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Palladium-Catalyzed Allylic Cross-Coupling Reactions of Primary- and Secondary Homoallylic Electrophiles

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Supporting Information Placeholder

Abstract

The Pd(0)-catalyzed allylic cross-coupling of homoallylic tosylate substrates using boronic acids and esters is reported. The reaction uses 2-(4,5-dihydro-2-oxazolyl)quinoline (quinox) as ligand and is performed at ambient temperature. The scope of the reaction is broad in terms of both the boronate transmetallating reagent and the substrate, and includes secondary tosylates. Mechanistic studies support an alkene-mediated S_N2-type stereoinvertive oxidative addition of unactivated primary- and secondary alkyl tosylates.

Transition metal-catalyzed cross-coupling reactions are widely recognized as among the most important class of synthetic transformations due to the ease with which diverse coupling partners can be combined to form specific carbon-carbon bonds.[1] While cross-coupling reactions of aryl- and vinylhalides have been extensively developed over four decades, strategies for the dependable cross-coupling of unactivated, β-hydrogen-containing alkyl electrophiles have been slower to develop.[2] The key mechanistic challenges in cross-couplings of alkyl electrophiles are slow oxidative addition to the metal[3] and subsequent competing β-hydride elimination.[4] Over the past decade, elegant ligand-controlled strategies for the Pd- and Ni-catalyzed cross-coupling of unactivated alkyl electrophiles have emerged.[1a,2a,2d] However, harnessing the propensity for β-hydride elimination from Pd-alkyl intermediates prior to cross-coupling has not been used as a strategy for carboncarbon bond-formation.

With this in mind, we sought to establish a Pd(0)-catalyzed reaction manifold whereby β-hydride elimination would be a mechanistic step *preceding* a carbon-carbon bond-forming event.[5] It was expected that homoallylic tosylates **A** would be potential substrates for such a reaction (Scheme 1). Oxidative addition of the substrate would form Pd-alkyl **B**, which is cationic in nature due to the weakly-coordinating tosylate counterion. β-Hydride elimination would then occur yielding the diene-Pd-H complex **C**. Subsequent migratory alkene insertion into the Pd-hydride would generate the stabilized π-allyl intermediate **D**.[6] Transmetallation of **D** followed by reductive elimination would afford the allylic C-H functionalization product **E**. This overall reaction transposes an unactivated electrophile to formally functionalize an allylic C-H bond[7] via a Pd-migration along an alkyl chain. Herein we report the successful development of this process, which is efficiently catalyzed by a unique ligand set for Pd-catalyzed cross-couplings of sp^3 electrophiles, specifically *N,N*-type ligands. Equally notably, this work also describes the first oxidative addition of unactivated secondary tosylates to Pd(0).

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ASSOCIATED CONTENT

Supporting Information. Optimization data, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The reaction was optimized using homostyrenyl tosylate **1** (Table 1). The central challenge was to identify a catalytic system capable of avoiding the formation of the Suzuki-Miyaura product, and instead accessing the diene intermediate through oxidative addition and rapid β-hydride elimination.

Additionally, the ligand would have to be capable of reinserting the putative 1,3-diene intermediate in order to subsequently access **2a**.[6,8] In light of the pioneering work of Fu and coworkers on Pd-catalyzed cross-couplings of primary alkyl electrophiles,[2a,2d] our initial efforts to optimize this reaction centered on the use of monodentate phosphine ligands (Table 1, entires 1-3). Pleasingly, the branched-to-linear selectivity of the reaction between homostyrenyl tosylate **1** and phenylboronic acid could be controlled by the choice of phosphine. For example, tri-*ortho*-tolylphosphine led to the predominant formation of the undesired cross-coupling product **3a** (entry 1), while tri-*tert*-butylphosphine delivered the desired product **2a** with excellent selectivity (entries 2 and 3). The contrasting selectivity despite similar cone angles (182° and 194°, respectively)[9] prompted the evaluation of a variety of ligands.[10] While we anticipated monodentate phosphines to be uniquely suited for this reaction, we surprisingly found that quinox, a ligand that has found utility in mechanistically distinct Wacker-type oxidations,[11] provided **2a** with the best selectivity and yield (entries 4 and 7). Notably, the Pd(quinox)Cl_2 precatalyst is easily prepared and air stable, thus obviating the use of rigorous air-free techniques in our studies. The pyrox ligand resulted in diminished yield (entry 5), and 2,2′-bipyridine failed to promote the reaction (entry 6).

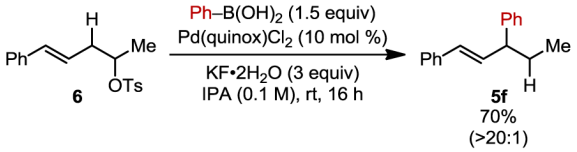
We next investigated the scope of boronate transmetallating reagents for the functionalization of substrate **1** under the optimized conditions (Table 2). Aryl- and vinylboronates were found to be generally well-tolerated. A variety of electronically-disparate *para*-substituted aryl boronic acids were found to be suitable for the transformation, affording branched/linear product ratios of ≥11:1 in each case for **2b**-**2e**. Additionally, *meta*-aminophenyl boronic acid afforded the desired product **2f** in good yield with good branched product selectivity. Aryl boronic acid pinacol esters are also suitable coupling partners for this reaction: *N*-methylindole-5-boronic acid pinacol ester delivered the branched indole product **2g** exclusively and in excellent yield, while **2h** was also produced with excellent selectivity and good yield from the corresponding pinacol ester. Finally, *E*-alkenyl boronic acids could be used to access skipped diene products **2i** and **2j** in good yields and with excellent selectivity. Strongly Lewis-basic boronate nucleophiles were not tolerated, presumably due to competitive coordination to Pd (see supporting information for details).

Turning our attention to the substrate, the role of the leaving group on the performance of the reaction was investigated (Table 3). While homostyrenyl bromide **4a** affected good yield but slightly diminished branched selectivity compared to the corresponding tosylate, reaction of homostyrenyl chloride **4b** resulted in only 19% yield. Next, the electronic nature of the styrene substituent was evaluated and was found to have minimal effect on the reaction outcome, as both electron-donating (**4c**) and electron-withdrawing (**4d**) functional groups were well-tolerated in terms of both yield and selectivity. Additionally, unstabilized alkenes could be used in place of styrenes, as **4e** afforded the desired product in good yield and excellent selectivity.

To evaluate the importance of the structural relationship of the tosylate to the alkene, bis-homostyrenyl tosylate **4f** was subjected to the optimized conditions. This resulted in a 30:70 ratio of **5f** to the linear product, as well as the recovery of the remaining starting material. While this shows that Pd can migrate to the allylic position through repeating β-hydride elimination/alkene insertion steps, the low yield suggests that this occurs inefficiently under

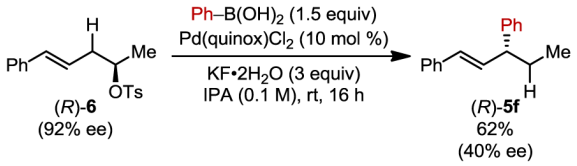
these conditions. The fact that the linear product is the major product in this case signifies that, after oxidative addition, the first β-hydride elimination is slower than transmetallation. This may be due to a more facile C-H breakage at the allylic position, a weaker C-H bond, compared to C-H cleavage at the homoallylic site. Alternatively, homoallylic substrates may be uniquely competent due to a favorable chelation event prior to oxidative addition.[12]

To further explore the role of the substrate in this reaction, homobenzylic tosylate **4g** (Table 3) was subjected to the reaction conditions. After 16 h, the starting material was completely recovered, which supports alkene chelation to Pd prior to oxidative addition.



(1)

Owing to the unique behavior of primary homoallylic tosylates detailed above, we hypothesized that secondary homoallylic tosylates might also be amenable substrates. However, this would require oxidative addition of Pd(0) into an unactivated secondary tosylate.[13] Pd(0)-catalyzed cross-couplings of activated alkyl electrophiles are known,[14] but to the best of our knowledge, no methods requiring Pd(0)-catalyzed oxidative addition into unactivated secondary alkyl electrophiles have been reported. This is generally ascribed to the high energy barrier of the predominant S_N2-type transition state proposed by Fu and coworkers in the oxidative addition event.[15] Therefore, it is surprising that the secondary tosylate **6** was found to convert into the corresponding allylic C-H phenylation product **5f** in moderate yield under the optimized conditions.

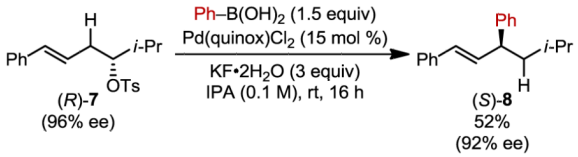


(2)

To gain insight into the stereochemical course of this reaction, an enantiomerically-enriched variant of **6** was synthesized. When (*R*)-**6** was subjected to the reaction conditions, a substantial erosion in enantiomeric excess was observed: starting from 92% ee of (*R*)-**6**, just 40% ee of (*R*)-**5f** was obtained (eq 2). The absolute configuration was determined by converting the product into a previously reported compound of known configuration (see supporting information for details).

Based on this result, the following detailed mechanism is proposed to account for the formation of the major product (*R*)-**5f** (Figure 1A). After coordination of the substrate (*R*)-**6**, stereoinvertive oxidative addition[15a,16] to Pd(0) would generate Pd-alkyl **F**, which then undergoes β-hydride elimination of H^b, affording **G**. Sequential alkene insertion without dissociation,[17] transmetallation with Ph-$B(OH)_2$, and stereoretentive reductive elimination[18] would afford the product. If oxidative addition occurs with high stereochemical fidelity, it is hypothesized that the β-hydride elimination step must therefore be responsible for the erosion of stereochemical integrity due to the existence of an equilibrium between Pd-alkyl **F** and its conformational isomer, **F'** (Figure 1B). Conformer **F** features an *anti* relationship

between the methyl and styrenyl functional groups, and only H^b is positioned *syn* to Pd for β-hydride elimination. In contrast, conformer **F'**, with the methyl and styrenyl groups oriented gauche, can eliminate either H^a or H^b. The observed modest 40% ee favoring (*R*)-**5f** suggests similar energetics for the selection of the two β-hydrogens.



(3)

It was thus envisioned that access to the problematic gauche conformer could be minimized by increasing the steric penalty of the gauche interaction, thereby achieving selective β-hydride elimination. To validate this hypothesis, substrate (*R*)-**7** was prepared via a Brown allylation and cross-metathesis sequence.[10] This substrate contains an isopropyl group in place of the methyl group of (*R*)-**6**. Upon subjection to identical reaction conditions, nearly complete chirality transfer in the formation of (*S*)-**8** was observed (92% ee, eq 3). The absolute configuration of (*S*)-**8** was determined by converting to a previously reported compound. Based on this, the overall stereochemical course of the reaction is strongly suggestive of an S_N2-type oxidative addition and conformationally enforced selective β-hydride elimination.

In conclusion, we have developed a general, mild, and procedurally simple Pd-catalyzed method for the functionalization of allylic C-H bonds from homoallylic tosylates. The key mechanistic features of this reaction are the stereoinvertive oxidative addition of unactivated primary- and secondary alkyl tosylates, and the migration of the Pd-alkyl intermediate via β-hydride elimination and migratory insertion. This reaction employs a simple *N,N*-ligand in a role generally presumed to be exclusive to monodentate phosphines. To facilitate further reaction development, experiments are being designed to probe the origin of this ligand-controlled process as well as the critical role of the substrate olefin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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18). Stereoretentive reductive elimination from these intermediates is well established. See: Stille JK. Hartley FR, Patai S. The Chemistry of the Metal-Carbon Bond. 1985; 2:625.WileyNew York

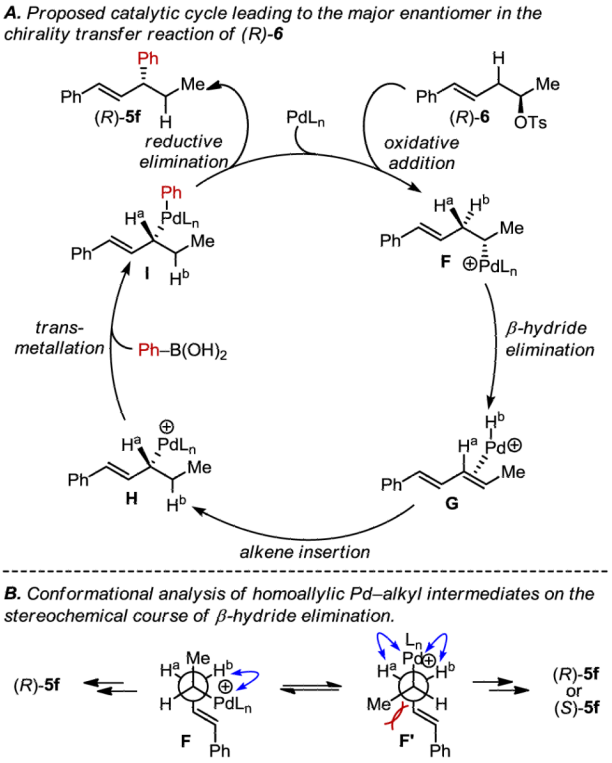
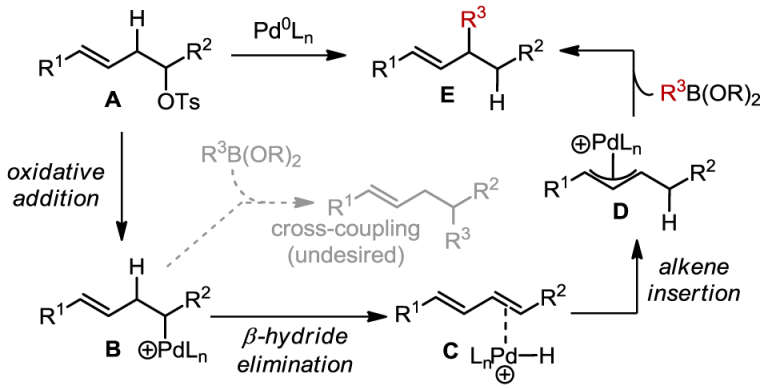


Figure 1.
Proposed Mechanism of Chirality Transfer Reactions

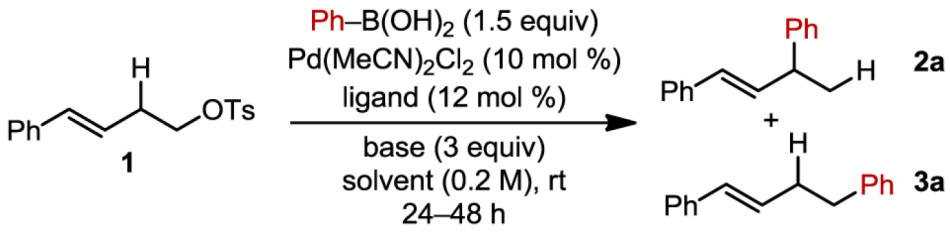


Scheme 1.

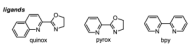
Proposed Mechanism of Pd(0)-Catalyzed Formal Allylic C-H Functionalization of Homoallylic Tosylates

Table 1

Reaction Optimization[a]



entry	ligand	base	solvent	% yield[b] (2a/3a)
1	P(*o*-tol)$_3$	Cs_2CO_3	PhMe	33 (<1:20)[c]
2	P(*t*-Bu)$_3$	Cs_2CO_3	PhMe	55 (>20:1)[c]
3	P(*t*-Bu)$_3$	K_2CO_3	*t*-AmOH	80 (>20:1)
4	quinox	Cs_2CO_3	*t*-AmOH	70 (>20:1)
5	pyrox	Cs_2CO_3	*t*-AmOH	48 (>20:1)
6	bpy	Cs_2CO_3	*t*-AmOH	no rxn
7	quinox	KF•2H_2O	*i*-PrOH	92 (>20:1)[d]



[a] Reactions performed on 0.1 mmol scale.

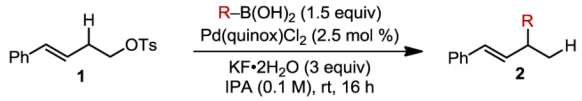
[b] Determined by GC analysis using an internal standard and response factor correction. The major byproduct was (*E*)-1-phenyl-1,3-butadiene.

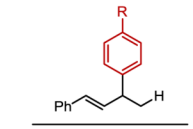
[c] Reaction carried out at 80 °C.

[d] Reaction carried out on 0.5 mmol scale using 2.5 mol % of pre-formed Pd(quinox)Cl_2 at [**1**] = 0.1 M.

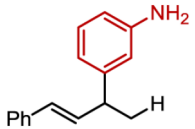
Table 2

Scope of Boronate Nucleophiles[a]

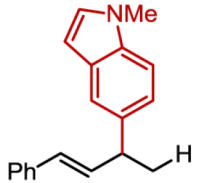




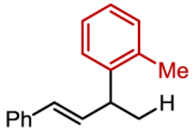
R = CF_3 (**2b**): 81% (12:1)
Cl (**2c**): 73% (11:1)
CO_2Me (**2d**): 82% (12:1)
OMe (**2e**): 72% (15:1)



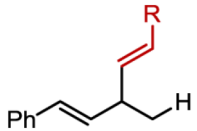
2f, 84%
(13:1)



2g, 94%[b]
(>20:1)



2h, 74%[b]
(>20:1)



2i (R = C_3H_7), 65% (>20:1)

2j (R = Ph), 74% (>20:1)[c]

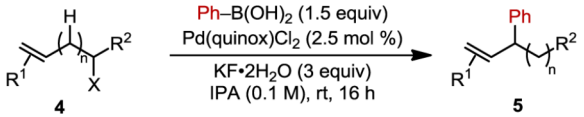
[a]Isolated yields of **2b–2j** are reported, with (B:L) selectivity determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

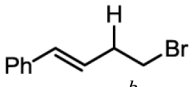
[b]Pinacol boronic ester used instead of boronic acid.

[c]^{1}H NMR yield, calculated using an internal standard.

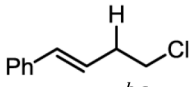
Table 3

Substrate Scope[a]

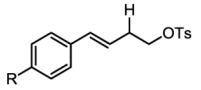




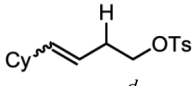
4a, 87%[b] (10:1)



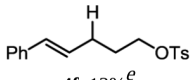
4b, 19%[b,c] (>20:1)



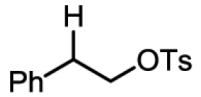
4c (R = OMe), 86% (15:1)
4d (R = CF_3), 78% (>20:1)



4e, 73%[d] (>20:1)



4f, 13%[e] (30:70)



4g, n.r.

[a]Isolated yields of **5a–5g** are shown, with (B:L) selectivity determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

[b]Determined by GC analysis using an internal standard and response factor correction.

[c]72 h reaction time.

[d]An 87:13 *E/Z* ratio of starting material isomers afforded a 93:7 *E/Z* ratio of products as determined by ^{1}H NMR spectroscopy.

[e]Both yield and selectivity determined by ^{1}H NMR spectroscopy.