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Nickel(0)-Catalyzed Hydroalkylation of 1,3-Dienes with Simple Ketones

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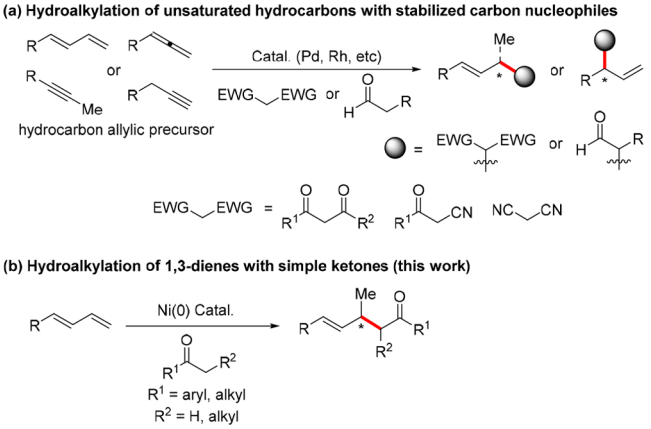
Supporting Information

ABSTRACT: We developed a highly regioselective addition of 1,3-dienes with simple ketones by nickel-hydride catalyst bearing DTBM-SegPhos ligand. A wide range of aromatic and aliphatic ketones directly coupled with 1,3-dienes, providing synthetically useful γ,δ-unsaturated ketones in high yield and regioselectivity. The asymmetric version of the reaction was also realized in high enantioselectivity by using novel chiral ligand DTBM-HO-BIPHEP. The utility of this hydroalkylation was demonstrated by facile product modification and enantioselective synthesis of (*R*)-flobufen.

Transition-metal-catalyzed addition of enols/enolates to unsaturated hydrocarbons is a useful and atom-economical method for construction of C−C bonds from readily available starting materials.[1] In particular, coupling reactions of enols/enolates with 1,3-dienes, allenes, and alkynes provide an efficient route to functionalized allylic compounds and have been attracting increasing attention.[2] These coupling reactions usually involve addition of M−H to the unsaturated hydrocarbon to generate an electrophilic metal-π-allyl intermediate, which reacts with the nucleophilic carbonyl compound. Since Hata et al. reported the palladium-catalyzed addition of 1,3-dicarbonyl compounds to dienes in the early 1970s,[3] significant progress has been made on palladium- and rhodium-catalyzed coupling of stabilized carbon nucleophiles with unsaturated hydrocarbons such as 1,3-dienes, allenes, and alkynes (Scheme 1a),[4] and the asymmetric version of this transformation has also been achieved.[5] However, the coupling of unstabilized carbon nucleophiles such as enols/enolates of simple ketones with these unsaturated hydrocarbons has not been well explored.[6]

Recently, we developed a protocol for nickel-catalyzed hydroarylation reactions of styrenes and 1,3-dienes with organoboron compounds.[7] In these reactions, an alcohol reacts with Ni(0) to generate the active catalyst species Ni−H. We reasoned that the Ni−H species could catalyze hydroalkylation reactions between 1,3-dienes and simple ketones to yield γ,δ-unsaturated ketones (Scheme 1b). Herein, we report the nickel-catalyzed addition of simple ketones to 1,3-dienes (i.e., hydroalkylation of 1,3-dienes) in high yield with excellent regioselectivity for the 1,2-addition product (that is, the product of Markovnikov addition).[8] We also accomplished an asymmetric version of this reaction with high enantioselectivity by using a C_2-symmetric biaryl bisphosphine ligand. This protocol allowed us to realize regio- and enantioselective addition of unstabilized carbon nucleophiles to unsaturated hydrocarbons.

Scheme 1. Transition-Metal-Catalyzed Hydroalkylation of Unsaturated Hydrocarbons with Carbonyl Compounds



We began by attempting to couple phenylbutadiene (**1a**) and acetophenone (**2a**) using a $Ni(COD)_2$/monophosphine catalyst under the previously reported hydroarylation conditions.[7] However, none of the desired 1,2-addition product (**3a**) was detected. We then explored different ligands and found that 2,2′-bis(diphenylphosphino)-1,1′-biphenyl (BIPHEP) gave **3a** in 5% yield. After extensive screening of additional ligands (see SI, Table S1), we were delighted to find that 5,5′-Bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (DTBM-SegPhos) was suitable, providing **3a** in 65% yield and none of the 1,4-addition product. In the hopes of further improving the yield, we evaluated several bases and found that the use of ^{t}BuOK (20 mol %) dramatically increased the yield of **3a** (to 93%).[9] A variety of ketones **2** were allowed to react with phenylbutadiene (**1a**) (Table 1). All of the tested ketones regioselectively gave products of 1,2-addition (>99:1). Aromatic ketones bearing substituents with various electronic and steric properties (**2b**−**2p**), as well as heteroaromatic ketones (**2q**, **2r**), were suitable substrates, providing the corresponding products in moderate to high yield (55−94%). Notably, relatively inert nucleophiles such as aliphatic ketones, cyclohexanecarboxaldehyde, and phenylacetate also showed good reactivity in the reaction with

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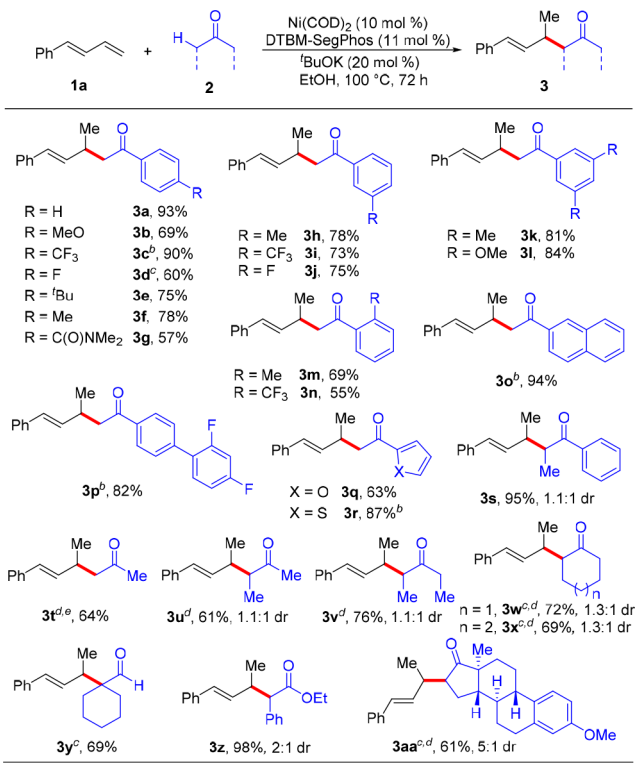
Table 1. Hydroalkylation of Phenylbutadiene with Various Ketones[a]



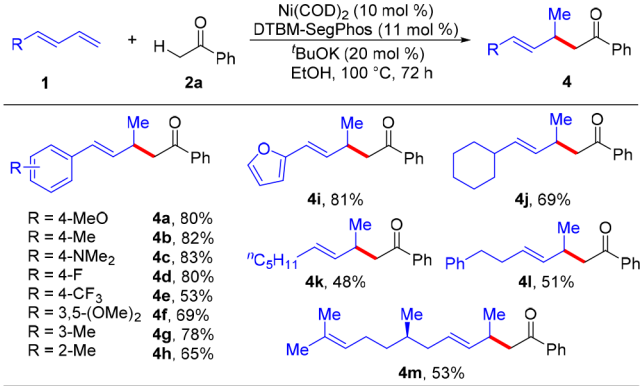
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), $Ni(COD)_2$ (10 mol %), DTBM-SegPhos (11 mol %), ^{t}BuOK (20 mol %), EtOH (1.0 mL), 100 °C, 72 h. Isolated yields. Diastereoselectivity were determined by ^{1}H NMR analysis. [b]1.2 equiv of diene. [c]Reacted at 80 °C. [d]Performed with DTBM-MeO-BIPHEP. [e]10 equiv of acetone.

1a, giving desired products **3t**–**3z** in 61–98% yield. In the reaction of nonsymmetric alkyl ketone, butan-2-one, coupling occurred at the CH_2 instead of CH_3 group (**3u**); this outcome differs from that of previously reported reactions involving an enamide directing strategy.[10] In addition, our protocol could be used to derivatize estrone 3-methyl ether (**2aa**), indicating that the reaction conditions are mild enough to be used for complex molecules.

We then examined the addition reactions of various 1,3-dienes **1** with acetophenone (**2a**) (Table 2). Aryl dienes gave corresponding 1,2-addition products **4a**–**4h** in moderate to good yield with excellent regioselectivity (>99:1). The presence of a strongly electron-withdrawing substituent, CF_3, on the phenyl ring of the aryl diene led to a decreased yield (53%, **4e**). Furyl diene **1i** provided desired product **4i** in 81% yield. Notably, alkyl 1,3-dienes also worked well, giving only 1,2-addition products **4j**–**4m** in moderate yield. In addition, the isolated C=C bond of substrate **1m** was tolerated under the reaction conditions.

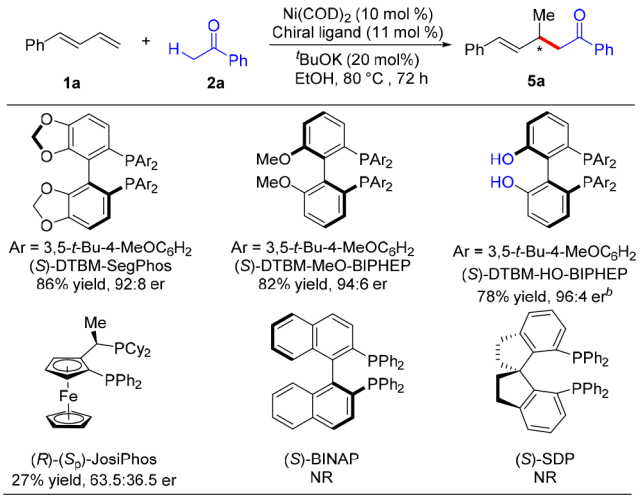
To further expand the utility of the reaction, we directed our efforts toward achieving an asymmetric version (Table 3). Systematic evaluation of chiral ligands in the reaction between **1a** and **2a** revealed that (*S*)-DTBM-SegPhos was an effective ligand, enantioselectively giving **5a** with an er of 92:8. The use of (*S*)-DTBM-MeO-BIPHEP increased the enantioselectivity of the reaction from 92:8 er to 94:6 er. We then prepared a novel ligand, (*S*)-DTBM-HO-BIPHEP, which bears two hydroxyl groups. This ligand gave an even higher enantioselectivity (96:4 er). In contrast, (R,S_p)-JosiPhos, (*S*)-BINAP, and (*S*)-SDP exhibited little or no chiral induction.

Table 2. Hydroalkylation of Various Dienes[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), $Ni(COD)_2$ (10 mol %), DTBM-SegPhos (11 mol %), ^{t}BuOK (20 mol %), EtOH (1.0 mL), 100 °C, 72 h. Isolated yields.

Table 3. Ligand Effect on Ni-Catalyzed Asymmetric Hydroalkylation of Phenylbutadiene and Acetophenone[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), $Ni(COD)_2$ (10 mol %), chiral ligand (11 mol %), ^{t}BuOK (20 mol %), EtOH (1.0 mL), 80 °C, 72 h. Isolated yields. Enantioselectivity determined by chiral HPLC. [b]40 mol % base was used.

By using (*S*)-DTBM-HO-BIPHEP as the ligand, we prepared a number of γ,δ-unsaturated ketones bearing a β-chiral center (Table 4). Aryl dienes reacted with acetophenone to give addition products **5a**–**5f** in moderate to good yield (42–78%) with high enantioselectivity (95.5:4.5–97:3 er). Notably, the stereochemistry of the diene had little influence on the yield, regioselectivity, or enantioselectivity. An approximately 2:1 mixture of *E*- and *Z*-phenylbutadienes exclusively yielded the 1,2-addition product with only an (*E*)-olefin (**5b**). Other aromatic ketones, including substituted acetophenones, 2-acetyl-naphthalene, and 2-acetyl-thiophene also showed moderate to good yield (**5g**–**5n**, 52–91%) and good enantioselectivity (91:9–96:4 er) in the reaction with phenylbutadiene. Phenyl-ethyl ketone, aliphatic ketones, and phenylacetate can also react with phenylbutadiene to give addition products (**5o**–**5t**) in good enantioselectivities (89.5:10.5–94:6 er), but with low diastereoselectivities (1.1:1–1.4:1 dr). Alkyl-substituted dienes reacted with ketones

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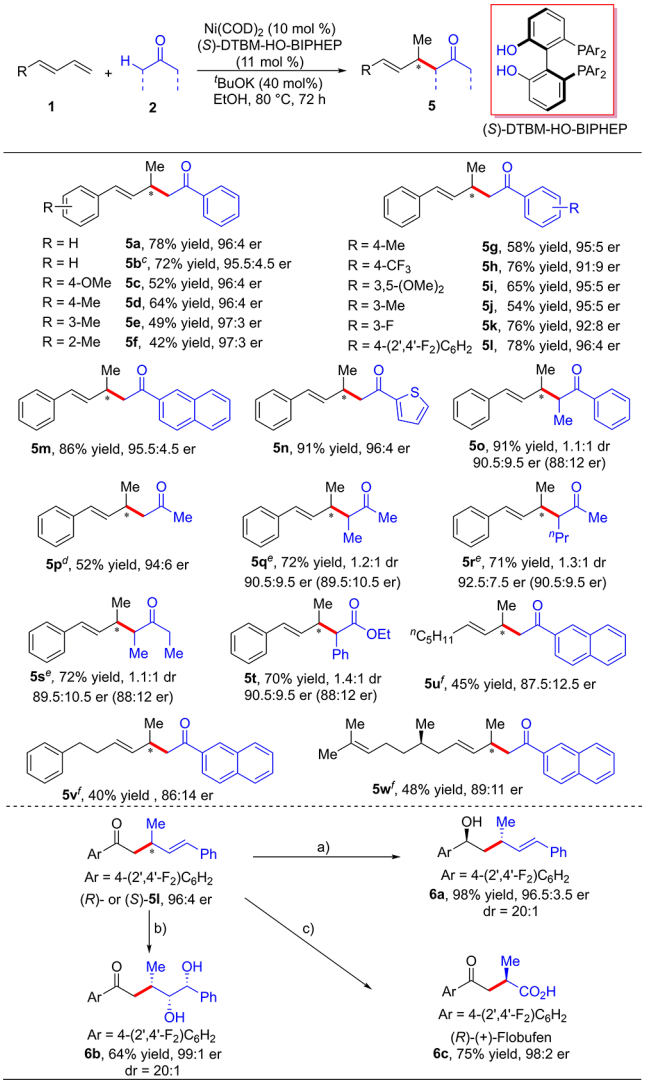
Table 4. Enantioselective Hydroalkylation[a] and Product Transformations[b]



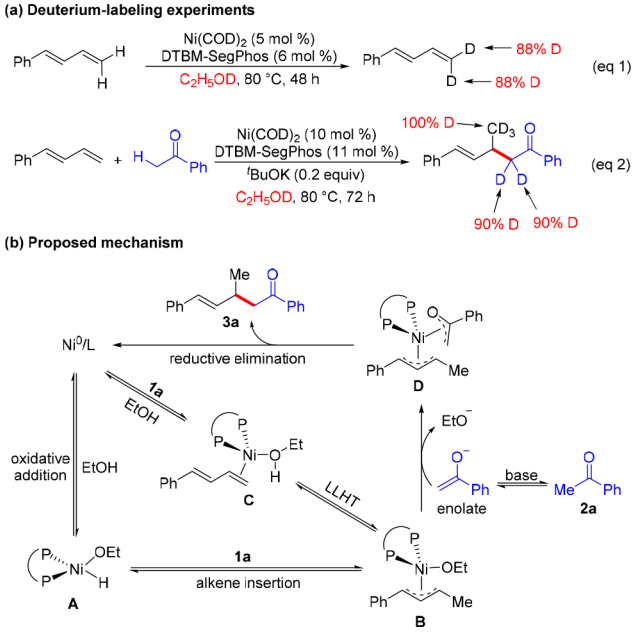
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), $Ni(COD)_2$ (10 mol %), Chiral ligand (11 mol %), ^tBuOK (20 mol %), EtOH (1.0 mL), 100 °C, 72 h. Isolated yields. Enantioselectivity and diastereoselectivity were determined by chiral HPLC. The data in parentheses are the enantioselectivity of minor isomers. [b]Reagents and conditions: (a) H_2 (10 atm), [Ir]-(*R*)-SpiroPAP, ^tBuOK, EtOH, rt, 1 h; (b) AD-mix β, $MeSO_2NH_2$, $^tBuOH/H_2O$ = 1:1, 0 °C, 48 h; (c) $KMnO_4$, $NaIO_4$, K_2CO_3, $^tBuOH/H_2O$ = 1:1, 0–20 °C, 24 h. [c]Use a mixture of phenylbutadienes formed from *Z*/*E* isomers. [d]10 equiv of acetone and reacted at 90 °C. [e]5 equiv of ketone. [f]Performed with (*S*)-DTBM-MeO-BIPHEP and reacted at 90 °C.

to afford addition products in lower yields and moderate enantioselectivities (**5u**–**5w**).

The chiral products contained carbonyl and olefin functional groups, which allowed them to be transformed to other useful compounds (Table 4). For example, the carbonyl group of **5l** could be hydrogenated in the presence of a chiral spiro iridium catalyst developed in our group,[11] yielding γ-methyl alcohol **6a** in 98% yield with high diastereoselectivity (dr = 20:1). The olefin group of **5l** could be converted to diol **6b** in 64% yield with high enantioselectivity and diastereoselectivity by means of Sharpless dihydroxylation.[12] Oxidative cleavage of the C=C bond of **5l** provided convenient, enantioselective access to (*R*)-flobufen, a nonsteroidal anti-inflammatory drug that also exhibits immunomodulatory properties.[13]

To gain some insight into the reaction mechanism, we conducted deuterium-labeling experiments with EtOD (Scheme 2a). The occurrence of H/D exchange in diene **1a**

Scheme 2. Deuterium-Labeling Experiments and Proposed Mechanism



(eq 1), and 100% deuterium incorporation into the methyl group of product **3a** (eq 2), revealed that a Ni—H intermediate was generated from the alcohol and that insertion of the terminal double bond of the diene into the Ni—H bond was reversible and faster than attack of the enol/enolate. On the basis of our experimental results and our previous work,[7,14] we propose the catalytic cycle shown in Scheme 2b. First, the oxidative addition of the alcohol to Ni(0) generates Ni—H intermediate **A**. Insertion of diene **1a** into the Ni—H bond of **A** affords π-allylnickel intermediate **B**. Another possible pathway to intermediate **B** is the complexation of Ni(0) with diene and alcohol to give intermediate **C**, followed by direct generation of **B** via LLHT mechanism.[14,15] Intermediate **D** is formed by a ligand exchange reaction in which the alcohol moiety of **B** is replaced by the enolate of ketone **2a**. Subsequent reductive elimination delivers hydroalkylation product **3a** and regenerates the Ni(0) catalyst.

In summary, we have developed a protocol for highly regioselective addition reactions between 1,3-dienes and simple ketones mediated by a nickel catalyst with DTBM-SegPhos as a ligand. A wide range of aromatic and aliphatic ketones could be directly coupled with 1,3-dienes, providing synthetically useful γ,δ-unsaturated ketones in high yield and regioselectivity. An asymmetric version of the reaction was also realized with high enantioselectivity by using the novel chiral ligand DTBM-HO-BIPHEP. Moreover, the chiral products of the reaction are versatile building blocks in synthetic chemistry, as demonstrated by the synthesis of the bioactive compound (*R*)-flobufen. Further studies will focus on elucidating the reaction mechanism and on application of Ni-BIPHEP catalysts to other enantioselective hydrofunctionalization reactions.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, optimization, characterization (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (b) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366. (c) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333.

(2) For reviews, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Craig, R. A., II; Stoltz, B. M. *Tetrahedron Lett.* **2015**, *56*, 4670. (d) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (e) Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524. (f) Haydl, A. M.; Breit, B.; Liang, T.; Krische, M. J. *Angew. Chem., Int. Ed.* **2017**, *56*, 11312.

(3) (a) Hata, G.; Takahashi, K.; Miyake, A. *J. Org. Chem.* **1971**, *36*, 2116. (b) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1183.

(4) For hydroalkylation of dienes, see: (a) Baker, R.; Popplestone, R. J. *Tetrahedron Lett.* **1978**, *19*, 3575. (b) Andell, O. S.; Bäckvall, J.-E.; Moberg, C.; Krautwurst, K. D.; Krogsgaard-Larsen, P.; Ryhage, R.; Isaksson, R. *Acta Chem. Scand.* **1986**, *40b*, 184. (c) Trost, B. M.; Zhi, L. *Tetrahedron Lett.* **1992**, *33*, 1831. (d) Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552. (e) Yang, X.-H.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1774. For hydroalkylation of allenes, see: (f) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (g) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. (h) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862. For hydroalkylation of alkynes, see: (i) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. (j) Patil, N. T.; Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *Adv. Synth. Catal.* **2004**, *346*, 800. (k) Cruz, F. A.; Chen, Z.; Kurtoic, S. I.; Dong, V. M. *Chem. Commun.* **2016**, *52*, 5836. (l) Beck, T.; Breit, B. *Org. Lett.* **2016**, *18*, 124.

(5) (a) Trost, B. M.; Jäkel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. (b) Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1029. (c) Zhou, H.; Wang, Y.; Zhang, L.; Cai, M.; Luo, S. *J. Am. Chem. Soc.* **2017**, *139*, 3631. (d) Beck, T. M.; Breit, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 1903. (e) Adamson, N. J.; Wilbur, K. C. E.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 2761.

(6) For a palladium/proline-catalyzed ketone-alkyne coupling via enamine intermediate, see: Yang, C.; Zhang, K.; Wu, Z.; Yao, H.; Lin, A. *Org. Lett.* **2016**, *18*, 5332.

(7) Xiao, L.-J.; Cheng, L.; Feng, W.-M.; Li, M.-L.; Xie, J.-H.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2018**, *57*, 461.

(8) For reviews on nickel-catalyzed diene hydrofunctionalization, see: (a) Kimura, M.; Tamaru, Y. *Top. Curr. Chem.* **2007**, *279*, 173. (b) RajanBabu, T. V.; Smith, C. R. Enantioselective Hydrovinylation of Alkenes. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: London, 2012, Vol. *5*, p 355.

(9) No reaction was observed when a Pd or Rh catalyst was used under the standard conditions.

(10) (a) Mo, F.; Dong, G. *Science* **2014**, *345*, 68. (b) Xing, D.; Dong, G. *J. Am. Chem. Soc.* **2017**, *139*, 13664.

(11) Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7329.

(12) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768.

(13) (a) Jegorov, A.; Hušák, M.; Ondřáček, J.; Kratochvíl, B.; Kuchař, M.; Bulej, P.; Gilar, M.; Tesařová, E. *J. Fluorine Chem.* **1997**, *83*, 111. (b) Trejtnar, F.; Král, R.; Pávek, P.; Wsól, V. *Chirality* **2003**, *15*, 724.

(14) Xiao, L.-J.; Fu, X.-N.; Zhou, M.-J.; Xie, J.-H.; Wang, L.-X.; Xu, X.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2957.

(15) For ligand-to-ligand hydrogen transfer (LLHT) mechanism in other nickel-catalyzed reactions, see: (a) Guihaumé, J.; Halbert, S.; Eisenstein, O.; Perutz, R. N. *Organometallics* **2012**, *31*, 1300. (b) Bair, J. S.; Schramm, Y.; Sergeev, A. G.; Clot, E.; Eisenstein, O.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 13098. (c) Nett, A. J.; Montgomery, J.; Zimmerman, P. M. *ACS Catal.* **2017**, *7*, 7352. (d) ref 14.

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