Palladium-Catalyzed Enantioselective Redox-Relay Heck Arylation of 1,1-Disubstituted Homoallylic Alcohols

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S *Supporting Information*

ABSTRACT: An enantioselective redox-relay oxidative Heck arylation of 1,1-disubstituted alkenes to construct β-stereocenters was developed using a new pyridyl-oxazoline ligand. Various 1,2-diaryl carbonyl compounds were readily obtained in moderate yield and good to excellent enantioselectivity. Additionally, analysis of the reaction outcomes using multidimensional correlations revealed that enantioselectivity is tied to specific electronic features of the 1,1-disubstituted alkenol and the extent of polarizability of the ligand.

Molecules containing a 1,2-diaryl motif are a common scaffold in various medicinally relevant molecules. For example, several 1,2-diaryl compounds target vitronectin receptor antagonists, implicated in the treatment of osteoporosis and breast cancer, and the urokinase receptor, an important cell surface GPI-anchored protein suggested to promote tumor metastasis (Figure 1a).[1] Accordingly, various synthetic methods have been developed, including benzylation of cinnamyl compounds,[2] diarylation of alkenes,[3] isomerization of trisubstituted styrene alcohols,[4] and arylation of *tert*-cyclobutanols via C−C bond cleavage.[5] Despite these advances, catalytic enantioselective variants to access 1,2-diaryl carbonyl compounds are rare and suffer from limited substrate scope.[6] We saw this dearth of examples as an opportunity to explore our recently developed enantioselective redox-relay Heck reaction of multisubstituted alkenols on 1,1-disubstituted alkenes (Figure 1b).[7,8] Successful development of such a protocol would provide direct and modular access to enantiomerically enriched 1,2-diaryl carbonyl structures.

In contrast to our previous reports, initial migratory insertion of the Pd−Ar species into 1,1-disubstituted alkenols forms a new C−C bond at the terminal position of the alkene, and the chiral center is established β to this site (**A**, Figure 1b).[9] A central concern for this substrate class involves selective β-hydride elimination. Specifically, β-hydride elimination of H_S ($H_{styrenyl}$) would yield the traditional Heck product, trisubstituted styrene **B**, or β-hydride elimination of H_R (H_{relay}) would ultimately lead to the desired aldehyde compound. The styrenyl product not only is thermodynamically more stable but also is historically formed using terminal alkenes under similar conditions.[10] Herein, we present the development of a successful enantioselective redox-relay Heck reaction of 1,1-homoallylic alcohols forming the desired 1,2-diaryl structures. This outcome required the use of a new pyridyl-oxazoline (PyrOx) ligand to overcome the
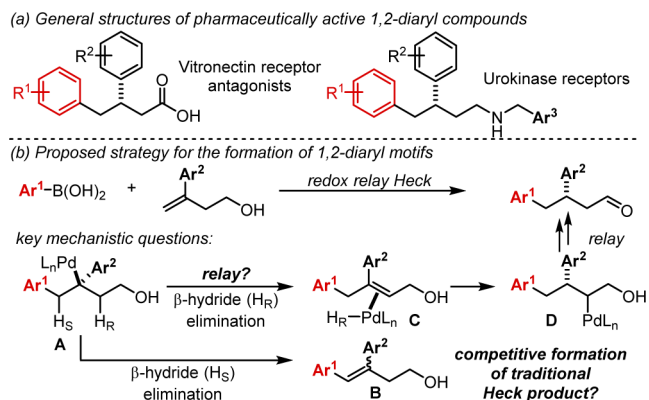

Figure 1. Effective drug candidates containing 1,2-diaryl motifs and proposed strategy.

propensity of trisubstituted styrene formation and achieve high enantioselectivity with this new alkene class.

On the basis of our previous success, chiral PyrOx ligand **L1** was first examined with $Pd(CH_3CN)_4(OTf)_2$ as a precatalyst under standard redox-relay oxidative Heck conditions[7c] using 1,1-disubstituted alkene **1a** and *p*-chlorophenylboronic acid as model coupling partners. When DMF was used as solvent, the desired relay product (**2e**) was produced in only 24% yield and a disappointing 69.5:30.5 er (Table 1, entry 1). The mass balance was a combination of unreacted starting material and the traditional Heck product. To improve the reaction outcome, we evaluated several PyrOx ligands with modifications (entries 2−4) to the oxazoline portion. By incorporating aryl groups into the ligand structure, potential involvement of noncovalent π interactions between the ligand substituent and the substrate became evident. A considerable enhancement was observed using ligand **L4** (89:11 er) in comparison to **L1** (69.5:30.5 er), which lacks an aryl group (a putative explanation is discussed below). In further optimization of the reaction conditions, solvent proved the most important variable, as illustrated with initial identification of MeOH as the reaction solvent (entries 7 and 8). Ultimately, a combination of MeOH and MTBE provided the best results in terms of both yield and enantioselectivity, yielding product **2e** in 63% and 95.5:4.5 er (entry 9).

Using these optimal conditions, the reaction scope was explored with a number of arylboronic acids (Table 2). In general, the desired 1,2-diaryl carbonyl compounds were obtained with moderate yields and good to excellent enantio-

Table 1. Optimization[a]

entry	ligand	solvent	% yield	er
1	L1	DMF	24	69.5:30.5
2	L2	DMF	30	80:20
3	L3	DMF	35	51:49
4	L4	DMF	30	89:11
5	L4	acetone	24	86:14
6	L4	dioxane	20	90:10
7	L4	MeOH	57	95.5:4.5
8[b]	L4	MeOH	49	96.5:3.5
9	L4	MeOH:MTBE = 3:1	63	95.5:4.5

Ligand 1   Ligand 2   Ligand 3   Ligand 4

[a]Each entry represents the isolated yield on 0.3 mmol scale at rt and used 3.0 equiv of *p*-chlorophenylboronic acid unless otherwise noted; er determined by SFC. [b]Reaction performed at 10 °C.

Table 2. Arylboronic Acid Scope[a]

2a, 43% 92.5:7.5 er
2b, 52% 94:6 er
2c, 55% 94.5:5.5 er
2d, 59% 95.5:4.5 er
2e, 63% 95.5:4.5 er
2f, 55% 95.5:4.5 er
2g, 64% 96:4 er
2h, 55% 96.5:3.5 er
2i, 63% 94:6 er
2j, 55% 93:7 er
2k, 50% 95:5 er
2l, 62% 96:4 er
2m, 40% 98:2 er
2n, 41% 92.5:7.5 er
2o, 52% 93:7 er

[a]Each entry represents the isolated yield on 0.3 mmol scale and used 3.0 equiv of arylboronic acid; er determined by SFC.

Table 3. Scope of the Homoallylic Alcohols[a]

2p, 62% 95.5:4.5 er
2q, 58%[b] 96.5:3.5 er
2r, 56% 91.5:8.5 er
2s, 63% 90:10 er
2t, 43% 93.5:6.5 er
2u, 51% 96:4 er
2v, 18% 80:20 er
2w, 36% 91.5:8.5 er
2x, 48% 96:4 er
2y, 52% 95:5 er
2z, 40% 95:5 er
2aa, 41% 95.5:4.5 er
2ab, 51%[c,d] 95:5 er
2ac, 24% 69.5:30.5 er
2ad, 34%[d] 67.5:32.5 er
2ae, 52% 51.5:48.5 er

[a]Each entry represents the isolated yield on 0.3 mmol scale and used 3.0 equiv of arylboronic acid; er determined by SFC. [b]On 3 mmol scale, **2q** was isolated in 55% yield and 95.5:4.5 er. [c]Phenylboronic acid was used. [d]Absolute configuration determined to be (*R*); thus the rest of the products, except **2ac** and **2ad**, were assigned as (*R*) by analogy. Absolute configuration of **2ad** determined to be (*S*); thus **2ac** was assigned as (*S*) by analogy.[12]

3,5-dichlorophenylboronic acid afforded the desired product **2m** in 98:2 er. It should also be noted that a simple heteroaromatic boronic acid, 2-dibenzofuranyl, was successfully incorporated, providing the corresponding product **2o** in 52% yield and 93:7 er. Other Lewis basic boronic acids were incompatible under these reaction conditions.[11]

Next, substituent effects on the alkenol (**1**) were evaluated under the standard reaction conditions (Table 3). The electronic nature of *para*-substituents on the styrenyl moiety had a greater influence on the enantioselectivity than was observed with substituted arylboronic acids. In this case, electron-donating groups led to higher enantioselectivity (**2q–2t**). Unfortunately, an *ortho*-fluorine was not well-tolerated, resulting in a significant decrease in yield and enantioselectivity (**2v**). It is noteworthy that a substrate containing a secondary alcohol gave 95.5:4.5 er, although in lower yield than observed with a primary alcohol (**2aa** compared to **2e**).

As the enantiodetermining step is likely migratory insertion of the alkene (**C** to **D**, Figure 1b),[9a] we hypothesized that the reaction of a 1,1-disubstituted alkene with two similar alkyl substituents would lead to low enantioselectivity due to a difficult differentiation of the substituents by the catalyst. Indeed, when alkyl-substituted alkenols were explored, the corresponding products were obtained with poor er and opposite face selection (**2ad**, **2ae**). Additionally, if the aryl group is not in conjugation with the alkene, low enantioselectivity was observed (**2ac**).

meric ratios (er). Again, the mass balance was mainly composed of the traditional Heck product. Compared with *p*-chlorophenylboronic acid, giving **2e**, the use of electron-rich arylboronic acids decreased the yield and the enantioselectivity (**2a**, **2b**), while electron-withdrawing groups in the *meta*- or *para*-position did not have a significant effect (**2c–2h**). This is consistent with a greater propensity for β-hydride elimination at H_S with adjacent electron-rich arenes observed previously in our laboratory.[3c,10] Substituents at the *ortho*-position led to a modest reduction in enantioselectivity (**2i**, **2j**). Finally, multisubstituted arylboronic acids were tested in this reaction (**2j–2o**). In particular, the use of

Table 4. Chain-Length Effect[a]

^{a}Each entry represents the isolated yield on 0.3 mmol scale and used 3.0 equiv of p-chlorophenylboronic acid; er determined by SFC.

In our previous redox-relay Heck reports, the chain length between the alcohol and the alkene minimally influenced the enantioselectivity, albeit none of these examples were styrenyl in nature and used ligand **1** exclusively. Thus, the profound effect of chain length on enantioselectivity in this system was surprising (Table 4). The bis-homoallylic alcohol substrate **1af** delivered desired product **2af** in 51% yield and 88.5:11.5 er, a significantly diminished result as compared to the model homoallylic substrate **1p**. The yields and enantioselectivities continued to decrease as a function of increasing chain length (**2ag**, **2ah**).

As the primary goal was to synthesize 1,2-diaryl compounds as described in Figure 1, we focused on the functionalization of homoallylic alcohols. Nonetheless, the observed product enantioselectivities with longer chain lengths are disappointing from the perspective of broadening the scope of the reaction. To facilitate a deeper understanding of the limitations of this system and potentially lend insight into future solutions, analysis of the data sets in terms of both the substrate and ligand effects on enantioselectivity was performed.

A multidimensional modeling strategy developed within our group was executed.[13] Through this iterative process, relevant molecular descriptors are related to the reaction output, enantioselectivity, through linear regression modeling techniques. When the effect of substrate identity on the enantioselectivity in this reaction was analyzed, a correlation was identified with three terms: the alkene C=C vibration ($\nu_{C=C}$), the O−H stretching frequency (ν_{O-H}), and the NBO charge of the allylic carbon (NBO$_{allyl-C}$, Figure 2a). The electronic nature of the alkene, modulated by the variable substituent, is likely described using the alkene stretching frequency, $\nu_{C=C}$, and thus plays a crucial role in the alkene face selection and enantio-determining step. The chain length effect can be expressed using ν_{O-H}, as demonstrated by the univariate correlation of this parameter to the enantioselectivities of products **2p** and **2ag**−**2ah** ($R^2 = 0.91$, Figure 2b). As this stretching frequency decreases based on the distance between the alcohol and the alkene, the observed enantioselectivities also decrease. A similar trend between the enantioselectivities of these products with varying chain lengths and NBO$_{allyl-C}$ was also identified, with increasingly negative charge of the allylic carbon correlating with higher enantioselectivity ($R^2 = 0.92$, Figure S6). Both of these trends suggest that the polarization of the alkyl chain due to the distance between the alcohol and the alkene is partially responsible for face discrimination of the substrate that is required for an enantioselective migratory insertion. We proposed a similar hypothesis in rationalizing site selectivity trends in the redox-relay Heck reaction of 1,2-disubstituted alkenols.[7b,9a] These trends could also indicate that the electronic and geometric nature of the alcohol itself is an important element for catalyst recognition. Overall, identifying these trends revealed several inherent properties of the
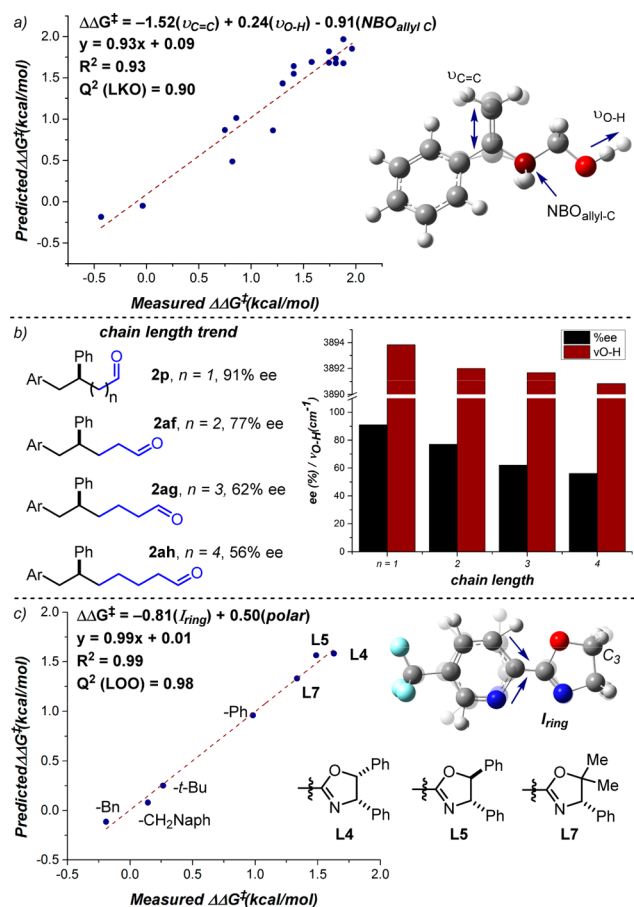

Figure 2. (a) Multidimensional correlation of substrate properties and enantioselectivities (Leave-K-Out (LKO), K = 6). (b) Univariate trend between the chain length and the alcohol stretching frequency. (c) Multidimensional correlation of ligand effects and enantioselectivies (Leave-One-Out (LOO)).

alkenol, including the electronic character of the alkene and the alcohol, that are required for high er.

To gain further insight into this process, the focus shifted to identifying the subtle structural effects of the ligand on the enantiodetermining step in this reaction. Using the same modeling strategy, properties of seven ligands with changes to the oxazoline were related to the measured enantioselectivities. An excellent correlation was identified with two terms: an IR intensity of a specific ring vibration on the pyridine (I_{ring}) and the ligand's computed polarizability (polar, Figure 2c). Upon closer examination of the corresponding ring stretch, it was observed that the C−C bond between heterocycles and the hydrogens or substituents at C_3 are also affected by this stretch. Consequently, the intensity of this frequency is likely accounting for steric effects as well as the electronic contributions from the substituents on the oxazoline. Additionally, the polarizability, or the extent of electron cloud distortion in the presence of an external electric field, could represent the ability of the ligand's substituents to interact in an attractive manner with the substrate.[14] As the electronic natures of the alkene and the alcohol were identified as significant influences in enabling a highly enantioselective method, a positive interaction between the aryl substituent or alcohol of the substrate and the ligand, such as a π-stacking or lone pair−π interaction, is plausible.[15] Certain geometric constraints are also observed within these data, including the requirement of a styrenyl substrate, homoallylic alcohol, and a Ph-substituted
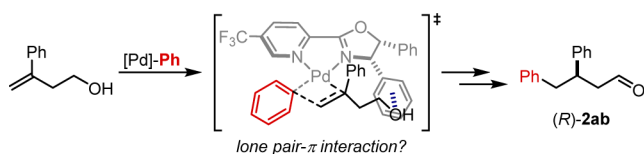
Figure 3. Proposed lone pair−π interaction as a controlling element in the transition state.

oxazoline for high er values. Since attractive interactions are more sensitive to the distance between the two interacting species,[16] these geometric requisites support the presence of an attractive noncovalent interaction between the ligand and the substrate. By combining the insight gained from the substrate and ligand effects as well as our previous computational report,[9a] a working hypothesis on the origin of enantioselectivity is proposed (Figure 3). The proposed transition state, which would lead to the observed product enantiomer, features a lone pair−π interaction between the alcohol and the phenyl group on the ligand.[15c] This interaction is consistent with the requirements described above.

In summary, we have successfully developed a method to synthesize enantiomerically enriched 1,2-diaryl carbonyl compounds, a common pharmacophore, in good to high enantioselectivity. The insight gained through uni- and multivariate correlations has revealed key properties in both the substrate and ligand, leading to a proposed attractive interaction responsible for achieving a highly selective process. Detailed mechanistic studies are in progress to investigate the unexpected effect of chain length on enantioselectivity and the potential role of noncovalent π interactions as controlling elements in the enantiodetermining step.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06994.

Experimental details, analytical data and NMR spectra of products, computations, and modeling details (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Manley, P. J.; Miller, W. H.; Uzinskas, I. N. (SmithKline Beecham Corp.). European Patent EP1218005A2, July 3, 2002. (b) Miller, W. H.; Manley, P. J.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1483. (c) Wang, F.; Li, J.; Sinn, A. L.; Knabe, W. E.; Khanna, M.; et al. *J. Med. Chem.* **2011**, *54*, 7193. (d) Hasui, T.; Matsunaga, N.; Ora, T.; Ohyabu, N.; Nishigaki, N.; et al. *J. Med. Chem.* **2011**, *54*, 8616. (e) Kim, M.; Ryu, J.; Hah, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1639. (f) Irannejad, H.; Unsal Tan, O.; Ozadali, K.; Dadashpour, S.; Tuylu Kucukkilinc, T.; Ahangar, N.; Ahmadnejad, M.; Emami, S. *Chem. Biol. Drug Des.* **2015**, *85*, 494. (g) Sun, J.; Chen, L.; Liu, C.; Wang, Z.; Zuo, D.; Pan, J.; Qi, H.; Bao, K.; Wu, Y.; Zhang, W. *Chem. Biol. Drug Des.* **2015**, *86*, 1541. (h) Koo, K. A.; Lorent, K.; Gong, W.; Windsor, P.; Whittaker, S. J.; Pack, M.; Wells, R. G.; Porter, J. R. *Chem. Res. Toxicol.* **2015**, *28*, 1519.

(2) (a) Lenz, G. R. *J. Org. Chem.* **1988**, *53*, 5791. (b) Mandal, S. K.; Jana, S.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 6115. (c) Franzoni, I. L.; Guénée, L.; Mazet, C. *Org. Biomol. Chem.* **2015**, *13*, 6338.

(3) (a) Trejos, A.; Fardost, A.; Yahiaoui, S.; Larhed, M. *Chem. Commun.* **2009**, 7587. (b) Lundin, M. P.; Esquivias, J.; Fu, C. G. *Angew. Chem., Int. Ed.* **2009**, *48*, 154. (c) Urkalan, B. K.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146. (d) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560. (e) Stokes, B. J.; Liao, L.; de Andrade, A. M.; Wang, Q.; Sigman, M. S. *Org. Lett.* **2014**, *16*, 4666. (f) You, W.; Brown, M. K. *J. Am. Chem. Soc.* **2014**, *136*, 14730. (g) Tang, C.; Xie, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 7662. (h) You, W.; Brown, M. K. *J. Am. Chem. Soc.* **2015**, *137*, 14578.

(4) (a) Li, H.; Mazet, C. *Org. Lett.* **2013**, *15*, 6170. (b) Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014**, *136*, 16882.

(5) Ziadi, A.; Martin, R. *Org. Lett.* **2012**, *14*, 1266.

(6) (a) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (b) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886. (c) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. *Chem. - Eur. J.* **2013**, *19*, 9147. (d) Dell'Amico, L.; Companyó, X.; Naicker, T.; Bräuer, T. M.; Jørgensen, K. A. *Eur. J. Org. Chem.* **2013**, *2013*, 5262. (e) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 4588. (f) Seo, W. S.; Kim, S. *Tetrahedron Lett.* **2012**, *53*, 2809. (g) Izquierdo, J.; Orue, A.; Scheidt, A. K. *J. Am. Chem. Soc.* **2013**, *135*, 10634. (h) Lu, P.; Jackson, J. J.; Eickhoff, J. A.; Zakarian, A. *J. Am. Chem. Soc.* **2015**, *137*, 656. (i) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2002**, 50. (j) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862. (k) Zhang, C.; Yun, J. *Org. Lett.* **2013**, *15*, 3416.

(7) Selected works from our group: (a) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. (b) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830. (c) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340.

(8) Selected works from other groups: (a) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629. (b) Bouquillon, S.; Ganchegui, B.; Estrine, B.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153. (c) Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron* **2006**, *62*, 4372. (d) Correia, C. R. D.; Oliveira, C. C.; Salles, A. G., Jr; Santos, E. A. F. *Tetrahedron Lett.* **2012**, *53*, 3325. (e) Oliveira, C. C.; Angnes, R. A.; Correia, C. R. D. *J. Org. Chem.* **2013**, *78*, 4373. (f) Angnes, R. A.; Oliveira, J. M.; Oliveira, C. C.; Martins, N. C.; Correia, C. R. D. *Chem. - Eur. J.* **2014**, *20*, 13117. (g) Oliveira, C. C.; Pfaltz, A.; Correia, C. R. D. *Angew. Chem., Int. Ed.* **2015**, *54*, 14036.

(9) (a) Xu, L.-P.; Hilton, M. J.; Zhang, X.; Norrby, P. O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960. (b) Hilton, M. J.; Xu, L.-P.; Norrby, P. O.; Wu, Y.-D.; Wiest, O.; Sigman, M. S. *J. Org. Chem.* **2014**, *79*, 11841.

(10) Selected recent works: (a) Parrish, J. P.; Jung, Y. C.; Shin, S.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 7127. (b) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 13981. (c) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692.

(11) No product was observed using 3-pyridinylboronic acid, 3-furanylboronic acid, and 3-thienylboronic acid.

(12) For details on the assignment of absolute configuration, please see the Supporting Information.

(13) Sigman, M. S.; Harper, K. C.; Bess, E. N.; Milo, A. *Acc. Chem. Res.* **2016**, *49*, 1292.

(14) (a) Guckian, K. M.; Schweitzer, B. A.; Ren, R. X.; Sheils, C. J.; Tahmassebi, D. C.; Kool, E. T. *J. Am. Chem. Soc.* **2000**, *122*, 2213. (b) Watt, M.; Hardebeck, L. K. E.; Kirkpatrick, C. C.; Lewis, M. *J. Am. Chem. Soc.* **2011**, *133*, 3854.

(15) (a) Raju, R. K.; Bloom, J. W. G.; An, Y.; Wheeler, S. E. *ChemPhysChem* **2011**, *12*, 3116. (b) Sherrill, C. D. *Acc. Chem. Res.* **2013**, *46*, 1020. (c) Singh, S. K.; Das, A. *Phys. Chem. Chem. Phys.* **2015**, *17*, 9596.

(16) Biedermann, F.; Schneider, H.-J. *Chem. Rev.* **2016**, *116*, 5216.