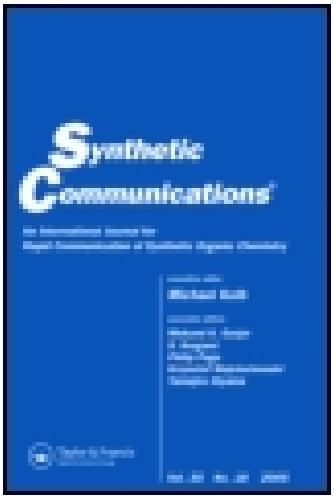

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Pd-Catalyzed Synthesis of Biphenyls with Methylthio Group

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Abstract: The synthesis of unsymmetrical biaryls with a methylthio group is achieved using the air-stable palladium–phosphinous acid complexes, $[(t\text{-Bu})_2P(OH)]_2\ PdCl_2$ (POPd), as the catalyst. A great variety of substituted bromobenzenes having electron-withdrawing and electron-donating functional groups in para and meta positions have been successfully coupled with 3-methylthiophenylboronic acid.

Keywords: cross-coupling, 3-methylthiophenylboronic acid, POPd, substituted bromobenzenes

Molecules that possess sulfur atoms are very important in living organisms.[1] Aryl compounds with a methylthio group are of interest as pesticide and synthetic intermediates used in the preparation of many pharmaceuticals. For example, methyl 2-methylthiobenzoate was used to identify the female-produced sex pheromone of *Phyllophaga crinita*. Interestingly, methyl

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Methyl 2-methylthiobenzoate Methyl 2-methoxybenzoate

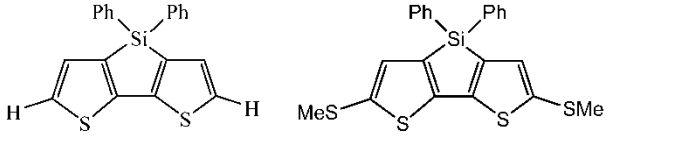
Scheme 1.

2-methoxybenzoate also captured *P. crinita* males, but only at a dose 10,000 times higher than the lowest tested dose of methyl 2-methylthiobenzoate (Scheme 1).[2]

Dithienosilole (DTS) is a very useful intermediate for preparing electron transporting and emissive materials. Introduction of methylthio groups on the α,α'-positions of DTS led to a red shift of the absorption maximum by 25 nm relative to nonsubstituted DTS, indicating that a substitution effect of -SMe groups lowers the HOMO-LUMO band gap of the molecule (Scheme 2).[3]

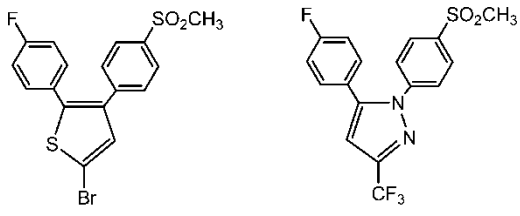
The methylthio group can be easily oxidized to form sulfinyl or sulfonyl groups, which are useful groups in pharmaceuticals. For example, Gans et al.[4] have reported that the thiophene DuP 697 ($ED_{50} = 0.18$ mpk) shows antiinflammatory activity in the rat adjuvant-induced arthritis model without the concomitant formation of gastric lesions at 400 mpk, which is the pharmacological profile expected of a selective COX-2 inhibitor. Isakson et al.[5] reported that the pyrazole SC-58125 (COX-1 $IC_{50} > 100$ pM, COX-2 $IC_{50} = 0.09$ pM) is a selective inhibitor of the inducible form of human recombinant cyclooxyge nase and is orally active ($ED_{50} = 0.4$ mpk) in rat adjuvant-induced arthritis (Scheme 3).

The synthesis of biaryl compounds by palladium-catalyzed cross-coupling reaction between aryl halides with arylboronic acids, which is commonly called Suzuki–Miyaura coupling, has developed into a powerful synthetic method in organic synthesis.[6,7] Suzuki–Miyaura cross-coupling reaction was widely used in the synthesis of many compounds because of its use of nontoxic and air-stable organoboron reagents.[8–10] The traditional palladium catalysts are mostly air sensitive and need the addition of a ligand. Li and coworkers developed a series of novel palladium–phosphinous acid complexes,



Dithienosilole (DTS) α,α'-dimethylthiodithienosilole (DTS(SMe)$_2$)

Scheme 2.

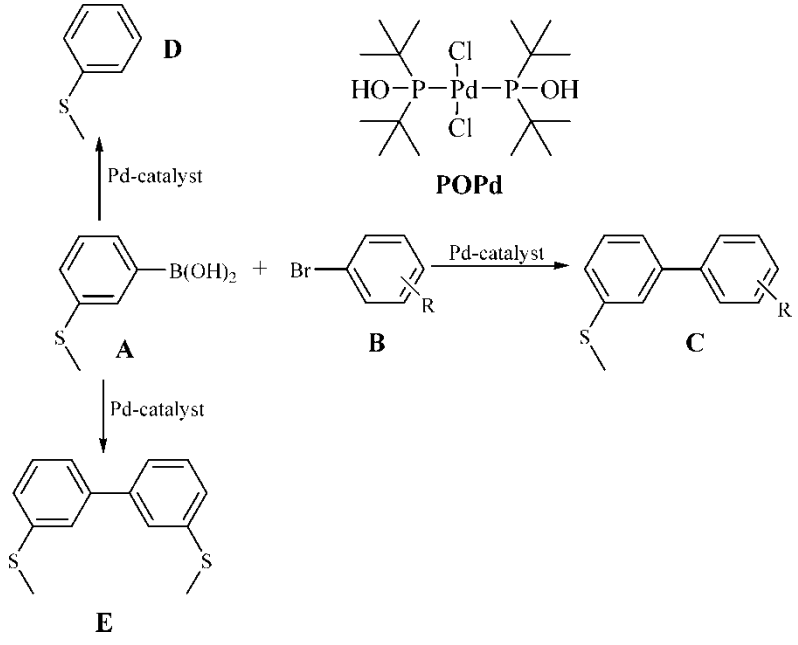


DuP 697 **SC-58125**

Scheme 3.

which were found to be efficient for variety of cross-coupling reactions.[11–14] These catalysts have advantages over the traditional catalysts, such as air and moisture stability, very high activity, and recyclability.

Herein, we investigated the reaction of 3-methylthiophenylboronic acid with substituted bromobenzenes catalyzed by one kind of Li's catalysts, $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (dihydrogendichlorobis(di-*tert*-butylphosphinito-*k*P) palladate(2-), CAS no. 391683-95-7), abbreviated as POPd (Scheme 4). (POPd catalysts are commercially available from Combi-phos Catalysts, Inc., Princeton, N.J.)



Scheme 4. POPd-catalyzed cross-coupling of 3-methylthiophenylboronic acid and aryl bromides

Table 1. POPd-catalyzed cross-coupling results of 3-methylthiophenylboronic acid and bromobenzene using dioxane as solvent

Entry	POPd (mol%)	Time (h)	Yield (%)[a] C	HPLC (%) C	D	E
1	2	6	35.1	52.5	29.5	12.3
2	0.5	6	72.1	67.6	6.0	2.8
3	0.2	3	90.0	80.1	3.0	1.2
4	0.1	5	92.0	81.1	2.3	1.5
5	0.05	16	79.7	74.5	5.3	4.9

[a]Isolated yields.

Our studies showed that the quantity of POPd used in the system significantly affected the reaction results. As shown in Table 1, there are two by-products: thioanisole (**D**) and 3,3′-dimethylthiobiphenyl (**E**) in this reaction. The reaction proceeded well while using 0.1–0.2 mol% POPd, and the amount of by-products increased when more catalysts were used.

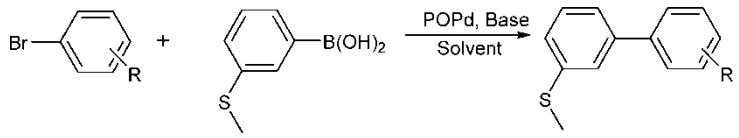
Dioxane was found to be the optimal solvent. The yield of the target product was also good while using toluene, but the solubility of 3-methylthiophenylboronic acid in toluene was poor and more by-products formed (Table 2, Scheme 4).

It can be seen that the present process, employing the air-stable POPd as catalyst, affects cross-couplings of 3-methylthiophenylboronic acid with substituted bromobenzenes (Table 3, Scheme 5). A variety of coupling reactions were catalyzed to yield the desired products with excellent isolated yields. The reactions of substituted bromobenzenes with electron-withdrawing groups give the desired product in excellent yields (Entries 2 and 3, Table 3), whereas the electron-donating substituted bromobenzenes with electron-rich groups give lower yields (Entries 6 and 7, Table 3).

In conclusion, we have demonstrated that Suzuki coupling of 3-methylthiophenylboronic acid with a variety of substituted bromobenzenes proceeds in good to excellent yield using the palladium–phosphinous acid

Table 2. POPd-catalyzed cross-coupling reactions of 3-methylthiophenylboronic acid and bromobenzene in different solvents

Entry	Solvent	Time (h)	HPLC (%) C	D	E
1	Tetrahydrofuran	5	0.4	0.4	0.3
2	Toluene	4	75.4	2.8	6.8
3	Dioxane	3	80.1	3.0	1.2



1a-g 2 3a-g

Scheme 5.

complex POPd as a catalyst. The further usefulness of this catalyst is currently under investigation in our laboratories.

EXPERIMENTAL

All reagents were purchased from commercial suppliers and used without further purification. POPd is available from Combi-phos Catalysts, Inc. Dioxane, tetrahydrofuran, and toluene were distilled from sodium benzophenone ketyl under nitrogen. Melting points were determined with an X-6 melting-point apparatus and are uncorrected. IR, NMR, and MS spectra were in agreement with the structure and were recorded on a Nicolet FT-IR 20 SX spectrometer, a Bruker AC 500 (TMS as internal standard) and Agilent 1100, respectively. High-resolution mass spectra were obtained with a Micromass GCT TOF mass spectrometer.

General Procedure for the Reaction of 3-(Methylthio) Phenylboronic Acid with Bromo Benzenes (Entry 1, Table 3)

A mixture of 3-methylthiophenylboronic acid (223.0 mg, 1.327 mmol), 4-bromobenzonitrile (161.0 mg, 0.8845 mmol), K_2CO_3 (366.7 mg, 2.657 mmol) and

Table 3. Experimental results of POPd-catalyzed cross-coupling

Entry	Reactant	R	Product	Time (h)	Yield (%) [a]
1	**1a**	H	**3a**	3	90.0
2	**1b**	4-CN	**3b**	3	99.7
3	**1c**	4-NO_2	**3c**	4	97.8
4	**1d**	3-OMe	**3d**	5	96.7
5	**1e**	4-COMe	**3e**	5	91.2
6	**1f**	4-OMe	**3f**	6	88.3
7	**1g**	4-Me	**3g**	5	85.7

[a]Isolated yields.

POPd (0.90 mg, 0.00177 mmol, 0.2 mol %) was stirred and refluxed in 2 mL of dioxane for 3 h. The reaction mixture was allowed to cool to room temperature, quenched with water, and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were removed under vacuum. The residue was purified by chromatography on silica gel eluting with hexane/EtOAc (60:1, v:v) to give the products **3a**–**g**.

Data

3-Methylthiobiphenyl (3a). Yield 90.0% as a colorless liquid; IR (KBr): 3028, 2932, 1586, 1562, 1466 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 2.55 (s, 3H), 7.27–7.25 (m, 1H), 7.39–7.36 (m, 3H), 7.49–7.45 (q, 3H, $J = 7.7$ Hz), 7.59 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 16.0, 124.1, 125.5, 127.3, 127.6, 128.9, 129.2, 139.1, 140.9, 142.0; HRMS (EI): M^+, found 200.0662. $C_{14}H_{11}NS$ requires 200.0660.

4-Cyano-3′-methylthiobiphenyl (3b). Yield 99.7% as a white acicular crystal. Mp 64.0–65.5°C. IR (KBr): 2230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 2.54 (s, 3H), 7.31 (d, 1H, $J = 7.8$ Hz), 7.34 (d, 1H, $J = 7.8$ Hz), 7.39–7.42 (t, 1H, $J = 7.8$ Hz), 7.45 (s, 1H), 7.67 (d, 2H, $J = 8.4$ Hz), 7.73 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 15.8, 124., 125.4, 126.7, 127.9, 129.6, 139.5, 139.9, 147.2, 147.3; HRMS (EI): M^+, found 225.0616. $C_{14}H_{11}NS$ requires 225.0612.

4-Nitro-3′-methylthiobiphenyl (3c). Yield 97.8% as a yellow solid. Mp 83.5–84.5°C. IR (KBr): 1515, 1349, 847 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 2.56 (s, 3H), 7.33 (d, 1H, $J = 7.8$ Hz), 7.38 (d, 1H, $J = 7.8$ Hz), 7.41–7.43 (t, 1H, $J = 7.8$ Hz), 7.49 (s, 1H), 7.73 (d, 2H, $J = 8.9$ Hz), 8.30 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 15.8, 124.1, 125.4, 126.7, 127.9, 129.6, 139.5, 139.9, 147.2, 147.3; HRMS (EI): M^+, found 245.0508. $C_{13}H_{11}NO_2S$ requires 245.0510.

4-Acetyl-3′-methylthiobiphenyl (3d). Yield 97.8% as a light yellow liquid. IR (KBr): IR (KBr): 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 2.54 (s, 3H), 2.64 (s, 3H), 7.25 (m, 1H), 7.37–7.39 (m, 2H), 7.49 (s, 1H), 7.66 (d, 2H, $J = 8.5$ Hz), 8.02 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 15.9, 26.7, 124.1, 125.4, 126.2, 127.3, 128.9, 129.4, 136.1, 139.4, 140.7, 145.3, 197.7; MS (m/z): 243.0 (M + 1); HRMS (EI): M^+, found 242.0760. $C_{15}H_{14}OS$ requires 242.0765.

3-Methoxy-3′-methylthiobiphenyl (3e). Yield 96.7% as a light yellow liquid. IR (KBr): 1300 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 2.56 (s, 3H), 3.89 (s, 3H), 6.96, 6.94 (d, 1H, $J = 10.7$ Hz), 7.146–7.154 (t, 1H, $J = 4.2$ Hz), 7.19–7.21 (d, 1H, $J = 9.9$ Hz), 7.27–7.29 (m, 1H), 7.37–7.40 (m, 3H),

7.51 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 15.8, 111.2, 118.8, 119.8, 124.0, 125.4, 125.5, 129.3, 129.9, 139.1, 141.9, 142.4, 160.0; HRMS (EI): M^+, found 230.0768. $C_{14}H_{14}OS$ requires 230.0765.

4-Methoxy-3′-methylthiobiphenyl (3f). Yield 88.3% as a white flakelike crystal. Mp 45.2–46.2°C. IR (KBr): 1260, 1040 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.46 (s, 3H), 3.78 (s, 3H), 6.90 (d, 2H, $J = 8.6$ Hz), 7.13 (d, 1H, $J = 7.1$ Hz), 7.25–7.26 (m, 2H), 7.36 (s, 1H), 7.44 (d, 2H, $J = 8.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 16.0, 55.4, 114.3, 123.7, 124.9, 125.1, 128.2, 129.2, 133.3, 138.9, 141.6, 159.4; HRMS (EI): M^+, found 230.0758. $C_{14}H_{14}S$ requires 230.0765.

4-Methyl-3′-methylthiobiphenyl (3g). Yield 85.7% as a colorless liquid. IR (KBr): 3075, 2960 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.43 (s, 3H), 2.56 (s, 3H), 7.266–7.274 (m, 3H), 7.37 (d, 2H, $J = 4.9$ Hz), 7.51 (d, 3H, $J = 8.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 16.0, 21.2, 124.0, 125.2, 125.3, 127.1, 129.2, 129.6, 137.4, 138.0, 139.0, 141.9; HRMS (EI): M^+, found 214.0816. $C_{14}H_{14}S$ requires 214.0816.

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