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Article

Nickel-Catalyzed Stereoselective Alkenylation of Ketones Mediated by Hydrazine

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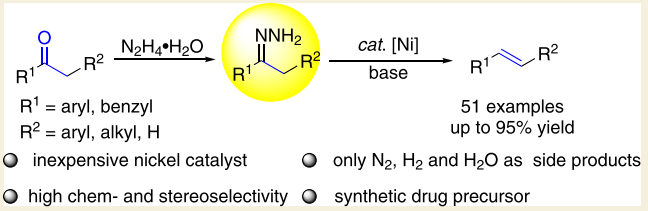
ABSTRACT: The direct conversion of naturally abundant carbonyl compounds provides a powerful platform for the efficient synthesis of valuable chemicals. In particular, the conversion of ketones to alkenes is a commonly encountered chemical transformation, often achieved via the multistep Shapiro reaction with tosylhydrazone and over stoichiometric organolithium or Grignard reagent. Herein, we report an earth abundant nickel-catalyzed alkenylation of naturally abundant methylene ketones to afford a wide range of alkene derivatives, mediated by hydrazine. The protocol features a broad substrate scope (including alkyl ketones, aryl ketones, and aldehydes), good functional group compatibility, mild reaction conditions, water tolerance, and only environmentally friendly N_2, H_2, and H_2O as theoretical byproducts. Moreover, gram-scale synthesis with good yield and generation of pharmaceutical intermediates highlighted its practical applicability.



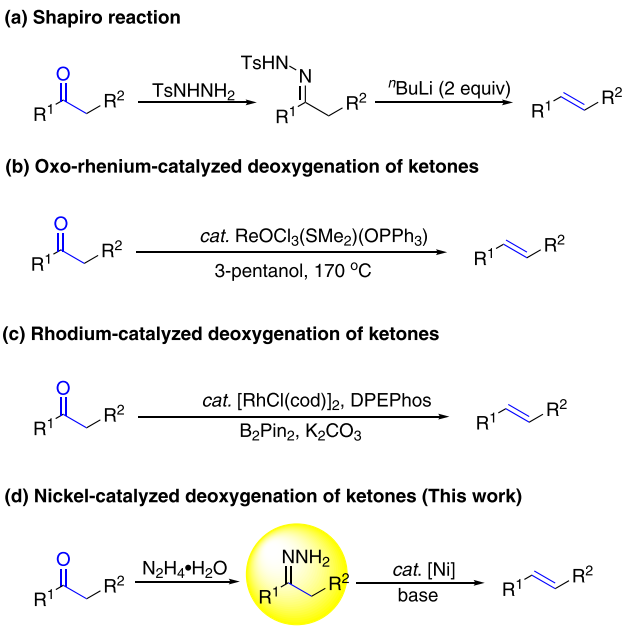
KEYWORDS: *alkenylation, ketones, hydrazone, hydrazine, nickel catalysis*

1. INTRODUCTION

Alkenes are basic constitutional units, which are prevalent in natural products, pharmaceuticals, and common organic molecules. In addition, alkenes act as versatile intermediates in chemical transformations.[1] Consequently, efficient methods toward facile synthesis of alkenes have long been a core pursuit in synthetic chemistry.[2] The carbonyl olefination has emerged as a powerful tool due to the easy availability and synthetic versatility of carbonyl compounds. Seminal discoveries include the Wittig reaction,[3] Homer–Wittig reaction,[4] Tebbe–Petasis olefination,[5] Peterson olefination[6] and Julia–Lythgoe olefination,[7] among others. In comparison to these classical Wittig-type reaction mechanisms involving the carbon-chain elongation, the direct alkenylation of aldehydes/ketones to deliver alkenes has received considerably less attention.

As early as in 1969, pioneered by Shapiro's work,[8] a reliable strategy based on a base-induced tosylhydrazone reaction realized the conversion of ketones to alkenes. Despite its remarkable importance, the requirement of an air-sensitive strong base (e.g., BuLi) resulted in a limited substrate scope and was accompanied by the formation of equivalent metal wastes (Scheme 1a). To pursuit a more maneuverable and general alkenylation process, Fernandes and co-workers demonstrated an elegant method allowing access to alkenes from ketones via oxo-rhenium catalysis with pentanol as the reducing agent (Scheme 1b).[9] More recently, a rhodium-catalyzed deoxygenation of ketones with B_2pin_2 to deliver alkenes has been established by Zhao and co-workers (Scheme 1c),[10] in which a boron enolate intermediate was proven to be the key for success. However, the existing alkenylation

Scheme 1. Strategies for Deoxygenation of Aldehydes and Ketones



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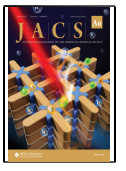

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strategies are relatively scarce and still have limitations for large scale synthesis and application due to the requirement of stoichiometric amounts of air/moisture-sensitive organometallic reagents, high temperature,[9] or noble metal catalyst.[11] Hence, a sustainable and practical strategy, using an inexpensive and ubiquitous first row transition-metal catalyzed system, to access high valued alkenes from naturally prevailing ketones (aldehydes) remains highly desirable and challenging.

Hydrazine, acting as an ideal mediator for the in situ hydrazone formation via its condensation with ketones/aldehydes, plays an important role in various organic transformations because of the inherent advantages of being readily available in large quantities and inexpensive as well as easy to handle (note: the hydrate form).[12] The classical Wolff−Kishner (WK) reduction mediated by hydrazine enables direct reduction of C═O bonds for facile preparation of methylene derivatives.[13] Inspired by the WK reduction, our group made significant progress in the development of umpolung aldehydes/ketones that act as carbanion equivalents in the catalytic addition reactions,[14] cross-couplings,[15] homocouplings,[16] and carboxylation with carbon dioxide.[17] In view of the significance of olefin structural motifs in chemical products and chemical transformations, we contemplated the feasibility of utilizing N_2H_4 as both the mediator and the reductant to realize the direct alkenylation to facilitate efficient synthesis of alkenes from carbonyl compounds.

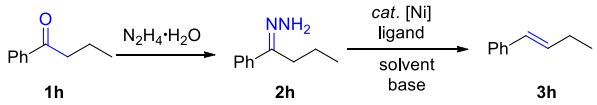
Herein, we describe a distinct strategy for the efficient preparation of alkenes via a nickel-catalyzed direct alkenylation of naturally rich ketones mediated by hydrazine (Scheme 1d), by successfully inhibiting the competing WK reduction, deoxygenative homocoupling reaction and direct coupling of hydrazones. The highlights of this novel olefination strategy are the following: (a) inexpensive and first-row abundant nickel catalyst; (b) broad substrate scope (aryl ketones and alkyl ketones, common in renewable feedstocks); (c) good functional group tolerance with high chem- and stereoselectivity; (d) low cost hydrazine as both key mediator and reductant; (e) only N_2, H_2, and H_2O as environmentally benign side (theoretical) products, and (f) synthetic demonstration of pharmaceutical intermediates.

2. RESULTS AND DISCUSSION

2.1. Optimization of the Reaction Conditions

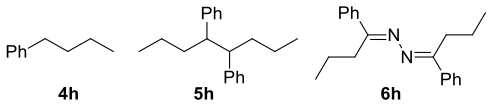
Initially, hydrazone **2h**, generated from 1-phenylbutan-1-one (**1h**), was chosen as the model substrate to explore the reaction conditions (Table 1). Inspired by ours and other group's recent achievements in the carbonyl conversions,[16,18] we evaluated various reaction factors including different nickel catalysts, ligands (phosphine- and carbene-based ligands), solvents, and temperatures (see SI for more details). The target product (*E*)-1-butenylbenzene (**3h**) was obtained in 32% yield with excellent stereoselectivity under a $NiCl_2$/IPr·HCl catalytic system mediated by hydrazine with DBU as the base at 100 °C (Table 1, entry 1), together with butylbenzene, octane-4,5-diyldibenzene, and azines as side products. Based on this promising result, various nickel catalysts with different ligands such as Ni(DME)Cl_2, Ni(dppe)Cl_2, Ni(dmpe)Cl_2, Ni$(PCy_3)_2Cl_2$, and Ni$(Py)_4Cl_2$ were examined and all gave comparable results, while Ni$(PPh_3)_2Cl_2$ afforded a 62% yield of product **3h** (Table 1, entries 2−7). Bases were subsequently investigated, considering their key role in the hydrazone deprotonation process according to our previous work.[16]

Table 1. Optimization of the Reaction Conditions[a,b]



entry	catalyst	ligand	base	solvent (mL)	**3h** yield (%)[c]
1	$NiCl_2$	IPr·HCl	DBU	1	32
2	Ni(DME)Cl_2	IPr·HCl	DBU	1	33
3	Ni(dppe)Cl_2	IPr·HCl	DBU	1	15
4	Ni(dmpe)Cl_2	IPr·HCl	DBU	1	31
5	Ni$(PCy_3)_2Cl_2$	IPr·HCl	DBU	1	45
6	Ni$(Py)_4Cl_2$	IPr·HCl	DBU	1	n.p.
7	Ni$(PPh_3)_2Cl_2$	IPr·HCl	DBU	1	62
8	Ni$(PPh_3)_2Cl_2$	IPr·HCl	TBD	1	73
9	Ni$(PPh_3)_2Cl_2$	IPr·HCl	Et_3N	1	15
10	Ni$(PPh_3)_2Cl_2$	IPr·HCl	DABCO	1	trace
11	Ni$(PPh_3)_2Cl_2$	IPr·HCl	KOH	1	8
12	Ni$(PPh_3)_2Cl_2$	IPr·HCl	*t*BuOK	1	trace
13	Ni$(PPh_3)_2Cl_2$	IPr·HCl	TBD	1.5	90 (85)
14	Ni$(PPh_3)_2Cl_2$	IPr·HCl	TBD	2	88
15	Ni$(PPh_3)_2Cl_2$	IPr·HCl	TBD	0.5	72
16[d]	Ni$(PPh_3)_2Cl_2$	IPr·HCl	TBD	1.5	63
17[e]	Ni$(PPh_3)_2Cl_2$	IPr·HCl	TBD	1.5	40
18	-	IPr·HCl	TBD	1.5	n.p.
19	Ni$(PPh_3)_2Cl_2$	-	TBD	1.5	15
20	Ni$(PPh_3)_2Cl_2$	IPr·HCl	-	1.5	n.p.

[a]Main byproducts:



[b]General conditions: 2 h (0.2 mmol), catalyst (0.04 mmol, 20 mol %), ligand (0.04 mmol, 20 mol %), base (0.2 mmol, 1 equiv), and solvent (*x* mL) at 100 °C for 24 h under an argon atmosphere; isolated yields in brackets. n.p.: no product. [c]Yields were determined by ^{1}H NMR with dibromomethane as internal standard. [d]16 h. [e]Air atmosphere.

Parallel experiments demonstrated that 1,5,7-triazabicyclo-[4,4,0]dec-5-ene (TBD), a relatively strong base, provided a higher yield than triethylenediamine (DABCO), Et_3N, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 1, entries 8−10), while inorganic bases like KOH and *t*-BuOK lowered the product yield, possibly due to their poor solubility in the reaction system (Table 1, entries 11−12). To our delight, increasing the amount of THF to 1.5 mL efficiently facilitated the desired transformation to give an optimal yield of product **3h**, while no further improvement was observed with more THF (Table 1, entries 13 and 14). Decreasing THF amount to 0.5 mL led to a significant drop in yield, due to the competing Wolff−Kishner reduction (Table 1, entry 15). Moreover, the transformation could also be performed for 16 h or under air atmosphere to give 63% and 40% yield of the desired product, respectively (Table 1, entries 16 and 17). Besides, no or only 15% yield of the alkenylation product was detected in the control experiments, demonstrating the indispensability of Ni catalyst/ligand and base (Table 1, entries 18−20).

2.2. Scope of the Alkenylation Reaction

With the optimized conditions identified, the scope of carbonyl compounds for the direct alkenylation was subsequently investigated. As shown in Table 2, for various aryl alkyl

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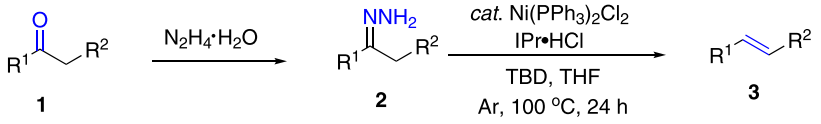
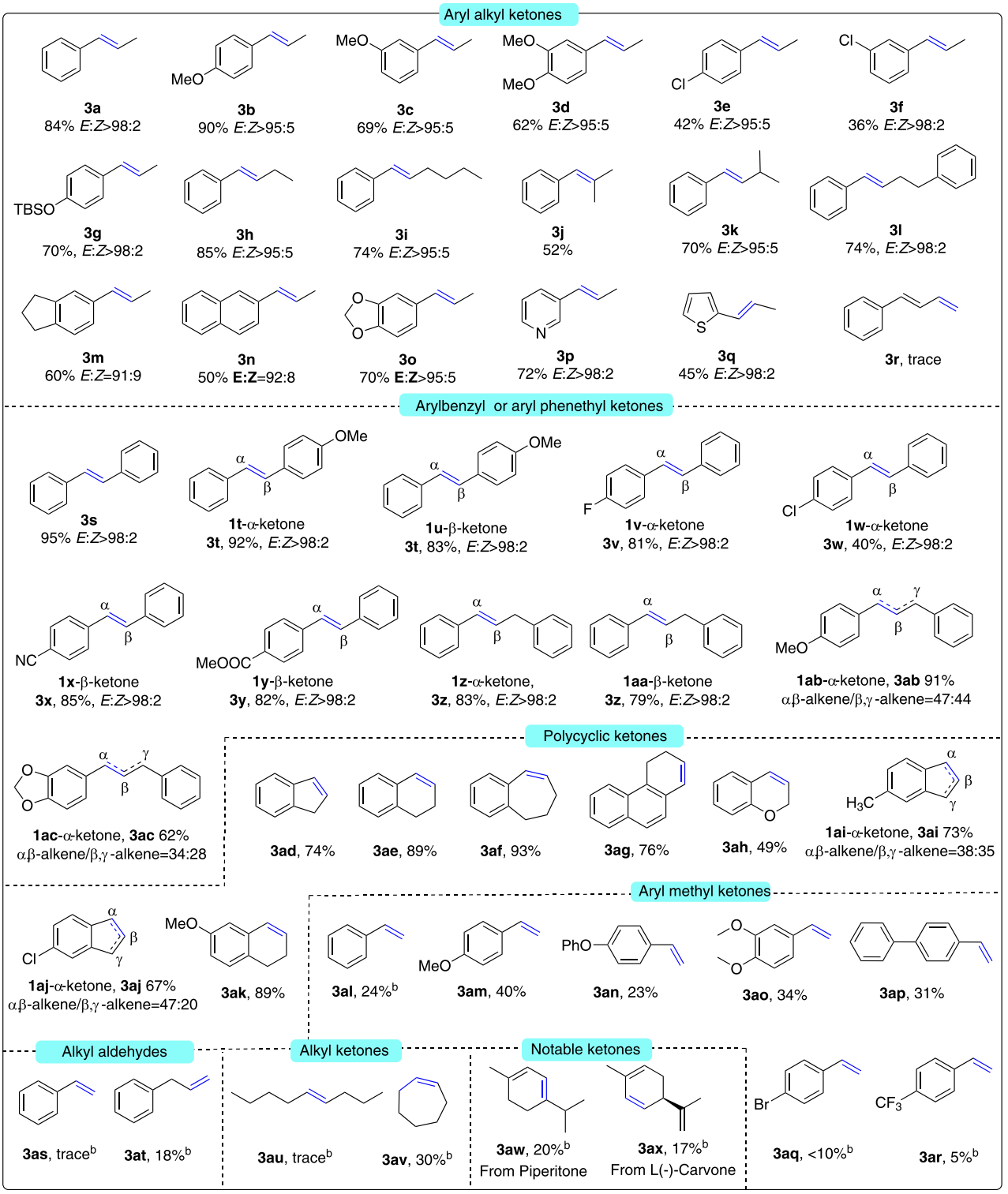
Table 2. Substrate Scope of the Alkenylation Reaction[a]





[a]General conditions: **2** (0.2 mmol), $Ni(PPh_3)_2Cl_2$ (0.04 mmol, 20 mol %), IPr·HCl (0.04 mmol, 20 mol %), TBD (0.2 mmol, 1 equiv), and THF (1.5 mL) at 100 °C for 24 h under an argon atmosphere; isolated yields. [b]Detected by GC-MS.

ketones, the alkenylation delivered (*E*)-alkenes as the main product, as confirmed by ^{1}H NMR and GC-MS analysis, with high stereoselectivity (generally *E*/*Z* > 90/10). Propiophenones bearing both electron-donating (MeO-, 3,4-dimethoxy-)

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and electron-withdrawing (Cl-) groups all proceeded smoothly to afford the corresponding (*E*)-alkenes **3a**−**3f**. The desired product **3g** could also be obtained in 70% yield when a substrate containing a protected phenolic hydroxyl group was tested. Aryl alkyl ketones with different chain lengths or branched chains were suitable substrates, providing the olefination products **3h**−**3l** in high yields. Notably, various polycyclic/heterocyclic (e.g., indene, naphthalene, dioxole, pyridine, thiophene) aryl alkyl ketones, as important motifs of pharmaceuticals, underwent the alkenylation efficiently in our system (**3m**−**3q**). Unfortunately, for the 4-phenyl-3-buten-2-one substrate, only a trace yield of the desired product **3r** was detected by GC-MS, probably due to the rapid competing formation of azines under high temperature. To our delight, regardless of the carbonyl group locating at the α- or the β-site, arylbenzyl/dibenzyl and aryl phenethyl ketones all worked well with moderate to excellent yields (**3s**−**3ac**). Among them, when the aromatic ring contains a substituent, mixed products were obtained. This protocol also worked well for the alkenylation of benzocyclic ketones: for example, benzo five-, six-, and seven-membered cyclic ketones could react smoothly to give the corresponding products **3ad**−**3af** in excellent yields. Moreover, naphthocyclohexanone, benzoheterocyclic ketone, and substituted benzocyclic ketones were also applicable in this transformation to generate the desired products **3ag**−**3ak**. It is worth noting that when the substituted benzo five-membered cyclic ketones were used as substrates, mixed products were also obtained during the reaction process. In addition, aryl methyl ketones containing electron-donating (MeO−, PhO−, 3,4-dimethoxy−, Ph−) and electron-withdrawing (Br−, CF_3−) groups all worked well to give the desired products **3al**−**3ar**, albeit with lower efficiency. Alkyl aldehydes such as phenyl acetaldehyde and phenylpropyl aldehyde were also investigated, affording the desired products **3as**−**3at** in trace and 18% yields. 5-Nonanone and cycloheptanone were also viable substrates **3au**−**3av**; however, several double-bond migration isomers were detected by GC-MS with 5-nonanone as the substrate. Furthermore, piperitone and carvone, as common ketones in medicines and fragrances, were converted into the corresponding olefin products **3aw**−**3ax** by the present nickel-catalyzed alkylenation system, albeit in low yield mainly due to the competing WK reduction products, homocoupling products, ketones, and azines.

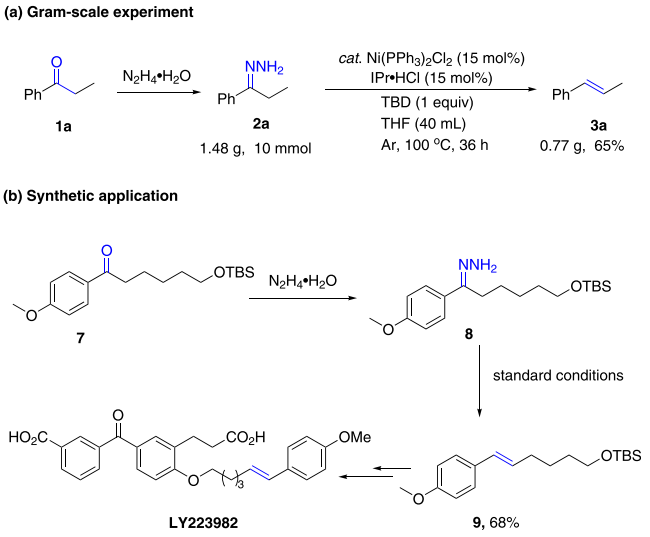
2.3. Application

To explore the practicality of the current protocol, a gram-scale experiment of **2a**, generated from propiophenone (**1a**), was performed, and the alkenylation product **3a** was obtained in 65% yield by prolonging the reaction time to 36 h (Scheme 2a). LY223982, a potent and selective antagonist of leukotriene B4, has been selected for clinical trials in human.[19] To evaluate the synthetic potentials of the present alkenylation reaction, alkene **9** was successfully synthesized under standard reaction conditions, which can be used as a precursor for the synthesis of LY223982 (Scheme 2b). These results exemplified the utility and generality of our protocol in the late-stage synthesis and modification of complex molecules.

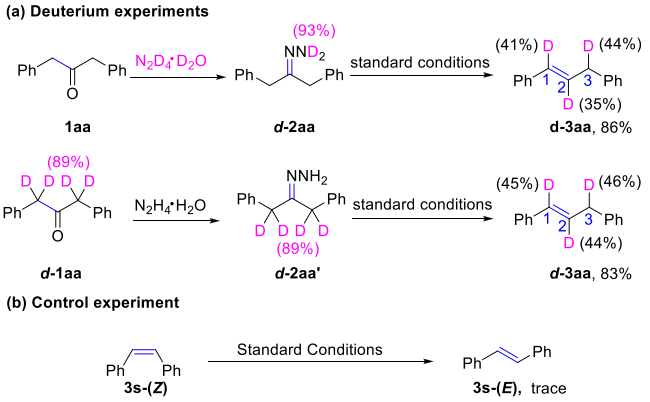
2.4. Mechanistic Investigation

To shed light on the mechanism of this alkenylation chemistry, we performed several control experiments (Scheme 3). When deuterated hydrazones (*d*-**2aa** and ***d***-**2aa**′) were subjected to the standard reaction conditions, similar deuterium incorporation at the 1-, 2-, and 3-positions of the corresponding alkene

Scheme 2. Applications of the Alkenylation Reaction



Scheme 3. Mechanistic Study



d-**3aa** was observed by ^{1}H NMR spectroscopic analysis, indicating the facile *H*/*D* exchanges of N−H with C−H bond of ketone (Scheme 3a). Furthermore, the isomerization experiments of cis-alkene **3s** was explored under the standard reaction conditions, and no **3s**-(*E*) was detected (Scheme 3b), indicating that the alkenylation process directly forms trans-alkenes without involving an isomerization of cis-alkene and further demonstrating the excellent stereoselectivity of the system.

Based on our previous works[12,14,16] and the above experimental results, a plausible reaction mechanism is depicted in Scheme 4. Initially, the potential coordination between the active nickel species **A** with hydrazone anion formed in situ from hydrazone with base affords nickel complex **B**. It is worth mentioning that complex **B** undergoes the deprotonation with the assistance of base to deliver the nickel hydrazine carbanion complex **C**, instead of directly releasing N_2 from intermediate **B** as reported in the previous work.[16] The intramolecular cyclization of complex **C** delivers a nickel pyrazole ring complex **D**, followed by extrusion release of N_2 and H_2 to afford the desired alkene derivatives **3**, and regenerates the active catalyst **A**. The formation of complex **D** rationalizes the generation of double-bond migration olefin isomers.

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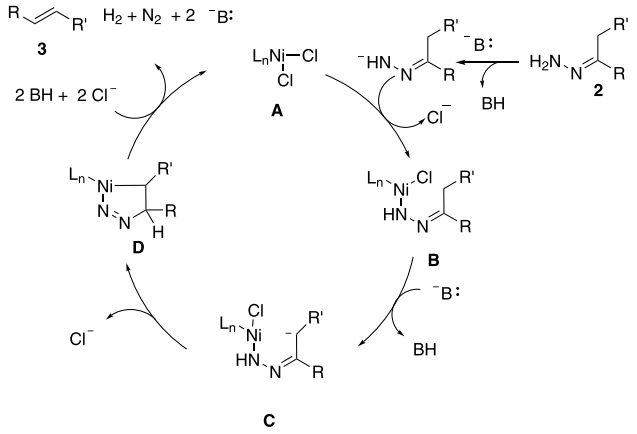
Scheme 4. Proposed Mechanism



3. CONCLUSIONS

In conclusion, we have established a simple and clean stereoselective alkenylation reaction of carbonyl compounds mediated by hydrazine and catalyzed by commercially available nickel catalyst as a sustainable protocol to access alkenes derivatives. Notably, prominent features of the strategy include broad substrate scope, earth-abundant metal catalyst, high chem- and stereoselectivity, only N_2, H_2, and H_2O as environmentally benign side products, and synthesis of a commercial pharmaceutical precursor for LY223982. This inexpensive Ni-catalyzed system offers an efficient and reliable alkenylation to access versatile alkenes, as well as a novel avenue for the conversion and utilization of naturally rich ketones in organic synthesis

4. METHODS

4.1. General Experimental Procedure

In a glovebox, a flame-dried reaction tube (10 cm^3) equipped with a magnetic stir bar was charged with $Ni(PPh_3)_2Cl_2$ (26.2 mg, 0.04 mmol, 20 mol %), IPr·HCl (17.0 mg, 0.04 mmol, 20 mol %), TBD (27.8 mg, 0.2 mmol), substrates (0.2 mmol), and THF (1.5 mL) before being sealed with a rubber septum. The tube was placed in a preheated oil bath at 100 °C, and the mixture was stirred under an argon atmosphere for 24 h. The reaction mixture was cooled to room temperature and concentrated; the NMR yield was determined by ^1H NMR using dibromomethane as an internal standard. The residue was purified by preparative TLC on silica gel eluting with hexane: EtOAc (200:1−2:1) to afford the products. (Note: For obtaining products' *E*/*Z* ratios, after the reaction, the mixture was cooled to room temperature and concentrated; then quantitative dibromomethane was added into the mixture as an internal standard, and the *E*/*Z* ratio was determined by ^1H NMR. In addition, for products whose *E*/*Z* ratio cannot be obtained by ^1H NMR, it is necessary to further determine the *E*/*Z* ratio by GC-MS using *n*-dodecane as the internal standard.)

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00320.

Experimental procedures, characterization data of products, and calculation details (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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