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Palladium-Catalyzed Hydroarylation of 1,3-Dienes with Boronic Esters via Reductive Formation of π-Allyl Palladium Intermediates under Oxidative Conditions

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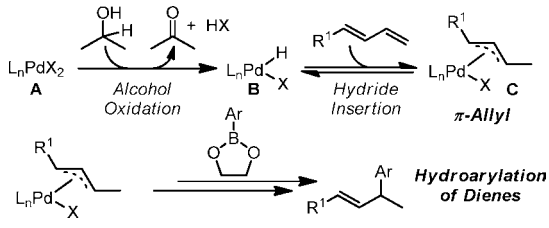
Abstract: A palladium-catalyzed reductive cross-coupling of 1,3-dienes with boronic esters in which a π-allyl Pd species is generated directly from a 1,3-diene via a Pd-catalyzed aerobic alcohol oxidation is reported. Both the scope of the process and the origin of a highly selective 1,2-addition are discussed.

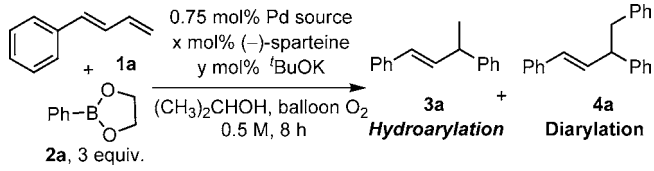
Since the first report in 1957,[1] the π-allyl complexes of palladium have played a central role in Pd catalysis because of the ease in which these complexes undergo nucleophilic substitution.[2] Classically, π-allyl Pd species are most commonly generated from reaction of Pd(0) with an allyl fragment containing a leaving group[2c,3] or from nucleophilic addition to a 1,3-diene promoted by Pd(II).[2e,4] More recently, efforts to directly access these intermediates via allylic oxidation have been reported.[5] On the basis of our programmatic focus on the development of Pd-catalyzed alkene hydrofunctionalization reactions coupled to the reduction of O_2,[6] we became interested in accessing π-allyl Pd species reductively directly from 1,3-dienes. These substrates have performed rather poorly in our previous reports.[6] To accomplish this, we hypothesized that a Pd hydride **B** formed from the oxidation of an alcohol could be intercepted by a 1,3-diene, yielding the desired π-allyl intermediate **C** (Scheme 1).[7] Herein we report the successful generation of these intermediates from dienes and an in situ-formed Pd hydride and their subsequent cross-coupling with aryl boronic esters to accomplish a highly regioselective diene hydroarylation reaction using O_2 as the terminal oxidant.

Scheme 1. Proposed Mechanism for Hydroarylation of 1,3-Dienes



Diene **1a** and boronic ester **2a** were selected as the substrates for optimization and initially evaluated under the conditions previously reported for styrene hydroarylation using $[Pd(\mathbf{SiPr})Cl_2]_2$ as the catalyst (Table 1, entry 1).[6] This catalyst system performed poorly with little conversion of the substrate, possibly because of the excellent stability of N-heterocyclic carbene allyl palladium species.[8] Therefore, we explored the use of Pd[(−)-sparteine]Cl_2, whose π-allyl complexes have previously been structurally characterized and successfully used in nucleophilic addition chemistry.[9] The use of this catalyst led to a significant improvement in conversion and GC yield of the desired product. It is important to note that the ratio of the 1,2- to 1,4-addition products was >99:1 on the basis of GC analysis. Removal of exogenous (−)-sparteine led to rapid decomposition of the catalyst. Therefore, the amount of excess sparteine was increased, with an observed improvement in selectivity and yield of the desired product (entry 3). Decreasing the amount of ^{t}BuOK (entry 4) as well as raising the temperature (entry 5) led to a noticeable increase in the product yield. Use of 3 equiv of the boronic ester was required because of the consumption of this reagent through oxidative homocoupling and formation of phenol by hydrogen peroxide produced from the reduction of O_2.[6c] It should be noted that ^{t}BuOK was required for adequate yields of product.

Table 1. Optimization of the Hydroarylation of **1a**

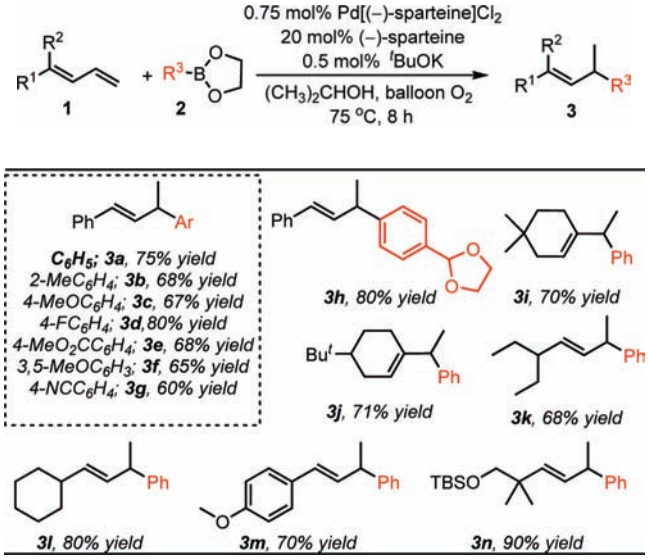


entry	Pd source	*x*	*y*	*T* (°C)	% conv.[a]	% **3a**[b]	**3a**/**4a**
1	$[Pd(\mathbf{SiPr})Cl_2]_2$	6	6	55	7	3	5:1
2	Pd[(−)-sparteine]Cl_2	6	6	55	70	42	22:1
3	Pd[(−)-sparteine]Cl_2	20	6	55	58	45	19:1
4	Pd[(−)-sparteine]Cl_2	20	0.5	55	96	63	>99:1
5	Pd[(−)-sparteine]Cl_2	20	0.5	75	>99	76	25:1

[a] Measured by GC using an internal standard. [b] GC yield using an internal standard.

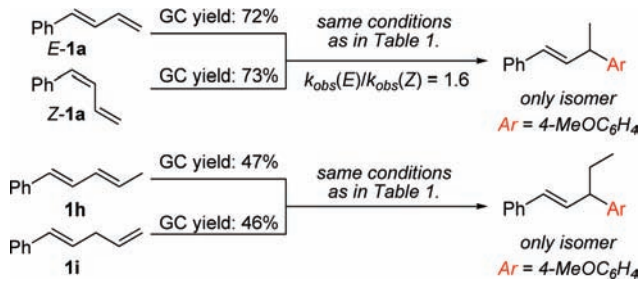
With this optimized catalyst system in hand, the substrate scope was explored (Table 2). First, the nature of the arylboronic ester was evaluated using diene **1a** (products **3a**−**h**). Isolated yields were generally good to excellent, and all of the reactions were highly regioselective for the 1,2-addition product (>95:5 by ^{1}H NMR). *o*-Substitution is allowed (**3b**), while the electronic nature of the boronic ester has a minimal impact on the yield of the reaction, in contrast to our previous reports (**3c**−**h**).[6c] This is highlighted by the incorporation of an ester (**3e**), a nitrile (**3g**), and an acid-sensitive acetal group (**3h**). Several substituted diene derivatives in the reaction with boronic ester **2a** were also examined. Moderate to good yields were achieved with simple hydrocarbons (**3i**−**l**). An electron-rich aryl-substituted diene gave the corresponding product in high yield (**3m**), and a TBS protected alcohol was tolerated using this catalyst system, giving the product in excellent yield (**3n**). It should be noted that acceptable yields were found only when using arylboronic esters.

Table 2. Substrate Scope[a]



[a] Yields are average isolated yields of at least two experiments. A >95:5 ratio of the 1,2- to 1,4-hydroarylation products was measured by ^{1}H NMR spectroscopy.

Scheme 2. Reactions To Probe the Intermediacy of a π-Allyl Pd Species



Classically, addition to π-allyl palladium complexes leads to a mixture of α- (1,2-addition in our case) and γ-coupled products.[10] The observation that high selectivity for the 1,2-addition product was found is not only synthetically attractive but also prompted us to investigate the intermediacy of a π-allyl Pd species. Therefore, a series of reactions was carried out. First, both stereochemically pure *Z* and *E* diene isomers of **1a** were submitted to the reaction conditions (Scheme 2). Although the observed rate of conversion for the *E* isomer was 1.6 times higher than that of the *Z* isomer, both led to only a single isomeric product, suggesting a π-allyl Pd intermediate. The *Z* isomer did not appreciably form the *E* isomer under the reaction conditions. Second, the reactions of conjugated diene **1h** and skipped diene **1i** both gave the same hydroarylation product, again consistent with a presumed π-allyl Pd intermediate. Conversion of **1i** to ∼10% **1h** was found by GC during the reaction, consistent with the formation of a Pd hydride. Finally, an experiment was carried out in which diene **1a** was mixed with Pd[(−)-sparteine]Cl_2 in the presence of isopropyl alcohol for 1 h at 60 °C, wherein a composition consistent with the [(−)-sparteine]Pd^{II}(π-allyl)(Cl) complex was confirmed by ESI-HRMS.[11]

To probe the nature of the high 1,2-selectivity, simple-hydrocarbon-substituted 1,3-dienes with differential steric impact were evaluated. Dienes with smaller substituents led to a poorer ratio of 1,2- to 1,4-addition products, although the formation of both is indicative of a π-allyl Pd intermediate (Figure 1). To confirm that the selectivity has a steric origin, the logarithm of the ratio of regioisomers was correlated to the Charton steric values of the

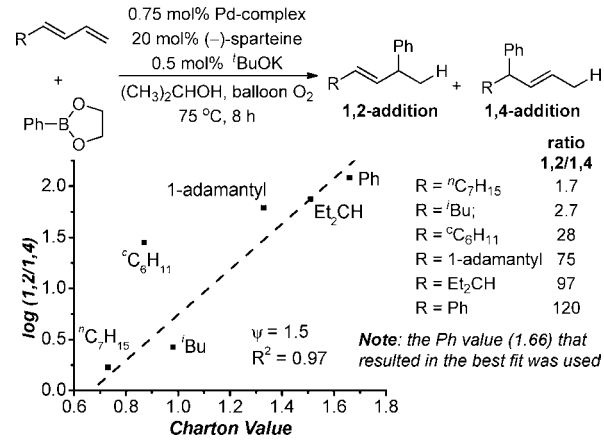


Figure 1. Linear free-energy relationship between Charton steric parameters and the logarithm of the ratio of regioisomers (1,2- to 1,4-addition).

substituents on the dienes.[12] A linear free-energy relationship was observed, consistent with steric effects dominating the selectivity in this reaction (Figure 1). However, the substrate containing a cyclohexyl substituent clearly did not fit in the correlation, and the reason for this is not obvious.

In summary, we have developed a novel approach for the hydroarylation of 1,3-dienes by accessing π-allyl intermediates directly using a coupled aerobic alcohol oxidation to access a Pd hydride. The scope of the process shows wide tolerance of functional groups on the boronic ester and on the diene. Moreover, high selectivity was observed for the 1,2-addition product and has been shown to have a steric origin. Although an enantioenriched chiral ligand was used in this chemistry, only poor enantioselectivity was achieved (<20% ee). Therefore, future work will be focused on identification of new ligand classes to promote this reaction with high enantioselectivity.

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Supporting Information Available: Experimental procedures and characterization data for substances. This material is available free of charge via the Internet at http://pubs.acs.org.

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