Nickel- and Palladium-Catalyzed Cross-Coupling Reaction of Polyfluorinated Arenes and Alkenes with Grignard Reagents

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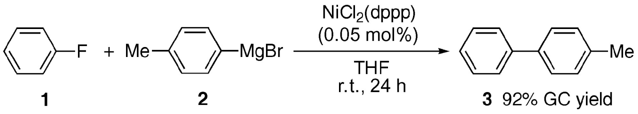
Abstract: The cross-coupling reaction of fluorobenzene with an aryl Grignard reagent has been reinvestigated which revealed that the reaction readily proceeds under ordinary conditions using a catalytic amount of $NiCl_2$(dppp) even at room temperature. The use of nickel catalysts and Grignard reagent is essential for the activation of the carbon–fluorine bond. The palladium catalyst is also effective for the 1,2-difluorobenzene and trifluorobenzenes to selectively produce the corresponding mono-coupled products while the nickel-based catalyst system affords a mixture of the mono-coupled product and di- or tri-coupled product.

Key words: cross-coupling, nickel, palladium, Grignard reagent, fluoroarene

Since the early study of the reaction of aryl and alkenyl halides with Grignard reagents in the presence of an iron or nickel catalyst was independently reported by the research groups of Kochi, Corriu, and Kumada in the early 1970s,[2] the transition metal-catalyzed cross-coupling reaction has become the most powerful and promising synthetic tool for the construction of carbon–carbon and carbon–heteroatom bonds.[3] A variety of organometallic reagents have already been successfully utilized for the catalytic system, as represented by the Suzuki–Miyaura (B), Hiyama (Si), Negishi (Zn), and Kosugi–Migita–Stille (Sn) reactions. On the other hand, recent interests in the cross-coupling reaction seems to be concentrated on the development of reaction systems involving less reactive substrates such as aryl chlorides,[4,5] aryl cyanides,[6] and aryl ethers.[7]

Until recently, aryl fluorides were regarded as an uncommon coupling partner for the transition metal-catalyzed cross-coupling reaction due to the strong carbon–fluorine bond (154 kcal/mol for C_6F_6), and the resulting lack of reactivity for oxidative addition.[8] Although the reaction conditions were not optimized at that time, however, one of us, together with Kumada, had already found in 1973 that the nickel-catalyzed cross-coupling reaction was also applicable to aryl fluorides.[2d,e] This was the first demonstration of the catalytic cleavage of the sp^2-carbon–fluorine bond. Twenty years later, the rhodium-catalyzed hydrogenation of aryl fluorides was reported by Aizenberg and Milstein in 1994.[9] Since then, several reports on the transition metal-catalyzed cross-coupling reactions utilizing a number of activated aryl fluorides such as *o*-fluorobenzaldimine,[10] fluoroarene–chromium complex,[11] fluoroazine and diazine,[12] *o*-fluoronitro-benzene,[13] and o-fluorobenzoates[14] have appeared. Very recently, the cross-coupling reaction of unactivated aryl fluorides was also reported using a nickel catalyst with a bulky and highly electron-donating carbene ligand by Herrmann[15] or a palladium catalyst with a microwave apparatus by Dankwardt.[16] These publications prompted us to report our recent results on the nickel- and palladium-catalyzed cross-coupling reaction of fluoroarenes and fluoroalkenes with Grignard or organozinc reagents.[17]

Monofluorobenzene Based on a previous observation we first reexamined the reaction conditions for the cross-coupling reaction of fluorobenzene (**1**) with 4-methylphenylmagnesium bromide (**2**) as a model reaction to reveal that the reaction readily proceeds under ordinary conditions using 0.05 equivalents of $NiCl_2$(dppp)[18] as a catalyst even at room temperature to afford 4-methylbiphenyl (**3**) in 92% GC yield after 24 hours (Scheme 1).



Scheme 1 Cross-coupling reaction of fluorobenzene with 4-MeC_6H_4MgBr

Other phosphine ligands examined in the screening of the catalyst system were less effective: $NiCl_2(PEt_3)_2$, 34%; $NiCl_2(PCy_3)_2$, 64%; $NiCl_2(PPh_3)_2$, 53%; $NiCl_2$(dppb), 26%; $NiCl_2$(dppf), 65%. The catalyst loading can be reduced to 0.01 equivalents without any loss in the product yield, as optimized in another experiment. It should be noted that the palladium catalysts, such as $PdCl_2(PPh_3)_2$, $PdCl_2$(dppb), and $PdCl_2$(dppf), were totally ineffective and the other organometallic reagents such as organoboron, silicon, zinc, zirconium, and tin compounds produced only a trace amount of the product.[19] The reason for the specificity to the organomagnesium compounds remains to be clarified, but the interaction between the magnesium atom and the fluorine atom might play an essential role in the oxidative addition process. The reaction conditions for the cross-coupling reaction of fluorobenzene (**1**) with *n*-butylmagnesium bromide were also screened in a similar manner to reveal that $NiCl_2$(dppp) is still the most

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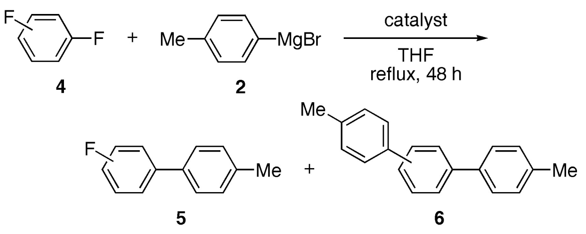
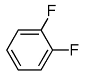
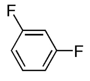
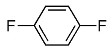
Table 1 Cross-Coupling Reaction of Difluorobenzenes with 4-MeC_6H_4MgBr[a]



a: 1,2-isomers, **b**: 1,3-isomers, **c**: 1,4-isomers

Entry	Substrate	Catalyst	Yield (%)[b]	
			5	**6**
1	 **4a**	$NiCl_2$(dppp)	38	40
2		$NiCl_2$(dppp)[c]	24	40
3		$PdCl_2$(dppf)	91	0
4	 **4b**	$NiCl_2$(dppp)	37	36
5		$NiCl_2$(dppp)[c]	11	78
6		$PdCl_2$(dppf)	15	0
7	 **4c**	$NiCl_2$(dppp)	23	45
8		$NiCl_2$(dppp)[c]	10	87
9		$PdCl_2$(dppf)	6	0

[a] Reaction conditions: difluorobenzene **4** (1.0 mmol), 4-MeC_6H_4MgBr (**2**, 1.5 mmol), and catalyst (0.01 mmol), THF (5.0 mL), reflux, 48 h.

[b] Determined by GC and NMR analysis with eicosane and 1,3,5-trimethoxybenzene as an internal standard, respectively.

[c] Larger amounts of catalyst (0.05 mmol) and the Grignard reagent (5.0 mmol) were employed.

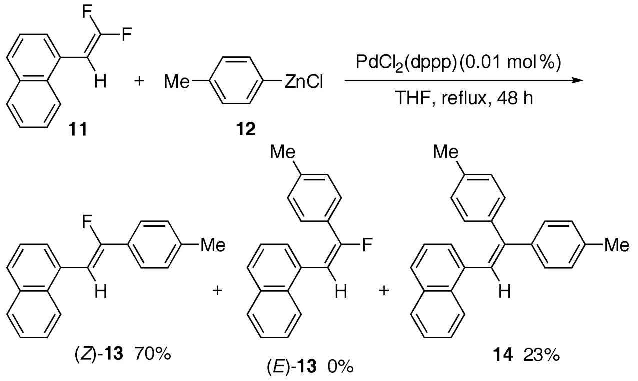
effective to afford *n*-butylbenzene in 93% yield after 24 hours of stirring under reflux.

Difluorobenzene We next examined the cross-coupling reaction of 1,2-, 1,3-, and 1,4-difluorobenzenes (**4a**–**c**) with the aryl Grignard reagent **2** as shown in Table 1. Under the optimized conditions using 0.01 equivalents of $NiCl_2$(dppp) and 1.5 equivalents of the Grignard reagent **2**, a mixture of the corresponding mono-coupled product **5** and di-coupled product **6** was obtained in the total yields ranging from 68% to 78% (entries 1, 4, and 7).[20] When the amounts of the nickel catalyst and the Grignard reagent were increased to 0.05 and 5 equivalents, respectively, the di-coupled product **6** dominated over the mono-coupled product **5** (entries 5 and 8), except for 1,2-difluorobenzene (**4a**) probably due to the steric hindrance between the *ortho* substituents (entry 2). In our efforts to determine the catalyst system suitable for the selective formation of the mono-coupled product **5**, $PdCl_2$(dppf) was found to be exceptionally effective for the coupling reaction of 1,2-difluorobenzene (**4a**) to exclusively afford the corresponding mono-coupled product **5a** in 91% yield (entry 3). Based on the observation that the other difluorobenzenes were ineffective in the palladium-based catalyst system (entries 6 and 9), a chelating effect of the adjacent fluorine atom was expected to play a crucial role in promoting the oxidative addition of the carbon–fluorine bond, but all attempted reactions with 2-methoxy-, 2-chloro-, and 2-hydroxyfluorobenzenes resulted only in the formation of undesired products.

Trifluorobenzene The coupling reaction was extended to the reaction of 1,2,3- and 1,3,5-trifluorobenzenes (**7a**,**b**) with the aryl Grignard reagent **2** as summarized in Table 2. In the reaction of 1,2,3-trifluorobenzene (**7a**) using the nickel catalyst, the corresponding di-coupled product **9a**[21] was exclusively obtained in 41% yield (entry 1), while the reaction of 1,3,5-trifluorobenzene (**7b**) afforded the tri-coupled product **10b** in 60% yield along with the di-coupled product **9b**[22] in 7% yield (entry 3): in the di-coupled product **9a**, the steric hindrance around the remaining *ortho*-fluorine atom could be responsible for preventing any further reaction. On the other hand, the reactions with palladium catalysts, such as $PdCl_2$(dppf) and $PdCl_2(PPh_3)_2$, almost exclusively afforded the corresponding mono-coupled products **8a**[23] and **8b** in 69% and 60% yields, respectively (entries 2 and 4).

The higher reactivity of the trifluorobenzenes than the difluorobenzenes (entry 4, Table 2 vs. entry 6, Table 1) is obviously attributable to the successive introduction of the electronegative fluorine atom.

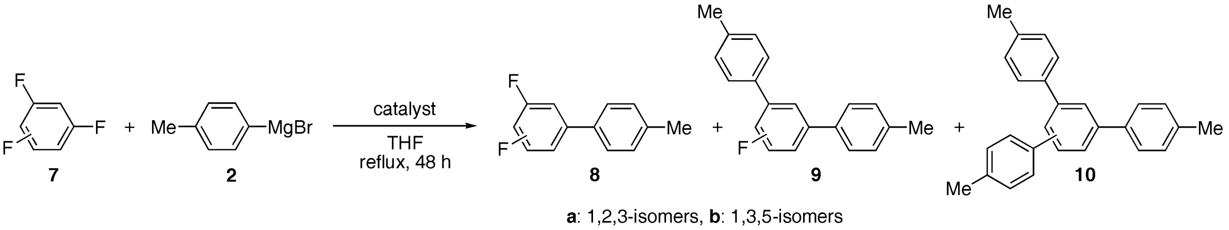
***gem*-Difluoroalkene** Finally, we applied the catalyst system to the cross-coupling reaction of *gem*-difluoroalkene **11** (Scheme 2).

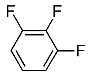
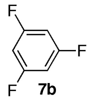


Scheme 2 Cross-coupling reaction of *gem*-difluoroalkene with an arylzinc reagent

The palladium-based catalyst system with $PdCl_2$(dppp) was most effective for the selective formation of mono-coupled product (*Z*)-**13**[24] and, in sharp contrast to the reactions of fluroarenes, arylzinc reagent **12** was found to be more effective than the Grignard reagent to produce the mono-coupled product (*Z*)-**13** in 70% yield after 48 hours of stirring under reflux, along with di-coupled product **14**[25] in 23% yield; the formation of an isomer (*E*)-**13** was not observed. In a similar reaction using $NiCl_2$(dppp) and an excess amount of the aryl Grignard reagent **2**, the di-coupled product **14** was obtained in 58% yield as a major product. It is noted that the coupling reaction of the difluoroalkene **11** with the aryl Grignard reagent **2** proceeded even in the absence of the transition metal catalysts

Table 2 Cross-Coupling Reaction of Trifluorobenzenes with 4-MeC$_6$H$_4$MgBr[a]



Entry	Substrate	Catalyst	Catalyst (equiv)	**2** (equiv)	Yield (%)[b]		
					8	**9**	**10**
1	 **7a**	NiCl$_2$(dppp)	0.05	6.0	0	41	0
2		PdCl$_2$(dppf)	0.01	1.5	69	9	0
3	 **7b**	NiCl$_2$(dppp)	0.05	6.0	0	7	60
4		PdCl$_2$(PPh$_3$)$_2$	0.01	1.5	60	9	0

[a] Reaction conditions: trifluorobenzene **7** (1.0 mmol), 4-MeC$_6$H$_4$MgBr (**2**, 6.0 or 1.5 mmol), catalyst (0.05 mmol or 0.01 mmol), THF (5.0 mL), reflux, 48 h.

[b] Determined by GC and NMR analysis with eicosane and 1,3,5-trimethoxybenzene as an internal standard, respectively.

probably due to the addition–elimination mechanism, but the geometry of the double bond was confused thereby producing a mixture of the isomers, (*Z*)-**13** and (*E*)-**13**,[26] in the ratio of 1:4 in 50% total yield (68% conversion after 48 h of stirring under reflux).

In summary, the cross-coupling reaction of fluoro-arenes with Grignard reagents was reexamined and revealed that the use of nickel catalysts and the Grignard reagent is essential for the activation of the carbon–fluorine bond. The palladium catalyst was also effective for the polyfluorinated arenes and alkenes to selectively afford the corresponding mono-coupled products.

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(18) Ligand abbreviation:
dppp = 1,3-bis(diphenylphosphino)propane,
dppb = 1,4-bis(diphenylphosphino)butane, and
dppf = 1,1′-bis(di-phenylphosphino)ferrocene.

(19) *n*-BuB(OH)$_2$, 4%; 4-MeC$_6$H$_4$SiF$_3$, trace; *n*-BuZnCl, 7%; *n*-C$_6$H$_{13}$CH=CHZrCp$_2$Cl, 0%; *n*-Bu$_4$Sn, trace.

(20) **A Typical Procedure for the Cross-Coupling Reactions.** To a suspension of PdCl$_2$(dppp) (7.8 mg, 0.01 mmol) and 1,2-difluorobenzene (**4a**, 115 mg, 1.0 mmol) in THF (3.0 mL) was added 4-MeC$_6$H$_4$MgBr (**2**, 1.0 M THF solution; 1.5 mL, 1.5 mmol) at r.t. and the mixture was heated under reflux for 48 h. The reaction was monitored by GC analysis with eicosane (54 mg) as an internal standard to reveal that the reaction completed within 48 h and 2-fluoro-4′-methylbiphenyl (**5a**) was formed in 91% yield. The further purification was performed with column chromatography on silica gel and high performance liquid chromatography (HPLC).

(21) **2-Fluoro-1,3-bis(4-methylphenyl)benzene (9a):** ^{1}H NMR (C$_6$D$_6$): δ = 2.16 (s, 6 H), 7.00 (t, *J* = 7.5 Hz, 1 H), 7.08 (d, *J* = 8.1 Hz, 4 H), 7.27 (dd, *J* = 7.5, 7.2 Hz, 2 H), 7.52 (d, *J* = 8.1 Hz, 4 H).

(22) **1-Fluoro-3,5-bis(4-methylphenyl)benzene (9b):** ^{1}H NMR (C$_6$D$_6$): δ = 2.18 (s, 6 H), 7.06 (d, *J* = 7.8 Hz, 4 H), 7.26 (dd, *J* = 9.6, 1.5 Hz, 2 H), 7.37 (d, *J* = 7.8 Hz, 4 H), 7.64 (t, *J* = 1.5 Hz, 1 H).

(23) **1,2-Difluoro-3-(4-methylphenyl)benzene (8a):** ^{1}H NMR (C$_6$D$_6$): δ = 2.13 (s, 3 H), 6.61 (tdd, *J* = 8.1, 4.8, 1.5 Hz, 1 H), 6.73 (dddd, *J* = 9.9, 8.1, 7.2, 1.5 Hz, 1 H), 6.89 (ddt, *J* = 8.1, 6.3, 1.5 Hz, 1 H), 7.02 (d, *J* = 7.8 Hz, 2 H), 7.35 (dd, *J* = 8.1, 1.8 Hz, 2 H).

(24) (*Z*)-**1-Fluoro-1-(4-methylphenyl)-2-(1-naphthyl)ethene [13-(*Z*)]:** ^{1}H NMR (C$_6$D$_6$): δ = 2.12 (s, 3 H), 6.89 (d, *J* = 37.2 Hz, 1 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 7.33–7.38 (m, 3 H), 7.56 (d, *J* = 8.7 Hz, 2 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 7.69–7.72 (m, 1 H), 8.02–8.05 (m, 1 H), 8.08 (d, *J* = 7.2 Hz, 1 H).

(25) **1,1-Bis(4-methylphenyl)-2-(1-naphthyl)ethene (14):** ^{1}H NMR (C$_6$D$_6$): δ = 2.01 (s, 3 H), 2.20 (s, 3 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 7.05 (dd, *J* = 8.4, 8.1 Hz, 1 H), 7.08 (d, *J* = 8.1 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.30–7.34 (m, 3 H), 7.46 (d, *J* = 8.1 Hz, 2 H), 7.45–7.49 (m, 1 H), 7.51 (s, 1 H), 7.65–7.69 (m, 1 H), 8.10–8.13 (m, 1 H).

(26) (*E*)-**1-Fluoro-1-(4-methylphenyl)-2-(1-naphthyl)ethene [13-(*E*)]:** ^{1}H NMR (C$_6$D$_6$): δ = 1.88 (s, 3 H), 6.64 (d, *J* = 8.1 Hz, 2 H), 6.86 (d, *J* = 21.0 Hz, 1 H), 7.09 (dd, *J* = 8.1, 7.5 Hz, 1 H), 7.28–7.32 (m, 3 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.63–7.69 (m, 1 H), 7.98–8.03 (m, 1 H).