Organic Process Research & Development

Review

pubs.acs.org/OPRD

Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to α,β-Unsaturated Cyclic Electrophiles

Samantha E. Shockley, Jeffrey C. Holder, and Brian M. Stoltz*

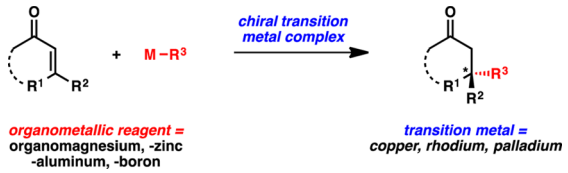
The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

ABSTRACT: This account describes our laboratory's efforts in the development of a palladium-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic conjugate acceptors. Specifically, we highlight the study of this transformation in the following areas: (a) construction of all-carbon quaternary stereocenters, (b) elucidation of the reaction mechanism, (c) addition to heterocyclic acceptors to generate tertiary stereocenters, and (d) application in the synthesis of natural products.

1. INTRODUCTION

Asymmetric conjugate addition has become a powerful synthetic tool for the assembly of structurally complex molecules.[1] Recently, new developments in this transformation have served as solutions to the persistent challenge of the catalytic, enantioselective synthesis of all-carbon quaternary stereocenters (Scheme 1).[2] To date, copper catalysis has dominated the field of asymmetric conjugate addition; however, these copper-catalyzed methods require the use of highly reactive organometallic reagents (e.g., diorganozinc,[3] triorganoaluminum,[4] and organomagnesium[5] reagents). Thus, these reactions typically require rigorously anhydrous reaction conditions and often operate at cryogenic temperatures. Alternatively, chiral rhodium catalysts in combination with air-stable, easily handled organoboron reagents have been shown to produce a wide array of conjugate addition adducts in very high yield and ee.[6−8] Although extremely effective, these rhodium catalysts are expensive and air-sensitive, and many of the most widely used precatalysts are not commercially available. Additionally, rhodium-catalyzed conjugate additions to form quaternary stereocenters require boroxine or tetraarylborate reagents and do not proceed with simple, widely available arylboronic acids. Furthermore, large excesses of the boron reagents are necessary to drive the reactions to completion. These factors diminish the appeal of such rhodium-catalyzed methods in complex molecule synthesis where custom aromatic units are often desired and thus the arene material is of high value.[8,9]

Scheme 1. Transition Metal Catalyzed Asymmetric Conjugate Addition

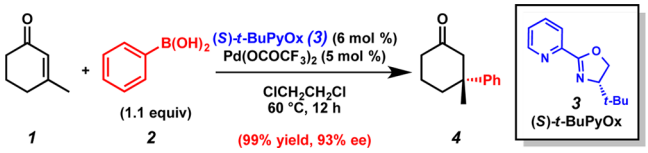


Palladium-catalyzed conjugate addition reactions are considerably less developed than those using copper and rhodium but offer significant advantages. For example, palladium-catalyzed conjugate addition reactions utilize air-stable and functional group-tolerant boron nucleophiles, which are commercially available. Furthermore, the reactions are typically not sensitive to water or oxygen. Together, these features comprise an operationally simple and robust transformation.[10] At the time we began our work in this area, there were only examples of the asymmetric synthesis of *tertiary* stereocenters in the palladium literature and a single report of the synthesis of quaternary stereocenters, albeit as a racemate.[11] It was not until our report in 2011 that a palladium-derived catalyst was employed to construct an asymmetric quaternary stereocenter via conjugate addition methodology.[12] Parallel to our studies, similar palladium-catalyzed conjugate additions to forge quaternary stereocenters were reported by Minnaard and de Vries.[13] This highlight provides an overview of our laboratory's efforts to develop the palladium-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic enone and other conjugate acceptors.

2. INITIAL DISCOVERIES

Our initial studies involved the asymmetric conjugate addition of arylboronic acids to β-substituted carbocyclic enones to generate benzylic all-carbon quaternary stereocenters.[12,14] We began these efforts by investigating the reaction of 3-methylcyclohexen-2-one (**1**) with phenylboronic acid (**2**, Scheme 2). Building on the precedent for bidentate dinitrogen ligands in conjugate addition chemistry,[11,15] we found that a catalyst formed in situ from the combination of $Pd(OCOCF_3)_2$ and the chiral pyridinooxazoline ligand, (*S*)-*t*-BuPyOx (**3**),[16]

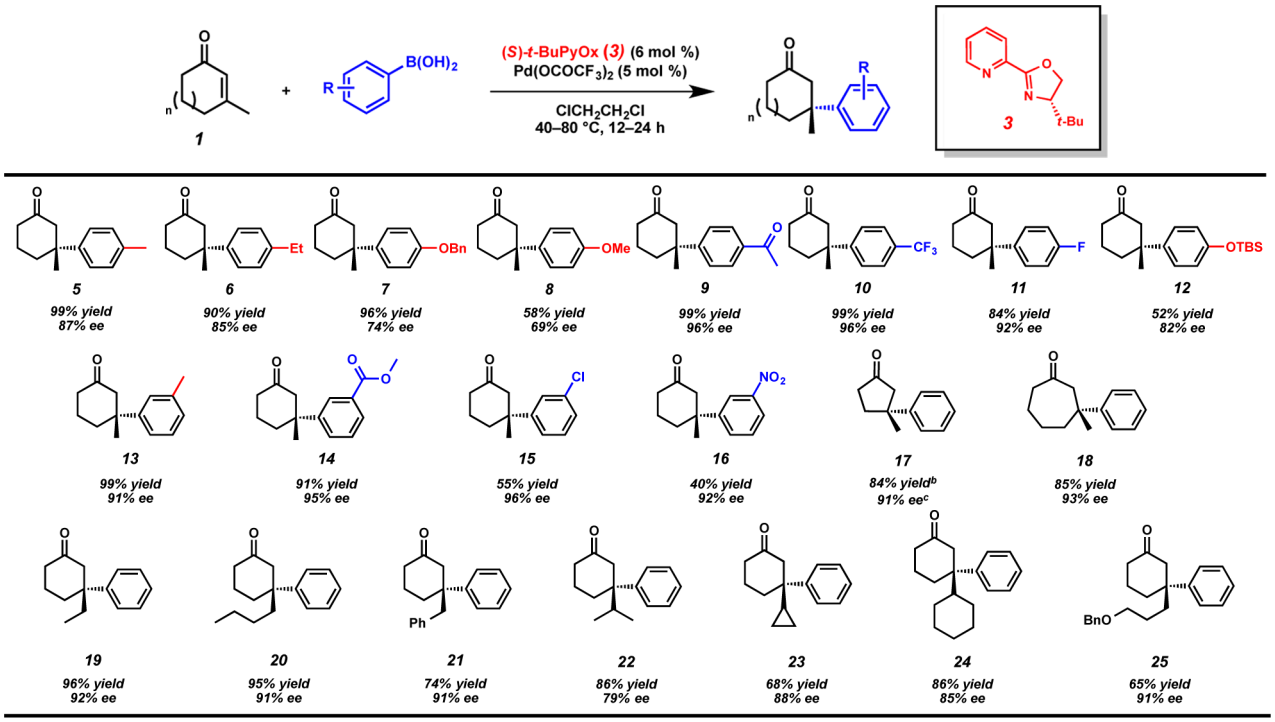
Scheme 2. Palladium-Catalyzed Asymmetric Conjugate Addition with (*S*)-*t*-BuPyOx (3)



Received: May 28, 2015

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 1. Scope of Arylboronic Acid and Enone Conjugate Acceptors[a]



[a]Conditions: reactions were performed with arylboronic acid (0.50 mmol), cycloalkenone (0.25 mmol), $Pd(OCOCF_3)_2$ (5 mol %), and ligand **3** (6 mol %) in $ClCH_2CH_2Cl$ (1 mL) at 60 °C for 12 h. Yields are isolated yields, ee determined by chiral HPLC.

proved effective in forming β-quaternary ketone product **4** in high yield and enantioselectivity.[17] Many other ligands were examined in the course of our studies, and *t*-BuPyOx was found to promote the highest enantioselectivity. Moreover, we observed that polar, coordinating solvents hindered the reaction while nonpolar solvents provided higher conversions and superior enantioinduction. Ultimately, we found that 1,2-dichloroethane allowed us to conduct reactions at temperatures up to 80 °C to achieve faster reaction times (12−24 h) while minimizing side products. Furthermore, the amount of phenylboronic acid could be reduced to 1.1 equiv with no detrimental effects on the reactivity other than increased reaction times.

Based on these initial studies, we found the reaction to be insensitive to adventitious moisture and air atmosphere; the high yield and enantioselectivity were maintained even upon addition of 10 equiv of water, and no improvements were noted under inert gas atmospheres. Therefore, the reactions may be conducted under ambient air in screw-top vials without the need for purification or distillation of any commercially obtained materials. Moreover, the optimal chiral ligand, (*S*)-*t*-BuPyOx, can be expediently prepared on relatively large laboratory scale in two steps from readily available starting materials.[18]

Gratifyingly, a wide range of arylboronic acids and enones undergo highly enantioselective reactions under the developed conditions (Table 1). With respect to the nucleophile scope, *para*-substituted arylboronic acids are well-tolerated. Alkyl-substituted arylboronic acids react with good yields and enantioselectivities to give products such as 4-methyl- and 4-ethyl-substituted ketones (**5** and **6**). However, electron-rich nucleophiles tend to furnish more modest yields and enantioselectivities (**7**, **8**, and **12**). Conversely, arylboronic acids bearing electron-withdrawing substituents produce ketone products in excellent ee and very high yields. Specifically, the electron-poor substitution can include carbonyl (**9**), fluoroalkyl (**10**), or halide (**11**) functional groups. Additionally, reactions involving *meta*-substituted nucleophiles fare well with alkyl (**13**), ester (**14**), halide (**15**), or even nitro groups (**16**) on the arylboronic acid. Notably, substituents at the 2-position of the arylboronic acid result in slower reactions and furnish poor yields of the ketone products in low ee (e.g., 2-methylphenylboronic acid resulted in 13% of its corresponding product in 22% ee). These *ortho*-arylboronic acid substrates react with higher yields and ee's in the palladium-catalyzed conjugate addition manifold described by Minnaard and de Vries.[13b]

Cyclic enones of different ring sizes, and with a range of β-substitution, react to afford enantioenriched β-quaternary ketone products (Table 1). Cyclohexanone products bearing both linear (**17**−**21**) and branched β-substituents (**22**−**24**) as well as functionalized side chains (**25**) are formed in good-to-excellent yields and ee's from their corresponding substituted conjugate acceptors. Moreover, altering the ring size has no deleterious effect on reactivity and furnishes products with five- (**17**) or seven-membered (**18**) cycloalkanones in high yield and ee. To the best of our knowledge, this represents the first example of a single catalyst system successfully constructing quaternary centers by asymmetric conjugate addition to 5-, 6-, and 7-membered enone conjugate acceptors.

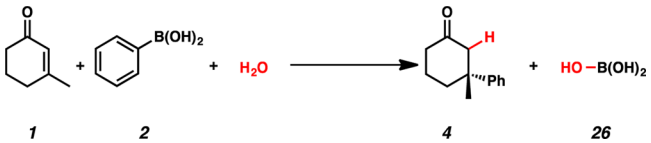
3. FURTHER REACTION DEVELOPMENT

Following our initial communication of the construction of quaternary stereocenters by asymmetric palladium-catalyzed conjugate addition,[12] we sought to further generalize the substrate scope, reduce the catalyst loading, and lower the reaction temperature.[14,19] While we noted that the addition of water had no deleterious effect in our initial report, we did not consider water as an important additive because we believed the

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

stoichiometric arylboronic acid, and adventitious water therein, to be an adequate proton source to turn over the catalyst. However, attempts to perform the reaction on large scale failed to fully convert enone **1** to product ketone **4**, resulting in only a moderate yield. We rationalized that, on small scale, the moisture in the air and on the glassware provided sufficient water to drive the reaction to completion. On larger scale this moisture was insufficient. Analysis of the balanced equation for the overall transformation indicated that the addition of water is necessary to achieve catalyst turnover (Scheme 3). Thus, we

Scheme 3. Water Is Required to Balance the Reaction Equation

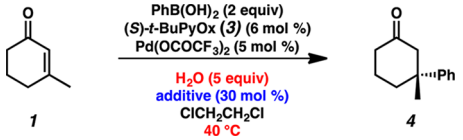


found that the addition of 5 equiv of water to the reaction mixture restored the reactivity when performing reactions on multigram scale. To date, reactions as large as 35 mmol-scale have been successfully conducted.

Examination of deuterium incorporation in the product ketone supported our hypothesis of water's role in reaction turnover. In reactions performed with deuterium oxide in place of water, we found significant deuterium incorporation at the α-methylene position of the carbonyl. This observation was true in reactions run to low conversion as well. These experiments, in combination with the scalability problems encountered without water as an additive, suggested that water is the reagent assisting product turnover, rather than the boron nucleophile (Scheme 3).

Based on literature reports detailing palladium-catalyzed conjugate addition employing cationic or dicationic precatalysts featuring weakly coordinating anions (PF_6^-, SbF_6^-, BF_4^-, etc.),[10] we sought to evaluate the effect of salt additives on the reaction rate (Table 2). At 40 °C, without additives, the addition of phenylboronic acid to 3-methylcyclohexenone is very slow and rarely goes to full conversion before the catalyst decomposes. At this same temperature, we observed that the addition of strongly coordinating anions (e.g., chloride, entry 1) obstructed the catalytic reaction while sodium salts with weakly

Table 2. Effect of Additives on Reaction Rate, Yield, and Enantioselectivity[a]



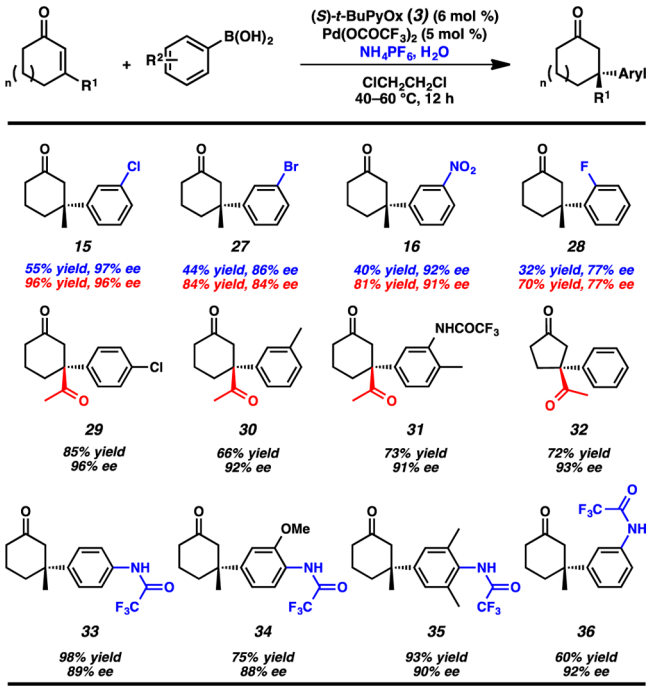
entry[a]	additive	time (h)	yield (%)[b]	ee (%)[c]
1	NaCl	24	trace	
2	$NaPF_6$	6	97	87
3	$(n\text{-Bu})_4NPF_6$	24	98	90
4	NH_4PF_6	12	96	91

[a]Conditions: reactions were performed with phenylboronic acid (0.5 mmol), 3-methylcyclohexen-2-one (0.25 mmol), NH_4PF_6 (30 mol %), water (5 equiv), $Pd(OCOCF_3)_2$ (5 mol %), and ligand **3** (6 mol %) in $ClCH_2CH_2Cl$ (1 mL) at 40 °C. [b]GC yield utilizing tridecane standard. [c]ee was determined by chiral HPLC.

coordinating anions greatly enhanced the reaction rate, but diminished enantioselectivity (e.g., $NaPF_6$, entry 2). Other additives required extended reaction times (e.g., $(n\text{-Bu})_4NPF_6$, entry 3). A larger examination of salt additives containing weakly coordinating counterions revealed that NH_4PF_6 gave the optimal combination of short reaction time with minimized loss of enantioselectivity (entry 4). We posit that these additives alter the catalyst resting state and result in a larger percentage of dissolved palladium species in the catalytic cycle.

Incorporation of the optimized additives (5 equiv of water, 30 mol % NH_4PF_6) into the reaction conditions allowed for reactions to be conducted at decreased temperatures (23–40 °C) and significantly broadened the substrate scope. Many of the previously studied substrates that contained temperature-sensitive functionalities (e.g., silyl ethers) or groups that may react with trace palladium(0) formed by off-cycle pathways (e.g., aryl bromides) afforded higher desired product yields under the modified conditions. For example, ketones **15**, **27**, **16**, and **28** were obtained in nearly double the yield under the new conditions (Table 3). Furthermore, at 40 °C, the

Table 3. Expanded Substrate Scope with Improved Reaction Conditions[a]



[a]Blue font: reported yield and ee of the product in the absence of NH_4PF_6 and water, with reactions performed at 60 °C. Red font: yield and ee of the product with additives. Conditions: reactions were performed with arylboronic acid (1.0 mmol), 3-methylcyclohexen-2-one (0.5 mmol), NH_4PF_6 (30 mol %), water (5 equiv), $Pd(OCOCF_3)_2$ (5 mol %), and ligand **3** (6 mol %) in $ClCH_2CH_2Cl$ (2 mL) at 40 °C. Reactions to synthesize products **29**–**36** were conducted at 60 °C. Yields are isolated yields, ee determined by chiral HPLC.

combination of additives allowed catalyst loadings of only 2.5 mol % of palladium and 3 mol % of ligand for most reactions. Moreover, the additives facilitated the reactions of two new substrate classes: (1) β-acyl cyclic enones and (2) arylboronic acids containing nitrogen substituents (Table 3). We were pleased to note that β-acyl enone substrates provided access to

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

asymmetric 1,4-dicarbonyl compounds, with only the olefin insertion process forming the quaternary stereocenter observed (**29**–**32**), as opposed to the isomeric insertion products that would afford tertiary stereocenters. We also observed that aniline-derived boronic acid substrates protected with a trifluoroacetyl group did not poison the catalyst and allowed for the synthesis of heteroatom-substituted products (**31**, **33**–**36**).

4. MECHANISTIC HYPOTHESIS

Studies have been conducted to elucidate the catalytic cycle active in our asymmetric conjugate addition chemistry.[19] A range of Lewis- and π-acidic metal salts were substituted for palladium with no product observed, signifying that palladium-catalyzed conjugate addition is not a Lewis-acid-catalyzed process. The reaction proceeds in the presence of mercury drops, which would poison a heterogeneous catalyst, indicating that a soluble complex likely catalyzes the reaction. Furthermore, a nonlinear effect study supported the action of a single, monomeric ML-type catalyst as the kinetically relevant species (Figure 1).[20] The linear relationship between catalyst ee

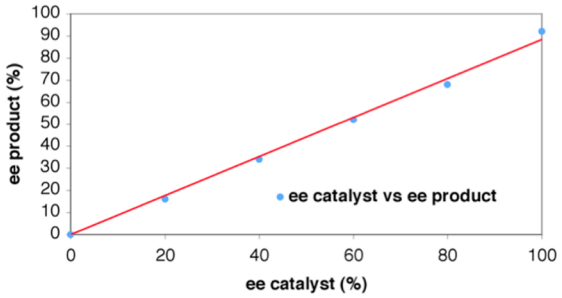


Figure 1. Linear relationship of catalyst ee to product ee.

and product ee argues against the kinetic relevance of palladium/ligand dimers in solution, as opposed to some catalysts that are known to aggregate in reservoirs.[11,21]

Density functional theory (DFT) calculations, performed in collaboration with the Houk laboratory, support the cationic catalytic cycle shown in Figure 2.[19,22] We postulate that the active catalyst is a cationic palladium(II) hydroxide species, which are known to undergo rapid transmetalation with arylboronic acids without added base.[23] We envision that arylpalladium **38** forms by transmetalation of the arylboronic acid with cationic catalyst **37**. Substrate association via the carbonyl yields an equilibrium mixture of carbonyl-bound complex **39** and olefin-bound complex **40**. *C*-bound enolate **43** is the initial product of alkene insertion into the aryl C–Pd bond. Notably, this insertion is calculated to be both the enantiodetermining and turnover-limiting step of the catalytic cycle. Subsequent isomerization to *O*-bound tautomer **42** under the reaction conditions followed by protonation affords the product ketone and regenerates the catalyst (**37**).[24] This proposed mechanism was experimentally substantiated by a recent collaboration with the Zare laboratory in which arylpalladium cation **38** and enone complex **39** were identified by DESI-MS monitoring of the reaction mixture.[25] No intermediates occurring after the predicted turnover-limiting step were observed. The observation of enone–arylpalladium complex **39** for a variety of arylboronic acid substrates led us to hypothesize that complex **39** may be the resting state.

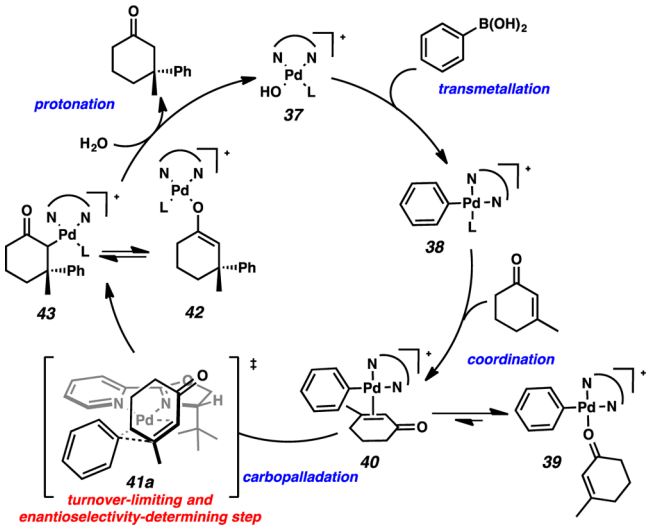


Figure 2. Proposed catalytic cycle for the asymmetric conjugate addition of arylboronic acids to cyclic enones catalyzed by the combination of $Pd(OCOCF_3)_2$ and (*S*)-*t*-BuPyOx.

The enantiodetermining alkene insertion step involves a four-membered cyclic transition state, with the lowest energy diastereomer calculated to be the transition state **41a**, which leads to the observed (*R*)-product. Diastereomer **41a** is the most stable as the bulky *t*-Bu group on the ligand is pointing away from the substrate. Analysis of the effects of substituents on the ligand at the four-position of the oxazoline revealed that replacing the *t*-Bu functionality with smaller groups, such as *i*-Pr, *i*-Bu, or Ph, significantly reduced the ee. If instead the oxazoline is substituted at the 5-position practically no enantioselectivity is afforded. Electronic perturbation of the pyridine moiety of the ligand did not markedly affect the observed enantioselectivity, though rates were greatly changed. Therefore, enantioselectivity is primarily attributed to the ligand/substrate steric interactions.

Transition state calculations suggested that stereocontrol predominantly arises from the repulsion of the α'-methylene hydrogens on the cyclohexenone substrate with the ligand (Figure 3). In the disfavored diastereomeric transition state (**41b**), these atoms are only 2.3 Å apart and thus incur a significant energetic penalty. Consequently, replacing the CH_2

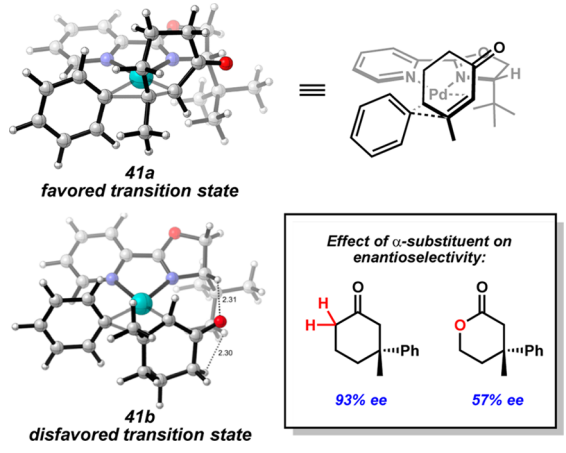
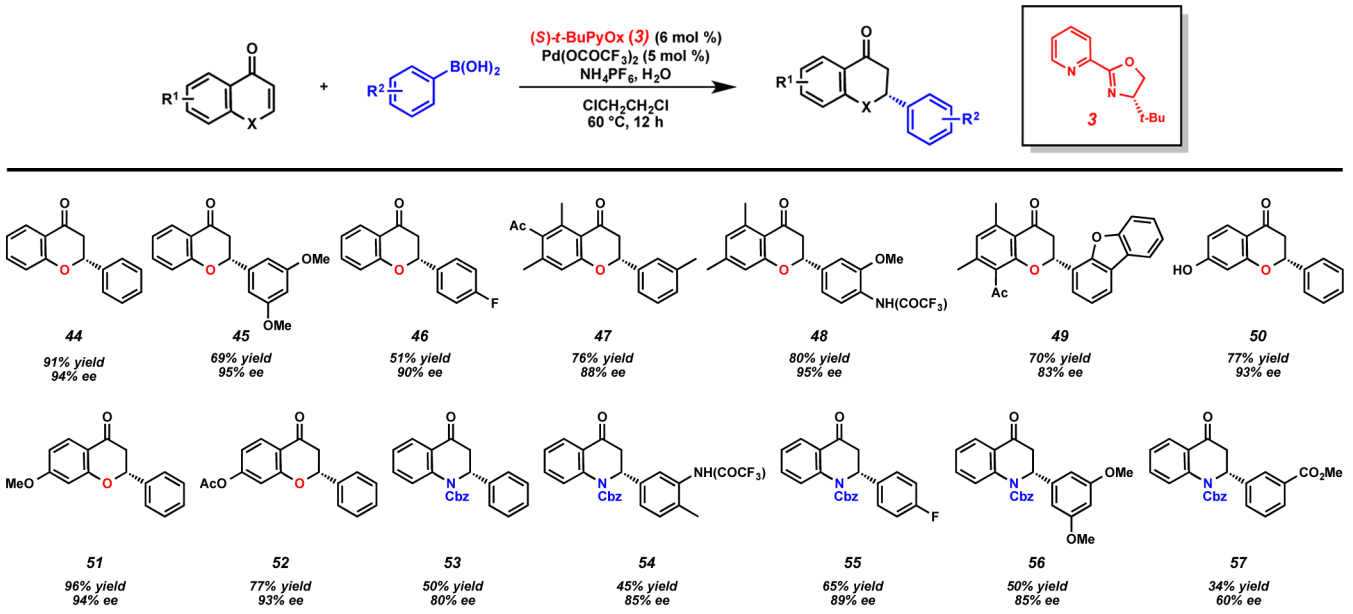


Figure 3. Calculated transition states and effect of α'-substituents on enantioselectivity.

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX–XXX

Table 4. Asymmetric Conjugate Addition of Arylboronic Acids to Heterocyclic Conjugate Acceptors[a]



[a]Conditions: reactions were performed with arylboronic acid (0.50 mmol), heterocyclic acceptor (0.25 mmol), NH_4PF_6 (30 mol %), water (5 equiv), $Pd(OCOCF_3)_2$ (5 mol %), and ligand **3** (6 mol %) in $ClCH_2CH_2Cl$ (1 mL) at 60 °C for 12 h. Yields are isolated yields, ee determined by chiral HPLC.

group with an O (e.g., lactone product, Figure 3) decreases the energy difference between the two diastereomeric transition states and leads to an observed decrease in enantioselectivity from 93% ee to 57% ee. Of note, α,β-unsaturated lactone substrates afford high enantioselectivity in the palladium-catalyzed asymmetric conjugate addition described by Minnaard and de Vries.[13a]

5. HETEROCYCLIC ACCEPTORS

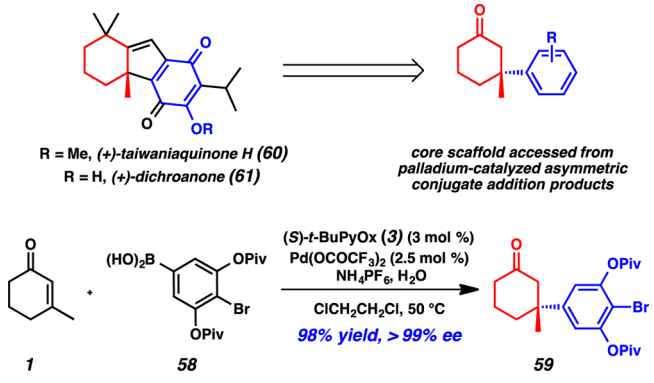
We wished to extend our conjugate addition methodology to the synthesis of stereochemically complex heterocyclic molecules. We found that the palladium-catalyzed conjugate addition of arylboronic acids to chromones and 4-quinolones delivered *tertiary* stereocenters in high yield and ee across multiple heterocyclic scaffolds with a wide range of arylboronic acids (Table 4).[26] While chromones[27,28] and 4-quinolones[29] have been successfully employed in rhodium-catalyzed conjugate addition, to our knowledge, these are the first examples of metal-catalyzed asymmetric conjugate additions to chromones and 4-quinolones using either palladium catalysis or arylboronic acid nucleophiles.[30]

Overall, a total of 38 adducts were prepared in moderate to excellent yield and high enantioselectivity. Furthermore, the stability of the reaction components to air and moisture affords unprecedented functional group tolerance. Hence, heterocyclic products bearing free phenolic groups (**50**), heterocyclic substitution (**49**), and *N*-substituted arenes (**48** and **54**) were realized via the conjugate addition methodology.

6. APPLICATION OF PALLADIUM-CATALYZED CONJUGATE ADDITION TOWARD THE SYNTHESIS OF NATURAL PRODUCTS

The formal synthesis of (+)-taiwaniaquinone H (**60**) and (+)-dichroanone (**61**) provided an optimal forum for demonstrating the breadth and generality of the palladium-catalyzed conjugate addition chemistry.[31] Here, we recognized that the β-benzylic ketone motif found in conjugate addition products mapped on to the scaffold of taiwaniaquinoid terpene natural products (Scheme 4).

Scheme 4. Synthetic Approach to Taiwaniaquinoid Terpene Natural Products by Palladium-Catalyzed Asymmetric Conjugate Addition



To rationally design a highly enantioselective conjugate addition substrate for the synthesis, we used our previous results to construct a plot of product enantioselectivity versus the Hammett constant (σ_p) for a variety of *para*-substituted arylboronic acids (Figure 4).[32] The resulting Hammett plot gave a strong positive linear correlation ($R^2 = 0.92$) and positive ρ (0.81), indicating that the difference in energy between the diastereomeric transition states leading to the enantiomeric (*S*) and (*R*) products increases as the boronic acid becomes increasingly electron-deficient. Therefore, the best selectivity in the conjugate addition reaction is achieved with electron-withdrawing substituents in the *para*-position. As a result we chose to mask the requisite isopropyl group of the natural

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

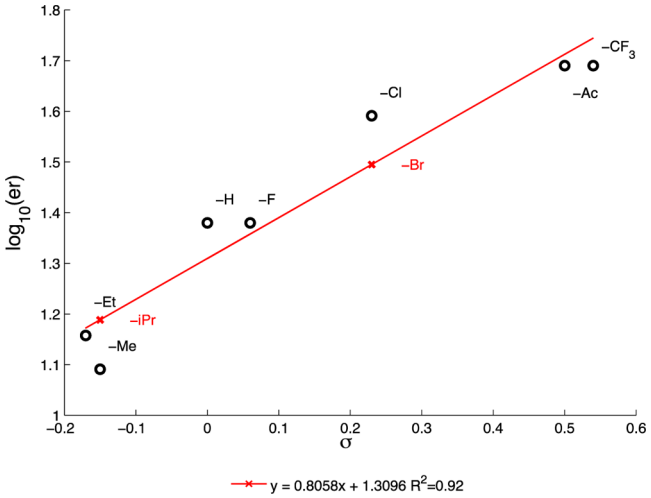
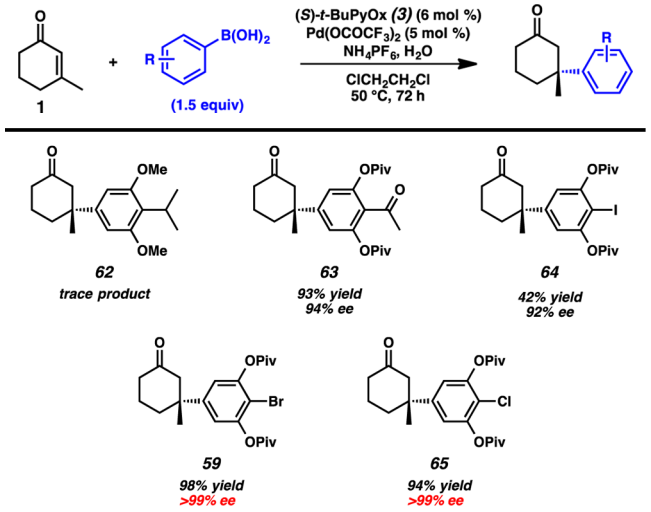


Figure 4. Hammett plot of $\log_{10}$(er) vs σ_p for select arylboronic acids.

products as either a methyl ketone or a halide to achieve a selective conjugate addition reaction.

Gratifyingly, we found that use of these boronic acids gave products bearing *para*-acetyl (**63**), *para*-iodo (**64**), *para*-bromo (**59**), and *para*-chloro (**65**) arenes in high ee and moderate-to-high yields (Table 5). Due to superior reactivity in subsequent

Table 5. Identification of a Suitable Conjugate Addition System for Synthesis of Taiwaniaquinoids[a]



[a]Conditions: reactions were performed with NH_4PF_6 (30 mol %), water (5 equiv), $Pd(OCOCF_3)_2$ (2.5 mol %), and ligand **3** (3 mol %) in $ClCH_2CH_2Cl$ at 50 °C for 72 h. Yields are isolated yields, ee determined by chiral SFC.

steps, *para*-bromo arene **59** was carried forward to complete the formal synthesis of (+)-dichroanone and (+)-taiwaniaquinone H in >99% ee, the highest reported ee to date.

7. CONCLUSION AND OUTLOOK

We have developed a palladium-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic β-substituted enones catalyzed by the combination of $Pd(OCOCF_3)_2$ and the chiral pyridinooxazoline ligand, (*S*)-*t*-BuPyOx. These reactions generate a wide array of benzylic all-carbon quaternary stereocenters while exhibiting high tolerance to both oxygen and water. Additionally, the transformation can be performed on multigram scale without complication, and the optimal chiral ligand can be rapidly accessed from commercially available materials in two steps.

The reaction scope has been expanded to heterocyclic conjugate acceptors to generate asymmetric flavanones and substituted dihydroquinolone products that are highly valuable to the pharmaceutical industry. Moreover, the reported method is amenable to the delivery of large quantities of material required for multistep synthesis, as demonstrated by the highly enantioselective formal syntheses of (+)-dichroanone and (+)-taiwaniaquinone H. Finally, intensive computational and experimental studies have elucidated a picture of the operative mechanism of the transformation, including hypotheses for the turnover-limiting step, enantiodetermining step, and resting state.

Despite the promise of the palladium-catalyzed asymmetric conjugate addition methodology described in this review, several challenges remain. Vinyl- and alkylboronic acids do not undergo productive conjugate addition, nor do many heteroarylboronic acid substrates. Additionally, several enone motifs are largely unreactive, including β-aryl and β-vinyl cyclic enones, and most acylic enones react slowly and yield products with low ee.[14] Future efforts to improve the reactivity of these substrates will continue to increase the widespread application of palladium-catalyzed asymmetric conjugate addition as a practical synthetic tool.

AUTHOR INFORMATION

Corresponding Author

*E-mail: stoltz@caltech.edu.

Notes

The authors declare no competing financial interest.

Biographies

Samantha E. Shockley was born in Birmingham, AL in 1990. She received her B.S. degree in Chemistry from the University of Chicago in 2012 where she conducted research for Professor Richard F. Jordan. After graduating from the College, she worked with Professor Martin Banwell at the Australian National University as a U.S. Fulbright scholar. She is now pursuing her graduate studies at the California Institute of Technology under the guidance of Professor Brian M. Stoltz. Her graduate research focuses on the total synthesis of novel natural products.

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Jeffrey C. Holder graduated from Harvard University in 2009 where he conducted research with Professors Daniel Kahne and E. J. Corey. In 2014, he completed his Ph.D. in the laboratory of Professor Brian M. Stoltz at the California Institute of Technology, where he studied palladium-catalyzed asymmetric conjugate addition reactions and their application in total synthesis. Currently, he is a National Institutes of Health Postdoctoral Fellow in the laboratory of Professor John F. Hartwig at the University of California, Berkeley. His research interests include the development and study of transition metal catalyzed reactions and their applications in natural product synthesis.

Brian M. Stoltz was born in Philadelphia, PA in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the laboratories of John L. Wood and an NIH postdoctoral fellowship at Harvard in the Corey laboratories, he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he currently is a Professor of Chemistry. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

■ ACKNOWLEDGMENTS

The authors thank the many past and present co-workers whose efforts have made our contributions in asymmetric conjugate addition possible: Michele Gatti, Emmett D. Goodman, Kotaro Kikushima, Bin Mao, Alexander N. Marziale, and Hideki Shimizu. Support for our program has been made available from the NIH-NIGMS (R01 GM080269), Amgen, and Caltech.

■ REFERENCES

(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series 9; Pergamon: Oxford, 1992. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (c) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*, Vol. 3; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag; New York, 1999; Chapter 31. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (e) Gini, F.; Hessen, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2007**, 710. (f) Cordova, A. *Catalytic Asymmetric Conjugate Reactions*; Wiley & Sons: Weinheim, 2010.

(2) For a comprehensive review, see: Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295.

(3) (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584. (c) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988. (d) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774. (e) Lee, K.-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182. (f) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097. (g) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801. (h) Wilsily, A.; Fillion, E. *J. Org. Chem.* **2009**, *74*, 8583. (i) Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440.

(4) (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. (b) Fuchs, N.; d'Augustin, M.; Humam, M.; Alexakis, A.; Taras, R.; Gladiali, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3143. (c) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. - Eur. J.* **2007**, *13*, 9647. (d) Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* **2007**, *2007*, 2057. (e) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462. (f) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358. (g) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211. (h) Ladjel, C.; Fuchs, N.; Zhao, J.; Bernardinelli, G.; Alexakis, A. *Eur. J. Org. Chem.* **2009**, *2009*, 4949. (i) Palais, L.; Alexakis, A. *Chem. - Eur. J.* **2009**, *15*, 10473. (j) Müller, D.; Hawner, C.; Tissot, M.; Palais, L.; Alexakis, A. *Synlett* **2010**, *2010*, 1694. (k) Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769.

(5) (a) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416. (b) Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem. - Eur. J.* **2010**, *16*, 9890. (c) Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122. (d) Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578.

(6) (a) For the seminal report in this area, see: Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) For an excellent review, see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(7) For select recent examples, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (c) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425. (d) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (e) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.

(8) (a) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961. (b) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628. (c) Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350.

(9) A paper describing the use of Rh·OlefOX (olefin-oxazoline) complex provided a single example of a phenylboronic acid addition to 3-methylcyclohexen-2-one (e.g. **1** + **2** → **4**). Unfortunately, ketone **4** was isolated in only 36% yield and 85% ee; see: Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.

(10) For review articles, see: (a) Gutnov, A. *Eur. J. Org. Chem.* **2008**, *2008*, 4547. (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, *2007*, 1279.

(11) Lin, S.; Lu, X. *Org. Lett.* **2010**, *12*, 2536.

(12) Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902.

(13) (a) Gottumukkala, A. L.; Matcha, K.; Lutz, M.; de Vries, J. G.; Minnaard, A. J. *Chem. - Eur. J.* **2012**, *18*, 6907. (b) Buter, J.; Moezelaar, R.; Minnaard, A. J. *Org. Biomol. Chem.* **2014**, *12*, 5883.

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(14) Holder, J. C.; Goodman, E. D.; Kikushima, K.; Gatti, M.; Marziale, A. N.; Stoltz, B. M. *Tetrahedron* **2014**, 10.1016/j.tet.2014.11.048 (accessed May 7, 2015).
(15) (a) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651. (b) Lin, S.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 7167.
(16) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499.
(17) The absolute stereochemistry for all products shown was assigned by analogy to the product from Table 2, entry 2 as described in ref 3c, and subsequently by crystal structure 24 in ref 31.
(18) (a) Shimizu, H.; Holder, J. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2013**, *9*, 1637. (b) Holder, J. C.; Shockley, S. E.; Wiesenfeldt, M. P.; Shimizu, H.; Stoltz, B. M. *Org. Synth.* **2015**, submitted.
(19) Holder, J. C.; Zou, L.; Marziale, A. N.; Liu, P.; Lan, Y.; Gatti, M.; Kikushima, K.; Houk, K. N.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 14996.
(20) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.
(21) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130.
(22) All calculations were performed with Gaussian 03. Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
(23) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116.
(24) Our initial hypothesis concerning the reaction mechanism was well-informed by the seminal work of Miyaura, see: Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317.
(25) Boeser, C. L.; Holder, J. C.; Taylor, B. L. H.; Houk, K. N.; Stoltz, B. M.; Zare, R. N. *Chem. Sci.* **2015**, *6*, 1917.
(26) Holder, J. C.; Marziale, A. N.; Gatti, M.; Mao, B.; Stoltz, B. M. *Chem. - Eur. J.* **2013**, *19*, 74.
(27) (a) Chen, J.; Chen, J.; Lang, F.; Zhang, X.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *J. Am. Chem. Soc.* **2010**, *132*, 4552. (b) Han, F.; Chen, G.; Zhang, X.; Liao, J. *Eur. J. Org. Chem.* **2011**, *2011*, 2928. (c) Korenaga, T.; Hayashi, K.; Akaki, Y.; Maenishi, R.; Sakai, T. *Org. Lett.* **2011**, *13*, 2022.
(28) For a recent example, see: He, Q.; So, C. M.; Bian, Z.; Hayashi, T.; Wang, J. *Chem. - Asian J.* **2015**, *10*, 540.
(29) (a) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5317. (b) Zhang, X.; Chen, J.; Han, F.; Cun, L.; Liao, J. *Eur. J. Org. Chem.* **2011**, *2011*, 1443.
(30) For an isolated example of a Pd-catalyzed non-enantioselective conjugate addition to a chromone, see: Huang, S.-H.; Wu, T.-M.; Tsai, F.-Y. *Appl. Organomet. Chem.* **2010**, *24*, 619.
(31) Shockley, S. E.; Holder, J. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 6362.
(32) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165 Red crosses in Figure 3 are interpolated from the linear least square regression using the known Hammett values (σ_p) for *p*-Br and *p*-iPr..

DOI: 10.1021/acs.oprd.5b00169
Org. Process Res. Dev. XXXX, XXX, XXX−XXX