

Sulfonium Salts. Participants *par Excellence* in Metal-Catalyzed Carbon–Carbon Bond-Forming Reactions

Jiri Srogl, Gary D. Allred, and Lanny S. Liebeskind*

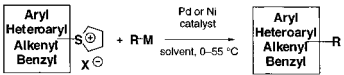
Sanford S. Atwood Chemistry Center
Emory University
1515 Pierce Drive, Atlanta, Georgia 30322



Received August 4, 1997

During the past decade, novel biological roles have been identified for metalloenzyme-induced transformations at the carbon–sulfur bond of biomolecules. *Since metal-mediated rupture of a carbon–sulfur bond is a key step in a number of these processes,*^{1–3} new and synthetically useful transformations of organosulfur compounds mediated by metals might be discovered by following nature's example.⁴ Consider, for example, the sulfonium salt.^{5,6} Although certain "onium" reagents^{7,8} have been used in transition metal-mediated cross-coupling reactions,^{9–14} it is surprising, given their biological relevance,¹⁵ that sulfonium salts have been neglected in the search for useful partners in this very powerful metal-catalyzed process.¹⁶

Sulfonium salts possess unique attributes that set them apart from other cross-coupling agents. Typically they are crystalline solids with excellent shelf-lives, they are easily and economically prepared by a variety of procedures, and they may well be superior to iodides or triflates in various applications. With appropriate non-nucleophilic counterions (PF₆⁻, BF₄⁻, ClO₄⁻),¹⁷ they possess good solubility and stability in both aprotic and protic solvents. As synthetically versatile *cationic* cross-coupling reactants, they offer a reactivity advantage through participation in attractive Coulombic interactions with approaching nucleophiles, and although cationic, sulfonium salts can coordinate to (and be activated by) a metal catalyst through the

Table 1. Metal-Catalyzed Cross-Coupling with Tetramethylenesulfonium Salts



Entry	Benzyl/Heterobenzyll	R	M	catalyst ^b / conditions	Cpd, Yld
1	benzyl ^f	2-thienyl	<i>n</i> -Bu ₃ Sn	A, EtOH, 45 °C, 12 h	1a, 82
2	2-bromobenzyl	(<i>E</i>)-β-styryl	<i>n</i> -Bu ₃ Sn	A, EtOH, 55 °C, 8 h	1b, 80
3	3-thienylmethyl	benzofuran-2-yl	<i>n</i> -Bu ₃ Sn	A, EtOH, 45 °C, 12 h	1c, 76
4	3-pyridylmethyl	(<i>E</i>)-β-styryl	<i>n</i> -Bu ₃ Sn	A, EtOH, 45 °C, 12 h	1d, 42
5	3,4-dimethoxybenzyl ^f	(<i>E</i>)-β-styryl	<i>n</i> -Bu ₃ Sn	A, EtOH, 45 °C, 10 h	1e, 75
6		benzofuran-2-yl	<i>n</i> -Bu ₃ Sn	A, EtOH, 45 °C, 14 h	1f, 76
7	2-bromobenzyl	2-(<i>N</i> -pyrrolyl)-phenyl	<i>n</i> -Bu ₃ Sn	B, EtOH, 40 °C, 5 h	1g, 81
8	3-pyridylmethyl	2-(<i>N</i> -pyrrolyl)-phenyl	<i>n</i> -Bu ₃ Sn	B, EtOH, 40 °C, 5 h	1h, 60
9	4-nitrobenzyl	4-thiomethylphenyl	B(OH) ₂	C, THF, 45 °C, 5 h	1i, 67
10	2-fluorobenzyl	<i>p</i> -tolyl	B(OH) ₂	C, 90% EtOH, 45 °C, 6 h	1j, 74
11	3,4-dimethoxybenzyl ^f	<i>p</i> -tolyl	B(OH) ₂	C, 90% EtOH, 45 °C, 8 h	1k, 72
12		<i>p</i> -tolyl	B(OH) ₂	C, DME, 45 °C, 14 h	1l, 58
13	benzyl ^f	(<i>E</i>)-1-hexenyl	B(OH) ₂	D, THF, 42 °C, 8 h	1m, 75
14	4-fluorobenzyl	2-thienyl	ZnCl	2% E, THF, 25 °C, 6 h	1n, 75
Entry	Aryl/Heteroaryl	R	M	catalyst ^b / conditions	Cpd, Yld
15	phenyl	<i>p</i> -tolyl	B(OH) ₂	F, THF, 40 °C, 14 h	2a, 95
16	2-pyridyl	<i>p</i> -tolyl	B(OH) ₂	F, THF/H ₂ O, 40 °C, 6 h	2b, 77
17	4-fluorophenyl	2-thienyl	B(OH) ₂	F, 95% EtOH, 40 °C, 3 h	2c, 74
18	2-methoxy-5-pyridyl	3-thienyl	B(OH) ₂	F, 95% EtOH, 40 °C, 3h	2d, 80
19	2-thienyl	(<i>E</i>)-β-styryl	B(OH) ₂	F, THF, 50 °C, 9 h	2e, 71
Entry	Alkenyl	R	M	catalyst ^b / conditions	Cpd, Yld
20	α-styryl	4-thiomethylphenyl	B(OH) ₂	D, THF, 40 °C, 8 h	3a, 73
21	α-styryl	<i>p</i> -tolyl	B(OH) ₂	D, THF, 40 °C, 8 h	3b, 82
22	α-styryl	Me	ZnMe	5% E, THF, 45 °C, 8 h	3c, 97
23	(<i>Z</i>)-octene-4-yl	3-methoxyphenyl	B(OH) ₂	D, THF, 40 °C, 8 h	3d, 72
24	(<i>Z</i>)-octene-4-yl	2-thienyl	B(OH) ₂	D, THF, 40 °C, 8 h	3e, 85
25	(<i>E</i>)-octene-4-yl	<i>p</i> -tolyl	B(OH) ₂	D, THF, 40 °C, 8 h	---

^a ClO₄⁻ as counterion; all others were PF₆⁻. ^b Catalysts: A: 0.2% generated *in situ* from Pd₂dba₃/8 trifurylphosphine. B: 0.1% catalyst generated *in situ* from Pd₂dba₃/8 trifurylphosphine with copper(I) diphenylphosphinate. C: 0.4–0.5% Pd(dppf)Cl₂, excess K₂CO₃. D: 0.9% Pd(PPh₃)₄. E: Ni(dppf)Cl₂. F: 4% Pd(dppf)Cl₂, 1 equiv of freshly ground K₂CO₃·H₂O. ^c GLC yield.

* Corresponding author. Phone: (404) 727-6604. FAX: (404) 727-0845. E-mail: CHEMLL1@emory.edu.

(1) Hausinger, R. P. In *Biochemistry of Nickel*; Plenum Press: New York, 1993; p 147.

(2) Ferry, J. G. *Annu. Rev. Microbiol.* **1995**, *49*, 305.

(3) Ragsdale, S. W.; Kumar, M. *Chem. Rev.* **1996**, *96*, 2515.

(4) Metal-catalyzed cross-coupling between Grignard reagents and aryl and alkenyl sulfides is known: Fiandanesse, V., Marchese, G., Naso, F. and Ronzini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 647. Wenkert, E., Leftin, M. and Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1984**, 617. Okamura, H., Miura, M. and Takei, H. *Tetrahedron Lett.* **1979**, 43. In addition, Luh and co-workers have extensively studied the nickel-catalyzed cross-coupling of Grignard reagents with various dithiane derivatives: Luh, T. Y. *Acc. Chem. Res.* **1991**, *24*, 257.

(5) *The Chemistry of the Sulphonium Group. Part 1*; Stirling, C. J. M., Ed.; John Wiley & Sons: New York, 1981; Vol. 1, p 385.

(6) *The Chemistry of the Sulphonium Group. Part 2*; Stirling, C. J. M., Ed.; John Wiley & Sons: New York, 1981; Vol. 2, p 847.

(7) Bumagin, N. A.; Sukhominova, L. I.; Igushkina, S. O.; Banchikov, A. N.; Tolstaya, T. P.; Beletskaya, I. P. *Bull. Russ. Acad. Sci. Ch-Engl. Tr.* **1992**, *41*, 2128.

(8) Moriarty, R. M.; Epa, W. R. *Tetrahedron Lett.* **1992**, *33*, 4095.

(9) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958.

(10) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340.

(11) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(12) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.

(13) Mitchell, T. N. *Synthesis* **1992**, 803.

(14) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(15) *S-Adenosylmethionine*, nature's premier methylating agent, is a sulfonium salt that acts as an alkylating agent for numerous biological molecules, and it is responsible for C-alkylations (*The Biochemistry of Adenosylmethionine*; Salvatore, F., Borek, E., Zappia, V., Williams-Ashman, H. G., Schlenk, F., Eds.; Columbia University Press: New York, 1977).

(16) Gendreau, Y.; Normant, J. F.; Villieras, J. J. *Organomet. Chem.* **1977**, *142*, 1.

(17) Sulfonium salts possessing perchlorate counterions are easily and economically prepared by substituting NaClO₄ for NaPF₆ or NH₄PF₆ in the experimental procedures described in the Supporting Information.

nonbonding pair of electrons on sulfur.^{18,19} These attractive features and the biological relevance of metal-mediated carbon–sulfur bond cleavage led to the current study, documented herein, which revealed the synthetic power of sulfonium salts in metal-catalyzed cross-coupling reactions (see Table 1).

A wide variety of tetramethylenesulfonium salts were easily prepared (Scheme 1). Various benzylic and heterobenzylic sulfonium salts (either PF₆⁻ or ClO₄⁻) were generated from the corresponding alcohols or halides and tetrahydrothiophene, while aromatic and heteroaromatic thiols were readily converted into tetramethylenesulfonium salts by reaction with Et₃N/1,4-dibromobutane in methyl *tert*-butyl ether or diethyl ether followed by counterion exchange with NH₄PF₆ in acetone.²⁰ Although few alkenylsulfonium salts are known,^{5,6} three representative alkenylsulfonium salts were prepared for this study (**4**, **5**, and **6**) from alkenes upon reaction with Br₂/tetrahydrothiophene (THT) followed by elimination of HBr and counterion exchange (see Scheme 1).^{21–24} With optimization, good synthetic potential should result from this stereocontrolled synthesis of

(18) Taube, H.; Stein, C. A. *J. Am. Chem. Soc.* **1978**, *100*, 336.

(19) Adams, R. D.; Blankenship, C.; Segmüller, B. E.; Shiralian, M. J. *Am. Chem. Soc.* **1983**, *105*, 4319.

(20) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H. *Tetrahedron Lett.* **1994**, *35*, 8659.

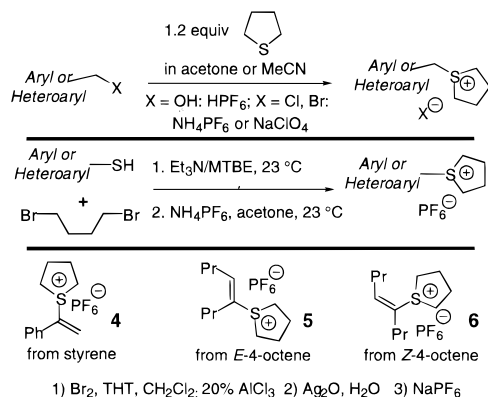
(21) Doering, W. v. E.; Schreiber, K. C. *J. Am. Chem. Soc.* **1955**, *77*, 514.

(22) Caserio, M. C.; Pratt, R. E.; Holland, R. J. *J. Am. Chem. Soc.* **1966**, *88*, 5747.

(23) Batty, J. W.; Howes, P. D.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 59.

(24) Chow, Y. L.; Bakker, B. H.; Iwai, K. *J. Chem. Soc., Chem. Commun.* **1980**, 521.

Scheme 1



alkenylsulfonium salts from geometrically pure alkenes by an *anti* addition–*anti* elimination sequence.

The sulfonium salts participated in efficient cross-coupling with a variety of organotin and -boron reagents (Pd-catalyzed) and organozinc reagents (Ni-catalyzed) (Table 1).²⁵ Attention is drawn to a number of special features of these cross-coupling reactions. (1) Of particular note is the observation that a wide range of *benzylic* and some *heterobenzylic* sulfonium salts are effective participants in cross-coupling reactions under mild conditions (Table 1, entries 1–14). This extends the scope of the cross-coupling protocol to a historically problematic, but significant, class of substrates.^{26–29} (2) Very low levels of palladium catalyst (0.01–0.5% Pd₂dba₃/8 TFP; dba = dibenzylideneacetone, TFP = tri-2-furylphosphine) are required to support acceptable rates of benzylic and heterobenzylic sulfonium/organostannane cross-coupling in ethanol at 42 °C (entries 1–8). (3) The efficiency of these organostannane cross-couplings was significantly improved by the use of Ph₂P(O)O[–]*n*-Bu₄N⁺ as a “*n*-Bu₃Sn” scavenger.³⁰ (4) Benzylic and hetero-

(25) **Representative Procedure. 2-(4-Fluorobenzyl)thiophene.** NH₄PF₆ (20.3 g, 124.5 mmol) in 50 mL of acetone was added to 4-fluorobenzyl chloride (10.0 g, 69.17 mmol) and tetrahydrothiophene (18.29 g, 207.5 mmol) in acetone (10 mL). After the solution was stirred for 16 h at 35 °C, the precipitated NH₄Cl was removed and washed with acetone. Evaporation of solvents and recrystallization of the residue from minimal acetone and Et₂O gave *S*-(4-fluorobenzyl)tetramethylenesulfonium hexafluorophosphate as colorless crystals (15.71 g, 66%): mp 118–120 °C. See the Supporting Information for characterization details. Next, *n*-BuLi (2.19 mmol, 1.14 mL of 2.5 M in hexanes) was added by syringe to thiophene (0.19 g, 2.22 mmol) in THF (7 mL) at 0 °C. After the solution was stirred for 15 min, ZnCl₂ (2.22 mmol, 2.22 mL of 1.0 M in ether) was added, and the mixture was warmed to room temperature. After 10 min, Ni(dppf)Cl₂ (2%, 0.02 g, 0.030 mmol; dppf = (diphenylphosphino)ferrocene) and *S*-(4-fluorobenzyl)tetramethylenesulfonium hexafluorophosphate (0.506 g, 1.48 mmol) were added. The mixture was stirred at room temperature for 6 h, then diluted with ether (100 mL), and washed with water (2 × 100 mL) and brine (100 mL). The organic layer was dried over Na₂SO₄, solvents were removed, and the crude product was purified by chromatography (Chromatotron, 4 mm SiO₂ rotor, 100% hexanes) to give 0.212 g (75%) of 2-(4-fluorobenzyl)thiophene as a colorless oil (Stoner, E. J.; Cothron, D. A.; Balmer, M. K.; Roden, B. A. *Tetrahedron* **1995**, *51*, 11043).

(26) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.

(27) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865.

(28) Vanasselt, R.; Elsevier, C. J. *Organometallics* **1994**, *13*, 1972.

(29) Lipshutz, B. H.; Bulow, G.; Lowe, R. F.; Stevens, K. L. *Tetrahedron* **1996**, *52*, 7265.

(30) Certain counterions facilitate the copper-mediated Stille cross-coupling reaction (Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748). The observation that *n*-Bu₃SnOP(O)Ph₂ precipitates from concentrated solutions led to the use of Ph₂P(O)O[–] in the current study.

benzylic sulfonium salts also participated in cross-coupling reactions with aryl- and heteroarylboronic acids (Table 1, entries 9–13); however, the use of K₂CO₃ in these reactions required an empirical match of substrate with solvent in order to minimize base-induced side reactions of the sulfonium salt (2,3-sigmatropic rearrangement of the sulfur ylide, nucleophilic opening of the tetramethylenesulfonium ring). (5) Of the few sulfonium salt/organozinc cross-coupling reactions attempted to date, the examples in Table 1, entries 14 and 22, suggest that this system will also prove useful, in particular in other benzylic cross-coupling reactions.

Aryl and heteroarylsulfonium salts also underwent efficient palladium-catalyzed cross-coupling reactions (Table 1, entries 15–19). However, in contrast to the benzylic and heterobenzylic substrates just described, where both organotin and -boron reagents were useful cross-coupling partners, boronic acids were noticeably superior to their organostannane counterparts in metal-catalyzed cross-coupling reactions with aryl- and heteroarylsulfonium salts. As before, the use of K₂CO₃ with solvent in order to achieve maximum efficiency of the reaction.

Three alkenylsulfonium salts have been studied as cross-coupling reaction partners (Table 1, entries 20–25). All three reactions of the *S*-α-styrylsulfonium salt **4** proceeded uneventfully (entries 20–22), and the sulfonium salt **5**, bearing a (*Z*)-*S*-(4-octen-4-yl) residue (generated stereospecifically from (*E*)-4-octene), participated in efficient and stereospecific cross-coupling reactions with 3-methoxyphenyl- and 2-thienylboronic acid (entries 23 and 24). However, a single attempt to induce a similar cross-coupling of the isomeric sulfonium salt **6** (prepared stereospecifically from (*Z*)-4-octene) failed (entry 25), perhaps a consequence of the greater steric demand of this system on oxidative addition. Metal catalysts with supporting ligand systems of lower steric requirements will be explored as a means of overcoming this current limitation.

In conclusion, tetramethylenesulfonium salts are easily prepared and are effective participants in palladium- and nickel-catalyzed cross-coupling reactions with organoboron, -tin, and -zinc reagents under mild conditions. Furthermore, stable sulfonium salts can be prepared and used in cross-coupling reactions from those substrates for which the corresponding halide or triflate would be unstable (various benzylic and heterobenzylic systems). It is notable that efficient palladium- and nickel-catalyzed processes occur even though tetrahydrothiophene is generated as a stoichiometric byproduct of the cross-coupling reaction, suggesting that other metal-catalyzed reactions of sulfonium salts are worth investigating (Heck reactions, carbonylations, allylic cross-couplings).

Acknowledgment. This investigation was supported by Grant No. CA40157, awarded by the National Cancer Institute, DHHS, and by partial funding from Bristol-Myers Squibb. We acknowledge the use of a VG 70-S mass spectrometer purchased through funding from the National Institutes of Health, Grant S10-RR-02478. This paper is dedicated to Professor Albert Padwa, colleague and confidant, on the occasion of his recent birthday.

Supporting Information Available: A complete description of the synthesis and characterization of all compounds in the paper (22 pages). See any current masthead page for ordering and Internet access instructions.

JA9726926