Cross-coupling between 3-Pyridylmagnesium Chlorides and Heteroaromatic Halides

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Abstract: Phenyl- and thienylpyridines were prepared by Pd(0)-catalyzed cross-coupling of 3-pyridylmagnesium chlorides with iodobenzene or iodothiophene at room temperature. Starting from bromo and chloro azines and diazines, the Ni(0)-catalyzed reaction proved more suitable to allow the synthesis of pyridylpyridines, pyridylquinolines and pyridyldiazines.

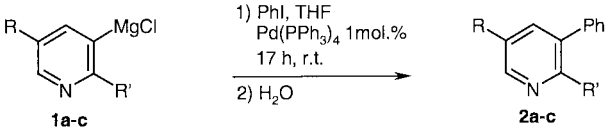
Key words: cross-coupling, heterocycles, magnesium, organometallic reagent, transition metals

Interest in azine (for example, pyridine, quinoline) and diazine natural products and pharmaceuticals,[1] as well as building blocks for various applications (such as material science and supramolecular chemistry)[2] has resulted in extensive efforts on synthetic methods.[3] Among the methods developed, the use of organometallics play an important role since such species can be either trapped with electrophiles (with metals such as lithium and magnesium) or involved in transition metal-catalyzed cross-coupling reactions (with metals such as magnesium,[4,5] zinc,[4,6] boron[4,7] and tin[4,7c,d,8]). As far as the reactivity of π-deficient heteroaromatic Grignard reagents in cross-coupling reactions is concerned, a survey of the literature revealed that few results have been reported.[9] Because of our interest in the synthesis of azine-containing natural products[1b,7d] and in the light of our knowledge of azine organometallics,[1b,10] we undertook the study of this reaction.

Recently, our laboratory developed an efficient access to pyridylmagnesium chlorides avoiding the use of lithiopyridines: bromine-magnesium exchange of bromopyridines could be effected using commercial isopropylmagnesium chloride (*i*-PrMgCl) in tetrahydrofuran at room temperature. Pyridylmagnesium chlorides thus obtained showed a good reactivity towards a large range of electrophiles.[11] We here describe the behavior of such pyridine Grignard reagents in catalyzed cross-coupling reaction with aromatic and heteroaromatic halides.

First of all, 3-pyridylmagnesium chlorides **1a**–**c** were prepared from the corresponding 3-bromopyridines and involved in the cross-coupling reaction with iodobenzene in a 'one-pot' procedure.[12] The reaction occurred at room temperature, in the presence of a catalytic amount of tetrakis(triphenylphosphine) palladium(0) [$Pd(PPh_3)_4$],[13] affording compounds **2a**–**c** in medium to good yields (Table 1).[12]

Table 1 Cross-Coupling Reactions of **1a**–**c** with Iodobenzene



1a-c **2a-c**

Entry	Pyridylmagnesium chloride	Product, Yield(%)[a]
1	**1a**: R = R′ = H	**2a**, 60[b]
2	**1b**: R = Br, R′ = H	**2b**, 52
3	**1c**: R = Br, R′ = F	**2c**, 58

[a] Isolated yields based on PhI.
[b] 61% using $Pd(PPh_3)_4$ 5mol %.

Starting from 3-pyridylmagnesium chloride, Pd(0)-catalyzed reaction with 2-iodothiophene was also performed under the same conditions, allowing the synthesis of thienylpyridine **3**.[14]

The study was then extended to π-deficient heteroaromatic halides. Since iodo derivatives are not commercially available, we turned to bromides and chlorides. Cross-coupling between pyridine Grignard **1a** and 2-bromopyridine could only be observed at THF reflux[15] when catalytic amounts of bis(dibenzylideneacetone) palladium(0) ($Pd(dba)_2$) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) were used[16] (Scheme).

In order to cross-couple quinolines and diazines, which are more prone to nucleophilic addition than pyridines due to their lower LUMO levels, we tried to find a more efficient catalyst. A survey of the literature[5] reveals that nickel, which is harder than palladium, is particularly efficient with bromides and chlorides, which are harder than iodides.[17] For this purpose, reactions between **1a** and 2,6- and 2,5-dibromopyridines were investigated under nickel

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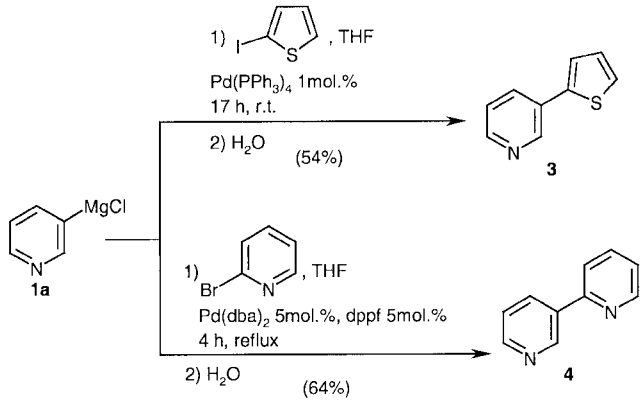
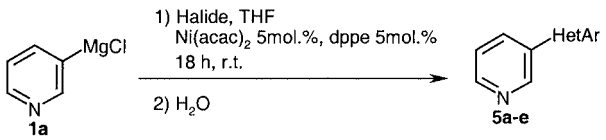


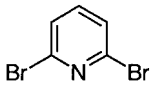
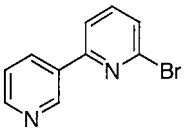
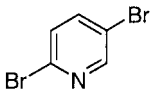
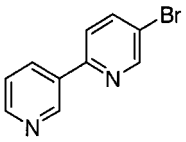
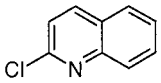
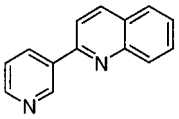
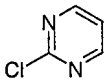
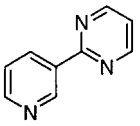
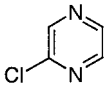
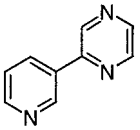
Scheme

catalysis. It was found that by using catalytic amounts of nickel(II) acetylacetonate [Ni(acac)$_2$] and diphenylphosphinoethane (dppe) in THF at room temperature, coupled products **5a**,**b** could be obtained, a complete regioselectivity at C2 being observed in the case of 2,5-dibromopyridine (entries 1 and 2). The coupling conditions were extended to the use of commercially available 2-chloroquinoline, 2-chloropyrimidine and 2-chloropyrazine to give the corresponding 3-pyridyl azines and diazines in good yields (entries 3 and 5) (Table 2).[18]

In conclusion, our methodology allowed cross-coupling reactions of 3-pyridylmagnesium chlorides catalyzed by palladium or nickel, starting from iodo, bromo, or chloro aromatics or heteroaromatics. Starting from 3-bromopyridines afforded, in a 'one-pot' procedure, pyridines, quinolines and diazines substituted by a pyridyl group. Our method is interesting since the other aryl organometallic substrates (with metals such as zinc, boron and tin) are usually prepared via their corresponding lithio derivatives, usually at low temperatures.[4]

Table 2 Cross-Coupling Reactions of **1a** with Haloazines and Halodiazines



Entry	Halo Substrate	Product	Yield(%)[a]
1		 **5a**	34[b]
2		 **5b**	61
3		 **5c**	76
4		 **5d**	69
5		 **5e**	69

[a] Isolated yields based on the halo substrate.
[b] 0% using Pd(dba)$_2$ 5mol.% and dppf 5mol%.

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(12) In a general procedure, the required 3-bromopyridine (1.2 mmol) was dissolved in THF (5 mL) and a solution of *i*-PrMgCl (1.4 mmol) in THF (0.70 mL) was added dropwise at r.t. to the mixture. After 1 h at the same temperature, the iodo derivative (1.0 mmol) and $Pd(PPh_3)_4$ (12 mg, 10 μmol) were introduced; the mixture was stirred for 17 h and quenched with an aqueous saturated NH_4Cl solution (5 mL). The aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, the solvents were evaporated under reduced pressure and the crude compound was chromatographed on a silica gel column. 3-Phenylpyridine(**2a**) starting from 3-bromopyridine and using iodobenzene (eluent: CH_2Cl_2–Et_2O, 90:10). Yield: 60%. The physical and spectral data are analogous to those obtained for a commercial sample. 3-Bromo-5-phenylpyridine(**2b**) starting from 3,5-dibromopyridine and using iodobenzene (eluent: CH_2Cl_2). Yield: 52%; the ^1H NMR data are in accordance with those of the literature;[19] ^{13}C NMR ($CDCl_3$) δ 120.7, 126.9 (2C), 128.4, 128.9 (2C), 135.9, 136.4, 137.7, 146.1, 149.1; IR (KBr): 3019, 1890, 1580, 1542, 1430, 1404, 1317, 1282, 1170, 1106, 1007, 880, 795, 763, 702, 670 cm^{-1}. Anal. Calcd for $C_{11}H_8BrN$ (234.10): C, 56.44; H, 3.44; N, 5.98. Found: C, 56.60; H, 3.51; N, 6.17%. 5-Bromo-2-fluoro-3-phenylpyridine(**2c**) starting from 3,5-dibromo-2-fluoropyridine and using iodobenzene (eluent: CH_2Cl_2). Yield: 58%; ^1H NMR ($CDCl_3$) δ 7.4 (m, 5 H, Ph), 7.9 (ddd, 1 H, J = 8.4, 2.5, 0.5 Hz, H_4), 8.15 (d, 1 H, J = 2.5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 116.5, 125.5, 128.5 (2C), 128.7 (2C), 128.9, 132.0, 142.5, 146.5, 159.0; IR (KBr): 3063, 1588, 1556, 1455, 1417, 1284, 1243, 1199, 1108, 1041, 1016, 901, 775, 731, 697, 636 cm^{-1}. Anal. Calcd for $C_{11}H_7BrFN$ (252.09): C, 52.41; H, 2.80; N, 5.56. Found: C, 52.19; H, 2.65; N, 5.48%.

(13) The toxicity of nickel salts led us to turn first to palladium-catalyzed cross-coupling reactions.

(14) 3-(2-Thienyl)pyridine(**3**)[20] using the general procedure,[12] starting from 3-bromopyridine and 2-iodothiophene (eluent: Et_2O–petroleum ether, 50:50). Yield: 54%; the ^1H NMR data are in accordance with those of the literature.[21]

(15) 2,3′-Bipyridine(**4**): $Pd(dba)_2$ (29 mg, 0.050 mmol), dppf (28 mg, 0.050 mmol) and, 10 min later, 2-bromopyridine (96 μL, 1.0 mmol) were added to THF (3 mL). After stirring for 30 min at r.t., this solution was transferred at r.t. to a freshly prepared (see general procedure 1) solution of 3-pyridylmagnesium chloride (1.2 mmol) in THF (5–6 mL). After 4 h at reflux, the mixture was quenched with an aqueous saturated NH_4Cl solution (5 mL) to give **4** (eluent: CH_2Cl_2–Et_2O, 90:10). Yield: 64%; the physical and spectral data are analogous to those obtained for a commercial sample.

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(18) In a general procedure, $Ni(acac)_2$ (13 mg, 0.050 mmol), dppe (20 mg, 0.050 mmol) and, 10 min later, the required 2-halo substrate (1.0 mmol) were added to THF (3 mL). After stirring for 30 min at r.t., this solution was transferred at r.t. to a freshly prepared (see general procedure 1) solution of 3-pyridylmagnesium chloride (1.2 mmol) in THF (5–6 mL). After 18 h at r.t., the mixture was quenched with an aqueous saturated NH_4Cl solution (5 mL). 6-Bromo-2-(3-pyridyl)pyridine(**5a**) starting from 2,6-dibromopyridine (eluent: CH_2Cl_2–Et_2O, 90:10). Yield: 34%; mp 82–84 °C (lit.[22] mp 73–74 °C). 5-Bromo-2-(3-pyridyl)pyridine (**5b**) starting from 2,5-dibromopyridine (eluent: CH_2Cl_2–Et_2O, 90:10). Yield: 61%; mp 72–74 °C (lit.[22] mp 75–77 °C); ^{13}C NMR ($CDCl_3$) δ 120.6, 121.9, 121.9, 124.3, 134.4, 139.1, 148.2, 150.4, 151.5, 153.6. Anal. Calcd for $C_{10}H_7BrN_2$ (235.08): C, 51.09; H, 3.00; N, 11.92. Found: C, 51.14; H, 3.06; N, 11.79%. 2-(3-Pyridyl)quinoline (**5c**) starting from 2-chloroquinoline (eluent: CH_2Cl_2–Et_2O, 90:10). Yield: 76%; mp 72 °C; the ^1H NMR data are in accordance with those of the literature;[6b] ^{13}C NMR ($CDCl_3$) δ 117.4, 122.6, 125.7, 126.3, 126.5, 128.7, 128.9, 133.9, 134.1, 136.1, 147.3, 147.7, 149.1, 153.5; IR (KBr): 2925, 2855, 1577, 1304, 1129, 1020, 811, 786, 755, 710 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2$ (206.25): C, 81.53; H, 4.89; N, 13.58. Found: C, 81.27; H, 5.02; N, 13.29%. 2-(3-Pyridyl)pyrimidine (**5d**) starting from 2-chloropyrimidine (eluent: CH_2Cl_2–Et_2O, 90:10). Yield: 69%; mp 52 °C (lit.[23] mp 48–49 °C); ^{13}C NMR ($CDCl_3$) δ 118.7, 122.3, 132.1, 134.4, 148.8, 150.3, 156.3 (2C), 161.9; IR (KBr): 3044, 2963, 2928, 2854, 1582, 1567, 1408, 1261, 1083, 1021, 787, 708 cm^{-1}. Anal. Calcd for $C_9H_7N_3$ (157.18): C, 68.78; H, 4.49; N, 26.73. Found: C, 68.54; H, 4.18; N, 26.42%. 2-(3-Pyridyl)pyrazine (**5e**)[24] starting from 2-chloropyrazine (eluent: CH_2Cl_2–Et_2O, 90:10). Yield: 69%; mp 92–94 °C; ^1H NMR ($CDCl_3$) δ 7.38 (dd, 1 H, J = 7.9, 4.5 Hz, $H_{5'}$), 8.27 (dt, 1 H, J = 7.9, 1.9 Hz, $H_{4'}$), 8.51 (d, 1 H, J = 1.5 Hz, H_5), 8.61 (d, 1 H, J = 1.5 Hz, H_6), 8.65 (dd, 4 H, J = 4.5, 1.9 Hz, $H_{6'}$), 9.00 (s, 1 H, H_3), 9.18 (d, 1 H, J = 1.5 Hz, $H_{2'}$); ^{13}C NMR ($CDCl_3$) δ 124.3, 130.1, 134.8, 142.4, 144.2, 144.9, 148.4, 150.8, 151.1; IR (KBr): 2925, 2854, 1416, 1082, 1013, 815, 702 cm^{-1}. Anal. Calcd for $C_9H_7N_3$ (157.18): C, 68.78; H, 4.49; N, 26.73. Found: C, 68.48; H, 4.19; N, 26.47%.

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