OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Asymmetric Synthesis of β-Aryl β-Imido Sulfones Using Rhodium Catalysts with Chiral Diene Ligands: Synthesis of Apremilast

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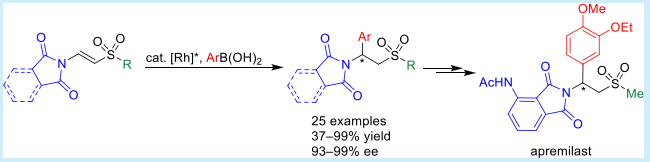
Supporting Information

ABSTRACT: A chiral rhodium(I)−diene catalyst enabled the one-step synthesis of β-aryl β-imido sulfones under mild reaction conditions. By selection of the chiral diene ligand **L1a** or **L2**, each enantiomer of the chiral β-aryl β-imido sulfone target can be accessed with high stereoselectivity. Demonstration of the scope of the reaction, which includes the synthesis of an *N*-protected chiral β-amino β-phenyl sulfone, culminated with the efficient synthesis of the heteroatom-rich active pharmaceutical ingredient apremilast.



Enantioenriched β-amino sulfone derivatives are versatile synthons in synthetic chemistry[1,2] and display a wide range of biological activities as compounds of medicinal importance.[3] For example, the oral drug apremilast (Otezla) (Figure 1), which is an inhibitor of phosphodiesterase 4

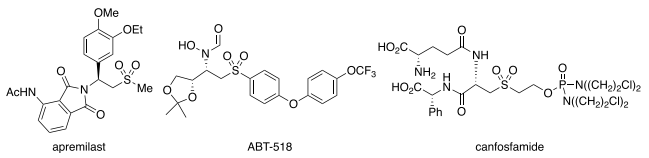


Figure 1. Drug molecules containing β-amino sulfone moieties.

(PDE4), is currently being used to treat active psoriatic arthritis and plaque psoriasis.[3b] ABT-518, a selective and potent matrix metalloproteinase inhibitor, has shown inhibition of cancer cell growth,[3c] while canfosfamide is a nitrogen mustard prodrug with potential antineoplastic activity that has been explored in phase 2 clinical trials for the treatment of several cancer indications.[3d]

Chiral β-amino sulfones and their derivatives are generally prepared from amino acids,[2a−d] by the diastereoselective addition of lithiated sulfone carbanions to chiral *N*-sulfinylimines,[2e,f,4] or through enantioselective aza-Michael additions to vinyl sulfones.[5] However, these methods require multistep manipulations and/or relatively expensive chiral auxiliaries. Transition-metal-catalyzed syntheses of β-amino sulfones are limited to Rh-catalyzed homogeneous enantioselective hydrogenations of β-sulfonyl enamines[6a] and β-acetylamino vinyl sulfones.[6b]

With a need to identify an efficient and enantioselective synthetic method for producing the active pharmaceutical ingredient apremilast, we set out to assess whether the Rh-catalyzed addition reaction could be applied to β-phthalimido vinyl sulfone Michael acceptor substrates. The Rh(I)-catalyzed asymmetric addition of organoboron reagents to electron-deficient conjugated alkenes, known as the Hayashi−Miyaura reaction, has emerged as the method of choice for the preparation of homochiral β-alkenyl- or β-aryl-substituted carbonyl compounds and electronic equivalents such as nitro- and phosphonyl alkenes, among others.[7] The first reported asymmetric addition of arylboronic acids to α,β-unsaturated sulfones was catalyzed by Rh(I)−diphosphine catalysts and relied, crucially, on the chelating effect of a strategically positioned *S*-(2-pyridyl) group directly adjacent to the sulfur atom.[8] Without the 2-pyridyl group, or a less effective 2,6-pyrimidyl or imidazoyl group, the vinyl sulfones were inert toward 1,4-addition[8c] or underwent nucleophilic *cine*-substitution when aryltitanium triisopropoxide reagents were used.[9] The recent development of chiral Rh(I)−diene catalysis,[7e−i] however, has paved the way for the arylation of unsaturated cyclic and acyclic sulfonates and sulfones without the necessity for a 2-pyridyl group.[10]

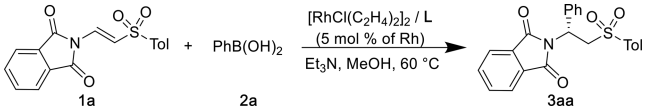
Despite these advances, to the best of our knowledge, no examples of 1,4-additions of arylboronic acids to β-imido vinyl sulfones catalyzed by Rh(I) salts have been reported. By analogy to the corresponding carbonyl compounds,[11] we envisioned that chiral β-aryl β-amino sulfone derivatives, such as apremilast, could be accessed by the Rh(I)-catalyzed arylation of α,β-unsaturated β-imido sulfones.[12] Here we describe a general approach that provides access to enantioenriched β-aryl β-phthalimido and -succinimido sulfones, which can be readily converted to β-amino sulfone derivatives, via a Rh(I)-catalyzed asymmetric addition reaction of arylboronic acids to β-imido vinyl sulfones.

Received: April 30, 2019

DOI: 10.1021/acs.orglett.9b01513
Org. Lett. XXXX, XXX, XXX−XXX

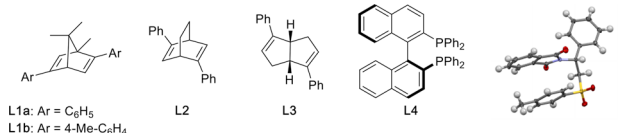
Investigations commenced with a model addition reaction of phenylboronic acid (**2a**) to β-phthalimido (*E*)-vinyl sulfone **1a** catalyzed by complexes formed from $[RhCl(C_2H_4)_2]_2$ (precatalyst) and chiral 2,5-diaryl-substituted bicyclo[2.2.1]-heptadiene ligands **L1a–e** previously developed in our laboratory[13] (Table 1). Ligands **L2**, **L3**, and **L4** have been

Table 1. Optimization of the Reaction Conditions[a]



entry	L	time	yield (%)	ee (%)
1	**L1a**	2	99	99
2	**L1b**	3	90	97
3	**L1c**	4.5	83	98
4	**L1d**	3	92	97
5	**L1e**	5	58	99
6[b]	**L1a**	3	80[c]	94
7	**L2**	3	91	−98
8	**L3**	24	N.R.	N.D.
9	**L4**	30	N.R.	N.D.
10[d]	**L1a**	7	89	98
11[e]	**L1a**	24	50	96

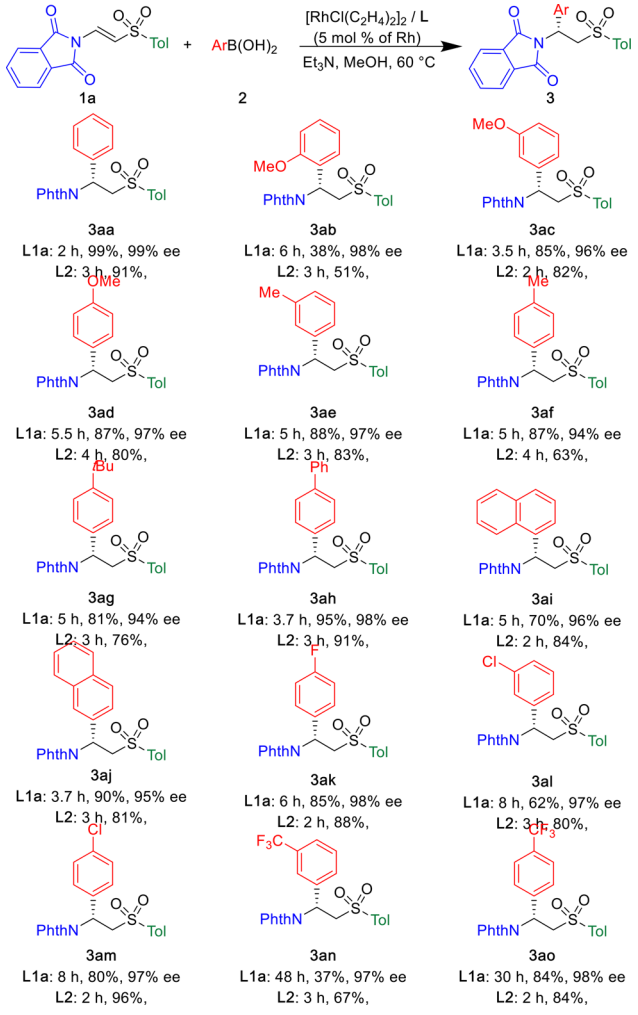
[a]Reaction conditions: **1a** (0.11 mmol), **2a** (0.22 mmol), $[RhCl(C_2H_4)_2]_2$ (2.5 mol %), ligand **L** (6 mol %), and Et_3N (0.11 mol). Isolated yields are reported (N.R. = no reaction). The ee values were determined by chiral HPLC analysis (N.D. = not determined). The absolute configuration of **3aa** was determined as (*R*) by single-crystal X-ray crystallography. [b](*Z*)-**1a** was used. [c]12% (*E*)-**1a** was recovered. [d]3 mol % catalyst. [e]1 mol % catalyst.



reported elsewhere as being useful in Hayashi–Miyaura reactions and were therefore examined also. Initial screening[14] of the reaction conditions involved a large array of inorganic or organic amine bases in dioxane, MeOH, EtOH, or *i*-PrOH as the solvent in the presence of Rh(I)/**L1a** (5 mol %) at 60 °C. While it was evident that some conditions provided poor yields, the combination of Et_3N[13c] and MeOH was found to furnish both an excellent yield (96%) and enantioselectivity (99% ee) of sulfone **3aa**. Single-crystal X-ray crystallography unequivocally determined that **3aa** was *R*-configured. Further screening under these conditions with diene ligands **L1b–e** revealed that moderate to good yields and high enantioselectivities of 97–99% ee were attainable (Table 1, entries 2–5); among the five dienes **L1a–e**, however, phenyl-substituted derivative **L1a** offered the best yield and enantioselectivity (entry 1). Contrary to our expectation, addition of **2a** to the *Z* isomer of **1a** gave rise to the same enantiomer of the addition product, (*R*)-**3aa**, albeit with slightly reduced selectivity and yield (entry 6). In situ isomerization of (*Z*)-**1a** to the thermodynamically more stable *E* isomer accounted for the production of (*R*)-**3aa** rather than the anticipated enantiomer (*S*)-**3aa**; this was supported by the recovery of unreacted (*E*)-**1a** from the reaction mixture. While the same reaction failed when chiral bicyclo[3.3.0]octadiene ligand **L3** or the chiral diphosphine ligand (*S*)-BINAP (**L4**) was employed (entries 8 and 9), the use of chiral bicyclo[2.2.2]octadiene ligand **L2** provided a 91% yield of **3aa** with −98% ee (entry 7), thereby allowing access to the other enantiomer of the product. While comparable enantioselectivities were observed when the reactions were conducted in the presence of 3 and 1 mol % Rh(I)/**L1a**, the chemical yield dropped to 89% and 50%, respectively (entries 10 and 11).

Next, the scope of the addition reaction of β-phthalimido α,β-unsaturated sulfone **1a** was examined by substituting variously adorned arylboronic acids for phenylboronic acid (**2a**) from the model reaction using diene ligand **L1a** or **L2** (Scheme 1). Electron-rich (**2c** and **2d**), electron-neutral (**2e–g**), and electron-deficient (**2k–o**) arylboronic acids all performed well, offering the corresponding chiral addition adducts in good yields (up to 99%) with excellent stereoselectivities (94–99% ee) of both enantiomers, except for 2-methoxyphenylboronic acid (**2b**), which furnished only a moderate yield of **3ab** as a result of the *ortho* substituent. Arylboronic acids harboring conjugated or extended π substituents (**2h–j**) also underwent efficient additions, giving

Scheme 1. Substrate Scope I[a]



[a]Reaction conditions: **1a** (0.11 mmol), **2** (0.22 mmol), $[RhCl(C_2H_4)_2]_2$ (2.5 mol %), ligand **L** (6 mol %), and Et_3N (0.11 mol). Isolated yields are reported. The ee values were determined by chiral HPLC analysis.

DOI: 10.1021/acs.orglett.9b01513
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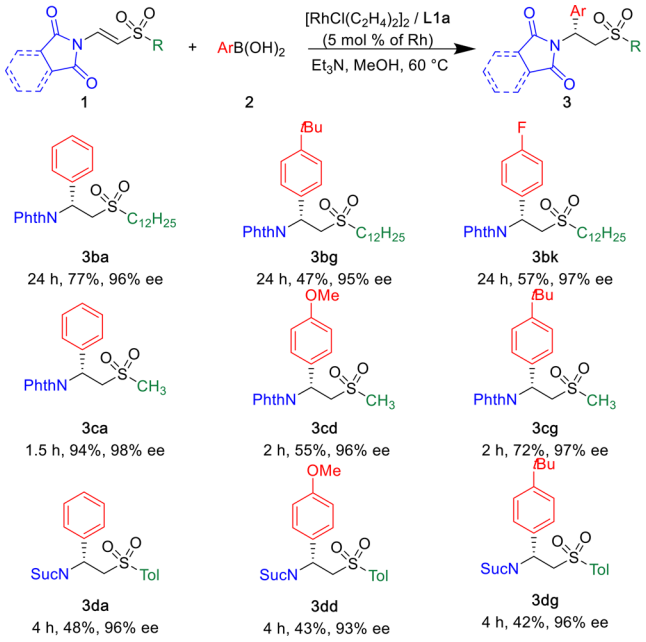
highly enantioenriched products in 70−95% yield with 95−98% ee.

The scope of the reaction was examined further using several *S*-substituted *β*-phthalimido vinyl sulfones as substrates (Scheme 2). As for the *S*-tolyl substrates described above, *S*-

Scheme 2. Substrate Scope II[a]



[a]Reaction conditions: **1** (0.11 mmol), **2** (0.22 mmol), $[RhCl(C_2H_4)_2]_2$ (2.5 mol %), ligand **L1a** (6 mol %), and Et_3N (0.11 mol). Isolated yields are reported. The ee values were determined by chiral HPLC analysis.

dodecyl (**1b**) and *S*-methyl (**1c**) derivatives were generally well-tolerated, supplying the corresponding addition products in 47−94% yield with 95−98% ee. Conversely, while the enantioselectivities were moderately high (93−96% ee), the yields of the *β*-succinimido-substituted derivatives **3da**, **3dd**, and **3dg** formed upon addition of boronic acids to **1d** were less pleasing (42−48%).[15]

With the aim of understanding the basis of the observed stereoselectivity, DFT calculations were performed with the putative phenylrhodium(I) complex using the B3LYP hybrid functional[16,17] in Gaussian 16[18] on two putative transition structures. The basis sets 6-31G (d,p)[19] and LAN2LDZ[20] were employed for the main-group elements and the Rh atom, respectively. As illustrated in Figure 2, transition structure **4a**

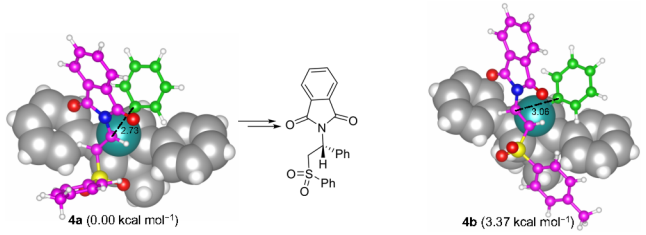
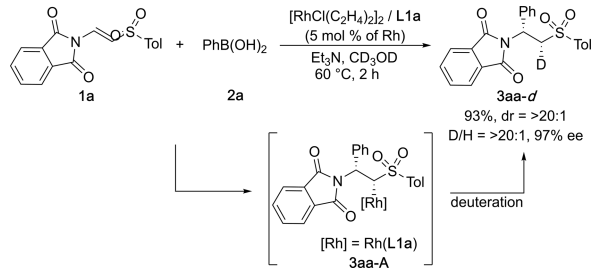


Figure 2. Calculated transition structures for the phenylation step with **1a**. **L1a** is shown in space-filling mode, and rhodium and reactants are presented in ball-and-stick mode. Interatomic distances are shown in Å.

wherein the Rh atom of the complex coordinates to the *Re* face of substrate **1a** is energetically favored, explaining the observed stereochemistry. The corresponding *Si*-face-coordinated complex **4b**, which would lead to the stereochemistry opposite to that observed ((*S*)-**3aa**), was calculated to be 3.37 kcal·mol^{-1} higher in energy than **4a**.

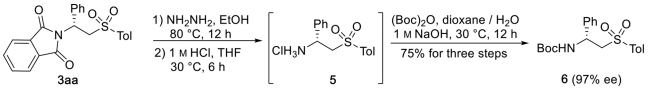
When the addition of **2a** to **1a** was conducted in CD_3OD at 60 °C, deuterated product **3aa**-*d* was isolated as a single diastereomer (according to ^1H NMR spectroscopy) in 93% yield with 97% ee; >95% of the deuterium was incorporated at the *α*-carbon with a *syn* relationship to the phenyl group. These results demonstrate that alkylrhodium intermediate **3aa-A** (Scheme 3), formed by *syn*-phenylrhodation, underwent deuteration (protonation) without *β*-hydrogen elimination[9] or isomerization.

Scheme 3. Deuterium Incorporation Experiment in the Addition of 2a to 1a



To illustrate the usefulness of the imido sulfone products of our method, phthalimido derivative **3aa** was treated with hydrazine and then acidified with HCl to liberate ammonium salt **5** (Scheme 4). This was converted to the corresponding *N*-

Scheme 4. Synthesis of Boc-Protected *β*-Amino Sulfone 6



Boc-protected chiral *β*-phenyl *β*-amino sulfone **6** without erosion of stereointegrity in 75% overall yield over three steps. Such compounds may serve as chiral building blocks or amino acid analogues.

Having demonstrated the scope of the addition reaction, we returned to the original inspiration for developing the method: the asymmetric synthesis of apremilast. To date, several synthetic approaches to apremilast have been published. In 2009, Man et al.[3b] constructed the racemic chiral *β*-amino *β*-aryl sulfone backbone required for this molecule and completed the synthesis by its resolution using *N*-acetyl-L-leucine and coupling with 3-*N*-acetylaminophthalic anhydride. Man's method, while able to provide apremilast with high ee, suffered from a <20% yield for the first two steps combined. This approach was later improved by Ruchelman and Connolly,[6a] who implemented the asymmetric hydrogenation of an enamine derivative of the *β*-amino *β*-aryl sulfone moiety using a Rh(I)−*t*-Bu-Josiphos complex followed by upgrading of the ee, again using *N*-acetyl-L-leucine. Overall, the yield was almost quadrupled. More recently, it was reported[6c] that asymmetric hydrogenation of a *β*-acetylamino vinyl sulfide using a Rh(I)−DuanPhos catalyst could be used to generate an apremilast precursor, thereby representing a formal synthesis of

DOI: 10.1021/acs.orglett.9b01513
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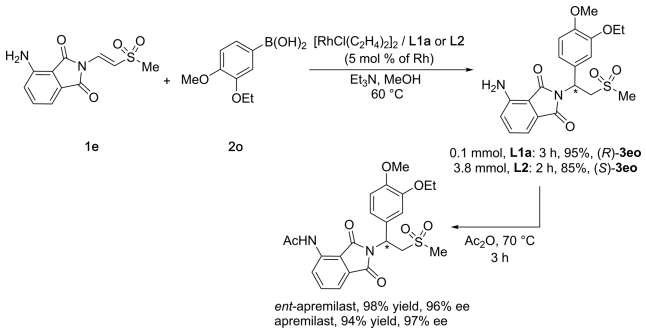
apremilast. None of these methods utilized a conjugate addition as described herein.

To our delight, vinyl methyl sulfone **1e** harboring a free amino group on the phthalimido group reacted smoothly with arylboronic acid **2o** under the reaction conditions described above using ligand **L1a** or **L2**, affording (*R*)- or (*S*)-**3eo** (prepared on a gram scale) in 95% or 85% yield, respectively (Scheme 5). Subsequent acetylation of (*S*)-**3eo** provided

Scheme 5. Synthesis of Apremilast and Its Enantiomer



apremilast in 94% yield with 97% ee. The enantiomer of apremilast was readily prepared in the same way from (*R*)-**3eo** in 98% yield with 96% ee.

In conclusion, with the original motivation being a need for an efficient and enantioselective method to access to the marketed drug apremilast, a general asymmetric Rh(I)-catalyzed arylation reaction of *β*-imido vinyl sulfones with arylboronic acids has been realized.[21] The reaction is mild and affords highly enantioenriched *β*-phthalimido and *β*-succinimido *β*-aryl sulfones in high yields. Electron-rich, -neutral, or -poor boronic acids are tolerated, as are modifications to the imido moiety and the sulfur substituent of the Michael acceptor. While a number of diene ligands (**L1a−e** and **L2**) were found to be useful in the transformation when it was conducted in the presence of 5 mol % Rh(I) precatalyst, chiral ligands **L1a** and **L2** permitted access to both enantiomers of the chiral *β*-aryl *β*-imido sulfone products, which themselves are prevalent motifs in biologically active molecules. Finally, conversion of **3aa** into *N*-Boc-protected *β*-aryl *β*-amino sulfone **6** and the conversion of (*S*)-**3eo** or (*R*)-**3eo** into apremilast or its enantiomer, respectively, demonstrate the utility of the method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01513.

Experimental procedures, additional condition screening table, complete characterization data, HPLC chromatograms and NMR spectra (PDF)

Accession Codes

CCDC 1907355 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Ministry of Science and Technology of the Republic of China (104-2628-M-003-001-MY3 and 107-2113-M-003-014-MY3) is gratefully acknowledged.

■ REFERENCES

(1) For reviews, see: (a) Bäckvall, J. E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291−2312. (b) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547−10658. (c) Prilezhaeva, E. N. *Russ. Chem. Rev.* **2000**, *69*, 367−408. (d) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793−814. (e) Back, T. G. *Can. J. Chem.* **2009**, *87*, 1657−1674.

(2) For selected examples using chiral *β*-amino sulfones in the synthesis, see: (a) Lehman de Gaeta, L. S.; Czarniecki, M.; Spaltenstein, A. *J. Org. Chem.* **1989**, *54*, 4004−4005. (b) Rama Rao, A. V.; Gurjar, M. K.; Pal, S.; Pariza, R. J.; Chorghade, M. S. *Tetrahedron Lett.* **1995**, *36*, 2505−2508. (c) Ermolenko, L.; Sasaki, N. A.; Potier, P. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 2465−2473. (d) Mirilashvili, S.; Chasid-Rubinstein, N.; Albeck, A. *Eur. J. Org. Chem.* **2010**, *2010*, 4671. (e) Kumareswaran, R.; Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **2000**, *41*, 8157−8162. (f) Kumareswaran, R.; Hassner, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2269−2276.

(3) (a) Zajac, M.; Peters, R. *Chem. - Eur. J.* **2009**, *15*, 8204−8222. (b) Man, H.-W.; Schafer, P.; Wong, L. M.; Patterson, R. T.; Corral, L. G.; Raymon, H.; Blease, K.; Leisten, J.; Shirley, M. A.; Tang, Y.; Babusis, D. M.; Chen, R.; Stirling, D.; Muller, G. W. *J. Med. Chem.* **2009**, *52*, 1522−1524. (c) Wada, C. K.; Holms, J. H.; Curtin, M. L.; Dai, Y.; Florjancic, A. S.; Garland, R. B.; Guo, Y.; Heyman, H. R.; Stacey, J. R.; Steinman, D. H.; Albert, D. H.; Bouska, J. S.; Elmore, I. N.; Goodfellow, C. L.; Marcotte, P. A.; Tapang, P.; Morgan, D. W.; Michaelides, M. R.; Davidsen, S. K. *J. Med. Chem.* **2002**, *45*, 219−232. (d) McIntyre, J. A.; Castaner, J. *Drugs Future* **2004**, *29*, 985−991.

(4) (a) Fustero, S.; Soler, J. G.; Bartolomé, A.; Roselló, M. S. *Org. Lett.* **2003**, *5*, 2707−2710. (b) Velázquez, F.; Arasappan, A.; Chen, K.; Sannigrahi, M.; Venkatraman, S.; McPhail, A. T.; Chan, T.-M.; Shih, N.-Y.; Njoroge, F. G. *Org. Lett.* **2006**, *8*, 789−792. (c) Zhang, H.; Li, Y.; Xu, W.; Zheng, W.; Zhou, P.; Sun, Z. *Org. Biomol. Chem.* **2011**, *9*, 6502−6505.

(5) (a) Enders, D.; Müller, S. F.; Raabe, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 195−197. (b) Enders, D.; Müller, S. F.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2000**, *2000*, 879−892.

(6) (a) Ruchelman, A. L.; Connolly, T. J. *Tetrahedron: Asymmetry* **2015**, *26*, 553−559. (b) Jiang, J.; Wang, Y.; Zhang, X. *ACS Catal.* **2014**, *4*, 1570−1573. For related work on asymmetric hydrogenation of *β*-acetylamino vinyl sulfides, see: (c) Gao, W.; Lv, H.; Zhang, Z. *Org. Lett.* **2017**, *19*, 2877−2880.

(7) For seminal reviews, see: (a) Hayashi, T. *Synlett* **2001**, *2001*, 879−887. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (d) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093−2105. (e) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364−3366. (f) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840−871. (g) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482−4502. (h) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31−38. (i) Tian, P.; Dong,

DOI: 10.1021/acs.orglett.9b01513
Org. Lett. XXXX, XXX, XXX−XXX

H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95−119. For some early representative studies on chiral dienes, see: (j) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850−10851. (k) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336−5337. (l) Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762−6766.

(8) (a) Mauleón, P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195−3198. (b) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961−4963. (c) Mauleón, P.; Alonso, I.; Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924−9935.

(9) (a) Yoshida, K.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 2872−2873. (b) So, C. M.; Kume, S.; Hayashi, T. *J. Am. Chem. Soc.* **2013**, *135*, 10990−10993. (c) Yang, Q.; Wang, Y.; Luo, S.; Wang, J. *Angew. Chem., Int. Ed.* **2019**, *58*, 5343−5347.

(10) (a) Nishimura, T.; Takiguchi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 9086−9089. (b) Lim, K. M.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2015**, *137*, 3201−3204.

(11) For a related arylation of *β*-phthalimido acrylates, see: Nishimura, T.; Wang, J.; Nagaosa, M.; Okamoto, K.; Shintani, R.; Kwong, F.-Y.; Yu, W.-Y.; Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464−465.

(12) Truce, W. E.; Brady, D. G. *J. Org. Chem.* **1966**, *31*, 3543−3550.

(13) (a) Wei, W.-T.; Yeh, J.-Y.; Kuo, T.-S.; Wu, H.-L. *Chem. - Eur. J.* **2011**, *17*, 11405−11409. (b) Huang, K.-C.; Gopula, B.; Kuo, T.-S.; Chiang, C.-W.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Org. Lett.* **2013**, *15*, 5730−5733. (c) Gopula, B.; Tsai, Y.-F.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Org. Lett.* **2015**, *17*, 1142−1145. (d) Gopula, B.; Yang, S.-H.; Kuo, T.-S.; Hsieh, J.-C.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Chem. - Eur. J.* **2015**, *21*, 11050−11055. (e) Fang, J.-H.; Jian, J.-H.; Chang, H.-C.; Kuo, T.-S.; Lee, W.-Z.; Wu, P.-Y.; Wu, H.-L. *Chem. - Eur. J.* **2017**, *23*, 1830−1838.

(14) See the Supporting Information for additional results on screening and optimization.

(15) Decompositions of substrate **1d** were observed during the reaction course.

(16) Becke, A. D. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098−3100.

(17) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789.

(18) Frisch, M. J.; et al. *Gaussian 16*, revision A.03; Gaussian, Inc.: Wallingford, CT, 2016.

(19) Andrae, D.; Häussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, *77*, 123−141.

(20) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299−310.

(21) No desired product was observed in the reaction of **1e** and *trans*-2-phenylvinylboronic acid under the optimized reaction conditions.

DOI: 10.1021/acs.orglett.9b01513
Org. Lett. XXXX, XXX, XXX−XXX