Synthesis of α-trifluoromethylstyrene derivatives *via* Pd-catalyzed cross-coupling of 2-bromo-3,3,3-trifluoropropene and arylmagnesium bromides

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ABSTRACT

Pd-catalyzed cross-coupling of 2-bromo-3,3,3-trifluoropropene (BTP) and arylmagnesium bromides was investigated. Diphenylphosphinomethane (dppm) was exclusively effective in the coupling among the phosphine ligands tested with Pd(0) and Pd(II) complexes. The use of diphenylphosphinomethane-coordinated Pd(II) complex, $PdCl_2(dppm)$, resulted in the highest yield of α-trifluoromethylstyrene (98%) from 2-bromo-3,3,3-trifluoropropene and phenylmagnesium bromide in 1,4-dioxane solvent at 50 °C for 30 min. The $PdCl_2(dppm)$-catalyzed coupling could be applied to the synthesis of α-trifluoromethylstyrene derivatives with satisfactory yields using arylmagnesium bromides.

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1. Introduction

α-Trifluoromethylstyrene derivatives are important fluorinated compounds used in medicinal, agricultural and material fields [1–3]. Of the previously reported synthetic methods [4–8], Pd-catalyzed cross-coupling using 2-bromo-3,3,3-trifluoropropene (BTP) [7,8] is one of the most promising methods from a practical point of view. Metallic reagents of BTP, such as 2-(3,3,3-trifluoropropenyl)zinc bromide [7] and 2-(3,3,3-trifluoropropenyl)boronic acid [8], have been known to be useful for the coupling with aryl halides. However, they are not favourable for practical use because their preparation method is somewhat difficult: the former is synthesized using a Zn–Ag alloy and BTP in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and the latter is synthesized using a Grignard reagent of BTP and a boronic compound.

We recently found that the oxidative addition of BTP to Pd(0) species occurs readily, resulting in coupling with alcohol in the presence of CO [9] or arylamines [10]. Similarly, cross-coupling of BTP and arylboronic acids using a palladium catalyst yields α-trifluoromethylstyrene derivatives [11,12]. Although arylboronic acids are versatile reagents for Pd-catalyzed coupling, their synthesis involves two steps: preparation of aryl metallic reagents and then reaction with boronic acid [13–15].

We began our investigation at the point that the coupling of BTP and arylmagnesium bromides should provide a simple and environmentally benign synthetic route to α-trifluoromethylstyrene derivatives. In this study, we successfully carried out Pd-catalyzed coupling of BTP and arylmagnesium bromides using diphenylphosphinomethane (dppm) as a ligand.

2. Experimental

2.1. General techniques

^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ on Bruker DRX-500 (^{1}H 500 MHz) and DRX-250 (^{19}F 235 MHz) using tetramethylsilane for ^{1}H NMR as an internal reference and fluorotrichloromethane for ^{19}F NMR as an external reference. Chemical shifts are expressed in ppm (δ). Multiplicities are indicated by s (singlet), d (doublet), dd (doublet of doublet), q (quartet), m (multiplet) and brs (broad singlet). IR and high-resolution mass spectra (HRMS) were recorded on HORIBA FT-720 and JEOL JMS-600H, respectively. Developed chromatograms were visualized by UV light. Flash chromatography was performed on silica gel (Kanto Chemical Co. N60). All commercially available reagents were used without further purification. The concentration of the THF solution of arylmagnesium bromide (ArMgBr) was *ca.* 1.1 mol/L.

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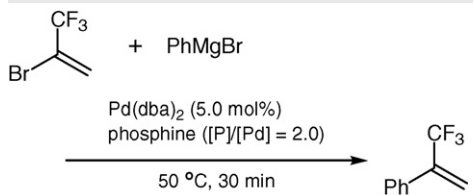
2.2. Typical procedure of the coupling

All reactions were carried out in flame-dried glassware under an argon atmosphere. To 1.0 mL of solvent containing palladium species (0.05 mmol), phosphine and BTP (1.0 mmol), 1.3 mL of THF solution of ArMgBr ([ArMgBr]/[BTP] = *ca.* 1.4) was added at a rate of 100 μL/min using a syringe pump at 50 °C. The reaction mixture was stirred for 30 min at the same temperature. After cooling to room temperature, an aliquot of the reaction mixture was diluted with pentane and subjected to quantitative analyses by GC and ^{19}F NMR. Tridecane and 2,2,2-trifluoroethanol were used as internal standards for GC and ^{19}F NMR, respectively. The reaction mixture was passed through a silica gel column, and the eluted solution was concentrated in vacuo or distilled to isolate the desired products. All the yields were calculated based on the initial concentration of BTP.

3. Results and discussion

First, we examined the reactions of BTP and phenylmagnesium bromide (PhMgBr) with a Pd(0) complex, Pd(dba)$_2$ (dba: dibenzylideneacetone), and various phosphines. The ratio of [P]/[Pd] was set at 2.0; 2.0 equiv. of monophosphine and 1.0 equiv. of diphosphine to palladium, respectively. The results are shown in Table 1. Only the combination of dppm and 1,4-dioxane as the solvent gave an excellent yield (entry 12). It is worth noting that the other sol-

Table 1
Pd-catalyzed coupling of BTP and PhMgBr using various phosphines.

Entry	Phosphine	Solvent	Yield (%)[a]
1	PPh$_3$	THF	5
2	PPh$_3$	1,4-Dioxane	24
3	P(4-F-C$_6$H$_4$)$_3$	THF	4
4	P(4-F-C$_6$H$_4$)$_3$	1,4-Dioxane	35
5	P(*p*-tolyl)$_3$	THF	17
6	P(*p*-tolyl)$_3$	1,4-Dioxane	32
7	P(*o*-tolyl)$_3$	THF	9
8	P(*o*-tolyl)$_3$	1,4-Dioxane	50
9	PCy$_3$	THF	43
10	PCy$_3$	1,4-Dioxane	30
11	dppm	THF	14
12	dppm	1,4-Dioxane	96
13	dppm	Et$_2$O	7
14	dppm	DME	48
15	dppe[b]	THF	5
16	dppe	1,4-Dioxane	28
17	dppp[c]	THF	0
18	dppp	1,4-Dioxane	3
19	dppb[d]	THF	0
20	dppb	1,4-Dioxane	3
21	dppf[e]	THF	0
22	dppf	1,4-Dioxane	3
23	dppm[f]	1,4-Dioxane	78
24	dppm[g]	1,4-Dioxane	6

[a] Determined by GC.
[b] 1,2-Bis(diphenylphosphino)ethane.
[c] 1,3-Bis(diphenylphosphino)propane.
[d] 1,4-Bis(diphenylphosphino)butane.
[e] 1,1′-Bis(diphenylphosphino)ferrocene.
[f] [P]/[Pd] = 1.0 ([dppm]/[Pd] = 0.5).
[g] [P]/[Pd] = 4.0 ([dppm]/[Pd] = 2.0).

Table 2
Coupling of BTP and PhMgBr using various Pd(II) complexes with dppm[a].

Entry	Pd(II) compound	[dppm]/[Pd]	Yield (%)[b]
1	PdCl$_2$(PhCN)$_2$	1.0	96
2	PdCl$_2$(PhCN)$_2$	0	3
3	PdCl$_2$(tmeda)	1.0	95
4	PdCl$_2$(tmeda)	0	2
5	Pd(acac)$_2$	1.0	94
6	Pd(acac)$_2$	0	7
7	PdCl$_2$	1.0	35
8	K$_2$PdCl$_4$	1.0	37
9	Pd(OAc)$_2$	1.0	80
10[c]	Pd(OAc)$_2$	1.0	94

[a] Solvent 1,4-dioxane.
[b] Determined by GC.
[c] 2.0 equiv. of NEt$_3$ to palladium was added.

vents such as THF, diethylether and 1,2-dimethoxyethane, which are commonly used in Grignard reactions were not suitable for the coupling even with dppm. Schlenk equilibrium in 1,4-dioxane is shifted to Ph$_2$Mg [16], which is less reactive (less nucleophilic) than PhMgBr [17]. It is conceivable that more nucleophilic PhMgBr abstracts bromine atom from BTP to 3,3,3-trifluoropropene and/or fluorine atom(s) from α-trifluoromethylstyrene [18] in the other solvents, resulting in the low yields. However, we have not detected these compounds by GC and ^{19}F NMR. Therefore, the positive solvent effect of 1,4-dioxane is probably caused by the other factors such as solubility of the substrate or the product, though the details are unknown at present.

The ratio of [dppm]/[Pd] = 0.5 ([P]/[Pd] = 1.0) gave the desired product in moderate yield (entry 23), whereas the yield was significantly small (entry 24) when the [dppm]/[Pd] ratio was 2.0 ([P]/[Pd] = 4.0).

It seems very rare that the combination of palladium and dppm is effective for the coupling [19]. Thereupon, various Pd(II) complexes were examined in order to establish the generality of the dppm-based reactions (Table 2). PdCl$_2$(PhCN)$_2$, PdCl$_2$(tmeda) and Pd(acac)$_2$ gave excellent yields in the presence of 1.0 equiv. of dppm to palladium ([P]/[Pd] = 2.0), while the yields obtained without dppm were very poor (entries 1, 3, 5 *vs.* 2, 4, 6). PdCl$_2$ and K$_2$PdCl$_4$ showed low activity probably due to their low solubility in 1,4-dioxane (entries 7 and 8). The yield obtained with Pd(OAc)$_2$, which is the conventional Pd(II) compound used in coupling, and dppm was less than 80% (entry 9). The addition of NEt$_3$ to the reaction mixture improved the yield to 94% (entry 10); NEt$_3$ is known to abstract acetate ligands from Pd(OAc)$_2$, thereby, facilitating the coordination of dppm [20].

The results in Tables 1 and 2 suggest that Pd(0) species having one dppm ligand is catalytically active and it is formed not only from Pd(0) but also from Pd(II). In the reactions shown in Table 2, the major reductant of Pd(II) to Pd(0) is PhMgBr.

The above results motivated us to use a dppm-coordinated Pd complex in the coupling reaction. In previous studies, Pd(dppm)$_2$ was the only reported example of a dppm-coordinated Pd(0) complex [21]. However, since only low activity was observed when the [dppm]/[Pd(0)] ratio is 2.0 (entry 24 in Table 1), this Pd(0) complex was not selected for our experiments. Considering that a [dppm]/[Pd] ratio of 1.0 gives excellent yields with both Pd(0) (Table 1) and Pd(II) (Table 2), we chose PdCl$_2$(dppm) [22] for our examination. It is evident from entry 1 in Table 3 that this complex gives excellent yield similar to that given by the combination of Pd(0) or Pd(II) complexes and 1.0 equiv. of dppm. Addition of an excess amount of dppm resulted in a drastic decline in the yield (entry 2). These results are consistent with the observation that the yield depends on the [dppm]/[Pd] ratio, as examined with Pd(dba)$_2$ (entry 24 in Table 1). The other Pd(II) complexes bearing phosphine ligands listed in Table 1 afforded the smaller amounts as compared

Table 3
Coupling of BTP and PhMgBr using various Pd(II) complexes possessing phosphine ligands[a].

Entry	Pd(II) complex	Yield (%)[b]
1	PdCl$_2$(dppm)	98
2[c]	PdCl$_2$(dppm)	18
3	PdCl$_2$(PPh$_3$)$_2$	37
4	PdCl$_2$[P(o-tolyl)$_3$]$_2$	27
5	PdCl$_2$(PCy$_3$)$_2$	3
6	PdCl$_2$(dppe)	15
7	PdCl$_2$(dppp)	2
8	PdCl$_2$(dppb)	3
9	PdCl$_2$(dppf)	3

[a] Solvent 1,4-dioxane.
[b] Determined by GC.
[c] 1.0 equiv. of dppm to palladium was added.

to those by PdCl$_2$(dppm). Thus, similar trends were observed in Tables 1 and 3.

Stockland et al. reported that a reaction mixture of PdCl$_2$(dppm) and PhMgBr in the ratio of *ca.* 1:1 primarily yields dark-red Pd$_2$Ph$_2$(μ-dppm)$_2$ *via* PdPh$_2$(dppm) at an ambient temperature in dichloromethane, and PdPh$_2$(dppm) is converted into "Pd(0)(dppm)" along with the formation of biphenyl in the side reaction [23]. Our colorless reaction mixture containing PdCl$_2$(dppm) turns yellow during the reaction, and 0.02 mmol of biphenyl was detected by GC after the reaction; 0.05 mmol of biphenyl should be ideally formed, assuming that all the PdCl$_2$(dppm) is completely converted into the dinuclear complex. Presumably, a similar partial conversion of PdCl$_2$(dppm) to Pd$_2$Ph$_2$(μ-dppm)$_2$ occurs, along with the formation an active Pd(0) species.

From the viewpoint of synthetic applicability, various ArMgBr were examined using PdCl$_2$(dppm) (Table 4). Satisfactory yields were obtained with aryl groups containing both electron-withdrawing (entries 1 and 2) and electron-donating (entries 3–5) substituents. The substituent at the *ortho* position retarded the reaction probably because of steric hindrance (entry 6). A naphtyl-magnesium bromide also gave the product in moderate yield as well (entry 7). When 4-fluorophenylmagnesium bromide or 4-chlorophenylmagnesium bromide was employed, the fluorine or chlorine atom remained unaffected under the given conditions. The high tolerance and selectivity suggests that a direct method for the synthesis of functionally substituted α-trifluoromethylstyrene derivatives is possible using BTP and ArMgBr.

In conclusion, we have demonstrated the Pd-catalyzed cross-coupling of BTP and ArMgBr to obtain α-trifluoromethylstyrene derivatives. We have found that dppm is exclusively effective in coupling. The present method for the synthesis of α-trifluoromethylstyrene derivatives will be more practical than previously reported methods.
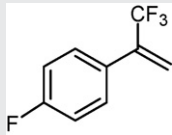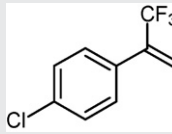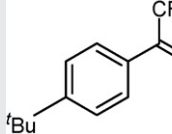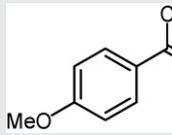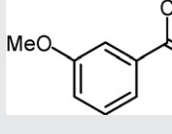
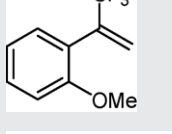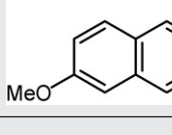## 4. Characterization of products

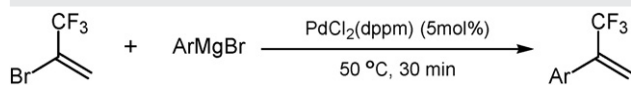### 4.1. α-Trifluoromethylstyrene (CAS No. 384-64-5 [4,11,24])

Full characterization of this compound is shown in Refs. [4,11,24]. ^{1}H NMR (CDCl$_3$) δ: 7.47–7.43 (m, 2H), 7.40–7.35 (m, 3H), 5.95 (q, J_{HF} = 1.4 Hz, 1H), 5.76 (q, J_{HF} = 1.4 Hz, 1H). ^{19}F NMR (CDCl$_3$) δ: −65.1. MS (m/z): 172 [M]$^+$.

4.2. 4-Methoxy-1-(trifluoromethyl)vinylbenzene (CAS No. 69843-08-9 [24])

Full characterization except ^{19}F NMR of this compound is shown in Ref. [24].

Table 4
The coupling of BTP with various arylmagnesium bromide using PdCl$_2$(dppm) catalyst[a].

Entry	Ar	Product	Yield (%)
1	4-Fluorophenyl		68
2	4-Chlorophenyl		56
3	4-*tert*-Butylphenyl		87
4	4-Methoxyphenyl		93
5	3-Methoxyphenyl		87
6	2-Methoxyphenyl		19
7	6-Methoxynaphtyl		52

Yield determined by ^{19}F NMR.

[a] Solvent 1,4-dioxane.

^{1}H NMR (CDCl$_3$) δ: 7.39 (d, J_{HH} = 8.7 Hz, 2H), 6.90 (d, J_{HH} = 8.7 Hz, 2H), 5.86 (q, J_{HF} = 1.3 Hz, 1H), 5.69 (q, J_{HF} = 1.7 Hz, 1H), 3.83 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −65.1. MS (m/z): 202 [M]$^+$.

4.3. 3-Methoxy-1-(trifluoromethyl)vinylbenzene (CAS No. 946614-13-7 [12])

^{1}H NMR (CDCl$_3$) δ: 7.32–7.27 (m, 1H), 7.05–7.02 (m, 1H), 6.98 (brs, 1H), 6.94–6.91 (m, 1H), 5.95 (q, J_{HF} = 1.3 Hz, 1H), 5.77 (q, J_{HF} = 1.6 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −65.1. IR (neat): 3082, 2943, 2839, 1601, 1491, 1348, 1242, 1159 cm^{-1}. HRMS (EI) m/z calcd for C$_{10}$H$_9$OF$_3$ 202.0605, found 202.0609.

4.4. 2-Methoxy-1-(trifluoromethyl)vinylbenzene (CAS No. 235780-29-7 [11])

Full characterization except ^{13}C NMR of this compound is shown in Ref. [11].

^{1}H NMR (CDCl$_3$) δ: 7.36–7.32 (m, 1H), 7.23–7.20 (m, 1H), 6.98–6.92 (m, 2H), 6.07 (d, J_{HF} = 1.4 Hz, 1H), 5.64 (d, J_{HF} = 1.0 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −65.9. MS (*m/z*): 202 [M]$^+$.

4.5. 4-tert-Butyl-1-(trifluoromethyl)vinylbenzene (CAS No. 185140-55-0 [25])

^{1}H NMR (CDCl$_3$) δ: 7.40 (brs, 4H), 5.91 (q, J_{HF} = 1.3 Hz, 1H), 5.75 (q, J_{HF} = 1.7 Hz, 1H), 1.33 (s, 9H). ^{19}F NMR (CDCl$_3$) δ: −65.1. IR (neat): 3041, 2964, 1612, 1518, 1365, 1352, 1165 cm^{-1}. HRMS (EI) *m/z* calcd for C$_{13}$H$_{15}$F$_3$ 228.1126, found 228.1129.

4.6. 4-Fluoro-1-(trifluoromethyl)vinylbenzene (CAS No. 655-29-8 [24])

Full characterization except ^{19}F NMR of this compound is shown in Ref. [24].
^{1}H NMR (CDCl$_3$) δ: 7.42 (dd, J_{HH} = 8.7 Hz, J_{HF} = 5.3 Hz, 2H), 7.06 (dd, J_{HH} = 8.7 Hz, J_{HF} = 8.7 Hz, 2H), 5.94 (d, J_{HF} = 1.3 Hz, 1H), 5.71 (d, J_{HF} = 1.7 Hz, 1H). ^{19}F NMR (CDCl$_3$) δ: −112.8, −65.4. MS (*m/z*): 190 [M]$^+$.

4.7. 4-Chloro-1-(trifluoromethyl)vinylbenzene (CAS No. 69843-10-3 [25,26])

^{1}H NMR (CDCl$_3$) δ: 7.41–7.34 (m, 4H), 5.97 (q, J_{HF} = 1.3 Hz, 1H), 5.76 (q, J_{HF} = 1.6 Hz, 1H). ^{19}F NMR (CDCl$_3$) δ: −65.2. IR (neat): 3051, 1903, 1597, 1496, 1398, 1350, 1093, 1167 cm^{-1}. HRMS (EI) *m/z* calcd for C$_9$H$_6$ClF$_3$ 206.0110, found 206.0119.

4.8. 6-Methoxy-2-[1-(trifluoromethyl)vinyl]naphthalene (CAS No. 136476-30-7 [7])

Full characterization except ^{13}C NMR of this compound is shown in Ref. [7].
^{1}H NMR (CDCl$_3$) δ: 7.86 (s, 1H), 7.76–7.71 (m, 2H), 7.54–7.50 (m, 1H), 7.19–7.15 (m, 1H), 7.14–7.11 (m, 1H), 5.99 (d, J_{HF} = 1.2 Hz, 1H), 5.86 (d, J_{HF} = 1.6 Hz, 1H), 3.92 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −64.6. MS (*m/z*): 252 [M]$^+$.

Acknowledgement

References

[1] A. Thompson, E.G. Corely, M.F. Huntington, E.J.J. Grabowski, J.F. Remenar, D.B. Collum, J. Am. Chem. Soc. 120 (1998) 2028.
[2] L. Tan, C.Y. Chen, R.D. Tillyer, E.J.J. Grabowski, P.J. Reider, Angew. Chem., Int. Ed. 38 (1999) 711.
[3] S. Kishimura, M. Endo, M. Sasago, M. Shirai, M. Kadooka, Kokai Tokkyo Koho, JP2002-311588.
[4] B.S. Nader, J.A. Cordova, K.E. Reese, C.L. Powell, J. Org. Chem. 59 (1994) 2898.
[5] H. Lebel, V. Paquet, Org. Lett. 4 (2002) 1671.
[6] J.M. Paratian, E. Labbé, S. Sibille, J. Périchon, J. Organomet. Chem. 489 (1995) 137.
[7] B. Jiang, Y. Xu, J. Org. Chem. 56 (1991) 7336.
[8] B. Jiang, Q. Wang, C. Yang, M. Xu, Tetrahedron Lett. 42 (2001) 4083.
[9] Y. Horino, N. Wakasa, T. Fuchikami, T. Yamakawa, J. Mol. Catal. A: Chem. 258 (2006) 152.
[10] T. Kino, Y. Nagase, Y. Horino, T. Yamakawa, J. Mol. Catal. A: Chem. 282 (2008) 34.
[11] R.Q. Pan, X.-X. Liu, M.Z. Deng, J. Fluorine Chem. 95 (1999) 167.
[12] K. Matoba, T. Mizukoshi, Y. Moriyama, PCT Int. Appl., WO2007094313.
[13] N. Miyaura, in: A. de Meijere, F. Diederich (Eds.), Metal-Catalyzed Cross-Coupling Reactions, vol. 2, Wiley, Weinheim, 2004, p. 41.
[14] J. Tsuji, Palladium Reagents and Catalysts, Wiley, West Sussex, 2004.
[15] D.G. Hall, in: D.G. Hall (Ed.), Boronic Acids, Wiley, Weinheim, 2005, p. 1.
[16] W. Schlenk, W. Schlenk Jr., Chem. Ber. 62B (1929) 920.
[17] G.F. Wright, J. Am. Chem. Soc. 61 (1939) 1152.
[18] H. Ito, A.F. Renaldo, M. Ueda, Macromolecules 22 (1989) 45.
[19] M.A. Campo, R.C. Larock, J. Am. Chem. Soc. 124 (2002) 14326.
[20] F. Ozawa, A. Kubo, T. Hayashi, Chem. Lett. (1992) 2177.
[21] Z. Wu, S. Yang, Y. Lin, J. Liu, L. Tian, Z. Pang, D. Cheng, M. Zhan, Huaxue Wuli Xuebao 17 (2004) 741.
[22] W.L. Steffen, G.J. Palenik, Inorg. Chem. 15 (1976) 2432.
[23] R.A. Stockland, G.K. Anderson Jr., N.P. Rath, Organometallics 16 (1997) 5096.
[24] T. Miura, Y. Ito, M. Murakami, Chem. Lett. 37 (2008) 1006.
[25] M. Mishima, H. Inoue, S. Itai, M. Fujio, Y. Tsuno, Bull. Chem. Soc. Jpn. 69 (1996) 3273.
[26] K.M. Koshy, D. Roy, T.T. Tidwell, J. Am. Chem. Soc. 101 (1979) 357.