

Efficient Pd-Catalyzed Heterobenzylic Cross-Coupling Using Sulfonium Salts as Substrates and (PhO)₃P as a Supporting Ligand

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S-(2-Furanylmethyl)tetramethylenesulfonium hexafluorophosphate, *S*-(2-thienylmethyl)tetramethylenesulfonium hexafluorophosphate, *S*-(3-thienylmethyl)tetramethylenesulfonium hexafluorophosphate, and *S*-(*N*-tert-butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate have been conveniently prepared from the corresponding alcohols. These stable heterobenzylic sulfonium salts participate in palladium-catalyzed Stille cross-couplings with organostannanes. All but the last mentioned sulfonium salt are also active participants in palladium-catalyzed cross-coupling reactions with boronic acids and organozinc halides. Because the heterobenzylic cross-coupling reactants are potent alkylating agents, they scavenge the typical phosphines and arsines that otherwise could be used to stabilize the palladium catalyst over extended reaction times. This problem was overcome by the use of (PhO)₃P as a unique supporting ligand for the palladium-catalyzed cross-coupling of heterobenzylic sulfonium salts.

Introduction

The formation of carbon–carbon and carbon–heteroatom bonds from a remarkably broad range of participating reactants using palladium- and nickel-catalyzed cross-coupling processes has led to widespread acceptance of these powerful protocols by synthetic chemists.^{1–14} Nevertheless, there is no general procedure for the carbon–carbon bond cross-coupling of benzylic and heterobenzylic reactants, two important classes of molecules.^{15–19} The recent discovery that benzylic sulfonium salts are effective participants in Stille and Suzuki cross-coupling reactions²⁰ provided the impetus to investigate heterobenzylic cross-couplings. That effort led to a convenient

preparation of heterobenzylic sulfonium salts and the development of a general Pd-catalyzed cross-coupling protocol. The results of cross-coupling of sulfonium salts with organotin, -boron, and -zinc nucleophiles are reported herein.

Results and Discussion

Preparation of Heterobenzylic Sulfonium Salts.

Many heterobenzylic halides are too unstable to serve in transition metal-catalyzed cross-couplings, and in synthesis in general. For example, the published preparation of 2-(chloromethyl)furan contains the following cautionary note: “*This compound should always be stored in solution (at –20 °C) because neat samples decompose slowly, even at –20 °C, to give hydrogen chloride which catalyzes polymerization of the furan ring with explosive violence.*”²¹ The isomeric 3-halomethylfuran darkens within 15 min at room temperature and must be stored in a freezer.

Stable benzylic sulfonium salts can be prepared from the corresponding benzylic halides through nucleophilic substitution with tetrahydrothiophene (THT) followed by counterion exchange.²⁰ A practical extension of the same procedure to the preparation of *electron-rich* heterobenzylic sulfonium salts is not feasible because of the instability of many of these heterobenzylic halides. However, ionization of the stable, *electron-rich* heterobenzylic alcohols, such as 2-furanylmethanol, 2-thienylmethanol, 3-thienylmethanol, and *N*-Boc-2-pyrrolylmethanol, with aqueous HPF₆ (60%) at 0 °C in the presence of excess THT produced good yields of the corresponding crystalline, stable sulfonium salts. Of these, only the preparation of the pyrrolylmethanol-derived sulfonium salt **2** was optimized. The results are summarized in Figure 1. Therefore, in distinct contrast to the instability of *electron-rich* heterobenzylic halides, the corresponding

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- (1) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.
- (2) 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.
- (3) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340.
- (4) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551.
- (5) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L., Ed.; John Wiley & Sons: New York, 1997; Vol. 50; p 1.
- (6) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.
- (7) Mitchell, T. N. *Synthesis* **1992**, 803.
- (8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- (9) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.
- (10) Ahman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363.
- (11) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.
- (12) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694.
- (13) Mann, G.; Hartwig, J. F.; Driver, f. M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827.
- (14) Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287.
- (15) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
- (16) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865.
- (17) Vanasselt, R.; Elsevier: C. J. *Organometallics* **1994**, *13*, 1972.
- (18) Lipshutz, B. H.; Bulow, G.; Lowe, R. F.; Stevens, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 5512.
- (19) Lipshutz, B. H.; Bulow, G.; Lowe, R. F.; Stevens, K. L. *Tetrahedron* **1996**, *52*, 7265.
- (20) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.
- (21) Divald, S.; Chun, M. C.; Joullié, M. M. *J. Org. Chem.* **1976**, *41*, 2835.

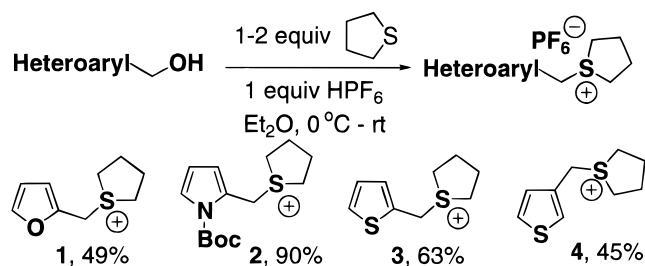


Figure 1. Preparation of stable, electron-rich heterobenzylic sulfonium salts.

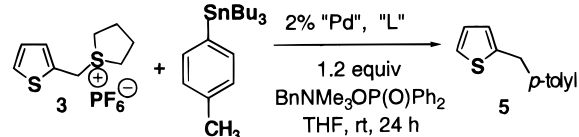
heterobenzylic sulfonium salts possessing nonnucleophilic counterions (PF_6^- , BF_4^- , ClO_4^-) can be easily prepared and are air and moisture stable in the solid state (Figure 1). This set the stage for evaluation of these compounds as substrates in transition metal-catalyzed cross-coupling reactions.

Cross-Coupling of Heterobenzylic Sulfonium Salts.

Exploratory Reactions. In nonprotic solvents (THF, CH_3CN , NMP, or toluene) with various palladium precatalysts and supporting ligands, sluggish to extremely slow cross-coupling reactions did proceed between heterobenzylic sulfonium salts **1–4** and 4-MeC₆H₅SnBu₃, in most cases giving only very low yields of the cross-coupling products. Reaction conditions previously optimized for the Stille cross-coupling of benzylic sulfonium salts (1% Pd₂(dba)₃, 4% tris(2-furanyl)phosphine, 1 equiv of Bu₄NOP(O)Ph₂ in EtOH at room temperature)²⁰ were effective only for **3**, the heterobenzylic sulfonium salts displaying greatest stability in solution.

It was apparent from the exploratory study that conventional catalyst/ligand systems did not efficiently catalyze a general cross-coupling process of heterobenzylic sulfonium salts with organometallic reagents. Consideration of the factors necessary to support a successful cross-coupling reaction provided insight into this failure. A successful heterobenzylic cross-coupling reaction should occur if an efficient rate of reaction can be sustained at a temperature low enough to minimize interference from both competitive decomposition of the thermally sensitive heterobenzylic coupling partners and catalyst deactivation. Unfortunately, a lower reaction temperature requires a longer reaction time, which necessarily increases the opportunity for catalyst deactivation. Catalyst deactivation has often been prevented by the use of strongly bound supporting ligands, but supporting ligands that bond strongly to the metal catalyst can also slow the rate of cross-coupling by retarding transmetalation, which is often the rate-limiting step of cross-coupling reactions.^{22,23} *Of particular significance to the case of heterobenzylic (and benzylic) cross-coupling, those ligands that are effective at stabilizing palladium in varying oxidation states (phosphines, arsines) are also effectively scavenged from the reaction mixture by the heterobenzylic cross-coupling reactants, since the latter are potent alkylating agents.*^{24,25} Herein lies the conundrum. The very reactivity of the heterobenzylic cross-coupling reactants pre-

Table 1. Ligand Effects in the Stille-Coupling of Sulfonium Salt **3**



entry	Pd source	L	Pd:L	GLC yield ^a (%)
1	Pd(PhCN) ₂ Cl ₂	none		46
2		(2,4,6-trimethoxyphenyl) ₃ P	1:2	10
3		(2,4,6-trimethylphenyl) ₃ P	1:2	39
4		(cyclohexyl) ₃ P	1:2	29
5		(<i>o</i> -tolyl) ₃ P	1:2	78
6		(<i>p</i> -tolyl) ₃ P	1:2	0
7		Ph ₃ P	1:2	0
8		(<i>p</i> -fluorophenyl) ₃ P	1:2	0
9		(2-furanyl) ₃ P	1:2	78
10		Ph ₃ As	1:2	54
11		(C ₆ F ₅) ₃ P	1:2	100
12		(EtO) ₃ P	1:2	36
13		(<i>p</i> -methylphenoxy) ₃ P	1:2	48
14		(<i>p</i> -nitrophenoxy) ₃ P	1:2	2
15		(PhO) ₃ P	1:1	84
16		(PhO) ₃ P	1:2	97
17		(PhO) ₃ P	1:4	0
18	Pd ₂ (dba) ₃	(PhO) ₃ P	1:2	93

^a All GLC yields were measured using 1,3,5-trimethoxybenzene as an internal reference.

cludes the use of typical phosphines and arsines that are required to stabilize the catalyst over extended reaction times.

Catalyst System Development and Application to Organostannane Coupling. If the above analysis is correct, then the key factor in developing a general system for the cross-coupling of benzylic and heterobenzylic reactants is the discovery of an effective supporting ligand for palladium that is not alkylated by heterobenzylic or benzylic sulfonium salts or halides. To that effect, a variety of metal precatalysts and supporting ligands with widely different steric and electronic character were screened using the Stille cross-coupling model system shown in Table 1. In the reaction of *S*-(2-thienylmethyl)-tetramethylenesulfonium hexafluorophosphate (**3**) with *p*-tolyltri-*n*-butylstannane (Table 1), the weak donors²⁶ (C₆F₅)₃P (entry 11) and (PhO)₃P (entry 15) gave excellent yields of the coupling product **5** within 24 h, while the very weak donor tri(4-nitrophenyl) phosphite (entry 14) was ineffective as a supporting ligand. The metal-to-ligand ratio was a critical reaction parameter for this specific cross-coupling. A dramatic difference was noted between the use of 4.0 equiv of (PhO)₃P per Pd (entry 17), which completely shut down the coupling reaction, and 2.0 equiv of (PhO)₃P per Pd (entry 16), which gave the product in excellent yield. Although the coupling product was produced in good yield by the use of 1 equiv of (PhO)₃P per Pd (entry 15), the ratio of 2.0 equiv of (PhO)₃P per Pd remained superior. A much earlier Pd black formation was observed in the former situation, which indicates a decreased catalyst stability at the lower ligand-to-metal ratio. Clearly, a successful cross-coupling reaction is dependent upon the competition between product formation and catalyst and sulfonium salt degradation, the rates of which are closely linked to the steric

(22) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(23) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243.

(24) Flowers, W. T.; Freitas, A. M.; Holt, G.; Purkiss, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1119.

(25) Kim, S.; Park, J. H.; Kim, Y. G.; Lee, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1188.

(26) Rahman, M. M.; Liu, H. Y.; Eriks, K.; Giering, W. P. *Organometallics* **1989**, *8*, 1.

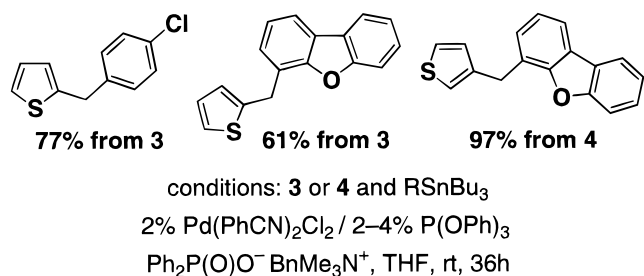


Figure 2.

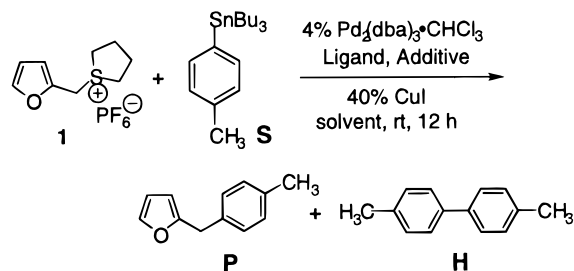
and electronic nature and stoichiometry of the supporting ligand. Given the sensitivity of the reaction system to many factors, the formation of some cross-coupling product in the absence of a strong supporting ligand for palladium (i.e., with $\text{Pd}(\text{PhCN})_2\text{Cl}_2$, as used in entry 1 of Table 1) is not inconsistent with our underlying premise and claims. Here, the absence of supporting ligands allows a fast *initial* palladium-catalyzed cross-coupling reaction to occur, but catalyst decomposition cannot be prevented and the process is not efficient.

Note the addition of $\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$ to these reactions. Its use as a highly effective tri-*n*-butylstannyl scavenger was derived from an earlier observation that *n*- $\text{Bu}_3\text{SnOP}(\text{O})\text{Ph}_2$ precipitated from concentrated solutions and facilitated the copper-catalyzed Stille cross-coupling reaction.²⁷ The efficacy of $\text{Ph}_2\text{P}(\text{O})\text{O}^-$ in sluggish Stille cross-coupling reactions has been confirmed in other laboratories,²⁸ suggesting its general consideration as a useful co-reactant in Stille reactions.

Efficient Stille cross-coupling reactions with the thiophene-derived sulfonium salts **3** and **4** did proceed in the presence of the catalyst system 2% $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ and 2–4% $(\text{PhO})_3\text{P}$ in THF at room temperature (Figure 2). Unfortunately, direct extension of the same conditions to the corresponding 2-furyl and *N*-Boc-pyrrolyl systems **1** and **2** was not feasible. Catalyst and substrate decomposition predominated with these more sensitive sulfonium salts. Since transmetalation is the rate-determining step in most Stille cross-coupling reactions, acceleration of this step could lead to an efficient and general protocol for heterobenzylic cross-couplings, and many means of accelerating the transmetalation step have been disclosed.^{5,29} Polar, aprotic solvents such as NMP increase the rate of cross-coupling by facilitating the requisite loss of a ligand prior to the transmetalation step.²² Also, the use of cocatalytic Cu(I) salts has been shown to accelerate problematic Stille couplings.^{30–32} Used in conjunction, these two reaction parameters led to a protocol in which sulfonium salts **1** and **2** cross-coupled efficiently with organostannanes at room temperature.

To elucidate the impact of these two parameters in heterobenzylic cross-coupling, a series of experiments was conducted (Table 2). With 40 mol % of CuI as a cocatalyst in THF, the reaction of sulfonium salt **1** with *p*-tolyl(tri-

Table 2. Survey of Some Cross-Coupling Reaction Parameters



entry	additive	CuI	ligand	solvent	P/H/S ^a
1	$\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$	X	$(\text{PhO})_3\text{P}$	THF	0/100/0
2	$\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$	X	$(\text{PhO})_3\text{P}$	NMP	94/6/0
3	$\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$		$(\text{PhO})_3\text{P}$	THF	30/11/59
4	$\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$		$(\text{PhO})_3\text{P}$	NMP	55/23/22
5	none	X	$(\text{PhO})_3\text{P}$	NMP	0/100/0
6	LiCl	X	$(\text{PhO})_3\text{P}$	NMP	9/24/66
7	NaOAc	X	$(\text{PhO})_3\text{P}$	NMP	20/18/62

^a Ratios determined by GLC. P, H, S = cross-coupling Product, Homocoupling side product, Stannane substrate.

n-butyl)stannane led only to homocoupling of the organostannane (entry 1),³³ while the same reaction in NMP produced a 94:6 ratio of the cross-coupling product to the organostannane homocoupling product (entry 2). In either THF or NMP under similar conditions, but in the absence of cocatalytic Cu(I), partial conversion of the stannane to the desired product was observed along with significant amounts of the homocoupling product (entries 3 and 4). Omission of the *n*- Bu_3Sn scavenger $\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$ led exclusively to the stannane homocoupling product (entry 5), while replacing $\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$ with LiCl or NaOAc depressed the reaction rate and led to mixtures of products (entries 6 and 7). Because of decomposition of sulfonium salt **1** in solution, its fate was not tracked for those cases where the yield of cross-coupled product was low.

For optimum results, the study depicted in Table 2 indicated the use of NMP as solvent, $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 / (\text{PhO})_3\text{P} / \text{CuI}$ as the catalyst system, and $\text{Ph}_2\text{P}(\text{O})\text{O}^- \text{BnMe}_3\text{N}^+$ as a *n*- Bu_3Sn scavenger. With this protocol, the coupling of the most sensitive heterobenzylic sulfonium salts, **1** and **2**, with a variety of organostannanes was investigated. The results are summarized in Table 3. Under the optimized conditions, sulfonium salt **1** coupled with *p*-tolyl(tri-*n*-butyl)stannane, 2-dibenzofuranyl(tri-*n*-butyl)stannane, and 1-methylenecyclohexane(tri-*n*-butyl)stannane in yields of 97%, 92%, and 87%, respectively (entries 1–3). However, when sulfonium salt **1** was treated with (*E*)-2-styryltri-*n*-butylstannane under the described conditions, considerable homocoupling of the organostannane was observed. Since unhindered alkenylstannanes are inherently reactive in Stille coupling reactions and also very sensitive to Cu(I)-induced homocoupling,^{34–36} the cocatalyst CuI was omitted in this

(27) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

(28) Smith, A. B., III.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.

(29) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 5; p 1.

(30) Liebeskind, L. S.; Foster, B. F. *J. Am. Chem. Soc.* **1990**, *112*, 8612.

(31) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408.

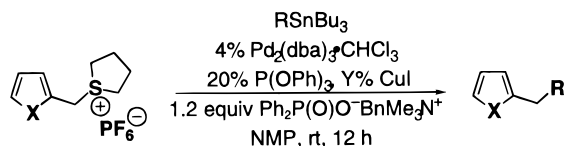
(32) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(33) The organostannane homocoupling product can form if there is a slow transmetalation of the stannane to the palladium intermediate (formed by oxidative addition of the sulfonium salt to Pd). A related process was described: Koo, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3389.

(34) Piers, E.; McEachern, E. J.; Gladstone, P. L. *Can. J. Chem.* **1997**, *75*, 694.

(35) Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609.

(36) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.

Table 3. Stille-Coupling of Heterobenzylic Sulfonium Salts 1 and 2

entry	X	R	CuI Y mol %	yield (%)
1	O	<i>p</i> -tolyl	40	97
2	O	2-dibenzofuranyl	40	92
3	O	methylenecyclohexan-1-yl	40	87
4	O	(<i>E</i>)-2-styryl	0	95
5	<i>N</i> -Boc	<i>p</i> -tolyl	40	64
6	<i>N</i> -Boc	2-furanyl	40	60
7	<i>N</i> -Boc	2-dibenzofuranyl	40	72
8	<i>N</i> -Boc	2-methyl-1-propenyl	40	78
9	<i>N</i> -Boc	(<i>E</i>)-2-styryl	0	49
10	<i>N</i> -Boc	(<i>E</i>)-2-styryl	10	97

specific case, and the cross-coupling product was obtained in 95% yield (entry 4).

Under the optimized conditions, the pyrrole-derived sulfonium salt **2** coupled with *p*-tolyltri-*n*-butylstannane (64%), 2-furanyltri-*n*-butylstannane (60%), 2-dibenzofuranyltri-*n*-butylstannane (72%), and 2-methyl(1-tri-*n*-butylstannyl)propene (78%) (entries 5–8). Once again, the coupling reaction with (*E*)-2-styryltri-*n*-butylstannane was sensitive to the amount of cocatalytic CuI. With 40 mol % of CuI, only reductive homocoupling of the stannane was observed, but omission of the copper cocatalyst gave only 49% yield of the product (entry 9). However, in the presence of 10 mol % CuI cocatalyst, the desired cross-coupling product was formed in 97% yield (entry 10)! These results suggest that fine-tuning of the Cu–Pd ratio will be essential in maximizing the cross-coupling/homo-coupling ratio for those organostannanes prone to homocoupling.

Boronic Acid Couplings. The Suzuki cross-coupling reaction of heterobenzylic sulfonium salts **1–3** with *p*-tolylboronic acid was assayed under a variety of conditions. Exploratory reactions were carried out with Pd(dppf)Cl₂, a catalyst used successfully in previous couplings of sulfonium salts with boronic acids.²⁰ In the presence of various bases (tetra-*n*-butylammonium fluoride, K₂CO₃, K₂CO₃·H₂O, KH₂PO₄, K₂HPO₄) and solvents (THF, *N*-methylpyrrolidone, CH₃CN) this catalyst system did not lead to a general protocol. However, by using 2% (PhO)₃P as a supporting ligand for 2% Pd(PhCN)₂Cl₂ in THF at room temperature, a successful cross-coupling reaction with sulfonium salt **3** was achieved in a model reaction (*p*-tolylboronic acid with K₂CO₃, 80%, GLC monitoring using 1,3,5-trimethoxybenzene as the internal standard).

The generality of this ligand system in the cross-coupling of heterobenzylic sulfonium salts with organoboronic acids was then investigated (Table 4). Sulfonium salt **3** reacted with arylboronic acids to give cross-coupling products in good yields (entries 1 and 2). Sulfonium salt **1** coupled with *p*-tolylboronic acid in moderate yield (55%) and with (*E*)-styrylboronic acid in good yield (84%) (entries 3 and 4). *S*-(3-Thiophenemethyl)tetramethylenesulfonium hexafluorophosphate, **4**, was also active in this reaction, producing the desired product in 84% yield (entry 8). The reaction of *S*-(*N*-Boc-2-pyrrolemethyl)tetramethylenesulfonium salt **2** with a

variety of boronic acids (*N*-Boc-2-pyrroleboronic acid, *p*-tolylboronic acid, (*E*)-2-styrylboronic acid, and 2-dibenzofuranylboronic acid) were uniformly sluggish and gave only low yields of the desired cross coupling products (entries 5–7).

Organozinc Reagent Couplings. Cross-coupling with organozinc reagents is a valuable procedure in organic synthesis.^{3,37} The synthetic utility of sulfonium salt/organozinc cross-coupling, demonstrated in an earlier study,²⁰ was explored using heterobenzylic sulfonium salts **1–3** in the presence of 2% Pd(PhCN)₂Cl₂/2–4% (PhO)₃P in THF at room temperature. As depicted in Table 5, the furan- and thiophene-derived sulfonium salts participated in organozinc cross-coupling reactions in acceptable yields (entries 3 and 4), but the problematic pyrrole system **2** was ineffective (entry 2).

Conclusions

Starting from readily available and inexpensive materials, a one-step method for the preparation of heterobenzylic sulfonium salts (derived from furan, thiophene, and pyrrole) has been developed. In contrast to their corresponding halides (which are often too unstable to be preparatively useful), these novel sulfonium salts undergo palladium-catalyzed cross-coupling with a variety of organostannanes, organoboronic acids, and organozinc halides. The organostannane coupling reactions proved most general, giving good to excellent yields of cross-coupling products from furan-, thiophene-, and pyrrole-derived sulfonium salts. The furan- and thiophene-based sulfonium salts participated in efficient cross-coupling with organoboron and organozinc reagents, but the pyrrole-based reactant gave only low yields of products.

The reactivity of heterobenzylic cross-coupling reactants as potent alkylating agents precludes the use of nucleophilic phosphines and arsines to stabilize the metal catalyst over extended reaction times. However, triphenyl phosphite, an effective supporting ligand that is not readily alkylated, was uniquely effective as ligand in heterobenzylic cross-couplings. It, or electronically similar supporting ligands, could prove generally useful in other cross-coupling protocols where one of the substrates is also a potent alkylating agent, such as a benzylic halide and α -halocarbonyl.

Experimental Section

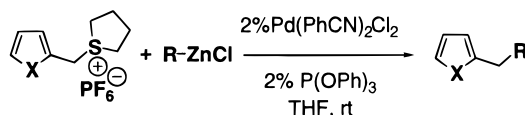
General Methods. All reactions were performed under an atmosphere of dry N₂ or Ar in flame-dried glassware unless otherwise noted. THF and CH₃CN were dried over 4 Å molecular sieves and titrated for water level prior to use with a Fisher Coulomatic K-F titrator. Anhydrous DMF and NMP were obtained from Aldrich in Sure-Seal bottles and titrated for H₂O prior to use. Purification by flash chromatography was performed using 32–63 μ m SiO₂ with compressed air as a source of positive pressure. Analytical thin-layer chromatography (TLC) was carried out using Merck Kieselgel 60F₂₅₄ plates with visualization by UV, phosphomolybdic acid, or iodine stain. Uncalibrated melting points taken on a Thomas-Hoover melting point apparatus in open capillary tubes were obtained from recrystallized samples or samples that crystallized during concentration of the chromatography eluents. In the latter case, no solvents of recrystallization are indicated. ¹H NMR spectra were recorded at 300 or 400 MHz and were

(37) Negishi, E.; Ay, M.; Gulevich, Y. V.; Noda, Y. *Tetrahedron Lett.* **1993**, *34*, 1437.

Table 4. Cross-Coupling of Heterobenzylic Sulfonium Salts with Boronic Acids

Entry	Sulfonium Salt	R'B(OH) ₂	Heteroaryl-CH ₂ R'	Yield (%)
1		3-methoxyphenyl	(2-thienyl)CH ₂ (3-methoxyphenyl)	72
2		<i>o</i> -tolyl	(2-thienyl)CH ₂ (<i>o</i> -tolyl)	81
3		<i>p</i> -tolyl	(2-furanyl)CH ₂ (<i>p</i> -tolyl)	55
4		(<i>E</i>)-2-styryl	(2-furanyl)CH ₂ (<i>E</i> -2-styryl)	84
5		<i>p</i> -tolyl	(<i>N</i> -Boc-2-pyrrolyl)CH ₂ (<i>p</i> -tolyl)	26
6		(<i>E</i>)-2-styryl	(<i>N</i> -Boc-2-pyrrolyl)CH ₂ (<i>E</i> -2-styryl)	11
7		2-dibenzofuranyl	(<i>N</i> -Boc-2-pyrrolyl)CH ₂ (2-dibenzofuranyl)	14
8		phenyl	(3-thienyl)CH ₂ (phenyl)	84

Table 5. Cross-Coupling of Heterobenzylic Sulfonium Salts with Organozinc Halides



entry	X	RZnCl	heteroaryl-CH ₂ R	yield (%)
1	O	<i>p</i> -tolyl	(2-furanyl)CH ₂ (<i>p</i> -tolyl)	67
2	<i>N</i> -Boc	<i>p</i> -tolyl	(<i>N</i> -Boc-2-pyrrolyl)CH ₂ (<i>p</i> -tolyl)	0
3	S	3-methoxyphenyl	(2-thienyl)CH ₂ (3-methoxyphenyl)	62
4	S	4-chlorophenyl	(2-thienyl)CH ₂ (4-chlorophenyl)	53

internally referenced to CHCl₃ (7.26 ppm), acetone (2.05 ppm), or DMSO (2.49 ppm); ¹³C NMR spectra were recorded at 75 and 80 MHz and were referenced to CDCl₃ (77.0 ppm) or DMSO-*d*₆ (39.7 ppm). Infrared (IR) spectroscopy was performed on a Nicolet 510 FT-IR with a resolution of 4 cm⁻¹.

Starting Materials. Benzyltrimethylammonium methoxide, diphenylphosphinic acid, 2-furanylmethanol, 2-thiophenylmethanol, 3-thiophenylmethanol, 3-furanylmethanol, 2-pyrrolicarboxaldehyde, tetrahydrothiophene, hexafluorophosphoric acid, phenylboronic acid, *p*-tolylboronic acid, *o*-tolylboronic acid, 2-tri-*n*-butylstannanylfuran, 4-methoxybenzyl chloride, *p*-tolylmagnesium bromide (1 M in Et₂O), 4-chlorophenylmagnesium bromide (1 M in Et₂O), zinc chloride (1 M in THF), tris(dibenzylideneacetone)dipalladium chloroform adduct, bis(benzonitrile)dichloropalladium(II), and all ligands were purchased from Aldrich and used as received. 3-Methoxybenzene boronic acid was purchased from Lancaster. 2-Dibenzofuran boronic acid was graciously provided by Frontier Scientific.³⁸ 4-Chlorophenyltri-*n*-butylstannane,³⁹ *p*-tolyltri-*n*-butylstannane,⁴⁰ (*E*)- β -styrylboronic acid,⁴¹ 2-methyl-1-tri-*n*-butylstannylpropene,⁴² (*E*)- β -tri-*n*-butylstannylstyrene,⁴² 1-methylenecyclohexyl tri-*n*-butylstannane,⁴³ 2-tri-*n*-butylstannyl-dibenzo-

furan,⁴⁴ *N*-Boc-pyrrolyl-2-methanol,⁴⁵ and 3-methoxyphenylmagnesium bromide⁴⁶ were prepared according to the literature procedures.

Preparation of Benzyltrimethylammonium Diphenylphosphinate. Benzyltrimethylammonium methoxide (45 wt % MeOH solution, 54.384 g, 120.0 mmol, 1.00 equiv) and diphenylphosphinic acid (26.183 g, 120.0 mmol, 1.00 equiv) were mixed together in 100 mL of MeOH, and the majority of the solvent was removed under reduced pressure, producing a suspended white solid. After being filtered, the mixture was evaporated to give benzyltrimethylammonium diphenylphosphinate (39.090 g, 104.4 mmol, 87%) as a white microcrystalline solid: mp 86–89 °C dec; IR (KBr pellet, cm⁻¹) 3385 (sb), 3047 (s), 3016 (s), 2197 (w), 1961 (w), 1905 (w), 1818 (w), 1767 (w); ¹H NMR ((CD₃)₂SO, 400 MHz) δ 7.70–7.67 (m, 4H), 7.55–7.45 (m, 5H), 7.26 (bs, 6H), 4.59 (s, 2H), 3.58 (bs, 5H, H₂O), 3.03 (s, 9H); ¹³C NMR ((CD₃)₂SO, 80.0 MHz) δ 132.9, 131.2 (d, *J* = 6.7 Hz ³⁹P–¹³C coupling), 130.2, 128.8, 128.7, 128.5, 127.4, 127.2, 67.6, 51.6. Anal. Calcd for C₂₂H₂₆NO₂P·2.5H₂O: C, 64.06; H, 7.58; N, 3.40. Found: C, 64.31; H, 7.25; N, 3.14.

(38) Mascarenas, J. L.; Garcia, A. M.; Castedo, L.; Mourino, A. *Tetrahedron Lett.* **1992**, *33*, 7589.

(44) Stang, P. J.; Tykwinski, R.; Zhdankin, V. V. *J. Heterocycl. Chem.* **1992**, *29*, 815.

(45) Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305.

(46) Ireland, R. E.; Thaisrinongs, S.; Dussalt, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768.

(38) Frontier Scientific Inc., P.O. Box 31, Logan, UT 84323-0031.

(39) Farina, V. *J. Org. Chem.* **1991**, *56*, 4985.

(40) Saa, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963.

(41) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4371.

(42) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.

Preparation of Heterobenzylic Sulfonium Salts 1–4. S-(2-Furanylmethyl)tetramethylenesulfonium Hexafluorophosphate, 1. Aqueous HPF₆ (60% by weight, 12.160 g, 50.0 mmol, 1.0 equiv) was slowly added to tetrahydrothiophene (4.410 g, 50.0 mmol, 1.0 equiv) in 30 mL of ether at 0 °C (CAUTION: exothermic!). The mixture was then slowly transferred to a solution of furfuryl alcohol (5.400 g, 55.0 mmol, 1.1 equiv) and tetrahydrothiophene (4.41 g, 50.0 mmol, 1.0 equiv) in 100 mL of ether at 0 °C. After 1 h, the precipitated solids were collected by filtration. This solid was washed with 30 mL of toluene, 30 mL of hexane, and 30 mL of ether and then dried under vacuum. *S*-(2-Furanylmethyl)tetramethylenesulfonium hexafluorophosphate was obtained as an off-white solid (7.760 g, 24.7 mmol, 49%): mp 93 °C dec; ¹H NMR ((CD₃)₂SO, 300 MHz) δ 7.83 (d, *J* = 0.9 Hz, 1 H), 6.78 (d, *J* = 3.0 Hz, 1 H), 6.57 (m, 1 H), 4.72 (s, 2 H), 3.52 (pent, *J* = 6.6 Hz, 2 H), 3.35 (pent, *J* = 6.6 Hz, 2 H), 1.92–2.13 (m, 4 H); ¹³C NMR ((CD₃)₂SO, 75.5 MHz) δ 145.7, 142.8, 114.0, 111.7, 42.5, 38.2, 28.1. Anal. Calcd for C₉H₁₃OSP₆: C, 34.40; H, 4.17; O, 5.09; S, 10.20; P, 9.86; F, 36.28. Found: C, 34.51; H, 4.23; S, 10.32.

S-(*N*-*tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium Hexafluorophosphate, 2. By the same procedure used for sulfonium salt 1, aqueous HPF₆ (60% by weight, 10.270 g, 42.25 mmol, 1.69 equiv) and tetrahydrothiophene (2.210 g, 25.00 mmol, 1.0 equiv) in 30 mL of ether at 0 °C (CAUTION: exothermic!) were slowly transferred to a mixture of *N*-*tert*-butoxycarbonyl-2-pyrrolemethanol (4.93 g, 25.00 mmol, 1.0 equiv) and tetrahydrothiophene (4.40 g, 50.00 mmol, 2.0 equiv) in 100 mL of ether at 0 °C. After 6 h, the precipitated solids were collected by filtration, washed with 30 mL each of toluene, hexane, and ether, and then vacuum-dried. *S*-(*N*-*tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate was obtained as a light yellow solid (7.8 g, 18.870 mmol, 90%): mp 103 °C dec; IR (KBr pellet, cm⁻¹) 1740 (s); ¹H NMR ((CD₃)₂CO, 300 MHz) δ 7.46 (dd, *J* = 3.3, 1.5 Hz, 1 H), 6.71–6.72 (m, 1 H), 6.27 (app t, *J* = 3.3 Hz, 1 H), 4.93 (s, 2 H), 3.63–3.79 (m, 4 H), 2.38–2.57 (m, 4 H), 1.65 (s, 9 H); ¹³C NMR ((CD₃)₂CO, 75.5 MHz) δ 151.2, 125.7, 122.4, 120.5, 111.9, 86.6, 44.2, 43.0, 29.5, 28.1. Anal. Calcd for C₁₄H₂₂NSP₆O₂: C, 40.68; H, 5.36; N, 3.39; S, 7.76; P, 7.49; F, 27.58; O, 7.74. Found: C, 40.79; H, 5.42; N, 3.40; S, 7.72.

S-(2-Thienylmethyl)tetramethylenesulfonium Hexafluorophosphate, 3. To a 100 mL round-bottomed flask charged with 2-thiophenemethanol (8.390 g, 73.50 mmol, 1.05 equiv) and tetrahydrothiophene (7.41 g, 84.00 mmol, 1.20 equiv) in 100 mL of ether at 0 °C was added slowly aqueous HPF₆ (60%, 17.03 g, 70.00 mmol, 1.00 equiv). The flask was removed from the cooling bath and stirred for 2 h at room temperature. The white solid that precipitated was collected by filtration, washed with 20 mL each of toluene and ether, and then dried under vacuum, giving 14.53 g (43.99 mmol, 63%) of *S*-(2-thienylmethyl)tetramethylenesulfonium hexafluorophosphate: mp 147.0 °C dec; ¹H NMR ((CD₃)₂SO, 300 MHz) δ 7.72 (d, *J* = 5.1 Hz, 1 H), 7.40 (d, *J* = 3.6 Hz, 1 H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 1 H), 4.85 (s, 2 H), 3.35–3.54 (m, 4 H), 2.11–2.20 (m, 4 H); ¹³C NMR ((CD₃)₂SO, 75.5 MHz) δ 131.4, 130.3, 129.7, 128.0, 42.6, 40.5, 28.2. Anal. Calcd for C₉H₁₃S₂PF₆: C, 32.73; H, 3.97; S, 19.42; P, 9.38; F, 34.51. Found: C, 32.89; H, 3.89; S, 19.34.

S-(3-Thienylmethyl)tetramethylenesulfonium Hexafluorophosphate, 4. By the same procedure used to prepare sulfonium salt 3, 3-thiophenemethanol (5.99 g, 52.5 mmol, 1.05 equiv) and tetrahydrothiophene (5.29 g, 60.0 mmol, 1.20 equiv) in 60 mL of ether at 0 °C was treated slowly with aqueous HPF₆ (60%, 12.16 g, 50.0 mmol, 1.00 equiv) at 0 °C. The flask was removed from the cooling bath and stirred for 2 h at room temperature. The precipitated white solid was collected by filtration, washed with 20 mL each of toluene and ether, and then dried under vacuum to give 7.4 g (22.4 mmol, 45%) of *S*-(3-thienylmethyl)tetramethylenesulfonium hexafluorophosphate: mp 98–100 °C; ¹H NMR ((CD₃)₂SO, 300 MHz) δ 7.83 (m, 1 H), 7.70 (dd, *J* = 4.8, 3.0 Hz, 1 H), 7.27 (d, *J* = 4.8 Hz, 1 H), 4.57 (s, 2 H), 3.33–3.52 (m, 4 H), 2.14 (br s, 4 H); ¹³C NMR ((CD₃)₂SO, 75.5 MHz) δ 129.3, 128.5, 128.4, 128.3, 42.4,

40.0, 28.1. Anal. Calcd for C₉H₁₃S₂PF₆: C, 32.73; H, 3.97; S, 19.42; P, 9.38; F, 34.51. Found: C, 33.82; H, 3.96; S, 19.32.

Ligand Effects on the Cross-Coupling of Sulfonium Salt 3 and *p*-tolyl(tri-*n*-butyl)stannane (Table 1 Study). *S*-(2-Thienylmethyl)tetramethylenesulfonium hexafluorophosphate (0.165 g, 0.500 mmol, 1.00 equiv) and benzyltrimethylammonium diphenylphosphinate (0.202 g, 0.538 mmol, 1.08 equiv) were placed in an oven-dried 50 mL flask containing 10 mL of degassed THF and *p*-tolyltri-*n*-butylstannane (0.210 g, 0.525 mmol, 1.05 equiv). To this was added (PhCN)₂PdCl₂ (0.004 g, 0.010 mmol, 0.020 equiv) and ligand (0.020 mmol, 0.040 equiv). This mixture was stirred under N₂ at room temperature for 24 h. To the crude reaction mixture was added 0.50 mL of a 0.25 M solution of 1,3,5-trimethoxybenzene (0.125 mmol, 0.25 equiv) in THF as an internal standard, and the reaction mixtures were analyzed by GLC (Hewlett-Packard 5890; column: J & W Scientific #128-5022; program: initial temperature = 80 °C static for 8 min, ramp 9 °C/min for 20 min to 260 °C).

4-Chlorophenyl-2-thienylmethane. *S*-(2-Thienylmethyl)tetramethylenesulfonium hexafluorophosphate 3 (0.660 g, 2.00 mmol, 1.00 equiv) and benzyltrimethylammonium diphenylphosphinate (0.81 g, 0.040 mmol, 1.10 equiv) were placed in an oven-dried 25 mL flask containing 4-chlorophenyl(tri-*n*-butyl)stannane (0.840 g, 2.100 mmol, 1.05 equiv) in 10 mL of degassed THF. To this were added (PhCN)₂PdCl₂ (0.015 g, 0.039 mmol, 0.020 equiv) and (PhO)₃P (10.1 μL, 0.012 g, 0.039 mmol, 0.020 equiv). This mixture was stirred under Ar at room temperature for 36 h and then transferred to a flask containing 20 mL of EtOAc and 20 mL of deionized H₂O. While the biphasic mixture was being stirred excess KF was added. After 20 min, the mixture was filtered through a plug of Celite and placed in a 60 mL separatory funnel. The organic phase was washed with 20 mL of NaHCO₃, 3 × 20 mL of H₂O, and 1 × 20 mL of brine. The organic phase was dried with MgSO₄, concentrated, and purified by SiO₂ column chromatography with a gradient of 0–2% Et₂O/hexane to provide 4-chlorophenyl-2-thienylmethane as a colorless oil (0.321 g, 1.54 mmol, 77%): ¹H NMR (CDCl₃, 300 MHz) δ 7.18–7.33 (m, 5 H), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1 H), 6.83 (dd, *J* = 3.3, 0.9 Hz, 1 H), 4.15 (s, 2 H). ¹³C NMR (CDCl₃, 75.5 MHz) δ 143.3, 138.8, 132.2, 129.9, 128.6, 126.8, 125.3, 124.1, 35.3. Anal. Calcd for C₁₁H₉ClS: C, 63.30; H, 4.35; Cl, 16.99; S, 15.36. Found: C, 63.54; H, 4.48; Cl, 16.81; S, 15.17.

2-Dibenzofuranyl-2-thienylmethane. Following the previously described procedure, *S*-(2-thienylmethyl)tetramethylenesulfonium hexafluorophosphate 3 (0.100 g, 0.300 mmol, 1.20 equiv), 2-tri-*n*-butylstannyldibenzofuran (0.114 g, 0.250 mmol, 1.00 equiv), benzyltrimethylammonium diphenylphosphinate (0.108 g, 0.300 mmol, 1.20 equiv), (PhCN)₂PdCl₂ (0.002 g, 0.005 mmol, 0.020 equiv), and (PhO)₃P (1.3 μL, 0.005 mmol, 0.020 equiv) gave, after SiO₂ chromatography with a gradient of 0–5% Et₂O/hexane, 2-dibenzofuranyl-2-thienylmethane as an oil (0.040 g, 0.172 mmol, 61%): ¹H NMR (CDCl₃, 400 MHz) δ 7.94 (ddd, *J* = 7.6, 0.4, 0.4 Hz, 1 H), 7.83 (dd, *J* = 6.0, 2.0 Hz, 1 H), 7.59 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.45 (ddd, *J* = 8.4, 8.4, 0.8 Hz, 1 H), 7.36–7.25 (m, 3 H), 7.15 (dd, *J* = 4.8, 1.2 Hz, 1 H), 6.84 (m, 2 H), 4.53 (s, 2 H). ¹³C NMR (CDCl₃, 80.0 MHz) δ 156.3, 154.4, 142.7, 127.6, 127.3, 127.1, 125.8, 124.7, 124.6, 124.3, 124.2, 123.1, 122.9, 120.9, 119.2, 112.0, 30.0.

2-Dibenzofuranyl-3-thienylmethane. Following the previously described procedure, *S*-(3-thienylmethyl)tetramethylenesulfonium hexafluorophosphate 4 (0.100 g, 0.300 mmol, 1.20 equiv), 2-tri-*n*-butylstannyldibenzofuran (0.114 g, 0.250 mmol, 1.00 equiv), benzyltrimethylammonium diphenylphosphinate (0.108 g, 0.300 mmol, 1.20 equiv), (PhCN)₂PdCl₂ (0.002 g, 0.005 mmol, 0.020 equiv), and (PhO)₃P (1.3 μL, 0.005 mmol, 0.020 equiv) gave, after SiO₂ chromatography with a gradient of 0–5% Et₂O/hexane, 2-dibenzofuranyl-3-thienylmethane as an oil (0.0643 g, 0.242 mmol, 97%): ¹H NMR (CDCl₃, 400 MHz) δ 7.95 (ddd, *J* = 7.6, 0.8, 0.4 Hz, 1 H), 7.83 (dd, *J* = 7.2, 1.6 Hz, 1 H), 7.60–7.57 (m, 1 H), 7.47 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1 H), 7.34 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1 H), 7.30–7.23 (m, 3 H), 7.05–7.03 (m, 2 H), 4.35 (s, 2 H); ¹³C NMR (CDCl₃, 80.0 MHz)

δ 156.3, 154.7, 140.3, 128.8, 127.7, 127.3, 125.8, 124.9, 124.8, 124.3, 123.1, 122.9, 121.8, 120.9, 118.9, 112.0, 30.5.

Other Reaction Parameters (Table 2 Study). A 10 mL round-bottomed flask containing 2.0 mL of degassed dry solvent under Ar was charged with $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.007 g, 0.007 mmol, 0.04 equiv) and $(\text{PhO})_3\text{P}$ (10.0 μL , 0.038 mmol, 0.24 equiv). The mixture was stirred until a yellow hue developed. The additive indicated in Table 2 (1.1 equiv) and 40 mol % CuI (for entries 1, 2, and 5–7) were introduced into the reaction flask, followed by the addition of *S*-(2-furanylmethyl)tetramethylenesulfonium hexafluorophosphate **1** (0.0560 g, 0.1800 mmol, 1.200 equiv). *p*-Tolyl(tri-*n*-butyl)stannane (0.060 g, 0.160 mmol, 1.00 equiv) in 1.0 mL of solvent was immediately added, and the reaction mixture was stirred at ambient temperature for 20 h. A portion of the reaction mixture was taken from the flask, partitioned between Et_2O and saturated NH_4Cl , and the organic phase was analyzed by GC–MS (Shimadzu GC-17A, Shimadzu MS-QP-5000; column: Restek XT1-5, 30 m, 0.25 mmID; program: initial temperature = 80 °C ramp at 18 °C/min to 260 °C, 260 °C static for 10 min, ramp at 10 °C/min to 310 °C; flow rate 2.2 mL/min) to determine the ratio of products (corrections for response factors were not applied).

Stille Cross-Coupling of Heterobenzylic Sulfonium Salts 1 and 2. Table 3 Study. Entry 1. Representative Stille Cross-Coupling Procedure of Sulfonium Salts 1 or 2. (2-Furanyl)-4-tolylmethane. A 10 mL round-bottomed flask containing 2.0 mL of dry NMP under Ar was deoxygenated four times with a freeze–thaw cycle and then charged with $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.007 g, 0.007 mmol, 0.04 equiv) and $(\text{PhO})_3\text{P}$ (10.0 μL , 0.038 mmol, 0.24 equiv). The mixture was stirred until a yellow hue developed. Benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.20 equiv) and CuI (0.012 g, 0.042 mmol, 0.40 equiv) were added, and then *S*-(2-furanylmethyl) tetramethylenesulfonium hexafluorophosphate **1** (0.056 g, 0.180 mmol, 1.20 equiv) was introduced. This was immediately followed by the addition of *p*-tolyltri-*n*-butylstannane (0.060 g, 0.160 mmol, 1.00 equiv) in 1.0 mL of NMP, which had been deoxygenated four times with a freeze–thaw cycle. The reaction mixture was stirred at ambient temperature for 12 h and then transferred to a flask containing 20 mL of EtOAc and 10 mL of deionized H_2O . Excess KF was added while the biphasic mixture was being stirred. After 20 min, the mixture was filtered through a plug of Celite and placed in a 60 mL separatory funnel. The organic phase was washed 20 mL of NaHCO_3 , 3 \times 20 mL of H_2O , and 1 \times 20 mL of brine. The organic phase was dried with MgSO_4 , concentrated, and purified by SiO_2 chromatography with a gradient of 0–5% Et_2O /hexanes to provide 2-furanyl-4-tolylmethane as a colorless oil (0.027 g, 0.156 mmol, 97%): ^1H NMR (CDCl_3 , 300 MHz) δ 7.39 (app s, $J = \text{Hz}$, 1 H), 7.20 (s, 4 H), 6.35 (dd, $J = 2.4, 1.8$ Hz, 1 H), 6.07 (d, $J = 2.4$ Hz, 1 H), 4.00 (s, 2 H), 2.41 (s, 3 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 154.8, 141.4, 135.9, 135.0, 129.1, 128.5, 110.2, 106.0, 34.0, 21.0. HRMS (EI) calcd for $\text{C}_{12}\text{H}_{12}\text{O}$ 172.0888, found 172.0882. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{O}$: C, 83.69; H, 7.02; O, 9.29. Found: C, 82.30; H, 7.14.

Entry 2. 2-Dibenzofuranyl-2-furanylmethane. *S*-(2-Furanylmethyl)tetramethylenesulfonium hexafluorophosphate **1** (0.056 g, 0.180 mmol, 1.200 equiv), 2-tri-*n*-butylstannyldibenzofuran (0.073 g, 0.160 mmol, 1.00 equiv), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.007 g, 0.007 mmol, 0.040 equiv), $(\text{PhO})_3\text{P}$ (10.0 μL , 0.038 mmol, 0.24 equiv), benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.20 equiv), and CuI (0.012 g, 0.042 mmol, 0.40 equiv) were reacted for 12 h as described in entry 1, above. Chromatography with a gradient of 0–5% Et_2O /hexanes provided 2-dibenzofuranyl-2-furanylmethane as a colorless oil (0.036 g, 0.147 mmol, 92%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.96 (d, $J = 7.6$ Hz, 1 H), 7.85 (app pent, $J = 4.0$ Hz, 1 H), 7.60 (d, $J = 8.4$ Hz, 1 H), 7.47 (ddd, $J = 7.2, 7.2, 1.2$ Hz, 1 H), 7.37–7.33 (m, 2 H), 7.30 (d, $J = 5.2$ Hz, 2 H), 6.32 (dd, $J = 3.2, 1.2$ Hz, 1 H), 6.11 (dd, $J = 3.2, 0.8$ Hz, 1 H), 4.37 (s, 2 H); ^{13}C NMR (CDCl_3 , 80.0 MHz) δ 156.3, 154.6, 153.5, 141.7, 127.7, 127.3, 124.7, 124.3, 123.1, 122.9, 122.4, 120.9, 119.2,

112.0, 110.5, 106.8, 28.4. Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{O}_2$: C, 82.24; H, 4.87; O, 12.89. Found: C, 82.04; H, 4.95.

Entry 3. (2-Furanyl)(1-methylenecyclohexyl)methane. *S*-(2-Furanylmethyl) tetramethylenesulfonium hexafluorophosphate **1** (0.056 g, 0.180 mmol, 1.20 equiv), 1-methylenecyclohexyl tri-*n*-butylstannane (0.062 g, 0.160 mmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.007 g, 0.007 mmol, 0.04 equiv), $(\text{PhO})_3\text{P}$ (10.0 μL , 0.038 mmol, 0.24 equiv), benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.20 equiv), and CuI (0.012 g, 0.042 mmol, 0.40 equiv) were reacted for 12 h as described in entry 1, above. Chromatography with a gradient of 0–2% Et_2O /hexanes provided (2-furanyl)(1-methylenecyclohexyl)methane as a colorless oil (0.0244 g, 0.1380 mmol, 87%): IR (neat, NaCl , cm^{-1}) 2925 (s), 2833 (s), 1453 (m), 1375 (w), 1261 (w), 1090 (w), 1019 (w), 791 (m); ^1H NMR (CDCl_3 , 400 MHz) δ 7.31 (br s, 1 H), 6.27 (app t, $J = 1.6$ Hz, 1 H), 5.96 (d, $J = 2.8$ Hz, 1 H), 5.26 (app t, $J = 4.0$ Hz, 1 H), 3.34 (d, $J = 7.6$ Hz, 2 H), 2.20–2.17 (m, 2 H), 2.12 (br s, 2 H), 1.57–1.53 (m, 6 H); ^{13}C NMR (CDCl_3 , 80.0 MHz) δ 156.6, 143.2, 142.0, 116.9, 111.2, 105.7, 38.1, 30.8, 29.8, 28.8, 27.9, 27.2; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{12}\text{O}$ 176.1201, found: 176.1194 (error 3.97 ppm).

Entry 4. 2-Furanyl-2-*E*-styrylmethane. *S*-(2-Furanylmethyl)tetramethylenesulfonium hexafluorophosphate (0.056 g, 0.180 mmol, 1.06 equiv), β -tri-*n*-butylstannylstyrene (*E/Z* 89:11 by GC–MS; 90:10 by NMR) (0.068 g, 0.170 mmol, 1.0 equiv), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.007 g, 0.007 mmol, 0.04 equiv), $(\text{PhO})_3\text{P}$ (10.0 μL , 0.0380 mmol, 0.22 equiv), and benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.06 equiv) were reacted for 14 h at room temperature as described in entry 1, above. Purification by SiO_2 column chromatography with a gradient of 0–5% Et_2O /hexanes provided 2-furanyl-2-*E*-styrylmethane (*E/Z* 88:12 by GC–MS) as a colorless oil (0.028 g, 0.152 mmol, 95%): IR (neat, NaCl , cm^{-1}) 1595 (m); ^1H NMR (CDCl_3 , 400 MHz) δ 7.42 (d, $J = 7.6$ Hz, 0.18 H), 7.35–7.12 (m, 5.82 H), 6.94 (dd, $J = 12.0, 2.8$ Hz, 0.8 H), 6.67–6.58 (m, 0.2 H), 6.47 (d, $J = 16.0$ Hz, 0.92 H), 6.32–6.25 (m, 0.8 H), 6.05 (d, $J = 2.8$ Hz, 0.88 H), 5.87–5.80 (m, 0.12 H), 3.63 (d, $J = 7.2$ Hz, 0.24 H), 3.53 (d, $J = 6.8$ Hz, 1.76 H); ^{13}C NMR (CDCl_3 , 80.0 MHz) δ 154.1, 141.6, 137.4, 132.2, 131.1, 129.4, 128.9, 128.7, 128.5, 127.8, 127.5, 127.1, 126.6, 126.4, 125.8, 110.5, 105.8, 105.5, 32.0, 27.9. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{O}$: C, 84.75; H, 6.57. Found: C, 84.52; H, 6.60.

Entry 5. 2-(Pyrrole-1-carboxylic acid *tert*-butyl ester)-4-tolylmethane. *S*-(*N-tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate (0.073 g, 0.180 mmol, 1.20 equiv), *p*-tolyltri-*n*-butylstannane (0.060 g, 0.160 mmol, 1.00 equiv), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.007 g, 0.007 mmol, 0.04 equiv), $(\text{PhO})_3\text{P}$ (10.0 μL , 0.038 mmol, 0.24 equiv), benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.20 equiv), and CuI (0.012 g, 0.063 mmol, 0.40 equiv) were reacted for 12 h as described in entry 1, above. Purification by SiO_2 chromatography with a gradient of 0–5% Et_2O /hexanes provided 2-(pyrrole-1-carboxylic acid *tert*-butyl ester)-4-tolylmethane as a colorless oil (0.028 g, 0.102 mmol, 64%): IR (neat, NaCl , cm^{-1}) 1737 (s); ^1H NMR (CDCl_3 , 400 MHz) δ 7.24 (dd, $J = 3.2, 1.6$ Hz, 1 H), 7.10 (d, $J = 8.0$ Hz, 2 H), 7.06 (d, $J = 8.4$ Hz, 2 H), 6.07 (app t, $J = 3.2$ Hz, 1 H), 5.74 (dd, $J = 3.2, 1.2$ Hz, 1 H), 4.17 (s, 2 H), 2.33 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR (CDCl_3 , 80.0 MHz) δ 149.8, 136.8, 135.7, 135.0, 129.1, 129.0, 121.5, 113.1, 110.2, 83.7, 34.9, 28.2, 21.3. Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: C, 75.25; H, 7.80; N, 5.16; O, 11.79. Found: C, 75.06; H, 7.83; N, 5.03.

Entry 6. 2-(Pyrrole-1-carboxylic acid *tert*-butyl ester)-2-furanylmethane. *S*-(*N-tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate (0.073 g, 0.180 mmol, 1.20 equiv), 2-tri-*n*-butylstannylfuran (57.1 g, 0.160 mmol, 1.00 equiv), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.007 g, 0.007 mmol, 0.04 equiv), $(\text{PhO})_3\text{P}$ (10.0 μL , 0.038 mmol), benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.20 equiv), and CuI (0.012 g, 0.063 mmol, 0.40 equiv) were reacted for 12 h as described in entry 1, above. Purification by SiO_2 chromatography with a gradient of 0–20% Et_2O /hexanes provided 2-(pyrrole-1-carboxylic acid *tert*-butyl ester)-2-furanylmethane as a colorless oil (0.024 g, 0.096 mmol, 60%): IR

(CH₂Cl₂, KCl, cm⁻¹) 1738 (s); ¹H NMR (CDCl₃, 400 MHz) δ 7.33 (d, *J* = 0.8 Hz, 1 H), 7.24 (dd, *J* = 3.2, 1.2 Hz, 1 H), 6.29 (dd, *J* = 2.0, 0.8 Hz, 1 H), 6.09 (app t, *J* = 3.6 Hz, 1 H), 5.96 (d, *J* = 3.2 Hz, 1 H), 5.92 (d, *J* = 1.2 Hz, 1 H), 4.22 (s, 2 H), 1.52 (s, 9 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 153.7, 149.6, 141.2, 131.3, 121.7, 113.1, 110.2, 106.2, 83.9, 29.9, 28.4, 28.1. Anal. Calcd for C₁₄H₁₇NO₃: C, 68.00; H, 6.93; N, 5.66; O, 19.41. Found: C, 68.23; H, 6.94; N, 5.50.

Entry 7. 2-Dibenzofuranyl-2-(pyrrole-1-carboxylic acid *tert*-butyl ester)methane. *S*-(*N*-*tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate (0.073 g, 0.180 mmol, 1.20 equiv), 2-*tri-n*-butylstannyldibenzofuran (0.073 g, 0.160 mmol, 1.00 equiv), Pd₂(dba)₃·CHCl₃ (0.007 g, 0.007 mmol, 0.04 equiv), (PhO)₃P (10.0 μL, 0.038 mmol, 0.24 equiv), benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.20 equiv), and CuI (0.012 g, 0.063 mmol, 0.40 equiv) were reacted for 12 h as described in entry 1, above. Purification by SiO₂ chromatography with a gradient of 0–20% Et₂O/hexanes provided 2-dibenzofuranyl-2-(pyrrole-1-carboxylic acid *tert*-butyl ester)methane as an oil (0.040 g, 0.115 mmol, 72%): IR (CH₂Cl₂, KCl, cm⁻¹) 1731 (s); ¹H NMR (CDCl₃, 400 MHz) δ 8.06–8.04 (m, 0.1 H), 7.96 (dd, *J* = 6.8 Hz, 1 H), 7.83 (dd, *J* = 7.6, 0.8 Hz, 0.9 H), 7.58 (d, *J* = 8.4 Hz, 1 H), 7.40 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1 H), 7.36–7.32 (m, 2 H), 7.31 (app t, *J* = 7.6 Hz, 1 H), 7.11 (d, *J* = 7.6 Hz, 1 H), 6.09 (app t, *J* = 3.2 Hz, 1 H), 5.79 (dd, *J* = 3.2, 1.2 Hz, 1 H), 4.58 (s, 2 H), 1.44 (bs, 9 H); ¹³C NMR (CDCl₃, 80.0 MHz) δ 156.2, 154.7, 149.8, 132.6, 127.4, 127.1, 124.8, 124.3, 124.0, 123.0, 121.8, 121.7, 120.9, 118.9, 118.8, 113.6, 112.1, 112.0, 110.3, 110.2, 83.9, 29.9, 29.5, 18.1, 28.0. Anal. Calcd for C₂₂H₂₁NO₃: C, 76.06; H, 6.09; N, 4.03; O, 13.82. Found: C, 76.23; H, 6.15; N, 3.88.

Entry 8. 3-(2-Methyl-1-butenyl)-2-(pyrrolyl-1-carboxylic acid *tert*-butyl ester). *S*-(*N*-*tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate **2** (0.073 g, 0.180 mmol, 1.20 equiv), 2-methyl-1-*tri-n*-butylstannypropene (0.055 g, 0.160 mmol, 1.00 equiv), Pd₂(dba)₃·CHCl₃ (0.007 g, 0.007 mmol, 0.04 equiv), (PhO)₃P (10.0 μL, 0.038 mmol, 0.238 equiv), benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.20 equiv), and CuI (0.012 g, 0.042 mmol, 0.40 equiv) were reacted for 12 h as described in entry 1, above. Purification by SiO₂ chromatography with a gradient of 0–20% Et₂O/hexanes provided 3-(2-methyl-1-butenyl)-2-(pyrrolyl-1-carboxylic acid *tert*-butyl ester) as a colorless oil (0.029 g, 0.125 mmol, 78%): IR (neat, NaCl, cm⁻¹) 1745 (s), 1596 (w); ¹H NMR (CDCl₃, 400 MHz) δ 7.19 (dd, *J* = 3.2, 1.2 Hz, 1 H), 6.07 (app t, *J* = 3.2 Hz, 1 H), 5.93 (m, 1 H), 5.36 (m, 1 H), 3.53 (d, *J* = 6.8 Hz, 2 H), 1.75 (br d, *J* = 0.8 Hz, 3 H), 1.66 (s, 3 H), 1.59 (s, 9 H); ¹³C NMR (CDCl₃, 80.0 MHz) δ 135.5, 133.4, 121.2, 121.1, 111.1, 110.2, 83.5, 28.3, 28.1, 26.0, 17.9. Anal. Calcd for C₁₄H₂₁NO₂: C, 71.46; H, 8.99; N, 5.95; O, 13.60. Found: C, 71.35; H, 9.04; N, 5.84.

Entry 9. 2-(Pyrrolyl-1-carboxylic acid *tert*-butyl ester)-(2-*E*-styryl)methane. *S*-(*N*-*tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate **2** (0.072 g, 0.180 mmol, 1.20 equiv), β-*tri-n*-butylstannyl styrene (*E/Z* 89:11 by GC–MS; 90:10 by NMR) (0.068 g, 0.170 mmol, 1.0 equiv), Pd₂(dba)₃·CHCl₃ (0.007 g, 0.007 mmol, 0.04 equiv), (PhO)₃P (10.0 μL, 0.038 mmol, 0.22 equiv), and benzyltrimethylammonium diphenylphosphinate (0.065 g, 0.180 mmol, 1.06 equiv) were reacted for 14 h at room temperature as described in entry 1, above. At this point, ¹H NMR analysis of the crude reaction product indicated an *E/Z* ratio of 87:13. Purification by SiO₂ chromatography with a gradient of 0–20% Et₂O/hexanes provided 2-(pyrrolyl-1-carboxylic acid *tert*-butyl ester)-(2-*E*-styryl)methane as a colorless oil (*E/Z* 79:21 by ¹H NMR) (0.024 g, 0.783 mmol, 49%). Data are presented with the next entry.

Entry 10. 2-(Pyrrolyl-1-carboxylic acid *tert*-butyl ester)-(2-*E*-styryl)methane. This experiment was run as described in entry 9, but with the addition of CuI (0.003 g, 0.015 mmol, 0.10 equiv). Chromatography with a gradient of 0–20% Et₂O/hexanes provided 2-(pyrrolyl-1-carboxylic acid *tert*-butyl ester)-(2-*E*-styryl)methane as a colorless oil (0.046 g, 0.155 mmol, 97%) (*E/Z* 79:21 by NMR): IR (neat, NaCl, cm⁻¹) 1738 (s), 1595

(w); ¹H NMR (CDCl₃, 400 MHz) δ 7.43 (d, *J* = 7.6 Hz, 0.12 H), 7.36–7.17 (m, 5.88 H), 6.99–6.91 (m, 0.08 H), 6.68–6.64 (m, 0.08 H), 6.58 (d, *J* = 11.6 Hz, 0.28 H), 6.44–6.33 (m, 1.56 H), 6.09 (app t, *J* = 2.0 Hz, 0.94 H), 6.04–6.03 (m, 0.28 H), 6.01–6.00 (m, 0.62 H), 5.92–5.85 (m, 0.24 H), 3.85 (d, *J* = 7.6 Hz, 0.42 H), 3.75 (d, *J* = 4.8 Hz, 1.58 H), 1.57 (s, 7.1 H), 1.55 (s, 1.9 H); ¹³C NMR (CDCl₃, 80.0 MHz) δ 149.7, 137.8, 134.1, 131.6, 131.5, 131.4, 128.8, 127.8, 125.7, 127.7, 127.2, 126.4, 126.2, 121.5, 121.3, 112.1, 111.9, 110.3, 110.2, 83.7, 32.7, 32.6, 32.6, 28.8, 28.3, 28.2. Anal. Calcd for C₁₈H₂₁NO₂: C, 76.30; H, 7.47; N, 4.94; O, 11.29. Found: C, 76.11; H, 7.42; N, 4.80.

Entry 1. 3-Anisyl-2-thienylmethane. A freshly prepared 0.01 M solution of (PhO)₃P (0.008 g, 0.02 mmol, 0.02 equiv) in THF (2 mL) was added to a flask charged with a freshly made solution of (PhCN)₂PdCl₂ (0.006 g, 0.02 mmol, 0.02 equiv) in THF (2 mL, 0.01 M). The solution turned from orange-brown to light yellow as the (PhO)₃P was added. This catalyst system was then transferred to a flask charged with *S*-(2-thienylmethyl)tetramethylenesulfonium hexafluorophosphate (0.33 g, 1.000 mmol, 1.00 equiv), 3-methoxyphenylboronic acid (0.167 g, 1.10 mmol, 1.10 equiv), and K₂CO₃ (0.690 g, 5.00 mmol, 5.00 equiv) in THF (6 mL) under nitrogen at room temperature. To avoid the formation of considerable amounts of the homo-coupling product of the arylboronic acid, the mixture was deoxygenated using three cycles of a vacuum-nitrogen purge. After 36 h, the mixture was diluted with 20 mL of Et₂O/hexane (1:1), filtered through a plug of silica gel, and concentrated. Purification by SiO₂ chromatography with hexane (100 mL) and then 2% Et₂O/hexane provided 3-anisyl-2-thienylmethane as a colorless oil (0.147 g, 0.720 mmol, 72%): ¹H NMR (CDCl₃, 300 MHz) δ 7.26 (t, *J* = 7.8 Hz, 1 H), 7.17 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.96 (dd, *J* = 7.8, 2.4 Hz, 1 H), 6.79–6.89 (m, 4 H), 4.16 (s, 2 H), 3.81 (s, 3 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 159.7, 143.7, 141.9, 129.5, 126.8, 125.1, 123.9, 120.9, 114.3, 111.8, 55.1, 36.0. Anal. Calcd for C₁₂H₁₂OS: C, 70.55; H, 5.92; O, 7.83; S, 15.70. Found: C, 70.52; H, 5.93.

Entry 2. 2-(Thienyl)phenylmethane. Following the procedure, workup, and purification described in entry 1, above, *S*-(2-thiophenemethyl)tetramethylenesulfonium hexafluorophosphate **3** (0.33 g, 1.00 mmol, 1.00 equiv), *o*-tolylboronic acid (0.15 g, 1.10 mmol, 1.10 equiv), K₂CO₃ (0.690 g, 5.00 mmol, 5.00 equiv), (PhCN)₂PdCl₂ (0.008 g, 0.02 mmol, 0.02 equiv), and (PhO)₃P (5.1 μL, 0.02 mmol, 0.02 equiv) at room temperature for 72 h provided 2-(thienyl)phenylmethane as a colorless oil (0.152 g, 0.81 mmol, 81%): ¹H NMR (CDCl₃, 300 MHz) δ 7.28 (s, 4 H), 7.22 (dd, *J* = 5.1, 0.9 Hz, 1 H), 7.01 (dd, *J* = 5.1, 3.3 Hz, 1 H), 6.82 (dd, *J* = 3.3, 0.9 Hz, 1 H), 4.24 (s, 2 H), 2.41 (s, 3 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 143.6, 138.4, 136.2, 130.3, 129.4, 126.8, 126.7, 126.1, 124.9, 123.6, 33.7, 19.4. Anal. Calcd for C₁₂H₁₂S: C, 76.55; H, 6.42; S, 17.03. Found: C, 76.47; H, 6.44; S, 17.12.

Entry 3. (2-Furanyl)phenylmethane. Following the procedure, workup, and purification described in entry 1, above, *S*-(2-furanylmethyl)tetramethylenesulfonium hexafluorophosphate (0.310 g, 1.00 mmol, 1.00 equiv), *p*-tolylboronic acid (0.150 g, 1.100 mmol, 1.10 equiv), K₂CO₃ (0.690 g, 5.00 mmol, 5.00 equiv), (PhCN)₂PdCl₂ (0.008 g, 0.02 mmol, 0.02 equiv), and (PhO)₃P (5.1 μL, 0.02 mmol, 0.02 equiv) at room temperature for 48 h provided (2-furanyl)phenylmethane as a colorless oil (0.094 g, 0.550 mmol, 55%). See entry 1 in Table 3 data, above, for characterization data.

Entry 4. (2-Furanyl)-(2-*E*-styryl)methane. Following the procedure, workup, and purification described in entry 1, above, *S*-(2-furanylmethyl)tetramethylenesulfonium hexafluorophosphate **2** (0.31 g, 1.00 mmol, 1.0 equiv), (*E*)-β-styrylboronic acid (0.160 g, 1.10 mmol, 1.10 equiv), K₂CO₃ (0.690 g, 5.00 mmol, 5.00 equiv), (PhCN)₂PdCl₂ (0.008 g, 0.020 mmol, 0.02 equiv), and (PhO)₃P (0.006 g, 0.020 mmol, 0.02 equiv) at room temperature for 24 h provided (2-furanyl)-(2-*E*-styryl)methane as a colorless oil (0.155 g, 0.840 mmol, 84%): ¹H NMR (CDCl₃, 300 MHz) δ 7.24–7.52 (m, 6 H), 6.55 (d, *J* = 14.7 Hz, 1 H), 6.32–6.42 (m, 2 H), 6.13–6.14 (m, 1 H), 3.61 (d, *J* = 6.6 Hz, 2 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 153.8, 141.3, 137.2,

131.9, 128.4, 127.2, 126.2, 125.5, 110.3, 105.6, 31.7. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57; O, 8.68. Found: C, 84.70; H, 6.54.

Entry 5. (2-Pyrrolyl-1-carboxylic acid *tert*-butyl ester)-(4-tolyl)methane. Following the procedure, workup, and purification described in entry 1, above, *S*-(*N*-*tert*-butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate (0.207 g, 0.50 mmol, 1.00 equiv), *p*-tolylboronic anhydride (0.124 g, 0.350 mmol, 0.07 equiv), K_2CO_3 (0.345 g, 2.50 mmol, 5.00 equiv), $(PhCN)_2PdCl_2$ (0.004 g, 0.01 mmol, 0.02 equiv), and $(PhO)_3P$ (2.6 μ L, 0.01 mmol, 0.02 equiv) at room temperature for 24 h provided (2-pyrrolyl-1-carboxylic acid *tert*-butyl ester)(4-tolyl)methane (0.0033 g, 0.13 mmol, 26%). See entry 5 in Table 3 data, above, for characterization data.

Entry 6. 2-(Pyrrolyl-1-carboxylic acid *tert*-butyl ester)-(2-*E*-styryl)methane. Following the procedure, workup, and purification described in entry 1, above, *S*-(*N*-*tert*-butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate **2** (0.207 g, 0.50 mmol, 1.00 equiv), (*E*)- β -styrylboronic acid (0.080 g, 0.563 mmol, 1.12 equiv), K_2CO_3 (0.345 g, 2.50 mmol, 5.00 equiv), $(PhCN)_2PdCl_2$ (0.004 g, 0.01 mmol, 0.02 equiv), and $(PhO)_3P$ (2.6 μ L, 0.01 mmol, 0.02 equiv) at room temperature for 24 h provided 2-(pyrrolyl-1-carboxylic acid *tert*-butyl ester)(2-*E*-styryl)methane (0.015 g, 0.055 mmol, 11%). See entry 10 in Table 3 data, above, for characterization data.

Entry 7. 2-Dibenzofuranyl-2-(pyrrolyl-1-carboxylic acid *tert*-butyl ester)methane. Following the procedure, workup, and purification described in entry 1, above, *S*-(*N*-*tert*-butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate (0.207 g, 0.50 mmol, 1.00 equiv), 2-dibenzofuranylboronic acid (0.127 g, 0.60 mmol, 1.20 equiv), K_2CO_3 (0.345 g, 2.50 mmol, 5.00 equiv), $(PhCN)_2PdCl_2$ (0.004 g, 0.01 mmol, 0.02 equiv), and $(PhO)_3P$ (2.6 μ L, 0.012 mmol, 0.02 equiv) at room temperature for 24 h provided 2-dibenzofuranyl-2-(pyrrolyl-1-carboxylic acid *tert*-butyl ester)methane (0.024 g, 0.07 mmol, 14%). See entry 7 in Table 3 data, above, for characterization data.

Entry 8. Phenyl-3-thienylmethane. Following the procedure, workup, and purification described in entry 1, above, *S*-(3-thiophenemethyl)tetramethylenesulfonium hexafluorophosphate (0.330 g, 1.00 mmol, 1.00 equiv), phenylboronic acid (0.130 g, 1.100 mmol, 1.10 equiv), K_2CO_3 (0.690 g, 5.00 mmol, 5.00 equiv), $(PhCN)_2PdCl_2$ (0.008 g, 0.02 mmol, 0.02 equiv), and $(PhO)_3P$ (5.1 μ L, 0.02 mmol, 0.02 equiv) at room temperature for 24 h provided phenyl-3-thienylmethane as a colorless oil (0.146 g, 0.84 mmol, 84%): 1H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.41 (m, 6 H), 7.00 (app d, $J = 4.2$ Hz, 2 H), 4.07 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 141.4, 140.5, 128.7, 128.4, 127.1, 126.1, 125.5, 121.2, 36.5; HRMS (EI) calcd for $C_{11}H_{10}S$ 174.0503, found 174.0496. Anal. Calcd for $C_{11}H_{10}S$: C, 75.82; H, 5.78; S, 18.40. Found: C, 76.68; H, 5.96; S, 17.36.

Entry 1. (2-Furanyl)-4-tolylmethane. To a 10 mL oven-dried flask under Ar was placed 1.0 M *p*-tolylmagnesium bromide in ether (0.750 mL, 0.750 mmol, 1.50 equiv). The solution was cooled to 5 $^{\circ}C$, and a 1.0 M $ZnCl_2$ solution in ether (0.750 mL, 0.750 mmol, 1.50 equiv) was added in a dropwise fashion. The mixture was allowed to stir for 30 min after

removal of the ice bath. Stirring was stopped, and 2.5 mL of dry hexane was added to precipitate the magnesium salts. The solution was separated from the salts and transferred to a flask containing *S*-(2-thiophenemethyl)tetramethylenesulfonium hexafluorophosphate (0.157 g, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of $(PhCN)_2PdCl_2$ (0.004 g, 0.010 mmol, 0.02 equiv) and $(PhO)_3P$ (2.6 μ L, 0.01 mmol, 0.02 equiv) in 4 mL of THF. The reaction mixture was subjected to three cycles of a vacuum-nitrogen purge, stirred for 36 h at room temperature, and then quenched with 10 mL of saturated NH_4Cl . The resulting biphasic mixture was diluted with 10 mL of ether and partitioned in a 60 mL separatory funnel. The organic phase was washed with 1×20 mL of brine and dried with $MgSO_4$. Chromatography with 0–2% Et_2O /hexanes gave (2-furanyl)-4-tolylmethane (0.057 g, 0.335 mmol, 67%); see entry 1 in Table 3 data for characterization.

Entry 2. 4-(*N*-Boc-2-pyrrolyl)toluene. *S*-(*N*-*tert*-Butoxycarbonyl-2-pyrrolylmethyl)tetramethylenesulfonium hexafluorophosphate (0.207 g, 0.50 mmol, 1.00 equiv), 1.0 M *p*-tolylmagnesium bromide solution in ether (0.750 mL, 0.750 mmol, 1.50 equiv), 1.0 M $ZnCl_2$ solution in ether (0.750 mL, 0.750 mmol, 1.50 equiv), $(PhCN)_2PdCl_2$ (0.004 g, 0.010 mmol, 0.02 equiv), and $(PhO)_3P$ (5.2 μ L, 0.02 mmol, 0.02 equiv) were subjected to the reaction conditions and workup described in entry 1. No coupling product was isolated.

Entry 3. 3-Anisyl-2-thienylmethane. *S*-(2-Furanylmethyl)tetramethylenesulfonium hexafluorophosphate (0.157 g, 0.50 mmol, 1.00 equiv), 0.3 M 3-methoxyphenylmagnesium bromide solution in THF (2.50 mL, 0.750 mmol, 1.50 equiv), 1.0 M $ZnCl_2$ solution in ether (0.750 mL, 0.750 mmol, 1.50 equiv), $(PhCN)_2PdCl_2$ (0.004 g, 0.010 mmol, 0.02 equiv), and $(PhO)_3P$ (2.6 μ L, 0.01 mmol, 0.02 equiv) in 5 mL of THF were subjected to the reaction conditions and workup described in entry 1 to give 3-anisyl-2-thienylmethane (0.057 g, 0.335 mmol, 62%) as a colorless oil: see entry 1 in Table 4 data for characterization.

Entry 4. 4-Chlorophenyl-2-thienylmethane. *S*-(2-Thiophenemethyl)tetramethylenesulfonium hexafluorophosphate (0.660 g, 2.00 mmol, 1.00 equiv), 1.0 M *p*-chlorophenylmagnesium bromide solution in ether (3.00 mL, 3.00 mmol, 1.50 equiv), 1.0 M ethereal solution of $ZnCl_2$ (3 mL, 3.00 mmol, 1.50 equiv), $(PhCN)_2PdCl_2$ (0.038 g, 0.10 mmol, 0.05 equiv), and $(PhO)_3P$ (26 μ L, 0.031 g, 0.10 mmol, 0.05 equiv) in 4 mL of THF were subjected to the reactions conditions and workup described in entry 1 to give 4-chlorophenyl-2-thienylmethane as a colorless oil (0.220 g, 1.06 mmol, 53%); refer to Table 1 data, above, for characterization.

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