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Preparation 2-Substituted-4-pyridylzinc Bromides *via* Direct Insertion of Active Zinc and Their Coupling Reactions

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Heterocyclic compounds which contain a pyridine moiety have played a very significant role in a wide range of organic compounds, such as pharmaceuticals, agrochemicals, medicinal chemistry, and material chemistry.[1] For example, bipyridine groups were found to be a key element in antibiotics, and pyridylpyrimidines were used as fungicides as well as tyrosine kinase inhibitors.[2] In addition, pyridine-containing oligomers are frequently found in liquid crystals.[3] More specific examples utilizing 4-pyridyl moiety are also found in a wide spread of fields in chemistry.[4] Consequently, new practical synthetic approaches for introducing a pyridine ring into complex organic molecules are of high value. To this end, transition-metal-catalyzed cross-coupling reactions of pyridylmetallic reagents have been frequently utilized. However, the preparation of electron-deficient pyridyl organometallic reagents has been a challenging subject mainly because of some difficulties such as instability and formation of by-products. In addition to those difficulties, the regiochemistry should be considered when the corresponding pyridylmetallic reagents were prepared because, unlike benzene, pyridine ring has unevenly distributed electrons.

To date, most of the studies utilizing pyridylmetallic reagents have been performed using 2-pyridylmetallics in the Suzuki,[5] Stille,[6] Grignard,[7] and Negishi[8] coupling reactions. Along with those works, a limited number of studies have been reported on the preparation of 3-pyridylmetallic halides such as 3-pyridylmagnesium,[9] 3-pyridylzinc,[10] 3-pyridylindium[11] halides, and 3-pyridylborates.[12] In contrast to those two pyridylmetallic reagents, the preparation and application of 4-pyridylmetallic reagent were not generally known. 4-Pyridylstananes were coupled with aryl halides in the presence of Pd-catalyst.[13] More extensive applications were performed with 4-pyridylborates in the fields of medicinal and material chemistry.[14] Contrary to our expectations, the usage of 4-pyridylzinc reagents, which have an exceptional functional group tolerance, has not been widely investigated.[15] In these studies, the organozinc reagents were prepared by typical lithiation of the pyridine ring followed by transmetallation with zinc halide. To the best of our knowledge, no report of the direct preparation of 4-pyridylzinc halide and its application has been revealed.

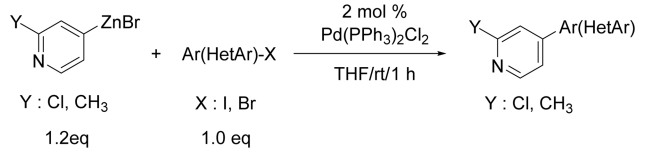
Interestingly, in association with our ongoing study on the preparation and application of organozinc reagents, we found that 4-pyridylzinc bromides were easily prepared by treatment of 4-bromopyridines with active zinc under mild conditions. Significantly, the resulting organozinc reagents were able to react with a variety of different electrophiles affording the corresponding coupling products in a reasonable manner.

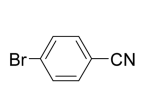
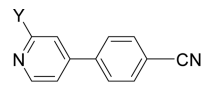
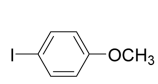
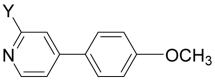
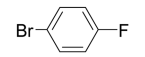
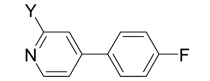
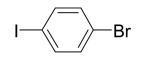
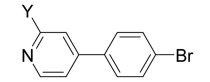
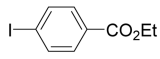
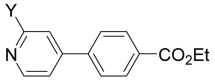
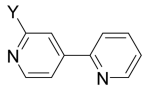
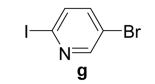
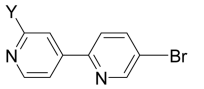
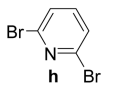
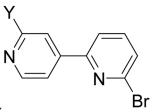
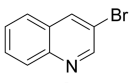
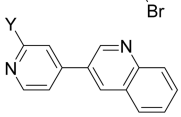
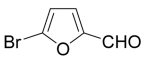
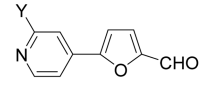
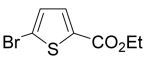
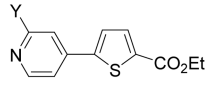
Prompted by our previous observation of 2- and 3-pyridylzinc bromides,[16] we have undertaken an expanded study on the pyridylzinc halide. This has been accomplished by the preparation and application of 4-pyridylzinc bromides, which were easily prepared by the treatment of the corresponding bromopyridines with active zinc. To this end, commercially available 4-bromopyridines, 4-bromo-2-chloropyridine and 4-bromo-2-methylpyridine, were chosen. Unfortunately, a simple 4-bromopyridine was sold as a salt which was not proper for our research scope. Readily available 4-bromo-2-chloropyridine was treated at room temperature with 2.0 equivalent of active zinc.[17] The oxidative addition of the active zinc to the carbon-bromine bond was completed in an hour in the presence of 20 mol % of LiCl affording the corresponding 2-chloro-4-pyridylzinc bromide (**A**). 2-Methyl-4-pyridylzinc bromide (**B**) was also prepared in the same manner used for **A**.

Investigation of the reactivity of the organozincs described above was performed first by the Pd-catalyzed carbon-carbon bond formation with various aryl halides. The results are summarized in Table 1. For the completion of cross-coupling reaction, Pd(II)-catalyst was used due to its easy of handling compared to $Pd(PPh_3)_4$. As depicted in Table 1, a better result was generally obtained from the coupling reaction using organozinc **A** in terms of isolated yield. The reason is not clear yet. Interestingly, the mild conditions worked well to complete the coupling reactions of organozincs both **A** and **B**. Several different types of functionalized aryl halides and heteroaryl halides were coupled with **A** and **B** in the presence of 2 mol % of $Pd(PPh_3)_2Cl_2$ at room temperature in THF, and most of the coupling reactions were completed within 1 h. An extended reaction time to 24 h did not help to improve the isolated yield throughout the whole coupling reactions. Functionalized iodo- and bromobenzenes (**a-e**) were first treated with **A** and **B**, and the coupling products (**1a-5a**, **1b-5b**) were obtained in moderate to good yields (entries 1-10, Table 1). Not only halogenated benzene

derivatives but also heteroaryl halides were efficiently coupled with **A** and **B** under the same conditions. Monobromopyridine (**f**) was also easily coupled with the organozincs to give rise to 2,4-bipyridines (**6a** and **6b**, Table 1) in 95% and 78% yields, respectively (entries 11 and 12). Dihalopyridines (**g** and **h**, entries 13-16, Table 1) were also good coupling partners to give interesting bipyridine derivatives (**7a**, **7b**, **8a**, and **8b**) leaving a bromine atom intact in moderate to good yields. 3-Bromoquinoline (**i**, Table 1) readily undergoes coupling reaction with organozincs **A** and **B** using a catalytic amount of $Pd(PPh_3)_2Cl_2$ to furnish **9a** and **9b** in moderate to good yields (entries 17 and 18, Table 1).

Table 1. Pd-Catalyzed coupling reactions with Aryl(HetAr) halides



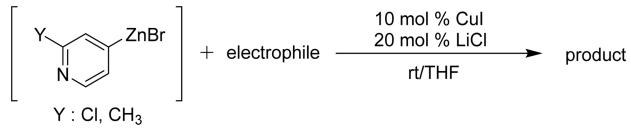
Entry	ArX	Product		Yield (%)[a]
1			**1a** Y : Cl	64
2	**a**		**1b** Y : CH_3	53
3			**2a** Y : Cl	56
4	**b**		**2b** Y : CH_3	54
5			**3a** Y : Cl	55
6	**c**		**3b** Y : CH_3	56
7			**4a** Y : Cl	79
8	**d**		**4b** Y : CH_3	43
9			**5a** Y : Cl	70
10	**e**		**5b** Y : CH_3	44
11			**6a** Y : Cl	95
12	**f**		**6b** Y : CH_3	78
13			**7a** Y : Cl	70
14	**g**		**7b** Y : CH_3	69
15			**8a** Y : Cl	59
16	**h**		**8b** Y : CH_3	44
17			**9a** Y : Cl	86
18	**i**		**9b** Y : CH_3	60
19			**10a** Y : Cl	66
20	**j**		**10b** Y : CH_3	62
21			**11a** Y : Cl	78
22	**k**		**11b** Y : CH_3	87

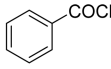
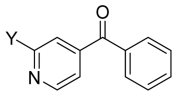
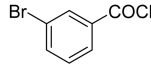
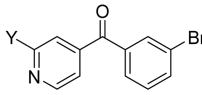
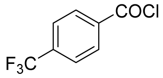
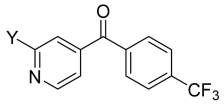
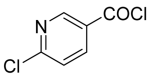
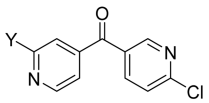
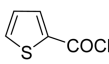
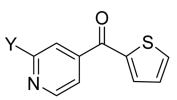
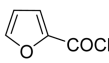
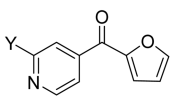
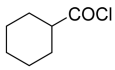
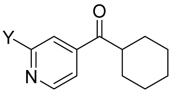
[a]Isolated yield (based on ArX)

The coupling reactions with a furan derivative (**j**, Table 1) resulted in the formation of **10a** and **10b** in moderate yields (entries 19 and 20, Table 1). Thiophene compound (**k**, Table 1) was also successfully employed as a coupling partner for the coupling reactions leading to the corresponding products (**11a** and **11b**, Table 1) in 78% and 87% yields, respectively.

Since many coupling reactions of organometallic reagents with acid chlorides have been frequently utilized to prove the formation of the organometallics and extend their applicability, we have also applied this strategy to our study. More coupling reactions of **A** and **B** with acid chlorides were carried out, and the results are summarized in Table 2. For the coupling reactions, a typical copper catalyst system (10 mol % CuI/20 mol % LiCl) was employed. Like other general reactions of organozinc reagents with acid chlorides, a copper-catalyst promoted the coupling reaction with benzoyl chloride to give the ketones (**12a** and **12b**, Table 2)

Table 2. Coupling reaction with acid chlorides



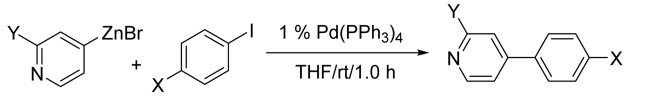
Entry	Electrophile[a]	Condition (time)	Product		Yield (%)[b]
1		1.0 h	 Y : Cl **12a**		92
2		24 h	CH_3 **12b**		53
3		1.0 h	 Y : Cl **13a**		59
4		24 h	CH_3 **13b**		nr[c]
5		1.0 h	 Y : Cl **14a**		68
6		24 h	CH_3 **14b**		48
7		1.0 h	 Y : Cl **15a**		66
8		24 h	CH_3 **15b**		59
9		24 h	 Y : Cl **16a**		79
10		24 h	CH_3 **16b**		53
11		24 h	 Y : Cl **17a**		79
12		24 h	CH_3 **17b**		60
13		1.0 h	 Y : Cl **18a**		59
14		1.0 h	CH_3 **18b**		48

[a]0.8 eq of electrophile used. [b]Isolated yield(based on electrophile). [c]no isolated product

in moderate to excellent yields. Again, in general, a longer reaction time was required in the case of 2-methyl-4-pyridylzinc bromide (**B**) to obtain a higher conversion to the product. Unfortunately, no coupling product was obtained from the coupling reaction of **B** with 3-bromobenzoyl chloride. In contrast, a moderate (59%) isolated yield was observed in the formation of **13a** under the same conditions. The reason is not yet clear. 4-Trifluoromethylbenzoyl chloride showed very similar reactivity giving rise to the ketones (**14a** and **14b**) in moderate yields (entries 5 and 6, Table 2). The treatment of **A** and **B** with 6-chloronicotinoyl chloride (entries 7 and 8, Table 2) at room temperature provided the corresponding ketones (**15a** and **15b**) in 66% and 59% yields, respectively. Other heteroaryl acid chlorides were effectively coupled with **A** and **B** in a similar manner affording ketones (**16-17**, Table 2). Alkyl carbonyl chlorides were also cross-coupled with 4-pyridylzincs (**A** and **B**) in a standard fashion generating **18a** and **18b** in 50% and 48% isolated yields, respectively (entries 13 and 14, Table 2).

Including our study, most of the aforementioned transition metal-catalyzed cross-coupling reactions of organozincs have been conducted with various coupling partners that contain relatively non-reactive functional groups toward organometallics, such as ester, ketone, nitrile, *etc.* For the preparation of a variety of 4-pyridyl derivatives, highly functionalized electrophiles are necessary as the coupling partner in the reactions. Therefore, we have performed the cross-coupling reactions of 4-pyridylzinc bromides with haloaromatic compounds containing relatively acidic protons. To this end, haloaromatic amines, and alcohols are reasonable candidates as coupling reactants, and the results are shown in Table 3. Since Pd(II)-catalysts have been used along with an appropriate ligand in the previous coupling reactions of organozinc reagents with haloaromatic amines and alcohols,[16] it seemed reasonable to apply these conditions to our study. Of interest, however, Pd(0)-catalyst turned out to be a more efficient catalyst than $Pd(PPh_3)_2Cl_2$ which was showing a very low conversion to the desired coupling product in this study. It was also found that increasing the reaction temperature affected neither the reaction progress nor the isolated yield. Notably, as described in Table 3, the $Pd(PPh_3)_4$-catalyzed coupling reactions were not affected by the presence of acidic protons (NH_2 and OH) providing the corresponding products (**19a**, **19b**, and **20a**, Table 3) in moderate yields. Surprisingly, it was found that both $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ were not effective for the coupling with 4-iodophenol,

Table 3. Coupling reaction with aniline and phenol

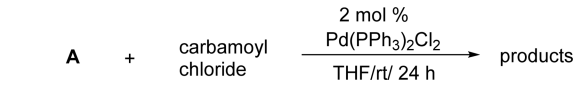


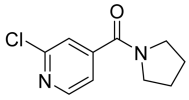
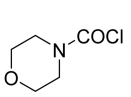
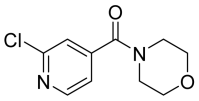
Y : Cl, CH_3 — 1.2 eq

X : NH_2, OH — 1.0 eq

Y : Cl	X : NH_2 (**19a**)	67%
Y : CH_3	X : NH_2 (**19b**)	37%
Y : Cl	X : OH (**20a**)	46%
Y : CH_3	X : OH (**20b**)	0%

Table 4. Coupling reaction of **A** with carbamoyl chloride



Entry	Electrophile	Product	Yield (%)[a]
1		 **21**	33
2		 **22**	36

[a]isolated yield (based on electrophile)

showing no detectable amount of coupling product.

For elucidation, a somewhat different type of coupling reaction was performed to synthesize the pyridine derivatives containing amide functionality. Amides are of special interest in synthetic organic chemistry because of their wide spectrum in natural compounds. This was accomplished by the coupling reaction of **A** with pyrrolidinecarbonyl chloride and morpholinecarbonyl chloride. As described in a previous study,[18] which showed the highest conversion to the product from the use of $Pd(PPh_3)_2Cl_2$, this catalytic system was employed furnishing the corresponding amides in moderate to good yields. The results are summarized in Table 4. The coupling reaction of organozinc **A** with 1-pyrrolidinecarbonyl chloride and morpholinecarbonyl chloride led to the desired products (**21** and **22**, Table 4) in 33% and 36% yields, respectively. To improve the yield, other conditions were tried (copper-catalyst system, elevated reaction temperature), but no significant change was observed.

In summary, we have described the development of a facile and general protocol for the synthesis of 4-substituted pyridine compounds. It has been accomplished by a transition-metal-catalyzed cross-coupling reaction of 4-pyridylzinc bromides prepared by the direct oxidative addition of active zinc into the corresponding bromopyridines under mild conditions. The use of typical Pd- and Cu-catalyst systems was important for the success to provide C-C bond forming products, such as biaryls, ketones, and tertiary amides in good to moderate yields. Even though some limitations have also been found in this study, this method provides an alternative protocol for the preparation of 4-substituted pyridine derivatives. Additional studies are currently in progress to optimize the reaction conditions and expand the scope to a variety of coupling partners.

Experimental

Preparation of 2-Chloro-4-pyridylzinc bromide (A). In an oven-dried 250 mL round-bottomed flask equipped with a stir bar was added 0.23 g of LiCl (20 mol %) under argon atmosphere. Next, 3.60 g of active zinc (Zn*, 110.0 mmol) were transferred into the flask. 4-Bromo-2-chloropyridine

(5.30 g, 55.0 mmol) was then cannulated into the flask at room temperature. The resulting mixture was stirred for 2 h at ambient temperature. The whole mixture was settled down and then the supernatant was used for the subsequent coupling reactions.

A Representative Procedure for Pd-catalyzed Coupling Reaction; 4-(4'-Methoxyphenyl)-2-methylpyridine (2b). A standard Pd(II)-catalyzed procedure was utilized for the coupling reaction. Purification by column chromatography on silica gel (5% ethyl acetate/95% heptane) afforded 4-(4'-methoxyphenyl)-2-methylpyridine (**2b**, 0.27 g) as a beige solid in 54% isolated yield. mp 96-97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, J = 5.2 Hz, 1H), 7.62-7.60 (m, 2H), 7.36 (br s, 1H), 7.31-7.29 (m, 1H), 7.03-7.01 (m, 2H), 3.88 (s, 3H), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 158.8, 149.6, 148.2, 130.7, 128.2, 120.6, 118.3, 114.5, 55.4, 24.6.

A Representative Procedure for Cu-catalyzed Coupling Reaction; (2-Methylpyridin-4-yl)-(4-(trifluoromethyl)-phenyl)methanone (14b). Carried out utilizing a standard CuI/LiCl catalytic system affording (2-methylpyridin-4-yl)-(4-(trifluoromethyl)phenyl)methanone (**14b**, 0.25 g) as a light yellow oil in 48% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.39 (dd, J = 0.8; 0.8 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 159.7, 149.9, 143.9, 139.0, 130.3, 128.1, 125.7 (q, CF_3), 124.8, 122.3, 119.9, 29.7; HRMS (*m/z*) calcd for $C_{14}H_{11}ONF_3$, 266.0793; found, 266.0796.

Preparation of 4-(2-Methylpyridin-4-yl)aniline (19b). Coupling reaction was carried out utilizing a standard Pd(0)-catalytic system. Purification by column chromatography on silica gel (10% ethyl acetate/90% heptane) afforded **19b** (0.14 g) as an orange solid in 37% isolated yield. mp 181-182 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.48 (d, J = 2.6 Hz, 1H), 7.50-7.48 (m, 2H), 7.33 (br s, 1H), 7.29-7.27 (m, 1H), 6.78-6.76 (m, 2H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.5, 149.3, 148.5, 147.5, 128.0, 120.1, 117.9, 115.2, 24.5.

Preparation of (2-Chloropyridin-4-yl)(morpholino)-methanone (22). Carried out utilizing a typical Pd(II)-catalyzed coupling procedure. Purification by column chromatography on silica gel (10% ethyl acetate/90% heptane) afforded 0.16 g of **22** as a yellow oil in 36% isolated yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 7.62 (s, 1H), 7.28 (s, 1H), 3.62 (br s, 2H), 3.49 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 149.8, 139.8, 129.7, 124.1, 66.7.

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