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Early Transition Metal-Catalyzed Cross-Coupling Reaction of Aryl Fluorides with a Phenethyl Grignard Reagent Accompanied by Rearrangement of the Phenethyl Group

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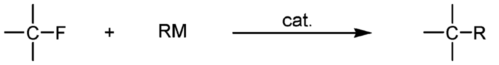
Defluorination of 1-fluoronaphthalene was catalyzed by $CpTiCl_3$ and an alkyl Grignard reagent system. The reaction of 1-fluoronaphthalene, however, with 3 equiv of phenethylmagnesium chloride in the presence of a catalytic amount of transition metal catalysts afforded 1-(1-phenethyl)naphthalene in good yield via isomerization of the phenethyl group. Among the examined catalysts, $CpTiCl_3$ and $TaCl_5$ showed much higher activity than the others. The similar coupling reactions of phenethylmagnesium chloride with substituted fluoroarenes proceeded with high regioselectivity at the *para*-position to produce the corresponding 1-phenethylarenes in good yields.

Introduction

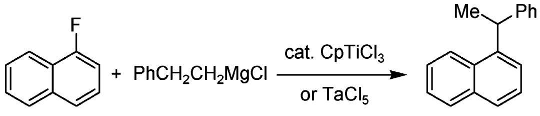
Recently activation of C−F bonds and carbon−carbon bond formation have attracted much attention in organic chemistry.[1]

Cross-coupling reactions of fluorocarbons with organometallic reagents have been achieved by late transition metal catalysts, such as nickel,[2] palladium,[2f,3] and copper.[2b] With early transition metal catalysts, however, cross-coupling reaction of organic fluorides is quite rare,[4] although defluorination of organic fluorides catalyzed or mediated by early transition metal complexes has been known.[5]



$$-\overset{|}{\underset{|}{C}}-F \quad + \quad RM \quad \xrightarrow{\text{cat.}} \quad -\overset{|}{\underset{|}{C}}-R \qquad (1)$$

Here, we report early transition metal-catalyzed cross-coupling reactions of phenethylmagnesium chloride with aryl fluorides accompanied by rearrangement of the phenethyl group as shown in eq 2.



(2)

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Results and Discussion

Table 1 summarizes the results of the reactions of 1-fluoronaphthalene with a series of Grignard reagents (3 equiv) in the presence of $CpTiCl_3$ (10 mol %) in THF at 50 °C. Using *n*-BuMgCl or *i*-PrMgCl, reduction of the C−F bond occurred to afford naphthalene (X = H) in 80 and 84% yields, respectively (entries 1 and 2). With *t*-BuMgCl or EtMgBr, the yields of naphthalene were reduced considerably (entries 3 and 4). When MeMgBr or $PhCH_2MgCl$ was employed, no reaction took place (entries 5 and 6). This suggests that the hydrogen source of the reduction is a β-hydrogen of the Grignard reagent. Such a tendency is quite similar to the zirconocene- or titanocene-catalyzed dehalogenation reaction of aryl bromides or chlorides as we reported previously.[6] The hydrodefluorination was applicable for reduction of the $C(sp^3)$−F bond: the reaction

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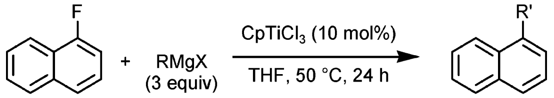
Table 1. Reactions of 1-Fluoronaphthalene with a Series of Grignard Reagents



entry	RMgX	R′	yield (%)
1	*n*-BuMgCl	H	80
2	*i*-PrMgCl	H	84
3	*t*-BuMgCl	H	46
4	EtMgBr	H	40
5	MeMgBr		N.R.
6	$PhCH_2MgCl$		N.R.
7[a]	$PhCH_2CH_2MgCl$	$PhCHCH_3$	85

[a] The reaction was carried out for 48 h.

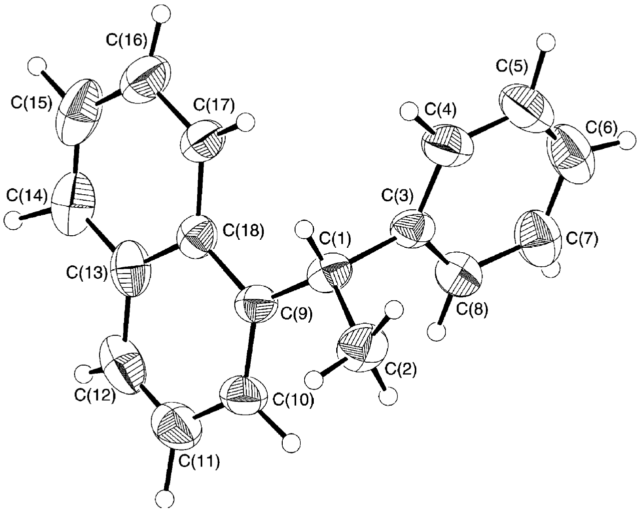


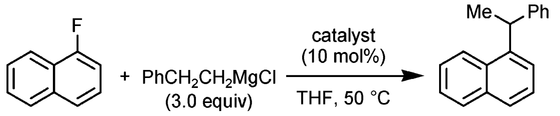
Figure 1. Molecular structure of 1-(1-phenethyl)naphthalene (**1**).

of 1-fluorooctane with *n*-PrMgCl and 10 mol % $CpTiCl_3$ in THF/DME (3:1) under reflux for 24 h afforded octane in 76% GC yield.

Unexpectedly, when phenethylmagnesium chloride was used for the reaction, a coupling product was obtained in 85% yield after hydrolysis of the reaction mixture (entry 7). The ^1H and ^{13}C NMR analyses proved that the product was 1-(1-phenethyl)-naphthalene (**1**). Moreover, the structure was unequivocally confirmed by X-ray crystallography (Figure 1). This means that the phenethyl group was rearranged to the corresponding secondary one during the reaction.[4] This is in sharp contrast to the other Grignard reagents shown in Table 1, which did not produce any coupling products. Without the catalyst neither reduction nor coupling reaction took place.

Table 2 showed the results of the coupling reactions in the presence of a variety of transition metals. The coupling products were identical. Among the examined group 4 catalysts, $CpTiCl_3$ showed the highest activity. With Cp_2TiCl_2 the yield was reduced to 60% (entry 2). The other titanium catalysts without cyclopentadienyl ligand showed only moderate activity (entries 3−5). Compared with these titanium catalysts, the zirconium analogues have lower efficiency in the reaction (entries 6−8). Other than group 4 metals, $TaCl_5$ was also effective to afford **1** in 86% yield (entry 11). Compared with the early transition metals, $FeCl_3$, $NiCl_2$, and $CuCl_2$ have little or no efficiency in the coupling reactions under the conditions used here (entries 13−15).

Table 2. Transition Metal-Catalyzed Coupling Reactions of 1-Fluoronaphthalene with 2-Phenethylmagnesium Chloride



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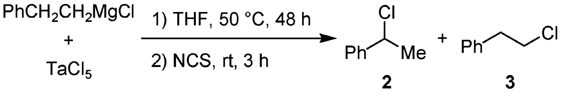
entry	catalyst	time (h)	yield (%)
1	$CpTiCl_3$	48	85
2	Cp_2TiCl_2	48	60
3	$TiCl_4$	24	22
4	$TiCl_3$	24	22
5	Ti(O-*i*-Pr)$_4$	48	40
6	$CpZrCl_3$	48	48
7	Cp*$ZrCl_3$	48	57
8	$ZrCl_4$	24	18
9	VCl_3	48	39
10	$NbCl_5$	48	60
11	$TaCl_5$	48	86
12	$CrCl_3$	24	27
13	$FeCl_3$	24	0
14	$NiCl_2$	24	5
15	$CuCl_2$	24	0

Scheme 1



with 0.1 equiv $TaCl_5$: 85% (**2**:**3** = 1:3)
1.0 equiv $TaCl_5$: 90% (**2**:**3** = 100:0)

The following results suggest a part of the mechanism. It seems that the active species of the reaction is an ate complex of the titanium catalyst. This was supported by the following experimental result: no coupling product was obtained in the stoichiometric reaction of 1-fluoronaphthalene (1.0 mmol) with 1.0 mmol of $CpTiCl_3$ and 3.0 mmol of phenethylmagnesium chloride under the same conditions. The existence of such an ate complex was also proposed in the Cp_2Ti-catalyzed alkylation reactions of arylalkenes with alkyl halides in the presence of *n*-BuMgCl.[5,7]

In addition, observation of a small amount of styrene in the reaction mixture suggests that the phenethylmagnesium group isomerizes to a secondary one via styrene on the catalyst.[2c,7,8] To clarify this phenomenon, reactions of 2-phenethylmagnesium chloride with $TaCl_5$ without aryl halides followed by quenching with NCS were performed as shown in Scheme 1. The reaction with 100 mol % $TaCl_5$ afforded the isomerized product (1-chloroethyl)benzene (**2**) in 90% as a sole product. On the other hand, the isomerization was not completed with 10 mol % $TaCl_5$. The results clearly showed that in the present cross-coupling reaction the isomerization of the phenethyl group occurred on the employed metal catalyst before coupling with aryl halides.

Probably, the isomerization proceeded via β-hydrogen elimination of the 2-phenethyl group on the metal to afford the corresponding styrene complex. In fact, when the reactions of 1-fluoronaphthalene with *n*-BuMgCl were examined in the presence of styrene and a catalytic amount of Cp_2TiCl_2, the expected coupling product with styrene was obtained in 20%

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Scheme 2

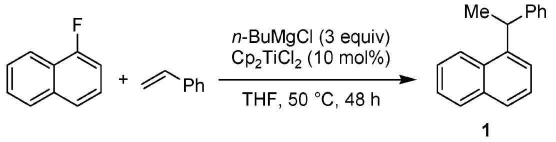
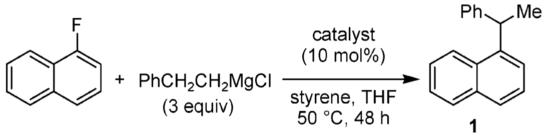


Table 3. Coupling Reactions in the Presence of Styrene



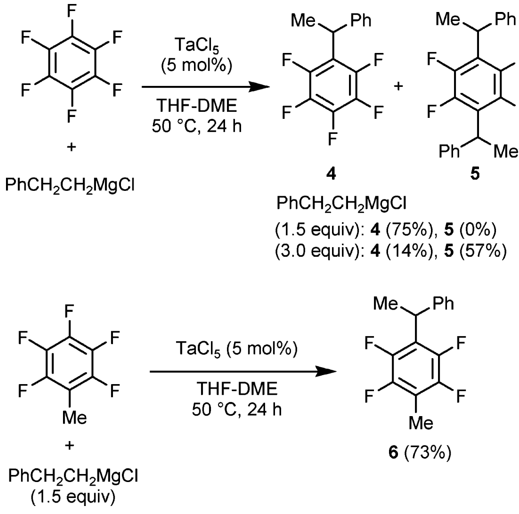
entry	catalyst	styrene (equiv)	GC yield (%)
1	$TaCl_5$	0	86
2	$TaCl_5$	0.2	41
3	$TaCl_5$	0.5	23
4	$TaCl_5$	1.0	11
5	Cp_2TiCl_2	0	60
6	Cp_2TiCl_2	0.2	81
7	Cp_2TiCl_2	0.5	63
8	Cp_2TiCl_2	1.0	62

yield (Scheme 2). This result strongly supports the intermediacy of styrene in the isomerization of the phenethyl group.

From the same reaction with $TaCl_5$, however, no coupling product was obtained. Actually, the presence of excess styrene retarded the tantalum-catalyzed coupling reactions even with 2-phenethylmagnesium chloride, as shown in Table 3. The yields of 1-phenethylnaphthalene **1** were decreased with increasing the amount of added styrene in the reaction system (entries 1−4), whereas little effect was observed for the Cp_2Ti-catalyzed reactions (entries 5−8). These negative effects of excess styrene toward the tantalum-catalyzed reaction may be due to formation of styrene−tantalum π-complexes.

The coupling reactions were further examined with polyfluorinated substrates, as shown in Scheme 3. The reaction of hexafluorobenzene with 2-phenethylmagnesium chloride in the presence of 5 mol % $TaCl_5$ afforded the corresponding coupling product **4** in 75% yield. When an excess amount of the Grignard reagent (3 equiv) was used, double-coupling product **5** was obtained in 57% yield along with the formation of monocoupled product **4** in 14% yield. Interestingly, only the *para*-disubstituted regioisomer was formed as the double-coupling product in this reaction; no other isomers were detected. Similar regioselectivity was observed in the reaction of 2,3,4,5,6-pentafluorotoluene with phenethylmagnesium chloride in the presence of $TaCl_5$. The substitution occurred only at the 4-position to afford 4-(1-phenethyl)-2,3,5,6-tetrafluorotoluene (**6**) in a good yield.

Scheme 3



In conclusion, it was found that early transition metal-catalyzed coupling reactions of fluoroarenes with phenethylmagnesium chloride proceeded in good yield accompanied by isomerization of the phenethyl group to afford the corresponding 1-phenethyl-substituted arenes. Further investigation on the reaction mechanism of the coupling is now in progress.

Experimental Section

General Procedures. All reactions were carried out under nitrogen using standard Schlenk techniques. All metal chlorides were handled under nitrogen atmosphere. THF was dried and distilled over sodium and benzophenone. Other chemicals were purchased from Aldrich Inc., TCI Co. Ltd., or Kanto Chemical Co. Ltd. and used without further purification.

^1H and ^{13}C NMR spectra were recorded on Bruker ARX-400 or JEOL JNM AL-300 NMR spectrometers. GC analyses were performed on a Shimadzu GC-14A equipped with a fused silica capillary column Shimadzu CBP1-M25-025 and Shimadzu C-R6A-Chromatopac integrator using hydrocarbons as internal standards.

Representative Procedure for Defluorination with a Grignard Reagent. To a solution of $CpTiCl_3$ (0.1 mmol) and 1-fluoronaphthalene (1 mmol) in 4 mL of THF was added *n*-BuMgCl (0.97 M solution in THF, 3.1 mL, 3.0 mmol) at −78 °C. Then the mixture was stirred at 50 °C for 24 h. The mixture was analyzed by NMR or GC spectrometers. The yield of naphthalene was determined by ^1H NMR spectroscopy in C_6D_6 with mesitylene as an internal standard.

Representative Procedure for Coupling Reactions of Aryl Fluorides with 2-Phenethylmagnesium Chloride. To a solution of $CpTiCl_3$ (22 mg, 0.1 mmol) and 1-fluoronaphthalene (146 mg, 1.0 mmol) in THF (4 mL) was added 2-phenethylmagnesium chloride (1.0 M solution in THF, 3.0 mL, 3.0 mmol) at −78 °C. Then the reaction mixture was stirred at 50 °C for 48 h. After cooling to room temperature, the mixture was quenched slowly with water and aqueous 3 N HCl solution and extracted with ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with hexane as an eluent to afford 1-(1-phenethyl)naphthalene (**1**) as a colorless solid (130 mg, GC yield: 85%, isolated yield: 56%). ^1H NMR ($CDCl_3$, δ) 1.76 (d, 3 H, $J = 7$ Hz), 4.91 (t, 1 H, $J = 7$ Hz), 7.12−8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, δ) 22.53, 40.54, 123.95, 124.32, 125.29, 125.42, 125.84, 125.95, 125.96, 127.60, 128.41, 128.76, 131.69, 133.96, 141.53, 146.63; HRMS calcd for $C_{18}H_{16}$ 232.1252, found 232.1259.

1,2,3,4,5-Pentafluoro-6-(1-phenethyl)benzene (4). To a solution of $TaCl_5$ (18 mg, 0.05 mmol) and 2,3,4,5,6-pentafluorotoluene (0.126 mL, 1.0 mmol) in DME (4 mL) was added 2-phenethylmagnesium chloride (1.0 M solution in THF, 1.5 mL, 1.5 mmol) at −78 °C. Then the mixture was stirred at 50 °C for 24 h. After cooling to room temperature, the mixture was quenched slowly with water and aqueous 3 N HCl solution and extracted with ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with hexane as an eluent to afford the title compound as a colorless oil (136 mg, GC yield: 75%, isolated yield: 50%). ^1H NMR ($CDCl_3$, δ) 1.75 (d, 3 H, $J = 7$ Hz), 4.58 (t, 1 H, $J = 7$ Hz), 7.14−7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, δ) 18.20, 34.47, 119.32 (t, $J = 16$ Hz), 126.87, 127.05, 128.57, 137.63 (d, $J = 252$ Hz), 139.73 (d, $J = 252$ Hz), 142.08, 145.04 (d, $J = 246$ Hz); HRMS calcd for $C_{14}H_9F_5$ 272.0624, found 272.0619.

1,2,4,5-Tetrafluoro-3,6-bis(1-phenethyl)benzene (5). To a solution of $TaCl_5$ (36 mg, 0.1 mmol) and hexafluorobenzene (0.12 mL, 1.0 mmol) in DME (4 mL) was added 2-phenethylmagnesium chloride (1.0 M solution in THF, 3.0 mL, 3.0 mmol) at −78 °C. The mixture was stirred at 50 °C for 24 h. After cooling to room temperature, the mixture was quenched slowly with water and aqueous 3 N HCl solution and extracted with ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with hexane as an eluent, affording the title compound as a colorless solid (161 mg, GC yield: 57%, isolated yield: 45%). ^{1}H NMR ($CDCl_3$, δ) 1.73 (d, 6 H, J = 7 Hz), 4.56 (q, 2 H, J = 7 Hz), 7.15−7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$, δ) 18.26, 34.73, 121.79−122.54 (m), 126.68, 127.06, 127.22, 128.46, 142.51, 144.85 (d, J = 250 Hz); HRMS calcd for $C_{22}H_{18}F_4$ 358.1345, found 358.1328.

2,3,5,6-Tetrafluoro-4-(1-phenethyl)toluene (6). To a solution of $TaCl_5$ (18 mg, 0.05 mmol) and 2,3,4,5,6-pentafluorotoluene (0.126 mL, 1.0 mmol) in DME (4 mL) was added 2-phenethylmagnesium chloride (1.0 M solution in THF, 1.5 mL, 1.5 mmol) at −78 °C. The mixture was stirred at 50 °C for 24 h. After cooling to room temperature, the mixture was quenched slowly with water and aqueous 3 N HCl solution and extracted with ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with hexane as an eluent, affording a colorless oil (196 mg, GC yield: 81%, isolated yield: 73%). ^{1}H NMR ($CDCl_3$, δ) 1.75 (d, 3 H, J = 7 Hz), 2.20 (t, 3 H, J = 2 Hz), 4.59 (q, 1 H, J = 7 Hz), 7.17−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, δ) 7.19−7.40 (m), 18.28 (t, J = 3 Hz), 34.61, 113.89 (t, J = 19 Hz), 121.40 (t, J = 16 Hz), 126.60, 127.12, 128.43, 142.69, 142.58−143.11 (m), 143.21−143.74 (m), 145.89−146.42 (m), 146.49−146.97 (m); HRMS calcd for $C_{22}H_{18}F_4$ 268.0875, found 268.0871.

Supporting Information Available: X-ray crystallographic data for **1** and **6**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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