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Cross-Coupling Reactions of Alkenylsilanols with Fluoroalkylsulfonates: Development and Optimization of a Mild and Stereospecific Coupling Process

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Abstract

The development of an effective protocol for the palladium-catalyzed cross-coupling of (*E*)- and (*Z*)-alkenylsilanols with aryl triflates is described. A critical component in the optimization of this method was balancing the stability and reactivity of the triflates in the presence of a nucleophilic promoter. This report highlights that the use of a slightly soluble Brønsted base promoter that allows for a low, steady-state concentration of alkenyl(dimethyl)silanolate in solution, thus facilitating cross-coupling in preference to S-O bond cleavage of the triflate.

Transition metal catalyzed cross-coupling reactions have revolutionized the construction of carbon-carbon and carbon heteroatom bonds.¹ The introduction of new organometallic donors and organic electrophiles has led to expanded functional group compatibility and has reduced formation of toxic by-products.² Initial reports on cross-coupling reactions focused on the use of highly active leaving groups such as iodides and diazonium ions. However, in recent years, advances in cross-coupling of aryl bromides and chlorides have been made possible by the development of ligands that facilitate the oxidative addition of the organic halide to a palladium(0) catalysts.³ By analogy to aliphatic substitution, alcohols need to be activated as leaving groups. Thus, the introduction of triflates,⁴ and in recent years mesylates,⁵ tosylates,⁶ phosphonates,⁷ carbonates and carboxylates,⁸ has enabled the use of such “activated” alcohols as cross-coupling electrophiles.

Triflates (R = CF₃) and nonaflates (R = C₄F₉) are the most widely employed class of pseudohalides in both the Kosugi-Migita-Stille⁹ and Suzuki-Miyaura¹⁰ cross-coupling reactions.¹¹ Such electrophiles are useful they can allow conversion of aromatic or enolic C-O bonds into carbon-carbon bonds by a simple two-step sequence (Scheme 1).¹²

In the past several years, reports from these laboratories have demonstrated that a number of organosilanol reagents undergo efficient cross-coupling with a variety of organohalides, under both fluoride-promoted¹³ and Brønsted base promoted¹⁴ cross-coupling conditions. The ability to access two different modes of activation, the mild reaction conditions, the ease in preparation and stability of these reagents, and the generation of benign by-products illustrate some of the advantages of organosilanol reagents. As in other coupling processes,

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the scope of electrophile is strongly influenced by the choice in the palladium/ligand combination. For example, bulky, electron-rich palladium complexes such as $(t\text{-Bu}_3\text{P})_2\text{Pd}$, are critical for the cross-coupling of arylsilanolates with aryl bromides¹⁵ whereas Buchwald type ligands allow for the cross-coupling of alkenylsilanolates with aromatic chlorides.¹⁶

The cross-coupling of organosilanes with triflates find precedent in the work of Hiyama who found that alkenyl, alkynyl, aryl, and alkyl mono-, di- and trifluorosilanes can combine with a range of alkenyl and aryl triflates.¹⁷ Moreover, a report from these laboratories described the coupling of alkenylsilanolates with aryl triflates under activation by hydrated fluoride sources.¹⁸

The current study focuses on evaluating Brønsted base activation of alkenyl(dimethyl)silanolates to expand the scope of the electrophile to include the use of sulfonates. Because silanol-based cross-coupling reactions involve a nucleophilic component, the development of such a method is challenging given the sensitivity of sulfonates toward basic and nucleophilic reagents.¹⁹ Therefore, two major issues need to be addressed to develop a protocol for a Brønsted base promoted cross-coupling reaction. First, the lower reactivity of an aromatic triflate, relative to aromatic halides, would require optimization of the palladium source and ligand. Second, the more challenging issue is to identify reaction conditions that would allow for Brønsted-base activation of the organosilanol while avoiding unproductive S-O bond cleavage of the aryl nonaflate or triflate (Scheme 2).

The starting point chosen was to survey a variety of Brønsted base activators for the reaction of phenyl nonaflate with heptenyl(dimethyl)silanol (*E*)-**1**.²⁰ Phenyl nonaflate was selected, rather than the corresponding triflate, because arylnonaflates are more reactive than the corresponding triflate in cross-coupling reactions and they are less prone to hydrolytic or basic cleavage of the S-O bond.²¹ The best starting point was to employ the palladium catalyst, ligand and solvent combination that was successful for the fluoride-promoted cross-coupling of aryl triflates and nonaflates.²² Therefore, in the presence of PdBr_2 , 2-biphenyldi(*t*-butyl)phosphine (BPTBP) in dioxane at room temperature a wide range of fluoride-free activators was tested (KOSiMe_3 , $\text{KO}t\text{-Bu}$, KH , NaH , NaOH , CsOH , NaOMe , etc.). Unfortunately, all of these activators gave low conversion and product yield with a significant amount of S-O cleavage. These results confirmed that S-O cleavage once again would be a major challenge. Therefore, a full optimization of reaction variables was required to identify a suitable activator that would significantly enhance the cross-coupling rate relative to the rate of S-O cleavage.

Because soluble Brønsted bases provided primarily the S-O cleavage product rather than the desired cross-coupling product, insoluble or sparingly soluble bases were investigated to decrease the concentration of the Brønsted base promoter in solution, thus suppressing the undesired S-O cleavage pathway (Table 1). For these studies 2-naphthyl triflate **2** was chosen, (because the potential side-products could be easily identified by GC analysis) along with (*E*)-**1** and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos)²³ in dioxane. Carbonate bases led to the formation of a significant amount of 2-naphthol and low conversion to the desired product (*E*)-**3a** (Table 1, entries 1–3). On the other hand, with Na_3PO_4 , K_3PO_4 , or $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$, low conversion to product was observed, but more importantly S-O cleavage was completely suppressed (Table 1, entries 4 and 5).

The next phase of the study was to identify a suitable combination of palladium source and ligand. These initial studies showed no significant differences between the palladium(II) sources and the ligands employed (Table 2, entries 1–5). Interestingly, when $[(\text{allyl})\text{PdCl}]_2$ was used in combination with X-Phos (Table 2, entry 3) fewer by-products were observed

by GC analysis compared to the combination with 2-dicyclohexylphosphino-2'-6'-dimethoxybiphenyl (S-Phos)²⁴ (Table 2, entry 4). In the case where Pd(OAc)₂ was employed the rate of cross-coupling was slightly faster than with the halides (Table 2, entry 5), however, the reaction appeared to stall after 6 h. Using Pd(dba)₂ at room temperature (Table 2, entry 6) led to a slight increase in product yield (44%) compared to palladium(II) salts. However, the reaction was still not complete and silanol was eventually consumed to disiloxane. Although this result was not optimal, it did demonstrate that a "ligandless" palladium(0) source was superior to palladium(II) sources. Accordingly, reaction optimization continued with Pd(dba)₂/X-Phos to increase the overall conversion to product. Heating the reaction to 50 °C increased the yield of (*E*)-**3a** to 57% along with 4% of 2-naphthol (Table 2, entries 7–8). Finally, acceptable product conversion was accomplished by heating the reaction mixture to 80 °C, giving 87% of (*E*)-**3a** along with 5% of 2-naphthol.

To determine the actual concentration of K₃PO₄/silanolate in solution at various temperatures, a series of titration experiments was performed. The concentration of these components was determined by mimicking the reaction conditions in Table 2 except adding only K₃PO₄ to dioxane and stirring the mixture at room temperature, 40 °C, 50 °C, 80 °C and 100 °C. Aliquots were removed and the concentration was determined by a total base titration. At 80 °C, the solution was approximately 0.07 M in K₃PO₄ (~12 mol% relative to triflate). This result suggests that at any given time the solution is ca. 0.07 M in silanolate. Thus, a low, steady state concentration of silanolate is maintained which is sufficient to the promote cross-coupling instead of the cleavage of **2**.

Although an acceptable yield of (*E*)-**3a** was achieved (by GC analysis), additional studies were needed to identify the ideal amounts of (*E*)-**1**, K₃PO₄, and ligand. Through extensive optimization it was found that increasing the amount of silanol (*E*)-**1** to 1.5 equiv, K₃PO₄ to 2.3 equiv and X-Phos to 0.052 equiv lead to complete conversion of 2-naphthyl triflate. Preparatively, this combination of reaction variables gave a 76% yield of **3a** after 4 h at 80 °C along with ~ 3% of 2-naphthol.

With a functioning catalytic system established, a survey of a series of aryl triflates possessing different electronic and steric properties was investigated to evaluate the generality of this cross-coupling reaction (Table 3). Overall, the reaction performed well with a series of electron-rich and sterically hindered aryl triflates, gave good yields exclusively as the *E*-isomer (Table 3, entries 1–7). It should also be noted that 7% or less of the phenol was observed in all cases. With electron-rich substrates, complete reaction was observed within 4 h (Table 3, entries 1–4). With sterically demanding substrates (Table 3, entries 5–6) the reaction proceeded smoothly; even the hindered 2,6-disubstituted arene was coupled to afford a 71% yield. Importantly the TBS protected benzyl alcohol gave the desired cross-coupling product in 80% yield (Table 3, entry 8). However, electron-deficient arenes were problematic (Table 3, entries 9–10). In these cases a significant amount of S-O cleavage was observed, giving rise to reduced yields. These unsatisfactory results suggested that the cross-coupling conditions required further optimization for application to electron poor triflates.

To improve the generality of the Brønsted base promoted cross-coupling of aryl triflates with (*E*)-**1**, the nucleophilicity of the silanolate was attenuated by the preparation of a variety of metal salts M⁺(*E*)-**1**[−] with the expectation that S-O bond cleavage would be attenuated (M = Li, MgBr, Cu, Ag). These silanolate salts were easily prepared by irreversible deprotonation of (*E*)-**1**. A solution of the corresponding salt could then be evaluated in the cross-coupling reaction with 4-(trifluoromethyl)phenyl triflate **4**. Unfortunately, the use of these salts did not significantly improve the cross-coupling

reaction. Either the reaction stalled at low conversion or was plagued by disiloxane formation or S-O cleavage.

These results warranted another round of optimization of all reaction variables, using **4** as the acceptor. Through extensive evaluation of solvent, additives, palladium pre-catalysts, ligands, and bases, the best result was obtained using a combination of K_3PO_4 , ((*o*-tol) $_3P$) $_2Pd$ and (Josi-Phos) 26 in toluene at 50 °C. Under these conditions a 48% yield (GC) of the desired cross-coupling product was obtained with approximately 20% S-O cleavage (Scheme 3).

In conclusion, the work presented here demonstrates that alkenyl silanols are capable of undergoing mild and smooth palladium-catalyzed cross-coupling with aryl triflates under Brønsted base activation. Key to the success of this method was the discovery that a sparingly soluble base (K_3PO_4) in dioxane allowed for a low-steady state concentration of the active silanolate in solution. This was found to suppress S-O bond cleavage. At this concentration high yield and stereospecificity was obtained for the cross-coupling of (*E*)-**1** with a range of electron-rich and sterically demanding aryl triflates.

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Scheme 1.
Cross-coupling via activated alcohols.

Scheme 2.
Divergent pathways for cross-coupling vs. S-O bond cleavage.

Scheme 3.
Cross-coupling of an electron-deficient aryl triflate.

Table 1Optimization of Brønsted Base for the Cross-Coupling of **2** with (*E*)-**1**.

entry ^a	base ^a	yield, % ^b	
		(<i>E</i>)- 3a	2-naphthol
1 ^c	Na ₃ CO ₃	4	11
2 ^c	K ₃ CO ₃	8	13
3 ^d	Cs ₂ CO ₃	10	15
4 ^d	Na ₃ PO ₄	17	—
5 ^d	K ₃ PO ₄	31	2
6 ^d	K ₃ PO ₄ •H ₂ O	16	12

^a Mass balance is unreacted starting material or disiloxane.^b Yields calculated by GC conversion relative to tetradecane as an internal standard.^c Reactions appear to have stalled after 4 h.^d Reactions stalled after 12 h.

Table 2

Optimization of Catalyst and Ligand for the Cross-Coupling of **2** and (*E*)-**1**.²⁵

entry	palladium source	ligand	temp., °C	time, h	yield, % ^a	
					(<i>E</i>)- 3a	2-naphthol
1	PdBr ₂	BPTBP	rt	24	24	1
2	PdBr ₂	X-Phos	rt	24	31	2
3	[(allyl)PdCl] ₂	X-Phos	rt	24	32	7
4	[(allyl)PdCl] ₂	S-Phos	rt	24	30	9
5	Pd(OAc) ₂	X-Phos	rt	24	31	15
6	Pd(dba) ₂	X-Phos	rt	24	44	12
7	Pd(dba) ₂	X-Phos	50	12	57	4
8	Pd(dba) ₂	X-Phos	80	4	87	5

^aYields calculated by GC conversion relative to tetradecane as an internal standard.

Table 3

Scope in Aryl Triflate.

entry	aryl-OTf	time, h	product	yield,% ^b
1	2-naphthyl	4	3a	76 ^e
2	C ₆ H ₅	4	3b	72 ^d
3	4-MeO(C ₆ H ₄)	4	3c	71 ^d
4	4-Me(C ₆ H ₄)	4	3d	78 ^d
5	2-Me(C ₆ H ₄)	4	3e	77 ^d
6	2-MeO(C ₆ H ₄)	4	3f	71 ^d
7	2,6-Me(C ₆ H ₃)	4	3g	72 ^d
8	4-CH ₂ OTBS(C ₆ H ₄)	4	3h	80 ^d
9	4-CF ₃ (C ₆ H ₄)	2	3i	30 ^d
10	4-NO ₂ (C ₆ H ₄)	2	3j	11 ^d

^aReactions employed 1.5 equiv of silanol.^bCrude product contained below 7% of the corresponding aryl alcohol.^dYield of chromatographed, distilled products.^eYield of analytically pure material.