Organic LETTERS

Letter

pubs.acs.org/OrgLett

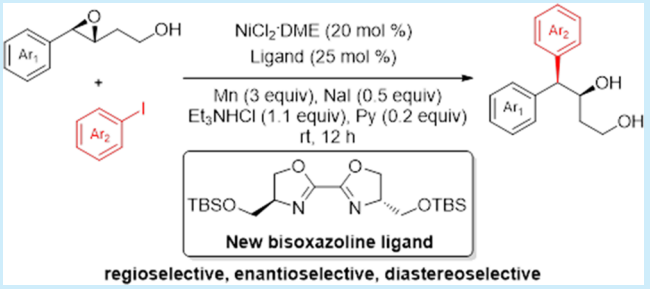
Nickel Catalyzed Regio-, Diastereo-, and Enantioselective Cross-Coupling of 3,4-Epoxyalcohol with Aryl Iodides

Amit Banerjee* and Hisashi Yamamoto*

Molecular Catalyst Research Center, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi 487-8501, Japan

Supporting Information

ABSTRACT: The first catalytic, regioselective cross-coupling of 3,4-epoxyalcohol with aryl iodides is reported. The combination of $NiCl_2$·DME and a newly developed C_2-symmetric oxazoline ligand plays a key role in selective ring opening of several 3,4-epoxy alcohols at the C4 position. This general protocol furnishes a new type of enantioenriched 4,4-diaryl alkane which also incorporates an additional 1,3-diol that can be easily transformed to a variety of functional groups. The products are formed with excellent regioselectivity (>99:1), diastereoselectivity (up to 99:1), and enantiopurity (up to >99.9% ee).



In recent years our group has been involved in the asymmetric epoxidation of allylic and homoallylic alcohols[1] followed by regio- and enantioselective ring opening by using nitrogen nucleophiles to generate enantiomerically pure amino alcohols.[2] The selective ring opening of 3,4-epoxy alcohols with carbon nucleophiles is a challenging task which would provide a straightforward access to 4,4-diaryl alkanes. As diaryl alkane moieties are present in various bioactive molecules, they play a significant role in living organisms that is reflected in their wide application in the pharmaceutical industry (Figure 1).[3]

Depending on their importance and synthetic utility, various attempts have been made toward the enantioselective synthesis of diaryl alkanes, including asymmetric hydrogenation of diaryl alkenes,[4] 1,4-addition to α,β-unsaturated carbonyl compounds,[5] and asymmetric cross-coupling at benzylic centers.[6] Meanwhile, transition metal catalyzed asymmetric cross-coupling methods have enormous scope, but enantioselective synthesis of 1,1-diaryl alkanes has rarely been investigated.[7] Recently, the

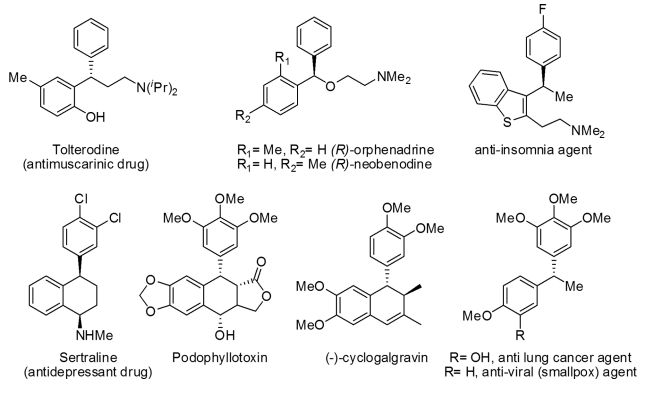
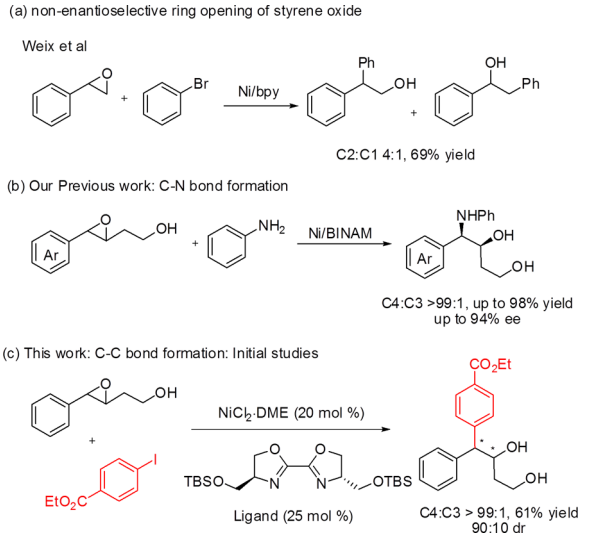


Figure 1. Biologically active chiral 1,1-diaryl alkane.

Scheme 1. Regio- and Enantioselective Opening of Epoxides

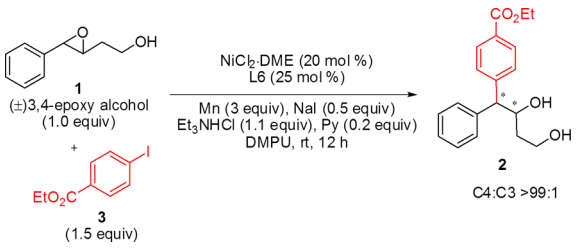


synthesis of enantioenriched diaryl alkanes reported by Fu,[8a] Doyle,[8b] and Reisman.[8c] Moreover, Weix reported cooperative Ni/Ti- catalyzed enantioselective cross-coupling of meso-epoxide with aryl bromides.[9a] Unfortunately, nickel catalyzed nonenantioselective cross-coupling of unsymmetrical aromatic epoxide suffers from regioselectivity issues (Scheme 1a).[9b] We envisioned that regioselective ring opening of epoxide by carbon nucleophiles can be controlled by using a hydroxy directing group in combination with nickel complexes (Scheme 1c).

Received: July 8, 2017

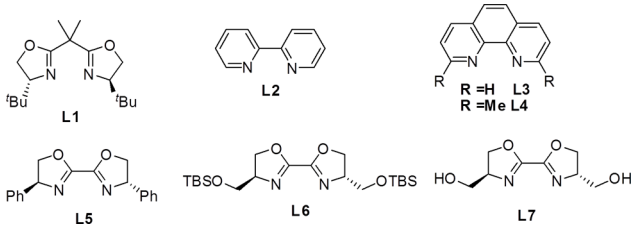
DOI: 10.1021/acs.orglett.7b02076
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimizaton of Nickel Catalyzed Cross-Coupling of 3,4-Epoxy Alcohol with Aryl Iodide[a]

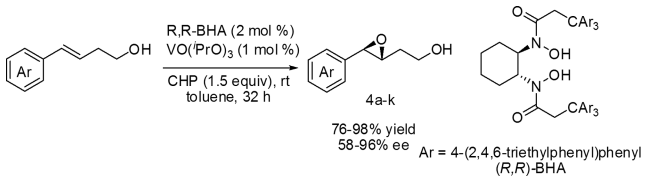


entry	reaction condition	yield (%)[b]	dr[c]
1	standard conditions	61	90:10
2	**L1** instead of **L6**	14	92:8
3	**L2** instead of **L6**	56	79:21
4	**L3** instead of **L6**	40	79:21
5	**L4** instead of **L6**	37	73:27
6	**L5** instead of **L6**	12	70:30
7	**L7** instead of **L6**	38	86:14
8	No $NiCl_2$·DME	0	–
9	No ligand	0	–
10	No Mn	0	–
11	Ar–Br instead of Ar–I	33	89:11
12	Zn instead of Mn	10	20:80
13	*m*-CO_2Et-PhI instead of *p*-CO_2Et-PhI	53	80:20
14	No Et_3NHCl, No NaI	21	92:8

[a]All the reactions were performed in 0.4 mmol scale, $NiCl_2$·DME (0.08 mmol, 0.2 equiv), Ligand (0.1 mmol, 0.25 equiv), Mn (1.2 mmol, 3.0 equiv), NaI (0.2 mmol, 0.5 equiv), Et_3NHCl (0.44 mmol, 1.1 equiv), Pyridine (0.8 mmol, 0.2 equiv), DMPU (3 mL), rt, 12 h. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy.



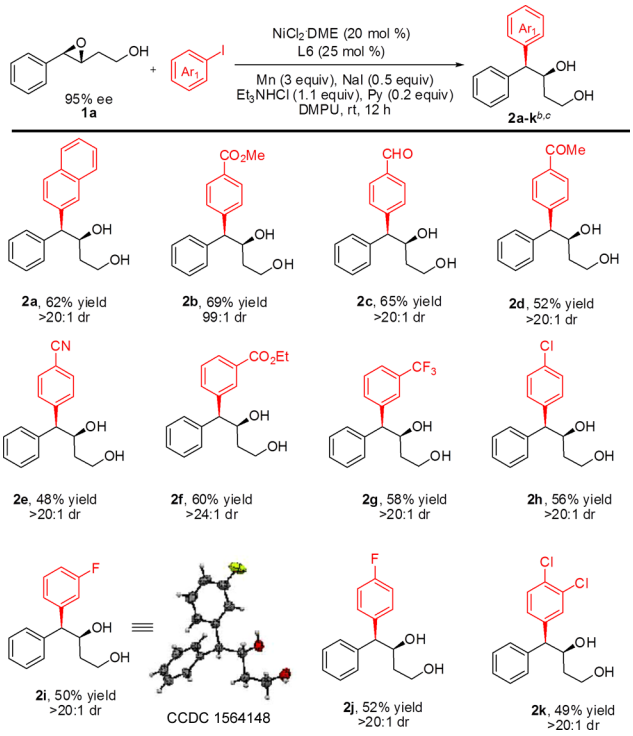
Scheme 2. Preparation of Chiral 3,4-Epoxy Alcohol



Very recently, our group reported Ni/BINAM complex-catalyzed regio- and enantioselective aminolysis of 3,4-epoxy alcohol with aryl amine directed by a hydroxyl group (Scheme 1b).[2] Based on these observation, we tested the regio-, diastereo-, and enantioselective cross-coupling of 3,4-epoxyalcohol with aryl iodides catalyzed by a new Ni/bisoxazoline complex (Table 1).

Initially, we commenced our investigation using *trans*-2-(3-phenyloxiran-2-yl)ethanol which is readily accessible from the corresponding olefin by *m*CPBA epoxidation and ethyl 4-iodobenzoate as substrate. To challenge this scheme, we first tested commercial **L1**; however, cross-coupling was observed with good diastereoselectivity but in very low yield (entry 2). Gratifyingly, **L2** provided the cross-coupling product in 56%

Scheme 3. Scope of Aryl Iodides[a]



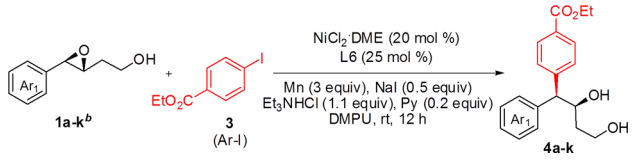
[a]Reaction conditions: epoxide **1** (0.4 mmol, 1.0 equiv), **3** (0.6 mmol, 1.5 equiv), $NiCl_2$·DME (0.08 mmol, 0.2 equiv), Ligand (0.1 mmol, 0.25 equiv), Mn (1.2 mmol, 3.0 equiv), NaI (0.2 mmol, 0.5 equiv), Et_3NHCl (0.44 mmol, 1.1 equiv), Pyridine (0.8 mmol, 0.2 equiv), DMPU (3 mL), rt, 12 h. [b]Isolated yield. [c]Diastereomeric ratio was determined by NMR of crude reaction mixture.

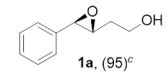
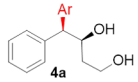
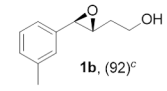
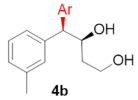
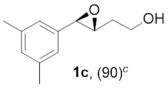
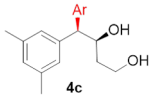
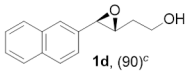
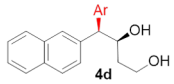
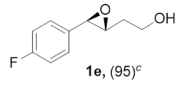
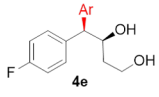
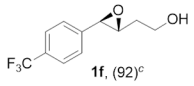
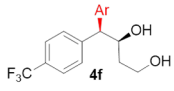
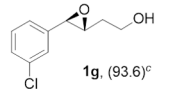
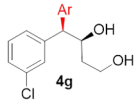
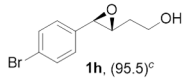
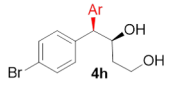
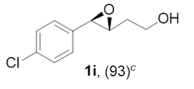
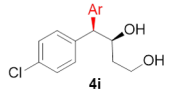
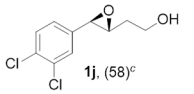
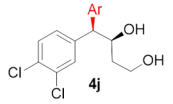
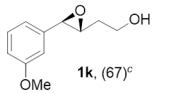
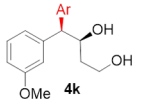
yield albeit moderate diastereoselectivity (entry 3). Further, **L3** and **L4** also show similar results with slightly lower yields of the product (entries 4, 5). Interestingly, **L5** also gave a very low yield of the product with poor *dr* (entry 6). We then hypothesized that steric hindrance at the α-position of nitrogen could be a deciding factor which ultimately effects the formation of a reactive nickel ligand complex to determine the selectivity and yield. Subsequent investigation showed that the presence of a methylene group at the α-position of the bis-oxazoline moiety is preferable to a tertiary carbon to improve yield and selectivity. Gratifyingly, promising diastereoselectivity (90:10) and excellent regioselectivity (>99:1) were observed with a 61% yield in the case of **L6**, which was derived from L-serine (entry 1), whereas **L7** also gave a similar *dr* albeit in a lower yield of the product (entry 7). Further, using ArBr instead of ArI did not improve the yield (entry 11). Again replacing *p*-CO_2Et-PhI with *m*-CO_2Et-PhI showed slight improvement in dr but a lower yield (entry 13). Furthermore, Zn instead of Mn provided a very low yield of the product (entry 12). The addition of Et_3NHCl and NaI were found to be necessary to improve the yield probably due to activation and ring opening of epoxide (entry 14).[9a,b] The complete conversion of epoxyalcohol **1** was observed under the reaction conditions in the given time. Notably, no cross-coupling product was observed in the absence of $NiCl_2$·DME (entry 8), Ligand (entry 9), and Mn (entry 10). From further investigation, DMPU was found to be the best solvent.[10]

Encouraged by these initial results we focused our attention toward the enantio- and diastereoselective cross-coupling of

DOI: 10.1021/acs.orglett.7b02076
Org. Lett. XXXX, XXX, XXX–XXX

Table 2. Scope of Chiral Epoxides[a]

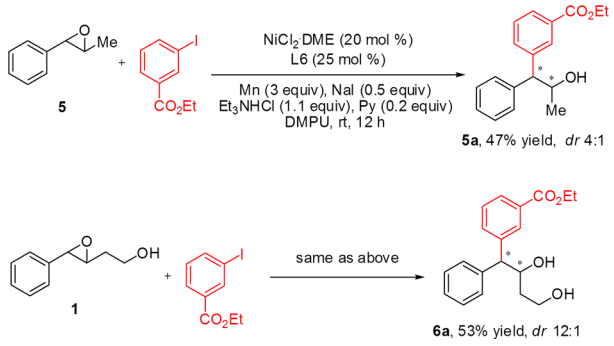


entry	epoxide (*ee*)	product	yield[d] (%)	*ee*[e] (%)	*dr*[f]
1	 **1a**, (95)[c]	 **4a**	63	96	96:4
2	 **1b**, (92)[c]	 **4b**	66	98	96:4
3	 **1c**, (90)[c]	 **4c**	61	98.4	96:4
4	 **1d**, (90)[c]	 **4d**	61	98.6	96:4
5	 **1e**, (95)[c]	 **4e**	55	98.8	95:5
6	 **1f**, (92)[c]	 **4f**	41	99	94:6
7	 **1g**, (93.6)[c]	 **4g**	52	98.9	95:5
8	 **1h**, (95.5)[c]	 **4h**	54	99.9	96:4
9	 **1i**, (93)[c]	 **4i**	57	98.9	95:5
10	 **1j**, (58)[c]	 **4j**	52	91.5	90:10
11	 **1k**, (67)[c]	 **4k**	66	99.9	96:4

[a]Reaction conditions: epoxide **1** (0.4 mmol, 1.0 equiv), **3** (0.6 mmol, 1.5 equiv), $NiCl_2$·DME (0.08 mmol, 0.2 equiv), Ligand (0.1 mmol, 0.25 equiv), Mn (1.2 mmol, 3.0 equiv), NaI (0.2 mmol, 0.5 equiv), Et_3NHCl (0.44 mmol, 1.1 equiv), Pyridine (0.8 mmol, 0.2 equiv), DMPU (3 mL), rt, 12 h. [b]Enantioenriched epoxide was synthesized using our previous report. [c]*ee* of epoxide. [d]Isolated yield. [e]Enantiomeric excess was determined by Chiral HPLC. [f]Diastereomeric ratio was determined by Chiral HPLC.

3,4-epoxyalcohol. We chose enantioenriched *trans*-2-(3-phenyloxiran-2-yl)ethanol (**1a**, 95% ee) which is easily prepared using our previous method and **3** for the ring opening reaction (Scheme 2).[1a] To our delight, cross-coupling of enantioenriched epoxide **1a** with **3** in the presence of Ni/**L6** complex provided the product (**4a**) with excellent regio- (>99:1) and

Scheme 4. Effect of Hydroxy Group in Cross-Coupling



diastereoselectivity (96:4) as well as enantioselectivity (96%) in 63% yield.

With this inspiring result in hand, we started to evaluate the substrate scope of this reaction. First, we tested commercially available aryl iodide to reveal the generality of this method (Scheme 3). For iodides, substitution at various positions of the aromatic ring is well tolerated to provide the 4,4-diaryl alkane product with moderate to good yields (48−69%) and with excellent diastereoselectivity. In order to check the accuracy of *dr*, chiral HPLC analysis was used for substrates **2b** and **2f**, and as anticipated, excellent *dr* was observed (99:1 and >96:4 respectively). Furthermore, a variety of functional groups including ester (**2b**, **2f**), aldehyde (**2c**) and ketone (**2d**), nitrile (**2e**), trifluoromethyl (**2g**), and halides such as fluoride (**2i**, **2j**) and chloride (**2h**, **2k**) were tolerated under these mild reaction conditions.

Encouraged by this broad iodide scope, we then began to evaluate the substrate scope of epoxides for this cross-coupling reaction (Table 2). A variety of enantioenriched 3,4-epoxyalcohols having different substituents were successfully synthesized by using our previous epoxidation method.[1a] Generally, all the reactions proceeded smoothly at ambient temperature affording products with excellent regioselectivity (>99:1) in good yields. Substrates **1b** and **1k** having substitution at the *m*-position of the aromatic ring provided a 66% yield, whereas *p*-substituted substrates such as **1e**, **1f**, **1g**, **1h**, **1i** and *m*-substituted ones such as **1g** provided a slightly diminished yield (42−57%). Interestingly, a significant improvement of *ee* of cross-coupling product was observed over the corresponding epoxy alcohol which might indicate that an unprecedented kinetic resolution occurs under the reaction conditions. As anticipated various functional groups such as halides, $-CF_3$, and −OMe were well tolerated under these reaction conditions. Gratifyingly, all the diaryl alkane products were achieved with excellent enantiopurity (up to 99.9%) and diastereoselectivity (up to 97:3). All the ee and dr were determined by chiral HPLC analysis (see Supporting Information).

In order to test the directing effect of the hydroxyl group of the substrate, we subjected 2-methyl-3-phenyloxirane (**5**) to the same reaction conditions furnishing a 4:1 diastereomeric mixture of cross-coupling product. However, *trans*-2-(3-phenyloxiran-2-yl)ethanol (**1**) furnished a 12:1 *dr* which clearly supports the hydroxy group playing a significant role to determine the diastereoselectivity (Scheme 4).

In conclusion, we have developed the first hydroxy directed, nickel catalyzed cross-coupling of a 3,4-epoxy alcohol with aryl iodides. The C4-selective opening approach shows excellent enantio- and diastereoselectivity for diverse epoxides with

DOI: 10.1021/acs.orglett.7b02076
Org. Lett. XXXX, XXX, XXX−XXX

various aryl iodides. Moreover, an enantioenriched 4,4-diaryl alkane with additional 1,3-diol functionality will provide a broad scope for further functionalization and can furnish new pathways for the synthesis of building blocks and synthetically useful intermediates. A new C_2-symmetric bisoxazoline ligand was identified to achieve excellent selectivity. Further study related to mechanism and application is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02076.

Experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: banerjeeam07@isc.chubu.ac.jp.
*E-mail: hyamamoto@isc.chubu.ac.jp.

ORCID

Hisashi Yamamoto: 0000-0001-5384-9698

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JST ACT-C Grant Number JPMJCR12ZD, Japan. The authors thank Dr. Y. Shimoda and Prof. E. Ishikawa for helpful discussions.

■ REFERENCES

(1) For enantioselective epoxidation of homoallylic alcohol, bis-homoallylic alcohol, and allylic alcohols, see: (a) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286. (b) Barlan, A. U.; Zhang, W.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 6075. (c) Li, Z.; Zhang, W.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7520. (d) Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*, 7878. (e) Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2013**, *135*, 3411. (f) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222. (g) Bhadra, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2015**, *137*, 15612. (h) Li, Z.; Yamamoto, H. *Acc. Chem. Res.* **2013**, *46*, 506.

(2) For 3,4-epoxyalcohol opening by amine nucleophile, see: (a) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2015**, *137*, 4308. For 2,3-epoxy alcohol opening by amine nucleophile, see: (b) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 6888. (c) Wang, C.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 13920.

(3) For references on various pharmaceuticals and biologically active molecules containing 1,1-diarylalkanes, see: (a) Hills, C. J.; Winter, S. A.; Balfour, J. A. *Drugs* **1998**, *55*, 813. (b) McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacother.* **2001**, *2*, 883. (c) Malhotra, B.; Gandelman, K.; Sachse, R.; Wood, N.; Michel, M. C. *Curr. Med. Chem.* **2009**, *16*, 4481. (d) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (e) Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; Rodrigo De Losada, J.; Bignon, J.; Liu, J.-M.; Wdzieczak- Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem* **2011**, *6*, 488. (f) Abad, A.; López-Pérez, J. L.; del Olmo, E.; García- Fernández, L. F.; Francesch, A.; Trigili, C.; Barasoain, I.; Andreu, J. M.; Díaz, J. F.; San Feliciano, A. *J. Med. Chem.* **2012**, *55*, 6724. (g) Silva, D. H. S.; Davino, S. C.; de Moraes Barros, S. B.; Yoshida, M. *J. Nat. Prod.* **1999**, *62*, 1475. (h) Ameen, D.; Snape, T. J. *MedChemComm* **2013**, *4*, 893.

(4) (a) Wang, Z.; Ai, F.; Wang, Z.; Zhao, W.; Zhu, G.; Lin, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 383. (b) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W.-M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855. (c) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912.

(5) (a) Yasukawa, T.; Suzuki, A.; Miyamura, H.; Nishino, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2015**, *137*, 6616. (b) Paquin, J.−F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.

(6) (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (b) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280. (c) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307. (d) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303.

(7) For selected review in nickel catalysis, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299. (b) Montgomery, J. Organonickel Chemistry. In *Organometallics in Synthesis*; Lipshutz, B. H., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2013; pp 319−428. (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (d) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587. For the selected reaction of racemic 1,1-diaryl alkane, see: (e) He, Y.; Cai, Y.; Zhu, S. *J. Am. Chem. Soc.* **2017**, *139*, 1061. (f) Arendt, K. M.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 9876.

(8) (a) Do, H.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288. (b) Woods, B. P.; Orlandi, M.; Huang, C.-Y.; Sigman, M. S.; Doyle, A. G. *J. Am. Chem. Soc.* **2017**, *139*, 5688. (c) Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2017**, *139*, 5684.

(9) (a) Zhao, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 3237. (b) Zhao, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 48. For the selected nonenantioselective cross-coupling of epoxides, see: (c) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130. (d) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442. (e) Nielsen, D. K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 6056. (f) Ikeda, Y.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Adv. Synth. Catal.* **2004**, *346*, 1631.

(10) DMPU and DMI were found to be the best solvents for this reaction, although DMI provided a slightly lower yield (54%), whereas DMF and DMA provided very low yields of the product (<15%). No cross-coupling product was observed in the case of DMSO, THF, toluene, and diethyl ether.

DOI: 10.1021/acs.orglett.7b02076
Org. Lett. XXXX, XXX, XXX−XXX