JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Palladium-Catalyzed Allylic Cross-Coupling Reactions of Primary and Secondary Homoallylic Electrophiles

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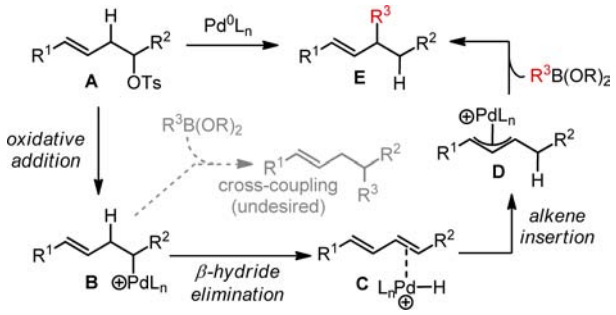
Supporting Information

ABSTRACT: The Pd(0)-catalyzed allylic cross-coupling of homoallylic tosylate substrates using boronic acids and pinacol esters is reported. The reaction uses 2-(4,5-dihydro-2-oxazolyl)quinoline (quinox) as a ligand and is performed at ambient temperature. The scope of the reaction is broad in terms of both the boronate transmetalating 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 because of the ease with which diverse coupling partners can be combined to form specific carbon−carbon bonds.[1] While cross-coupling reactions of aryl and vinyl halides 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,d] However, harnessing the propensity for β-hydride elimination from Pd−alkyl intermediates prior to cross-coupling has not been used as a strategy for carbon−carbon 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 because of 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] Transmetalation of **D** followed by reductive elimination would afford the allylic C−H functionalization product **E**. This overall reaction transposes an unactivated electrophile to achieve formal functionalization of an allylic C−H bond[7] via the migration of Pd 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 unactivated sp^3 electrophiles,

Scheme 1. Proposed Mechanism of Pd(0)-Catalyzed Formal Allylic C−H Functionalization of Homoallylic Tosylates



specifically N,N-type ligands. Equally notably, this work also reports the first oxidative addition of unactivated secondary tosylates to Pd(0).

The reaction was optimized using homostyrenyl tosylate **1** (Table 1). The central challenge was to identify a catalytic system that could avoid the formation of the Suzuki−Miyaura product and instead access the diene intermediate through oxidative addition and rapid β-hydride elimination. Additionally, the catalyst would have to be able to reinsert the putative 1,3-diene intermediate in order to subsequently access **2a**.[6,8] In light of the pioneering work of Fu and co-workers on Pd-catalyzed cross-couplings of primary alkyl electrophiles,[2a,d] 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 (B:L) selectivity of the reaction between homostyrenyl tosylate **1** and phenylboronic acid could be controlled by the choice of phosphine. For example, tri-*o*-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 selectivities 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 reactions,[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

Received: June 4, 2012
Published: June 28, 2012

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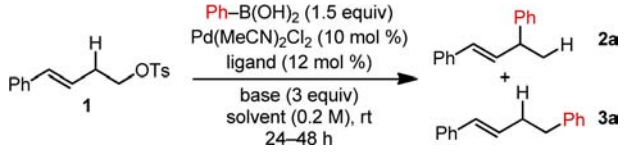
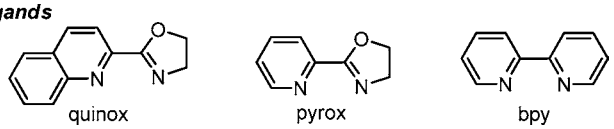
Table 1. Reaction Optimization[a]



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$_2$O	*i*-PrOH	92 (>20:1)[d]

[a]Reactions were performed on a 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]The reaction was carried out at 80 °C. [d]The reaction was carried out on a 0.5 mmol scale using a 2.5 mol % loading of preformed Pd(quinox)Cl$_2$ at [**1**] = 0.1 M.

ligands



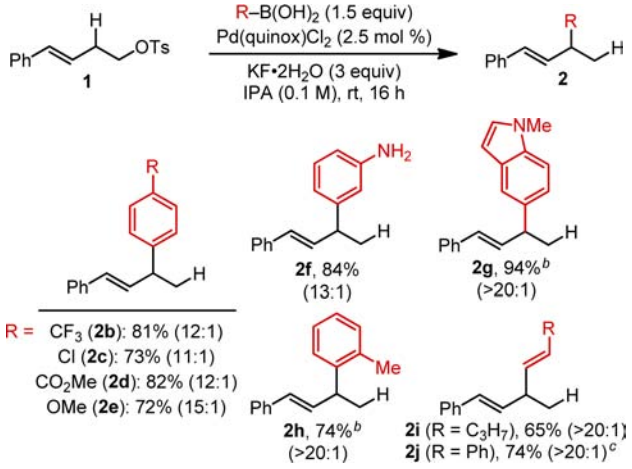
diminished yield (entry 5), and 2,2′-bipyridine failed to promote the reaction (entry 6).

We next investigated the scope of boronate transmetalating 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 arylboronic acids were found to be suitable for the transformation, affording product B:L ratios of ≥11:1 in each case for **2b**–**e**. Additionally, *m*-aminophenylboronic acid afforded the desired product **2f** in good yield with good branched product selectivity. Arylboronic 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 in excellent yield, while **2h** was also produced with excellent selectivity and good yield from the corresponding pinacol ester. Finally, (*E*)-alkenylboronic acids could be used to access skipped diene products **2i** and **2j** in good yields with excellent selectivity. Strongly Lewis basic boronate nucleophiles were not tolerated, presumably because of competitive coordination to Pd (see the Supporting Information for details).

In regard to the substrate, the role of the leaving group on the performance of the reaction was investigated (Table 3). While homostyrenyl bromide **4a** is a good substrate but slightly diminished B:L selectivity relative to the corresponding tosylate, the reaction of homostyrenyl chloride **4b** resulted in a yield of only 19%. Next, the electronic nature of the styrene substituent was evaluated and 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 with excellent selectivity.

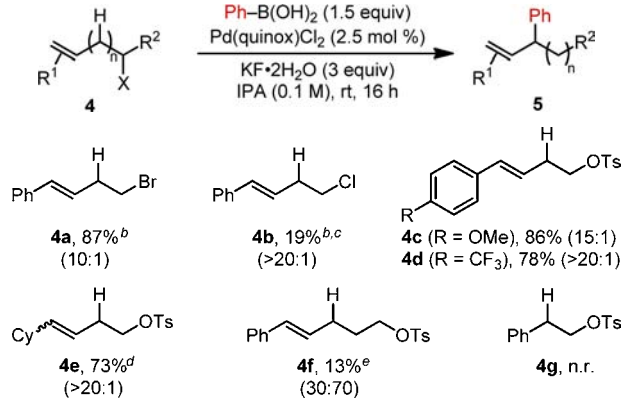
To evaluate the importance of the structural relationship of the tosylate to the alkene, bis-homostyrenyl tosylate **4f** was

Table 2. Scope of Boronate Nucleophiles[a]



[a]Isolated yields of **2b**–**j** are reported, along with (in parentheses) B:L selectivities determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [b]The pinacol boronic ester was used instead of the boronic acid. [c]^{1}H NMR yield calculated using an internal standard.

Table 3. Substrate Scope[a]



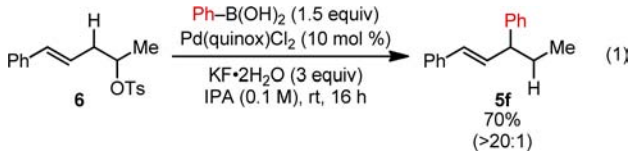
[a]Isolated yields of **5a**–**g** are shown, along with (in parentheses) B:L selectivities determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [b]Determined by GC analysis using an internal standard and response factor correction. [c]72 h reaction time. [d]An 87:13 *E*/*Z* ratio of starting-material isomers afforded a 93:7 *E*/*Z* ratio of products, as determined by ^{1}H NMR spectroscopy. [e]Both the yield and selectivity were determined by ^{1}H NMR spectroscopy.

subjected to the optimized conditions. This resulted in a 13% yield with a 30:70 ratio of **5f** to the linear product, along with recovery of the remaining starting material. While this shows that Pd can migrate to the allylic position through repeated *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 transmetalation. This may be due to more facile C–H cleavage (i.e., a weaker C–H bond) at the allylic position than at the homoallylic site. Alternatively, homoallylic substrates may be uniquely competent because of a favorable chelation event prior to oxidative addition.[12]

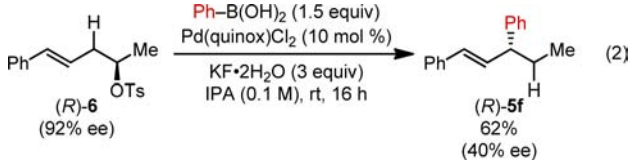
To explore further the role of the substrate in this reaction, homobenzylic tosylate **4g** (Table 3) was subjected to the reaction conditions. After 16 h, the starting material was completely recovered, which supports alkene chelation to Pd prior to oxidative addition.

dx.doi.org/10.1021/ja305403s | J. Am. Chem. Soc. 2012, 134, 11408–11411

Because of 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 in the oxidative addition event, as proposed by Fu and co-workers.[15] Therefore, we were surprised to find that secondary tosylate **6** was converted into the corresponding allylic C–H phenylation product **5f** in moderate yield under the optimized conditions (eq 1).



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 (*R*)-**6** with 92% ee, (*R*)-**5f** with just 40% ee was obtained (eq 2). The absolute configuration was determined by converting the product into a previously reported compound of known configuration (see the Supporting Information for details).



On the basis of this result, the detailed mechanism shown in Figure 1A is proposed to account for the formation of the major product (*R*)-**5f**. After coordination of the substrate (*R*)-**6**, stereoinvertive oxidative addition[15a,16] to Pd(0) would generate Pd–alkyl **F**, which would then undergo *β*-hydride elimination of H^b, affording **G**. Sequential alkene insertion without dissociation,[17] transmetalation with Ph–$B(OH)_2$, and stereoretentive reductive elimination[18] would afford the product. If the oxidative addition occurs with high stereochemical fidelity, it is hypothesized that the *β*-hydride elimination step would be responsible for the erosion of stereochemical integrity as a result of 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.

It was thus envisioned that access to the problematic gauche conformer could be minimized by increasing the steric penalty of the gauche interaction, resulting in selective *β*-hydride elimination. To validate this hypothesis, substrate (*R*)-**7** was prepared via a Brown allylation and cross-metathesis sequence

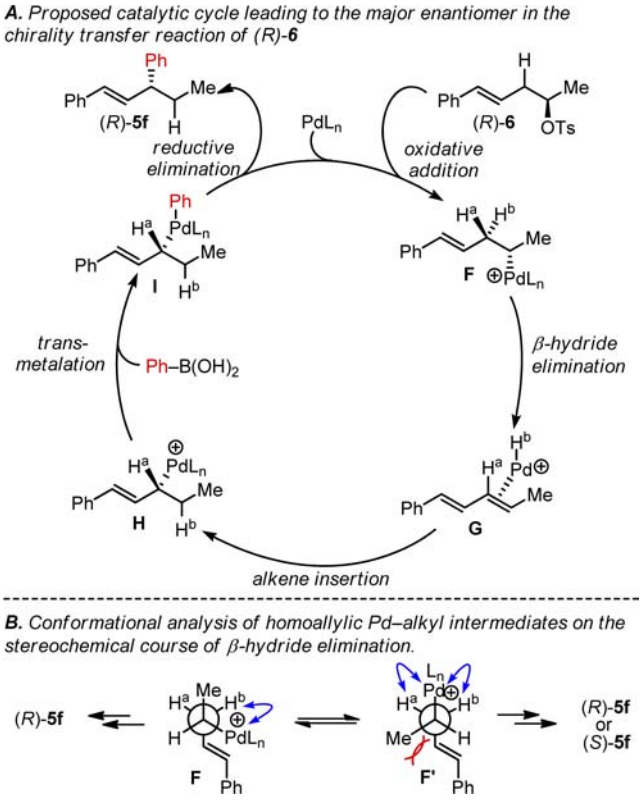
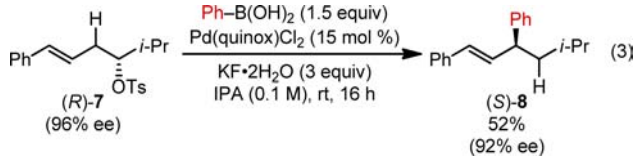


Figure 1. Proposed Mechanism of Chirality Transfer Reactions.

(see Supporting Information for details). This substrate contains an isopropyl group in place of the methyl group of (*R*)-**6**. When (*R*)-**7** was subjected 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 it to a previously reported compound. On this basis, 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-type ligand in a role generally presumed to be exclusive to monodentate phosphines. To facilitate further reaction development, experiments to probe the origin of this ligand-controlled process as well as the critical role of the substrate olefin are being designed.

dx.doi.org/10.1021/ja305403s | J. Am. Chem. Soc. 2012, 134, 11408–11411

■ 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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (R01GM063540 and F32GM099254).

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