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Letter

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

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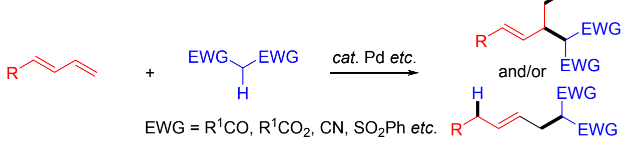
ABSTRACT: Hydroalkylation of unsaturated hydrocarbons with unstabilized carbon nucleophiles is difficult and remains a major challenge. The disclosed examples so far mainly focused on the involvement of heteroatom and/or stabilized carbon nucleophiles as efficient reaction partners. Reported here is an unprecedented regioselective nickel-catalyzed hydrobenzylation of 1,3-dienes with hydrazones, generated *in situ* from abundant aryl aldehydes and ketones and acted 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(sp^3)-C(sp^3) bonds.

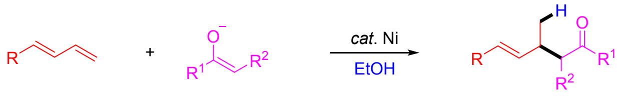
KEYWORDS: hydroalkylation, 1,3-diene, hydrazone, nickel catalysis, C(sp^3)-C(sp^3) bond

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 nucleophiles[3] or electrophiles.[4] Recently, metal-hydride mediated hydroarylation of dienes has been developed rapidly, either through C-H bond activation of arenes[5] or by adding additional hydride reagents when aryl boronic acids[6] or aryl halides[7] were used. In comparison, hydroalkylation of dienes remains less explored. As early as 1970s, Hata and coworkers 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 (Fig. **1a**).[8] Great efforts made by Trost,[9] Hartwig[10] et al.[11] 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 higher acidic methylene C-H bond allows the direct and easy deprotonation to generate metal hydride. In 2018, Zhou and coworkers 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 (Fig. **1b**).[12] Recently, our group disclosed that the reversal of electronic character of non-substituted hydrazones facilitated the development of unstablized carbanion chemistry in the nucleophilic addition[13] 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 H_2.[15] To harness the Ni-H species efficiently (i.e., incorporate into product) and towards 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) (Fig. **1c**). This strategy features umpolung of aryl aldehydes and ketones serving as not only precusors 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(sp^3)-C(sp^3) bonds. Notably, organometallic reagents such as organomagnesium,[16] organozinc[17] and organosilicon[18] mediated hydroalkylation of dienes also provides an efficient and reliable access to the construction of C(sp^3)-C(sp^3) bond at the internal carbon of 1,3-dienes.

(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)

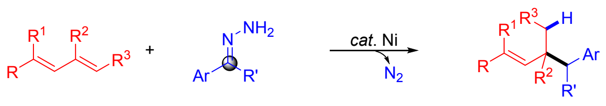
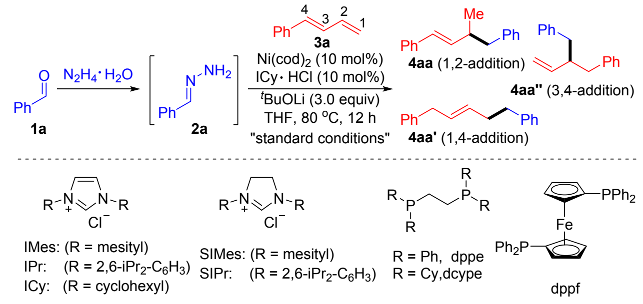


Fig. 1. Strategies for the transition-metal-catalyzed hydroalkylations of 1,3-dienes

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_3PO_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	$P^{t}Bu_2Me$ 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.

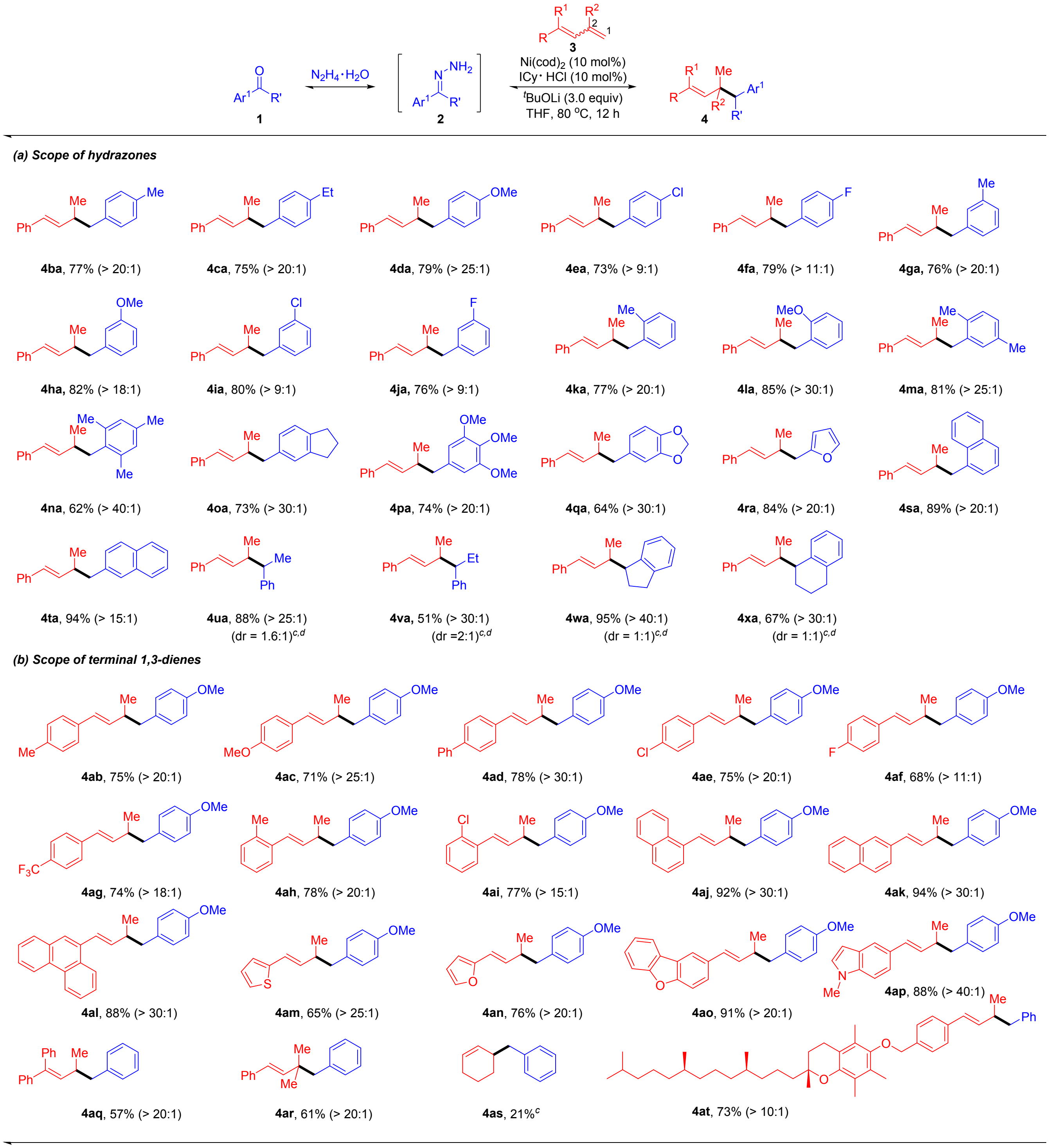
[a] Standard reaction conditions: phenyl hydrazone **2a** (0.2 mmol, 1.0 M generated *in situ* from benzaldehyde and hydrazine), phenyl butadiene **3a** (0.1 mmol), $Ni(cod)_2$ (10 mol%), ICy•HCl (10 mol%) and ^{t}BuOLi (3.0 equiv) in THF (1.0 mL) at 80 °C for 12 h under N_2. [b] The yields of **4aa**, **4aa′** and **4aa"** were determined by ^1H NMR using mesitylene as an internal standard (isolated yield of **4aa** in parenthesis). N. D. = not detected. DIPEA = *N*,*N*-diisopropyl ethylamine.

Our initial attempt towards the proposed hydrobenzylation of 1,3-diene was commenced by using phenyl hydrazone **2a** and phenyl butadiene **3a** as the model substrates (Table 1). 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 ^{t}BuOLi (**4aa**/**4aa′**/**4aa"** = 82/4/1, entry 1). Based on 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 K_3PO_4 or ^{t}BuOK failed to facilitate this transformation possibly due to the rapidly competing Wolff-Kishner reduction of phenyl hydrazone (entries 4 and 5), while NaOH delieved 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 mono-dentate phosphine ligands such as PCy_3 and $^{t}Bu_3P$ facilitated the desired transformamtion, yet 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 absence of $Ni(cod)_2$, ICy•HCl or ^{t}BuOLi (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, methylenedioxyl, 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 a 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* configuation 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%). Thienyl 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 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-disubstitued dienes were tested as suitable reaction parters (**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.

Table 2. Scope of hydrazones and terminal 1,3-dienes[a,b]



(a) Scope of hydrazones

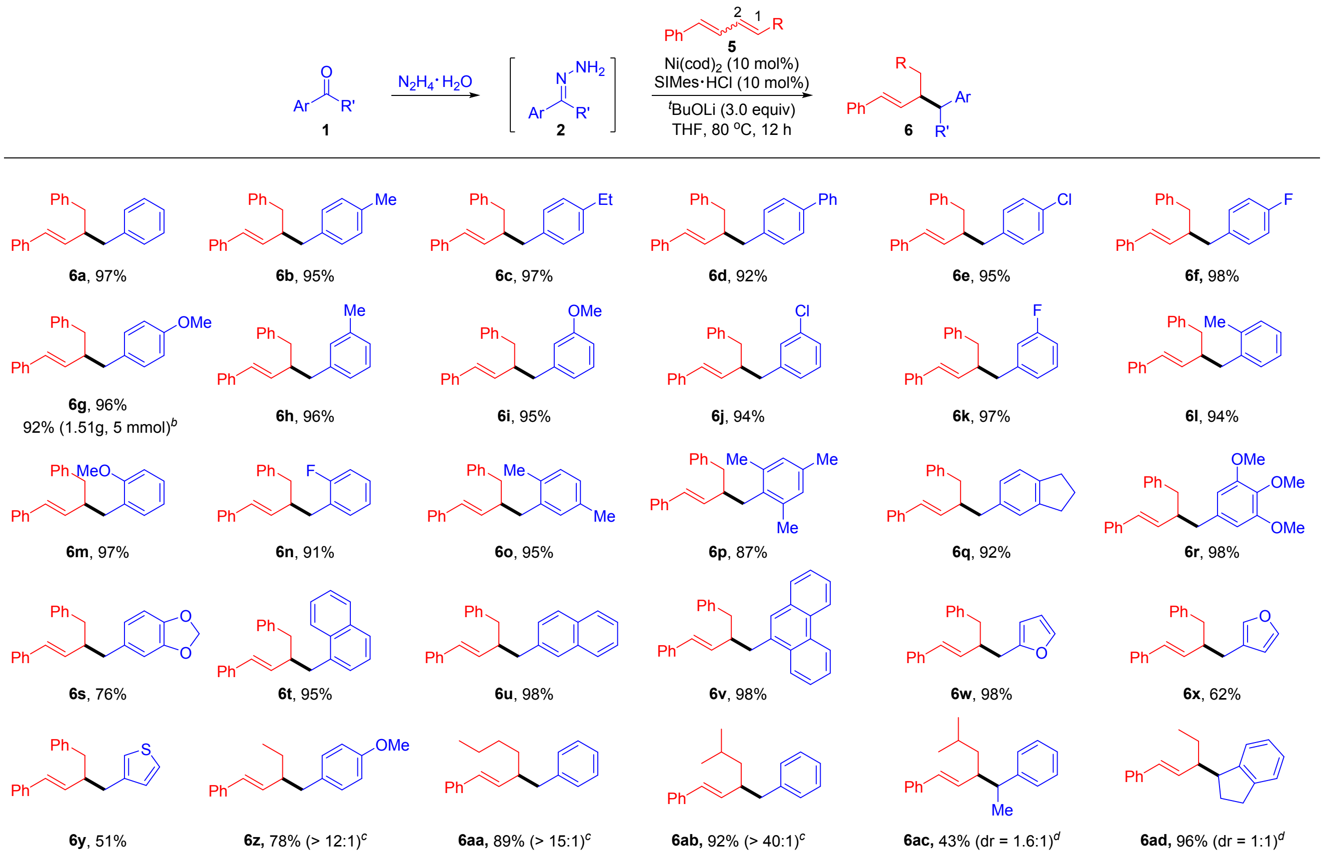
4ba, 77% (> 20:1)
4ca, 75% (> 20:1)
4da, 79% (> 25:1)
4ea, 73% (> 9:1)
4fa, 79% (> 11:1)
4ga, 76% (> 20:1)
4ha, 82% (> 18:1)
4ia, 80% (> 9:1)
4ja, 76% (> 9:1)
4ka, 77% (> 20:1)
4la, 85% (> 30:1)
4ma, 81% (> 25:1)
4na, 62% (> 40:1)
4oa, 73% (> 30:1)
4pa, 74% (> 20:1)
4qa, 64% (> 30:1)
4ra, 84% (> 20:1)
4sa, 89% (> 20:1)
4ta, 94% (> 15:1)
4ua, 88% (> 25:1) (dr = 1.6:1)[c,d]
4va, 51% (> 30:1) (dr =2:1)[c,d]
4wa, 95% (> 40:1) (dr = 1:1)[c,d]
4xa, 67% (> 30:1) (dr = 1:1)[c,d]

(b) Scope of terminal 1,3-dienes

4ab, 75% (> 20:1)
4ac, 71% (> 25:1)
4ad, 78% (> 30:1)
4ae, 75% (> 20:1)
4af, 68% (> 11:1)
4ag, 74% (> 18:1)
4ah, 78% (> 20:1)
4ai, 77% (> 15:1)
4aj, 92% (> 30:1)
4ak, 94% (> 30:1)
4al, 88% (> 30:1)
4am, 65% (> 25:1)
4an, 76% (> 20:1)
4ao, 91% (> 20:1)
4ap, 88% (> 40:1)
4aq, 57% (> 20:1)
4ar, 61% (> 20:1)
4as, 21%[c]
4at, 73% (> 10:1)

[a] Reaction 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 ^{t}BuOLi (3.0 equiv) in THF (1.0 mL) at 80 °C for 12 h under N$_2$. Reported yields are the isolated ones. [b] The ratio of 1,2-/1,4- addition was in parenthesis and determined by ^{1}H NMR analysis of the crude mixture. [c] SIMes•HCl (10 mol%) was use instead. [d] The diastereoisomeric ratios of 1,2-addition was determined by ^{1}H NMR analysis of the crude mixtures.

Table 3. Scope of hydrazones and internal 1,3-dienes[a]



[a] Reaction 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 ^{t}BuOLi (3.0 equiv) in THF (1.0 mL) at 80 °C for 12 h under N_2. Reported yields are the isolated ones. [b] Diene (5.0 mmol), hydrazone (8.0 mmol), $Ni(cod)_2$ (5 mol%), SIMes•HCl (5 mol%) and ^{t}BuOLi (3.0 equiv) in THF (15.0 mL) at 80 °C for 24 h under N_2. [c] The ratios of 1,2-/1,4- addition were determined by ^{1}H NMR analysis of the crude mixtures. [d] The diastereoisomeric ratio of 1,2-addition was determined by ^{1}H NMR analysis of the crude mixtures.

Notably, many previous reports on the hydrofunctionalizations of unsaturated hydrocarbons were mostly focused on 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. Towards 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 none of 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-adddition 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 (Fig. 2). Both ^{1}HNMR and ^{2}HNMR 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, 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.

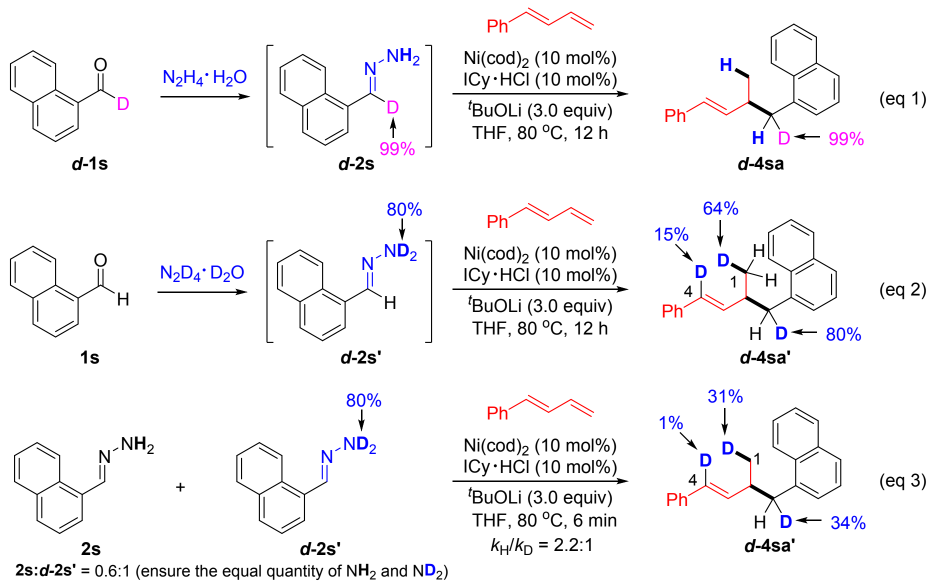


Fig. 2. Deuterium-labeling experiments

Based on the experimental results and previous reports,[13-15,19] a possible reaction mechanism was proposed (Fig. 3). Initially, oxidative addition of the N-H bond of hydrazone to the nickel generates the Ni-H adduct species **B**. The analogous N-H bond activation mode was also disclosed with a iridium[20] or manganese pincer complex.[21] In the presence of strong base such as ^{t}BuOLi, 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.[3i] 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 ^{t}BuOLi.

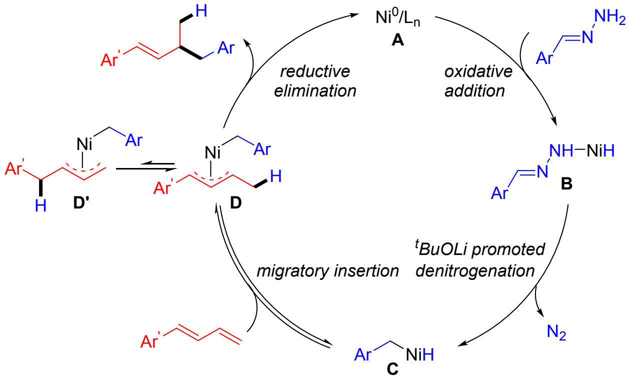


Fig. 3. Proposed mechanism

In summary, we have accomplished a nickel-catalyzed highly regioselective hydrobenzylation of both terminal and internal dienes with hydrazones to construct C(sp^3)-C(sp^3) 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 unstablized carbon nucleophiles. Deuterium-labeling experiments demonstrated that the hydride was generated *via* nickel-catalyzed selective N-H activation rather than C-H bond of hydrazone. These outcomes shed light on the new reactivities of hydrazones and may stimulate further development of unstablized 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.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Screening data, experimental details, characterization of new compounds and NMR spectra (PDF)

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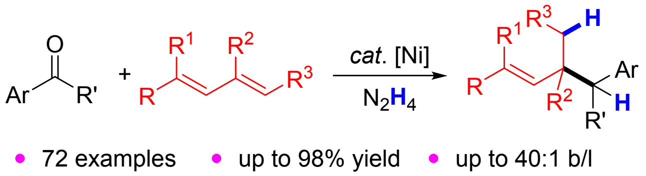

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