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Applications of α-Phosphonovinyl Tosylates in the Synthesis of α-Arylethenylphosphonates via Suzuki−Miyaura Cross-Coupling Reactions

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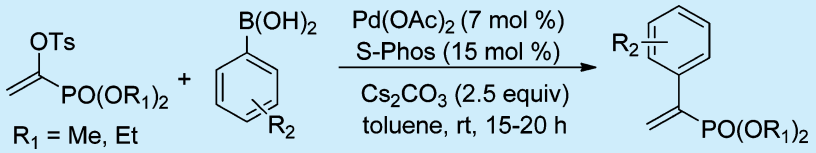
Supporting Information



ABSTRACT: It has been demonstrated for the first time that α-phosphonovinyl tosylates could efficiently couple with a range of arylboronic acids to access α-arylethenylphosphonates. The unprecedented procedure exhibits excellent functional group tolerance, giving the terminal vinylphosphonates in good to excellent isolated yields (60−99%) under mild reaction conditions.

Cross-coupling has been established as one of the preferred methods for generating C−C bonds in synthetic chemistry.[1] Within this broad family of transformations, the Suzuki−Miyaura reaction[2] is perhaps the most popular owing to the low toxicity, air and water stability, functional group compatibility, and commercial availability of the organoboron compounds. In addition to the vast advancements of the preparations of boron reagents[3] and supporting ligands,[4] the development of pseudohalides as the alternative or complementary electrophiles for the C−C cross-coupling reactions also received much attention.[5] Among various pseudohalides, alkyl,[6] alkenyl,[7] and aryl[8] tosylates are indeed highly attractive because they are easy to purify, thermally stable, and persistent to hydrolysis. Moreover, the reactivity alkenyl/aryl tosylates show good reactivity compared to corresponding bromides in cross-coupling reactions.[9]

Terminal vinylphosphonates are a class of vinylphosphonates[10] that exhibit a wide range of applications in organic synthesis and medicinal and agricultural chemistry. Given the interest in terminal vinylphosphonates and their applications as reagents to prepare a host of useful molecules,[11] there is a significant demand for their synthesis. Despite the numerous reported synthetic methods,[12] procedures about transition-metal-catalyzed synthesis of terminal vinylphosphonates are still highly desirable.[13] Presently, most of the protocols for the synthesis of α-arylethenylphosphonates are based on metal-catalyzed C−P bond formation.[13] However, a mixture of α- and β-alkenylphosphorus isomers is always produced via the well-known metal-catalyzed hydrophosphorylation of terminal alkynes. There is no specific procedure[14] describing the synthesis of α-arylethenylphosphonates with C−C bond formation as the strategy. Moreover, α-phosphonovinyl sulfonates have been less investigated, and there is only one report about the applications of α-phosphonovinyl nonaflate **1** in Sonogashira cross-coupling reactions (Figure 1).[15] Intrigued

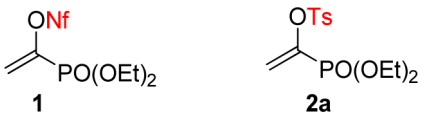


Figure 1. α-Phosphonovinyl nonaflate **1** and tosylate **2a**.

with our continuing interest in cross-coupling reactions,[16] we became interested in the preparation of more economical α-phosphonovinyl arylsulfonates **2** and their applications in Suzuki−Miyaura cross-coupling reaction. Herein, we report for the first time that α-phosphonovinyl arylsulfonates **2** could efficiently couple with a set of aryl- and heteroarylboronic acids to synthesize α-arylethenylphosphonates.

The current study began with the preparation of α-phosphonovinyl arylsulfonates **2a−c** using an adaptation of the Doğan procedure.[17] To our delight, α-phosphonovinyl arylsulfonates **2** could be easily prepared by treatment of acetyl phosphonates **3** with DBU and arylsulfonyl chlorides **4** in 74−83% yields (Scheme 1). Importantly, **2** are highly crystalline free-flowing solids.

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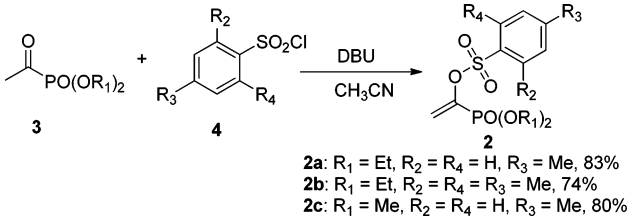
Scheme 1. Preparations of α-Phosphonovinyl Arylsulfonates 2a–c



2a: R_1 = Et, R_2 = R_4 = H, R_3 = Me, 83%
2b: R_1 = Et, R_2 = R_4 = R_3 = Me, 74%
2c: R_1 = Me, R_2 = R_4 = H, R_3 = Me, 80%

With the α-phosphonovinyl arylsulfonates **2** in hand, we set out to optimize the reaction parameters. Using the reaction between α-phosphonovinyl tosylate **2a** and phenylboronic acid **5a** as the template, a wide variety of ligands, bases, and solvents were screened. First, screening of various phosphorus ligands was carried out with $Pd(OAc)_2$ as the palladium source and toluene as the solvent at room temperature. As apparent from Table 1, bidentate phosphine ligands *rac*-BINAP and DPE-Phos showed very poor reactivity (entries 1 and 2). Interestingly, using the simple PPh_3 ligand afforded the desired coupled product in 36% isolated yield (entry 3). Encouraged by this result, the subsequent reaction optimization focused on the monophosphine ligands (entries 4–6). Gratifyingly, with Buchwald's S-Phos or X-Phos as the ligand (entries 5 and 6), full conversion and nearly quantitative yield could be achieved. Indeed, we decided to use two different ligands, S-Phos and X-Phos, because they were often complementary in their reactivity under Pd-catalyzed Suzuki–Miyaura cross-coupling reaction conditions.[18] In the next step of the screening procedure, different bases were examined for the ability to promote the cross-coupling of the model substrates. Cs_2CO_3 and K_3PO_4 displayed similar results, and excellent yields could be obtained (entries 6 and 7). However, the use of K_2CO_3 and Na_2CO_3 resulted in a drop in the yield (entries 8 and 9). THF and CH_3CN were observed to be ineffective solvents (entries 10 and 11). Interestingly, with potassium trifluoroborate as the nucleophilic cross-coupling partner, the expected reaction could proceed well in a 4:1 toluene and water mixture, giving **6a** in 99% yield (entry 12). On the basis of these results, the combination of 7 mol % of $Pd(OAc)_2$, 15 mol % of S-Phos or X-Phos, and 2.5 equiv of Cs_2CO_3 in toluene for 15 h emerged as the best reaction conditions.

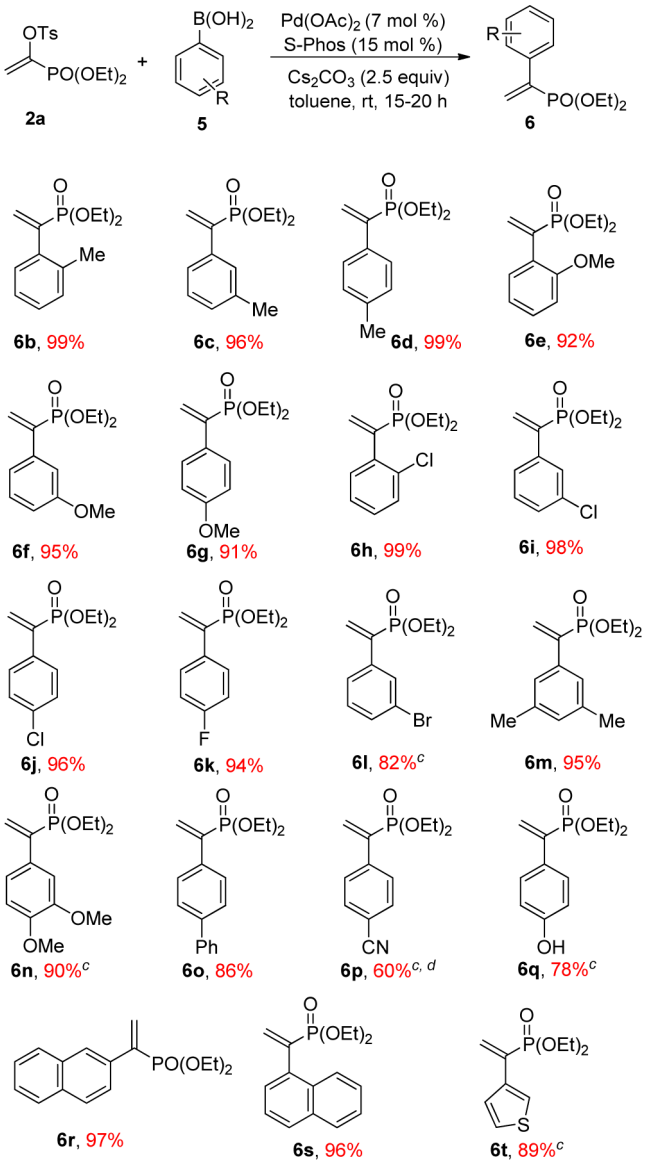
Table 1. Optimization of α-Phosphonovinyl Tosylate 2a and Phenylboronic Acid 5a[a]

entry	ligand	base	solvent	yield[b] (%)
1	DPE-Phos	Cs_2CO_3	toluene	trace
2	*rac*-BINAP	Cs_2CO_3	toluene	<10
3	PPh_3	Cs_2CO_3	toluene	36
4	*t*-$Bu_3P{\cdot}HBF_4$	Cs_2CO_3	toluene	45
5	X-Phos	Cs_2CO_3	toluene	98
6	S-Phos	Cs_2CO_3	toluene	99
7	S-Phos	K_3PO_4	toluene	98
8	S-Phos	K_2CO_3	toluene	79
9	S-Phos	Na_2CO_3	toluene	43
10	S-Phos	Cs_2CO_3	THF	42
11	S-Phos	Cs_2CO_3	CH_3CN	14
12[c,d]	S-Phos	Cs_2CO_3	toluene:H_2O	99

[a]Reaction conditions: **2a** (0.3 mmol), **5a** (0.6 mmol), $Pd(OAc)_2$ (7.0 mol %), ligand (15.0 mol %), base (2.5 equiv), solvent (2.0 mL), room temperature, 15 h. [b]Isolated yield. [c]Used toluene/H_2O (4:1, 0.15 M) as the solvent. [d]Potassium phenyltrifluoroborate (0.6 mmol) was used. DPE-Phos: bis(2-diphenylphosphinophenyl)ether. *rac*-BINAP: *rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. X-Phos: 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl. S-Phos: 2-dicyclohexylphosphinohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl.

With the optimized reaction conditions in hand, we next tested the substrate scope of arylboronic acids. As indicated in Scheme 2, electron-neutral, electron-donating, and electron-withdrawing groups were suitable coupling partners in Suzuki–Miyaura cross-coupling reactions. Surprisingly, sterically hindered *ortho*-substituted (Me, OMe, and Cl) arylboronic acids provided as high a yield as the less hindered *meta*- and *para*-substituted arylboronic acids (**6b–j**). The present reaction protocol was applicable to the coupling of halo-substituted

Scheme 2. Applications of α-Phosphonovinyl Arylsulfonates 2a in Suzuki–Miyaura Cross-Coupling Reactions[a,b]



[a]Reaction conditions: **2a** (0.3 mmol), **5** (0.6 mmol), $Pd(OAc)_2$ (7.0 mol %), S-Phos (15.0 mol %), Cs_2CO_3 (2.5 equiv), toluene (2.0 mL), room temperature, 15–20 h. [b]Isolated yield. [c]The reaction was carried out at 60 °C. [d]X-Phos (15 mol %) used as the supporting ligand.

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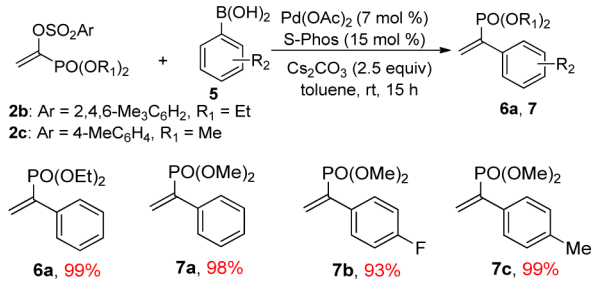
arylboronic acids, including substrates bearing fluoro, chloro, and bromo groups (**6h–l**). Of particular note, 3-bromophenylboronic acid showed inferior reactivity compared to the corresponding 3-chlorophenylboronic acid, and a higher temperature (60 °C) was required. Additionally, 3,5-dimethylphenylboronic acid, 3,4-dimethoxyphenylboronic acid, and 4-biphenylboronic acid all underwent the reaction to deliver the expected coupled products **6m–o** in excellent yields (86–95%). Satisfyingly, the base-sensitive cyano and hydroxyl groups were well-tolerated under these conditions, affording the coupled products **6p** and **6q** in moderate yields. As far as the size of aryl group is concerned, 1- and 2-naphthaleneboronic acids with larger aryl moieties also worked uneventfully to afford **6r** and **6s** in excellent isolated yields. Likewise, heteroaromatic 3-thienylboronic acid was also a good cross-coupling partner to give **6t** in 89% yield.

To expand the substrate scope further, we next tested the feasibility of the replacement of **2a** (Scheme 3). Indeed, under

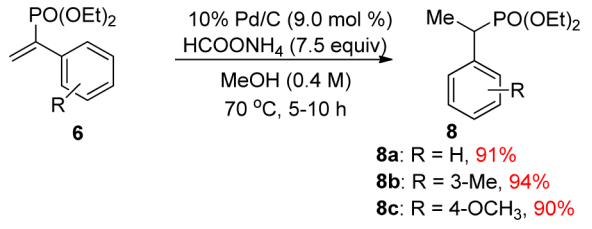
Scheme 3. C–C Cross-Coupling Reactions of α-Phosphonovinyl Tosylates 2b and 2c



identical conditions, the cross-coupling reaction using mesitylenesulfonate **2b** furnished the product **6a** in 99% yield. Moreover, the $Pd(OAc)_2$/S-Phos-based catalyst allowed the coupling of α-phosphonovinyl tosylate **2c** with arylboronic acids bearing electron-donating and electron-withdrawing groups at the phenyl ring to produce **7a–c** in 93–99% yields.

It is well-known that 1-arylethylphosphonates have received much attention during the past few years in bioorganic and medicinal chemistry.[19] As a synthetic application of the present method, hydrogenation of α-arylethenylphosphonates **6** using a $HCOONH_4$/Pd/C system[20] was explored (Scheme 4). The

Scheme 4. Hydrogenation of α-Arylethenylphosphonates by Ammonium Formate/Pd/C



reduction was conducted in the presence of 10% palladium on charcoal (9.0 mol %) and $HCOONH_4$ (7.5 equiv) in methanol at 70 °C, and the corresponding saturated phosphonates **8a–c** were obtained in excellent yields (90–94%).

In summary, we have disclosed for the first time that α-phosphonovinyl tosylates could be employed as the electrophilic coupling partners under Pd-catalyzed Suzuki–Miyaura cross-coupling reactions. High efficiency, mildness of the reaction conditions, great functional group tolerance, and easily accessible starting materials can make this reaction a method of choice for the synthesis of α-arylethenylphosphonates. Extensions of the application of the α-phosphonovinyl tosylates in C–C bond formation reactions are currently being pursued and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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