Enantioselective hydroalkoxylation of 1, 3-dienes via Ni-catalysis

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ABSTRACT: As an advance in hydrofunctionalization, we herein report that alcohols add to 1,3-dienes with high regio- and enantioselectivity. Using a Ni-DuPhos, we access enantioenriched allylic ethers. Through the choice of solvent-free conditions, we control the reversibility of C-O bond formation. This work showcases a rare example of methanol as a reagent in asymmetric synthesis.

Drawing inspiration from ether-containing pharmaceuticals,[1] agrochemicals,[2] and natural products,[3] chemists strive to identify useful C-O bond forming methods. Hydrofunctionalization represents an attractive approach to construct C–X bonds from feedstock olefins.[4] In contrast to carbon and nitrogen-based nucleophiles, chalcogen nucleophiles are underdeveloped as coupling partners.[5] In most cases, alkynes or allenes have been used as substrates for hydroalkoxylation, with high regioselectivity and enantioselectivity,[5a, 6] albeit using precious metal catalysts, such as Rh,[7] Ru,[8] Pd,[9] or Au[10] (Figure 1A). The addition of alcohols to conjugated dienes has attracted significant attention.[11] However, asymmetric hydroalkoxylation of readily available dienes warrants further studies, especially using earth abundant catalysts. With Ni-catalysis, Mazet and coworkers demonstrated the promising addition of alcohols to 2-substitued 1,3-dienes to yield racemic allylic ethers (Figure 1B).[11c] By applying a chiral phosphinooxazoline ligand, they achieved an isolated enantioselective example. However, they observed decreasing enantiomeric ratio during the course of the experiment. Sauthier and coworkers disclosed a Ni-catalyzed enantioselective hydroalkoxylation of butadiene using ethanol; racemization and isomerization occured to decrease enantioselectivity and regioselectivity with reaction going (Figure 1C). [11b, d] Through our independent investigations, we have discovered a complementary and enantioselective Ni-catalyzed hydroalkoxylation of dienes. Petroleum feedstocks and readily available dienes can be transformed into chiral allylic ether building blocks, with high regio- and enantiocontrol via Ni- catalysis under solvent-free conditions (Figure 1D).[12]

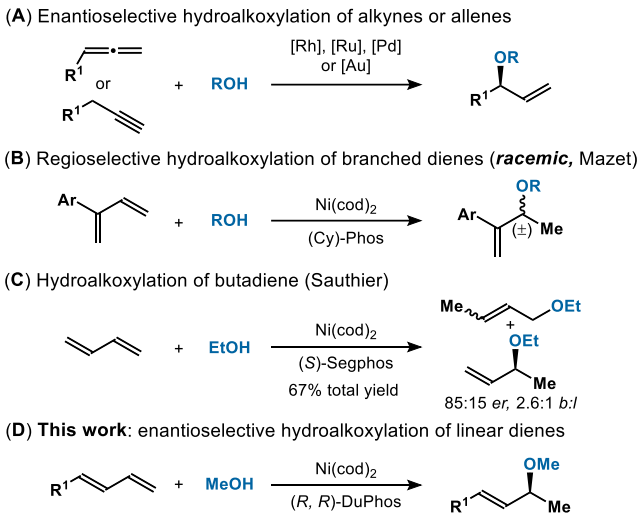


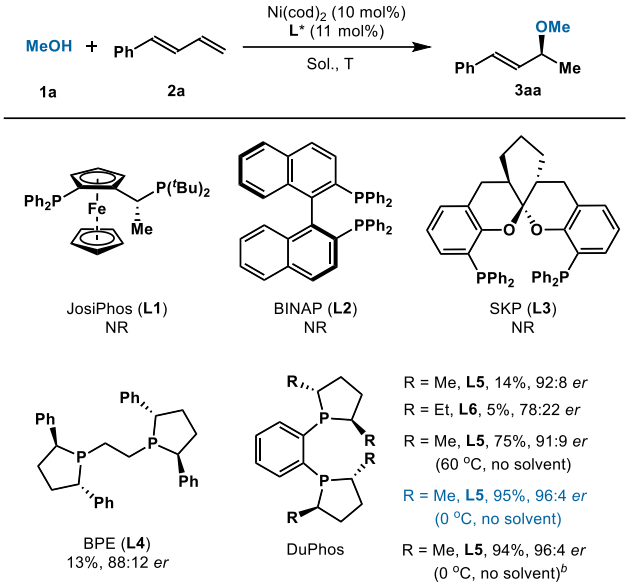
Figure 1. Inspiration for the asymmetric hydroalkoxylation of 1,3-diene.

Our laboratory has pursued the hydrofunctionalization of 1.3-dienes, including hydroamination,[13] hydrothiolation,[14] and hydrophosphinylation[15]. In these reports, conjugated dienes could be transformed via metal-π-allyl intermediates to produce the corresponding 1,2- and/or 1,4-addition products. Compared to amines (with nucleophilicities N = 13.2 on Mayr scale[16]) and thiols (N = 23.4), alcohols (N = 9.6) present a unique challenge and opportunity due to their lower nucleophilicity.

With this challenge in mind, we chose methanol (**1a**) and 1-phenyl-1,3-butadiene (**2a**) as the model substrates and surveyed a wide-range of metal catalysts. Metals such as Pd, Rh, and Ir, showed no reactivity. In contrast, we found that the desired branched allylic ether was obtained by using Ni catalysis with ethereal solvents. We studied the hydroalkoxylation of diene **2a** with methanol (**1a**) using different bidentate phosphine ligands in the presence of $Ni(cod)_2$ (Table 1). With JosiPhos (**L1**), BINAP (**L2**), and SKP (**L3**) ligands, no product formation was detected. Yet, the BPE (**L4**) and DuPhos family (**L5** and **L6**) afforded promising results. With **L5** as the ligand, we obtained excellent regioselectivity for the allylic ether **3aa** (>20:1 *rr*)

with 14% yield and 92:8 *er* by using $^{i}Pr_2O$; other ethereal solvents (such as THF, cyclopentyl methyl ether) showed lower reactivity and enantioselectivity. The linear diene **2a** showed no reactivity under the conditions previously reported by Mazet.[11c] However, in accordance with Mazet[11c] and Sauthier's[11b, d] studies, we found that the enantioselectivity decreased dramatically with prolonged reaction times (vide infra). To our delight, we discovered that this decrease in enantioselectivity over time could be overcome by performing the experiment neat (i.e., without solvent). Under solvent-free conditions, we isolated the enantioenriched ether **3aa** in 75% yield and 91:9 *er*. When the temperature was lowered to 0 °C, the enantioselectivity was increased to 96:4 *er* with excellent yield (95%, 4 h). Furthermore, the catalyst loading could be decreased to 2.5 mol% (94% yield, 96:4 *er*, 10 h). This represents a rare example of methanol as a reagent in asymmetric synthesis.[17]

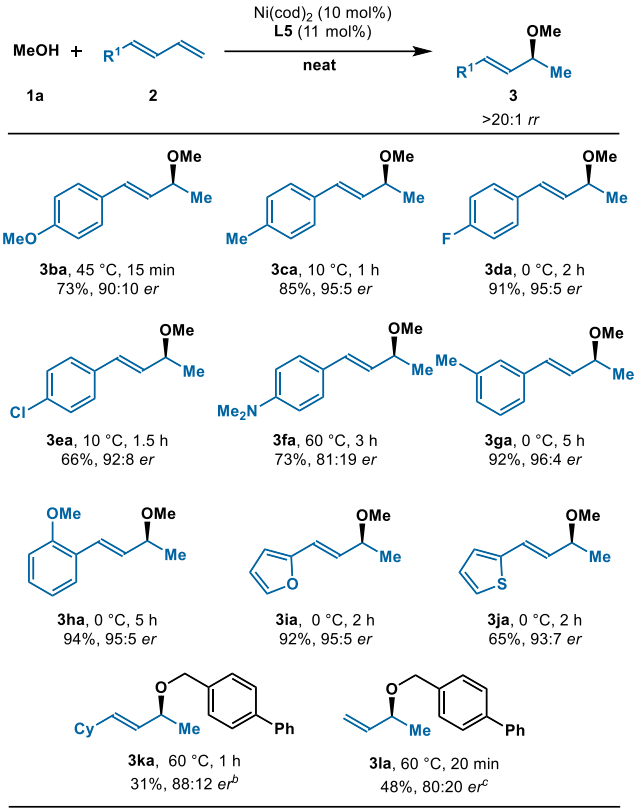
Table 1. Reaction Condition Optimization[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Ni(cod)$_2$ (10 mol%), ligand (11 mol%), $^{i}Pr_2O$ (0.1 mL), 60 °C, 4 h. Isolated yields. Enantiomeric ratio (*er*) was determined by HPLC. [b]Using 2.5 mol% Ni(cod)$_2$ and 2.8 mol% **L5**, 10 h.

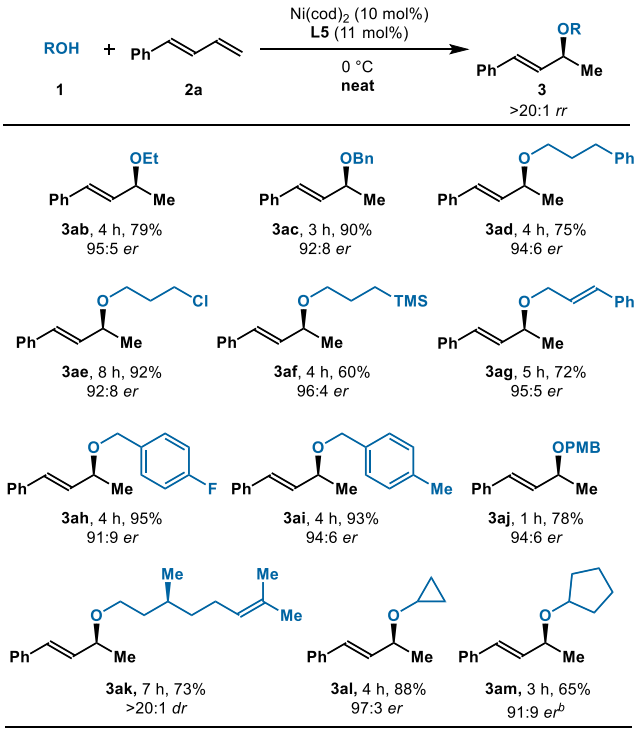
With these conditions in hand, we investigated the hydroalkoxylation of various 1,3-dienes with methanol **1a** (Table 2). Products bearing both electron-donating and electron-withdrawing groups on the phenyl ring were obtained in high reactivity and enantioselectivities (**3ba**–**3ha**, 66–94% yield, 81:19–96:4 *er*). This protocol tolerates a heterocycle substituted 1,3-dienes such as **2i** (R^1 = 2-furyl) and **2j** (R^1 = 2-thienyl) and afforded the corresponding allylic ethers **3ia** (92% yield, 95:5 *er*) and **3ja** (65% yield, 93:7 *er*). In addition, hydroalkoxylation of alkyl-substituted 1,3-diene **2k** and feedstock butadiene (**2l**) provided the corresponding products **3ka** and **3la** in 31% and 48% yield with 88:12 *er* and 80:20 *er*.[18] Overall, these results demonstrate the first asymmetric hydroalkoxylation of dienes without erosion of enantiomeric ratio.

Table 2. Hydroalkoxylation of Various Dienes[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), Ni(cod)$_2$ (10 mol%), **L5** (11 mol%). Isolated yields. Enantiomeric ratio (*er*) is determined by HPLC. [b] $^{i}Pr_2O$ (2 M) as solvent. [c]Butadiene (2.0 mmol) in hexane (20%) is used.

Table 3. Hydroalkoxylation with Various Alcohols[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), Ni(cod)$_2$ (10 mol%), **L5** (11 mol%), 0 °C. Isolated yields. Enantiomeric ratio (*er*) is determined by HPLC. [b]60 °C. PMB = *p*-methoxybenzyl.

Next, we examined the addition of various alcohols **1** to diene **2a** (Table 3). We found that a variety of alcohols could be transformed to chiral ethers with good reactivity and selectivity. High reactivities (60–95% yield) and enantioselectivities (91:9–96:4 *er*) are obtained by using alcohols that bear phenyl, chloro, and trimethylsilyl groups (**3ab**–**3aj**). Addition of natural product (–)-citronellol (**1k**) to diene (**2a**) furnishes the desired ether (*S*, *S*)-**3ak** in 73% yield with >20:1 *dr*. Moreover, hydroalkoxylation with secondary alcohols, such as cyclopropanol (**1l**) and cyclopentanol (**1m**), provides the corresponding allylic ether **3al** and **3am** in high efficiencies (88% and 65% yield, respectively) and enantioselectivities (97:3 *er* and 91:9 *er*, respectively). In all cases, only one constitutional isomer is obtained.

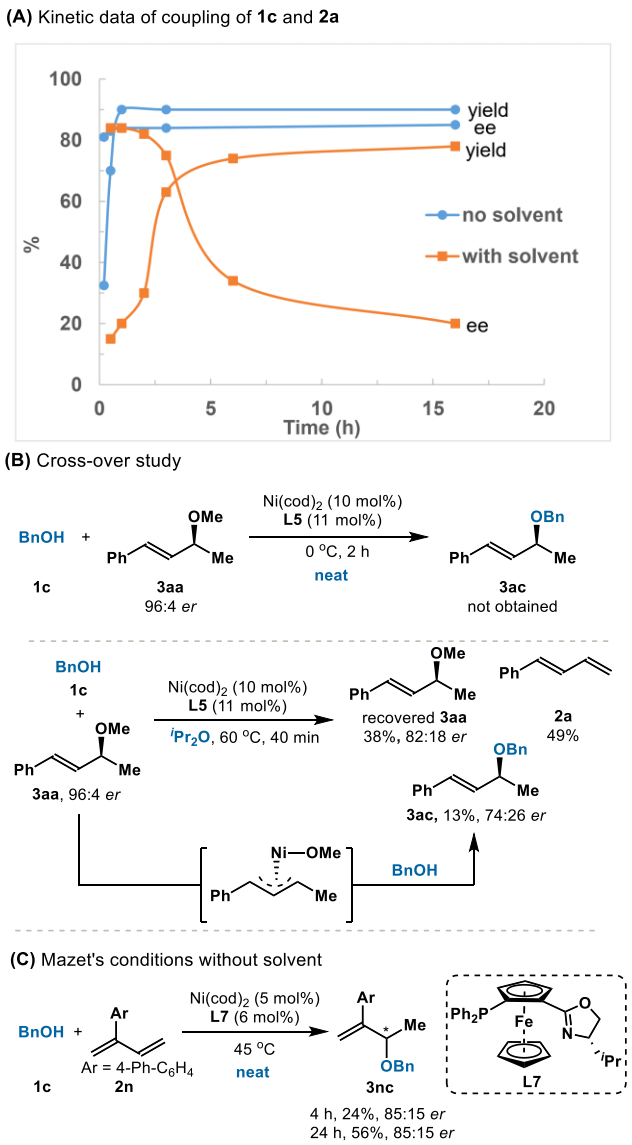


Figure 2. Reversibility studies.

We monitored the hydroalkoxylation of diene **2a** with benzyl alcohol **1c** with and without solvent, as shown in Figure 2A. When using $^{i}Pr_2O$ as solvent, the reaction plateaued after 6 h and the amount of **3ac** remained nearly constant. Meanwhile, the *ee* of product **3ac** is decreased to 20% after 16 hours. The transformation proceeds faster and is complete within one hour without solvent. The enantioselectivity is maintained at a high level, even after prolonged reaction time (up to 16 h).

We speculated that the erosion of the *er* of product may be linked to the reversibility of the C-O bond formation. To test our hypothesis, we performed a cross-over study to understand the reversibility of C-O bond formation (Figure 2B). When product **3aa** was subjected to otherwise standard reaction conditions, in the presence of one equivalent of benzyl alcohol **1c**, no trace of **3ac** was detected after 2 h; the *er* value of recovered starting material **3aa** (96:4 *er*) is unchanged. However, when a related cross-over experiment was performed in the presence of the solvent $^{i}Pr_2O$, we observed formation of **3ac** (74:26 *er*) and recovered **3aa** with decreased *er* (82:18). The activation of C-O bonds under Ni-catalysis in solvent has been investigated both theoretically and experimentally.[19] While a number of pathways are possible for racemization, we observe that the major isomer of **3ac** generated from **3aa** has same sense of absolute stereochemistry as the starting 3**aa** at an early time-point (40 min). The net retention of stereochemistry initially observed could result from an S_N2 pathway involving double inversion.[19g] Alternatively, stereoretentive oxidative additions have also been observed by Watson and Jarvo.[19a, c, d] In regards to racemization in solvent, Doyle has shown the feasibility of S_N1-like pathways.[19e] While further studies are warranted, we demonstrate that solvent-free conditions prevent reversible C-O bond formation and this phenomenon may have broader applications. As an example, we investigated Mazet's conditions for transforming **2n** to **3nc**; without solvent, we found racemization did not occur as previously observed when using mesitylene as the solvent of choice (Figure 2C).[11c]

Hydroalkoxylation represents an attractive way to transform dienes into allylic ethers. By using Ni-catalysis, we have achieved the first enantioselective hydroalkoxylation of linear dienes with various alcohols without racemization. The allylation works well with a broad range of alcohols and tolerates different functional groups such as halogens, esters, and silanes. Future studies will include a detailed mechanistic investigation. Insights from this study will guide future olefin couplings with chalcogen nucleophiles.

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Notes

The authors declare no competing financial interest.

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SYNOPSIS TOC