

Nickel-Catalyzed Regioselective Hydrobenzylation of 1,3-Dienes with Hydrazones

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Supporting Information

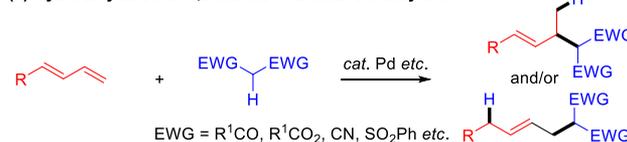
ABSTRACT: Hydroalkylation of unsaturated hydrocarbons with unstabilized carbon nucleophiles is difficult and remains a major challenge. The disclosed examples so far have mainly focused on the involvement of heteroatom and/or stabilized carbon nucleophiles as efficient reaction partners. Reported here is an unprecedented regioselective nickel-catalyzed hydrobenzylation of 1,3-dienes with hydrazones, generated in situ from abundant aryl aldehydes and ketones and acting as both the sources of unstabilized carbanion equivalent and hydride. With this strategy, both terminal and sterically hindered internal dienes are hydroalkylated efficiently in a highly selective manner, thus providing a reliable catalytic method to construct challenging C(sp³)-C(sp³) bonds.

KEYWORDS: hydroalkylation, 1,3-diene, hydrazone, nickel catalysis, C(sp³)-C(sp³) bond

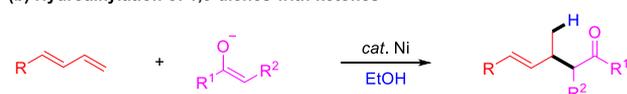


Transition-metal-catalyzed hydrofunctionalization of unsaturated hydrocarbons has emerged as an efficient and atom-economical protocol to produce a variety of value-added molecules.¹ In particular, selective hydrocarbo-functionalization of dienes offers a straightforward access to the construction of functionalized allylic compounds via C–C bond formation.² These hydrofunctionalizations typically involve addition of M–H to the unsaturated systems to generate metal- π -allyl intermediates, which then react with nucleophiles³ or electrophiles.⁴ Recently, metal-hydride-mediated hydroarylation of dienes has been developed rapidly, either through C–H bond activation of arenes⁵ or by adding additional hydride reagents when aryl boronic acids⁶ or aryl halides⁷ were used. In comparison, hydroalkylation of dienes remains less explored. As early as the 1970s, Hata and co-workers reported the first palladium-catalyzed addition of 1,3-dicarbonyl compounds to dienes, although the products contain mixtures of both 1,2- and 1,4-additions (Figure 1a).⁸ Great efforts made by Trost,⁹ Hartwig¹⁰, and others¹¹ disclosed that the regioselectivity issue could be controlled by tuning the combination of metal and ligand. However, the carbon nucleophiles were strictly restricted to the active methylene compounds, and further extension to other relatively inert carbon nucleophiles remains sluggish in the past few decades. The major barrier stems from the fact that only the more highly acidic methylene C–H bond allows the direct and easy deprotonation to generate a metal hydride. In 2018, Zhou and co-workers demonstrated an elegant nickel-catalyzed coupling of less-stabilized carbon nucleophiles such as enols/enolates of simple ketones with dienes using alcohol as the hydride source (Figure 1b).¹² Recently, our group disclosed that the reversal of electronic character of non-substituted hydrazones facilitated the development of unstabi-

(a) Hydroalkylation of 1,3-dienes with active methylenes



(b) Hydroalkylation of 1,3-dienes with ketones



(c) Hydrobenzylation of 1,3-dienes with simple hydrazones (this work)

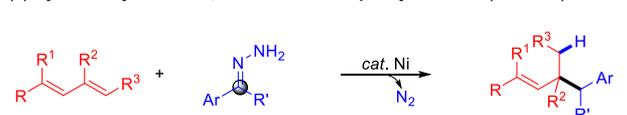


Figure 1. Strategies for the transition-metal-catalyzed hydroalkylations of 1,3-dienes.

lized carbanion chemistry in the nucleophilic addition¹³ and cross-coupling reactions.¹⁴ Very recently, we also realized a nickel-catalyzed direct dehydrogenative Heck coupling of styrenes with hydrazones, in which Ni–H intermediate was generated and eventually evolved as H₂.¹⁵ To harness the Ni–H species efficiently (i.e., incorporate into product) and toward the challenging hydroalkylation chemistry with unstabilized carbon nucleophiles, herein, we wish to report an unprecedented nickel-catalyzed regioselective 1,2-addition of hydrazones to 1,3-dienes (i.e., hydrobenzylation of 1,3-dienes)

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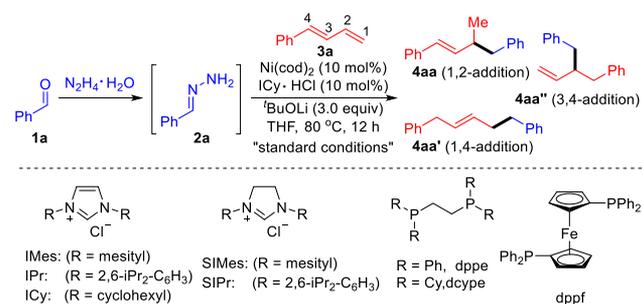
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(Figure 1c). This strategy features umpolung of aryl aldehydes and ketones serving as not only precursors of equivalent unstabilized carbon nucleophiles but also hydride donors, which allows selective and efficient hydroalkylation of both terminal and sterically hindered internal dienes. It also overcomes the long-standing limitations in hydroalkylation reactions of requiring auxiliary electron-withdrawing groups attached to carbon nucleophiles, thus providing a new and reliable catalytic method to form C(sp³)-C(sp³) bonds. Notably, organometallic reagents such as organomagnesium,¹⁶ organozinc,¹⁷ and organosilicon¹⁸ have mediated hydroalkylation of dienes and also provided an efficient and reliable access to the construction of C(sp³)-C(sp³) bond at the internal carbon of 1,3-dienes.

Our initial attempt toward the proposed hydrobenzylation of 1,3-diene was commenced by using phenyl hydrazone **2a** and phenyl butadiene **3a** as the model substrates (Table 1).

Table 1. Optimization of the Reaction Conditions^a



entry	variations from "standard conditions"	4aa/4aa'/4aa'' (yield, %) ^b
1	none	82/4/1 (79)
2	DIPEA instead of ^t BuOLi	N.D.
3	DBU instead of ^t BuOLi	N.D.
4	K ₃ PO ₄ instead of ^t BuOLi	N.D.
5	^t BuOK instead of ^t BuOLi	N.D.
6	NaOH instead of ^t BuOLi	34/7/1
7	PCy ₃ instead of ICy-HCl	46/26/6
8	P ^t Bu ₂ Me instead of ICy-HCl	57/34/7
9	dppe, dcype, dppf, bpy instead of ICy-HCl	5/3/0.5 ~24/16/2
10	IMes-HCl instead of ICy-HCl	53/44/2
11	SIMes-HCl instead of ICy-HCl	54/42/2
12	IPr-HCl instead of ICy-HCl	64/2/34
13	SIPr-HCl instead of ICy-HCl	63/2/34
14	without Ni(cod) ₂	N.D.
15	without ICy-HCl	N.D.
16	without ^t BuOLi	N.D.

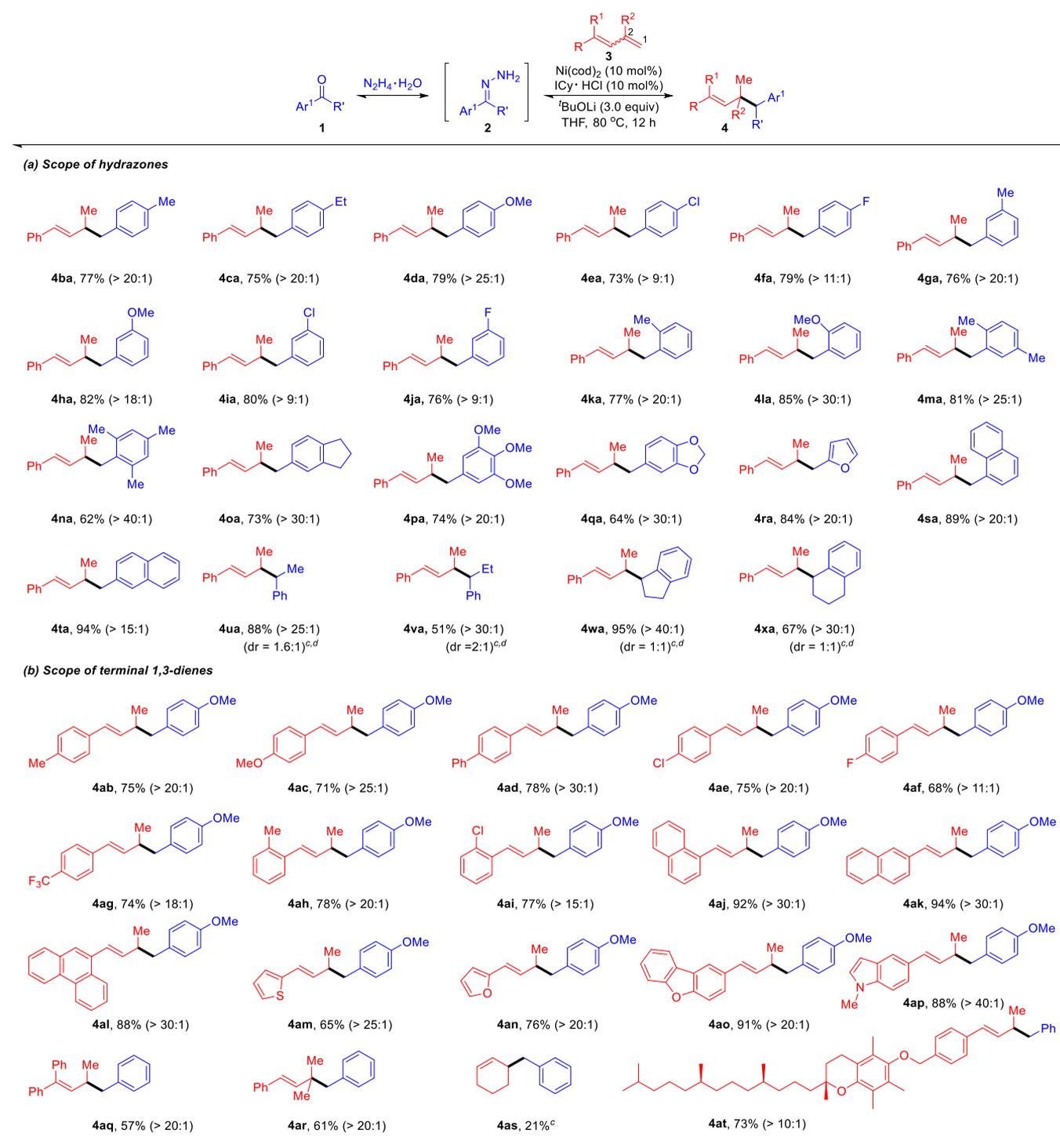
^aStandard reaction conditions: phenyl hydrazone **2a** (0.2 mmol, 1.0 M generated in situ from benzaldehyde and hydrazine), phenyl butadiene **3a** (0.1 mmol), Ni(cod)₂ (10 mol %), ICy-HCl (10 mol %), and ^tBuOLi (3.0 equiv) in THF (1.0 mL) at 80 °C for 12 h under N₂. ^bThe yields of **4aa**, **4aa'**, and **4aa''** were determined by ¹H NMR using mesitylene as an internal standard (isolated yield of **4aa** in parentheses). N.D. = not detected. DIPEA = *N,N*-diisopropyl ethylamine.

Inspired by the previously established dehydrogenative Heck-coupling conditions and upon extensive preliminary evaluations of various reaction parameters (see Supporting Information for more details), the desired product **4aa** was obtained in 82% yield with excellent 1,2-addition selectivity under a Ni(cod)₂/ICy-HCl catalytic system in the presence of

^tBuOLi (**4aa/4aa'/4aa''** = 82/4/1, entry 1). On the basis of the optimal conditions, a set of control experiments were conducted to understand the role of each component. The choice of base plays an important role in the efficiency of this transformation. For example, organic base such as *N,N*-diisopropyl ethylamine (DIPEA) or DBU did not give any hydrobenzylation product, leaving most of the starting 1,3-diene **3a** unchanged (entries 2 and 3). Inorganic base such as K₃PO₄ or ^tBuOK failed to facilitate this transformation possibly because of the rapidly competing Wolff-Kishner reduction of phenyl hydrazone (entries 4 and 5), while NaOH delivered the desired product **4aa** in 34% yield (entry 6). Notably, the selectivity of this transformation was largely controlled by the choice of ligand. For example, the sterically hindered, strong σ -donor alkyl monodentate phosphine ligands such as PCy₃ and ^tBu₃P facilitated the desired transformation yet were accompanied by a large amount of competing 1,4-addition product **4aa'** (entries 7 and 8). Bidentate phosphine or nitrogen ligands such as dppe, dcype, dppf, and bipyridine delivered the hydrobenzylation products in low yield and selectivity (entry 9). Among the different NHC ligands being tested, the bulky ICy did not give the highest yield but dramatically increased the regioselectivity. For example, IMes and SIMes favored both 1,2- and 1,4-additions (entries 10 and 11), while IPr and SIPr preferred both 1,2- and 3,4-additions (entries 12 and 13). Although the combined isomers **4aa**, **4aa'**, and **4aa''** were obtained in quantitative yields with these NHC ligands, poor selectivity renders it less appealing in synthetic chemistry. Finally, this transformation did not proceed in the absence of Ni(cod)₂, ICy-HCl, or ^tBuOLi (entries 14–16).

With the optimized conditions identified, the substrate scope of hydrobenzylation of terminal 1,3-dienes with hydrazones was investigated (Table 2). In general, hydrazones bearing both electron-donating and electron-withdrawing groups all reacted smoothly with phenyl butadiene **3a** to afford the 1,2-addition products in good to excellent yields, with the former giving higher regioselectivity (>20:1) (Table 2a). Various substituents, such as methyl, ethyl, methoxyl, methylenedioxy, fluoro, and chloro, regardless the *para*-, *meta*-, *ortho*-, or multiple substitutions, were all tolerated to give the corresponding products **4ba–qa** in 64–85% yields under the optimized conditions. Hydrazone generated from furan-2-carbaldehyde was also compatible in this transformation (**4ra**). Moreover, hydrazones prepared from polycyclic aromatic aldehydes such as 1-naphthaldehyde and 2-naphthaldehyde delivered the desired product **4sa** and **4ta** smoothly in high yields with excellent selectivity. Gratifyingly, hydrazones derived from ketones also reacted smoothly with **3a**, affording the 1,2-addition products **4ua–xa** in 51–95% yields under slightly modified reaction conditions. Hydrazones derived from aliphatic aldehydes/ketones afforded various inseparable regioisomer mixtures detected in GC-MS in low yields (<10%).

Subsequently, the scope of terminal dienes was investigated (Table 2b). It is noteworthy that the *E/Z* configuration of dienes has no effect on the yield and/or selectivity of this reaction. Aromatic dienes bearing substituents with various electronic and steric properties (**3b–i**), as well as polycyclic aromatic dienes (**3j–l**), were suitable substrates, providing the corresponding products **4ab–al** in high yields (68–94%). Thieryl and furyl dienes **3m** and **3n** also worked well, giving the 1,2-addition products **4am** and **4an** in 65% and 76% yields, respectively. Dienes **3o** and **3p**, bearing a dibenzofuran or

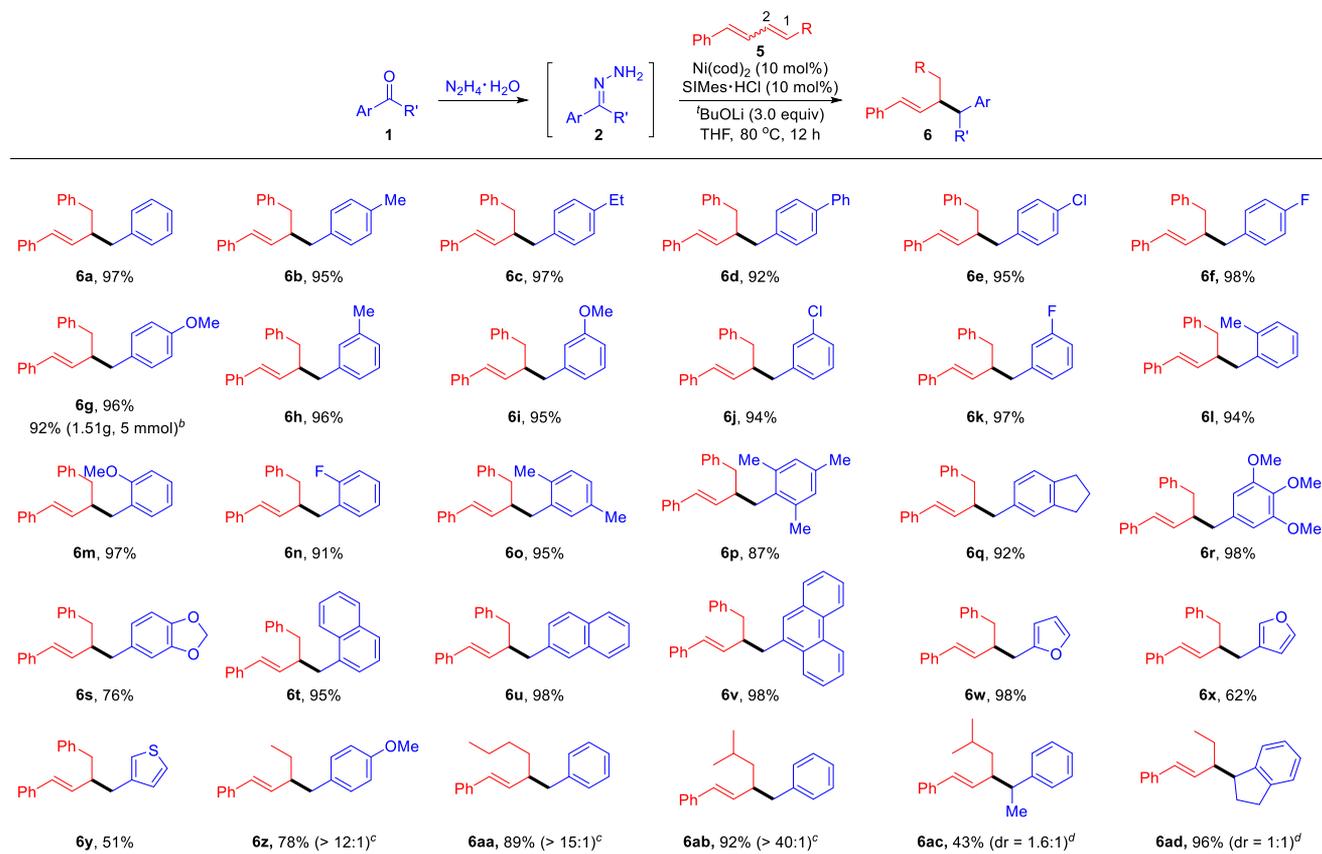
Table 2. Scope of Hydrazones and Terminal 1,3-Dienes^{a,b}

^aReaction conditions: hydrazone **2** (0.2 mmol, 1.0 M generated in situ from aldehyde and hydrazine), terminal diene **1** (0.1 mmol), Ni(cod)₂ (10 mol %), ICy·HCl (10 mol %), and ^tBuOLi (3.0 equiv) in THF (1.0 mL) at 80 °C for 12 h under N₂. Reported yields are the isolated ones. ^bThe ratio of 1,2-/1,4- addition was in parentheses and determined by ¹H NMR analysis of the crude mixture. ^cSIMes·HCl (10 mol %) was used instead. ^dThe diastereoisomeric ratios of 1,2-addition was determined by ¹H NMR analysis of the crude mixtures.

indole skeleton that are important motifs in natural products and pharmaceuticals, underwent efficient and selective hydrobenzylation under the established conditions (**4ao** and **4ap**). In addition, the 4,4- and 2,4-disubstituted dienes were tested as suitable reaction partners (**4aq** and **4ar**) as well. Cyclohexa-1,3-diene afforded exclusively allylic alkylated product **4as**, while

aliphatic 1,3-dienes gave moderate yields of both 1,2- and 1,4-addition mixtures. Gratifyingly, diene derived from α -Tocopherol reacted smoothly to give the desired product **4at** in 73% yield.

Notably, many previous reports on the hydrofunctionalizations of unsaturated hydrocarbons were mostly focused on

Table 3. Scope of Hydrazones and Internal 1,3-Dienes^a

^aReaction conditions: hydrazone 2 (0.2 mmol, 1.0 M generated in situ from aldehyde and hydrazine), internal diene 5 (0.1 mmol), Ni(cod)₂ (10 mol %), SIMes·HCl (10 mol %), and ^tBuOLi (3.0 equiv) in THF (1.0 mL) at 80 °C for 12 h under N₂. Reported yields are the isolated ones. ^bDiene (5.0 mmol), hydrazone (8.0 mmol), Ni(cod)₂ (5 mol %), SIMes·HCl (5 mol %), and ^tBuOLi (3.0 equiv) in THF (15.0 mL) at 80 °C for 24 h under N₂. ^cThe ratios of 1,2-/1,4-addition were determined by ¹H NMR analysis of the crude mixtures. ^dThe diastereoisomeric ratio of 1,2-addition was determined by ¹H NMR analysis of the crude mixtures.

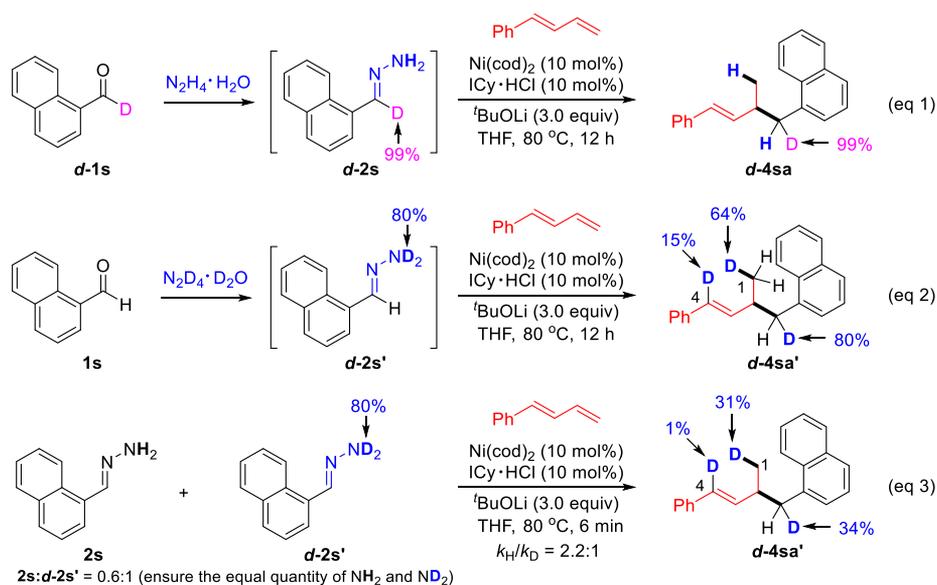


Figure 2. Deuterium-labeling experiments.

terminal dienes as suitable substrates. No reaction or poor results were observed when internal (1,4-disubstituted) dienes were tested due to the steric hindrance. Nevertheless, we still

wondered if our methodology was also applicable to the hydroalkylation of challenging internal dienes with hydrazones. Toward this goal, 1,4-diphenylbutadiene 5a and phenyl

hydrazone **2a** were selected as the model substrates to study this transformation. However, none of the 1,2-, 1,4-, or 3,4-addition product was detected under the above optimized hydrobenzylation conditions. We then explored different ligands and delightfully found that the less-sterically hindered NHC ligand such as SIMes was suitable, providing **6a** in 97% yield, with no 1,4- or 3,4-addition product detected. A variety of hydrazones **2** were allowed to react with 1,4-diphenylbutadiene **5a** smoothly and efficiently (Table 3). All of the tested hydrazones, regardless of electronic or steric properties and (hetero) aromatic or polycyclic skeletons, regioselectively gave the 1,2-addition products (**6a–y**) in moderate to excellent yields (51–98%). Gratifyingly, when phenyl alkyl substituted 1,3-dienes were tested, the 1,2-addition products **6z**, **6aa**, and **6ab** were obtained in 78–92% yields with excellent regioselectivity. 1-Alkyl-, 1,4-dialkyl 1,3-dienes, and simple 1,3-butadiene did not afford the hydrobenzylation products under the standard conditions. Hydrazones prepared in situ from ketones were also applicable (**6ac** and **6ad**). To highlight the practicality of this methodology, gram-scale synthesis was performed, giving the product **6g** in 92% yield (1.51 g).

To gain preliminary mechanistic insight into the hydrobenzylation reaction, deuterium-labeling experiments using deuterated hydrazone (*d*-**2s** and *d*-**2s'**) were conducted (Figure 2). Both ¹H NMR and ²H NMR spectroscopic analysis of the products revealed that the Ni–H intermediate was generated from the N–H group in hydrazine instead of the C–H bond of aldehyde (eqs 1 and 2). The observation of H/D scrambling at the C1 (64% D) and C4 (15% D) in product *d*-**4sa'** suggested that insertion of the double bond of diene into the Ni–H bond was reversible (see migratory insertion step in the mechanism). Furthermore, the kinetic isotope experiment ($k_H/k_D = 2.2$) (eq 3) indicated that cleavage of the N–H bond might be involved in the rate-determining step.

On the basis of the experimental results and previous reports,^{13–15,19} a possible reaction mechanism was proposed (Figure 3). Initially, oxidative addition of the N–H bond of

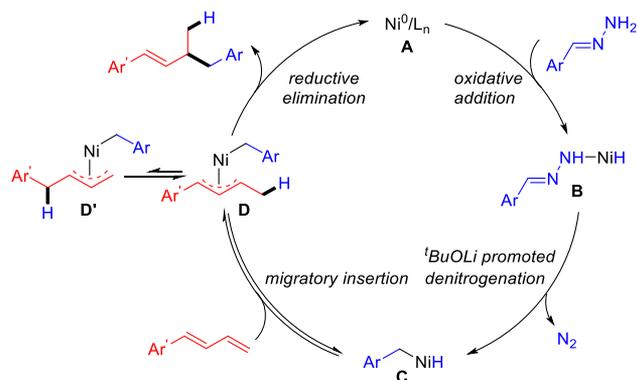


Figure 3. Proposed mechanism.

hydrazone to the nickel generates the Ni–H adduct species **B**. The analogous N–H bond activation mode was also disclosed with an iridium²⁰ or manganese pincer complex.²¹ In the presence of a strong base such as ^tBuOLi, the resulting species **B** undergoes rapid Wolff–Kishner reductive denitrogenation to afford the intermediate **C**, which then adds to the 1,3-diene to give a metal- π -allyl intermediate **D** or **D'**. Finally, reductive elimination provides the thermodynamically more stable conjugated product.³¹ It should be noted that the hydrazone

deprotonated or denitrogenated directly prior to the oxidative addition with Ni(0) cannot be fully excluded especially in the presence of excess strong base such as ^tBuOLi.

In summary, we have accomplished a nickel-catalyzed highly regioselective hydrobenzylation of both terminal and internal dienes with hydrazones to construct C(sp³)–C(sp³) bonds. A new strategy in which umpolung carbonyls provide both the alkyl moieties and hydride was developed, thus offering an approach to overcome the challenging hydroalkylation of unsaturated hydrocarbons with equivalent unstabilized carbon nucleophiles. Deuterium-labeling experiments demonstrated that the hydride was generated via nickel-catalyzed selective N–H activation rather than the C–H bond of hydrazone. These outcomes shed light on the new reactivities of hydrazones and may stimulate further development of unstabilized carbon nucleophiles in other transformations. Further studies on elucidating the mechanism and asymmetric versions are ongoing in our lab and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b02483.

Screening data, experimental details, characterization of new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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