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Ligand-Enabled Ni-Catalyzed Enantioselective Hydroarylation of Styrenes and 1,3-Dienes with Arylboronic Acids

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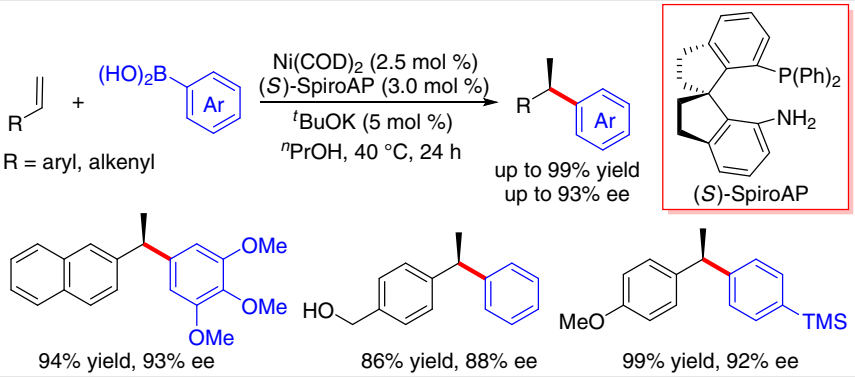
We report an enantioselective hydroarylation reaction of styrenes and 1,3-dienes with arylboronic acids catalyzed by nickel complexes bearing chiral spiro aminophosphine ligands. The reaction serves as an efficient, straightforward, and mild method for the preparation of enantioenriched 1,1-diarylalkanes, which are important building blocks for the synthesis of many biologically active molecules. This redox neutral reaction uses only catalytic amounts of the reagents and is, therefore, atom economical and environmentally benign.



Keywords: **nickel catalyst, enantioselective hydroarylation, alkene, organoboron, chiral spiro aminophosphine**

Introduction

The development of efficient methods for the enantioselective construction of tertiary stereogenic centers via C–C bond formation is an essential task in organic synthesis. One method for this purpose is the transition-metal-catalyzed enantioselective functionalization of alkenes, which has attracted considerable research interest in the last few decades.[1-4] For example, the enantioselective hydroarylation of styrenes via C–H functionalization has been developed for the synthesis of enantioenriched 1,1-diarylalkanes,[5-8] which often show biological activity.[9-11] Although boronic acids and esters have been demonstrated to be very efficient reagents for the hydroarylation of alkenes,[12-18] enantioselective hydroarylation reactions of styrenes with boronic reagents are

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rare. Sigman et al.[12,13] pioneered palladium-catalyzed hydroarylation of styrenes with aryl boron esters using isopropanol as the hydride source and reported an asymmetric version of this reaction with moderate enantioselectivity.[18] In addition, Buchwald et al.[19] reported an Cu/Pd-cooperatively catalyzed asymmetric hydroarylation of styrenes with arylbromides using silane as the hydride source, affording 1,1-diarylethenes in good yields with excellent enantioselectivities.

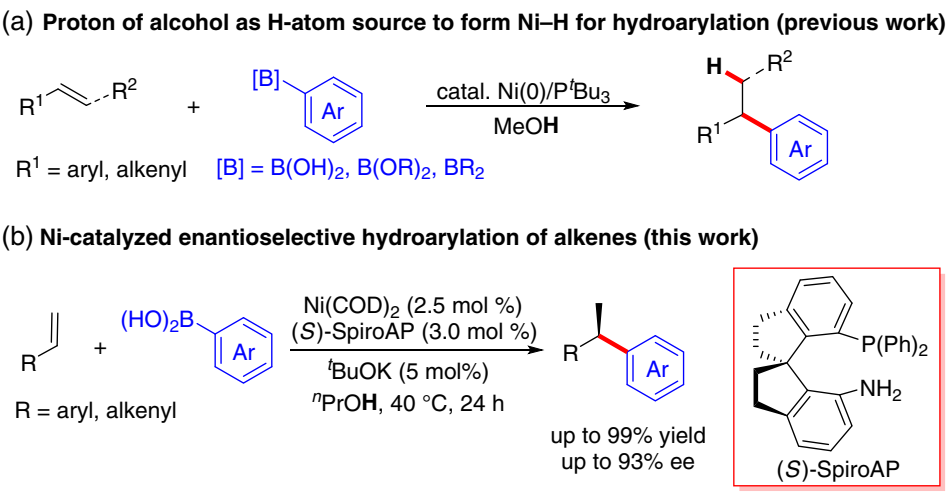
Recently, we developed a protocol for nickel-catalyzed hydroarylation of styrenes and dienes with organoboron compounds; in this reaction, the methanolic proton generates the active Ni–H catalyst species (Scheme 1a).[14,20] Using this strategy and the chiral ligand DTBM-HO-BIPHEP, we achieved the enantioselective hydroalkylation of 1,3-dienes with simple ketones.[21] In contrast, when we applied the Ni-DTBM-HO-BIPHEP catalyst to the hydroarylation of styrenes with organoboron compounds, none of the desired 1,1-diarylalkane products were obtained. Systematic exploration of chiral ligands revealed that the spiro aminophosphine (SpiroAP) ligands have been described previously,[22] are efficient for Ni-catalyzed enantioselective hydroarylation of styrenes and 1,3-dienes with arylboronic acids. The advantages of the reaction are that (1) it could be conducted under redox neutral conditions and (2) all the reagents used are catalytic. Herein, we report the details of this Ni-catalyzed enantioselective hydroarylation of styrenes and 1,3-dienes with arylboronic acids, which affords 1,1-diarylalkanes and allylarenes with good to excellent enantioselectivities.

Experimental Methods

General procedure for Ni-catalyzed enantioselective hydroarylation: We employed an argon-filled glove box with oven-dried sealed tube charged with a stir bar. Boronic acid **2** (0.3 mmol), ^{t}BuOK (0.01 mmol), ligand (*S*)-SpiroAP (**L1**, 2.5 mg, 0.006 mmol), catalyst precursor Ni(COD)$_2$ (1.4 mg, 0.005 mmol), alkene **1** (0.2 mmol), and *n*-propanol (1.0 mL) were injected into the tube. Then, the tube was sealed and removed from the glove box. Subsequently, the reaction mixture was stirred at room temperature for 2 min and heated at 40 °C for 24 h. After cooling to room temperature, the solvent was removed under vacuum, and pure product **3** was obtained by column chromatography using silica gel column and eluted with petroleum ether (PE) and ethyl acetate (EA) (PE/EA = 100:1). Unless otherwise specified, the racemic product was prepared according to a previously reported procedure.[14] More experimental details and characterization are available in Supporting Information (Scheme S1).

Results and Discussion

The reaction of styrene hydroarylation (**1a**) with (4-methoxyphenyl)-boronic acid (**2a**) was performed for optimizing the reaction conditions (Table 1). The reaction was initially carried out in methanol at 60 °C in the presence of a Ni catalyst generated in situ from 5 mol % Ni(COD)$_2$ and 6 mol % chiral ligand. After evaluation of various chiral ligands, we were delighted to find that the SpiroAP ligands (**L1**–**L4**), which were developed in our laboratory,[23,24] gave high yields and moderate enantioselectivities, with **L1** being the most enantioselective (entries 1–11). Chiral spiro ligands **L5**–**L8**, oxazoline ligand **L9**, Josiphos ligand **L10,** and Phox ligand **L11** exhibited either extremely low yield or low enantioselectivity. Subsequent experiments focused on the systematic optimization of the reaction conditions using ligand **L1** (entries 12–18). Our solvent variation experiments showed that ^{n}PrOH was better than MeOH or EtOH, increasing the ee to 85% (entry 13), whereas ^{n}BuOH was inferior, giving a low yield



Scheme 1 | *Ni-Catalyzed hydroarylation of styrenes with arylboronic acids.*

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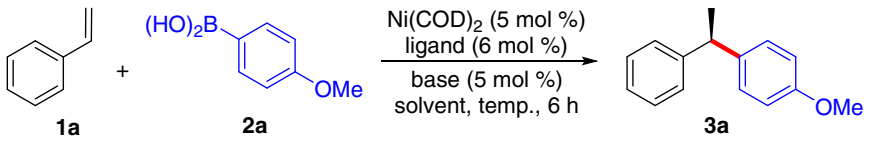
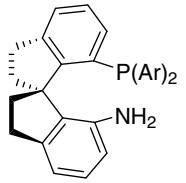
Table 1 | *Optimization of the Reaction Conditions of Styrene Hydroxylation*[a]

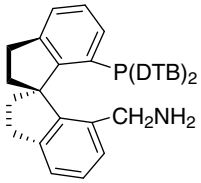


1a 2a 3a

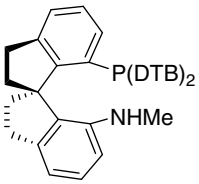
Entry	Ligand	Solvent	Temp. (°C)	Base (5 mol%)	Yield (%)	ee (%)
1	**L1**	MeOH	60	–	95	67
2	**L2**	MeOH	60	–	76	53
3	**L3**	MeOH	60	–	95	49
4	**L4**	MeOH	60	–	95	50
5	**L5**	MeOH	60	–	82	27
6	**L6**	MeOH	60	–	<5	ND
7	**L7**	MeOH	60	–	<5	ND
8	**L8**	MeOH	60	–	87	38
9	**L9**	MeOH	60	–	95	31
10	**L10**	MeOH	60	–	74	7
11	**L11**	MeOH	60	–	11	0
12	**L1**	EtOH	60	–	95	68
13	**L1**	^{n}PrOH	60	–	95	85
14	**L1**	^{n}BuOH	60	–	14	50
15[b,c]	**L1**	^{n}PrOH	60	–	95	86
16[b,c]	**L1**	^{n}PrOH	40	–	68	92
17[b,c]	**L1**	**^{n}PrOH**	**40**	**^{t}BuOK**	**98(98)**[d]	**92**
18[b,c]	**L1**	^{n}PrOH	40	K_3PO_4	84	91
19[b,c]	**L1**	^{n}PrOH	40	K_2CO_3	78	93



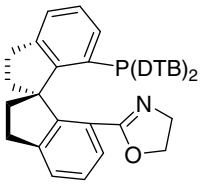
L1: Ar = C_6H_5
L2: Ar = 4-$MeOC_6H_4$
L3: Ar = 3,5-$Me_2C_6H_3$
L4: Ar = 3,5-$^{t}Bu_2C_6H_3$



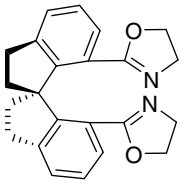
L5



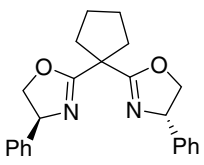
L6



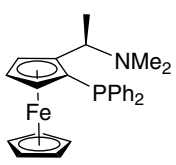
L7



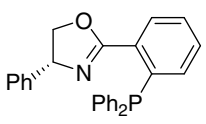
L8



L9



L10



L11

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Ni(COD)_2$ (5 mol %), ligand (6 mol %), base (5 mol %) at 60 °C for 6 h. The yield was determined by NMR using CH_2Br_2 as an internal standard. Enantiomric excess (ee) was determined by chiral High performance liquid chromatography (HPLC). [b]2.5 mol % catalyst. [c]24 h. [d]Isolated yield in parenthesis.

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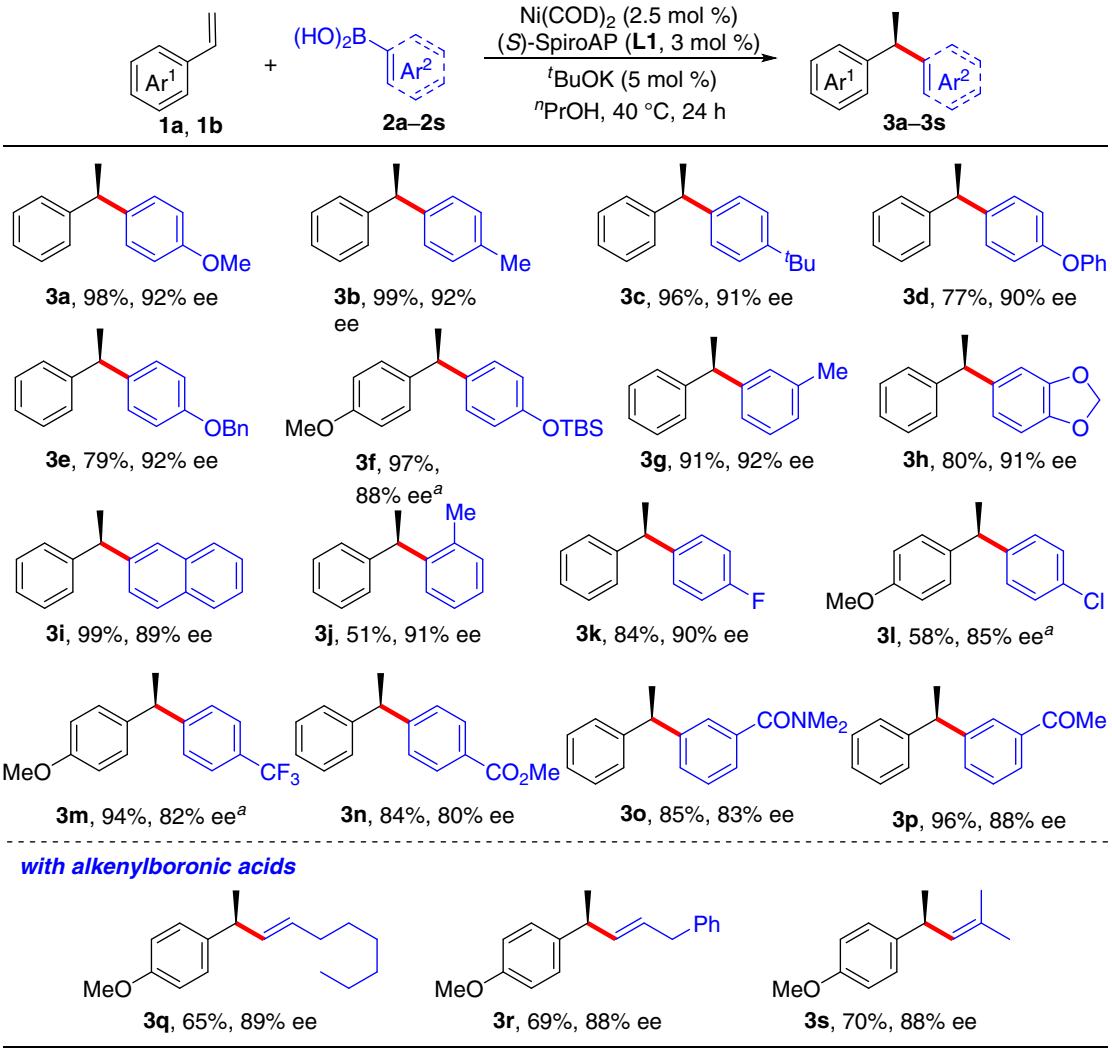
and a low ee (entry 14). Notably, the Ni(0)/**L1** catalyst displayed such high activity that the reaction could be performed in ^{n}PrOH at a catalyst loading as low as 2.5 mol % without a decrease in the yield or ee (entries 13 and 15). When the reaction was carried out at 40 °C, the enantioselectivity increased to 92% ee, although the yield decreased to 68% (entry 16). Adding 5 mol % of a base increased the yield (entries 17–19), with ^{t}BuOK being the best choice (98% yield; 92% ee).

Using the above optimized reaction conditions, we evaluated the substrate scope by carrying out reactions of a variety of arylboronic acids **2** with styrene (**1a**) or 4-methoxystyrene (**1b**) (Table 2). All the tested arylboronic acids which bear substituents with different steric and electronic properties, worked well, affording hydroarylation products **3a**–**3p** in moderate to excellent yields (51–99%) with good to high enantioselectivities (80–92% ee). Ethers (**2a**, **2d**, and **2e**), silyl ether (**2f**), a benzodioxole moiety (**2 h**), fluorine and chlorine atoms (**2k** and **2l**), a trifluoromethyl group (**2m**), an ester (**2n**), an amide (**2o**), and a ketone (**2p**) were all tolerated under the standard reaction conditions. Generally, arylboronic acids with electron-donating groups (**2a**–**2j**) gave higher enantioselectivities than those with electron-withdrawing groups (**2k**–**2p**). Importantly, arylboronic acid **2j**, which has an *ortho*-methyl group, exhibited high enantioselectivity (91% ee); nonetheless, the yield was only moderate (51%). Finally, the reaction was also carried out with alkenylboronic acids to afford hydroalkenylation products **3q**–**3s** in good yields with high ee values of 88–89%.

Next we examined the scope of substrate with respect to styrene by allowing various styrenes **4a**–**4l** to react with phenylboronic acid (**2**) (Table 3). Styrenes-bearing amino groups (**4a**, **4b**), alcohols (**4c**), ethers (**4d**, **4e**), and esters (**4f**) worked well, giving the corresponding hydroarylation products in good to excellent yields. Electron-rich styrenes (**4a**–**4e**) showed higher yields (80–99%) and enantioselectivities (88–92% ee) than a

Table 2 | *Scope of Arylboronic Acids*[a]



[a]Isolated yield.

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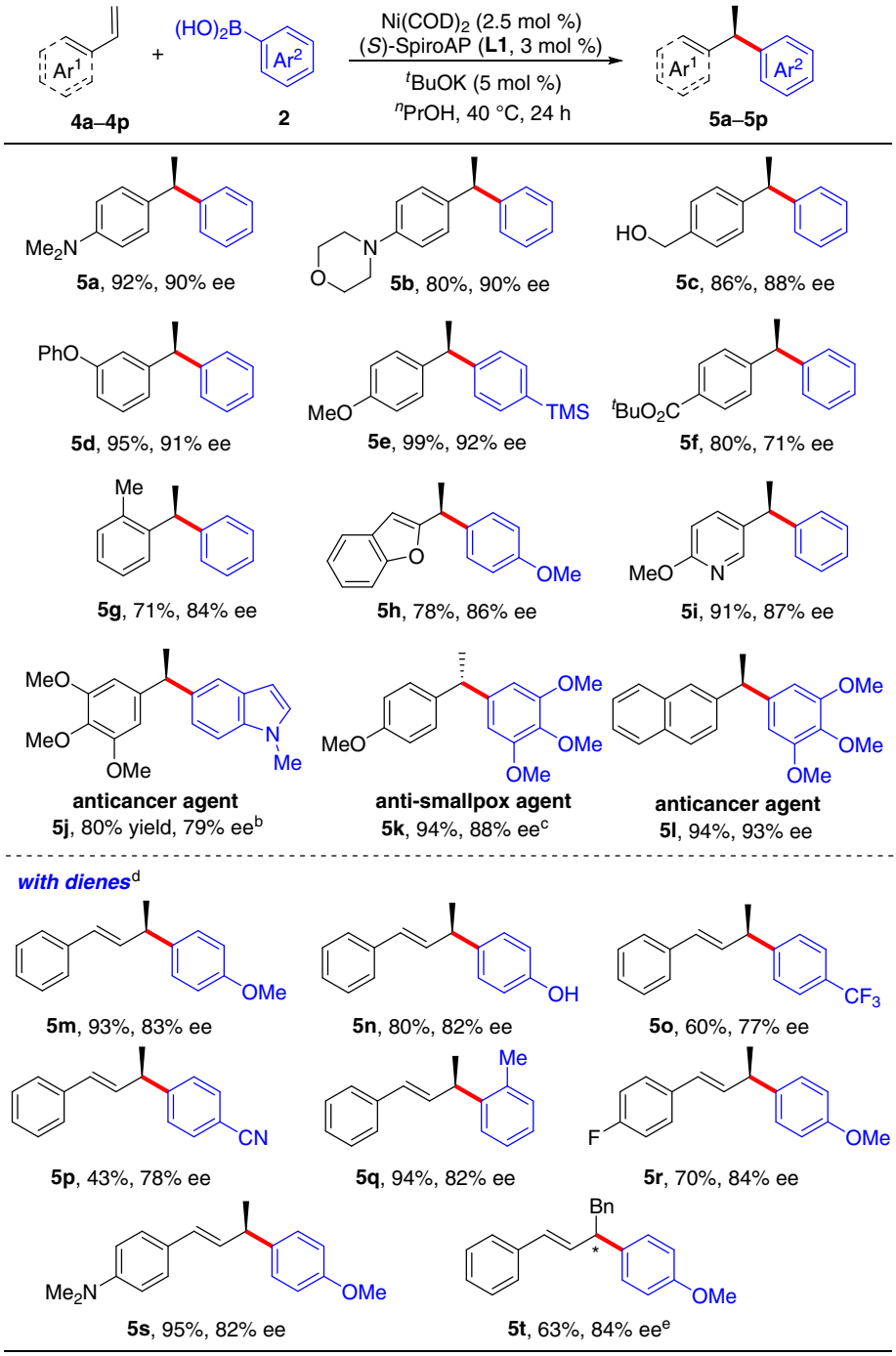
styrene with a strong electron-withdrawing ester group (**4f**; 80% yield and 71% ee). Particularly, the *ortho*-methyl group in styrene **4g** was also tolerated, affording a 71% yield with an 84% ee. It is worth pointing out that the heteroaromatic alkenes 2-vinylbenzofuran (**4 h**) and 2-vinyl-5-methoxypyridine (**4i**) were also acceptable coupling partners. We demonstrated the synthetic utility of this catalytic enantioselective hydroarylation reaction by synthesizing several biologically active molecules—anti-smallpox **5k**[9] and anticancer agents, **5j**[10] and **5l,**[10] in high yields with good to high enantioselectivities (Table 3). In addition, 1,3-dienes such as 1-arylbuta-1,3-dienes **4m**–**4s** and 1,4-diphenylbuta-1,3-diene (**4t**) also reacted with boronic acids **2** to give the desired hydroarylation products in moderate to excellent yields (43–95%) and good enantioselectivities (77–84% ee). However, internal alkenes, for instance, *trans*-β-methylstyrene and indene and aliphatic alkenes

Table 3 | *Scope of Styrenes and their Applications*[a]



[a]Isolated yield. [b]5% catalyst at 30 °C. [c]With (*R*)-SpiroAP. [d]5% catalyst with **L4** at 25 °C for 24 h. [e]2.5% catalyst with **L1** at 25 °C for 48 h.

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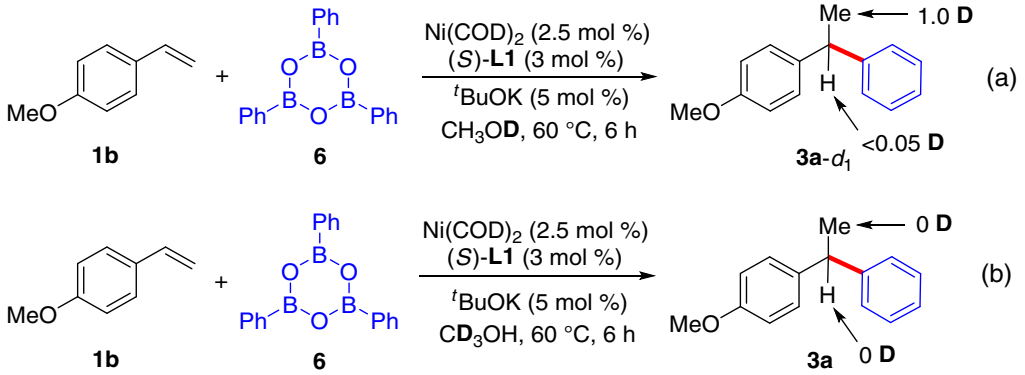

Scheme 2 | *Deuterium-labeling experiments.*

(e.g., 1-hexene) were inert under our standardized conditions.[25]

To confirm that the proton of the alcohol solvent was the hydrogen source for generating the Ni–H species, we carried out a deuterium-labeling study using CH_3OD or CD_3OH as the solvent (Scheme 2). When CH_3OD was used, deuterium was incorporated into the product, indicating that the Ni–H species was generated from the O–H hydrogen atom rather than the C–H hydrogen atom. This result is consistent with our previous observations,[14] except hydrogen/deuterium (H/D) scrambling between the methyl and benzyl positions of the hydroarylation product was not observed in the reaction carried out with P^tBu_3 as the ligand. This difference suggests that the current reaction involves the irreversible formation of MeO–Ni–H and MeO–Ni–R intermediates, which might explain the superiority of the bidentate SpiroAP ligands in controlling the enantioselectivity of the reaction.

Conclusions

We have developed a method for Ni-catalyzed enantioselective hydroarylation of styrenes and 1,3-dienes with arylboronic acids using SpiroAP ligands. This efficient, straightforward, and mild method affords chiral 1,1-diarylalkanes in high yields with high enantioselectivities. The fact that the reaction uses only catalytic reagents under redox neutral conditions make this method atom economical, environmentally benign, and potentially useful for a wide variety of applications, including fabrications of bioactive compounds such as therapeutic agents for smallpox and cancer.

Supporting Information

Supporting information is available including experimental details and characterization.

Conflicts of Interest

The authors declare no competing interests.

Acknowledgments

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References

1. van Leeuwen, P. W. N. HydroformylationHydrocarbonylationHydrocyanation, and Hydroacylationof Carbon–Carbon Double Bonds. In *Science of Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme: Stuttgart, **2011**; Vol. 1, pp 477–519.
2. Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. *Angew. Chem. Int. Ed.* **2016**, *55*, 48–57.
3. Coombs, J. R.; Morken, J. P. Catalytic Enantioselective Functionalization of Unactivated Terminal Alkenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 2636–2649.
4. Chen, J.; Guo, J.; Lu, Z. Recent Advances in Hydrometallation of Alkenes and Alkynes via the First Row Transition Metal Catalysis. *Chin. J. Chem.* **2018**, *36*, 1075–1109.
5. Lee, P.-S.; Yoshikai, N. Cobalt-Catalyzed Enantioselective Directed C–H Alkylation of Indole with Styrenes. *Org. Lett.* **2015**, *17*, 22–25.
6. Ebe, Y.; Onoda, M.; Nishimura, T.; Yorimitsu, H. Iridium-Catalyzed Regio- and Enantioselective Hydroarylation of Alkenyl Ethers by Olefin Isomerization. *Angew. Chem. Int. Ed.* **2017**, *56*, 5607–5611.
7. Loup, J.; Zell, D.; Oliveira, J. C. A.; Keil, H.; Stalke, D.; Ackermann, L. Asymmetric Iron-Catalyzed C–H Alkylation Enabled by Remote Ligand meta-Substitution. *Angew. Chem. Int. Ed.* **2017**, *56*, 14197–14201.
8. Grélaud, S.; Cooper, P.; Feron, L. J.; Bower, J. F. Branch-Selective and Enantioselective Iridium-Catalyzed Alkene

DOI: 10.31635/ccschem.019.20190026
CCS Chem. **2019**, *1*, 328–334

Hydroarylation via Anilide-Directed C–H Oxidative Addition. *J. Am. Chem. Soc.* **2018**, *140*, 9351–9356.
9. Cheltsov, A. V.; Aoyagi, M.; Aleshin, A.; Yu, E. C.-W.; Gilliland, T.; Zhai, D.; Bobkov, A. A.; Reed, J. C.; Liddington, R. C.; Abagyan, R. Vaccinia Virus Virulence Factor NIL is a Novel Promising Target for Antiviral Therapeutic Intervention. *J. Med. Chem.* **2010**, *53*, 3899–3906.
10. Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; De Losada, J. R.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. Discovery of Isoerianin Analogues as Promising Anticancer Agents. *ChemMedChem* **2011**, *6*, 488–497.
11. Soussi, M. A.; Provot, O.; Bernadat, G.; Bignon, J.; Desravines, D.; Dubois, J.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Iso*CombretaQuinazolines: Potent Cytotoxic Agents with Antitubulin Activity. *ChemMedChem* **2015**, *10*, 1392–1402.
12. Iwai, Y.; Gligorich, K. M.; Sigman, M. S. Aerobic Alcohol Oxidation Coupled to Palladium-Catalyzed Alkene Hydroarylation with Boronic Esters. *Angew. Chem. Int. Ed.* **2008**, *47*, 3219–3222.
13. Liao, L.; Sigman, M. S. Palladium-Catalyzed Hydroarylation of 1,3-Dienes with Boronic Esters via Reductive Formation of π-Allyl Palladium Intermediates Under Oxidative Conditions. *J. Am. Chem. Soc.* **2010**, *132*, 10209–10211.
14. Xiao, L.-J.; Chen, L.; Feng, W.-M.; Li, M.-L.; Xie, J.-H.; Zhou, Q.-L. Nickel(0)-Catalyzed Hydroarylation of Styrenes and 1,3-Dienes with Organoboron Compounds. *Angew. Chem. Int. Ed.* **2018**, *57*, 461–464.
15. Lv, H.; Xiao, L.-J.; Zhao, D.; Zhou, Q.-L. Nickel(0)-Catalyzed Linear-Selective Hydroarylation of Unactivated Alkenes and Styrenes with Aryl Boronic Acids. *Chem. Sci.* **2018**, *9*, 6839–6843.
16. Matsuura, R.; Jankins, T. C.; Hill, D. E.; Yang, K. S.; Gallego, G. M.; Yang, S.; He, M.; Wang, F.; Marsters, R. P.; McAlpine, I.; Engle, K. M. Palladium(II)-Catalyzed γ-Selective Hydroarylation of Alkenyl Carbonyl Compounds with Arylboronic Acids. *Chem. Sci.* **2018**, *9*, 8363–8368.
17. So, C. M.; Kume, S.; Hayashi, T. Rhodium-Catalyzed Asymmetric Hydroarylation of 3-Pyrrolines Giving 3-Arylpyrrolidines: Protonation as a Key Step. *J. Am. Chem. Soc.* **2013**, *135*, 10990–10993.
18. Podhajsky, S. M.; Iwai, Y.; Cook-Sneathen, A.; Sigman, M. S. Asymmetric Palladium-Catalyzed Hydroarylation of Styrenes and Dienes. *Tetrahedron* **2011**, *67*, 4435–4441.
19. Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 8372–8375.
20. Xiao, L.-J.; Ye, M.-C.; Zhou, Q.-L. Nickel-Catalyzed Highly Atom-Economical C–C Coupling Reactions with π Components. *Synlett* **2019**, *30*, 361–369.
21. Cheng, L.; Li, M.-M.; Xiao, L.-J.; Xie, J.-H.; Zhou, Q.-L. Nickel(0)-Catalyzed Hydroalkylation of 1,3-Dienes with Simple Ketones. *J. Am. Chem. Soc.* **2018**, *140*, 11627–11630.
22. Xie, J.-B.; Xie, J.-H.; Liu, X.-Y.; Kong, W.-L., Li, S.; Zhou, Q.-L. Highly Enantioselective Hydrogenation of α-Arylmethylene Cycloalkanones Catalyzed by Iridium Complexes of Chiral Spiro Aminophosphine Ligands. *J. Am. Chem. Soc.* **2010**, *132*, 4538–4539.
23. Xie, J.-H.; Zhou, Q.-L. Chiral Diphosphine and Monodentate Phosphorus Ligands on a Spiro Scaffold for Transition Metal-Catalyzed Asymmetric Reactions. *Acc. Chem. Res.* **2008**, *41*, 581–593.
24. Xie, J.-H.; Zhou, Q.-L. Magical Chiral Spiro Ligands. *Acta Chim. Sinica* **2014**, *72*, 778–797.
25. During the preparation of this manuscript, a Ni-catalyzed enantioselective hydroarylation of styrenes with arylboronic acids using bisoxazoline ligand was reported by Mei et al.: Chen, Y.-G.; Shuai, B.; Xu, X.-T.; Li, Y.-Q.; Yang, Q.-L.; Qiu, H.; Zhang, K.; Fang, P.; Mei, T.-S. Nickel-catalyzed Enantioselective Hydroarylation and Hydroalkenylation of Styrenes. *J. Am. Chem. Soc.* **2019**, *141*, 3395–3399.

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