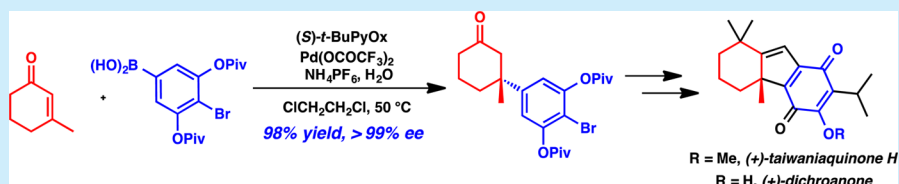


# A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

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## Supporting Information



**ABSTRACT:** A catalytic, enantioselective formal synthesis of (+)-dichroanone and (+)-taiwaniaquinone H is reported. The all-carbon quaternary stereocenter was constructed by asymmetric conjugate addition catalyzed by a palladium(II) (*S*)-*tert*-butylpyridinoxazoline complex. The unexpected formation of a [3.2.1] bicyclic intermediate required the identification of a new route. Analysis of the Hammett constants for *para*-substituted arenes enabled the rational design of a highly enantioselective conjugate addition substrate that led to the completion of the formal synthesis.

First isolated in 1995, the taiwaniaquinoid natural products are a family of tricyclic diterpenoids with a unique [6,5,6]-*abeo*-abietane skeleton (Figure 1, 1–7).<sup>1</sup> Since their isolation, the

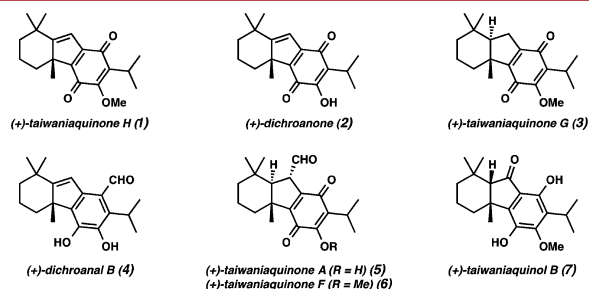


Figure 1. Taiwaniaquinoid natural products.

taiwaniaquinoids have attracted significant attention from the synthetic community, resulting in a multitude of total and formal syntheses.<sup>2</sup> Interest in these compounds stems from their purported biological activity,<sup>3</sup> in addition to their unique architecture containing a benzylic quaternary stereocenter. Due to the limited number of methodologies capable of installing benzylic quaternary stereocenters, only four catalytic, enantioselective syntheses of taiwaniaquinoids have been published to date.<sup>2e,m,q,t</sup>

Our laboratory has a long-standing interest in the asymmetric synthesis of quaternary stereocenters. Previously, our group reported the first catalytic, enantioselective total synthesis of (+)-dichroanone (2) via asymmetric palladium-catalyzed allylic alkylation (Figure 2).<sup>2e</sup> This work featured a linear synthetic sequence, elaborating allylic alkylation product 9 to bicyclic enone 8 by Wacker oxidation and subsequent aldol condensation.

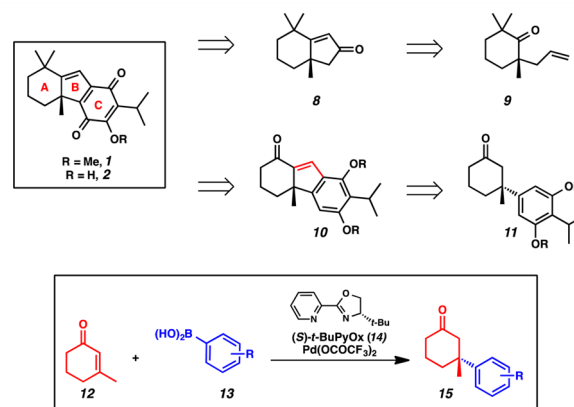


Figure 2. Comparative retrosynthetic analysis of (+)-taiwaniaquinone H (1) and (+)-dichroanone (2).

The final ring was appended by another aldol condensation, and a novel series of oxidations provided the natural product in only 11 steps.

Recently, we developed a new catalyst for the enantioselective conjugate addition of arylboronic acids (Figure 2, 13) to cyclic enones to form  $\beta$ -quaternary ketones (15) in high yields and enantioselectivities.<sup>4</sup> We observed that these  $\beta$ -aryl ketone products closely resembled the core of the taiwaniaquinoids, and we envisioned that a more convergent synthesis of these natural products could be achieved by employing  $\beta$ -aryl ketone 11 as the key intermediate. This modified retrosynthetic analysis

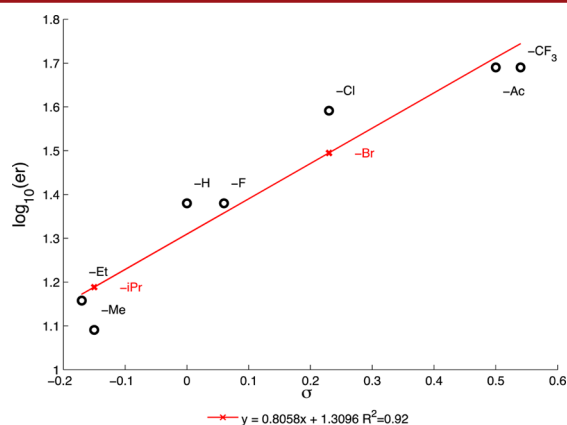
Received: October 28, 2014

Published: December 9, 2014

facilitates a highly convergent, catalytic, enantioselective key step that joins together 13 of the 19 core carbons of the taiwaniaquinoid tricyclic core, including the quaternary stereocenter, in a single chemical transformation. Herein, we present the rational design of high-yielding and highly enantioselective conjugate addition reactions of arylboronic acids to 3-methyl-2-cyclohexenone that facilitated the catalytic, asymmetric formal synthesis of (+)-dichroanone and (+)-taiwaniaquinone H in greater than 99% enantiomeric excess.

Our preliminary strategic disconnections of (+)-dichroanone (**2**) and (+)-taiwaniaquinone H (**1**) involved late stage introduction of the gem-dimethyl functionality and oxidation of the C-ring of enone **10** to the quinone (Figure 2).<sup>5,2f</sup> The B-ring of tricycle **10** was envisioned to be established through *ortho*-formylation of the phenol **11** and subsequent aldol condensation. We anticipated that the all-carbon quaternary center could be constructed by palladium-catalyzed asymmetric conjugate addition of 3-methyl-2-cyclohexenone (**12**) with an appropriate arylboronic acid **13**.<sup>4</sup>

We first selected *para*-acetylphenylboronic acid **19** as our conjugate addition substrate. In our previous work we noted that electron-withdrawing substituents at the *para* position of the arylboronic acid often afforded highly enantioenriched  $\beta$ -quaternary ketone products (**15**).<sup>4</sup> A plot of the enantiomeric ratio versus the Hammett value ( $\sigma_p$ ) for a variety of *para*-substituted phenylboronic acids (**15**) demonstrates a strong positive linear correlation,  $R^2 = 0.92$  (Figure 3).<sup>6</sup> The positive

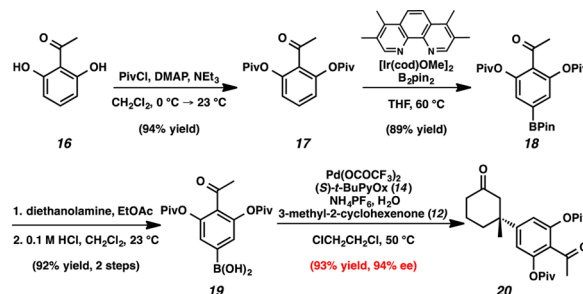


**Figure 3.** Hammett plot of  $\log_{10}(er)$  vs  $\sigma_p$  for select boronic acids in the palladium-catalyzed conjugate addition reaction.

value of  $\rho$  (0.81) suggests 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. Thus, the best selectivity in the conjugate addition reaction is achieved with electron-withdrawing substituents in the *para*-position. Therefore, we chose to mask the isopropyl group as a methyl ketone to achieve a selective conjugate addition reaction.

Access to *para*-acetylphenylboronic acid **19** (Scheme 1) began with acylation of 2,6-dihydroxyacetophenone (**16**) with pivaloyl chloride to provide arene **17**. Installation of the boryl substituent was accomplished through an Ir-catalyzed C–H borylation.<sup>7</sup> This reaction provided pinacol boronate ester **18** as the exclusive product in 89% yield. Empirically, we identified that protecting the *meta*-hydroxyl substituents with pivalate groups allowed for the highest yields in this borylation chemistry. After exhaustive exploration of deprotection conditions, we found that treatment

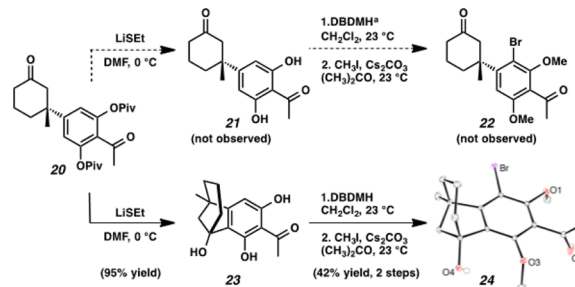
## Scheme 1. Synthesis of Acetyl Conjugate Addition Product **20**



with diethanolamine and subsequent acid-catalyzed hydrolysis of the transesterified intermediate afforded arylboronic acid **19** in 92% yield.<sup>8</sup> Boronic acid **19** was treated with 3-methyl-2-cyclohexenone in the presence of  $\text{Pd}(\text{OCOCF}_3)_2$ , (*S*)-*t*-BuPyOx, and  $\text{NH}_4\text{PF}_6$  at 50 °C to afford enantioenriched ketone **20**, in 93% yield and 94% ee.<sup>4b</sup>

With ketone **20** in hand, we turned our attention to the installation of the final carbon of the tricyclic core and the completion of the B-ring. Regrettably, attempts to formylate arene **20** were unsuccessful. We rationalized that the sterically congested environment surrounding the arene C–H bonds prohibited installation of a functional group handle. Moreover, deprotection of the hydroxyl groups of ketone **20** was not facile and required treatment with LiSEt to cleanly remove both pivaloyl groups, affording what we predicted to be resorcinol **21** (Scheme 2). Though HRMS data matched the molecular formula

## Scheme 2. Unexpected Cyclization of Phenolic Intermediate



<sup>a</sup>DBDMH = 1,3-dibromo-5,5-dimethylhydantoin.

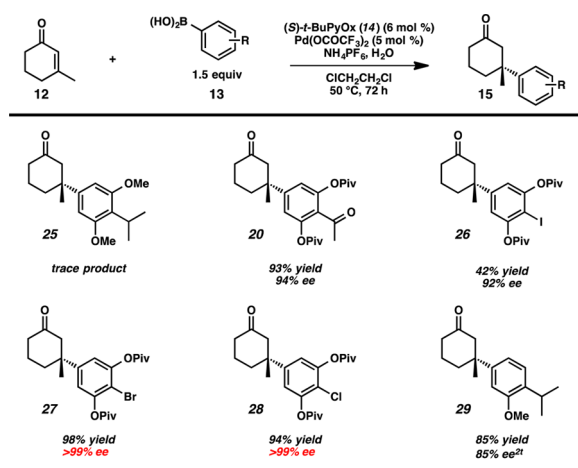
of desired resorcinol **21**, the <sup>1</sup>H NMR spectra did not match that of a typical  $\beta$ -quaternary ketone conjugate addition product. We suspected that an unproductive cyclization may have occurred and sought to crystallize derivatives of ketone **23** to confirm the new structure by single crystal X-ray diffraction. Bromination and methylation of compound **23** provided bromoarene **24** as a white crystalline solid. As we suspected, a cyclization had occurred and the structure proved to be [3.2.1]bicycle **24**. Thus, we were able to properly assign the structures of cyclization product **23** and arene bromination adduct **24**. This X-ray structure also confirms the absolute stereochemistry imparted in asymmetric conjugate addition reactions of arylboronic acids to cyclic conjugate acceptors facilitated by the catalyst derived from the combination of (*S*)-*t*-BuPyOx and  $\text{Pd}(\text{OCOCF}_3)_2$ .

Cyclizations of  $\beta$ -aryl ketones to form [3.2.1] bicycles are rare; the few other reports of this transformation require treatment with strong Lewis<sup>9</sup> or Brønsted acids<sup>10</sup> at elevated temperatures. These reactions presumably operate via an electrophilic aromatic substitution mechanism. While it is possible that our noted

cyclization proceeds through a similar mechanism, we did not observe cyclization with substrates bearing protected phenols, which suggests that the hydroxyl group or phenoxide may be involved in the cyclization mechanism. This observation led us to propose that this unexpected cyclization may instead occur through a carbonyl ene or lithium phenoxide aldol reaction pathway.

As we were unable to functionalize ketone **20** without causing the undesired cyclization, we decided to redesign the arylboronic acid substrate and began examining alternative conjugate addition reactions. Removing the acetyl group would obviate the need to differentiate the benzylic carbonyl from the cyclic ketone while installing the requisite isopropyl group in the first-generation conjugate addition product **20**. We envisioned that a *para*-halogenated arylboronic acid derivative would allow for facile installation of the isopropyl group via cross-coupling chemistry. Additionally, based on our Hammett plot analysis, we posited that the *para*-halide would serve as a necessary *para*-electron-withdrawing group to impart high enantioselectivity in the Pd/PyOx conjugate addition chemistry (Figure 3).<sup>4</sup> Gratifyingly, we found that use of these boronic acids furnished products bearing *para*-iodo (**26**), *para*-bromo (**27**), and *para*-chloro (**28**) arenes in high ee and moderate to high yields (Scheme 3).

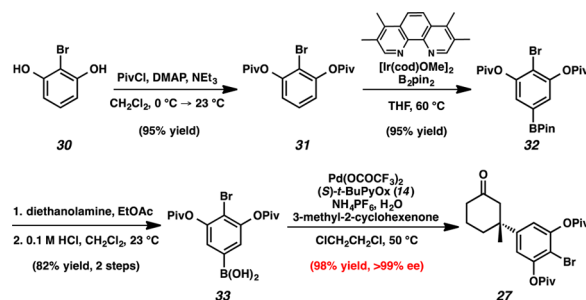
**Scheme 3. Identification of a Suitable Conjugate Addition System**



We consequently pursued a revised approach to the natural products via bromoarene **27**, selected for both its superior reactivity in palladium-catalyzed conjugate addition chemistry and facile cross-coupling ability. To access this intermediate, 2-bromoresorcinol **30** was converted to *para*-bromophenyl boronic acid derivative **33** in 73% yield over four steps (Scheme 4). Subsequent catalytic, asymmetric conjugate addition furnished ketone **27** in 98% yield and >99% ee.

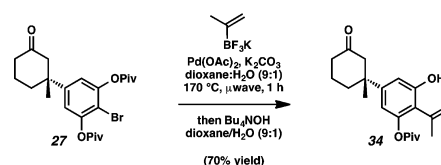
Having set the absolute stereochemistry of the quaternary center, we next sought to install the isopropyl group. Attempts to directly cross-couple an isopropyl zinc reagent with bromide **27** gave an inseparable mixture of iso- and *n*-propyl products.<sup>11</sup> The steric hindrance of the nearby pivaloyl groups frustrated our attempts to cross-couple **27** with isopropenyl organometallic reagents, but we ultimately achieved success using Molander's protocol for Suzuki–Miyaura couplings of potassium isopropenyltrifluoroborate salts.<sup>12</sup> Our optimized conditions (170 °C, 1 h, microwave) gave a crude mixture of both cross-coupled product and monodeprotected cross-coupled product

**Scheme 4. Synthesis of Ketone 27**



that could be stirred with tetrabutylammonium hydroxide to furnish isopropenyl phenol **34** in 70% yield (Scheme 5).

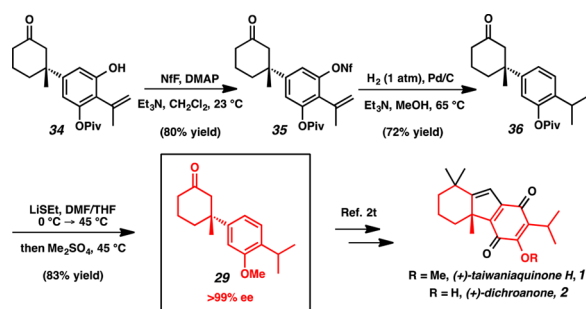
**Scheme 5. Isopropenyl Cross-Coupling**



With a route to monodeprotected arene **34** established, we turned our efforts once more toward the formation of the B-ring. However, despite the successful removal of one pivaloyl group, the system proved resistant to a number of metal and nonmetal mediated *ortho*-formylations, directed *ortho*-metalations, and halogenations, regardless of protection of the ketone. We speculate that the failure of these efforts may again be attributed to the formidable steric environment of the arene C–H bonds.

Recognizing that significant steric hindrance would prevent the formation of the B-ring, we sought to diminish the steric environment of the arene by reductive removal of the free phenol. Activation of phenol **34** by exposure to excess perfluorobutanesulfonyl fluoride led to the generation of nonaflate **35** in 80% yield (Scheme 6). Subsequent hydrogenation with Pd/C simulta-

**Scheme 6. Synthesis of Key Intermediate 29<sup>a</sup>**



<sup>a</sup>NfF = perfluorobutanesulfonyl fluoride.

neously cleaved the nonaflate and reduced the isopropenyl functionality to afford isopropyl arene **36** in 72% yield.<sup>13</sup> Finally, the pivaloyl group was replaced with a methyl group by one-pot deprotection and methylation with LiSEt and Me<sub>2</sub>SO<sub>4</sub> to provide ketone **29** in 83% yield. With the less substituted arene **29** in hand, we believed that the necessary tricycle could now be readily formed by *ortho*-formylation.

Concurrent with our synthetic efforts, Qin and co-workers reported a formal total synthesis of (+)-dichroanone and



(+)-taiwaniaquinone **1** via asymmetric conjugate addition of (4-isopropyl-3-methoxyphenyl)boronic acid to 3-methyl-2-cyclohexenone (**12**) in 85% yield and 85% ee (Scheme 3, **29**) using the catalyst developed in our laboratory.<sup>2i,4a</sup> However, Qin was unable to optimize the conjugate addition substrates to achieve yields or enantiomeric excesses over 85%. This result aligns well with our Hammett plot analysis; the determined linear relationship predicts an ee of 88% for the electron-donating isopropyl group (Figure 3). Moreover, this study demonstrated that our common intermediate **29** could be further transformed into the taiwaniaquinoid tricyclic skeleton by *ortho*-formylation followed by aldol condensation. Therefore, our synthesis of ketone **29** in >99% ee constitutes a formal synthesis of (+)-dichroanone (**2**) and (+)-taiwaniaquinone **1** in the highest reported ee to date.

In summary, we have presented the formal catalytic, asymmetric total syntheses of (+)-dichroanone and (+)-taiwaniaquinone **1** in 35% overall yield, starting from commercially available 2-bromoresorcinol (**30**). Investigation of electronic effects of arylboronic acid substituents on enantioselectivity enabled the rational design of a highly enantioselective reaction that furnished established intermediate **29** in exceptionally high yield and ee. Additionally, an unexpected cyclization to form a [3.2.1] bicycle permitted the unambiguous determination of the absolute stereochemistry of the quaternary stereocenter installed by the Pd/PyOx-catalyzed conjugate addition reaction by X-ray diffraction analysis. Currently, efforts to apply *para*-halogen conjugate addition substrates to the synthesis of a range of [6,6,6] and [6,7,6] tricyclic scaffolds are underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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†S.E.S. and J.C.H. contributed equally.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors thank NIH-NIGMS (B.M.S., R01 GM080269), Caltech, and the American Chemical Society Division of Organic Chemistry (predoctoral fellowship J.C.H.) for financial support. Dr. Scott Virgil is thanked for helpful discussions and assistance with chiral chromatography. Dr. David VanderVelde of the Caltech NMR facility is thanked for invaluable assistance with NMR experiments and helpful discussions. Lawrence Henling and Dr. Michael K. Takase (Caltech) are gratefully acknowledged for X-ray crystallographic structural determination. Dr. Mona Shahgholi is thanked for mass spectroscopy determination. Niklas B. Thompson is thanked for his assistance with crystallographic and Hammett plot analysis. The Bruker KAPPA APEXII X-ray diffractometer was purchased via an NSF CRIF:MU award to Caltech. The Varian 400 MHz NMR spectrometer at Caltech was purchased via an NIH grant (RR027690).

## ■ REFERENCES

- (1) (a) Majetich, G.; Shimkus, J. M. *J. Nat. Prod.* **2010**, *73*, 284. (b) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 871. (c) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1996**, *42*, 1657. (d) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493. (e) Chang, C.-I.; Chien, S.-C.; Lee, S.-M.; Kuo, Y.-H. *Chem. Pharm. Bull.* **2003**, *51*, 1420. (f) Chang, C.-I.; Chang, J.-Y.; Kuo, C.-C.; Pan, W.-Y.; Kuo, Y.-H. *Planta Med.* **2005**, *71*, 72.
- (2) (a) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Org. Lett.* **2003**, *5*, 3931. (b) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144. (c) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2006**, *71*, 2787. (d) Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896. (e) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738. (f) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022. (g) Li, S.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741. (h) Tang, S.; Xu, Y.; He, J.; He, Y.; Zheng, J.; Pan, X.; She, X. *Org. Lett.* **2008**, *10*, 1855. (i) Majetich, G.; Shimkus, J. M. *Tetrahedron Lett.* **2009**, *50*, 3311. (j) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Meneses, R.; Es-Samti, H.; Fernández, A. *J. Org. Chem.* **2009**, *74*, 3384. (k) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Charrah, Y.; Es-Samti, H. *Org. Biomol. Chem.* **2009**, *7*, 5146. (l) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592. (m) Node, M.; Ozeki, M.; Planas, L.; Nakano, M.; Takita, H.; Mori, D.; Tamatani, S.; Kajimoto, T. *J. Org. Chem.* **2010**, *75*, 190. (n) Jana, C. K.; Scopelliti, R.; Gademann, K. *Synthesis* **2010**, 2223. (o) Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem.—Eur. J.* **2010**, *16*, 7692. (p) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. *Chem. Commun.* **2010**, 46, 9244. (q) Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088. (r) Tapia, R.; Guardia, J. J.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *J. Org. Chem.* **2012**, *77*, 573. (s) Deng, J.; Li, R.; Luo, Y.; Li, J.; Zhou, S.; Li, Y.; Hu, J.; Li, A. *Org. Lett.* **2013**, *15*, 2022. (t) Li, L.-Q.; Li, M.-M.; Chen, D.; Liu, H.-M.; Geng, H.-C.; Lin, J.; Qin, H.-B. *Tetrahedron Lett.* **2014**, *55*, 5960.
- (3) (a) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911. (b) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742. (c) Katoh, T.; Akagi, T.; Noguchi, C.; Kajimoto, T.; Node, M.; Tanaka, R.; Nishizawa, M.; Ohtsu, H.; Suzuki, N.; Saito, K. *Bioorg. Med. Chem.* **2007**, *15*, 2736.
- (4) (a) Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902. (b) 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. (c) Holder, J. C.; Marziale, A. N.; Gatti, M.; Mao, B.; Stoltz, B. M. *Chem.—Eur. J.* **2013**, *19*, 74.
- (5) Reetz, M. T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* **1981**, 237.
- (6) 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 ( $\sigma_p$ ) for *para*-Br and *para*-iPr.
- (7) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyauchi, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.
- (8) Sun, J.; Perfetti, M. T.; Santos, W. L. *J. Org. Chem.* **2011**, *76*, 3571.
- (9) Johnston, M. D.; Shapiro, B. L.; Shapiro, M. J.; Proulx, T. W.; Godwin, A. D.; Pearce, H. L. *J. Am. Chem. Soc.* **1975**, *97*, 542.
- (10) Takeda, M.; Inoue, H.; Noguchi, K.; Honma, Y.; Kawamori, M.; Tsukamoto, G.; Yamawaki, Y.; Saito, S. *Chem. Pharm. Bull.* **1976**, *24*, 1514.
- (11) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532.
- (12) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.
- (13) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1990**, *55*, 991.