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# Palladium(II)-catalyzed $\gamma$ -selective hydroarylation of alkenyl carbonyl compounds with arylboronic acids†

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A catalytic  $\gamma$ -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.

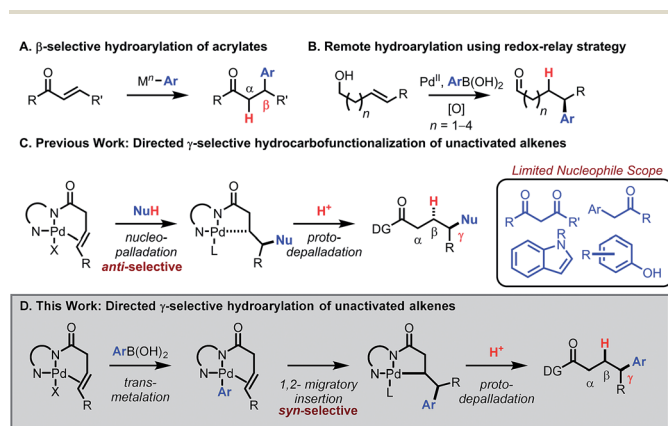
## Introduction

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  $\beta$  position of a carbonyl compound or functional group equivalent. In 1997 Miyaura reported a seminal study describing Rh(I)-catalyzed  $\beta$ -selective hydroarylation of enones using arylboronic acids (Scheme 1A).<sup>1</sup> In 1998, Miyaura and Hayashi reported an asymmetric version of this reaction.<sup>2</sup> Since then,

Hayashi has reported an array of  $\beta$ -selective hydroarylation methods for many classes of alkenes in conjugation with electron-withdrawing groups, including esters,<sup>3</sup> aldehydes,<sup>4</sup> phosphonates,<sup>5</sup> and sulfonyls.<sup>6</sup> Hayashi has also achieved  $\delta$ -selective functionalization by utilizing conjugation in  $\alpha,\beta,\gamma,\delta$ -unsaturated systems.<sup>7,8</sup> However, expanding this mode of reactivity to C–C  $\pi$  bonds remote from and out of conjugation with a carbonyl group (*e.g.*, the  $\gamma$ -position) remains a challenge.<sup>9</sup> 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).<sup>10,11</sup> The goal of the present study was to develop a redox-neutral method for  $\gamma$ -selective hydroarylation of  $\beta,\gamma$ -unsaturated carboxylic acid derivatives with arylboronic acids using a substrate directivity approach, a mode of reactivity that would complement existing methods.<sup>12</sup>

Previously, our group<sup>13–18</sup> and others<sup>19,20</sup> have developed a suite of chelation-controlled regioselective alkene functionalization reactions using Daugulis's 8-aminoquinoline (AQ)<sup>21,22</sup> directing group under palladium(II) catalysis. With 3-butenic acid-derived substrates, the AQ directing group forces an incoming nucleophile to attack the  $\gamma$ -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).<sup>14,19b</sup> 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.<sup>20</sup>

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  $\pi$ -bond hydrocarbofunctionalization.

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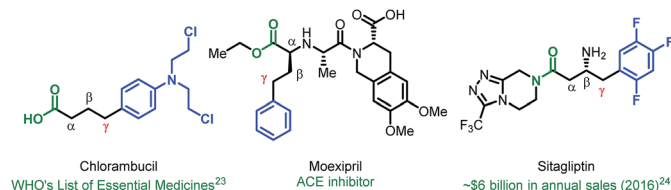


Fig. 1 FDA approved drug molecules containing  $\gamma$ -aryl acid motifs.

envisioned that such a transformation would be useful given that the  $\gamma$ -aryl carboxylic acid motif is found in multiple FDA-approved drugs (e.g., chlorambucil, moexipril and sitagliptin, Fig. 1). The proposed approach would allow such molecules to be synthesized in a modular fashion using synthetic logic that is appealing to medicinal chemists and would allow for facile synthesis of analogues.

Moreover, we envisioned that after substrate coordination, the complex would undergo transmetalation with the arylboronic acid, allowing for mechanistically distinct Heck-type *syn*-selective delivery of the aryl group *via* 1,2-migratory insertion. Afterwards, the intermediate would undergo protodepalladation to yield the  $\gamma$ -arylated product (Scheme 1D).

## Results and discussion

Based on our past work, we initiated our investigation using AQ-masked 3-butenic acid (**1a**) as the pilot alkene and phenylboronic acid as the nucleophile. Gratifyingly, we were able to observe the desired hydroarylated product in 27% yield under acidic conditions (Table 1, entry 1). Notably, during preliminary screening we found that AQ out-performed various alternative directing groups (see ESI†). Hence, subsequent optimization

focused on AQ-containing alkene **1a**. Aromatic solvents were found to be beneficial for the reaction and could be used in combination with common polar solvents (entry 2). Various acids and bases were then screened, leading to the identification of NaF as a comparable alternative to benzoic acid as a promoter (entries 2–6). Interestingly, other fluoride bases did not have a similarly beneficial effect on the reaction (entries 3 and 4). Switching to 100% *m*-xylene as solvent and lowering the concentration improved the mass balance (entry 7).

Further optimization of reaction temperature and time, and rescreening of aromatic solvents led to 91% yield of the desired product with NaF in 0.1 M benzotrifluoride (entries 8–10). Decreased catalyst loading lowered the yield and conversion (entry 11). When the reaction was run in toluene, the yield decreased substantially, illustrating the importance of the trifluoromethyl group on benzotrifluoride, perhaps for increased polarity (entry 12). Among several arylboron reaction partners that were attempted (see ESI†), only triphenylboroxine behaved similarly to phenylboronic acid (see ESI†). Boronic esters, on the other hand, did not lead to formation of the desired product.

Having optimized the reaction, we proceeded to investigate the substrate scope and functional group tolerance.<sup>25</sup> As commercial boronic acids can contain varying amounts of water, for each example we screened 0, 1.5, or 2.5 equivalents of water to find the optimal amount (see ESI†). Additionally, some boronic acids with polar functional groups were found to be visibly insoluble in benzotrifluoride. In these cases, a 1 : 4 mixture of *t*-BuOH and benzotrifluoride was effective (see ESI†).

The reaction was found to tolerate an array of functional groups on the aromatic ring of the boronic acid, including both electron-donating and -withdrawing substituents, in both the *para* and *meta* positions (Table 2, **3b–3v**). Substituents in the *ortho* position led to diminished yields, presumably due to steric effects, yet in most cases yields were still moderate (**3w–z**). Our method also tolerated multi-substituted benzenes (**3aa–3ad**), protected catechols (**3ae**), naphthalenes (**3af**), various heterocycles including furans, protected pyrroles, and indoles (**3ag–3as**), and alkenylboronic acids (**3at, 3au**). Though pyridine-type heterocycles were not generally compatible, 6-fluoro-3-pyridinylboronic acid was an exception and provided 16% yield (**3ap**).

We then probed the alkene scope for our method. Substituents on the  $\alpha$ -position were generally well tolerated (Table 3, **4a–e**). Internal alkenes were also compatible, providing moderate to good yield (**4f–4m**). Other sterically hindered alkenes, such as 1,1-disubstituted alkenes (**4n**) and trisubstituted alkenes (**4o**) were reactive, albeit in low yields. Alcohols and protected amines on the substrate did not exhibit an inhibitory effect on the transformation (**4e, 4m**). When cyclic substrates were subjected to the reaction conditions, the corresponding *syn*-hydroarylated products were exclusively formed (**4p, 4q**).

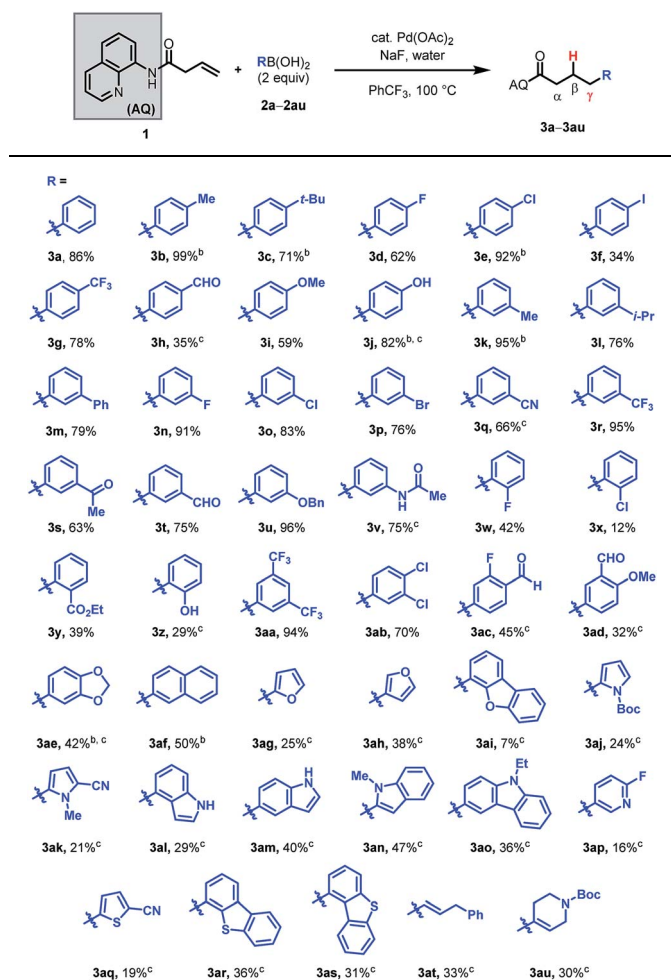
To demonstrate the practicality and utility of this method, two large-scale reactions were performed. When run on 1 mmol scale or 7.1 mmol scale (1.5 g), the reaction gave comparable yields to the small-scale reaction (Scheme 2A). After

Table 1 Reaction optimization<sup>a</sup>

	Acid/base	Solvent	Temp	<b>1a</b>	<b>3a</b>
1	PhCO <sub>2</sub> H	MeCN (0.5 M)	120 °C	5%	27%
2	PhCO <sub>2</sub> H	1 : 1 MeCN : <i>m</i> -xylene (0.5 M)	120 °C	3%	58%
3 <sup>b</sup>	KF	1 : 1 MeCN : <i>m</i> -xylene (0.5 M)	120 °C	39%	22%
4 <sup>b</sup>	CsF	1 : 1 MeCN : <i>m</i> -xylene (0.5 M)	120 °C	51%	12%
5 <sup>b</sup>	Na <sub>2</sub> CO <sub>3</sub>	1 : 1 MeCN : <i>m</i> -xylene (0.5 M)	120 °C	52%	11%
6 <sup>b</sup>	NaF	1 : 1 MeCN : <i>m</i> -xylene (0.5 M)	120 °C	6%	56%
7	NaF	<i>m</i> -xylene (0.1 M)	120 °C	41%	40%
8 <sup>c</sup>	NaF	<i>m</i> -xylene (0.1 M)	80 °C	37%	55%
9 <sup>c</sup>	PhCO <sub>2</sub> H	<i>m</i> -xylene (0.1 M)	80 °C	93%	3%
10 <sup>d</sup>	NaF	PhCF <sub>3</sub> (0.1 M)	100 °C	0%	91%
11 <sup>d,e</sup>	NaF	PhCF <sub>3</sub> (0.1 M)	100 °C	39%	63%
12 <sup>d</sup>	NaF	Toluene (0.1 M)	100 °C	33%	58%

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)<sub>2</sub> (10 mol%), acid or base (2 equiv.), water (2.5 equiv.), solvent, temperature, 5 h. <sup>b</sup> Base (1 equiv.). <sup>c</sup> 24 h. <sup>d</sup> 12 h. <sup>e</sup> 5% catalyst loading.



Table 2 Boronic acid scope<sup>a</sup>

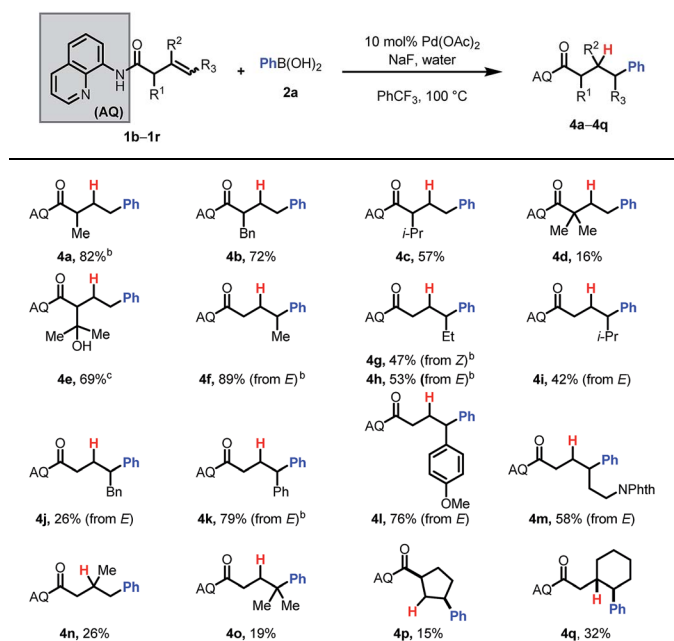
<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2a–2at** (0.2 mmol), Pd(OAc)<sub>2</sub> (10 mol%), NaF (0.2 mmol), var. water in PhCF<sub>3</sub> (0.1 mL), 100 °C, 12 h. All percentages correspond to isolated yields. <sup>b</sup> 80 °C. <sup>c</sup> In 1 : 4 *t*-BuOH : PhCF<sub>3</sub> (0.1 mL).

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).<sup>26</sup>

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.

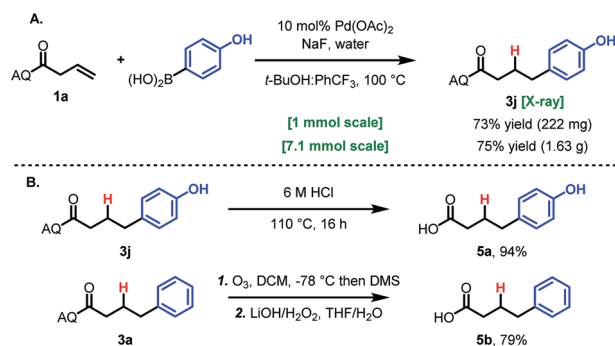
## Mechanistic studies

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<sup>a</sup>

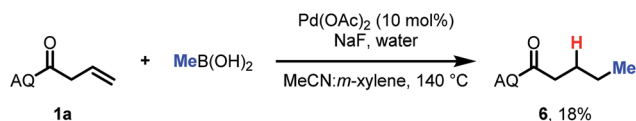
<sup>a</sup> Reaction conditions: **1b–1r** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)<sub>2</sub> (10 mol%), NaF (0.2 mmol), water (0.25 mmol) in PhCF<sub>3</sub> (0.1 mL), 100 °C, 12 h. All percentages correspond to isolated yields. <sup>b</sup> 80 °C. <sup>c</sup> In 1 : 4 *t*-BuOH : PhCF<sub>3</sub> (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 D<sub>2</sub>O in place of H<sub>2</sub>O, H/D exchange was observed exclusively at the alkenyl position (Scheme 4A).<sup>27</sup> 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 D<sub>2</sub>O, 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

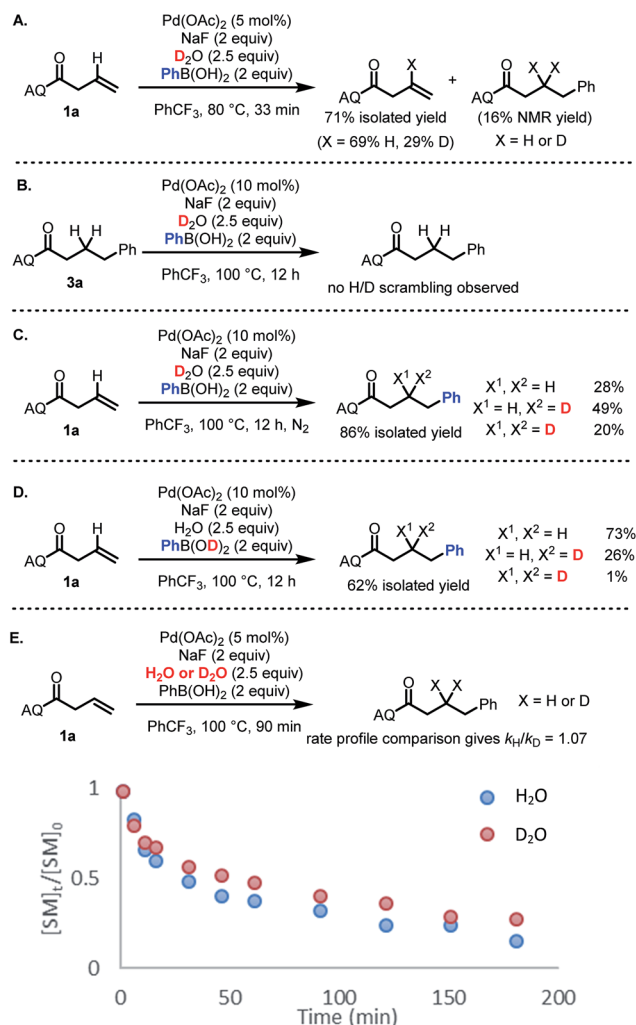


Scheme 2 Large-scale synthesis and deprotection.





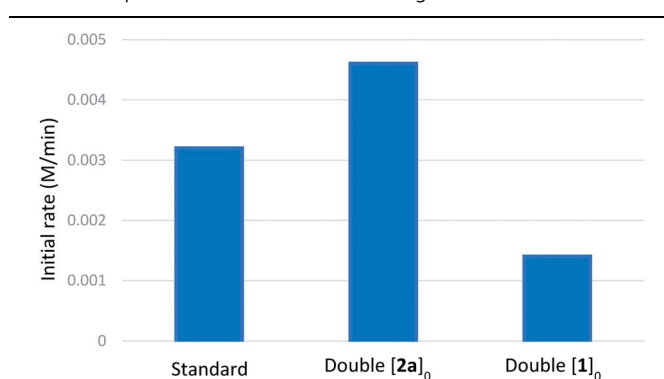
Scheme 3 Preliminary result for alkyl boronic acids.



Scheme 4 Deuterium-labeling studies.

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

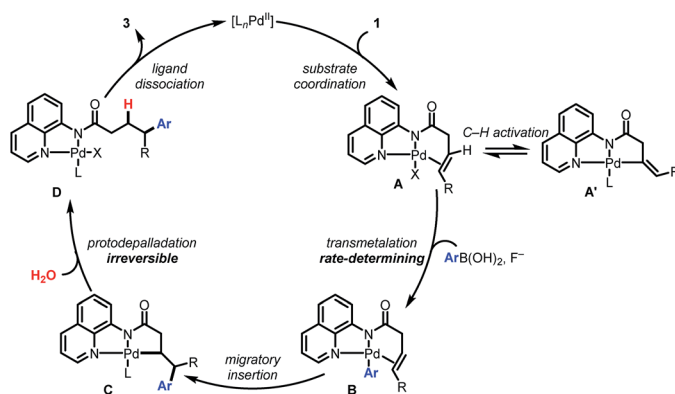
Interestingly, upon using  $\text{PhB}(\text{OD})_2$  as the source of deuterons, the reaction gave a dramatically different product distribution, suggesting that while there is some H/D exchange between the boronic acid and reaction medium, not all protons/deuterons in the reaction system are in equilibrium (Scheme 4D). Finally, a comparison of global rate profile between reactions using  $\text{H}_2\text{O}$  versus  $\text{D}_2\text{O}$  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),<sup>28</sup> suggesting that protodepalladation is not the rate-determining step in the present catalytic cycle.

Table 4 Dependence of initial rate on reagent concentration<sup>a</sup>

<sup>a</sup> 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 =  $\text{PhCF}_3$ ; 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.<sup>29</sup> 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 method<sup>30</sup> 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.



A. The observed H/D scrambling in **1a** (Scheme 4A) and the negative order in [**1a**] are consistent with the formation of an off-cycle complex **A'** via C(alkenyl)–H activation. Intermediate **A** reacts via base-promoted, rate-controlling transmetalation to form the aryl palladium complex **B** which then undergoes syn-selective 1,2-migratory insertion to form Pd(II) complex **C**. An irreversible protodepalladation step involving water gives product-bound palladium complex **D**, which dissociates to release the product and regenerate the catalyst.

## Conclusions

In conclusion, we have developed a regioselective hydroarylation of 3-butenic acid derivatives using readily available arylboronic acids and a removable 8-aminoquinoline directing group. Unlike previous methods that utilize *anti*-nucleopalladation, this reaction proceeds via transmetalation and *syn*-insertion. This reactivity paradigm dramatically broadens the range of nucleophiles that can be employed and allows for the preparation of diastereoisomeric products that are distinct from previous methods. The reaction was found to tolerate a wide range of substituents and functional groups on the boronic acid and was completely regio- and stereoselective. This method can also be run on larger scales without significant decrease in yield, and facile removal of the directing group was also demonstrated. Future investigation will focus on expanding the scope to include more alkenyl and alkyl boronic acids.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

- M. Sakai, H. Hayashi and N. Miyaoura, *Organometallics*, 1997, **16**, 4229.
- Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai and N. Miyaoura, *J. Am. Chem. Soc.*, 1998, **120**, 5579.
- Y. Takaya, T. Senda, H. Kurushima, M. Ogasawara and T. Hayashi, *Tetrahedron: Asymmetry*, 1999, **10**, 4047.
- T. Hayashi, N. Tokunaga, K. Okamoto and R. Shintani, *Chem. Lett.*, 2005, **34**, 1480.
- T. Hayashi, T. Senda, Y. Takaya and M. Ogasawara, *J. Am. Chem. Soc.*, 1999, **121**, 11591.
- T. Nishimura, Y. Takiguchi and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 9086.
- T. Hayashi, S. Yamamoto and N. Tokunaga, *Angew. Chem., Int. Ed.*, 2005, **44**, 4224.
- T. Nishimura, Y. Yasuhara and T. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 5164.
- For representative reports on Pd(II)-catalyzed  $\beta$ -selective hydroarylation using arylboronic acids, see: (a) T. Nishikata, Y. Yamamoto, I. D. Gridnev and N. Miyaoura, *Organometallics*, 2005, **24**, 5025; (b) T. Nishikata, Y. Yamamoto and N. Miyaoura, *Adv. Synth. Catal.*, 2007, **349**, 1759; (c) T. Nishikata, Y. Yamamoto and N. Miyaoura, *Angew. Chem., Int. Ed.*, 2003, **42**, 2768; (d) X. Lu and S. Lin, *J. Org. Chem.*, 2005, **70**, 9651; (e) B. Zhao and X. Lu, *Org. Lett.*, 2006, **8**, 5987; (f) F. Gini, B. Hessen and A. J. Minnaard, *Org. Lett.*, 2005, **7**, 5309; (g) K. Kikushima, J. C. Holder, M. Gatti and B. M. Stoltz, *J. Am. Chem. Soc.*, 2011, **133**, 6902; (h) A. L. Gottumukkala, K. Matcha, M. Lutz, J. G. de Vries and A. J. Minnaard, *Chem.-Eur. J.*, 2012, **18**, 6907; (i) F. Wang, F. Chen, M. Qu, T. Li, Y. Liu and M. Shi, *Chem. Commun.*, 2013, **49**, 3360; (j) Q. He, F. Xie, G. Fu, M. Quan, C. Shen, G. Yang, I. D. Gridnev and W. Zhang, *Org. Lett.*, 2015, **17**, 2250; (k) S. Chen, L. Wu, Q. Shao, G. Yang and W. Zhang, *Chem. Commun.*, 2018, **54**, 2522.
- E. W. Werner, T.-S. Mei, A. J. Burckle and M. S. Sigman, *Science*, 2012, **338**, 1455.
- T.-S. Mei, E. W. Werner, A. J. Burckle and M. S. Sigman, *J. Am. Chem. Soc.*, 2013, **135**, 6830.
- For representative recent reports on alternative catalytic approaches to alkene hydroarylation, see: (a) S. M. Podhajsky, Y. Iwai, A. Cook-Sneathen and M. S. Sigman, *Tetrahedron*, 2011, **67**, 4435; (b) Y. Schramm, M. Takeuchi, K. Semba, Y. Nakao and J. F. Hartwig, *J. Am. Chem. Soc.*, 2015, **137**, 12215; (c) K. Semba, K. Ariyama, H. Zheng, R. Kameyama, S. Sakaki and Y. Nakao, *Angew. Chem., Int. Ed.*, 2016, **55**, 6275; (d) S. A. Green, J. L. M. Matos, A. Yagi and R. A. Shenvi, *J. Am. Chem. Soc.*, 2016, **138**, 12779; (e) S. D. Friis, M. T. Pirnot, L. N. Dupuis and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2017, **56**, 7242; (f) L.-J. Xiao, L. Cheng, W.-M. Feng, M.-L. Li, J.-H. Xie and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2018, **57**, 461.
- J. A. Gurak Jr, K. S. Yang, Z. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2016, **138**, 5805.
- K. S. Yang, J. A. Gurak Jr, Z. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2016, **138**, 14705.
- Z. Liu, T. Zeng, K. S. Yang and K. M. Engle, *J. Am. Chem. Soc.*, 2016, **138**, 15122.
- J. A. Gurak Jr, V. T. Tran, M. M. Sroda and K. M. Engle, *Tetrahedron*, 2017, **73**, 3636.
- Z. Liu, Y. Wang, Z. Wang, T. Zeng, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2017, **139**, 11261.
- Z. Liu, H.-Q. Ni, T. Zeng and K. M. Engle, *J. Am. Chem. Soc.*, 2018, **140**, 3223.
- (a) E. P. A. Talbot, T. d. A. Fernandes, J. M. McKenna and F. D. Toste, *J. Am. Chem. Soc.*, 2014, **136**, 4101; (b)



- H. Wang, Z. Bai, T. Jiao, Z. Deng, H. Tong, G. He, Q. Peng and G. Chen, *J. Am. Chem. Soc.*, 2018, **140**, 3542.
- 20 Two related studies were disclosed while this manuscript was in revision. For a report using nickel(0) catalysis, see: (a) H. Lv, L.-J. Xiao, D. Zhao and Q.-L. Zhou, *Chem. Sci.*, 2018, **9**, 6839. For a reductive Heck approach, see: (b) C. Wang, G. Xiao, T. Guo, Y. Ding, X. Wu and T.-P. Loh, *J. Am. Chem. Soc.*, 2018, **140**, 9332.
- 21 For a representative review, see: O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074.
- 22 For representative reports on Pd(II)-catalyzed directed  $\gamma$ -arylation of carbonyl compounds *via* C(sp<sup>3</sup>)-H activation, see: (a) B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391; (b) G. He, S.-Y. Zhang, W. A. Nack, R. Pearson, J. Rabb-Lynch and G. Chen, *Org. Lett.*, 2014, **16**, 6488; (c) A. Dey, S. Pimparkar, A. Deb, S. Guin and D. Maiti, *Adv. Synth. Catal.*, 2017, **359**, 1301.
- 23 The 2017 WHO Essential Medicines List can be found at <http://www.who.int/medicines/publications/essentialmedicines/en/>.
- 24 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>.
- 25 For low-yielding examples, the reactions typically only reached low conversion. In these cases, roughly 90% of the material could be accounted for as starting alkene (1) or product (3); the remaining material (approximately 10%) was consumed *via* alkene reduction.
- 26 M. Berger, R. Chauhan, C. A. B. Rodrigues and N. Maulide, *Chem.-Eur. J.*, 2016, **22**, 16805.
- 27 For an example of similar reactivity involving a six-membered palladacycle, see: M. Liu, P. Yang, M. K. Karunananda, Y. Wang, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2018, **140**, 5805.
- 28 J. Derosa, A. L. Cantu, M. N. Boulous, M. L. O'Duill, J. L. Turnbull, Z. Liu, D. M. De La Torre and K. M. Engle, *J. Am. Chem. Soc.*, 2017, **139**, 5183.
- 29 D. G. Blackmond, *Angew. Chem., Int. Ed.*, 2005, **44**, 4302.
- 30 J. Burés, *Angew. Chem., Int. Ed.*, 2016, **55**, 2028.

