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γ-Selective Cross-Coupling of Allylic Silanolate Salts with Aromatic Bromides Using Trialkylphosphonium Tetrafluoroborate Salts Prepared Directly from Phosphine•Borane Adducts

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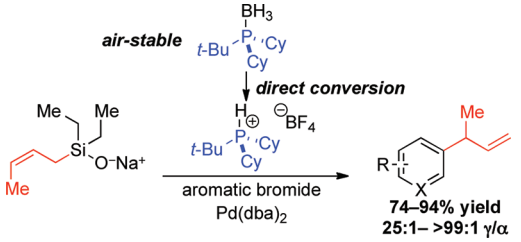
ABSTRACT



The γ-selective, palladium-catalyzed cross-coupling of sodium (*Z*)-2-butenyldiethylsilanolate with a variety of aromatic bromides is reported. The protocol provides high yields (73−94%) and site selectivity (γ/α, 25:1 → > 99:1) in the coupling of electron-rich, electron-poor, sterically hindered, and heteroaromatic bromides. The use of a configurationally homogeneous (*Z*)-silanolate, nontransferable ethyl groups, and a sterically bulky trialkylphosphonium tetrafluoroborate salt (*t*-Bu$Cy_2PH^+BF_4^-$) prepared directly from the corresponding air-stable phosphine•borane adduct are critical to the success of the method.

The trend toward more active and selective palladium catalysts has fueled efficient and selective synthetic reactions.[1] Specifically, palladium catalysts incorporating sterically bulky, electron-rich trialkylphosphine ligands for use in C−C bond-forming cross-coupling reactions has allowed for milder reaction conditions and the inclusion of previously inaccessible substrates.[2,3] However, the synthesis and handling of these highly air-sensitive phosphines poses a technical challenge. The introduction of tetrafluoroborate salts provides bench-stable precursors to air-sensitive trialkylphosphines with no significant change in reactivity when used under basic reaction conditions.[4]

Previous reports from these laboratories describe the remarkable effect of π-acidic olefin ligands on the site selectivity of C−C bond formation in the palladium-catalyzed cross-coupling of allylic silanolate salts with aromatic bromides.[5] These reaction conditions did however display some sensitivity to the electronic properties of the substrate. Furthermore, stereochemical correlation of products from couplings with an enantioenriched, α,γ-disubstituted allylic silanolate established that these reagents stereospecifically transfer the allyl group to palladium

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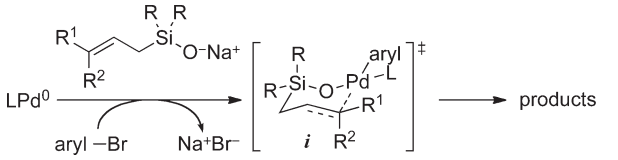
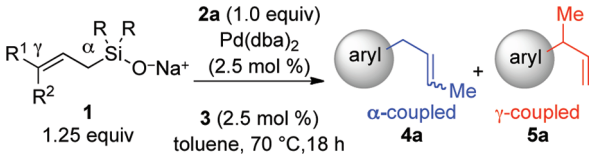
through a *syn* S_E' process with complete stereochemical fidelity.[6] Taken together, these studies provide a structural model of transmetalation that invokes a tetracoordinate Pd(II) intermediate bearing a single ancillary ligand, and also highlights the importance of the *E* vinylic substituent R^1 in its placement relative to the palladium ligand periphery (Scheme 1). In addition, recent mechanistic studies with isolated palladium(II) silanolate complexes indicate that nucleophilic attack at silicon to form hypervalent 10-Si-5 species can have a dramatic effect on the rate of transmetalation.[7] This model prompted our investigation of the effect of the silanolate olefin geometry and nontransferable group on reaction generality, rate, and selectivity when combined with bulky, monodentate phophine ligands. Our ultimate goal was to identify catalysts that are both more active and less sensitive to the electronic properties of the substrate.

Scheme 1. Summary of the Proposed Mechanism Illustrating the Key Transmetalation Transition-State Structure ***i***



In a preliminary evaluation of bulky monodentate phosphine ligands, the combination of $Pd(dba)_2$ and *t*-$BuCy_2PH^+BF_4^-$ (**3**) provided a highly reactive catalyst for the cross-coupling of allylic silanolate salts with aromatic bromides. Therefore, this ligand was used to study the effect of the nontransferable group and olefin geometry of the allylic silanolate on the efficiency and selectivity of the cross-coupling reaction (Table 1). The use of an allylic silanolate with nontransferable methyl groups and (*E*)-olefin geometry (*E*)-**1a** provided a 57% yield of **5a** and 42:1 site selectivity favoring the γ-coupled product (entry 1). Changing the olefin geometry to *Z* raised the yield of **5a** to 92% with slightly lower γ-selectivity (entry 2). Low reactivity was exhibited by the more bulky, diethyl substituted silanolate (*E*)-**1b** with only 15% conversion of the aromatic bromide observed (entry 3). Strikingly, the combination of (*Z*)-olefin geometry and nontransferable ethyl groups (*Z*)-**1b** led to higher reaction efficiency (conversion) and exquisite γ-selectivity at a slightly reduced reaction conversion (entry 4). The superior reactivity of (*Z*)-silanolates relative to (*E*)-silanolates under these conditions supported our hypothesis that the disposition of the vinylic methyl group in the transmetalation transition-state structure ***i*** is important. The lower conversion observed for diethylsilanolates suggests a slower displacement by the bulkier silanolate at the palladium center to form the requisite Si–O–Pd linkage; however the excellent γ-selectivity of (*Z*)-**1b** warranted further study.

Table 1. Effect of Silanolate Nontransferable Group and Olefin Geometry[a]



entry	**1**, R	R^1	R^2	conv, %	yield γ,[b] %	γ/α[c]
1	**1a**, Me	Me	H	96	57	42:1
2	**1a**, Me	H	Me	100	92	18:1
3	**1b**, Et	Me	H	15	4	–
4	**1b**, Et	H	Me	69	67	>99:1

[a] Reactions performed on 0.1 mmol scale, **2a** = 3,5-dimethylbromobenzene, and aryl = 3,5-dimethylbenzene. [b] Determined by GC analysis. [c] GC peak area ratio of crude reaction mixtures.

Determining the effect of other bulky, monodentate phosphonium tetrafluoroborate salts required ready access to a variety of ligands. The tetrafluoroborate salts provide a number of technical advantages and similar reactivity (after in situ deprotonation) to the corresponding trialkylphosphines.[4] These technical advantages are offset when an air-sensitive phosphine is needed that requires purification or further synthetic elaboration. A significant drawback of these salts is the inability to purify them by silica gel chromatography or recover them from alkaline or ionic reaction conditions. Conversely, benchstable phosphine•borane adducts can be carried through multistep synthesis, employing reductive, oxidative, aqueous acidic, or strongly basic conditions, and be easily purified by recrystallization, sublimation, or silica-gel chromatography.[8] Moreover, trialkylphosphine•borane adducts can be handled without the use of rigorous Schlenk technique or a drybox.

To achieve the synthesis of trialkylphosphonium tetrafluoroborate salts that bypasses the handling of pyrophoric trialkylphosphines, experimental conditions were developed to transform air-stable phosphine•borane adducts directly into phosphonium tetrafluoroborate salts (Scheme 2). Preparation of **3** began by treatment of Cy_2PCl[9] with *t*-BuLi at −78 °C,[10] followed by addition of BH_3•THF

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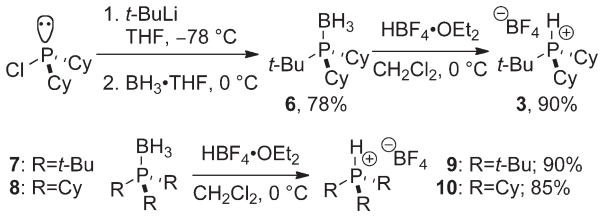
(11) (a) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319–9322. (b) McKinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 7655–7666. (c) McKinstry, L.; Overberg, J. J.; Soubra-Ghaoui, C.; Walsh, D. S.; Robins, K. A.; Toto, T. T.; Toto, J. L. *J. Org. Chem.* **2000**, *65*, 2261–2263.

at 0 °C, to provide the trialkylphosphine•borane adduct **6** in 78% yield after recrystallization (mp 122−123 °C). Treatment of **6** with HBF_4•OEt_2[11] in CH_2Cl_2 at 0 °C followed by an aqueous fluoroboric acid wash provided a 90% yield of analytically pure **3** (mp 230−231 °C). Likewise, **9** and **10** were prepared from the corresponding trialkylphosphine•borane adducts (**7** and **8**)[12] in high yield under these conditions.

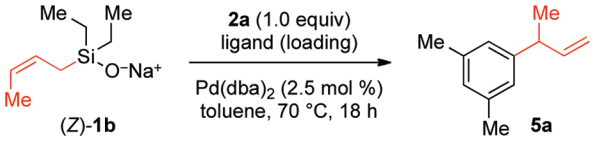
Scheme 2. Preparation of Trialkylphosphonium Tetrafluoroborate Salts from Phosphine•Borane Adducts



With the trialkylphosphonium salts in hand, the reaction parameters for cross-coupling of (*Z*)-**1b** were optimized (Table 2). The use of **9** provided a low yield of the desired product (entry 1). The less bulky ligand **10** provided a similar result to that of **3**; however a better γ-selectivity and yield of **5a** were achieved with **3**. The higher yield and γ-selectivity provided by **3** relative to the other ligands examined suggest this ligand provides an ideal steric environment that allows for transmetalation but retards α-coupling by obstruction of the tetracoordinate π-allyl intermediate. Increasing the reaction concentration provided a better conversion and yield (entries 3−5). The use of 1.5 equiv of silanolate provided optimal results (entries 5−7), and $Pd(dba)_2$ was a superior palladium source compared to $[allylPdCl]_2$ (APC) (cf. entries 5 and 8). The increased γ-selectivity provided by $Pd(dba)_2$ suggests the π-acidic olefin ligand dba continues to serve a beneficial role.[13] Reactions were slightly slower at ligand stoichiometries greater than 1:1 with respect to palladium (entries 11 and 12). Only a small decrease in product yield was noted when the reaction temperature was increased to 90 °C (entry 14).

The results from 1.0 mmol scale reactions of a variety of aromatic bromides with (*Z*)-**1b** are compiled in Table 3. The model substrate **2a** provided the coupling product with excellent γ-selectivity (determined prior to purification) and isolated yield (after aqueous workup, chromatography, and distillation) (entry 1). Likewise, the electron-neutral aromatic bromides **2b**−**d** are excellent substrates in this reaction (entries 2−4). Substrates bearing electron-donating groups provided high yields and γ-selectivities under these conditions (entries 4−6). Noteworthy are the good yields and excellent selectivities observed with substrates containing sterically bulky *ortho*-substitution, including **2i** and the di-*ortho*-substituted **2h** (entries 7 and 8). Substrates bearing electron-withdrawing substituents also reacted smoothly (entries 10 and 11). Heterocyclic bromides, like **2l** and **2m**, are good substrates for allylations under these conditions (entries 12 and 13). Moreover, the racemic precursor[14a] **5n** to the nonsteroidal anti-inflammatory drug naproxen[14b] was prepared in high yield with excellent γ-selectivity under these conditions (entry 14).

Table 2. Optimization of Cross-Coupling Reaction Using Trialkylphosphonium Tetrafluoroborate Salts[a]



entry	(*Z*)-**1b** (equiv)	ligand, mol %	concn (M)	conv,[b] %	yield γ-**5a**,[b] %	γ/α[c]
1[d]	1.5	**9**, 2.5	0.5	100	50	38:1
2[d]	1.5	**10**, 2.5	0.5	100	88	51:1
3	1.5	**3**, 2.5	0.5	100	94	>99:1
4	1.5	**3**, 2.5	0.25	92	85	>99:1
5	1.5	**3**, 2.5	1.0	100	99	>99:1
6	1.25	**3**, 2.5	1.0	69	67	>99:1
7	2.0	**3**, 2.5	1.0	100	96	>99:1
8[e]	1.5	**3**, 2.5	1.0	97	86	17:1
9[f]	1.5	**3**, 1.25	1.0	18	18	>99:1
10[g]	1.5	**3**, 5.0	1.0	100	99	>99:1
11	1.5	**3**, 5.0	1.0	93	91	>99:1
12	1.5	**3**, 10	1.0	89	88	>99:1
13[h]	1.5	**3**, 2.5	1.0	18	18	>99:1
14[i]	1.5	**3**, 2.5	1.0	100	93	>99:1

[a] Reactions performed on 0.1 mmol scale. [b] Determined by GC analysis. [c] GC peak area ratio of crude reaction mixture. [d] Average of 2 experiments. [e] APC (1.25 mol %) used as the catalyst. [f] $Pd(dba)_2$ (1.25 mol %). [g] $Pd(dba)_2$ (5.0 mol %). [h] 50 °C. [i] 90 °C.

The judicious combination of allylic silanolate olefin geometry, nontransferable group, and trialkylphosphonium tetrafluoroborate salt allows for the γ-selective palladium-catalyzed allylation reaction of allylic silanolates with a variety of electronically and sterically differentiated aromatic bromides. Moreover, (*Z*)-**1b** is easily prepared from configurationally homogeneous (*Z*)-crotyltrichlorosilane obtained from the palladium-catalyzed silylation of 1,3-butadiene with trichlorosilane.[15] Additionally, the direct conversion of phosphine•borane adducts to useful

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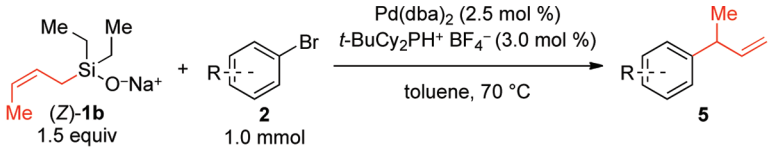
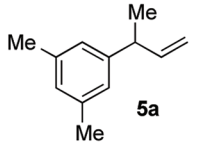
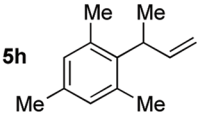
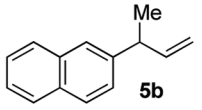
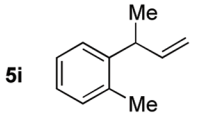
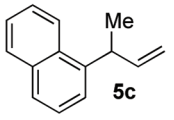
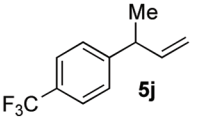
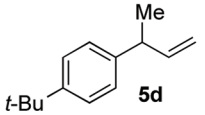
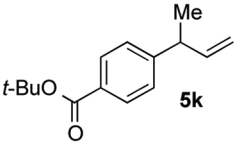
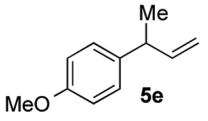
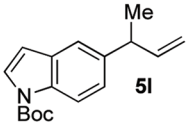
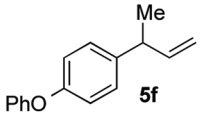
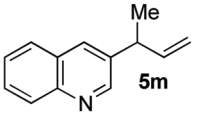
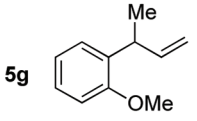
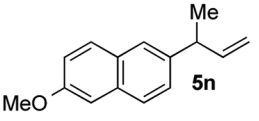
Table 3. Preparative Palladium-Catalyzed Allylations of Substituted Aromatic Bromides Using (*Z*)-**1b** and **3**[a]



entry	product	yield,[b] %	γ/α[c]	entry	product	yield,[b] %	γ/α[c]
1	 **5a**	90	>99:1	8	 **5h**	73	>99:1
2	 **5b**	92	>99:1	9	 **5i**	74	>99:1
3	 **5c**	89	>99:1	10[d]	 **5j**	82	>99:1
4	 **5d**	94	>99:1	11	 **5k**	91	>99:1
5	 **5e**	85	>99:1	12	 **5l**	88	99:1[e]
6	 **5f**	84	>99:1	13[d,f]	 **5m**	82	25:1
7	 **5g**	85	>99:1	14	 **5n**	91	>99:1

[a] Reactions performed on 1.0 mmol scale. [b] Yield of isolated, purified product. [c] GC peak area ratio of crude reaction mixture. [d] 5% $Pd(dba)_2$ and 6% *t*-$BuCy_2PH^+BF_4^-$ used. [e] Determined by ^1H NMR analysis (> 100:1 *S*/*N*). [f] 90 °C reaction temperature used.

trialkylphosphonium tetrafluoroborate salts should find widespread utility to chemists interested in the synthesis and application of trialkylphosphine ligands.

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Supporting Information Available. Detailed experimental procedures and spectral characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.