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Palladium(II)-catalyzed γ -selective hydroarylation of alkenyl carbonyl compounds with arylboronic acids†

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A catalytic γ -selective *syn*-hydroarylation of alkenyl carbonyl compounds using arylboronic acids has been developed using a substrate directivity approach with a palladium(II) catalyst. This method tolerates a wide range of functionalized (hetero)arylboronic acids and a variety of substitution patterns on the alkene. Preliminary mechanistic studies suggest that transmetalation is rate-limiting.

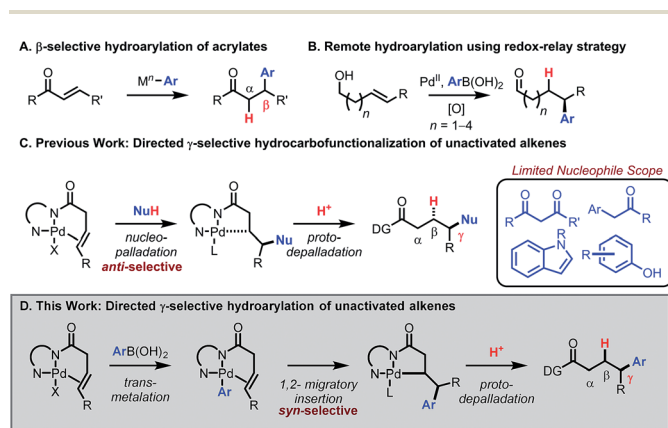
Introduction

Transition-metal catalyzed 1,4-addition of arylboronic acids to enones and related conjugated alkenes has emerged as a reliable and robust method to introduce an aryl group at the β position of a carbonyl compound or functional group equivalent. In 1997 Miyaura reported a seminal study describing Rh(I)-catalyzed β -selective hydroarylation of enones using arylboronic acids (Scheme 1A).¹ In 1998, Miyaura and Hayashi reported an asymmetric version of this reaction.² Since then,

Hayashi has reported an array of β -selective hydroarylation methods for many classes of alkenes in conjugation with electron-withdrawing groups, including esters,³ aldehydes,⁴ phosphonates,⁵ and sulfonyls.⁶ Hayashi has also achieved δ -selective functionalization by utilizing conjugation in $\alpha,\beta,\gamma,\delta$ -unsaturated systems.^{7,8} However, expanding this mode of reactivity to C–C π bonds remote from and out of conjugation with a carbonyl group (*e.g.*, the γ -position) remains a challenge.⁹ Notably, Sigman and co-workers have recently developed a powerful toolkit of remote arylation reactions to access enantioenriched arylated aldehydes from alkenyl alcohols using a redox-relay strategy (Scheme 1B).^{10,11} The goal of the present study was to develop a redox-neutral method for γ -selective hydroarylation of β,γ -unsaturated carboxylic acid derivatives with arylboronic acids using a substrate directivity approach, a mode of reactivity that would complement existing methods.¹²

Previously, our group^{13–18} and others^{19,20} have developed a suite of chelation-controlled regioselective alkene functionalization reactions using Daugulis's 8-aminoquinoline (AQ)^{21,22} directing group under palladium(II) catalysis. With 3-butenic-acid-derived substrates, the AQ directing group forces an incoming nucleophile to attack the γ -position to form the preferred five-membered palladacycle. The intermediate then reacts with an electrophile to yield the hydro- or difunctionalized product. In particular, the hydrocarbofunctionalization of 3-butenic acid derivatives using various carbon nucleophiles has been reported (Scheme 1C).^{14,19b} Thus far, nucleophile scope has been limited to 1,3-dicarbonyls, aryl carbonyls, indoles, phenols, and related nucleophiles capable of engaging in a Wacker-type *anti*-nucleopalladation mechanism. The addition of general aryl nucleophiles in this mode of catalysis remains an unmet challenge.²⁰

Given the vast structural diversity of arylboronic acids and their widespread commercial availability, we sought to achieve analogous reactivity with this family of nucleophiles. We

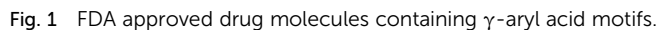


Scheme 1 Past and current work in C–C π -bond hydrocarbofunctionalization.

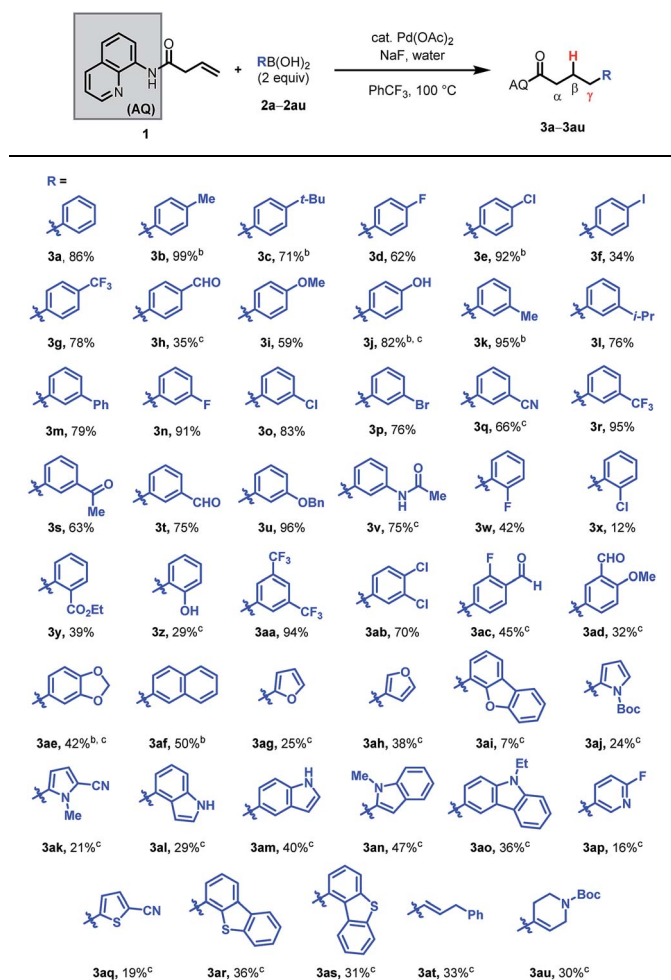
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Table 2 Boronic acid scope^a

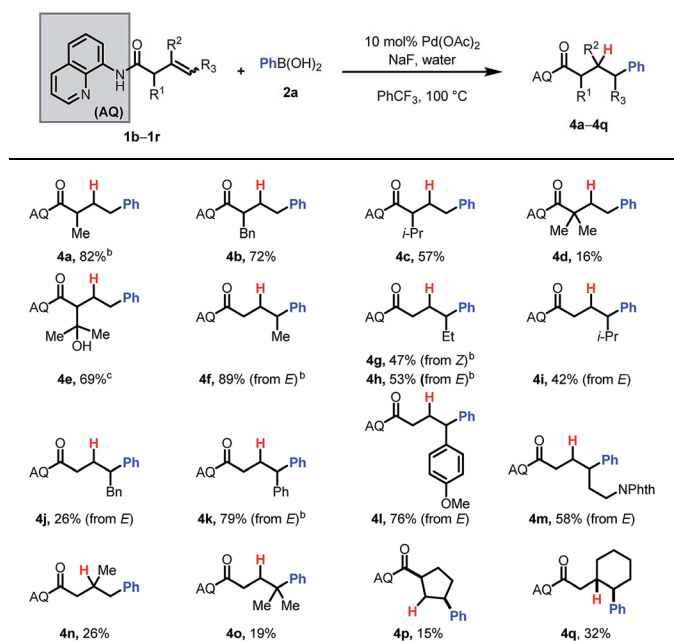
^a Reaction conditions: **1a** (0.1 mmol), **2a-2at** (0.2 mmol), Pd(OAc)₂ (10 mol%), NaF (0.2 mmol), var. water in PhCF₃ (0.1 mL), 100 °C, 12 h. All percentages correspond to isolated yields. ^b 80 °C. ^c In 1 : 4 *t*-BuOH : PhCF₃ (0.1 mL).

hydroarylation, the AQ directing group was readily cleaved to yield the free acid **6a** in 94% yield (Scheme 2B). Deprotection using Maulide's milder ozonolysis conditions was also viable, providing free acid **6b**, albeit in lower yield (Scheme 2B).²⁶

Finally, a preliminary result indicates that this approach can also be extended to alkyl coupling partners. Using slightly modified conditions with methylboronic acid as the nucleophile, we were able to observe formation of the desired hydro-methylation product in 18% yield (Scheme 3). This is a promising finding for future expansion of the reaction scope.

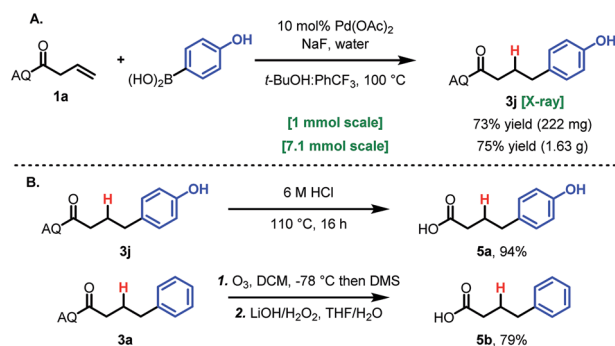
Mechanistic studies

The broad scope of this transformation combined with the critical role of water stoichiometry in catalytic efficiency prompted us to perform several experiments to shed light on key aspects of the reaction mechanism.

Table 3 Alkene scope^a

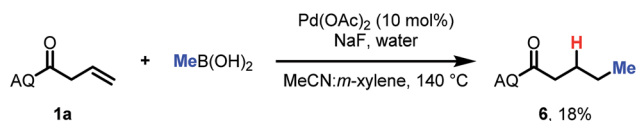
^a Reaction conditions: **1b-1r** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (10 mol%), NaF (0.2 mmol), water (0.25 mmol) in PhCF₃ (0.1 mL), 100 °C, 12 h. All percentages correspond to isolated yields. ^b 80 °C. ^c In 1 : 4 *t*-BuOH : PhCF₃ (0.1 mL).

To identify the origin of the hydrogen atom in the hydroarylated product, deuterium incorporation studies were performed using deuterated reaction components. First, we sought to probe potential H/D exchange reactivity of the starting material and product. When starting material **1a** was subjected to reaction conditions using D₂O in place of H₂O, H/D exchange was observed exclusively at the alkenyl position (Scheme 4A).²⁷ In contrast, H/D exchange with the hydroarylated product **3a** was not observed (Scheme 4B). When alkene **1a** was then subjected to the standard reaction conditions with D₂O, a mixture of bis-protio, mono-protio-mono-deutero, and bis-deutero products was obtained (Scheme 4C). The formation of bis-deutero product combined with the observation that the product does not undergo H/D exchange establishes that water

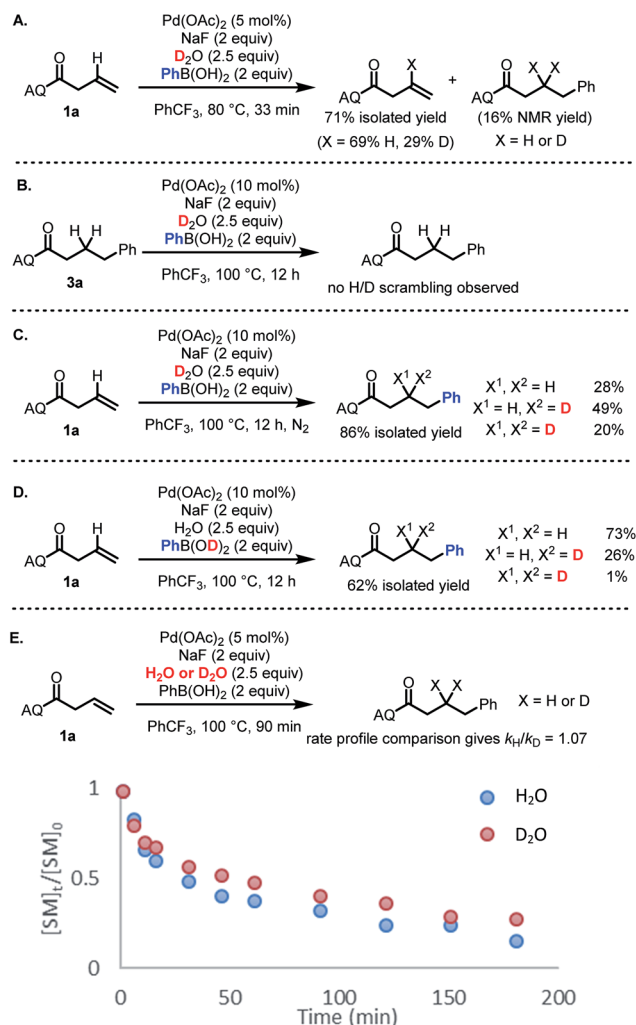


Scheme 2 Large-scale synthesis and deprotection.





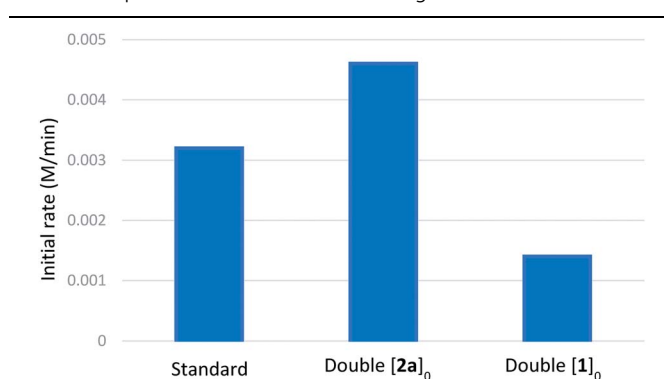
Scheme 3 Preliminary result for alkyl boronic acids.



Scheme 4 Deuterium-labeling studies.

is a competent source of protons/deuterons, consistent with a protodepalladation mechanism.

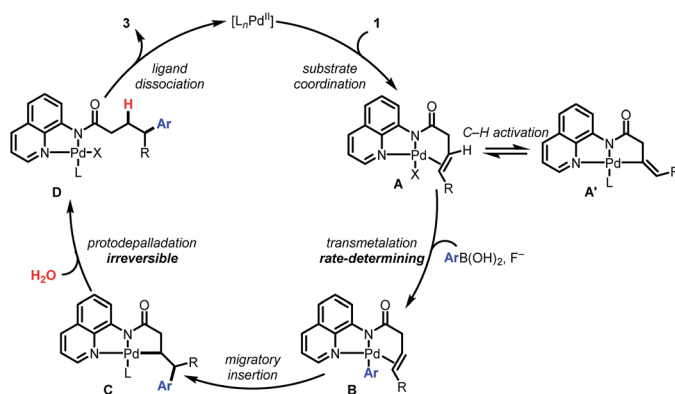
Interestingly, upon using $\text{PhB}(\text{OD})_2$ as the source of deuterons, the reaction gave a dramatically different product distribution, suggesting that while there is some H/D exchange between the boronic acid and reaction medium, not all protons/deuterons in the reaction system are in equilibrium (Scheme 4D). Finally, a comparison of global rate profile between reactions using H_2O versus D_2O gave $k_{\text{H}}/k_{\text{D}} = 1.07$ (Scheme 4E). If protodepalladation were the rate-determining step, we would expect to see a larger KIE (even factoring in the possibility of exchangeable protons/deuterons),²⁸ suggesting that protodepalladation is not the rate-determining step in the present catalytic cycle.

Table 4 Dependence of initial rate on reagent concentration^a

^a Standard conditions: $[\mathbf{1a}]_0 = 0.1 \text{ M}$; $[\mathbf{2a}]_0 = 0.2 \text{ M}$; $[\text{Pd}(\text{OAc})_2] = 0.01 \text{ M}$; $[\text{NaF}] = 0.2 \text{ M}$; $[\text{H}_2\text{O}] = 0.25 \text{ M}$; solvent = PhCF_3 ; 100 °C.

We then performed reaction progress kinetic analysis (RPKA), which is a powerful method to determine the driving forces of a reaction from a minimal number of experiments.²⁹ Same-excess experiments indicated that catalyst deactivation takes place during the reaction and that there is some degree of product inhibition (see ESI†). The general form of the kinetic profiles (as can be seen in the representative cases of the H versus D rate profiles, Scheme 4E), shows a sharp transition between a faster initial rate and a slower rate at higher conversions, which often indicates catalyst deactivation. A plausible pathway for catalyst deactivation is arylboronic acid homocoupling to generate catalytically inactive palladium(0). Indeed, biphenyl was observed by GC-FID during kinetic experiments. A series of different-excess experiments were also performed to determine the orders of the various reactants (summarized in Table 4, see ESI† for complete rate profiles). These experiments indicated positive order in $[\mathbf{2a}]$ and negative order in $[\mathbf{1a}]$ (see ESI†). Burés's graphical method³⁰ was used to compare rate profiles from experiments with different catalyst amounts, and the results suggested that the reaction is first-order in palladium (see ESI†).

Collectively the above experimental observations are consistent with the catalytic cycle depicted in Scheme 5. The $\text{Pd}(\text{II})$ catalyst coordinates to the AQ directing group to generate



Scheme 5 Proposed catalytic cycle.



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- 6 The annual sales for Januvia® (Sitagliptin) can be found at <http://investors.merck.com/news/press-release-details/2017/Merck-Announces-Fourth-Quarter-and-Full-Year-2016-Financial-Results>.
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