Notes

Palladium-Catalyzed Coupling of Aryl Arenesulfonates with Organostannanes†

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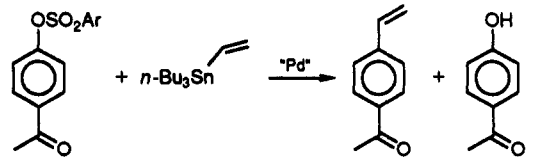
Introduction

The palladium-catalyzed cross-coupling reaction of organostannanes with aryltriflates is a versatile, high-yield method for selective carbon–carbon bond formation.[1] However, the synthesis of aryl triflates from phenols is costly, and the products are sometime unstable.[2,3] To the best of our knowledge, aryl fluorosulfonates are the only reported alternatives[4] to aryl triflates in palladium-catalyzed coupling using phenols as starting materials. However, aryl fluorosulfonates are prepared using the noncommercial, highly toxic fluorosulfonic anhydride.[5,6] Aryl arenesulfonates are potentially useful organic electrophiles for this cross-coupling reaction because they are more stable and cost less than aryl triflates. A recent paper on palladium-catalyzed reduction of aryl arenesulfonates[7] prompted us to study the related coupling with organostannanes. We now report our results on this palladium-catalyzed coupling.

Results and Discussion

A series of reactions with *p*-acetylphenyl sulfonates **1a–d** and vinyltri-*n*-butylstannane was examined to establish the best reaction conditions. A halide source (e.g., LiCl)



1a–d 2 3

Ar = a, phenyl; b, mesitylene; c, *p*-nitrophenyl; d, *p*-fluorophenyl

is essential for coupling to occur, as Stille pointed out.[1a] The reaction works well with *p*-fluorobenzenesulfonate as the leaving group (Table I). With arylsulfonates **1b–c**, conversion of 1 was incomplete or substantial amounts of cleavage products **3** were formed.[8]

The solvent affects the overall rate of reaction (Table II); in agreement with Stille,[1a] polar aprotic solvents enhance the rate dramatically (entry 1 vs 4). As the catalyst, $Pd(OAc)_2$ and $PdCl_2(CH_3CN)_2$ produce complete conversion of **1d** (Table III), but reactions were cleaner with $Pd(OAc)_2$ (entry 2 vs 4).

We also studied the influence of the palladium ligands on the coupling (Table IV). The results obtained with monodentate phosphines show that more basic ligands give higher product yields (entries 2, 3 vs 1). We also tested tris(*p*-fluorophenyl)phosphine and tri(*p*-tolyl)phosphine, but in these cases, to our surprise, many byproducts were formed. The results with electronically similar chelating

Table I. Effect of Varying Arenesulfonate on the Coupling Reaction[a]

entry	Ar	2[b]	3[b]	1a–d[b]
1	1a	89.6		10.4
2	1b	52.5		47.5
3	1c	77.8	22	0.2
4	1d	99.3	0.7	

[a] Reactions were run with 5 mol % of Pd $(OAc)_2$, 5.5 mol % of DPPP, and LiCl (3 equiv) in DMF under N_2 at 90 °C for 24 h. [b] Molar ratio, determined by GLC.

Table II. Effect of Varying Solvent on the Coupling Reaction[a]

entry	solvent	2[b]	3[b]	1d[b]
1	dioxane			100
2	DMSO	60.9		39.1
3	CH_3CN[c]	22.9		77
4	DMF	99.3	0.7	

[a] Reactions were run with 5 mol % of $Pd(OAc)_2$, 5.5 mol % of DPPP and LiCl (3 equiv) under N_2 at 90 °C for 24 h. [b] Molar ratio, determined by GLC. [c] Reaction run at 70 °C.

Table III. Effect of Varying Catalyst on the Coupling Reaction[a]

entry	catalyst[c]	2[b]	3[b]	1d[b]
1	$PdCl_2$	60.9	0.2	38.9
2	$Pd(OAc)_2$	99.3 (86)	0.7	
3	$PdCl_2(Ph_3P)_2$	79.1	5.5	15.4
4	$PdCl_2(CH_3CN)_2$	98.9 (60)		1

[a] Reactions were run with 5 mol % of DPPP and LiCl (3 equiv) in DMF under N_2 at 90 °C for 24 h. [b] Molar ratio, determined by GLC. Numbers in parentheses are for pure, isolated **2**. [c] 5 mol %.

Table IV. Effect of Varying Ligand on the Coupling Reaction[a]

monodentate phosphine[b]					
entry	ligand	cone angle θ,[c] deg	2[d]	3[d]	1d[d]
1	PPh_3	145	65	0.7	34.3
2	$P(p\text{-}CH_3OPh)_3$	145	97.3	1.4	1.3
3	Ph_2PCH_3[e]	136	100		
bidentate phosphine[f]					
entry	ligand	P–Pd–P angle, deg	2[d]	3[d]	1d[d]
4	$Ph_2PCH_2CH_2PPh_2$	~85[g]	80.7	18	17.5
5	$Ph_2PCH_2CH_2CH_2PPh_2$	~90[g]	99.3	0.7	
6	$Ph_2PCH_2CH_2CH_2CH_2PPh_2$	≥90[h]	88.5	1.9	9.6
7	$Me_2PCH_2CH_2PMe_2$		93.2		6.8

[a] Reactions were run with 5 mol % of Pd $(OAc)_2$ and LiCl (3 equiv) in DMF under N_2 at 90 °C for 24 h. [b] 11 mol %. [c] See ref 19. [d] Molar ratio, determined by GLC. [e] Reaction quenched after 14 h. [f] 5.5 mol %. [g] See ref 20. [h] See ref 21.

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(2) For a review of the chemistry of triflates, see: Stang, P. G.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

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Table V. Palladium-Catalyzed Coupling of Aryl *p*-Fluorobenzenesulfonates with Organostannanes[a]

entry	*p*-fluorobenzene sulfonate	organostannane	ligand[b]	*T*, °C	reaction time, h	product(s)	isolated yield, %
1	1d	n-Bu_3Sn	DPPP	90	24	2	86
2			Ph_2PCH_3	90	14	2	56
3		n-Bu_4Sn	DPPP	100	48	4	50
4			Ph_2PCH_3	120	26	4	67
5		n-Bu_3Sn	Ph_2PCH_3	100	26	5 + 6 (Ratio 100:0)	45
6			DPPP	100	18	5 + 6 (Ratio 65:35)	80
7		n-Bu_3SnPh	DPPP	110	24	7	85
8			Ph_2PCH_3	110	22	7	72
9		n-Bu_3Sn (Ph)	DPPP	100	20	8	69
10	9	n-Bu_3Sn	DPPP	100	30	10	50
11	11	n-Bu_3SnPh	Ph_2PCH_3	130	26	12	68
12	13	n-Bu_3Sn	Ph_2PCH_3	90	26	14	25
13			DPPP	90	19	14	50
14	15	n-Bu_3SnPh	Ph_2PCH_3	110	76	16	41[c]
15			DPPP	110	72	17	70
16	18	n-Bu_3Sn	DPPP	110	96	19 + 20	12 + 13
17			Ph_2PCH_3	110	88	20	34[d]

[a] Reactions were run with 5 mol % of Pd $(OAc)_2$ ligand and LiCl (3 equiv) in DMF under N_2. [b] DPPP 5.5 mol %, Ph_2PCH_3 11 mol %. [c] Conversion 76%. [d] Conversion 72%.

biphosphines 1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), and 1,4-bis-(diphenylphosphino)butane (DPPB) show that steric effects also play an important role in the coupling. The best

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(4) Roth, G. P.; Fuller, C. E. *J. Org. Chem.* **1991**, *56*, 3493.
(5) Kongpricha, S.; Preusse, W. C.; Schwarer, R. *Inorg. Synth.* **1968**, *11*, 151.

ligands are DPPP and methyldiphenylphosphine, which is intriguing in view of the opposite results obtained with these ligands in the Stille reaction.[9,10]

Generally, aryl *p*-fluorobenzenesulfonates couple with aryl-, vinyl-, and alkyltin reagents more sluggishly than with aryl triflates, but with comparable yields (Table V). An exception is the allyltin reagent (entry 6), which couples faster (18 h at 100 °C vs 43 h at 98 °C) giving a 65:35 mixture of **5** and **6**.[11] Using methyldiphenylphosphine as the palladium ligand in the reaction with allyltin, pure **5** is obtained in moderate yields (entry 5). Allyltri-*n*-butyltin and aryltri-*n*-butyltin couple without transfer of the alkyl group. Vinylstannane reacts with *p*-bromophenyl *p*-fluorobenzenesulfonate chemoselectively at the bromine atom (entries 12, 13), with fairly good yields. Aryl *p*-fluorobenzenesulfonates with electron-donating groups react slowly, and sometimes appreciable amounts of starting materials are recovered (entries 14, 17) and products of reaction at the *p*-fluorobenzene moiety **17** and **20** are also obtained. Displacement of the halogen of aryl fluoride by nucleophilic nitrogen species is a well-known reaction.[12] On the other hand, attempts to couple **15** with tri-*n*-butylphenyltin without palladium catalyst gave only starting material after 80 h, suggesting that palladium assists the formation of nucleophilic nitrogen species.[13]

Conclusion

The results of palladium-catalyzed cross-coupling of aryl *p*-fluorobenzenesulfonates with organostannanes differ according to the substitution on the aryl group: electron-donating groups give very poor yields and/or undesidered products, while with other substituents cross-coupling is efficient with alkyl-, vinyl-, allyl-, and arylstannanes. Utilization of *p*-fluorobenzenesulfonates in the Stille reaction offers two advantages over triflates: they cost less and starting materials are crystalline instead of oils.

Experimental Section

Elemental analyses were performed by the microanalytical laboratory of the Department of Chemistry of the University of Milan. The GLC analyses were carried out with an Ultra 1HP column (25-m length, 0.32-mm i.d.) and a flame ionization detector. Preparative column chromatography was done by the flash technique.[14] All reactions were carried out under positive argon pressure. 1,4-Dioxane was distilled from sodium and stored over activated 4-Å sieves. Dry DMF, DMSO, and CH_3CN were obtained by distillation from calcium hydride and stored over molecular sieves.

Organostannanes. Phenyltri-*n*-butylstannane and (*E*)-styryltri-*n*-butylstannane were prepared according to published procedures.[15,16] Vinyltri-*n*-butylstannane, allyltri-*n*-butylstannane, and tetra-*n*-butylstannane (Aldrich) were used as purchased.

Aryl Arenesulfonates. General Procedure. 1-Naphthyl *p*-Fluorobenzenesulfonate (9). A solution of 4-fluorobenzenesulfonyl chloride (3.00 g, 15.3 mmol) in 2 mL of pyridine was slowly added to a solution of 1-naphthol (2.00 g, 13.9 mmol) in 4 mL of pyridine at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was poured into water and extracted with ethyl ether. The ether extract was washed sequentially with water, 5% aqueous hydrochloric acid solution, and water, dried (Na_2SO_4), and concentrated to yield an oil which solidified on standing. Recrystallization from isopropyl ether afforded 3.8 g (90%) of **9** as a white solid: mp 87–89 °C; IR (KBr) 1590, 1492, 1371, 1186 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.10–7.73 (m, 5 H), 7.63–7.37 (m, 5 H), 7.29–7.16 (m, 1 H). Anal. Calcd for $C_{16}H_{11}FO_3S$: C, 63.57; H, 3.67. Found: C, 63.41; H, 3.65.

8-Quinolyl *p*-fluorobenzenesulfonate (11) (85%): white solid; mp 120–122 °C; IR (KBr) 1591, 1490, 1378, 1188, 837, 777 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.81–8.73 (m, 1 H), 8.45–8.35 (m, 1 H), 8.10–7.84 (m, 3 H), 7.73–7.37 (m, 5 H). Anal. Calcd for $C_{15}H_{10}FNO_3S$: C, 59.39; H, 3.32. Found: C, 59.21; H, 3.30.

4-Bromophenyl *p*-fluorobenzenesulfonate (13) (88%): white solid; mp 62–64 °C; IR (KBr) 1589, 1494, 1373, 1155, 838 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.89–7.77 (m, 2 H), 7.41 (dd, J = 9.8, 3.5 Hz, 2 H), 6.86 (dd, J = 9.8, 3.5 Hz, 2 H). Anal. Calcd for $C_{12}H_8BrFO_3S$: C, 43.52; H, 2.43. Found: C, 43.65; H, 2.45.

Cross-Coupling Reactions with Organostannanes. General Procedure. 4-Acetylbiphenyl (7). LiCl (215 mg, 5.07 mmol), DPPP (38.5 mg, 0.093 mmol), and $Pd(OAc)_2$ (19 mg, 0.084 mmol) were added to a solution of **1d** (500 mg, 1.7 mmol) in 7.5 mL of DMF. After 5 min of stirring, the resulting suspension became a pale yellow solution, and phenyltri-*n*-butylstannane (748 mg, 2.04 mmol) was added. The mixture was heated at 110 °C with stirring for 24 h. Then pyridine (1 mL) and 1.8 mL of pyridinium fluoride (1.4 M solution in THF, 2.52 mmol)[17] were added to the cooled reaction mixture, which was stirred overnight. The solution was diluted with ether (50 mL), filtered, washed with water, dried (Na_2SO_4), and concentrated to give the crude product. Chromatography (hexane–EtOAc, 99:1) yielded **7** as a white solid (285 mg, 85%): mp 119–120 °C (lit.[18] mp 121 °C). Anal. Calcd for $C_{13}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.44; H, 6.12. Yields of products synthesized by this methodology are listed in Table V.

3-Tolyl 4-(dimethylamino)benzenesulfonate (17) (70%): white solid; mp 120–122 °C; IR (KBr) 1593, 1360, 1176, 1159 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.55–7.45 (m, 2 H), 7.26–7.03 (m, 2 H), 6.87–6.63 (m, 4 H), 3.01 (s, 3 H), 2.24 (s, 3 H). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88. Found: C, 61.78; H, 5.86.

Registry No. **1a**, 64101-66-2; **1b**, 143858-70-2; **1c**, 55660-68-9; **1d**, 123412-35-1; **2**, 10537-63-0; **4**, 37920-25-5; **5**, 17417-03-7; **6**, 62926-84-5; **7**, 92-91-1; **8**, 3112-03-6; **9**, 123412-32-8; **10**, 826-74-4; **11**, 143858-71-3; **12**, 605-04-9; **13**, 143858-72-4; **14**, 143858-73-5; **15**, 143858-74-6; **16**, 643-93-6; **17**, 143858-75-7; **18**, 143858-76-8; **19**, 5459-40-5; **20**, 143858-77-9; DPPP, 6737-42-4; *n*-$Bu_3SnCH{=}CH_2$, 7486-35-3; *n*-Bu_4Sn, 1461-25-2; *n*-$Bu_3SnCH_2CH{=}CH_2$, 24850-33-7; *n*-Bu_3SnPh, 960-16-7; *n*-$Bu_3SnCH{=}CHPh$, 79159-76-5; Ph_2PCH_3, 1486-28-8; $Pd(OAc)_2$, 3375-31-3; 4-fluorobenzenesulfonyl chloride, 349-88-2; 1-naphthol, 90-15-3; 8-quinolinol, 148-24-3; 4-bromophenol, 106-41-2.

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