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Introduction of (2-CF_3)Phenyl Group via Nickel-catalyzed C–Cl Bond Activation and Arylation

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Keywords: C–Cl activation; Nickel; Trifluoromethyl; Organozinc reagent; C,C-coupling; Chlorinated benzalimine

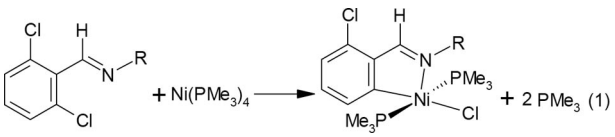
Abstract. A simple and mild catalytic arylation via C–Cl bond activation is described. The phenyl group containing a 2-trifluoromethyl group was introduced into the aromatic imine molecules through C,C-coupling reaction between chloroarenes and the organozinc reagent, bis(2-(trifluoromethyl)phenyl)zinc, with tetrakis(trimethylphosphine)-nickel(0) complex as an effective catalyst. Under catalytic conditions chlorinated benzalimines were quantitatively converted into the expected benzalimines with trifluoromethyl group(s).

1 Introduction

Although chloroarenes have been widely used in chemical industry, medicine, pesticide, leatherworking, and many other fields, their bioaccumulation, toxicity, carcinogenicity, and stability lead to globally environmental problems.[1] For this reason, several methods have been developed to activate C–Cl bonds in order to transform chloroarenes into useful, environmentally-friendly substances.[2] In general, the reaction conditions of traditional methods are harsh and the scope is very narrow. In contrast, the use of transition metal complexes as catalysts in this process is a useful exploration, such as the Suzuki,[3] Kumada,[4] and Negishi coupling.[5] Some palladium,[3–9] rhodium,[10–11] iron,[12–14] cobalt,[15–17] and nickel,[18,19] complexes have been applied in the catalytic activation of C–Cl bonds.

Organic fluorides have many unique excellent properties, such as excellent thermal stability, chemical inertness, unusual surface property, low dielectric constant, and high transparency as well as low refractive index. Therefore, they have been widely used in many fields.[20] In some cases, the introduction of trifluoromethyl group(s) into an organic molecule plays a decisive role for its property because the electronic structure and reactivity of trifluoromethyl group are different from those of other substituents.[21] The molecular moieties with CF_3-containing group(s) have been introduced to fine-tune biochemical properties in the design of drug molecules, agricultural chemicals, and other functional materials.[22] In recent years, the report on trifluoromethylation was disclosed.[23] In addition to direct trifluoromethylation,[24,25] indirect trifluoromethylation was also explored through the reaction of organometallic reagent with CF_3-containing reactant.[26]

We studied cyclometalation reaction involving C–Cl bond activation at a central nickel(II) atom with an aldazine nitrogen atom as an anchoring group to obtain the *ortho*-chelated nickel(II) complexes with a [C–Ni–Cl] fragment [Equation (1)].[27]



In this paper, we extend our work from C–Cl bond activation to arylation of chloroarenes catalyzed by nickel(0) complex with CF_3-containing organozinc reagent to prepare novel CF_3-containing aromatic compounds.

2 Results and Discussion

According to the mechanism of C–Cl bond functionalization and C,C-coupling reaction, the key step is the C–Cl bond activation. We realized the C–Cl bond activation of the chlorinated imine with $Ni(PMe_3)_4$.[27] As a continuation of our work in the field of C–Cl bond activation, the expected C,C-coupling reaction via C–Cl arylation with CF_3-containing organozinc reagent was explored. Several novel CF_3-containing aromatic compounds were synthesized.

At the beginning of the research, (2,6-dichlorobenzylidene)-aniline (**1a**) was selected as a model substrate to optimize the catalytic reaction conditions [Equation (2)]. The experimental results on the optimization of the reaction conditions are listed in Table 1. Entry 6 is the control experiment. Entries 1–5 indicate that the most suitable solvent is toluene among the five tested reaction media. With the increasing of the reaction temperature from 30 °C to 100 °C, 80 °C is the optimized reaction temperature (entries 7–9). Five equivalents of organozinc reagent are more appropriate because the yield did not increase

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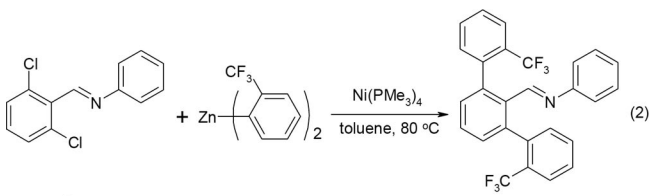
Table 1. Optimization of the catalytic reaction conditions.

Entry	Catalyst /mol%	Zn reagents	Solvent	*T* /°C	Time /h	Yield /%
1	10%	2.0 eq	THF	60	24	54
2	10%	2.0 eq	toluene	60	24	56
3	10%	2.0 eq	MeCN	60	24	trace
4	10%	2.0 eq	dioxane	60	24	49
5	10%	2.0 eq	DMSO	60	24	47
6	none	2.0 eq	toluene	60	24	trace
7	10%	2.0 eq	toluene	30	24	45
8	10%	2.0 eq	toluene	80	24	69
9	10%	2.0 eq	toluene	100	24	63
10	10%	3.0 eq	toluene	80	24	79
11	10%	5.0 eq	toluene	80	24	88
12	10%	6.0 eq	toluene	80	24	88
13	2.0%	5.0 eq	toluene	80	24	89
14	0.5%	5.0 eq	toluene	80	24	trace
15	2.0%	5.0 eq	toluene	80	5	60
16	2.0%	5.0 eq	toluene	80	15	93
17	2.0%	5.0 eq	toluene	80	30	93

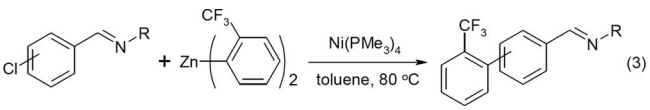
with more organozinc reagent (entries 10–12). When the loading of the catalyst was changed, it was found that 2.0 mol% of $Ni(PMe_3)_4$ are sufficient for the desired yields (entries 10–14). Entries 15–17 verified that this catalytic reaction had finished within 15 h. According to the experimental results in Table 1, the optimized catalytic reaction conditions can be summarized as follows: (2,6-dichlorobenzylidene)aniline (1.0 equiv.), bis(2-(trifluoromethyl)phenyl)zinc (5.0 equiv.), $Ni(PMe_3)_4$ (2.0 mol%), 1.5 mL toluene, 80 °C, 15 h.



(2)

After optimization of the catalytic reaction conditions, more substrates of the chlorinated benzalimines were selected to explore the scope of this catalytic system under the optimized reaction conditions [Equation (3)] (Table 2). The substrates in Table 2 were prepared from the reaction of 2,4-dichlorobenzaldehyde, 2,6-dichlorobenzaldehyde, or 2-chlorobenzaldehyde with aniline, 4-methylaniline, benzylaniline, 2,6-diisopropylaniline, and 1-naphthylamine. In general, the conjugated aromatic imines as substrates have higher yields than those of the unconjugated aromatic imines. Additionally, the reaction could proceed for both mono-chlorinated and di-chlorinated phenyl imines. With di-chlorinated phenyl imine as a substrate, no mono-(C–Cl) bond arylation product could be isolated. However, based on the results in Table 2, it is difficult to find more regularity of this nickel(0)-catalyzed C–Cl bond arylation.

All of the products (**1b**–**8b**) were characterized by NMR and HRMS spectra. It should be noted that two single signals in the ^{19}F NMR spectra of **1b**–**4b** were observed with different integral intensities in the ratio of 1:1.34 to 1:1.73. This may be caused by the *trans*- and *cis*-isomers of the imines. This result could be attributed to the stronger steric hindrance effect of the di-arylation products. Compounds **5b** and **6b** as mono-arylation products have less steric hindrance effect. Therefore, they have only one single signal in the ^{19}F NMR spectra. Entries 7 and 8 indicated that the *para*-(C–Cl) bonds of the imines could also be activated and it is not indispensable that the imine group plays a role as a directing group in this process. In comparison with the result of entry 5, the result of entry 9 shows that the low yield might be caused by the steric effect of the *isopropyl* groups.



(3)

The molecular structure of compound **2b** was confirmed by X-ray single crystal diffraction. A view of the structure of **2b** is shown in Figure 1. This structure shows a *trans*-configuration with regard to the imine double bond in the crystal state.

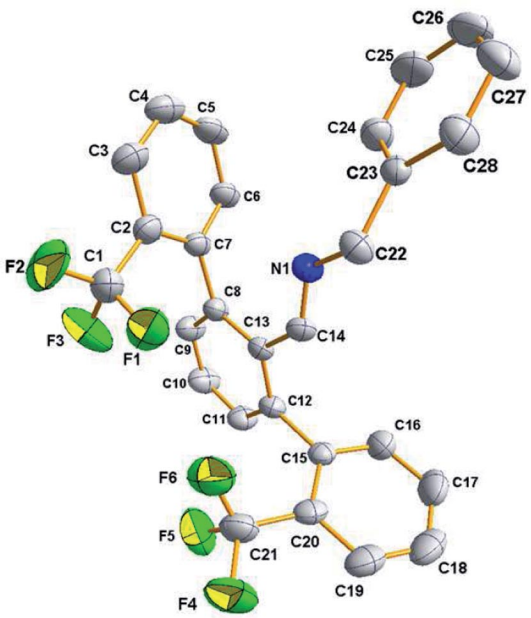
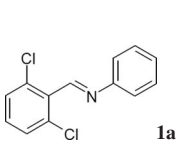
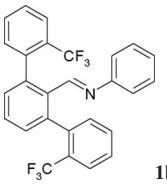
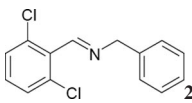
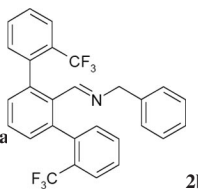
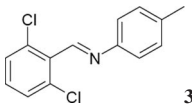
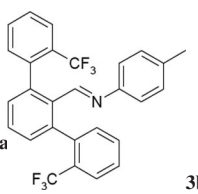
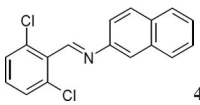
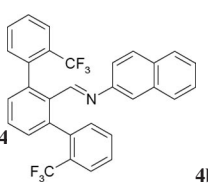
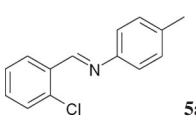
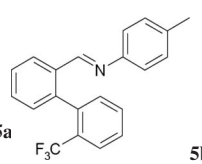
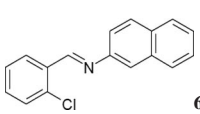
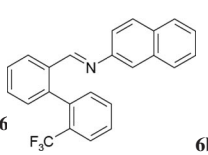
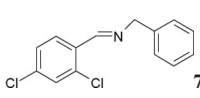
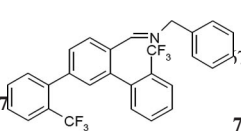
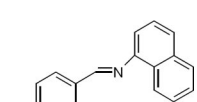
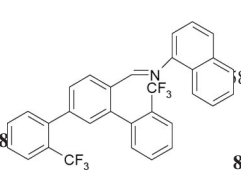
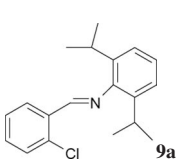
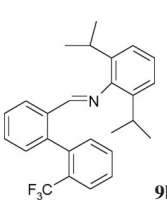


Figure 1. Molecular structure of **2b**.

Table 2. Ni-catalyzed arylation of chlorinated benzalimines [a].

Entry	Substrate	Product	Yield /% [b] A/B
1	 **1a**	 **1b**	93/88
2	 **2a**	 **2b**	50/46
3	 **3a**	 **3b**	67/63
4	 **4**	 **4b**	68/64
5	 **5a**	 **5b**	98/93
6	 **6**	 **6b**	90/86
7	 **7**	 **7b**	7/56
8	 **8**	 **8b**	8/50
9	 **9a**	 **9b**	11/ [c]

a) Reaction conditions: 1.0 equiv. imine, 5.0 equiv. bis(2-(trifluoromethyl)phenyl)-zinc, 2 mol % $Ni(PMe_3)_4$, toluene, 80 °C, 15 h, N_2. b) Yield A based on in situ ^{19}F NMR spectra; yield B is the isolated yield. c) No isolated yield was determined.

Unexpectedly, the two phenyl rings (C1–C7 and C15–C20) with the *ortho*-trifluoromethylphenyl groups are not in the conjugated phenyl-imine plane [N1=C14–(C8–C13)]. Two *ortho*-trifluoromethyl groups orientate toward to the same direction concerning the (C8–C13) phenyl ring. This structure might be resulted from the packing effect in the crystal state. Owing to the methylene group (C22) of the benzyl group, the conjugation of the (C23–C28) phenyl ring with the [N1=C14–(C8–C13)] group is excluded.

3 Conclusions

A simple and efficient catalysis for C–Cl bond activation and arylation is described. Trifluoromethyl group(s) were introduced into the aromatic imine molecules through the C,C-coupling reaction between chloroarenes and organozinc reagent, bis(2-(trifluoromethyl)phenyl)zinc. Nickel(0) complex, tetrakis(trimethylphosphine)nickel(0), is a good catalyst for this process. Nine chlorinated benzalimines were transformed to the expected benzalimines with trifluoromethyl group(s). We believe that this catalytic system can be expanded to more related substrates.

4 Experimental Section

4.1 General Procedures

All experiments for C,C-coupling reaction were performed using standard Schlenk techniques in an atmosphere of nitrogen. ^1H and ^{19}F NMR spectra were recorded with a 300 MHz Bruker NMR instrument. Mass spectra were recorded with an Agilent Q-TOF 6510 mass spectrometer. Melting points were measured in capillaries and were uncorrected. X-ray crystallography was performed with a Bruker Smart 1000 diffractometer.

4.2 Materials and Methods

Na_2SO_4 was obtained from commercial source and used as received. Acetonitrile, DME, DMF, and DMSO were dried by refluxing over CaH_2. Toluene, pentane, THF, and diethyl ether were dried with sodium and used after distillation. $Ni(PMe_3)_4$ was synthesized according to the method by *Klein*.[28] $(C_7H_4F_3)_2Zn$ was prepared from $C_7H_4F_3MgBr$ and $ZnCl_2$ in THF. $C_7H_4F_3MgBr$ was synthesized by $C_7H_4F_3Br$ and Mg in THF. Imines were prepared by corresponding aldehyde and amines in small amount of ethanol, and recrystallized from diethyl ether, pentane or THF. All imines are light yellow crystals. The yields of imines are from 40 % to 70 %.

4.3 General Experimental Procedure of Catalytic Study

$(C_7H_4F_3)_2Zn$ (1.0 mmol) was injected to a solution of an aryl halide (0.2 mmol) and $Ni(PMe_3)_4$ (0.004 mmol) in toluene (1.5 mL). The mixture was stirred at 80 °C for 15 h. The reaction mixture was dried under reduced pressure. The residue was extracted by pentane and diethyl ether. The crude product was re-crystallized in pentane or diethyl ether.

4.4 Analytical Data for the Products

***N*-((2,2′′-Bis(trifluoromethyl)-(1,1′:3′,1′′-terphenyl)-2′-yl)methylene)aniline (1b):** Yield: 88 %. M.p.: 92–93 °C. **^1H NMR** ($CDCl_3$,

300 MHz, ppm): δ = 7.90–7.88 (m, 1 H), 7.77–7.72 (m, 2 H), 7.58–7.40 (m, 6 H), 7.36–7.31 (m, 3 H), 7.12–7.0 (m, 2 H), 7.02–6.96 (m, 1 H), 6.33–6.30 (m, 2 H). **^{19}F NMR** ($CDCl_3$, 282 MHz, ppm): δ = –58.38 (s), 58.80 (s) (1.00 : 1.43). **HRMS** (EI): *m/z* calculated for $C_{27}H_{17}F_6N$: 469.4203; found: 470.1319.

***N*-((2,2′′-Bbis(trifluoromethyl)-(1,1′:3′,1′′-terphenyl)-2′-yl)methylene)-1-phenylmethanamine (2b):** Yield: 46 %. M.p.: 85–86 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz, ppm): δ = 7.90–7.87 (m, 1 H), 7.69–7.62 (m, 2 H), 7.58–7.32 (m, 7 H), 7.26–7.24 (m, 2 H), 7.12–7.08 (m, 3 H), 6.64–6.62 (m, 2 H), 4.19–4.17 (m, 2 H). **^{19}F NMR** ($CDCl_3$, 282 MHz, ppm): δ = –58.38 (s), 58.90 (s) (1.00 : 1.73). **HRMS** (EI): *m/z* calculated for $C_{28}H_{19}F_6N$: 483.4468; found: 484.1505.

***N*-((2,2′′-Bis(trifluoromethyl)-(1,1′:3′,1′′-terphenyl)-2′-yl)methylene)-4-methylaniline (3b):** Yield: 63 %. M.p.: 97–98 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz, ppm): δ = 7.90–7.88 (m, 1 H), 7.75–7.70 (m, 2 H), 7.57–7.39 (m, 6 H), 7.35–7.24 (m, 3 H), 6.91–6.88 (m, 2 H), 6.26–6.24 (m, 2 H), 2.20 (s, 3 H). **^{19}F NMR** ($CDCl_3$, 282 MHz, ppm): δ = –58.37 (s), 58.80 (s) (1.00 : 1.36). **HRMS** (EI): *m/z* calculated for $C_{28}H_{19}F_6N$: 483.5071; found: 484.1491.

***N*-((2,2′′-Bis(trifluoromethyl)-(1,1′:3′,1′′-terphenyl)-2′-yl)methylene)naphthalen-1-amine (4b):** Yield: 64 %. M.p.: 127–128 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz, ppm): δ = 8.09–8.07 (m, 1 H), 7.81–7.75 (m, 2 H), 7.67–7.59 (m, 2 H), 7.54–7.47 (m, 6 H), 7.42–7.33 (m, 4 H), 7.19–7.14 (m, 2 H), 6.90–6.82 (m, 1 H), 6.26–6.21 (m, 1 H). **^{19}F NMR** ($CDCl_3$, 282 MHz, ppm): δ = –58.32 (s), 58.81 (s) (1.00 : 1.34). **HRMS** (EI): *m/z* calculated for $C_{31}H_{19}F_6N$: 519.4789; found: 520.2537.

4-Methyl-*N*-((2′-(trifluoromethyl)-(1,1′-biphenyl)-2-yl)methylene)-aniline (5b): Yield: 93 %. M.p.: 46–47 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ = 8.33–8.31 (m, 1 H), 8.03 (m, 1 H), 7.79–7.77 (m, 1 H), 7.59–7.45 (m, 4 H), 7.32–7.28 (m, 2 H), 7.10–7.08 (m, 2 H), 6.91–6.89 (m, 2 H), 2.30 (s, 3 H). ^{19}F NMR ($CDCl_3$, 282 MHz, ppm): δ = –58.29 (s, 3F). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{16}F_3N$: 339.3530; found: 340.1999.

***N*-((2′-(Trifluoromethyl)-(1,1′-biphenyl)-2-yl)methylene)naphthalen-1-amine (6b):** Yield: 86 %. M.p.: 108–109 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 8.51–8.48 (m, 1 H), 8.25–8.22 (m, 1 H), 8.14 (s, 1 H), 7.81–7.76 (m, 2 H), 7.64–7.46 (m, 7 H), 7.35–7.30 (m, 3 H), 6.73–6.70 (m, 1 H). **^{19}F NMR** ($CDCl_3$, 282 MHz): δ = –58.23 (s). **HRMS** (EI): *m/z* calculated for $C_{24}H_{16}F_3N$: 375.3851; found: 376.2095.

***N*-((2,2′′-Bis(trifluoromethyl)-(1,1′:3′,1′′-terphenyl)-4′-yl)methylene)-1-phenylmethanamine (7b):** Yield: 63 %. m.p.: 83–84 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 8.24–8.21(m, 1 H), 8.01 (s, 1 H), 7.79–7.72 (m, 2 H), 7.65–7.28 (m, 9 H), 7.24–7.21 (m, 4 H), 4.64 (s, 2 H). **^{19}F NMR** ($CDCl_3$, 282 MHz): δ = –56.87 (s, 3F), –58.37 (s, 3F). **HRMS** (EI): *m/z* calculated for $C_{28}H_{19}F_6N$: 483.4552; found: 484.2095.

***N*-((2,2′′-Bis(trifluoromethyl)-(1,1′:3′,1′′-terphenyl)-4′-yl)methylene)naphthalen-1-amine (8b):** Yield: 54 %. M.p.: 106–107 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 8.56–8.53 (m, 1 H), 8.29–8.25 (m, 1 H), 8.18 (s, 1 H), 7.82–7.76 (m, 3 H), 7.66–7.30 (m, 12 H), 6.76–6.73 (m, 1 H). **^{19}F NMR** ($CDCl_3$, 282 MHz): δ = –56.78 (s, 3F), –58.28 (s, 3F). **HRMS** (EI): *m/z* calculated for $C_{31}H_{19}F_6N$: 519.4882; found: 520.2537.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository number CCDC-968364 (**2**) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

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