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Rhodium-Catalyzed Hydrofunctionalization: Enantioselective Coupling of Indolines and 1,3-Dienes

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Supporting Information

ABSTRACT: We communicate a strategy for the hydrofunctionalization of 1,3-dienes via Rh-hydride catalysis. Conjugated dienes are coupled to nucleophiles to demonstrate the feasibility of novel C−C, C−O, C−S, and C−N bond forming processes. In the presence of a chiral JoSPOphos ligand, hydroamination generates chiral allylic amines with high regio- and enantioselectivity. Tuning both the pK_a and steric properties of an acid-additive is critical for enantiocontrol.

Conjugated dienes are raw materials for polymerization and attractive building blocks for medicinal and natural product synthesis.[1,2] Inventing enantioselective strategies for functionalizing dienes is an important challenge that has inspired Pd-catalyzed hydroamination,[3] Co-catalyzed hydrovinylation,[4] and Ru-catalyzed hydrohydroxyalkylation.[5] To expand the power of hydrofunctionalization, we envisioned using Rh-hydride catalysis to couple 1,3-dienes and nucleophiles (Figure 1).[6] Iridium and rhodium-hydrides have been used to transform allenes and/or alkynes into electrophilic metal-π-allyl intermediates, which undergo nucleophilic attack to form branched products (Figure 1A).[7] Building on this strategy, our laboratory achieved the first enantioselective C−N and C−C bond forming reactions with alkynes.[8] In analogy to allenes and alkynes, we reasoned that conjugated dienes could be transformed via Rh-π-allyl intermediates to produce the corresponding 1,2- and/or 1,4-addition products (Figure 1B). Herein, we report the generality of Rh-hydride catalysis for enabling atom-economic C−C, C−O, C−N, and C−S bond forming reactions with dienes. In addition, we demonstrate the first hydroamination of unsymmetric dienes with excellent regio- and enantiocontrol.[9]

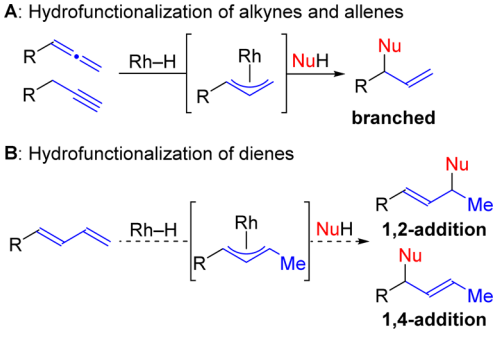


Figure 1. Rh-hydride catalyzed hydrofunctionalization of unsaturated compounds.

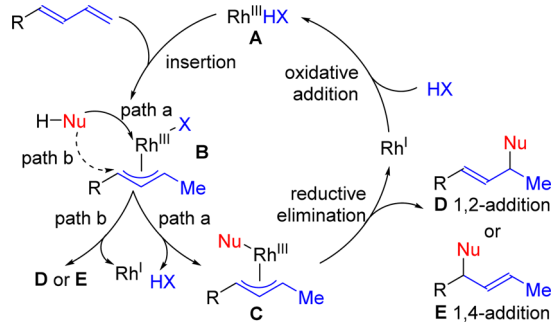
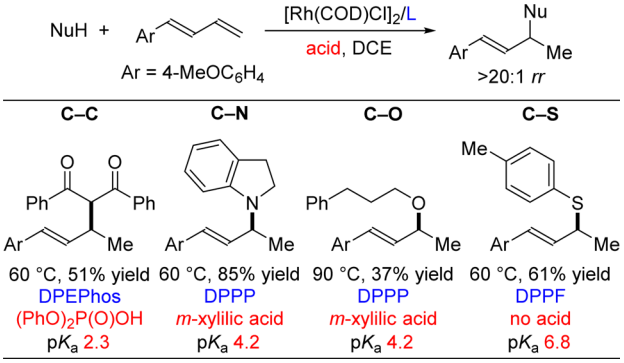


Figure 2. Reaction design for the hydrofunctionalization of 1,3-dienes.

Table 1. Constructing Different C−X Bonds *via* Hydrofunctionalization of 1,3-Diene[a]



[a]Reaction conditions: NuH (0.2 mmol), 1,3-diene (0.3 mmol), $[Rh(COD)Cl]_2$ (2 mol %), ligand (4 mol %), acid (50 mol %), DCE (0.4 mL), 24 h. Isolated yields.

The mechanism for our proposed hydrofunctionalization of dienes is depicted in Figure 2. It would be critical to identify the right combination of a rhodium catalyst and Brønsted acid (HX) to generate a Rh-hydride catalyst **A** capable of diene insertion. On the basis of steric preference, we reasoned that this Rh-hydride insertion would favor the terminal double bond to form Rh-π-allyl intermediate **B**. From this intermediate, there are two likely pathways for nucleophilic addition. One pathway (path a) involves anion exchange of **B** with nucleophiles to provide complex **C**. Reductive elimination of

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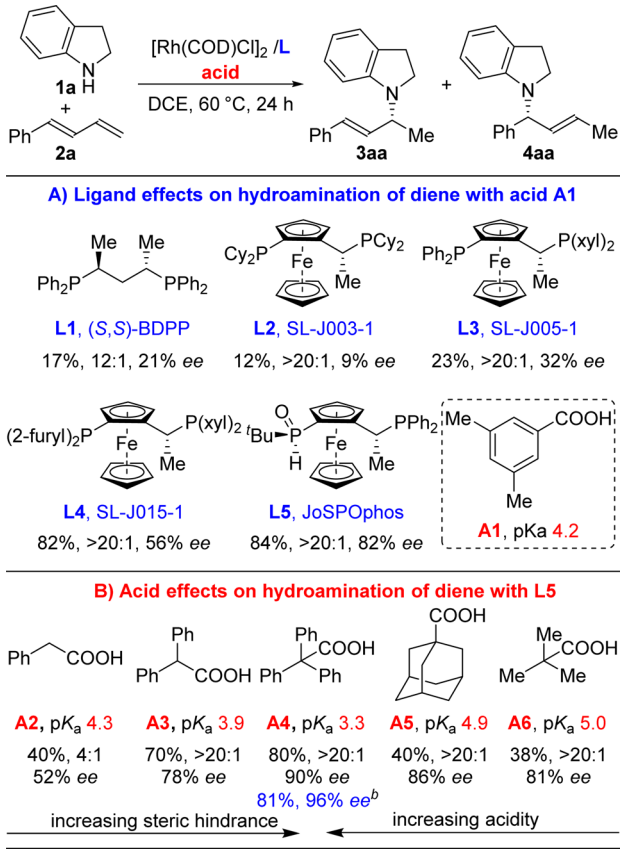
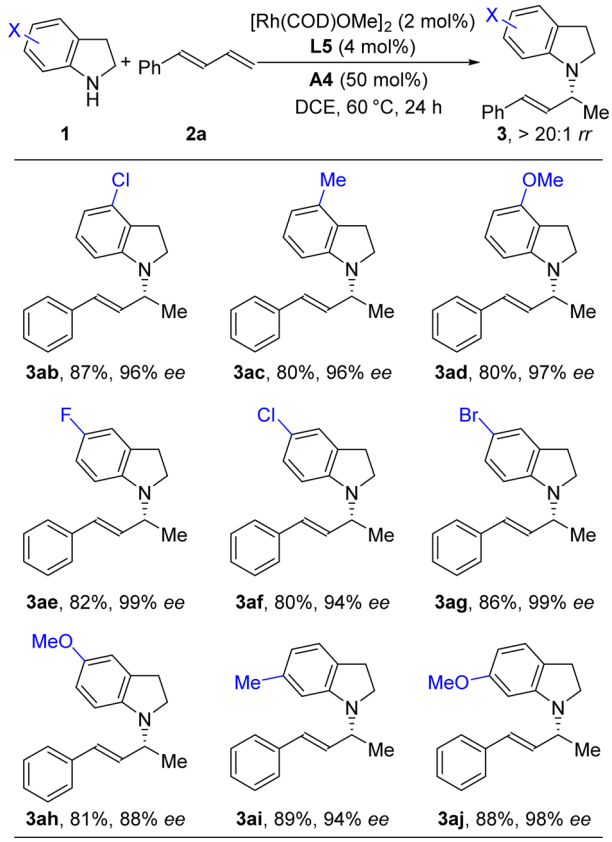
Table 2. Ligand and Acid Effects on Asymmetric Hydroamination of 1,3-Diene[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Rh(COD)Cl]_2$ (2 mol %), ligand (4 mol %), acid (50 mol %), DCE (0.2 mL), 60 °C, 24 h. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. Regioselectivity determined by ^1H NMR analysis of the unpurified reaction mixture. Enantioselectivity determined by chiral SFC. [b]Using $[Rh(COD)OMe]_2$ instead of $[Rh(COD)Cl]_2$.

Table 3. Hydroamination Using Various Indolines[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[Rh(COD)OMe]_2$ (2 mol %), JoSPOphos (4 mol %), Ph_3CCOOH (50 mol %), DCE (0.4 mL), 60 °C, 24 h. Isolated yields. Regioselectivity determined by ^1H NMR analysis of the unpurified reaction mixture. Enantioselectivity determined by chiral SFC.

C releases 1,2-addition product **D** or 1,4-addition product **E**. Alternatively, the nucleophile can attack via an S_N2' or S_N2 type step (path b) to generate product **D** or **E**.

With this hypothesis in mind, we chose to investigate (*E*)-1-(4-methoxyphenyl)-1,3-butadiene as the model substrate. We investigated a range of achiral bidentate phosphine ligands and acid additives. A summary of our most relevant findings is in Table 1. The 1,3-diene can be cross-coupled with various nucleophiles; promising yields were observed for C−C bond (51% yield), C−N bond (85% yield), C−O bond (37% yield), and C−S bond (61% yield) formations. In all cases, excellent regioselectivity for the 1,2-Markovnikov product was observed (>20:1 *rr*). Using acids with a wide pK_a range (2.3 to 6.8) was necessary to encompass nucleophiles such as diketones,[10] indolines,[8a] alcohols,[11] and thiophenols.[12] It appears that weaker nucleophiles performed better in the presence of stronger acid additives. With this promising reactivity established, we chose to optimize hydroamination due to the value of enantiopure amines in drug discovery.[13]

Although there has been interest in enantioselective hydroamination of 1,3-dienes,[14] most studies have focused on intramolecular variants.[15] Prior to our study, Hartwig demonstrated the only example of an enantioselective, intermolecular hydroamination of 1,3-dienes; this study focused on cyclohexadiene.[3] In contrast, enantioselective hydroamination of unsymmetric dienes had yet to be achieved. In considering this challenge, we chose indoline **1a** and (*E*)-1-phenyl-1,3-butadiene **2a** as model substrates (Table 2A). Given our previous work on alkyne hydroamination,[8a] our initial studies focused on using $[Rh(COD)Cl]_2$ as the precatalyst and *m*-xylylic acid **A1** as the additive. Ligand (*S,S*)-BDPP **L1**, which gave high enantioselectivity for alkyne hydroamination, promoted diene hydroamination to form allylic amine **3aa** in only 21% *ee* (17% yield, 12:1 *rr*). From an extensive ligand evaluation, we found the Josiphos ligand family **L2**−**L4** gave excellent regioselectivity (>20:1 *rr*) but only modest reactivity and enantiocontrol. In comparison, the related JoSPOphos ligand **L5**[16] afforded **3aa** in 84% yield, 82% *ee*, and >20:1 *rr*.

With ligand **L5** in hand, we next investigated the effect of the acid additive (Table 2B). The structure and acidity of the carboxylic acid had a marked effect on both yields and enantioselectivities. As highlighted in Table 2, we found that the optimal acid additive was **A4** (80% yield, 90% *ee*, >20:1 *rr*). In comparison, acids bearing less α-substitution, such as 2-phenylacetic acid **A2** and 2,2-diphenylacetic acid **A3**, provided lower *ee*'s, 52% and 78%, respectively. On the other hand, bulky acids that were less acidic, such as **A5** and **A6**, gave diminished yields (40% and 38%, respectively). These results show the significance of tuning both the pK_a and steric properties of the acid-additive in Rh-hydride catalysis. We anticipated that the carboxylate would undergo exchange more effectively with a

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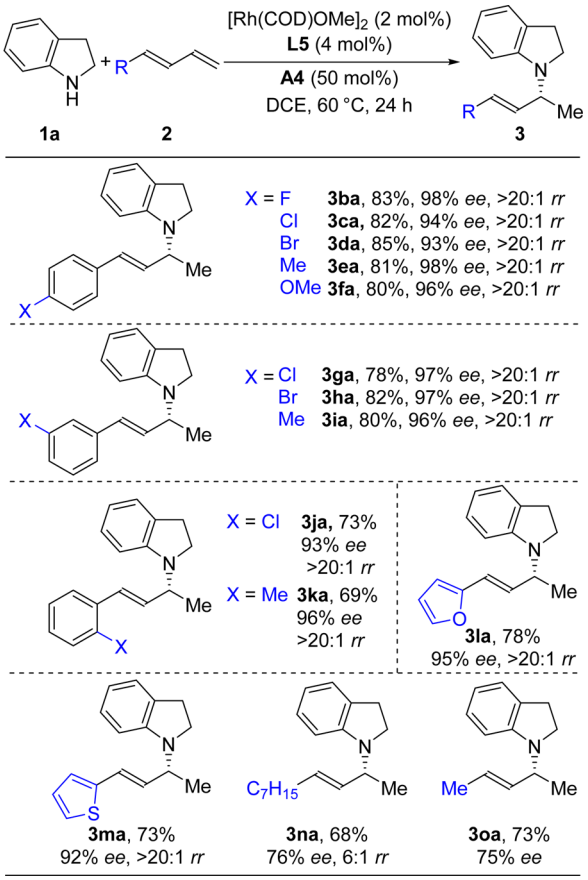
Table 4. Hydroamination of Various 1,3-Dienes[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $[Rh(COD)OMe]_2$ (2 mol %), JoSPOphos (4 mol %), Ph_3CCOOH (50 mol %), DCE (0.4 mL), 60 °C, 24 h. Regioselectivity determined by ^1H NMR analysis of the unpurified reaction mixture. Isolated yields. Enantioselectivity determined by chiral SFC.

methoxide versus chloride ligand.[17] Thus, in an effort to improve selectivity further, we switched from using $[Rh(COD)Cl]_2$ to $[Rh(COD)OMe]_2$ and observed the desired product in 81% yield and 96% *ee*.

With this protocol, we explored the hydroamination of 1,3-diene **2a** with various indolines **1** (Table 3). The substituent on the indoline had a negligible impact on the yield, regio- and enantioselectivity. In all cases, we observed excellent regioselectivity (>20:1 *rr*) for the Markovnikov 1,2-addition isomers in preference to the *anti*-Markovnikov 1,2-addition or 1,4-addition isomers. This type of regioselectivity was observed by Meek, although via π-acidic Rh-catalysis.[9h] In addition, we obtained the allylic amines with high enantioselectivities (>94% *ee*). A slight decrease in enantioselectivity was observed with indolines containing electron-donating substituents at the 5-position (**3ah**, 81% yield, 88% *ee*) compared with other substituents. Together, these results represent the first intermolecular hydroamination of unsymmetric 1,3-dienes with high regio- and enantiocontrol.

Next, we studied the hydroamination of various 1,3-dienes **2** with indoline **1a** (Table 4). Products bearing both electron-donating and electron-withdrawing groups on the phenyl ring were observed in high regio- and enantioselectivities. Due to steric effects, the coupling of indoline with ortho-substituted substrates **2j** and **2k** gave a slight decrease in yields (73% and 69%, respectively). This protocol tolerated a heterocycle substituted 1,3-dienes such as **2l** (R = 2-furyl) and **2m** (R = 2-thienyl) and afforded the corresponding allylic amines (*R*)-**3la** (78% yield, 95% *ee*) and (*R*)-**3ma** (73% yield, 92% *ee*). In addition, alkyl-substituted 1,3-diene **2n** provided the product **3na** in 68% yield; however, the regioselectivity (6:1 *rr*) and enantioselectivity (76% *ee*) were lower compared to aryl substituted 1,3-dienes. For 1,3-pentadiene **2o**, the desired product **3oa** was obtained in 73% yield with 75% *ee*. We derivatized indoline **3oa** via oxidation with DDQ to generate the corresponding indole **5**,[18] whose absolute configuration has been reported.[19]

Hydrofunctionalization represents a promising way to transform dienes into enantiopure allylic motifs. Krische established the use of Ru- and Ir-hydrides to generate nucleophilic π-allyl species.[5,20] As a complementary approach, we developed Rh-hydride catalysts that transform dienes into electrophilic π-allyl species. By tuning the Rh-hydride's structure and acidity, we achieved an enantioselective hydroamination for indolines and terminal dienes.[21] Future studies will focus on understanding the origin of 1,2-addition vs 1,4-addition. Moreover, we plan to design catalysts to expand scope and variants for enantioselective and regioselective C−C, C−N, C−O, and C−S bond formations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12307.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(21) Under this protocol, amines that differ in basicity from indolines (e.g., aniline, morpholine, and dibenzylamine) showed no reactivity. Internal dienes, such as (1*E*,3*E*)-1,4-diphenyl-1,3-butadiene and (1*E*,3*E*)-1-phenyl-1,3-pentadiene, also showed no reactivity, presumably due to increased steric bulk.

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