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Cross-Coupling Reactions of Phenylmagnesium Halides with Fluoroazines and Fluorodiazines

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The first nickel-catalyzed cross-coupling reactions between fluoroarenes and aryl organometallics using commercially available ligands are described. The nickel-catalyzed cross-coupling reactions between aryl Grignard reagents and fluoroazines and -diazines occurred in THF at room temperature using commercially available 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, or 1,1′-bis(diphenylphosphino)ferrocene as ligand. Various fluoro substrates such as pyridines, diazines (pyrazine, pyridazine), benzodiazines (quinoxaline), and quinolines were successfully involved in the reaction with phenylmagnesium halides (phenylmagnesium chloride, 2-methoxyphenylmagnesium bromide, and 4-methoxyphenylmagnesium bromide). The conditions used also allowed the cross-coupling of 4-fluorotoluene with arylmagnesium reagents.

Introduction

We describe here the first nickel-catalyzed cross-couplings between fluoroarenes and aryl organometallics using common ligands, such reactions being only known using N-heterocyclic carbene ligands.[1]

Interest in azine and diazine natural products either for pharmaceuticals or as building blocks for various applications within materials science and supramolecular chemistry has led to extensive efforts devoted to a variety of synthetic methodologies.[2] Transition-metal-catalyzed cross-couplings have proven to be an important method for preparing a number of complex heterocycles. In the azine and diazine series, several Negishi,[3,4] Suzuki,[3,5] Stille,[3,5b,d,6] and Kharasch[3,7] cross-coupling reactions have already been reported. The usefulness of cross-coupling chemistry to form unsymmetrical biaryls has been driven by the development of catalyst systems that have successively allowed the activation of aryl iodides, bromides, and chlorides, even at ambient temperature.

The activation of carbon−fluorine bonds is of importance since this reaction contributes to the fundamental understanding of the reactivity of such very stable bonds.[8] A variety of methods for the activation of carbon−fluorine bonds under mild conditions by stoichiometric amounts of soluble transition-metal complexes have been established in the last two decades.[9] However, homogeneous stoichiometric or catalytic transformations of aromatic fluorides are mainly limited to defluorination reactions.[10] Few examples have been reported in which carbon−fluorine bond cleavage has been followed by carbon−carbon bond formation.[11] Since the development of the nickel-catalyzed cross-coupling of Grignard reagents (Kharasch) in the early 1970s,[7c,12] very few reac-

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tions with fluoro substrates have been reported. The nickel-mediated cross-coupling reactions of fluorobenzene with alkylmagnesium chlorides were reported in 1973[13] and 1999.[11h] Much more recently, the selective cross-coupling of aryl fluorides with arylmagnesium halides at room temperature, mediated by the complex bis[1,3-di-(2′,6′-diisopropylphenyl)imidazolin-2-ylidene]nickel(0), has been reported.[1]

Under palladium catalysis, cross-coupling reactions between arylmagnesium halides and aryl chlorides, bromides, or iodides are possible at rt.[7f,l−k,14] Nickel, which is harder than palladium, was most often chosen for chlorides[7d,h,k] and fluorides,[1,11h,13] which are harder than bromides and iodides. So we turned to nickel catalysis for the reactions between phenylmagnesium halides and fluoroazines and -diazines. For the activation of C−F bonds, the low-valent metal must be combined with a strongly Lewis basic, electron-donating, and sterically demanding ligand.[15] The cross-coupling of phenylmagnesium halides with fluorobenzenes was found to be feasible using N-heterocyclic carbene ligands.[1] Nevertheless, the use of π-deficient substrates, for which the oxidative addition step is easier, led us to consider the use of commercially available ligands such as 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), and 1,1′-bis(diphenylphosphino)-ferrocene (dppf). We therefore decided to study the cross-coupling reaction of phenylmagnesium halides with fluoroazines and -diazines using these commercially available ligands.

TABLE 1. Cross-Coupling of Phenylmagnesium Halides with Fluoroazines and Fluorodiazines

entry	fluoro substrate	product	yield[a]
1	**1a**	**2a**:[b]	82%[c]
2	**1b**	**2b**:[b]	64%[c,d]
3	**1c**	**2c**:[b]	61%[c]
4	**1a**	**3a**:[e]	80%[c]
5	**1b**	**3b**:[e]	89%[c]
6	**1b**	**3c**:[f]	30%[c] 79%[g]
7	**4a**	**5a**:[b]	81%[c]
8	**4b**	**5b**:[e]	59%[c]
9	**4c**	**5c**:[e]	67%[h]
10	**6a**	**7a**:[b]	97%[c]
11	**6b**	**7b**:[b]	91%[h]

[a] Isolated yields based on the fluoro substrate. [b] Using PhMgCl. [c] Using $NiCl_2$(dppe). [d] The same result was obtained using Ni(acac)$_2$ (5 mol %) and dppe (5 mol %). [e] Using 4-MeOPhMgBr. [f] Using 2-MeOPhMgBr. [g] Using Ni(acac)$_2$ (5 mol %) and dppp (5 mol %). [h] Using Ni(acac)$_2$ (5 mol %) and dppf (5 mol %).

Results and Discussion

The reaction of phenylmagnesium chloride with fluoropyridines **1a**−**c** was carried out in THF using [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) [$NiCl_2$(dppe)] as ligand. Under these conditions, the corresponding phenylpyridines **2a**−**c** were formed at ambient temperature. Compared to well-defined $NiCl_2$(dppe), an in situ catalyst system using bis(acetylacetonate)nickel(II) [Ni(acac)$_2$] and dppe gave the same results (Table 1, entries

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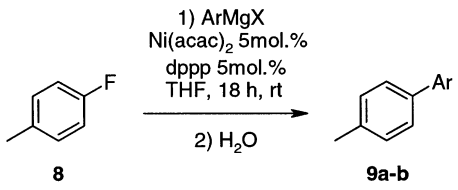
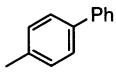
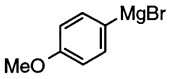
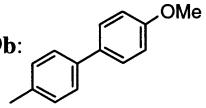
TABLE 2. Cross-Coupling of Phenylmagnesium Halides with 8



8 **9a-b**

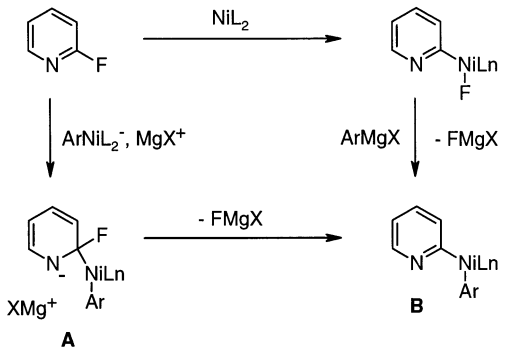
entry	ArMgX	product	yield[a]
1	PhMgCl	**9a**: 	59%
2		**9b**: 	61%

[a] Isolated yields based on 4-fluorotoluene.

1−3). To evaluate the scope of this reaction, experiments employing different fluorides and phenylmagnesium halides were conducted. 4-Methoxyphenylmagnesium bromide was likewise successfully used in the reaction with **1a,b** to afford compounds **3a,b** in good yields (Table 1, entries 4 and 5). For more hindered 2-methoxyphenylmagnesium bromide, dppp, which usually gives better results than dppe,[7] was employed and improved the yield of the reaction (Table 1, entry 6). Due to their lower LUMO levels, diazines and quinolines are more prone to nucleophilic addition than pyridines. Nevertheless, under the remarkably mild conditions used, no nucleophilic addition was observed and the reaction was also feasible. Fluoropyrazine (**4a**), 3-fluoro-6-phenylpyridazine (**4b**), and 4-fluoro-2-phenylquinazoline (**4c**) were synthesized from the corresponding chlorides according to published procedures[16] and submitted to cross-coupling reactions with phenylmagnesium halides. The reactions proceeded in yields comparable to those obtained in the pyridine series (Table 1, entries 7−9). 3-Fluoroquinoline (**6a**) was also prepared[17] and shown to react with phenylmagnesium chloride under the same reaction conditions in an excellent yield. Concerning 6-fluoro-2-methylquinoline (**6b**), the result was largely dependent on the ligand used: dppe did not afford the coupled product **7b** satisfactorily, whereas dppf allowed the product to be formed in a high yield (Table 1, entries 10 and 11).

With these efficient conditions in hand for the reaction with activated, electron-poor fluoro substrates, we then investigated the reaction with less activated 4-fluorotoluene (**8**). In this case, we have also shown that it is advantageous to use dppp as ligand instead of dppe; the reaction performed under these conditions afforded the coupled products **9a,b** in medium to good yields (Table 2). The yields obtained in the benzene series are slightly lower than those reported by Herrmann.[1] This may be attributed to the poorer electron-donating ability of phosphine ligands compared to N-heterocyclic carbenes.[18]

SCHEME 1



Since fluoropyridines are known to react directly with nucleophiles including aryllithiums,[19] a reaction mechanism involving nucleophilic aromatic substitution[20] was suspected. However, it could be discarded since reactions of the fluoro derivatives **1a,b** conducted without catalyst did not allow the cross-coupling products **2a,b** to be formed. Elimination−addition via azyne or diazyne intermediates[21] was also unlikely considering the selectivity of the reaction. Herrmann suggests a polar reaction through oxidative addition[22] instead of radical pathways[23] for the cross-coupling between arylmagnesium bromides and fluorobenzenes.[1] Another possibility is an addition−elimination mechanism to the π-deficient fluoro substrate (instead of oxidative addition followed by transmetalation) for the reaction of compounds **1b,c** and **4a**−**c**.[7i] The initial addition step of the "ate" species $ArNiL_2^-$,MgX^+ (obtained by the reaction of NiL_2 with the Grignard reagent) to the fluoro substrate could lead to the stabilized magnesium amide **A**, which could furnish the intermediate **B** after elimination of magnesium halide (Scheme 1).

Conclusion

We have described the first cross-coupling reactions of fluoroazines and -diazines with aryl Grignard reagents. These nickel-catalyzed reactions were accomplished in THF at rt using commercially available ligands such as dppe, dppp, and dppf. The conditions used were suitable for the reaction of electron-poor fluoro substrates but also, albeit to a lesser extent, for the reaction of fluorobenzenes.

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Experimental Section

General Procedures. The NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75 MHz). The main IR absorptions of the IR spectra are given.

Starting Materials. THF was distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[24] Reactions were carried out under dry N_2. Petrol refers to petroleum ether (bp 40−60 °C). Fluoropyrazine (**4a**),[16a] 3-fluoro-6-phenylpyridazine (**4b**),[16b] 4-fluoro-2-phenylquinazoline (**4c**),[16a] and 3-fluoroquinoline (**6a**)[17] have been prepared following procedures described in the literature.

After the reaction, the organic layer was dried over $MgSO_4$, the solvents were evaporated under reduced pressure, and, unless otherwise noted, the crude compound was chromatographed on a silica gel (Geduran Si 60, 0.063−0.200 mm) column (the eluent is given in the product description).

3-Phenylpyridine (2a). $NiCl_2$(dppe) (26 mg, 50 μmol) was suspended in 3 mL of dry and degassed THF under an atmosphere of dry nitrogen. After addition of 3-fluoropyridine (87 μL, 97 mg, 1.0 mmol) the mixture was stirred for 5 min at rt until catalysis was commenced by dropwise addition of PhMgCl (1.2 mmol) in THF (0.60 mL). After 18 h at rt, the solvent was removed under reduced pressure. The residue was dissolved in concd NH_4OH (0.5 mL) and AcOEt (50 mL) to give 82% **2a** (eluent CH_2Cl_2/Et_2O, 90:10). The physical and spectral data are analogous to those obtained for a commercial sample.

2-Phenylpyridine (2b). The procedure is as described for **2a** but using 2-fluoropyridine (87 μL, 97 mg, 1.0 mmol) instead of 3-fluoropyridine: yield 64% (eluent CH_2Cl_2). The physical and spectral data are analogous to those obtained for a commercial sample.

4-Methyl-2-phenylpyridine (2c). The procedure is as described for **2a** but using 2-fluoro-4-methylpyridine (111 mg, 1.0 mmol) instead of 3-fluoropyridine: yield 61% (eluent CH_2Cl_2/Et_2O, 95:5). The physical and spectral data are analogous to those obtained for a commercial sample.

3-(4-Methoxyphenyl)pyridine (3a). The procedure is as described for **2a** but using 4-methoxyphenylmagnesium bromide (1.2 mmol) in THF (2.4 mL) instead of PhMgCl: yield 80% (eluent CH_2Cl_2/Et_2O, 85:15); mp 57 °C. The physical and spectral data are analogous to those previously described.[25]

2-(4-Methoxyphenyl)pyridine (3b). The procedure is as described for **2a** but using 2-fluoropyridine (87 μL, 97 mg, 1.0 mmol) instead of 3-fluoropyridine, and 4-methoxyphenylmagnesium bromide (1.2 mmol) in THF (2.4 mL) instead of PhMgCl: yield 89% (eluent CH_2Cl_2/Et_2O, 95:5); mp 47−49 °C (lit.[26] mp 47−50 °C). The physical and spectral data are analogous to those previously described.[27]

2-(2-Methoxyphenyl)pyridine (3c).[26] The procedure is as described for **2a** but using 2-fluoropyridine (87 μL, 97 mg, 1.0 mmol) instead of 3-fluoropyridine, 2-methoxyphenylmagnesium bromide (1.2 mmol) in THF (1.2 mL) instead of PhMgCl, and $Ni(acac)_2$ (13 mg, 50 μmol) and dppp (21 mg, 50 μmol) instead of $NiCl_2$(dppe): yield 79% (eluent CH_2Cl_2/Et_2O, 95:5); ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 7.02 (d, 1H, J = 8.3 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.2 (m, 1H), 7.37 (td, 1H, J = 7.8, 1.7 Hz), 7.7 (m, 3H), 8.71 (dd, 1H, J = 4.3, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 56.0, 111.7, 121.4, 122.0, 125.5, 129.5, 130.3, 131.5, 136.0, 149.8, 156.4, 157.2; IR (KBr) ν 3062, 3005, 2938, 2836, 1602, 1586, 1495, 1463, 1438, 1424, 1259, 1242, 1026, 754 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO$ (185.23): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.60; H, 6.08; N, 7.41.

2-Phenylpyrazine (5a). The procedure is as described for **2a** but using fluoropyrazine (98 mg, 1.0 mmol) instead of 3-fluoropyridine: yield 81% (eluent CH_2Cl_2/Et_2O, 90:10); mp 75 °C (lit.[28] mp 73 °C). The physical and spectral data are analogous to those previously described.[29,7j]

3-(4-Methoxyphenyl)-6-phenylpyridazine (5b).[30] The procedure is as described for **2a** but using 3-fluoro-6-phenylpyridazine (174 mg, 1.0 mmol) instead of 3-fluoropyridine, and 4-methoxyphenylmagnesium bromide (1.2 mmol) in THF (2.4 mL) instead of PhMgCl: yield 59% (eluent CH_2Cl_2/Et_2O, 95:5); mp 202−203 °C; ^1H NMR ($CDCl_3$) δ 4.89 (s, 3H), 7.00 (m, 2H), 7.45 (m, 3H), 7.83 (m, 2H), 8.07 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 55.8, 114.8, 123.9, 124.5, 127.1, 127.2, 128.7, 129.0, 129.4, 130.3, 136.6, 157.4; IR (KBr) ν 3053, 2967, 2936, 2837, 1608, 1511, 1428, 1400, 1260, 1248, 1175, 1035, 1024, 821, 791, 749, 693 cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_2O$ (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.69; H, 5.44; N, 10.45.

4-(4-Methoxyphenyl)-2-quinazoline (5c). The procedure is as described for **2a** but using 4-fluoro-2-phenylquinazoline (224 mg, 1.0 mmol) instead of 3-fluoropyridine, 4-methoxyphenylmagnesium bromide (1.2 mmol) in THF (2.4 mL) instead of PhMgCl, and $Ni(acac)_2$ (13 mg, 50 μmol) and dppf (27 mg, 50 μmol) instead of $NiCl_2$(dppe): yield 67% (eluent CH_2Cl_2/petrol, 70:30). The physical and spectral data are analogous to those previously described.[31]

3-Phenylquinoline (7a).[32] The procedure is as described for **2a** but using 3-fluoroquinoline (147 mg, 1.0 mmol) instead of 3-fluoropyridine: yield 97% (eluent CH_2Cl_2/Et_2O, 95:5); ^1H NMR ($CDCl_3$) δ 7.5 (m, 7H), 7.83 (dd, 1H, J = 8.1, 1.0 Hz), 8.08 (d, 1H, J = 8.4 Hz), 8.25 (d, 1H, J = 2.1 Hz), 9.13 (d, 1H, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 127.4, 127.8, 128.4, 128.5, 129.6, 129.6, 129.8, 130.0, 133.7, 134.3, 138.2, 147.7, 150.3. Anal. Calcd for $C_{15}H_{11}N$ (205.26): C, 87.77; H, 5.40; N, 6.82. Found: C, 87.82; H, 5.41; N, 6.69.

2-Methyl-6-phenylquinoline (7b). The procedure is as described for **2a** but using 6-fluoro-2-methylquinoline (161 mg, 1.0 mmol) instead of 3-fluoropyridine, and $Ni(acac)_2$ (13 mg, 50 μmol) and dppf (27 mg, 50 μmol) instead of $NiCl_2$(dppe): yield 91% (eluent CH_2Cl_2/Et_2O, 90:10); mp 90−91 °C; ^1H NMR ($CDCl_3$) δ 2.77 (s, 3H), 7.32 (d, 1H, J = 8.4 Hz), 7.35 (m, 3H), 7.64 (m, 2H), 7.87 (m, 2H), 8.02 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 122.8, 125.6, 127.0, 127.7, 128.0, 129.3, 129.3, 129.5, 136.8, 138.8, 140.7, 147.5, 159.3; IR (KBr) ν 3051, 2989, 2922, 1596, 1489, 1450, 1371, 1314, 1223, 1126, 892, 842, 815, 782, 764, 701 cm^{-1}. Anal. Calcd for $C_{16}H_{13}N$ (219.29): C, 87.64; H, 5.98; N, 6.39. Found: C, 87.71; H, 6.10; N, 6.14.

1-Methyl-4-phenylbenzene (9a). The procedure is as described for **2a** but using 4-fluorotoluene (110 μL, 110 mg, 1.0 mmol) instead of 3-fluoropyridine, and $Ni(acac)_2$ (13 mg, 50 μmol) and dppp (21 mg, 50 μmol) instead of $NiCl_2$(dppe): yield 59% (eluent petrol/CH_2Cl_2, 90:10). The physical and spectral data are analogous to those obtained for a commercial sample.

4-Methoxy-4′-methylbiphenyl (9b). The procedure is as described for **2a** but using 4-fluorotoluene (110 μL, 110 mg, 1.0 mmol) instead of 3-fluoropyridine, 4-methoxyphenylmagnesium bromide (1.2 mmol) in THF (2.4 mL) instead of PhMgCl, and $Ni(acac)_2$ (13 mg, 50 μmol) and dppp (21 mg, 50 μmol) instead of $NiCl_2$(dppe): yield 59% (eluent petrol/CH_2Cl_2, 90:10); mp 110−111 °C (lit.[33] mp 107 °C). The physical and spectral data are analogous to those previously described.[33]

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