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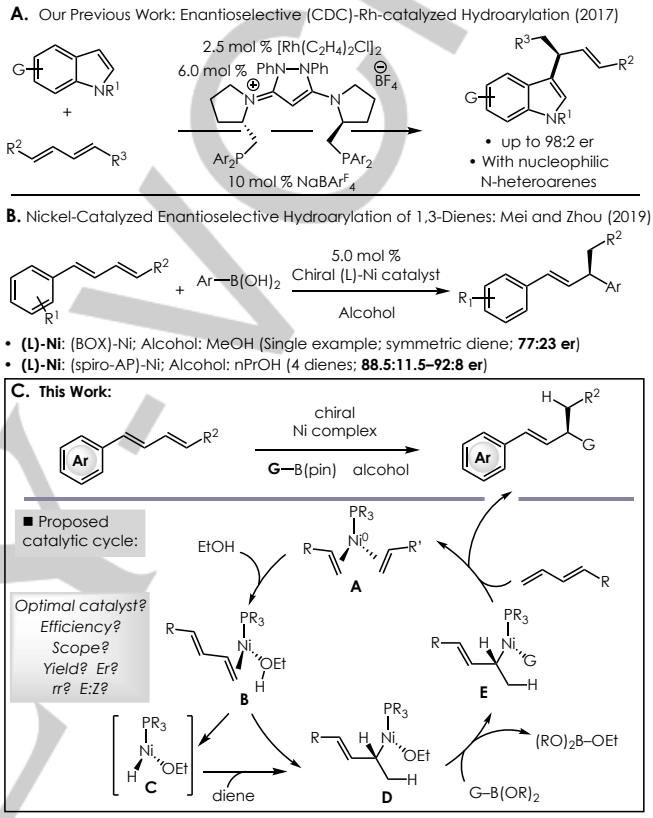
Enantioselective Synthesis of Functionalized Arenes by Nickel-Catalyzed Siteselective Hydroarylation of 1,3-Dienes with Aryl-Boronates

Justin S. Marcum, Tiffany R. Taylor, and Simon J. Meek*[a]

Abstract: A catalytic method for the site- and enantioselective synthesis of functionalized arenes by the intermolecular hydroarylation of terminal and internal 1,3-dienes with aryl pinacolato boronates is disclosed. Reactions are promoted by 5.0 mol % of a readily available monodentate phosphoramidite-Ni complex in ethanol, affording a variety of enantioenriched products in up to 96% yield and 99:1 er. Mechanistic studies indicate Ni-allyl formation is irreversible and related to the nature of the arylboronate.

Catalytic carbon-carbon bond forming methods that efficiently convert unsaturated hydrocarbons into chiral organic molecules in a site- and enantioselective manner has long been recognized as important processes in organic synthesis.[1] Thus, catalytic hydroarylation of olefins, transformations that formally add C(sp^2)–H across C–C π-bonds, has attracted considerable interest as an attractive, atom economical approach for the generation of functionalized arenes.[2] Consequently, several catalytic enantioselective protocols (intra- and intermolecular) have been developed in response.[3–4] In contrast, corresponding methods for the enantioselective hydroarylation of 1,3-dienes are scarce.[5, 6] The reasons for this is related to several challenges associated with identifying catalysts that are able to control multiple aspects of selectivity to synthetically useful levels (>95:5 er, dr, and rr). Nonetheless, transformations involving 1,3-dienes are particularly noteworthy as they deliver products that contain a pendant alkene for further chemical elaboration. [7, 8, 9] And yet, there are only a few catalytic methods for the hydroarylation of 1,3-dienes in high enantiomeric purity. In spite of these challenges, a few catalytic enantioselective examples are known.

We have previously reported catalytic site- and enantioselective reactions between N-heteroarenes to terminal and internal 1,3-dienes promoted by (CDC)-Rh-complex that proceeds via an electrophilic Rh(III)-π-allyl (Scheme 1A).[10,11] Although the method is efficient, site- and enantioselective, the scope of the reaction centers on nucleophilic arenes, since C–C bond formation occurs by outer sphere nucleophile addition. In 2019, Zhou reported a strategy for the catalytic hydroarylation of alkenyl arenes that involves reaction between an olefin, aryl boronic acid, and an alcohol in the presence of a (phosphine)-nickel complex.[6f] Subsequently, Mei[12] and Zhou[13] independently disclosed enantioselective versions through development and application of chiral N,N and P,N bidentate ligands. Included in



Scheme 1. Catalytic Enantioselective Hydroarylations of 1,3-Dienes.

both of these studies 1,3-dienes provide low levels of enantioselectivity (Scheme 1B). In the case of the (bis-oxazoline)-Ni catalyst system, a single example of a symmetric 1,3-diene is described in 77:23 er.[12] In the closely related report by Zhou, several examples of 1,3-dienes promoted by a spiro-N,P-Ni complex are reported, with products formed in 88.5:11.5–92:8 er.[13] In the case of the nickel-catalyzed processes, substrate scope is very limited, with methods relying on relatively unfunctionalized or symmetric 1,3-dienes, and enantioselectivities lower than synthetically desirable (>95:5 er). Our previous (CDC)-Rh method requires nucleophilic N-heteroarenes and, due to the electrophilic nature of the cationic Rh(I)/(III) intermediates and catalytic acid, is less tolerant of Lewis basic functionality.[10]

With these limitations in mind, we hypothesized that development of an efficient and enantioselective Ni-catalyzed hydroarylation would be complementary, more functional group tolerant (vs Rh), and enable access to a broader array of chiral arenes. The ability to employ readily accessible aryl boronic esters, as well as control the site of C–C bond formation by inner

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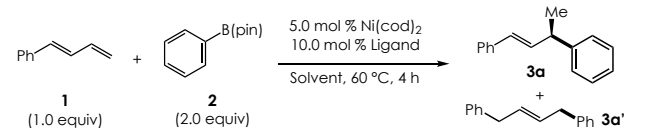
sphere reductive elimination, would be advantageous. In light of these goals, we set out to pursue the development of a general nickel catalyst system for the enantioselective hydroarylation of 1,3-dienes. We reasoned that identification of new ligand scaffolds that promote hydroarylation with high levels of site- and enantioselectivity was a crucial objective.

The proposed mechanism for the Ni-catalyzed olefin hydroarylation reaction is outlined in Scheme 1C.[6f] The transformation proceeds via the intermediacy of a Ni(II)–H (**C**) generated by O–H oxidative addition by Ni(0) (**B**→**C**) (or ligand-to-ligand proton transfer).[14] Subsequent, Ni(II)-alkyl formation (**D**) followed by transmetalation (**E**) and reductive elimination affords product and regenerates the Ni(0) catalyst **A**.



Entry	Ligand	Solvent	% Yield[a]	rr (**3a**:**3a'**)[a]	E/Z[a]	er[b]
1[c]	**L1**	MeOH/THF (1:1)	42	75:25	>95:5	55:45
2[c]	**L2**	MeOH/THF (1:1)	72	90:10	>95:5	51:49
3	**L3**	MeOH	<2	–	–	–
4	**L4**	MeOH	<2	–	–	–
5	**L5**	MeOH	60	67:33	>95:5	52:48
6	**L6**	MeOH	71	83:17	>95:5	68:32
7	**L7**	MeOH	90	88:12	>95:5	55:45
8	**L8**	MeOH	73	>95:5	>95:5	69:31
9	**L9**	MeOH	43	92:8	>95:5	95:5
10	**L9**	EtOH	95	92:8	>95:5	97:3
11[d]	**L9**	EtOH	90	>95:5	95:5	97:3

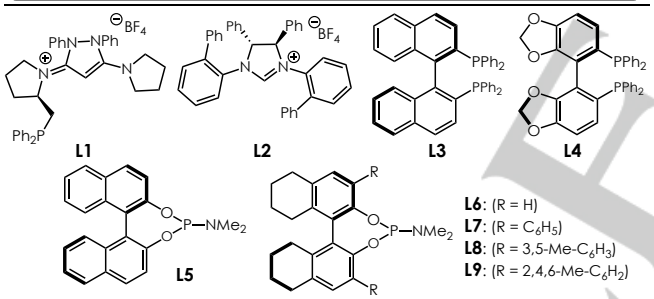
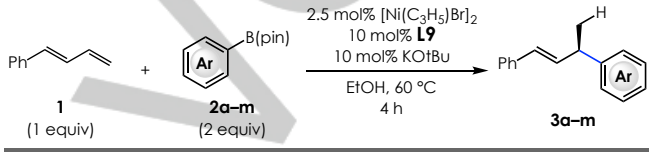
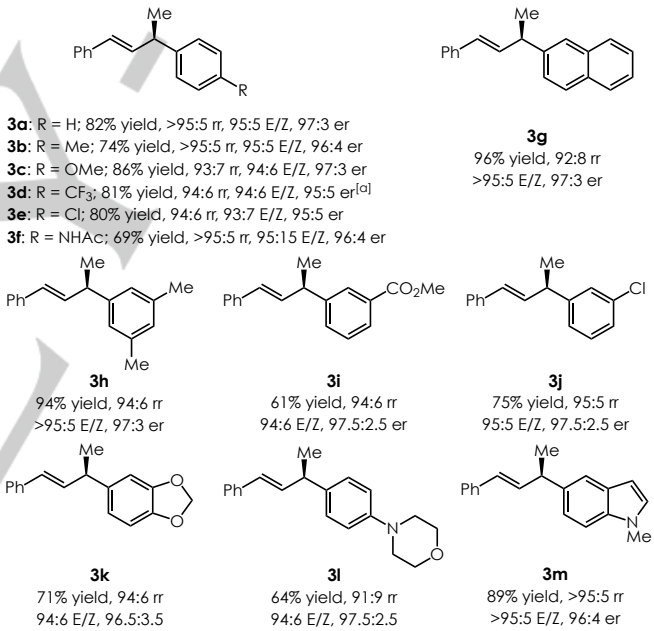


Table 1. Optimization of Nickel-Catalyzed Hydroarylation of 1,3-Dienes. Reactions performed under an N_2 atmosphere on a 0.1 mmol scale with 1.0 equiv of **1** and 2.0 equiv **2**. [a] Yields, regioselectivity, and E/Z ratios determined by analysis of the crude reaction mixture using hexamethyldisiloxane as an internal standard. [b] Enantiomeric ratios were obtained by chiral SFC or HPLC analysis; see Supporting Information for details. [c] 10 mol % KOtBu used. [d] Reaction with 2.5 mol % $[Ni(C_3H_5)Br]_2$ and 10 mol % KOtBu.

We initiated our studies by investigating the reaction of phenylbuta-1,3-diene (**1**) with phenyl-B(pin) (**2**) in the presence of 5.0 mol % $Ni(cod)_2$ and MeOH at 60 °C (Table 1). Drawing from our previous work on diene hydrofunctionalization with carbodicarbene ligands,[7,8] we began by screening bidentate CDC–phosphine **L1**, which resulted in conversion to **3a** but with low site- and enantioselectivity (entry 1). An improvement in conversion and site-selectivity (90:10 rr) for **3a** was observed by switching to chiral NHC **L2**, but enantioselectivity remained absent (51:49 er) (entry 2). Reactions performed with bis-phosphine ligands, are particularly noteworthy, as a <2% conversion is detected, an observation also noted by Zhou (entries 3–4).[6f] In contrast, switching to monodentate phosphoramidite ligands **L5–L6**, led to increased reactivity and selectivity with partially hydrogenated **L6** (vs binaphthyl **L5**) furnishing **3a** in 83:17 rr and 68:32 er (entry 6). Further ligand modification, for example incorporation of 3,3'-aryl units onto the diol backbone (e.g., **L7–8**), resulted in marked improvement in rr (>95:5) likely due to increased sterics, however, enantioselectivity remained unchanged (entries 7–8). In an effort to improve the facial selectivity of **1** binding to the nickel catalyst, sterically hindered **L9** bearing 3,3'-mesityl groups was examined. The effect of increasing sterics is significant; reaction of 5.0 mol % $Ni(cod)_2$ with 10.0 mol % **L9** affords **3a** in 43% conversion, 92:8 rr, and 95:5 er (entry 9). The use of ethanol as alcohol led to slight increase in selectivity to 97:3 er (entry 10), while EtOH in combination with $[Ni(C_3H_5)Br]_2$ and KOtBu yielded optimal conditions (entry 11).[15]





Scheme 2. Aryl-Boronate Scope. Reactions performed under an N_2 atmosphere on 0.1 mmol scale with 1.0 equiv of **1** and 2.0 equiv Ar–B(pin). Yields, rr, er, and E/Z ratio of the purified products are indicated beneath each entry and are the averages of two runs; see supporting information for crude ratios. [a] i-PrOH used as solvent.

Next, we set out to explore the scope of the transformation, beginning with the arylboronate fragment (Scheme 2). Under optimized conditions a variety of aryl pinacolato borons reacted efficiently, and with high site- (>91:9 rr) and enantioselectively (>95:5 er), including those with an electron-donating (**3b-c**, **3f**, **3h**, **3k–l**), electron-withdrawing (**3d–e**, **3i–j**), or a naphthyl moiety (**3g**). In all cases examined, substitution is well tolerated with no loss in catalytic activity or site- and enantioselectivity. Moreover, products are generated as the E alkene isomer in >93:7 E/Z selectivity. Other noteworthy features of the method include, the

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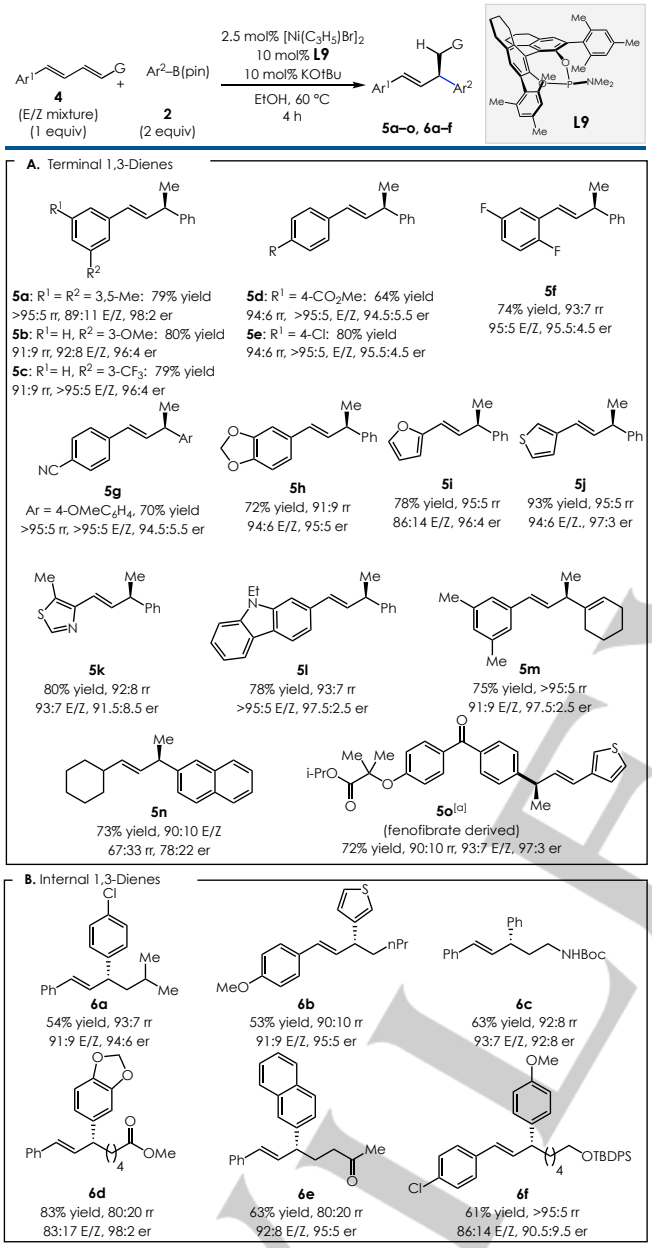
tolerance of aryl boronates containing an aryl chloride, as well as a heteroarene moiety; for example, the selective formation of m-chloro **3j** in 97.5:2.5 er and 5-substituted indole **3m** in 96:4 er, are illustrative. Lastly, the stereochemical assignment of the products as (*R*) was determined though correlation of **3a** to known compound.[16]



Scheme 3. Scope of Reaction with 1,3-Dienes. Reactions performed under an N_2 atmosphere on a 0.1 mmol scale with 1.0 eq of **4** and 2.0 eq **2**. Yields, regioselectivity, and *E/Z* ratio of the purified products are indicated beneath each entry; see supporting information for crude ratios. The isolated yields, rr, er, and *E/Z* ratio are the average of two runs. [a] With 1.5 equivalents of Ph-B(pin)

Reactions were also extended to variations of the 1,3-diene component (Scheme 3). Substituted aryl 1,3-dienes bearing electron-donating (**5a**, **h**, **m**) and electron-withdrawing (**5b–g**) groups at various positions furnish allyl-substituted arenes in up >95:5 rr and 99:1 er. Particularly noteworthy, is the observation that 1,3-dienes can be used as impure E/Z mixture of isomers, without detriment to reaction efficiency, site- and enantioselectivity. Such an attribute is highly advantageous from a practicality standpoint as methods for the synthesis of stereodefined *E*- or *Z*-dienes are not always highly selective. Heteroarene substituted dienes also undergo efficient and enantioselective hydroarylation, including those containing a furan (**5i**), thiophene (**5j**), thiazole (**5k**), and carbazole (**5l**) moiety. As illustrated by **5n**, products derived from alkyl dienes can be prepared in good yield but with significantly reduced selectivity. Cyclohexenyl **5m**, formed in 75% yield, >95:5 rr, and 97.5:2.5 er, illustrates reactions with alkenyl boronates proceed with high er and rr. Lastly, application of the Ni-catalyzed protocol to the enantioselective derivatization of bioactive molecules is highlighted by the formation of fenofibrate-derived **5o**, in 90:10 rr and 97:3 er.

Reactions of internal 1,4-disubstituted dienes are synthetically desirable, however, the presence of an additional substituent renders site-selectivity more difficult due to the closer steric parity of the 1- and 4-positions that the Ni catalyst needs to differentiate. Nonetheless, treatment of a variety of *E/Z* mixtures of internal dienes with 5.0 mol % (**L9**)-Ni and an aryl-B(pin) in EtOH at 60 °C delivers functionalized aryl products efficiently and selectively (Scheme 3B). For example, products containing an alkyl (**6a–b**), allylic NBoc carbamate (**6c**), ester (**6d**), ketone (**6e**), and silylether (**6f**) moiety are tolerated. In general, high levels of enantioselectivity are maintained, however, **6d** and **6e** are generated in diminished 80:20 rr, possibly resulting from the carbonyl interacting with the catalyst. Of note, the method is compatible with enolizable ketones and esters.

During the course of our study a number of mechanistic questions were raised. (1) Does the nickel catalyst isomerize the mixture of E/Z dienes prior to hydroarylation? (2) If the reaction is run in deuterated alcohol which positions, if any, of the product have deuterium incorporated? (3) Does the structure of the boron reagent play a role in reaction selectivity? To answer these questions, first we compared reactions conducted with isomerically enriched E and Z diene **7** (Scheme 4A). Under standard conditions **5e** is formed in identical 95.5:4.5 er but reaction with *E*-**7** furnishes the product in slightly diminished 92:8 rr vs 94:6 rr from Z enriched **7**. In both cases the same major enantiomer *(R)* of product is formed. These results indicates either the diene is isomerized prior to reaction, or a stereoconvergent process where the Z-diene initially reacts to afford a *(S)–Z*–Ni-π-allyl with the opposite sense of enantioselectivity. Fast isomerization of *(S)–Z*–Ni-π-allyl via π–σ–π to the *(R)–E*–Ni-π-allyl, then affords *(R)–E*–stereoisomer as the major product (Scheme 4B). To determine if the latter scenario is taking place we analyzed product **5i** formed in 90:10 *E:Z*, and determined the enantioselectivity of ***Z*-5i** as 98:2 er (Scheme 4B). To assess whether the relative configuration of the allylic stereocenter in ***E*-5i** and ***Z*-5i** is formed with opposite sense of enantioinduction, the inseparable mixture was reduced with Pd/C in MeOH. Unfortunately, reduction of the alkene resulted in partial reduction of the furan; as such, for analysis purposes, the

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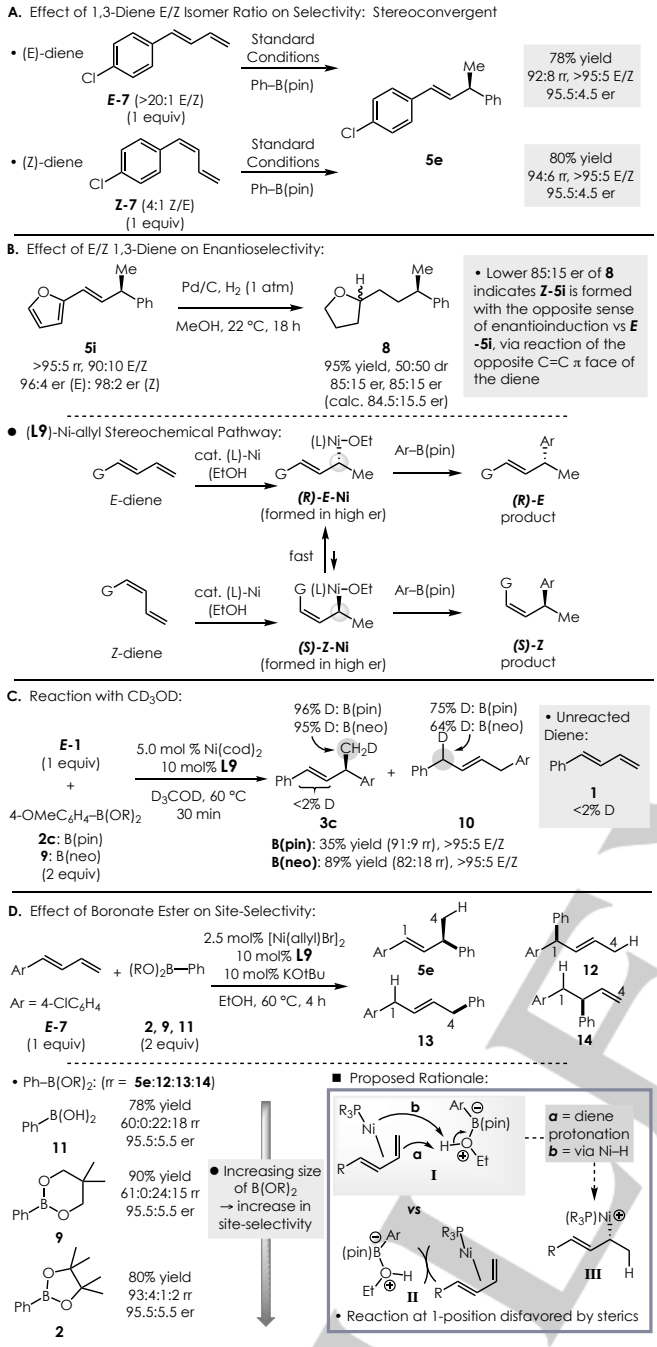

Scheme 4. Mechanistic insight into the enantioselective 1,3-diene hydroarylation. [a] 24 h reaction; see supporting information for more details.

substrate was fully reduced to **8**. Hydrogenation of the furan afforded **8** in 50:50 dr, with both diastereomers formed in 85:15 er. The theoretical calculated selectivity for opposite enantiomers is 84:16 er, confirming that *Z*-dienes react with the opposite facial selectivity but Ni-π-allyl isomerizes faster than transmetalation and C–C bond formation. Further evidence for an irreversible Ni-π-allyl formation followed by rapid isomerization was garnered by analyzing reactions run with CD_3OD (Scheme 4C). Treatment of ***E*-1** with either **2c** or **9** with 5.0 mol % (**L9**)-Ni in CD_3OD affords **3c** and **10** with high deuterium incorporation at the expected homoallylic and allylic positions: >95%-D incorporation into the methyl group of the 1,2-arylation product and 64–75% deuterium incorporation into the methylene group of the 1,4-arylation product. In addition, analysis of unreacted ***E*-1** showed <2% deuterium indicating lack of scrambling prior to transmetalation. Lastly the effect of the boron reagent on site-selectivity was investigated (Scheme 4D). Catalytic enantioselective reaction of ***E*-7** in the presence of either **2**, **9**, or **11** revealed an significant variance in site-selectivity. With all three Ph–$B(OR)_2$ reagents, **5e** is formed in high yield and 95.5:4.5 er, however, the site-selectivity of the reactions with phenyl boronic acid and neopentyl glycol ester **9**, are significantly worse compared to pinacol ester **11**. It should be emphasized, that the difference in site-selectivity arises from hydrogen incorporation at either carbon-4 (**5e** and **12**) or carbon-1 (**13** and **14**), which occurs in the Ni-π-allyl formation step of the mechanism. The trend follows the size of the $B(OR)_2$ group, and an argument could be made for transmetalation being controlled by sterics; however, this explanation does not agree with the data in **6B**. If transmetalation determines site-selectivity then deuterium incorporation would be expected at the styrenyl position in **3c** as hydrogen incorporation at C1 reverses to C4. Furthermore, the Ni-π-allyl leading to the formation of **13** is sterically less hindered compared to the Ni-π-allyl that afforded **5e**, and would favour transmetalation. Nevertheless, these results indicate that the identity of the boronate plays an important role in determining site-selectivity. A possible rationale is that site-selective protonation occurs at the sterically least hindered position of a (L)-Ni-diene complex (e.g., **I** vs **II**) by EtOH activated by Ph–B(pin), either at the diene or at nickel followed by rapid hydride migratory insertion (Scheme 4D).[17]

In summary, we show that enantioselective Ni-catalyzed hydroarylations of 1,3-dienes provides efficient access to functionalized arenes. The protocol is tolerant of aryl halides, heterocycles, and Lewis basic functionality. In addition, the above findings indicate reactions proceed via an *E/Z* stereoconvergent enantioselective process that is influenced by the identity of the aryl boronate. Further studies of enantioselective hydrofunctionalization reactions are ongoing.

Keywords: Hydroarylation • Hydrofunctionalization • Nickel • Enantioselective • Catalysis

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[1] E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds. *Comprehensive Asymmetric Catalysis*; Springer Verlag: Berlin, Germany, 1999.

[2] (a) X. Zeng, *Chem. Rev.* **2013**, *113*, 6864–6900. (b) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, *Chem. Rev.* **2017**, *117*, 9333–9403.

[3] (a) X. Han, R. A. Widenhoefer, *Org. Lett.* **2006**, *8*, 3801–3804. (b) C. Liu, R. A. Widenhoefer, *Org. Lett.* **2007**, *9*, 1935–1938. (c) G. Pattison, G. Piraux, H. W. Lam, *J. Am. Chem. Soc.* **2010**, *132*, 14373–14375. (d) J.

Bexrud, M. Lautens *Org. Lett.* **2010**, *12*, 3160–3163. (e) A. Saxena, H. W. Lam, *Chem. Sci.* **2011**, *2*, 2326. (f) S. M. Podhajsky, Y. Iwai, A. Cook-Sneathen, M. S. Sigman, *Tetrahedron* **2011**, *67*, 4435–4441. (g) E. W. Werner, T.-S. Mei, A. J. Burckle, M. S. Sigman, *Science* **2012**, *338*, 1455–1458. (h) T.-S. Mei, E. W. Werner, A. J. Burckle, M. S. Sigman, *J. Am. Chem. Soc.* **2013**, *135*, 6830–6833. (i) C. M. So, S. Kume, T. Hayashi, *J. Am. Chem. Soc.* **2013**, *135*, 10990–10993. (j) T.-S. Mei, H. H. Patel, M. S. Sigman, *Nature* **2014**, *508*, 340–344. (k) I. D. Roy, A. R. Burns, G. Pattison, B. Michel, A. J. Parker, H. W. Lam, *Chem. Commun.* **2014**, *50*, 2865. (l) C. Zhang, C. B. Santiago, J. M. Crawford, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 15668–15671. (m) S. D. Friis, M. T. Pirnot, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 8372–8375. (n) L. Oxtoby, Z.-Q. Li, V. Tran, T. Erbay, R. Deng, P. Liu, K. M. Engle, *Angew. Chem. Int. Ed.* **2020**, DOI 10.1002/anie.202001069; *Angew. Chem.* **2020**, DOI 10.1002/ange.202001069.

[4] (a) R. K. Thalji, J. A. Ellman, R. G. Bergman, *J. Am. Chem. Soc.* **2004**, *126*, 7192–7193. (b) S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 13496–13497. (c) R. M. Wilson, R. K. Thalji, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2006**, *8*, 1745–1747. (d) H. Harada, R. K. Thalji, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2008**, *73*, 6772–6779. (e) C. S. Sevov, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2116–2119. (f) T. Shibata, T. Shizuno, *Angew. Chem. Int. Ed*. **2014**, *53*, 5410–5413; *Angew. Chem.* **2014**, *126*, 5514-5517. (g) G. Song, W. W. N. O., Z. Hou, *J. Am. Chem. Soc.* **2014**, *136*, 12209–12212. (h) T. Shirai, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2015**, *54*, 9894–9897; *Angew. Chem.* **2015**, *127*, 10032-10035. (i) T. Shibata, N. Ryu, H. Takano, *Adv. Synth. Catal.* **2015**, *357*, 1131–1135. (j) P.-S. Lee, N. Yoshikai, *Org. Lett.* **2015**, *17*, 22–25. (k) M. Hatano, Y. Ebe, T. Nishimura, H. Yorimitsu, *J. Am. Chem. Soc.* **2016**, *138*, 4010–4013. (l) S. Grélaud, P. Cooper, L. J. Feron, J. F. Bower, *J. Am. Chem. Soc.* **2018**, *140*, 9351–9356. (m) K. Ozols, Y.-S. Jang, N. Cramer, *J. Am. Chem. Soc*. **2019**, *141*, 5675-5680. (n) J. Diesel, D. Grosheva, S. Kodama, N. Cramer, *Angew. Chem. Int. Ed.* **2019**, *58*, 11044-11048; *Angew. Chem.* **2019**, *131*, 11160-11164. (o) K. Sakamoto, T. Nishimura, *Adv. Syn. Catal.* **2019**, *361*, 2124–2128.

[5] For recent reviews on enantioselelctive diene functionalizations, see: (a) Y. Xiong, Y. Sun, G. Zhang, *Tetrahedron Lett.* **2018**, *59*, 347–355. (b) X. Wu, L.-Z. Gong, *Synthesis* **2019**, *51*, 122–134. (c) N. J. Adamson, S. J. Malcolmson, *ACS Catal.* **2020**, *10*, 1060–1076.

[6] For catalytic non-enantioselective hydroarylation reactions of 1,3-dienes, see: (a) M.-Z. Wang, M.-K. Wong, C.-M. Che, *Chem. Eur. J.* **2008**, *14*, 8353–8364. (b) L. Liao, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 10209–10211. (c) M. Niggemann, N. Bisek, *Chem. Eur. J.* **2010**, *16*, 11246–11249. (d) C. C. Roberts, D. M. Matías, M. J. Goldfogel, S. J. Meek, *J. Am. Chem. Soc.* **2015**, *137*, 6488–6491. (e) L. Gu, L. M. Wolf, A. Zieliński, W. Thiel, M. Alcarazo, *J.Am. Chem. Soc.* **2017**, *139*, 4948–4953. (f) L.-J. Xiao, L. Cheng, W.-M. Feng, M.-L. Li, J.-H. Xie, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2018**, *57*, 461–464; ; *Angew. Chem.* **2017**, *130*, 470-473.

[7] For representative examples of enantioselective C–C hydrofunctionalization of 1,3-dienes that proceed via electrophilic metal-allyl intermediates, see: Hydroarylation: (a) S. M. Podhajsky, Y. Iwai, A. Cook-Sneathen, M. S. Sigman, *Tetrahedron* **2011**, *67*, 4435–4441. For a recent related enantioselective hydroarylation of alkynes, see: (b) Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 10641–10644. Hydroalkylation: (c) Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552–7557. (d) N. J. Adamson, K. C. E. Wilbur, S. J. Malcolmson, *J. Am. Chem. Soc.* **2018**, *140*, 2761–2764. (e) L. Cheng, M.-M. Li, L.-J. Xiao, J.-H. Xie, Q.-L. Zhou, *J. Am. Chem. Soc.* **2018**, *140*, 11627–11630. (f) Q. Zhang, H. Yu, L. Shen, T. Tang, D. Dong, W. Chai, W. Zi, *J. Am. Chem. Soc.* **2019**, *141*, 14554–14559. (g) N. J. Adamson, S. Park, P. Zhou, A. L. Nguyen, S. J. Malcolmson, *Org. Lett.* **2020**, *22*, 2032–2037. (h) C. I. Onyeagusi, X. Shao, S. J. Malcolmson, *Org. Lett.* **2020**, *22*, 1681–1685. Hydroalkynylation: (i) M. Shirakura, M. Suginome, *Angew. Chem. Int. Ed.* **2010**, *49*, 3827–3829; *Angew. Chem.* **2010**, *122*, 3915-3917. (j) T. Sawano, A. Ashouri, T. Nishimura, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 18936–18939. Hydrocyanation: (k) B. Saha, T. V. RajanBabu, *Org. Lett.* **2006**, *8*, 4657–4659.

[8] For examples of enantioselective hydrovinylation of 1,3-dienes, see: (a) A. Zhang, T. V. RajanBabu, *J. Am. Chem. Soc.* **2006**, *128*, 54–55. (b) B. Saha, C. R. Smith, T. V. RajanBabu, *J. Am. Chem. Soc.* **2008**, *130*, 9000–9005. (c) R. K. Sharma, T. V. RajanBabu, *J. Am. Chem. Soc.* **2010**, *132*, 3295–3297. (d) J. P. Page, T. V. RajanBabu, *J. Am. Chem. Soc.* **2012**, *134*, 6556–6559. (e) Y. N. Timsina, R. K. Sharma, T. V. RajanBabu, *Chem. Sci.* **2015**, *6*, 3994–4008.

[9] For a review of reductive couplings of 1,3-dienes, see: (a) M. Holmes, L. A. Schwartz, M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026–6052. For examples of enantioselective reductive couplings of 1,3-dienes, see: (b) Y. Yang, S.-F. Zhu, H.-F. Duan, C.-Y. Zhou, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 2248–2249. (c) Y. Sato, Y. Hinata, R. Seki, Y. Oonishi, N. Saito, *Org. Lett.* **2007**, *9*, 5597–5599. (d) J. R. Zbieg, J. Moran, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 10582–10586. (e) J. R. Zbieg, E. Yamaguchi, E. L. McInturff, M. J. Krische, *Science* **2012**, *336*, 324–327. (f) E. L. McInturff, E. Yamaguchi, M. J. Krische, *J. Am. Chem. Soc.* **2012**, *134*, 20628–20631. (g) K. D. Nguyen, D. Herkommer, M. J. Krische, *J. Am. Chem. Soc.* **2016**, *138*, 14210–14213. (h) Y.-Y. Gui, N. Hu, X.-W. Chen, L. Liao, T. Ju, J.-H. Ye, Z. Zhang, J. Li, D.-G. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 17011–17014. (i) C. Li, R. Y. Liu, L. T. Jesikiewicz, Y. Yang, P. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2019**, *141*, 5062–5070. (j) B. Fu, X. Yuan, Y. Li, Y. Wang, Q. Zhang, T. Xiong, Q. Zhang, *Org. Lett.* **2019**, *21*, 3576–3580. (k) C. Li, K. Shin, R. Y. Liu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2019**, *58*, 17074; *Angew. Chem.* **2019**, *131*, 17230-17236. (l) X.-W. Chen, L. Zhu, Y.-Y. Gui, K. Jing, Y.-X. Jiang, Z.-Y. Bo, Y. Lan, J. Li, D.-G. Yu, *J. Am. Chem. Soc.* **2019**, *141*, 18825–18835.

[10] J. S. Marcum, C. C. Roberts, R. S. Manan, T. N. Cervarich, S. J. Meek, *J. Am. Chem. Soc.* **2017**, *139*, 15580–15583.

[11] For a related (CDC)-Rh-catalzyed hydroallyltion, see: Marcum, J. S.; Cervarich, T. N.; Manan, R. S.; Roberts, C. C.; Meek, S. J. *ACS Catal.* **2019**, *9*, 5881–5889.

[12] Y.-G. Chen, B. Shuai, X.-T. Xu, Y.-Q. Li, Q.-L. Yang, H. Qiu, K. Zhang, P. Fang, T.-S. Mei, *J. Am. Chem. Soc.* **2019**, *141*, 3395–3399.

[13] X.-Y. Lv, C. Fan, L.-J. Xiao, J.-H. Xie, Q.-L. Zhou, *CCS Chem.* **2019**, *1*, 328–334.

[14] For references on the mechanism of ligand-to-ligand hydrogen transfer, see: (a) J. Guihaumé, S. Halbert, O. Eisenstein, R. N. Perutz, *Organometallics* **2012**, *31*, 1300–1314. (b) J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 13098–13101. (c) L.-J. Xiao, X.-N. Fu, M.-J. Zhou, J.-H. Xie, L.-X. Wang, X.-F. Xu, Q.-L. Zhou, *J. Am. Chem. Soc.* **2016**, *138*, 2957–2960. (d) A. J. Nett, J. Montgomery, P. M. Zimmerman, *ACS Catal.* **2017**, *7*, 7352–7362. (e) S. Tang, O. Eisenstein, Y. Nakao, S. Sakaki, *Organometallics* **2017**, *36*, 2761–2771.

[15] A difference in solubility was observed with MeOH in comparison to EtOH. The **L9**–Ni complex appears to be partially insoluble in MeOH, which likely results in lower yields, but no significant change in rr.

[16] H. Fang, Z. Yang, L. Zhang, W. Wang, Y. Li, X. Xu, S. Zhou, *Org. Lett.* **2016**, *18*, 6022–6025.

[17] For protonation at the diene of a (bis-phosphine)-Ni-diene complex, see: A. Mifleur, D. S. Mérel, A. Mortreux, I. Suisse, F. Capet, X. Trivelli, M. Sauthier, S. A. Macgregor, *ACS Catal.* **2017**, *7*, 6915–6923.

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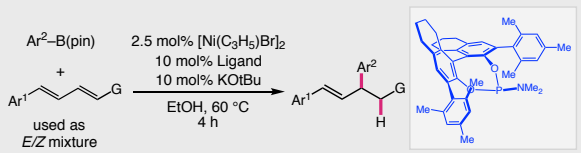

A catalytic method for the site- and enantioselective synthesis of functionalized arenes by the intermolecular hydroarylation of 1,3-dienes with aryl pinacolato boronates is disclosed. Reactions are promoted by 5.0 mol % of a readily available phosphoramidite-Ni complex in ethanol, affording a variety of enantioenriched products in up to >95:5 rr and 99:1 er. Mechanistic studies indicate Ni-allyl formation is irreversible and related to the nature of the arylboronate.

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