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

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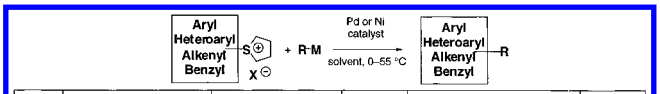
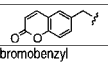
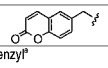
During the past decade, novel biological roles have been identified for metalloenzyme-induced transformations at the carbon−sulfur bond of biomolecules. *Since metal-mediated rupture of a carbon−sulfur bond is a key step in a number of these processes,*[1−3] new and synthetically useful transformations 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 (PF_6, BF_4, ClO_4[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 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).

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



Entry	Benzyl/Heterobenzyl	R	M	catalyst[b] / conditions	Cpd, Yld
1	benzyl[a]	2-thienyl	*n*-Bu_3Sn	A, EtOH, 45 °C, 12 h	**1a**, 82
2	2-bromobenzyl	(*E*)-β-styryl	*n*-Bu_3Sn	A, EtOH, 55 °C, 8 h	**1b**, 80
3	3-thienylmethyl	benzofuran-2-yl	*n*-Bu_3Sn	A, EtOH, 45 °C, 12 h	**1c**, 76
4	3-pyridylmethyl	(*E*)-β-styryl	*n*-Bu_3Sn	A, EtOH, 45 °C, 12 h	**1d**, 42
5	3,4-dimethoxybenzyl[a]	(*E*)-β-styryl	*n*-Bu_3Sn	A, EtOH, 45 °C, 10 h	**1e**, 75
6		benzofuran-2-yl	*n*-Bu_3Sn	A, EtOH, 45 °C, 14 h	**1f**, 76
7	2-bromobenzyl	2-(*N*-pyrrolyl)-phenyl	*n*-Bu_3Sn	B, EtOH, 40 °C, 5 h	**1g**, 81
8	3-pyridylmethyl	2-(*N*-pyrrolyl)-phenyl	*n*-Bu_3Sn	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	*p*-tolyl	$B(OH)_2$	C, 90% EtOH, 45 °C, 6 h	**1j**, 74
11	3,4-dimethoxybenzyl[a]	*p*-tolyl	$B(OH)_2$	C, 90% EtOH, 45 °C, 8 h	**1k**, 72
12		*p*-tolyl	$B(OH)_2$	C, DME, 45 °C, 14 h	**1l**, 58
13	benzyl[a]	(*E*)-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	*p*-tolyl	$B(OH)_2$	F, THF, 40 °C, 14 h	**2a**, 95
16	2-pyridyl	*p*-tolyl	$B(OH)_2$	F, THF/H_2O, 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	(*E*)-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	*p*-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[c]
23	(*Z*)-octene-4-yl	3-methoxyphenyl	$B(OH)_2$	D, THF, 40 °C, 8 h	**3d**, 72
24	(*Z*)-octene-4-yl	2-thienyl	$B(OH)_2$	D, THF, 40 °C, 8 h	**3e**, 85
25	(*E*)-octene-4-yl	*p*-tolyl	$B(OH)_2$	D, THF, 40 °C, 8 h	----

[a] ClO_4^- as counterion; all others were PF_6^-. [b] Catalysts. A: 0.2% generated *in situ* from Pd_2dba_3/8 trifurylphosphine. B: 0.1% catalyst generated *in situ* from Pd_2dba_3/8 trifurylphosphine with copper(I) diphenylphosphinate. C: 0.4−0.5% Pd(dppf)Cl_2, excess K_2CO_3. D: 0.9% $Pd(PPh_3)_4$. E: Ni(dppf)Cl_2. F: 4% Pd(dppf)Cl_2, 1 equiv of freshly ground $K_2CO_3 \cdot H_2O$. [c] GLC yield.

A wide variety of tetramethylenesulfonium salts were easily prepared (Scheme 1). Various benzylic and heterobenzylic sulfonium salts (either PF_6^- or ClO_4^-) were generated from the corresponding alcohols or halides and tetrahydrothiophene, while aromatic and heteroaromatic thiols were readily converted into tetramethylenesulfonium salts by reaction with Et_3N/1,4-dibromobutane in methyl *tert*-butyl ether or diethyl ether followed by counterion exchange with NH_4PF_6 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 Br_2/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

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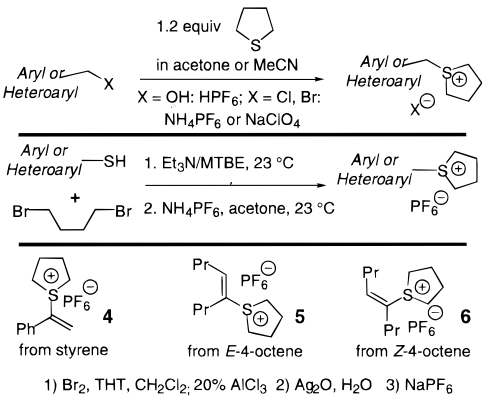
Scheme 1



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% Pd_2dba_3/8 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 $Ph_2P(O)O^-$ *n*-Bu_4N^+ as a "*n*-Bu_3Sn" scavenger.[30] (4) Benzylic and heterobenzylic sulfonium salts also participated in cross-coupling reactions with aryl- and heteroarylboronic acids (Table 1, entries 9−13); however, the use of K_2CO_3 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 K_2CO_3 with the boronic acid reactants required an empirical match 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).

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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.

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(25) **Representative Procedure. 2-(4-Fluorobenzyl)thiophene.** NH_4PF_6 (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 NH_4Cl was removed and washed with acetone. Evaporation of solvents and recrystallization of the residue from minimal acetone and Et_2O 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, $ZnCl_2$ (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)Cl_2 (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 Na_2SO_4, solvents were removed, and the crude product was purified by chromatography (Chromatotron, 4 mm SiO_2 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).

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