

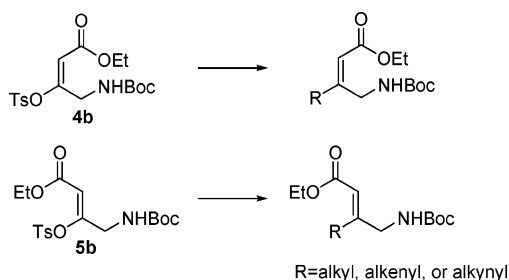
Enol Tosylates as Viable Partners in Pd-Catalyzed Cross-Coupling Reactions

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Herein we demonstrate functionalized enol tosylates to be robust substrates that undergo Suzuki–Miyaura, Sonogashira, and Stille cross-coupling reactions to provide stereodefined trisubstituted unsaturated esters.

Enol tosylates are emerging as important alternatives to enol triflates and vinyl halides in Pd-catalyzed cross-coupling reactions. Enol tosylates are often more stable than the corresponding enol triflates both in the solid state and in solution. In addition, the preparation of enol tosylates possesses distinct advantages over the preparation of enol triflates. On a large scale, Ts_2O is relatively inexpensive compared to $\text{ Tf}_2\text{O}$, and the fact that it is a stable solid renders it easier to handle than $\text{ Tf}_2\text{O}$. In comparison to vinyl halides, which often require multiple steps to prepare, enol tosylates are easily prepared by enolization of the corresponding ketone followed by treatment with $\text{ Ts}_2\text{O}$. This enolization strategy allows for the selective formation of either (*E*)- or (*Z*)-enol tosylates in high isomeric purity simply by choosing the appropriate reaction parameters. As a direct result of these described advantages, enol tosylates are becoming prominent substrates in cross-coupling reactions.

Enol tosylates have been demonstrated to be effective coupling partners in a variety of Pd-catalyzed cross-coupling reactions.¹ Despite these recent successful reports, a broad study on the generality of an architecturally defined enol tosylate to participate in a variety of

transition-metal-catalyzed coupling reactions has not been reported. Although cross-coupling reactions involving aryl tosylates with aryl boronic acids have been reported by several groups, to our knowledge there are no reports of coupling alkyl boronic acids, and reports of coupling vinyl boronic acids with enol tosylates are rare.² The increasing number of reports involving enol tosylates in carbon–carbon bond-forming reactions merits an investigation into the general applicability of these substrates as viable coupling partners in Pd-catalyzed cross-coupling reactions. Herein we demonstrate enol tosylates **4b** and **5b** to be effective coupling partners with commercially available reagents in Suzuki–Miyaura, Sonogashira, and Stille cross-coupling reactions. Also presented in this report is a rare example of a Suzuki coupling reaction of an enol tosylate with methylboronic acid and potassium trifluoroorganoborates.

Recently, we reported the Pd-catalyzed coupling of enol tosylates **4b** and **5b** with electron-withdrawing, electron-donating, and electron-neutral aryl boronic acids as a general method for the preparation of trisubstituted α,β -unsaturated esters.³ Under those conditions, good yields (50–97%) are obtained for all of the cross-coupling reactions. Because of our success with the cross-coupling of various aryl boronic acids, we were interested in the scope and limitations of Suzuki–Miyaura cross-coupling reactions of these enol tosylates. From Tables 1 and 2, our results show that both *cis*- and *trans*-vinyl boronic acids undergo effective coupling with enol tosylates **4b** and **5b** to yield the corresponding trisubstituted α,β -unsaturated esters.^{4,5} Historically, Suzuki–Miyaura cross-coupling reactions involving methyl boronic acids have been difficult to achieve. The cross-coupling reaction of methylboronic acid with alkenyl triflates is reported to require 40 mol % of triphenylarsine.⁶ More recently, cross-coupling of aryl triflates with methyl boronic acid was achieved under milder, less toxic conditions.⁷ In our studies, the coupling reaction of (*Z*)-enol tosylate **5b** with methylboronic acid affords the desired coupled product in 59% assay yield and 49% isolated yield (Table 1, entry 1). In contrast, when (*E*)-enol tosylate **4b** and methylboronic acid were subjected to these coupling conditions (3 equiv of $\text{ Cs}_2\text{CO}_3$, THF, 45 °C, $\text{ PdCl}_2(\text{ Ph}_3\text{ P})_2$) the major product obtained was the methylated pyrrolidinone **10**. However, using $\text{ Na}_2\text{CO}_3$ as base (THF, 45 °C, $\text{ PdCl}_2(\text{ Ph}_3\text{ P})_2$) under biphasic conditions afforded **9** in 45% isolated yield and pyrrolidinone **10** was not observed in the reaction.

Over the past several years, organotrifluoroborate derivatives have emerged as more robust, stable alternatives to boronic acids. Organotrifluoroborate compounds

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(4) Control experiment: 46% decomposition of **4b** is observed after 15 h in THF with 2 equiv of $\text{ Cs}_2\text{CO}_3$ at ambient temperature.

(5) No product is observed in the coupling reaction of *cis*-propenyl boronic acid and **5b** with 5 mol % $\text{ Pd}(\text{ PPh}_3)_2\text{ Cl}_2$ and 4 equiv of $\text{ Na}_2\text{CO}_3$ in THF.

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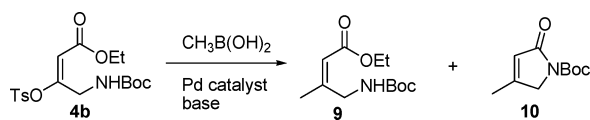
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TABLE 1. Pd-Catalyzed Cross-Coupling Results for Enol Tosylate **5b**

Entry	Substrate	Product	Isolated Yield (%)
1			49 ^a
2			69 ^b
3			81 ^a
4			81 ^c
5			69 ^d
6			50 ^b
7			78 ^e
8			67 ^f

^a 1.2 equiv of borate derivative, 5 mol % Pd(PPh₃)₂Cl₂, Cs₂CO₃ (3 equiv) in THF (0.1 M), 60 °C. ^b 1.2 equiv of borate derivative, 10 mol % PdCl₂(dppf)-CH₂Cl₂, Cs₂CO₃ (2 or 3 equiv) in 10:1 THF/water (0.1 M), 60 °C. ^c 1.2 equiv of borate derivative, 5 mol % Pd(PPh₃)₂Cl₂, aqueous 2 M Na₂CO₃ (3.5 equiv) in THF (0.12 M), 60 °C. ^d 1.2 equiv of borate derivative, 5 mol % PdCl₂(dppf)-CH₂Cl₂, Et₃N (1 equiv), *n*-PrOH (0.06 M), 65 °C. ^e 1.2 equiv of acetylene, 2.5 mol % [Pd(allyl)Cl]₂, 10 mol % di-*tert*-butylphosphinobiphenyl, 15 mol % CuI, DABCO (2 equiv), CH₃CN, ambient temperature. ^f 1.2 equiv of tributylphenyltin, 5 mol % Pd(PPh₃)₄, KF (3 equiv), THF, 60 °C.

SCHEME 1



are considered more nucleophilic than the corresponding boronic acids⁸ and show good reactivity in Suzuki–Miyaura cross-coupling reactions with alkenyl halides

and both aryl halides and triflates.^{7,9,10} Thus, we decided to investigate these borate derivatives in the Suzuki cross-coupling reaction with enol tosylates **4b** and **5b**. Moderate yields were obtained for the desired coupled product from reaction with potassium benzyltrifluoroborate (Table 1, entry 6; Table 2, entry 6). Coupling of potassium phenyltrifluoroborate with both (*E*)- and (*Z*)-enol tosylates provides the desired ester product in good yields, which are comparable to that of the cross-coupling

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TABLE 2. Pd-Catalyzed Cross-Coupling Results for Enol Tosylate **4b**

Entry	Substrate	Product	Yield (%)
1	$\text{H}_3\text{C}-\text{B}(\text{OH})_2$		45 ^a
2			54 ^b
3			56 ^b
4	$\text{Ph}-\text{BF}_3\text{K}$		78 ^a
5			67 ^a
6			31 ^a
7	$\text{Ph}-\text{C}\equiv\text{C}-\text{H}$		57 ^c
8	$\text{Ph}-\text{Sn}(\text{Bu})_3$		89 ^d

^a 1.2 equiv of borate derivative, 5 mol % Pd(PPh₃)₂Cl₂, aqueous 2 M Na₂CO₃ (3.5 equiv) in THF (0.12 M), 60 °C. ^b 1.2 equiv of borate derivative, 10 mol % PdCl₂(dppf)-CH₂Cl₂, Cs₂CO₃ (2 or 3 equiv) in 10:1 THF/water (0.1 M), 60 °C. ^c 1.2 equiv of phenyl acetylene, 2.5 mol % [Pd(allyl)Cl]₂, 10 mol % di-*tert*-butylphosphinobiphenyl, 15 mol % CuI, DABCO (1 equiv), CH₃CN, ambient temperature. ^d 1.2 equiv of tributylphenyltin, 5 mol % Pd(PPh₃)₄, KF (3 equiv), THF, 60 °C.

reaction with phenylboronic acid (Table 1, entry 4; Table 2, entry 4).¹¹ Employing the optimal conditions for coupling as identified by Molander et al.,¹⁰ good yields are obtained in the cross-coupling reaction of potassium styrenyltrifluoroborate with (*Z*)-enol tosylate **5b** (Table 1, entry 5). However, over the course of the coupling reaction of this borate salt with (*E*)-enol tosylate **4b**, complete isomerization of the (*Z*)-ester product was

(11) Twelve percent isomerization is observed in cross-coupling reaction of KPhBF₃ with **5b** as compared to <3% isomerization observed in the cross-coupling reaction of PhB(OH)₂ with **5b** (see ref 3).

observed,¹² to afford only the (*E*)-ester product at the end of the reaction. Because these coupling conditions call for use of *n*-PrOH as the solvent,¹³ this isomerization is thought to be the result of an addition/elimination of the alcoholic solvent. Therefore, the reaction was performed in a THF/water (10:1) media.¹⁴ A good yield of the (*Z*)-

(12) After 6 h, 87% conversion of **5b** is observed and 27% of the undesired (*E*)-ester is present. Only the (*E*)-ester is detected after heating overnight.

(13) Reaction conditions: 1.2 equiv of styrenyltrifluoroborate, 5 mol % PdCl₂(dppf)-CH₂Cl₂, and Et₃N (1 equiv) in *n*-PrOH (0.06 M).

(14) Reaction conditions: 1.2 equiv styrenyltrifluoroborate, 5 mol % PdCl₂(Ph₃P)₂ and 3 equiv of Cs₂CO₃.

ester is obtained in the absence of the alcoholic solvent with only about 5% isomerization (19:1 *Z/E* selectivity).¹⁵ Because pure geometrical isomers are obtained and control experiments performed in the absence of Pd show no conversion of starting material, an addition/elimination pathway to form the ester product can be ruled out.¹⁶

Preparation of 2-alken-4-yn-1-carbonyl compounds as intermediates to enediyne antibiotics,¹⁷ substituted furans,¹⁸ and conducting polymeric materials¹⁹ is of recent interest. Reactions of enol tosylates with alkyne derivatives under Sonogashira cross-coupling conditions allows rapid access to geometrically defined 1,3-enynes.^{17,20} Cross-coupling of phenylacetylene with (*Z*)-enol tosylate **5b** provides the desired enyne in 78% isolated yield (Table 1, entry 7).²¹ Coupling of the (*E*)-enol tosylate with phenylacetylene under the same conditions used for the (*Z*)-isomer results in a 32% assay yield and formation of the enyne pyrrolidinone. Modification of the reaction conditions²² gives the desired enyne ester in 72% assay yield and 57% isolated yield (Table 2, entry 7). Recent work from our labs demonstrated efficient Sonogashira cross-coupling of aryl bromides with acetylenes in the absence of Cu salts.²³ In line with these results, the reaction of phenylacetylene and enol tosylate **4b** proceeds without CuI to give a 44% assay yield of the desired enyne. The lower yield is attributed to the slower coupling rate in the absence of CuI making the decomposition pathway competitive.

We were also interested in examining other widely used cross-coupling reactions including the Stille, Negishi, and silanol cross-coupling reactions. Reaction of tributylphenyltin with (*Z*)-enol tosylate **5b** gives the desired ester in a 67% isolated yield. Stille coupling of the (*E*)-enol tosylate **4b** with the same substrate gives an 89% isolated yield (Table 2, entry 8). Organozinc compounds are also commonly used as cross-coupling partners. However, Negishi coupling of enol tosylate **5b** to phenylzinc bromide was unsuccessful.^{24,25} Interest in silanols as cross-coupling partners led us to investigate the potential of cross-coupling reactions between tosylates **4b** and **5b** with aryl silanols. Successful silanol couplings

often employ alkoxides²⁶ or TBAF²⁷ to activate the substrate. Because of the base sensitivity of enol tosylates **4b** and **5b**, we were limited in our choice of activators for these reactions.²⁸ Many attempts were made to couple enol tosylate **5b** with *p*-methoxy dimethylsilanol, but our best results show only a 5% conversion to the desired product.^{29,30}

In summary, enol tosylates have been found to have good reactivity toward Suzuki cross-coupling reactions with aryl, alkenyl, and alkyl boronic acids. The mild coupling conditions employed allow for a range of functionality on the aryl boronic acids to be tolerated. In light of the limited number of reports involving the successful coupling of methylboronic acid, our demonstration of Pd-catalyzed methylation via enol tosylates reveals that synthetic opportunities exist with these types of substrates. Yields for the aryl and alkenyl trifluoroborates are comparable to those of boronic acids, while a moderate yield was obtained for potassium benzyltrifluoroborate. Sonogashira coupling with phenylacetylene proceeds smoothly and in good yield with the (*Z*)-enol tosylate. The propensity of (*E*)-enol tosylate **4b** to undergo cyclization to form pyrrolidinone products during the coupling reactions is eliminated through a change in Pd catalyst and solvent system or a decrease in the amount of base for the case of Sonogashira coupling. Typically, the (*Z*)-enol tosylate **5b** exhibits greater reactivity toward Pd-catalyzed coupling reactions than the (*E*)-enol tosylate **4b**. As a result of the competent reactivity and crystallinity of enol tosylates, we expect these substrates to continue to find importance in a variety of applications.

Experimental Procedure

A Schlenk flask was charged with enol tosylate (0.5 g, 1.25 mmol), *cis*-propenyl boronic acid (1.2 equiv, 1.50 mmol), and PdCl₂(dppf)-CH₂Cl₂ (10 mol %, 0.125 mmol). THF (13 mL), deionized water (1.3 mL), and Cs₂CO₃ (3 equiv, 3.75 mmol) were added, and the flask was evacuated and backfilled with N₂ three times. The resulting reaction was stirred overnight at 60 °C under N₂. HPLC of the reaction mixture indicated complete conversion. The mixture was cooled to room temperature, and 15 mL of EtOAc was added followed by 15 mL of NaHCO₃ (saturated aqueous solution). After the phase cut, the organic layer was washed with 2 × 15 mL of brine. The organic layer was dried over MgSO₄, treated with KB-B Darco (50 mg), and filtered through Solka Floc. Evaporation and chromatography on silica gel afforded the product.

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Supporting Information Available: Experimental procedures for the preparation of all reported new compounds and ¹H and ¹³C NMR spectra of these products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) No product is formed in THF with 5 mol % Pd(PPh₃)₂Cl₂, 2 equiv Cs₂CO₃, and 1.2 equiv of styrenyltrifluoroborate.

(16) Table 1, entry 4 gives 12% isomerization. Table 2, entry 1 gives 5% isomerization, entry 2 gives 4% isomerization, entry 3 gives 9% isomerization, and entry 5 gives 5% isomerization. All other entries, <3% isomerization is observed. These values are quoted for the experimental conditions listed in the footnotes to Tables 1 and 2. Control experiments: **5b**, KPhBF₃, and 2 M Na₂CO₃ in THF were heated for 20 h at 60 °C; **5b**, methylboronic acid, and Cs₂CO₃ in THF were heated for 20 h at 60 °C. No conversion to product was observed.

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(22) Only 1 equiv, instead of 2 equiv, of DABCO is used in the coupling of the (*E*)-enol tosylate.

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(28) Complete decomposition of **5b** is observed after 2 h in THF at room temperature with TBAF-*n*-H₂O.

(29) Reaction conditions: 1.2 equiv of silanol, 2 equiv of KF, 5 mol % [Pd(allyl)Cl]₂, and 20 mol % PPh₃ in toluene, 85 °C overnight.

(30) Significant decomposition of enol tosylate **5b** did not occur under reactions conditions.