Communication

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

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

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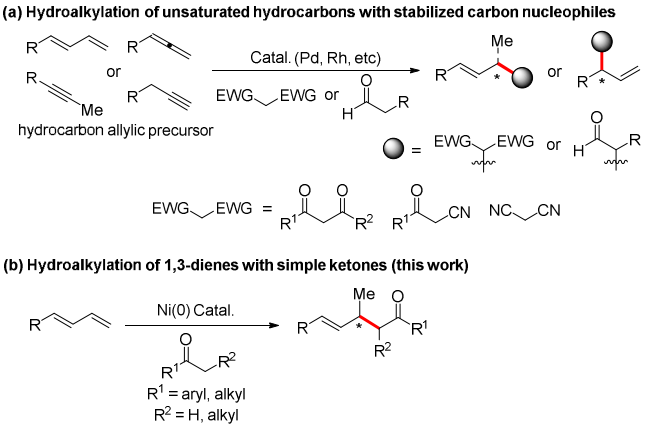
Supporting Information Placeholder

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.

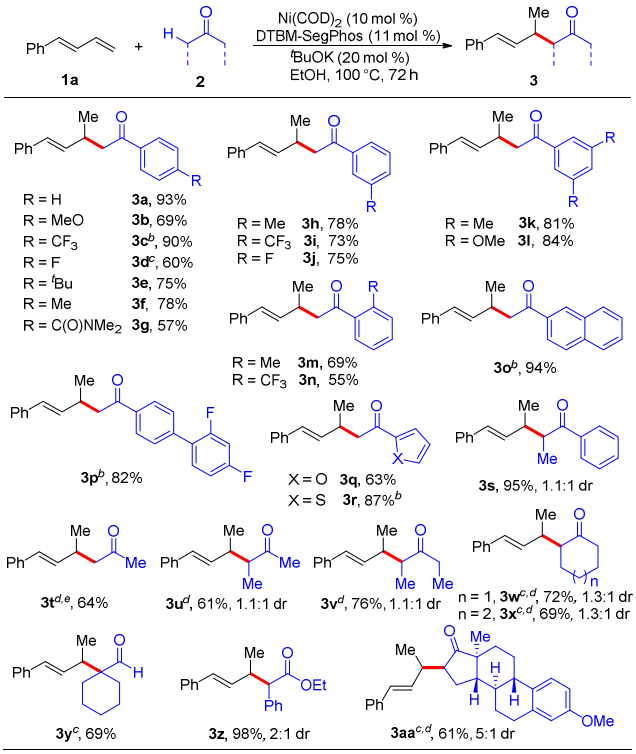
Scheme 1. Transition-Metal-Catalyzed Hydroalkylation of Unsaturated Hydrocarbons with Carbonyl Compounds



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 **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.

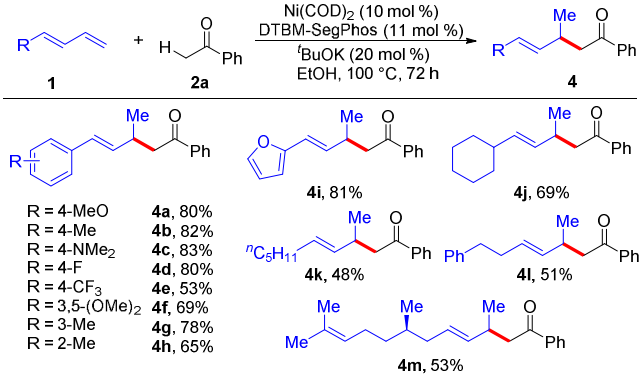
Table 1. Hydroalkylation of Phenylbutadiene with Various Ketones[a]



[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 equivalent of diene. [c] Reacted at 80 °C. [d] Performed with DTBM-MeO-BIPHEP. [e] 10 equivalent of acetone.

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.

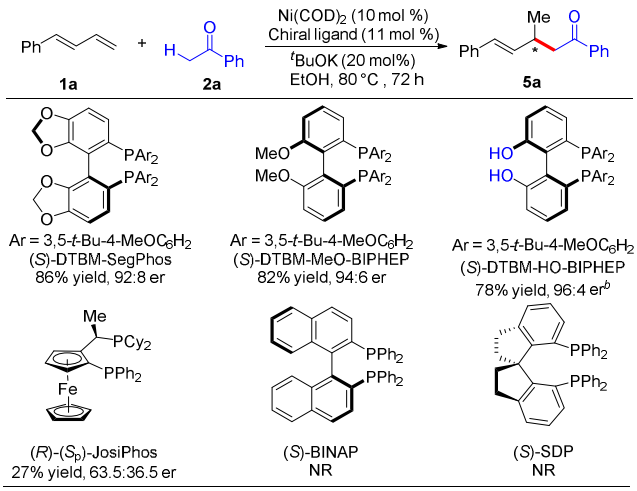
Table 2. Hydroalkylation of Various Dienes[a]



[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.

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

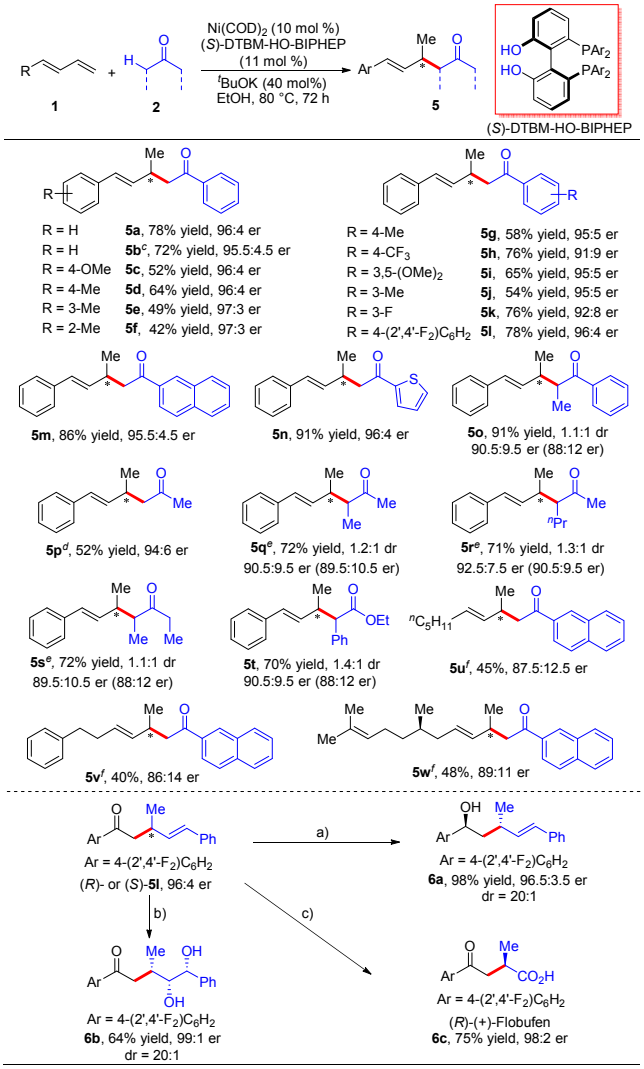


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), Ni(COD)$_2$ (10 mol %), chiral ligand (11 mol %), ^{t}BuOK (20 mol %), EtOH (1.0 mL), 80 °C, 72 h. Isolated yields. Enantioselectivity determined by chiral HPLC. [b] 40 mol % base was used.

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 (**5p–5t**) in good enantioselectivities (89.5:10.5–92.5:7.5 er), but with low diastereoselectivities (1.1:1–1.4:1 dr). Alkyl-substituted dienes reacted with ketones to afford addition products in lower yields and moderate enantioselectivities (**5u–5w**).

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

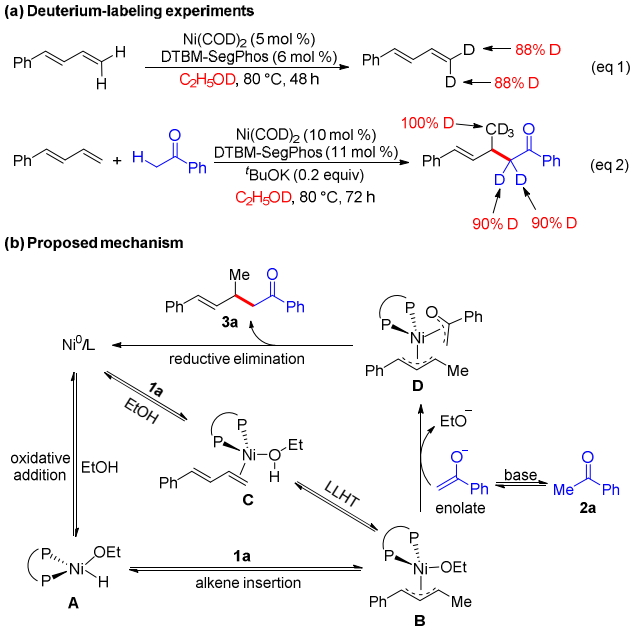


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), $Ni(COD)_2$ (10 mol %), Chiral ligand (11 mol %), ^tBuOK (20 mol %), EtOH (1.0 mL), 100 °C, 72 h. Isolated yields. Enantioselectivity and diastereoselectivity were determined by chiral HPLC. The data in parentheses are the enantioselectivity 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 equivalent of acetone and reacted at 90 °C. [e] 5 equivalent of ketone. [f] Performed with (*S*)-DTBM-MeO-BIPHEP and reacted at 90 °C.

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** (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.

Scheme 2. Deuterium-Labeling Experiments and Proposed Mechanism



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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx

Experimental procedures, optimization, characterization (PDF)

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Notes

The authors declare no competing financial interests.

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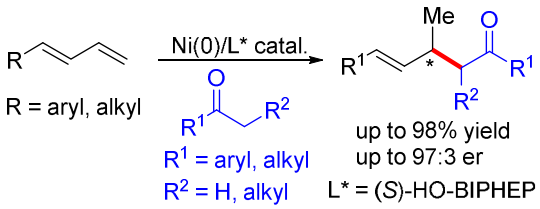

•simple ketones • atom-economical
• high regio- and enantioselectivity