Cross-coupling reaction of cyclopropylboronic acids with aryl ω-halo-oxo-perfluoroalkyl-sulfonates

YAO Minliang, WANG Jiapo & DENG Minzhi

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China
Correspondence should be addressed to Deng Minzhi (e-mail: Dengmz@pub.sioc.ac.cn)

Abstract **The cross-coupling reaction of cyclopropylboronic acids with aryl ω-halo-oxo-perfluoroalkylsulfonates is investigated. It was found that the stereodefined cyclopropylboronic acids can readily react with aryl ω-halo-oxo-perfluoroalkylsulfonates to give the corresponding cross-coupling products in high yields under the appropriate conditions and in the presence of transition metal catalysts. For the reaction of various aryl perfluoroalkylsulfonates bearing the substituents, the use of corresponding bases was essential. During these reactions, the cyclopropyl configurations of cyclopropylboronic acids are retained. Thus, the procedure provides a new convenient route to stereodefined cyclopropane derivatives from phenols and commerce-available ω-chloro-oxo-perfluoroalkylsulfonyl fluoride.**

Keywords: cross-coupling reaction, cyclopropylboronic acid, cyclopropane derivatives, ω-halo-oxo-perfluoroalkylsulfonates.

Suzuki-type cross-coupling reaction[1,2] catalyzed by the transition metal compounds is one of the main methods of C-C bond formation, with the advantages of mild reaction conditions, retention of many functions, excellent stereoselectivity, regioselectivity, etc. Especially, cross- coupling reactions of aryl and alkenylboronic acids have been violently developed[3—7] and widely applied to the synthesis of liquid crystals, drugs and natural compounds in the past two decades[8—12].

Because many natural compounds contain cyclopropyl subunit[13—15], to extend the scope of Suzuki-type cross-coupling reactions, we have investigated the synthesis of stereodefined cyclopropylboronic acids (esters) and their cross-coupling reactions during the past years[16—21]. Recently, we accomplished the cross-coupling reactions of cyclopropylboronic acids with alkenyl triflates successively[22—24], providing novel methods to prepare stereodefined cyclopropyl derivatives from phenols and arylam- ines. Considering that triflic anhydride, which is a necessary starting material for preparing various aryl and alkenyl triflates, is too expensive, we used commerce- avaliable ω-halo-oxo-perfluoroalkylsulfonyl fluoride instead of triflic anhydride to react with phenols giving corresponding aryl perfluorosulfates, and explored their cross-coupling with cyclopropylboronic acids.

Initially, using *trans*-2-butylcyclopropylboronic acid and aryl ω-halo-oxo-perfluoroalkylsulfonates **1** and **2** (the reaction products of phenols with ω-halo-oxo-perfluoroal- kylsulfonyl fluoride) as the substrates, the effects of catalysts, solvents and bases on the cross-coupling were investigated (fig. 1).

After many experiments, it was found that the reaction of **1** did not provide the desired coupling product perhaps due to the reason that the C-I bond could also participate in oxidative-addition to the catalysts, while **2** was used as the substrate, since Cl-C bond is difficult to take part in the oxidative-addition, the cross-coupling was readily conducted to give the expected coupling products in medial yield by using $Pd(PPh_3)_4$ (3 mol%) as a catalyst, $K_3PO_4 \cdot 3H_2O$ as a base and toluene as the solvent.

In order to investigate the effect of the substitutent group and the length of perfluoroalkyl chain on the cross-coupling reactions, various aryl ω-halo-oxo-perfluoroalkylsulfonates 3—6 (fig. 2) were prepared and their reactions with the cyclopropylboronic acids were explored.

1 Experimental

(i) Reagents and apparatus. All reactions were carried out under a dry nitrogen or argon atmosphere. The solvents and the starting materials were dried and purified according to the standard methods in literature before use. Melting points were uncorrected. IR spectra were recorded on IR-400 and FTS-185 infrared spectrometers. MS were obtained on HP5989A. ^1H NMR and ^{19}F NMR were recorded on 60 MHz (Varian-360), 90 MHz (Varian-360) and 300 MHz (Brucker AMX-300) instruments. The elemental analysis was accomplished in the Analytic Center of Shanghai Institute of Organic Chemistry.

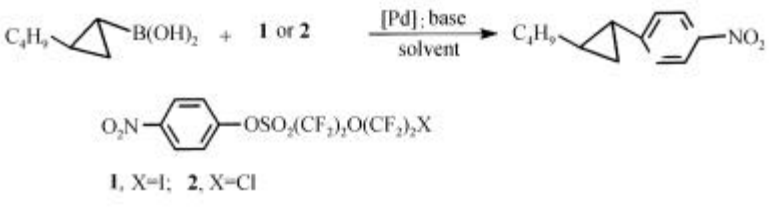


Fig. 1

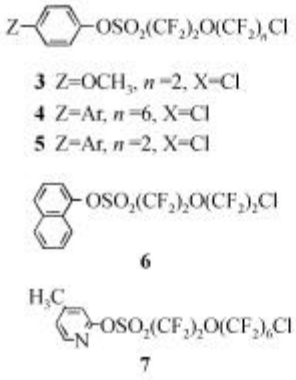
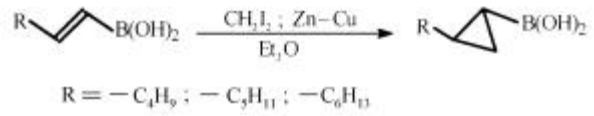


Fig. 2

(ii) Preparation of starting materials and reagents.

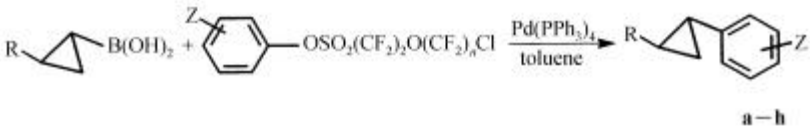
Starting materials were $BH_3 \cdot THF$[27], catecholborane (CB)[27] and *trans*-2-alkenylboronic acids[27]. ω-Halo-oxo-perfluoroalkylsulfonates[28] and $Pd(PPh_3)_4$[29] were prepared respectively according to the literature procedure.

(iii) Preparation of *trans*-2-alkyl(aryl)-cyclopropylboronic acids[16](scheme 1). A 3-neck flask was charged with Zn-Cu alloy (3.3 g) and dry ether (3 mL). To the mixture $(CH_3)_3SiCl$ (0.3 mL) was syringed under stirring. After 5 min, CH_2I_2 (0.1 mL) and Et_2O (0.5 mL) were added. The solution was heated to reflux. The mixture of CH_2I_2 (1.67 mL), alkenyl boronic acids (10 mmol) and dry ether (10 mL) was added dropwise at such a rate as to keep the solvent refluxing. After the addition, the solution of CH_2I_2 (0.85 mL) in Et_2O (2 mL) was added and the reaction mixture was stirred for 10—12 h under refluxing. Then, ether (15 mL) was added. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The mixture was filtered and the solid residue was washed with ether (4×15 mL). The combined organic layer was washed with saturated aqueous NH_4Cl (3×10 mL) and brine, and dried with $MgSO_4$. After the solvent was removed, the solid was recrystalized from water to give the pure products (yield: 65%—83%).



Scheme 1

(iv) The cross-coupling reaction of *trans*-2-substituted-cyclopropylboronic acids with triflates analogues (scheme 2). In a flask, cyclopropylboronic acids (1.1 mmol), triflates analogues (1 mmol), $K_3PO_4 \cdot 3H_2O$ (3 mol%) NaBr (1 mmol), toluene (4 mL) were placed, then under argon, $Pd(PPh_3)_4$ (35 mg, 3 mol%) was added. The reaction mixture was stirred at 100℃. After the reaction was completed (about 18—25 h), the mixture was cooled to room temperature and water (1 mL) was added. The mixture was extracted with petroleum ether (3×10 mL). Then the combined organic layer was washed with brine (3×10 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo*, followed by silica gel chromatography, gave the corresponding coupling products **a**—**h** (table 1). Their microanalyses and spectra are given as follows.



Scheme 2

Compound **a**: yield, 75%; colorless oil; IR (film) ν_{max}/cm^{-1}: 2979, 1602, 1518, 1405, 1114, 858, 751, 697. ^{1}H NMR-400 MHz δ_H: 8.09 (d, 2H); 7.13 (d, 2H); 1.68—1.72 (ddd, 1H); 1.34—1.42 (m, 6H, 3×CH_2); 1.11—1.15 (m, 1H); 0.97—1.03 (m, 1H); 0.94—0.96 (m, 1H); 0.88—0.92 (t, 3H, CH_3). MS(EI) *m*/*z*: 149 (100), 116 (26.14), 119 (22.54), 115 (18.15), 150 (15.04), 219 (12.11), 91 (11.18); 103 (8.49). Anal. Calcd. for $C_{13}H_{17}NO_2$: C%, 71.20; H%, 7.81; N%, 6.39. Found: C%, 71.30; H%, 7.91; N%, 6.60.

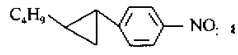
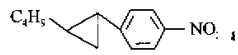
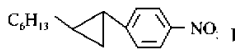
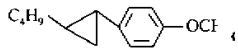
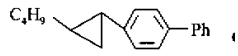
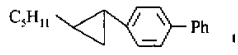
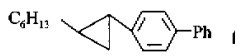
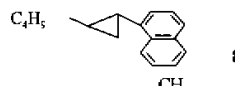
Compound **b**: yield, 82%; colorless oil; IR (film) ν_{max}/cm^{-1}: 2979, 1602, 1518, 1343, 1113, 859, 751, 697. ^{1}H NMR δ_H: 8.10 (d, 2H); 7.13 (d, 2H); 1.69—1.72 (ddd, 1H); 1.28—1.42 (m, 10H, 5×CH_2); 1.12—1.15 (m, 1H); 0.87—1.05 (m, 5H, H+H+CH_3). MS(EI) *m*/*z*: 149 (100), 119 (36.79), 115 (36.11), 41 (35.70), 116 (30.67), 43 (27.56), 91 (22.95), 150 (19.31). Anal. Calcd. for $C_{15}H_{21}NO_2$: C%, 72.84; H%, 8.56; N%, 5.66. Found: C%, 73.33; H%, 8.86; N%, 5.58.

Compound **c**: yield, 68%; colorless oil; IR (film) ν_{max}/cm^{-1}: 1618, 1518, 1470, 1245, 1039, 824. ^{1}H NMR δ_H: 6.95—7.24 (d, 2H); 6.76—6.81 (d, 2H); 3.76 (s, 3H, OCH_3); 1.51—1.75 (ddd, 1H); 1.25—1.47 (m, 6H, 3×CH_2); 0.86—0.97 (m, 4H, CH_3+H); 0.75—0.81 (ddd, 1H); 0.64—0.70 (ddd, 1H). MS (EI) *m*/*z*: 45 (100), 147 (78.10), 44 (43.65), 57 (25.52), 204 (23.03), 43 (21.36), 91 (21.00), 69 (18.85). Anal. Calcd. for $C_{14}H_{20}O$: C%, 82.29; H%, 9.87. Found: C%, 81.92; H%, 10.13.

Compound **d**: yield, 81%; solid; IR (KBr) ν_{max}/cm^{-1}: 2953, 2916, 1612, 1487, 1448, 834, 757, 688. ^{1}H NMR δ_H: 7.08—7.60 (m, 9H, Ar); 1.60—1.66 (ddd, 1H); 1.26—1.41 (m, 6H, 3×CH_2); 1.02—1.10 (ddd, 1H); 0.87—0.96 (m, 4H, H+CH_3); 0.75—0.82 (ddd, 1H). MS (EI)

6 (m, 4H, H+CH_3); 0.75—0.82 (ddd, 1H). MS (EI) *m*/*z*: 250 (100), 193 (74.45), 178 (43.00), 180 (33.81), 165 (31.76),

Table 1 The cross-coupling reaction of cyclopropylboronic acids with aryl ω-halo-oxo-perfluoroalkylsulfonates[a)]

Entry No.	Cyclopropylboronic acids	Perfluoroalyl-sulfonates **2**—**7**	Products		Yield (%)[a)]
A		**2**		**a**	75
B		**2**		**a**	84[c)]
C		**2**		**b**	82[c)]
D		**3**		**c**	66[c)]
E		**4**		**d**	81[c)]
F		**5**		**d**	82[c)]
G		**4**		**e**	76
H		**4**		**f**	84[c)]
M		**6**		**g**	78
N		**7**		**h**	70[c)]

a) Cyclopropylboronic acids: 1.1 mmol; triflates analogues, 1 mmol; 3.3 eq. $K_3PO_4 \cdot 3H_2O$; $Pd(PPh_3)_4$, 0.03 mmol; toluene, 4 mL. b) Isolated yield (based on aryl perfluoroalkylsulfonates). c) 3.3 eq. $KF \cdot 2H_2O$.

251 (25.46), 179 (24.86), 167 (18.29). Anal. Calcd. for $C_{19}H_{22}$: C%, 91.14; H%, 8.86. Found: C%, 91.00; H%, 9.05.

Compound **e**: yield, 78%; solid; IR (KBr) ν_{max}/cm^{-1}: 2956, 2919, 1488, 1448, 832, 758, 689. ^{1}H NMR δ_H: 7.10—7.58 (m, 9H, Ar); 1.58—1.65 (ddd, 1H); 1.28—1.42 (m, 8H, 4×CH_2); 1.04—1.11 (ddd, 1H); 0.86—0.95 (m, 4H, H+CH_3); 0.76—0.83 (ddd, 1H). MS (EI) *m*/*z*: 264 (100), 193 (56.70), 265 (27.94), 178 (22.50), 165 (21.42), 180 (18.61), 167 (17.65), 179 (14.23). Anal. Calcd. for $C_{20}H_{24}$: C%, 90.85; H%, 9.15. Found: C%, 91.04; H%, 9.31.

Compound **f**: yield, 84%; solid; IR (KBr) ν_{max}/cm^{-1}: 2954, 2918, 1612, 1488, 1448, 821, 758, 688. ^{1}H NMR δ_H: 7.11—7.59 (m, 9H, Ar); 1.61—1.68 (ddd, 1H); 1.30—1.43 (m, 10H, 5×CH_2); 1.05—1.11 (ddd, 1H); 0.86—0.95 (m, 4H, H+CH_3); 0.76—0.83 (ddd, 1H). MS (EI) *m*/*z*: 278 (100), 193 (76.88), 180 (50.47), 178 (40.70), 165 (31.20), 279 (30.53), 167 (26.41), 179 (19.97). Anal. Calcd. for $C_{21}H_{26}$: C%, 90.59; H%, 9.41. Found: C%, 90.34; H%, 9.52.

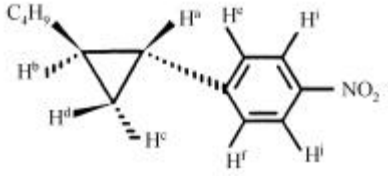
Compound **g**: yield, 78%; colorless oil; IR (film) ν_{max}/cm^{-1}: 2979, 1602, 1518, 1407, 1113, 859, 756, 697. ^{1}H NMR δ_H: 7.25—8.41 (m, 7H, Ar); 2.12—2.15 (ddd, 1H); 1.68—1.75 (ddd, 1H); 1.42—1.57 (m, 6H, 3×CH_2); 1.12—1.18 (ddd, 1H); 0.97—1.06 (t, 3H, *J*=6.7; CH_3); 0.87—0.92 (ddd, 1H). MS (EI) *m*/*z*: 167 (100), 153 (46.07), 165 (38.06), 152 (32.23), 224 (32.14), 154 (32.12), 166 (22.47), 168 (20.86). Anal. Calcd. for $C_{17}H_{20}$: C%, 91.01; H%, 8.99. Found: C%, 90.77; H%, 8.92.

Compound **h**: yield, 70%; colorless oil; IR (film) ν_{max}/cm^{-1}: 2958, 2954, 1606, 1562, 1456, 818. ^{1}H NMR δ_H: 8.27 (d, 1H, *J*=5.0); 6.90 (s, 1H); 6.83 (d, 2H, 3.6); 2.28 (s, 3H); 1.68—1.71 (ddd, 1H); 1.31—1.43 (m, 7H, 3×CH_2+H); 1.15—1.19 (ddd, 1H); 0.89 (t, 3H, CH_3, *J*=7.2); 0.74—0.77 (ddd, 1H). MS (EI) *m*/*z*: 146 (100), 132 (89.38), 131 (73.01), 133 (66.10), 130 (40.45), 41 (32.08), 147 (29.75), 144 (28.83). Anal. Calcd. for $C_{13}H_{19}N$: C%, 82.48; H%, 10.12; N%, 7.40. Found: C%, 82.09; H%, 10.33; N%, 7.36.

2 Results and discussion

Using $K_3PO_4 \cdot 3H_2O$ (3 mol%) as a base and $Pd(PPh_3)_4$ (3 mol%) as a catalyst, the cross-coupling of various aryl ω-chloro-oxo-perfluoroalkylsulfonates with *trans*-cyclopropylboronic acids in toluene was accomplished and the results are shown in table 1.

Table 1 demonstrates that the cross-coupling reactions of various aryl ω-chloro-oxo-perfluoroalkylsulfonates with *trans*-cyclopropylboronic acids can readily proceed under the appropriate conditions to give the desired cross-coupling products in good yields. The length of perfluoroalkyl chain did not influence the reaction (entries E *vs*. F, and **4** *vs*. **5**). The aryl ω-chloro-oxo-perfluoroalkylsulfonates of heterocyclic phenol can also take part in the reaction, readily to give the corresponding coupling products (entry N). Moreover, it was found that in the case of electron-withdrawing group, the use of KF instead of $K_3PO_4 \cdot 3H_2O$ as a base can offer higher yield of corresponding coupling products (entries A *vs.* B). However, for the aryl ω-chloro-oxo-perfluoroalkylsulfonates with electron-donating group, KF as a base provided only a trace of coupling products (entry D), due to the occurrence of exchange between the aryl group of ω-chloro-perfluoroalkylsulfonates and the phenyl group of the catalyst[23,25,26]. ^{1}H-^{1}H NOESY of compound **a** and ^{1}H NMR spectra of products showed that the configurations of the cyclopropyl group of the products were *trans*- isomer (scheme 3).



Scheme 3. Compound **a**.

^{1}H-^{1}H NOESY spectra of compound **a** are as follows. δ_H ($CDCl_3$, TMS, 400 MHz): 0.88—0.92 (t, 3H, CH_3), 0.94—0.96 (m, 1H, H^d), 0.97—1.03 (m, 1H, H^c), 1.11—1.15 (m, 1H, H^b), 1.34—1.42 (m, 6H, 3×CH_2), 1.69—1.72 (m, 1H, H^a), 7.13 (d, 2H, H^e, H^f), 8.09(d, 2H, H^i, H^j). Two of the aryl protons (δ7.13, H^e, H^f) showed very strong NOE interactions with three of the cyclopropyl protons (H^a, H^b, H^c), but no NOE interactions with the fourth (H^d). Furthermore, there are NOE interactions between H^a and H^d, H^b and H^c, H^c and H^d. The facts suggested that the cyclopropyl subunit of compound **a** has *trans*-configuration. The cyclopropylboronic acids used, generated from the cyclopropanation of *trans*-alkenyl- boronic acids, are pure *trans*-isomer. The configurations confirmation of compound **a** proved again that cyclopropyl configuration was retentive during the coupling process.

Since the ω-chloro-oxo-perfluoroalkylsulfonates could be obtained from phenols and commerce-available ω-chloro-oxo-perfluoroalkylsulfonyl flouride, the success of the reaction makes the method of preparing stereodefined cyclopropylarenes from phenols via the corresponding perfluoroalkylsulfonates more practical.

Acknowledgements This work was supported by the National Natural Science Foundation of the China (Grant Nos. 29672043 and 29872050).

References

1. Miyaura, N., Suzuki, A., Palladium-catalyzed cross-coupling reaction of organoboron, Chem. Rev., 1995, 95: 2457.
2. Suzuki, A., Recent advances in the cross-coupling reactions of organoboron derivatives with organic electrophiles, 1995—1998, J. Orgnometallic Chem., 1999, 576: 147.
3. Old, D. W., Wolfe, J. P., Buchwald, S. L., A highly active catalyst for palladium-catalyzed cross-coupling reaction: Room temperature Suzuki couplings and amination of unactivated aryl chlorides, J. Am. Chem. Soc., 1998, 120: 9722.
4. Yang, N., Zhen, Y., Nickel-catalyzed cross-couplings of cyclohexenyl phosphate and arylboronic acids, Tetrahedron Lett., 1999, 40: 3321.
5. Sengupta, S., Bhattacharyya, S., Palladium-catalyzed cross-coupling of arenediazonium salts with arylboronic acid, J. Org. Chem., 1997, 62: 3405.
6. Bumagin, N. A., Korolev, D. N., Synthesis of unsymmetric ketones via ligandless Pd-catalyzed reaction of acyl chlorides with organoboranes, Tetrahedron Lett., 1999, 40: 3057.
7. Haddach, M., McCarthy, J. R., A new method for the synthesis of ketones: the palladium-catalyzed cross-coupling of acid chlorides with arylboronic acids, Tetrahedron Lett., 1999, 40: 3109.
8. Miyaura, N., Suginome, H., Suzuki, A., New stereospecific synthesis of pheromone bombykol and its three geometrical isomers, Tetrahedron Lett., 1983, 24: 1527.
9. Miyaura, N., Suginome, H., Suzuki, A., Stereospecific synthesis of (2Z,4E,6E)-3,7,11-trimethyl-2,4,6,10-dodecatetraene [*trans*(C_{10})-allofarnesene], Bull. Chem. Soc. Jpn., 1982, 55: 2221.
10. Gordon, D. W., An improved synthesis of YC-1, Synlett., 1998, 1065.
11. Havelkova, M., Hocek, M., Cesrk, M. et al., The Suzuki-miyaura cross-coupling reactions of 6-halopurines with boronic acids leading to 6-aryl- and 6-alkenylpurines, Synlet., 1999(7): 1145.
12. Bussolari, J. C., Rehborn, D. C., Preparation of 5-arylfurfurals and arylthiophene-2-carboxaldehydes via Pd-catalyzed C-C bond formation in aqueous media, Org. Lett., 1999(1): 965.
13. Levy, B. D., Petasis, N. A., Serhan, C. N., Polyisoprenyl phosphates in intracellular signaling, Nature, 1997, 389: 985.
14. Mohapatra, D. K., Datta, A., Stereoselective synthesis of a key precursor of halicholactone and neohalicholactone, J. Org. Chem., 1998, 63: 642, and references cited therein.
15. Connor, D. T., Von Strandtmann, M., Antibiotics from polyangium cellulosum var fulvum, J. Org. Chem., 1978, 43: 4606.
16. Wang, X. Z., Deng, M. Z., Cross-coupling reaction of cyclopropylboronic acid with bromoarenes, J. Chem. Soc., Perkin. Trans 1., 1996, 2663.
17. Ma, H. R., Wang, X. H., Deng, M. Z., Pd-catalyzed cross-coupling reaction of stereodefined cyclopropylboronic acids with N-hetero- cyclic bromides, Synth. Commun., 1999, 29(14): 2477.
18. Zhou, S. M., Yan, Y. L., Deng, M. Z., A novel stereocontrolled synthesis of cyclopropyl-substituted α,β-unsaturated esters, Synlett., 1998(2): 198.
19. Zhou, S. M., Deng, M. Z., A novel route to stereodefined cyclopropyl-substituted alkenes, Tetrahedron Lett., 2000, 41: 3951.
20. Chen, H., Deng, M. Z., A novel Suzuki-type cross-coupling reaction of cyclopropylboronic esters with benzyl bromides, J. Chem. Soc., Perkin. Trans 1., 2000, 1609.
21. Chen, H., Deng, M. Z., A novel stereocontrolled synthesis of 1,2-

transcyclopropyl ketones via Suzuki-type coupling of acid chlorides with cyclopropylboronic acids, Org. Lett., 2000, 2: 1649.
22. Yao, M. L., Deng, M. Z., A Pd-catalyzed cross-coupling reaction of cyclopropylboronic acids with aryl triflates, Synthesis, 2000(8): 1095.
23. Yao, M. L., Deng, M. Z., A practical approach to stereodefined cyclopropyl-substitued heteroarenes using a Suzuki-type reaction, New J. Chem., 2000, 24(6): 425.
24. Yao, M. L., Deng, M. Z., Facile approach to 4-substituted 2(5H)-furanones, J. Org. Chem., 2000, 65: 5034.
25. Kong, K. C., Chang, C. H., Facile aryl-aryl exchange between the palladium centre and phosphine ligands in palladium(II) complexes, J. Am. Chem. Soc., 1991, 113: 6313.
26. O'Keefe, D. F., Dannock, M. C., Marcuccio, S. M., Palladium catalyzed coupling of halobenzenes with arylboronic acids: Role of the triphenylphosphine ligand, Tetrahedron Lett., 1992, 33: 6679.
27. Brown, H. C., Organic Synthese via Boranes, New York: Wiley, 1975, 18, 63, 64.
28. Chen Qingyun, Yang Zhenyu, Improved method for the synthesis of phenyl fluoroalkanesulfonates, Organic Chemistry (in Chinese), 1987(2): 143.
29. Covsion, D. R., Tetrakis(triphenylphosphine)palladium(0), Inorg. Synth., 1972, 13: 121.

(Received November 30, 2000; accepted February 7, 2001)