ACS Catalysis

Letter

Cite This: ACS Catal. 2019, 9, 1−6

pubs.acs.org/acscatalysis

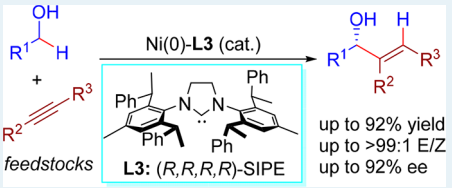
Nickel/N-Heterocyclic Carbene Complex-Catalyzed Enantioselective Redox-Neutral Coupling of Benzyl Alcohols and Alkynes to Allylic Alcohols

Yuan Cai, Jia-Wen Zhang, Feng Li, Jia-Ming Liu, and Shi-Liang Shi*

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: The nickel-catalyzed enantioselective redox-neutral coupling of alcohols and alkynes to access chiral allylic alcohols is reported. The reaction proceeds via a hydrogen transfer process under ambient temperature, converting abundant feedstock alcohols and alkynes to chiral allylic alcohols with high stereoselectivities in one chemical step. Key to the success of this process was the development of a bulky chiral N-heterocyclic carbene, (*R*,*R*,*R*,*R*)-SIPE, a chiral version of SIPr, as the ligand for nickel. Notably, we found that the utilization of $P(OPh)_3$ as secondary ligand for nickel was crucial to inhibit the isomerization of products.

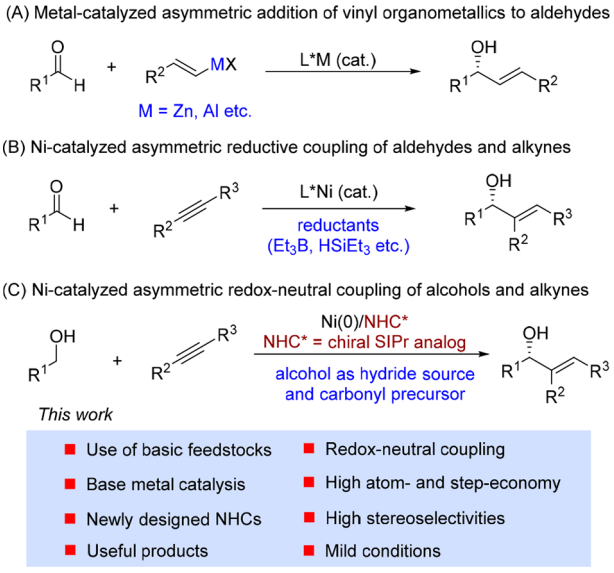


KEYWORDS: *asymmetric catalysis, nickel, ligand design, N-heterocyclic carbenes, transfer hydrogenation, redox-neutral coupling, alkynes, alcohols*

Enantioenriched allylic alcohols represent important chiral building blocks because of their synthetic versatility and the common occurrence of this substructure in a variety of pharmaceuticals and natural products. Consequently, the general asymmetric construction of chiral allylic alcohols is an important objective in organic synthesis.[1] Among the reported methods, the classical asymmetric addition of vinyl organometallics to carbonyl compounds[2] is a general method to synthesize chiral allylic alcohols, although vinyl organometallics need to be preformed, often through multistep procedures (Scheme 1A). Alternatively, the nickel-catalyzed asymmetric reductive coupling of aldehydes and alkynes[3] has been advanced as a more efficient approach for the preparation of chiral allylic alcohols (Scheme 1B).[4] While the direct use of widely available alkynes as coupling partner in lieu of a vinyl organometallic in this process is advantageous, stoichiometric organometallic reductants (e.g., $ZnEt_2$ or Et_3B) are still required.

Recently, we questioned whether an alcohol could serve as both a "greener" hydride source and also as a precursor for a transient aldehyde for the overall redox-neutral asymmetric coupling of alkynes and alcohols to form chiral allylic alcohols (Scheme 1C).[5−7] If successful, such a direct asymmetric C−H alkenylation of alcohols via hydrohydroxyalkylation of alkynes represents a nearly ideal method to access chiral allylic alcohols given the abundance of both starting materials and excellent atom-, step-, and redox economy of the process.[8] We noted that the Krische group,[9] and the Matsubara group,[10] has developed elegant alcohol-alkyne coupling reactions for the synthesis of achiral allylic alcohols using ruthenium and nickel-based catalysts, respectively. However, the methods for the enantioselective C−H alkenylation of alcohols with alkynes to form chiral allylic alcohols, have previously not been reported.

Scheme 1. Synthesis of Chiral Allylic Alcohols



Despite recent advances made in the field of asymmetric redox-neutral coupling of alcohols and unsaturated hydrocarbons,[5−7] base metal-catalyzed enantioselective examples

Received: October 18, 2018
Revised: November 19, 2018

DOI: 10.1021/acscatal.8b04198
ACS Catal. 2019, 9, 1−6

remain elusive.[11] One factor that has impeded the development of asymmetric base metal-catalyzed reactions is the lack of suitable chiral ligands with efficient control of both reactivity and selectivity.

Chiral N-heterocyclic carbenes (NHCs) have become increasingly common in asymmetric catalysis,[12] especially for nickel(0)-catalysis,[3b,c,13] as a result of their modular preparation, steric and electronic tunability, and robustness as monodentate ligands for transition-metals. We recently developed a bulky chiral NHC ligand, namely, ANIPE (Figure 1, **L1**),[14] which could be considered a chiral version of IPr,

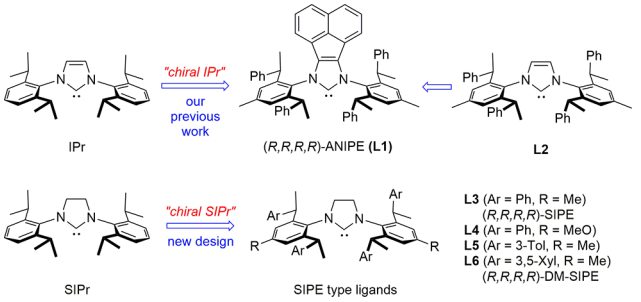
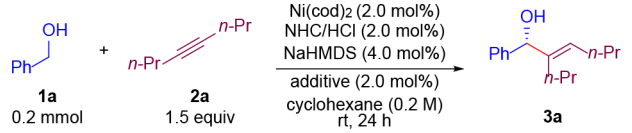


Figure 1. NHCs designed and applied in this study.

whose design draws inspiration from Gawley's carbene (**L2**).[15] The use of **L1** enabled a highly enantioselective copper catalyzed hydroboration of α-olefins.[14] Subsequently, Cramer reported a nickel-catalyzed enantioselective intramolecular alkylation of pyridone substrates based on a similar ligand system.[13g] Herein, we describe the development of SIPE ligands (Figure 1), a new class of bulky chiral analogues of saturated NHCs, like SIPr. It is practically important that the precursor of SIPE ligands, air- and moisture-stable salts, could be easily prepared on multigram scale.[16] The SIPE ligands were successfully applied to the nickel-catalyzed enantioselective redox-neutral coupling of alcohols and alkynes to form chiral allylic alcohols. To the best of our knowledge, this is the first example of base metal-catalyzed enantioselective transfer hydrogenative C−C bond forming reactions.

We began our study by examining the coupling of benzyl alcohol (**1a**) and 4-octyne (**2a**) to form chiral allylic alcohol **3a** in the presence of 2 mol % $Ni(cod)_2$ and chiral ligand. Initially, a range of commonly used chiral phosphine and N-heterocyclic carbene ligands were tested, none of which provided the desired product **3a** (see Supporting Information (SI)). The use of our previously disclosed ligand **L1**, however, gave encouraging results, providing product **3a** in 68% yield and 92.5:7.5 e.r. with an E/Z selectivity of 88:12 (Table 1, entry 1). Although the use of **L2** resulted in lower yield (entry 2), the use of **L3**, a newly design saturated NHC led to an improvement in the yield and selectivity (entry 3, E/Z 94:6, 95.5:4.5 e.r.). During the course of optimization, we found that partial isomerization[17] of **3a** occurred under the reaction conditions, which we ascribed to a sequential hydronickelation and β-H elimination process initiated by a nickel hydride species.[18] Various Lewis basic additives, such as PPh_3, ethyl acrylate, Et_3N, and phosphites, were investigated as secondary ligands, whose coordination might stabilize the nickel catalyst and thus suppress isomerization events (entries 4−9). We were pleased to find that the electron-deficient phosphite ligand $P(OPh)_3$[19] in combination with **L3** at room temperature delivered **3a** in 76% isolated yield and 95.5:4.5 e.r., with a

Table 1. Ligand Screening and Reaction Optimization



entry	NHC	additive	yield (%)[a]	E/Z[a]	e.r.[b]
1	**L1**	--	68	88:12	92.5:7.5
2	**L2**	--	42	88:12	91.5:8.5
3	**L3**	--	84	94:6	95.5:4.5
4	**L3**	PPh_3	<2	nd	nd
5	**L3**	ethyl acrylate	68	93:7	nd
6	**L3**	dimethyl fumarate	<2	nd	nd
7	**L3**	NEt_3	60	90:10	nd
8	**L3**	$P(OEt)_3$	69	93:7	nd
9	**L3**	$P(OPh)_3$	82(76)	99:1	95.5:4.5
10	**L4**	$P(OPh)_3$	84	97:3	94.5:5.5
11	**L5**	$P(OPh)_3$	72	96:4	94.5:5.5
12	**L6**	$P(OPh)_3$	70	96:4	95:5

[a]Determined by NMR analysis with 1,1,2,2-tetrachloroethane as internal standard using crude sample; isolated yield shown in parentheses. [b]Determined by HPLC analysis with a chiral stationary phase.

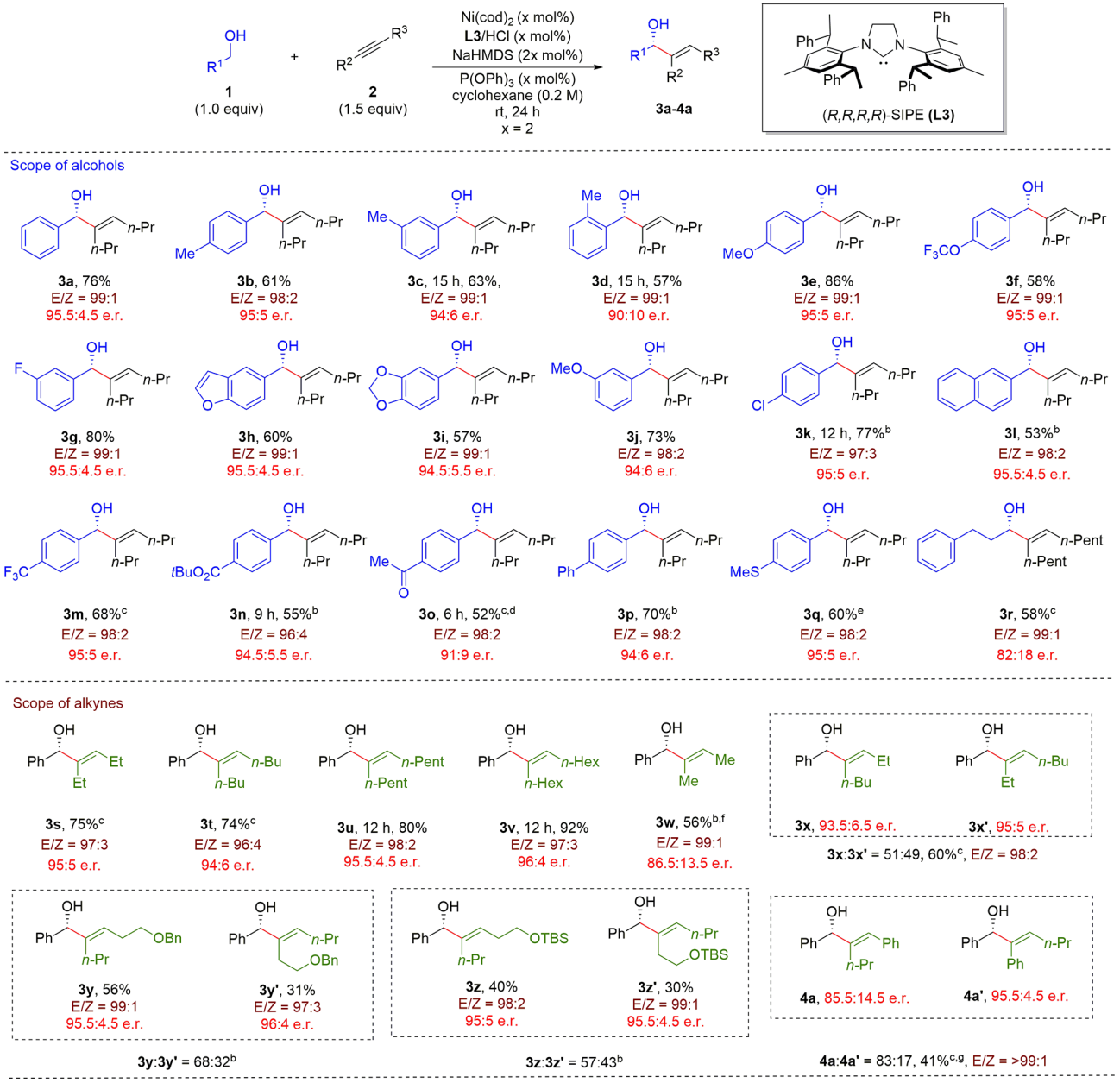
dramatically improved E/Z ratio of 99:1 (entry 9). Interestingly, other members of the SIPE family of ligands exhibited slightly lower levels of selectivity (**L4**−**L6**, entries 10−12).

With our optimized conditions, we next set out to investigate the scope of this novel enantioselective alcohol-alkyne coupling protocol (Table 2). First, various benzylic alcohols were coupled with 4-octyne. Both electron-rich and electron-poor benzylic alcohols were suitable, and electronic properties had little influence on the enantioselectivity, although electron-poor benzylic alcohols required a higher catalyst loading to achieve good conversion. Generally, chiral allylic alcohol products were obtained in moderate to high yields (52−86%) and high stereoselectivities (≥96:4 E/Z) and enantioselectivities (94:6−95.5:4.5 e.r. in most cases). Importantly, this mild protocol tolerated many functional groups, such as ethers (**3e**, **3i**, **3j**, and **3y**) and silyl ethers (**3z**), a thioether (**3q**), a trifluoromethyl ether (**3f**), aryl halides (F, Cl) (**3g** and **3k**), a benzofuran (**3h**), a trifluoromethyl (**3m**), an ester (**3n**), and a ketone (**3o**). It is noteworthy that an aryl chloride was compatible with reaction conditions (**3k**), considering well-established, mild protocols for nickel-catalyzed cross coupling of aryl chlorides.[4] Remarkably, simple aliphatic alcohol (phenylpropanol) could also be employed in this transformation, providing the coupling product **3r** with moder ate enantioselectivity, though with excellent control of double bond geometry.

Next, we examined the scope of alkynes coupling partner. In addition to 4-octyne, we found that symmetric internal alkynes, including 3-hexyne, 5-decyne, 6-dodecyne, and 7-tetradecyne, were all competent substrates, providing products in 94:6−96:4 e.r. and 74−92% yields (**3s**−**3v**). In the case of 2-butyne (the smallest internal alkyne), bulkier ligand **L6** was employed, affording product **3w** in 86.5:13.5 e.r.[20] Given that efficient enantiocontrol of a nickel-catalyzed reductive coupling of dialkyl internal alkynes and aldehydes is challenging, the enantioselectivities obtained in this novel protocol are considerably high.[3] Moreover, the use of unsymmetric internal

DOI: 10.1021/acscatal.8b04198
ACS Catal. 2019, 9, 1−6

Table 2. Substrate Scope[a]



[a]Yields of isolated products on 0.2 mmol scale. [b]Using 5 mol % catalyst (x = 5). [c]Using 10 mol % catalyst (x = 10). [d]toluene as the solvent. [e]Using 20 mol % catalyst (x = 20, without $P(OPh)_3$). [f]Using **L6**/HCl as the ligand. [g]20 mol % benzaldehyde was added.

alkynes, 3-octyne and an aryl-substituted alkyne, gave products as regioisomeric mixtures with high stereoselectivities for both regioisomers (**3x** and **3x′**, **4a** and **4a′**). In the case of an alkynylarene, 20 mol % benzaldehyde was added to promote the initial oxa-nickelacycle formation. Finally, regioisomeric products (**3y** and **3y′**, **3z** and **3z′**) from alkynes containing ethers could also be obtained in good yields and stereoselectivities. The absolute configuration of the product **3a** was determined as the R-configuration by Mosher ester analysis (see SI).

A series of experiments were performed to get insight into the mechanism. First, a deuterium-labeling experiment using *d2*-**1a** in the model reaction gave 87% deuterium incorporation at the olefinic position of **3a** (Figure 2A). On the basis of this result and previous observations,[10] we proposed a catalytic cycle as outlined in Figure 2B: (1) Alcohol dehydrogenation initially generates the corresponding aldehyde. (2) A subsequent oxidative cyclization of aldehyde, alkyne and Ni(0) catalyst furnishes oxanickelacyle **A**,[21] which is protonated by alcohol to afford acyclic vinylnickel intermediate **B**. (3) A subsequent β-H elimination of **B** provides nickel hydride complex **C** and regenerates the aldehyde. (4) Finally, reductive elimination affords the allylic alcohol product and regenerates the nickel catalyst. In support of this proposal, when *d2*-**1a** and nondeuterated **1e** was used in a crossover reaction, partial incorporation at olefinic position was observed for both products, indicative of scrambling (Figure 2C). In contrast, no deuterium scrambling on benzylic position of *d2*-**3a** and *d1*-**3e** was observed, which suggest the dehydrogenation step of benzylic alcohols is probably irreversible and

DOI: 10.1021/acscatal.8b04198
ACS Catal. 2019, 9, 1−6

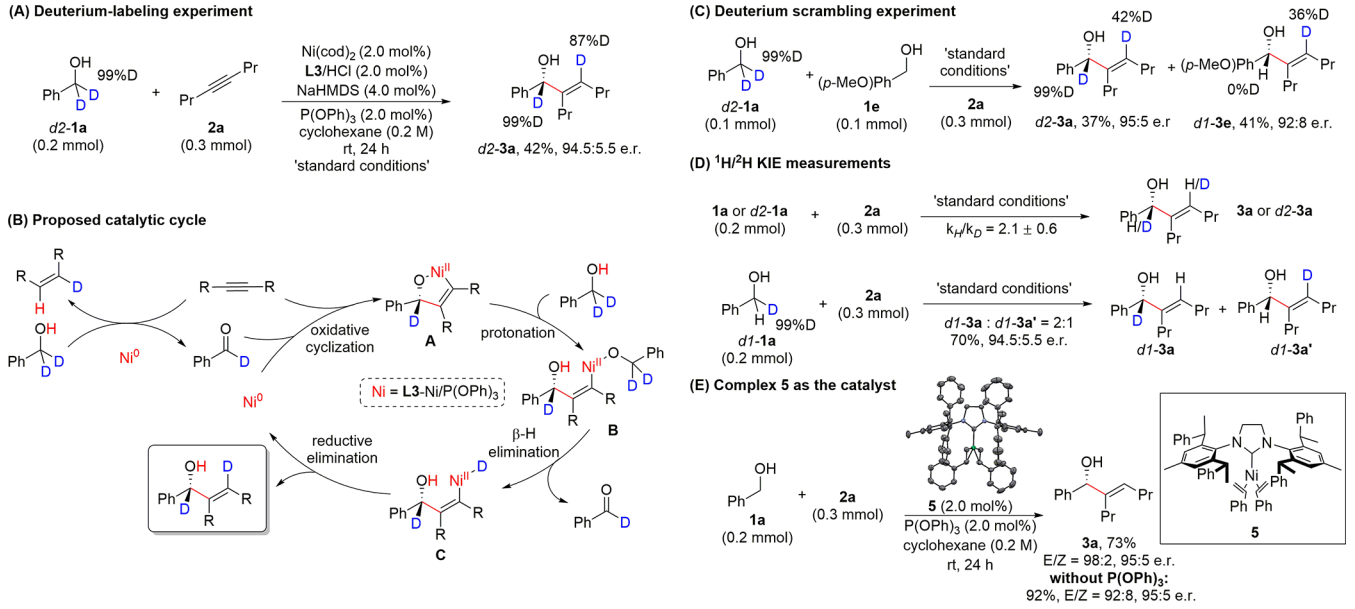


Figure 2. Mechanistic studies and proposed catalytic circle

oxidative cyclization is fast. In addition, both intermolecular and intramolecular KIEs were observed (KIE = 2.1 or 2.0, Figure 2D). Moreover, the X-ray crystal structure of Ni(0)-complex **5** was obtained. The use of **5** as catalyst gave similar results to the reaction using nickel catalyst generated in situ, consistent with monomeric nickel-**L3** complex being the active catalyst (Figure 2E). Finally, an erosion in *E*/*Z* ratio of **3a** was observed in the control experiment in the absence of $P(OPh)_3$ using **5** as catalyst, further confirm the important role of the additive (Figure 2E).

In summary, we have developed the first nickel-catalyzed enantioselective redox-neutral coupling of alcohols and alkynes, which also represents the first enantioselective base metal-catalyzed transfer hydrogenative C−C bond forming reaction. This mild protocol utilizes two feedstock chemicals and earth-abundant nickel catalysts to form chiral allylic alcohols with high stereoselectivities in one chemical step. Essential for the success of the process was the development of SIPE-type ligands and the utilization of a basic additive to suppress the product isomerization. Efforts to expand the scope of the reaction by further ligand design and exploration of wider application of these ligands are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b04198.

Experimental procedures, spectroscopic data, and NMR spectra of all products (PDF)

Crystallographic data for **5** (CCDC 1843290) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shiliangshi@sioc.ac.cn.

ORCID

Shi-Liang Shi: 0000-0002-0624-6824

Notes

The authors declare the following competing financial interest(s): A patent has been filed.

■ ACKNOWLEDGMENTS

This work was financially supported by the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB 20000000), the "1000 Talents Plan", the National Natural Science Foundation of China (Grant No. 21690074, 21871288, 21821002). We thank Prof. Yiming Wang (University of Pittsburgh) for proofreading this manuscript.

■ DEDICATION

Dedicated to Prof. Xiyan Lu on the occasion of his 90th birthday.

■ REFERENCES

(1) For recent reviews, see: (a) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. Enantiomerically Enriched Allylic Alcohols and Allylic Amines via C−C Bond-Forming Hydrogenation: Asymmetric Carbonyl and Imine Vinylation. *Acc. Chem. Res.* **2007**, *40*, 1394−1401. (b) Lumbroso, A.; Cooke, M. L.; Breit, B. Catalytic Asymmetric Synthesis of Allylic Alcohols and Derivatives and their Applications in Organic Synthesis. *Angew. Chem., Int. Ed.* **2013**, *52*, 1890−1932.

(2) For selected examples of enantioselective catalytic addition of vinyl organometallics to carbonyl compounds, see: Zn: (a) Oppolzer, W.; Radinov, R. N. Catalytic Asymmetric Synthesis of Secondary (*E*)-Allyl Alcohols from Acetylenes and Aldehydes *via* (1-Alkenyl) zinc Intermediates. Preliminary Communication. *Helv. Chim. Acta* **1992**, *75*, 170−173. (b) Wipf, P.; Xu, W. Preparation of Allylic Alcohols by Alkene Transfer from Zirconium to Zinc. *Tetrahedron Lett.* **1994**, *35*, 5197−5200. (c) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. A General, Highly Enantioselective Method for the Synthesis of D and L α-Amino Acids and Allylic Amines. *J. Am. Chem. Soc.* **2002**, *124*, 12225−12231. (d) Li, H.; Walsh, P. J. Catalytic Asymmetric Vinylation of Ketones. *J. Am. Chem. Soc.* **2004**, *126*, 6538−6539 Al: . (e) Biradar, D. B.; Gau, H.-M. Highly Enantioselective Vinyl Additions of Vinylaluminum to etones Catalyzed by a Titanium (IV) Catalyst of (*S*)-BINOL. *Org. Lett.* **2009**, *11*, 499−502 B: . (f) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. Enantioselective Alkenylation and Phenylation Catalyzed by a Chiral CuF Complex. *J. Am. Chem. Soc.* **2005**, *127*, 4138−4139. (g) Shono, T.; Harada, T. Catalytic

DOI: 10.1021/acscatal.8b04198
ACS Catal. 2019, 9, 1−6

Enantioselective Synthesis of Secondary Allylic Alcohols from Terminal Alkynes and Aldehydes *via* 1-Alkenylboron Reagents. *Org. Lett.* **2010**, *12*, 5270−5273. (h) Huang, Y.; Huang, R.-Z.; Zhao, Y. Cobalt-Catalyzed Enantioselective Vinylation of Activated Ketones and Imines. *J. Am. Chem. Soc.* **2016**, *138*, 6571−6576 Si: . (i) Aikawa, K.; Hioki, Y.; Mikami, K. Highly Enantioselective Alkenylation of Glyoxylate with Vinylsilane Catalyzed by Chiral Dicationic Palladium (II) Complexes. *J. Am. Chem. Soc.* **2009**, *131*, 13922−13923.

(3) For selected examples, see: (a) Miller, K. M.; Huang, W.-S.; Jamison, T. F. Catalytic Asymmetric Reductive Coupling of Alkynes and Aldehydes: Enantioselective Synthesis of Allylic Alcohols and α-Hydroxy Ketones. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443. (b) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. New *N*-Heterocyclic Carbene Ligand and Its Application in Asymmetric Nickel-Catalyzed Aldehyde/Alkyne Reductive Couplings. *J. Am. Chem. Soc.* **2007**, *129*, 9568−9569. (c) Wang, H.; Lu, G.; Sormunen, G. J.; Malik, H. A.; Liu, P.; Montgomery, J. NHC Ligands Tailored for Simultaneous Regio- and Enantiocontrol in Nickel-Catalyzed Reductive Couplings. *J. Am. Chem. Soc.* **2017**, *139*, 9317−9324. (d) Yang, Y.; Zhu, S.-F.; Zhou, C.-Y.; Zhou, Q.-L. Nickel-Catalyzed Enantioselective Alkylative Coupling of Alkynes and Aldehydes: Synthesis of Chiral Allylic Alcohols with Tetrasubstituted Olefins. *J. Am. Chem. Soc.* **2008**, *130*, 14052−14053. (e) Fu, W.; Nie, M.; Wang, A.; Cao, Z.; Tang, W. Highly Enantioselective Nickel-Catalyzed Intramolecular Reductive Cyclization of Alkynones. *Angew. Chem., Int. Ed.* **2015**, *54*, 2520−2524.

(4) For selected reviews on Ni-catalyzed C−C coupling reactions, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, *509*, 299−309. (b) Moragas, T.; Correa, A.; Martin, R. Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-Type Compounds. *Chem. - Eur. J.* **2014**, *20*, 8242−8258. (c) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767−1775. (d) Gu, J.; Wang, X.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Other Electrophiles: Concept and Mechanistic Considerations. *Org. Chem. Front.* **2015**, *2*, 1411−1421. (e) Henrion, M.; Ritleng, V.; Chetcuti, M. J. Nickel *N*-Heterocyclic Carbene-Catalyzed C−C Bond Formation: Reactions and Mechanistic Aspects. *ACS Catal.* **2015**, *5*, 1283−1302. (f) Choi, J.; Fu, G. C. Transition Metal−Catalyzed Alkyl-Alkyl Bond Formation: Another Dimension in Cross-Coupling Chemistry. *Science* **2017**, *356*, No. eaaf7230.

(5) For recent reviews on enantioselective alcohol-mediated transfer hydrogenation, see: (a) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. Catalytic Enantioselective C−H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142−9150. (b) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. Metal-Catalyzed Reductive Coupling of Olefin-Derived Nucleophiles: Reinventing Carbonyl Addition. *Science* **2016**, *354*, aah5133. (c) Kim, S. W.; Zhang, W.; Krische, M. J. Catalytic Enantioselective Carbonyl Allylation and Propargylation via Alcohol-Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier. *Acc. Chem. Res.* **2017**, *50*, 2371−2380. (d) Holmes, M.; Schwartz, L. A.; Krische, M. J. Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes, and Enynes with Carbonyl Compounds and Imines. *Chem. Rev.* **2018**, *118*, 6026−6052.

(6) For examples on enantioselective C−H allylation of alcohols with alkynes, see: (a) Liang, T.; Nguyen, K. D.; Zhang, D.; Krische, M. J. Enantioselective Ruthenium-Catalyzed Carbonyl Allylation via Alkyne-Alcohol C−C Bond-Forming Transfer Hydrogenation: Allene Hydrometalation *vs* Oxidative Coupling. *J. Am. Chem. Soc.* **2015**, *137*, 3161−3164. (b) Liang, T.; Zhang, W.; Krische, M. J. Iridium-Catalyzed C−C Coupling of a Simple Propargyl Ether with Primary Alcohols: Enantioselective Homoaldol Addition via Redox-Triggered (*Z*)-Siloxyallylation. *J. Am. Chem. Soc.* **2015**, *137*, 16024−16027. (c) Liang, T.; Zhang, W.; Chen, T.-Y.; Nguyen, K. D.; Krische, M. J. Ruthenium Catalyzed Diastereo- and Enantioselective Coupling of Propargyl Ethers with Alcohols: Siloxy-Crotylation *via* Hydride Shift Enabled Conversion of Alkynes to π-Allyls. *J. Am. Chem. Soc.* **2015**, *137*, 13066−13071.

(7) For selected examples on asymmetric coupling of alcohols and unsaturated hydrocarbons under hydrogen transfer conditions, see: (a) Holmes, M. T.; Nguyen, K. D.; Schwartz, L. A.; Luong, T.; Krische, M. J. Enantioselective Formation of CF_3-Bearing All-Carbon Quaternary Stereocenters via C−H Functionalization of Methanol: Iridium Catalyzed Allene Hydrohydroxymethylation. *J. Am. Chem. Soc.* **2017**, *139*, 8114−8117. (b) Nguyen, K. D.; Herkommer, D.; Krische, M. J. Enantioselective Formation of All-Carbon Quaternary Centers *via* C−H Functionalization of Methanol: Iridium-Catalyzed Diene Hydrohydroxymethylation. *J. Am. Chem. Soc.* **2016**, *138*, 14210−14213. (c) Nguyen, K. D.; Herkommer, D.; Krische, M. J. Ruthenium-BINAP Catalyzed Alcohol C−H *tert*-Prenylation via 1,3-Enyne Transfer Hydrogenation: Beyond Stoichiometric Carbanions in Enantioselective Carbonyl Propargylation. *J. Am. Chem. Soc.* **2016**, *138*, 5238−5241. (d) Sam, B.; Luong, T.; Krische, M. J. Ruthenium-Catalyzed C−C Coupling of Fluorinated Alcohols with Allenes: Dehydrogenation at the Energetic Limit of β-Hydride Elimination. *Angew. Chem., Int. Ed.* **2015**, *54*, 5465−5469. (e) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. Chiral-Anion-Dependent Inversion of Diastereo- and Enantioselectivity in Carbonyl Crotylation *via* Ruthenium-Catalyzed Butadiene Hydrohydroxyalkylation. *J. Am. Chem. Soc.* **2012**, *134*, 20628−20631. (f) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. Enantioselective C−H Crotylation of Primary Alcohols *via* Hydrohydroxyalkylation of Butadiene. *Science* **2012**, *336*, 324−327. (g) Geary, L. M.; Woo, S. K.; Leung, J. C.; Krische, M. J. Diastereo- and Enantioselective Iridium-Catalyzed Carbonyl Propargylation from the Alcohol or Aldehyde Oxidation Level: 1,3-Enynes as Allenylmetal Equivalents. *Angew. Chem., Int. Ed.* **2012**, *51*, 2972−2976. (h) Zbieg, J. R.; Moran, J.; Krische, M. J. Diastereo- and Enantioselective Ruthenium-Catalyzed Hydrohydroxyalkylation of 2-Silyl-butadienes: Carbonyl syn-Crotylation from the Alcohol Oxidation Level. *J. Am. Chem. Soc.* **2011**, *133*, 10582−10586. (i) Han, S. B.; Kim, I.-S.; Han, H.; Krische, M. J. Enantioselective Carbonyl Reverse Prenylation from the Alcohol or Aldehyde Oxidation Level Employing 1,1-Dimethylallene as the Prenyl Donor. *J. Am. Chem. Soc.* **2009**, *131*, 6916−6917.

(8) (a) Trost, B. M. The Atom Economy−a Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471−1477. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. Function-Oriented Synthesis, Step Economy, and Drug Design. *Acc. Chem. Res.* **2008**, *41*, 40−49. (c) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Redox Economy in Organic Synthesis. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854−2867.

(9) (a) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. Direct Vinylation of Alcohols or Aldehydes Employing Alkynes as Vinyl Donors: A Ruthenium Catalyzed C−C Bond-Forming Transfer Hydrogenation. *J. Am. Chem. Soc.* **2009**, *131*, 2066−2067. (b) McInturff, E. L.; Nguyen, K. D.; Krische, M. J. Redox-Triggered C−C Coupling of Diols and Alkynes: Synthesis of β,γ-Unsaturated α-Hydroxyketones and Furans by Ruthenium-Catalyzed Hydrohydroxyalkylation. *Angew. Chem., Int. Ed.* **2014**, *53*, 3232−3235. (c) Sato, H.; Bender, M.; Chen, W.; Krische, M. J. Diols, α-Ketols, and Diones as $2_{2\pi}$ Components in [2 + 2+2] Cycloadditions of 1,6-Diynes via Ruthenium (0)-Catalyzed Transfer Hydrogenation. *J. Am. Chem. Soc.* **2016**, *138*, 16244−16247. (d) Luong, T.; Chen, S.; Qu, K.; McInturff, E. L.; Krische, M. J. Ruthenium(0)-Catalyzed C−C Coupling of Alkynes and 3-Hydroxy-2-oxindoles: Direct C−H Vinylation of Alcohols. *Org. Lett.* **2017**, *19*, 966−968.

(10) Nakai, K.; Yoshida, Y.; Kurahashi, T.; Matsubara, S. Nickel-Catalyzed Redox-Economical Coupling of Alcohols and Alkynes to Form Allylic Alcohols. *J. Am. Chem. Soc.* **2014**, *136*, 7797−7800.

(11) For a review on base metal-catalyzed alcohol C−C couplings under hydrogen transfer conditions, see: (a) Cai, Y.; Li, F.; Li, Y.-Q.; Zhang, W.-B.; Liu, F.; Shi, S.-L. Base metal-catalyzed alcohol C−C couplings under hydrogen transfer conditions. *Tetrahedron Lett.* **2018**, *59*, 1073−1079. For racemic examples, see: (b) Zhang, S. Y.; Tu, Y. Q.; Fan, C. A.; Zhang, F. M.; Shi, L. Iron-Catalyzed $C(sp^3)$−$C(sp^3)$

DOI: 10.1021/acscatal.8b04198
ACS Catal. 2019, 9, 1−6

Bond Formation through C(sp^3)−H Functionalization: A Cross-Coupling Reaction of Alcohols with Alkenes. *Angew. Chem., Int. Ed.* **2009**, *48*, 8761−8765. (c) Bausch, C. C.; Patman, R. L.; Breit, B.; Krische, M. J. Divergent Regioselectivity in the Synthesis of Trisubstituted Allylic Alcohols by Nickel- and Ruthenium-Catalyzed Alkyne Hydrohydroxymethylation with Formaldehyde. *Angew. Chem., Int. Ed.* **2011**, *50*, 5687−5690. (d) Zheng, Y. L.; Liu, Y. Y.; Wu, Y. M.; Wang, Y. X.; Lin, Y. T.; Ye, M. C. Iron-Catalyzed Regioselective Transfer Hydrogenative Couplings of Unactivated Aldehydes with Simple Alkenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 6315−6318.

(12) (a) Perry, M. C.; Burgess, K. Chiral *N*-Heterocyclic Carbene-Transition Metal Complexes in Asymmetric Catalysis. *Tetrahedron: Asymmetry* **2003**, *14*, 951−961. (b) Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. Chiral *N*-Heterocyclic Carbenes as Stereodirecting Ligands in Asymmetric Catalysis. *Chem. Soc. Rev.* **2004**, *33*, 619−636. (c) Wang, F.; Liu, L.-J.; Wang, W.; Li, S.; Shi, M. Chiral NHC−Metal-Based Asymmetric Catalysis. *Coord. Chem. Rev.* **2012**, *256*, 804−853. (d) Janssen-Müller, D.; Schlepphorst, C.; Glorius, F. Privileged Chiral N-Heterocyclic Carbene Ligands for Asymmetric Transition-Metal Catalysis. *Chem. Soc. Rev.* **2017**, *46*, 4845−4854.

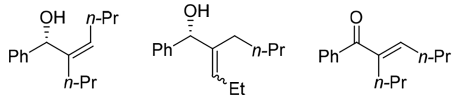
(13) (a) Sato, Y.; Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. Nickel-Catalyzed Enantio- and Diastereoselective Three-Component Coupling of 1,3-Dienes, Aldehydes, and Silanes Using Chiral N-Heterocyclic Carbenes as Ligands. *Org. Lett.* **2007**, *9*, 5597−5599. (b) Ahlin, J. S. E.; Donets, P. A.; Cramer, N. Nickel(0)-Catalyzed Enantioselective Annulations of Alkynes and Arylenoates Enabled by a Chiral NHC Ligand: Efficient Access to Cyclopentenones. *Angew. Chem., Int. Ed.* **2014**, *53*, 13229−13233. (c) Kumar, R.; Hoshimoto, Y.; Yabuki, H.; Ohashi, M.; Ogoshi, S. Nickel(0)-Catalyzed Enantio- and Diastereoselective Synthesis of Benzoxasiloles: Ligand-Controlled Switching from Inter- to Intramolecular Aryl-Transfer Process. *J. Am. Chem. Soc.* **2015**, *137*, 11838−11845. (d) Ho, C.-Y.; Chan, C.-W.; He, L. S. Catalytic Asymmetric Hydroalkenylation of Vinylarenes: Electronic Effects of Substrates and Chiral N-Heterocyclic Carbene Ligands. *Angew. Chem., Int. Ed.* **2015**, *54*, 4512−4516. (e) Ahlin, J. S. E.; Cramer, N. Chiral N-Heterocyclic Carbene Ligand Enabled Nickel(0)-Catalyzed Enantioselective Three-Component Couplings as Direct Access to Silylated Indanols. *Org. Lett.* **2016**, *18*, 3242−3245. (f) Kumar, R.; Hoshimoto, Y.; Tamai, E.; Ohashi, M.; Ogoshi, S. Two-step Synthesis of Chiral Fused Tricyclic Scaffolds from Phenols *via* Desymmetrization on Nickel. *Nat. Commun.* **2017**, *8*, 32. (g) Diesel, J.; Finogenova, A. M.; Cramer, N. Nickel-Catalyzed Enantioselective Pyridone C−H Functionalizations Enabled by a Bulky N-Heterocyclic Carbene Ligand. *J. Am. Chem. Soc.* **2018**, *140*, 4489−4493.

(14) Cai, Y.; Yang, X.-T.; Zhang, S.-Q.; Li, F.; Li, Y.-Q.; Ruan, L.-X.; Hong, X.; Shi, S.-L. Copper-Catalyzed Enantioselective Markovnikov Protoboration of α-Olefins Enabled by a Buttressed N-Heterocyclic Carbene Ligand. *Angew. Chem., Int. Ed.* **2018**, *57*, 1376−1380.

(15) (a) Albright, A.; Gawley, R. E. Application of a C_2-Symmetric Copper Carbenoid in the Enantioselective Hydrosilylation of Dialkyl and Aryl-Alkyl Ketones. *J. Am. Chem. Soc.* **2011**, *133*, 19680−19683. (b) Albright, A.; Eddings, D.; Black, R.; Welch, C. J.; Gerasimchuk, N. N.; Gawley, R. E. Design and Synthesis of C_2-Symmetric N-Heterocyclic Carbene Precursors and Metal Carbenoids. *J. Org. Chem.* **2011**, *76*, 7341−7351. (c) Spahn, E.; Albright, A.; Shevlin, M.; Pauli, L.; Pfaltz, A.; Gawley, R. E. Double-Asymmetric Hydrogenation Strategy for the Reduction of 1,1-Diaryl Olefins Applied to an Improved Synthesis of CuIPhEt, a C_2-Symmetric N-Heterocyclic Carbenoid. *J. Org. Chem.* **2013**, *78*, 2731−2735.

(16) The key intermediate chiral aniline could be readily prepared in 45-g scale (>99.5% ee); see SI for the details.

(17) The following byproducts generated from E/Z isomerization, double bond shift, and dehydrogenation of allylic product **3a** respectively, were observed.



(18) For selected examples involving NiH-catalyzed alkene isomerization, see: (a) Lee, W.-C.; Wang, C.-H.; Lin, Y.-H.; Shih, W.-C.; Ong, T.-G. Tandem Isomerization and C−H Activation: Regioselective Hydroheteroarylation of Allylarenes. *Org. Lett.* **2013**, *15*, 5358−5361. (b) Bair, J. S.; Schramm, Y.; Sergeev, A. G.; Clot, E.; Eisenstein, O.; Hartwig, J. F. Linear-Selective Hydroarylation of Unactivated Terminal and Internal Olefins with Trifluoromethyl-Substituted Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 13098−13101. (c) Buslov, I.; Becouse, J.; Mazza, S.; Montandon-Clerc, M.; Hu, X. Chemoselective Alkene Hydrosilylation Catalyzed by Nickel Pincer Complexes. *Angew. Chem., Int. Ed.* **2015**, *54*, 14523−14526. (d) He, Y.; Cai, Y.; Zhu, S. Mild and Regioselective Benzylic C−H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 1061−1064. (e) Chen, F.; Chen, K.; Zhang, Y.; He, Y.; Wang, Y.-M.; Zhu, S. Remote Migratory Cross-Electrophile Coupling and Olefin Hydroarylation Reactions Enabled by in Situ Generation of NiH. *J. Am. Chem. Soc.* **2017**, *139*, 13929−13935. (f) Gaydou, M.; Moragas, T.; Juliá-Hernández, F.; Martin, R. Site-Selective Catalytic Carboxylation of Unsaturated Hydrocarbons with CO_2 and Water. *J. Am. Chem. Soc.* **2017**, *139*, 12161−12164. (g) Peng, L.; Li, Y.; Li, Y.; Wang, W.; Pang, H.; Yin, G. Ligand-Controlled Nickel-Catalyzed Reductive Relay Cross-Coupling of Alkyl Bromides and Aryl Bromides. *ACS Catal.* **2018**, *8*, 310−313.

(19) The use of triphenylphosphite additive was found to promote Ni(0)/NHC-catalyzed coupling reaction of alkenes and aldehydes. see: Ho, C.-Y.; Jamison, T. F. Highly Selective Coupling of Alkenes and Aldehydes Catalyzed by [Ni(NHC){$P(OPh)_3$}]: Synergy between a Strong σ Donor and a Strong π Acceptor. *Angew. Chem., Int. Ed.* **2007**, *46*, 782−785.

(20) To our knowledge, this challenging substrate (2-butyne) has never been used as a coupling partner even in a nickel-catalyzed asymmetric reductive coupling with aldehydes. Besides, the use of **L3** (5 mol%) gave product **3w** in 45% yield and 84:16 e.r.. We attributed this moderate enantiocontrol to insufficient interaction between small alkyne substituents and the ligand in the oxa-nickelacycle formation step.

(21) (a) Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. Nickeladihydrofuran. Key Intermediate for Nickel-Catalyzed Reaction of Alkyne and Aldehyde. *Chem. Commun.* **2008**, 1347−1349. (b) Liu, P.; Montgomery, J.; Houk, K. N. Ligand Steric Contours to Understand the Effects of *N*-Heterocyclic Carbene Ligands on the Reversal of Regioselectivity in Ni-Catalyzed Reductive Couplings of Alkynes and Aldehydes. *J. Am. Chem. Soc.* **2011**, *133*, 6956−6959. (c) Baxter, R. D.; Montgomery, J. Mechanistic Study of Nickel-Catalyzed Ynal Reductive Cyclizations through Kinetic Analysis. *J. Am. Chem. Soc.* **2011**, *133*, 5728−5731.

DOI: 10.1021/acscatal.8b04198
ACS Catal. 2019, 9, 1−6