

Cross-Coupling Reactions of Alkenylsilanols with Fluoroalkylsulfonates

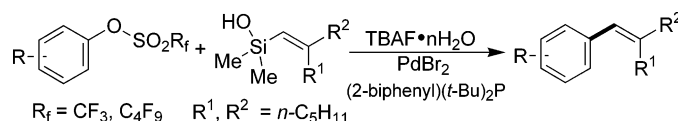
Scott E. Denmark* and Ramzi F. Sweis

Roger Adams Laboratory, Department of Chemistry, University of Illinois,
600 South Mathews Avenue, Urbana, Illinois 61801

denmark@scs.uiuc.edu

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ABSTRACT



The design and development of an effective protocol for the palladium-catalyzed cross-coupling of (*E*)- and (*Z*)-heptenyldimethylsilanols with organo-triflates and nonaflates is described. Optimization of this coupling focused on the issues of both reactivity and stability of the pseudohalides in the presence of the nucleophilic fluoride promoter for the coupling. The crucial role of varying amounts of water to modulate the reactivity of the fluoride ion is highlighted.

Palladium-catalyzed cross-coupling reactions are among the most highly revered methods for the efficient construction of carbon–carbon bonds. Soon after the breakthroughs in organostannane (Stille–Miyaura–Kosugi)¹ and organoboron (Suzuki–Miyaura)² cross-coupling with organohalides, an extremely valuable alternative to these protocols was recognized, namely, the cross-coupling to sulfonate electrophiles.^{3–5} Since such “pseudohalides” are readily prepared from aryl alcohols or ketones,⁶ this development significantly expanded the range of compatible electrophiles in cross-coupling reactions and further enhanced the synthetic utility of this method.

(1) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1. (c) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 4.

(2) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(3) For organotin coupling to triflates, see: (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (c) Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114. For organoboron coupling to triflates, see: (d) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (e) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(4) Vinylstannane coupling to phosphates has also been reported: (a) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gartner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467.

The recent development of organosilanol cross-coupling presents a viable (often superior) alternative to the use of organotin or organoboron compounds.⁷ The advantages of these agents include the ease of synthesis of organosilanols, their mild coupling conditions, and the harmless byproducts that they generate. To date, most reports have described the versatility of this reaction with regard to the silanol coupling partner. Herein, we disclose our initial studies on the extension to nonhalide-based electrophiles (Scheme 1).⁸

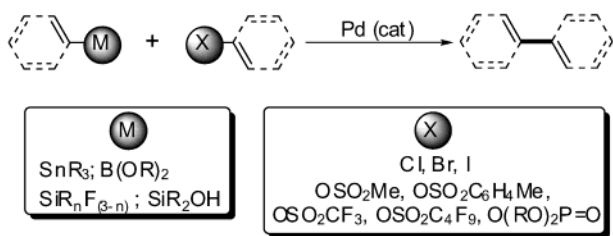
(5) Other nonhalide coupling partners for palladium-catalyzed cross-couplings include iodonium salts: (a) Hinkle, R. J.; Poulter, G. T.; Stang, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 11626. (b) Moriarty, R. M.; Epa, W. R. *Tetrahedron Lett.* **1992**, *33*, 4095. (c) Kang, S. K.; Lee, H. W.; Jang, S. B.; Ho, P. S. *J. Org. Chem.* **1996**, *61*, 4720. (d) Kang, S. K.; Yamaguchi, T.; Hong, R. K.; Kim, T. H.; Pyun, S. J. *Tetrahedron* **1997**, *53*, 3027. Diazonium salts: (e) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405. (f) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761. (g) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 6271. (h) Babudri, F.; Farinola, G. M.; Naso, F.; Panessa, D. *J. Org. Chem.* **2000**, *65*, 1554.

(6) For reviews on the synthesis of organo-triflates and nonaflates, see: (a) Stang, P. J.; Hanack, M.; Subrmanian, L. R. *Synthesis* **1982**, 85. (b) Ritter, K. *Synthesis* **1993**, 735.

(7) (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (c) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (d) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

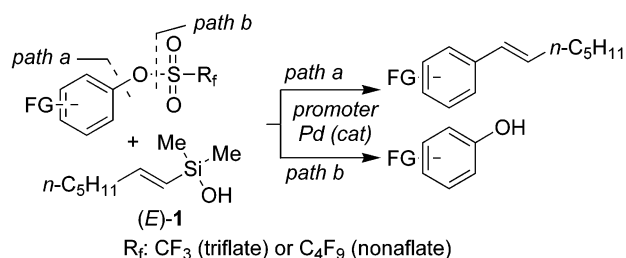
(8) Hiyama has reported the cross-coupling of fluorosilanols to aryl and alkenyl triflates. Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 2719.

Scheme 1



Our approach toward development of a successful protocol addressed two obstacles associated with this type of coupling. First, the low reactivity of triflates relative to the iodides employed in our previously developed coupling methods was immediately apparent. Second, aryl triflates were expected to be unstable under the reaction conditions in the presence of a nucleophilic promoter (Scheme 2). Because these cross-couplings require a promoter, our challenge was clearly defined: to devise a system wherein the difference between the rate of desired C–O bond cleavage for cross-coupling (path a) was significantly greater than the rate of undesired S–O bond cleavage (path b) back to the aryl alcohol.

Scheme 2



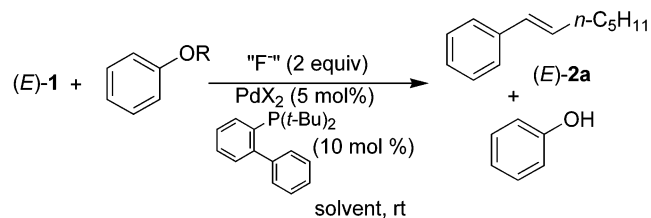
At the outset, we chose to employ phenyl nonaflate in the cross-coupling reaction with (*E*)-**1**, rather than the corresponding triflate, because it was less prone to phenol formation.⁹ A survey of promoters also revealed that tetraabutylammonium fluoride (TBAF), supplied as a crystalline trihydrate, in either dioxane or DMF was unique in its ability to effectively induce this type of coupling.¹⁰

The particular palladium catalyst/ligand combination employed was crucial to the success of this coupling. In addition to the unique properties of TBAF as a promoter, high conversion could only be obtained when either PdBr₂ or PdCl₂ was used in conjunction with 1,1-di-*tert*-butylphosphinobiphenyl (BPDTBP), a crystalline air-stable ligand developed by Buchwald (Table 1).¹¹

(9) It has been reported that nonaflates are less susceptible than triflates to nucleophilic attack at the sulfur atom, which we believe to be the source of undesired phenol formation. See: Neuville, L.; Bigot, A.; Dau, M. E. T. H.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 7638.

(10) Other potential promoters surveyed include KOSiMe₃, KH, KF, KHF₂, KO^{*t*}-Bu, CsF, Cs₂CO₃, CsOH, and NaOMe.

(11) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

Table 1. Optimization of the Cross-Coupling of (*E*)-**1** with Phenyl Sulfonates

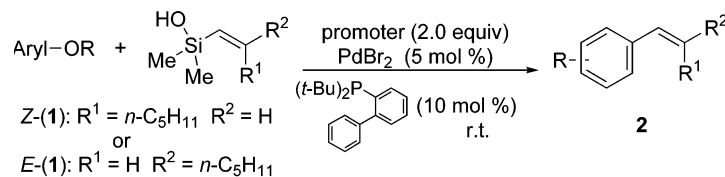
entry	R	fluoride source ^a	X	solvent	time, h	(<i>E</i>)- 2 yield, % ^b	phenol yield, % ^b
1	Nf	TBAF·3H ₂ O	Cl	dioxane	12	40	22 ^d
2	Nf	TMAF·4H ₂ O	Cl	DMF	24	95	5
3	Nf	TBAF·4H ₂ O	Cl	dioxane	12	71	19 ^d
4	Nf	TBAF·6H ₂ O	Cl	dioxane	12	95	5
5	Nf	TBAF·8H ₂ O	Cl	dioxane	12	89	1 ^d
6	Nf	TBAF·10H ₂ O	Cl	dioxane	12	76	1 ^d
7	Nf	TMAF ^c	Cl	DMF	24	1	20 ^d
8	Nf	TMAF·6H ₂ O	Cl	DMF	24	99	1
9	Nf	TMAF·8H ₂ O	Cl	DMF	24	83	1
10	Nf	TBAF·6H ₂ O	Br	dioxane	8	97	3
11	Tf	TBAF·3H ₂ O	Br	dioxane	3	78	22 ^d
12	Tf	TBAF·4H ₂ O	Br	dioxane	8	84	16
13	Tf	TBAF·6H ₂ O	Br	dioxane	8	93	7
14	Tf	TBAF·8H ₂ O	Br	dioxane	8	97	3

^a Hydrated levels of TBAF and TMAF were made by premixing the appropriate amount of water with either TMAF·4H₂O or TBAF·3H₂O. ^b Yields calculated by GC conversion relative to naphthalene as an internal standard. ^c Prepared by dehydration of TMAF·4H₂O. ^d Mass balance is unreacted starting material.

The optimal promoter, solvent, catalyst, and ligand combination were then employed in the cross-coupling between (*E*)-**1** and phenyl nonaflate. At 12 h, the product ratio was approximately 2:1 in favor of the cross-coupling compared to the phenolic cleavage product (Table 1, entry 1). Although encouraging, this was not a synthetically useful result. However, when we employed tetramethylammonium fluoride (TMAF), which is supplied as a crystalline tetrahydrate, a dramatically improved product ratio of 95:5 in favor of the desired cross-coupling product was observed (Table 1, entry 2).

This striking result prompted an investigation into the origin of the superiority of TMAF over TBAF. The two limiting possibilities would be the effect of either the alkyl group or the extra water contained within the crystalline tetraalkylammonium salt (TMAF·4H₂O and TBAF·3H₂O).¹² These factors were easily addressed by adding water to the coupling reaction to achieve various levels of hydration of the nucleophilic salt (Table 1, entries 3–6). By comparing the tetrahydrate of TBAF with the trihydrate (Table 1, entries 1 and 3), it became apparent that the addition of water reduces the amount of phenol formation (from 22 to 19%) and also increases the extent of cross-coupling (from 40 to 79%).¹³ Using TBAF as a hexahydrate (Table 1, entry 4)

(12) For a review on water-accelerated organic transformations, see: Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

Table 2. Palladium-Catalyzed Coupling of (*E*)- and (*Z*)-**1** with Aryl Triflates and Nonaflates^a

entry	silanol	aryl	R	promoter	solvent	time, h ^b	product	yield, %	<i>E/Z</i> ^c
1	(<i>E</i>)- 1	C ₆ H ₅	SO ₂ CF ₃	TBAF·8H ₂ O	dioxane	8	(<i>E</i>)- 2a	91 ^d	99.5/0.5
2	(<i>Z</i>)- 1	C ₆ H ₅	SO ₂ C ₄ F ₉	TBAF·6H ₂ O	dioxane	14	(<i>Z</i>)- 2a	88 ^d	2.9/97.1
3	(<i>E</i>)- 1	1-naphthyl	SO ₂ CF ₃	TBAF·6H ₂ O	dioxane	14	(<i>E</i>)- 2b	82 ^d	99.1/0.9
4	(<i>Z</i>)- 1	1-naphthyl	SO ₂ CF ₃	TBAF·6H ₂ O	dioxane	15	(<i>Z</i>)- 2b	82 ^d	1.1/98.9
5	(<i>E</i>)- 1	2-(CH ₃)C ₆ H ₄	SO ₂ CF ₃	TBAF·6H ₂ O	dioxane	16	(<i>E</i>)- 2c	85 ^{e,f}	>99.9/0.1
6	(<i>Z</i>)- 1	2-(CH ₃)C ₆ H ₄	SO ₂ CF ₃	TBAF·6H ₂ O	dioxane	25	(<i>Z</i>)- 2c	86 ^{e,f}	0.4/99.6
7	(<i>E</i>)- 1	4-(CH ₃ O)C ₆ H ₄	SO ₂ CF ₃	TBAF·6H ₂ O	dioxane	5	(<i>E</i>)- 2d	93 ^d	98.9/1.1
8	(<i>Z</i>)- 1	4-(CH ₃ O)C ₆ H ₄	SO ₂ CF ₃	TBAF·6H ₂ O	dioxane	13	(<i>Z</i>)- 2d	87 ^d	1.5/98.5
9	(<i>E</i>)- 1	4-(CH ₃ CO)C ₆ H ₄	SO ₂ C ₄ F ₉	TMAF·30H ₂ O	DMF	27	(<i>E</i>)- 2e	87 ^{d,g}	93.2/6.7
10	(<i>Z</i>)- 1	4-(CH ₃ CO)C ₆ H ₄	SO ₂ C ₄ F ₉	TMAF·30H ₂ O	DMF	24	(<i>Z</i>)- 2e	91 ^{d,h,i}	80.0/20.0

^a Reactions employed 1.1 equiv of silanol. ^b Solvent: TBAF, dioxane; TMAF, DMF. ^c Crude product contained less than 6% of the corresponding aryl alcohol. ^d Determined by GC analysis. ^e Yield of chromatographed, distilled products. ^f Yield of analytically pure material. ^g 10 mol % Pd, 20 mol % ligand. ^h 50 °C. ⁱ 70 °C. ^j Crude product contained 26% 4-hydroxyacetophenone, 49% product, and 25% nonaflate; yield was based on 49% conversion to product.

resulted in a 95:5 ratio of the desired product to phenol.¹⁴ Further addition of water reduces the amount of phenol to 1% or less. However, the yield of coupling product also begins to decrease due to the reduced rate of cross-coupling (Table 1, entries 5 and 6).

A similar effect of water was observed when using TMAF (Table 1, entries 7–9). Unlike TBAF, however, TMAF can be obtained in an anhydrous form.¹⁵ The absence of water almost completely suppressed the coupling reaction while still promoting a significant amount of phenol formation (Table 1, entry 7). The TMAF hexahydrate, on the other hand, is not only superior to the tetrahydrate (Table 1, entries 2 and 8), but it is superior to TBAF hexahydrate in minimizing phenol formation (1 vs 5%) (Table 1, entries 4 and 8). However, the rate of cross-coupling with TMAF·6H₂O is much lower than that with TBAF·6H₂O. As was the case with TBAF, increasing the amount of water further reduces the rate and, hence, yields of cross-coupling products (Table 1, entry 9).

Having established the importance of fluoride hydration, we next examined the TBAF·6H₂O-promoted coupling using PdBr₂ instead of PdCl₂. A significant increase in the reaction rate was observed, with the cross-coupling now complete in 8 h compared to 12 h with PdCl₂ (Table 1, entries 4 and 10). A re-examination of the hydration of TBAF employing PdBr₂ was then conducted with phenyl triflate (Table 1, entries 11–14). As stated above, the triflate yielded slightly

more phenol (7%) than the nonaflate (3%) under similar reaction conditions (Table 1, entries 10 and 13). Nonetheless, the triflate proved to be a viable coupling partner and responded in a similar way, with respect to TBAF hydration levels, as the nonaflate. In this case, TBAF octahydrate gave the lowest amount of phenol formation (3%) relative to cross-coupling product (97%) (Table 1, entry 14).

From these optimization studies, it is apparent that *there is not one optimal set of conditions*. If short reaction time is desired, then high levels of fluoride hydration are not necessary. On the other hand, if the starting pseudohalide is precious, then high levels of hydration are imperative to completely suppress phenol formation, albeit at the expense of the coupling rate. Either a nonaflate or a triflate can be used with either TBAF or TMAF hydrates, and the starting points will be substrate dependent.

On the basis of these results, we next investigated a series of aryl nonaflates and triflates possessing different electronic and steric properties to establish the generality of the coupling reaction and the ability to customize the procedure for different substrates. The results of this survey are collected in Table 2. As in our previously reported cross-couplings of silanols to aryl iodides,^{7c–d} these reactions were generally high-yielding, proceeded under mild conditions, and showed a high degree of stereospecificity (e.g., Table 2, entries 1 and 2). We observed slightly lower rates of coupling for more sterically demanding substrates such as the 1-naphthyl and 2-methylphenyl derivatives (Table 2, entries 3–6). In general, the rate of coupling with silanol (*Z*)-**1** was slower than that with (*E*)-**1**. With sterically demanding (Table 2, entries 3–6) and electron-rich substrates (Table 2, entries 7–8), the TBAF hexahydrate was sufficient to promote that coupling since the rate of aryl alcohol formation was not competitive. In the case of electron-deficient arenes, however, the more

(13) Reduced nucleophilicity of tetrahexylammonium fluoride with increasing levels of hydration has been reported: Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1989**, *54*, 328.

(14) It has been suggested that a stable geometry exists as six water molecules around the fluoride ion of TBAF in an aqueous solution. See: Craig, J. D. C.; Booker, M. H. *J. Solution Chem.* **2000**, *29*, 879.

(15) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. J. *Am. Chem. Soc.* **1990**, *112*, 7619.

robust nonaflate had to be used with the milder promoter, TMAF (Table 2, entries 9–10). In addition, 30 equiv of water was necessary to suppress the cleavage of the triflate. Since this also attenuated the cross-coupling rate, the reaction had to be heated to 50 °C to reach completion (Table 2, entry 9). With the corresponding coupling of (*Z*)-**1**, however, an effective balance between the rates of cross-coupling and aryl alcohol formation could not be achieved. This case notwithstanding, the cross-coupling between silanols and aryl sulfonates proves to be quite general, tolerating functional groups as well as arenes possessing various steric and electronic properties.

Finally, this method is also compatible with alkenyl triflates. The cross-coupling (*E*)- and (*Z*)-**1** proceeded readily and with high stereospecificity at 50 °C with cycloalkenyl triflate, **3**, in the presence of TBAF (Scheme 3).¹⁶ While TBAF trihydrate was adequate for the coupling to (*E*)-**1**, the

corresponding hexahydrate was necessary for the slower coupling to (*Z*)-**1** to reduce ketone formation to ~10%.

The work presented here demonstrates that silanols are capable of undergoing mild and facile palladium-catalyzed cross-coupling reactions to alkenyl and aryl triflates. Unlike most prior examples, these particular pseudohalide coupling reactions generally do not require elevated temperatures.¹⁷ With few exceptions, the high yields and stereospecificity obtained with substrates possessing a wide range of steric and electronic properties exemplify the generality of this method. As a result of our initial optimizations, the variables affecting the success of this reaction have been delineated, providing the user with clear guidelines by which to employ this method for a particular sulfonate substrate of choice.

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Supporting Information Available: Representative procedures for optimization studies and coupling reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Lower yields of these couplings result from problematic separation of the hydrocarbon product from the polymethylsiloxane byproducts.

(17) Fu has developed a mild, general method for the Suzuki coupling of triflates.^{3c}

Scheme 3

