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Report

Nickel catalysis, Ketone synthesis, Hydrogen transfer, Alkynes, Alcohols, *N*-heterocyclic carbene ligand

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Expedient Synthesis of Ketones via NHC/Nickel-Catalyzed Redox-Economical Coupling of Alcohols and Alkynes

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An NHC/nickel-catalyzed direct coupling of alcohols and internal alkynes to form α-branched ketones has been developed. This methodology provides a new approach to afford branched ketones, which is difficult to access through the hydroacylation of simple internal alkenes with aldehydes. This redox-neutral and redox-economical coupling is free from any oxidative or reductive additives as well as stoichiometric byproducts. These reactions convert both benzylic and aliphatic alcohols and alkynes, two basic feedstock chemicals, into various α-branched ketones in a single chemical step.

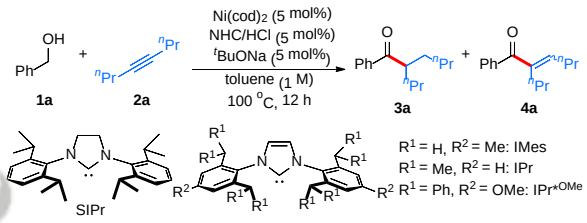
The ketone is a fundamental functional group of high synthetic utility. The direct preparation of ketones from readily available starting materials via carbon-carbon bond formations represents one of the most critical challenges in organic synthesis. The transition-metal-catalyzed hydroacylation of alkenes, usually achieved by the addition of an aldehyde C-H bond across an olefin π-bond, is one straightforward strategy for the construction of ketones from simple precursors.[1] Despite the high efficiency of this transformation, however, several longstanding limitations exist. For instance, these processes are typically catalyzed by noble metals, most often Rh.[2] Moreover, a coordinating group is usually needed on either the alkene or aldehyde substrate to provide chelation assistance and suppress the undesired decarbonylation reaction.[3] More importantly, most current hydroacylation methods are only applicable to terminal alkenes, strain-activated cyclic alkenes, or electronically activated alkenes (Figure 1a). [2d, 3d,e, f] Unactivated internal alkenes continue to pose a formidable challenge to hydroacylation chemistry.[5]

As an alternative strategy to access the hydroacylation products of simple internal alkenes, we considered changing the oxidation state of the starting materials. In particular, we reasoned that the direct coupling of alcohols and alkynes, two basic feedstock chemicals, would probably lead to the same product as alkene hydroacylation (Figure 1b). In more detail, we envisioned that a direct hydrogen transfer of an alcohol in the presence of a nickel catalyst would give catalytic amounts of nickel hydride species and an aldehyde.[6] The alkyne would then be hydroacylated by the aldehyde via an oxanickelacyclic intermediate[7,8] to form a carbon-carbon bond affording an enone.[9] We further postulated that the enone would be eventually hydrogenated by the initially formed nickel hydride species to deliver the α-branched ketone product.

We noted that in our proposed catalytic cycle, a single nickel catalyst would have to perform two catalytic cycles simultaneously, and it was unclear whether a suitable ligand could be found to allow this single-catalyst, dual-catalytic process to take place. Furthermore, the success of our strategy was hinged on addressing three challenges (Figure 1b): (i) competitive trimerization of

Figure 1. Direct synthesis of ketones from internal alkenes and alkynes. (a) Hydroacylation of internal alkenes. (b) Direct coupling of alcohols with alkynes to form ketones.

Table 1. Optimization of reaction conditions[a]

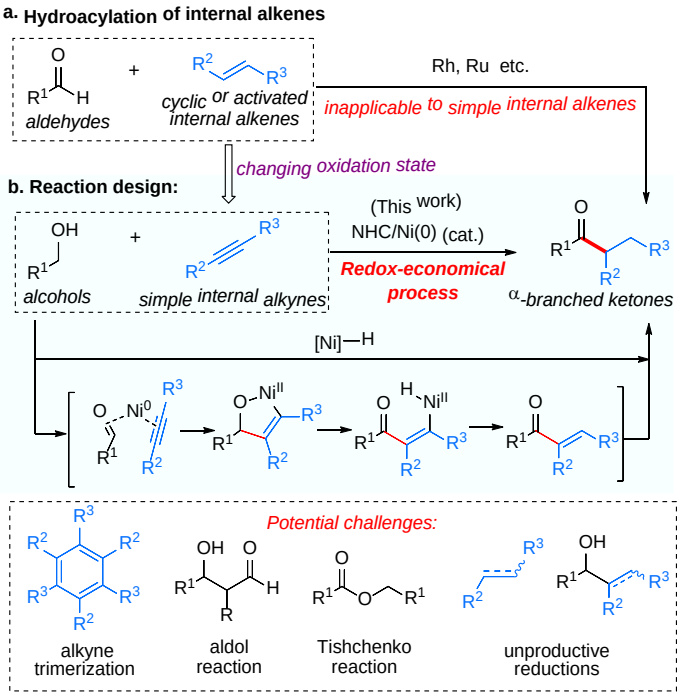


Entry	1a/2a	NHC	Yield of 3a (%)[b]	3a/4a[b]
1	1:1.2	none	0	--
2	1:1.2	SIPr	84	88:12
3	1:1.2	IPr	79	88:12
4	1:1.2	IMes	67	79:21
5	1:1.2	IPr*OMe	64	73:27
6	1:1	SIPr	88	94:6
7	1.2:1	SIPr	91	98:2
8	1.5:1	SIPr	92 (90)[c]	>99:1

[a] Reactions were performed on 0.2 mmol scale.[b] Determined by ^{1}H NMR analysis using an internal standard. [c] Isolated yield.

alkynes[10], which is facile under nickel catalysis, would need to be suppressed; (ii) desired formation of oxametallacyclic intermediates should be fast enough to avoid competitive aldol reaction and Tishchenko reaction of transient aldehydes[11]; (iii) the conjugate reduction catalyzed by the nickel hydride species, which has been rarely studied[12], would need to be highly chemo- and regioselective to avoid unproductive reductions of alkynes[13], transiently formed aldehydes and enones, as well as ketone products. Capitalizing on newly designed *N*-heterocyclic carbene (NHC) ligands[14], we recently reported a Ni-catalyzed redox-economical coupling of benzylic alcohols and alkynes for the direct preparation of chiral allylic alcohols.[6a] As part of our continuing effort in the field of NHC/metal catalysis, we report here the use of an NHC-ligated nickel catalyst to achieve the alcohol-alkyne coupling as a means of obtaining the ketone products of an elusive hydroacylation of unactivated internal olefins.[15] This base-metal-catalyzed hydrogenative transfer process[16] free from any additives makes the reaction atom-, step- and redox-economical.[17]

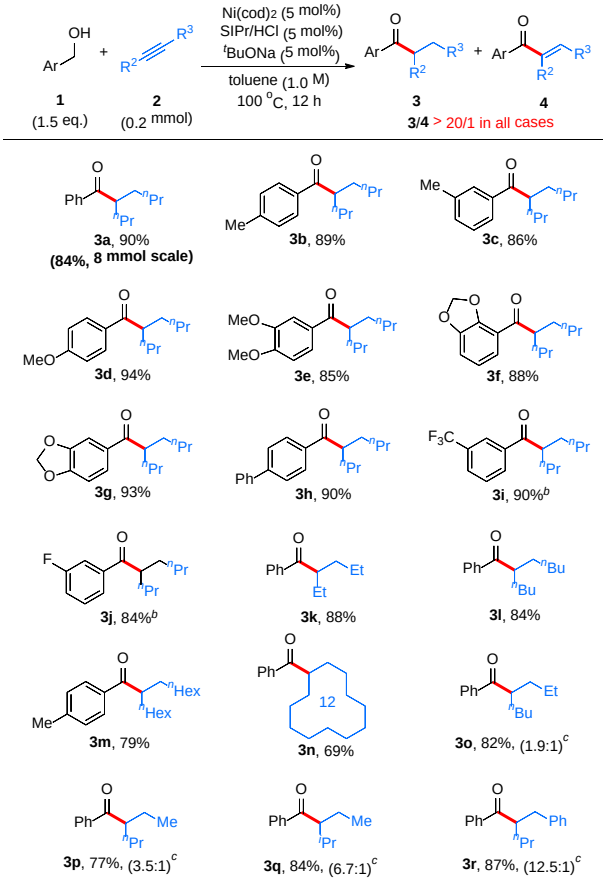
We first test the feasibility of the proposed redox-economical coupling utilizing benzylic alcohol (**1a**) and 4-octyne (**2a**) as the model substrates to form ketone **3a** in the presence of 5 mol% of $Ni(cod)_2$, ^{t}BuONa, and a range of NHC precursor imidazolium salts under heating conditions (100 °C). We found that the *in-situ* generated Ni/NHC catalyst indeed deliver the desired ketone product (**3a**), while no reaction occurred in the absence of NHC ligands (Table 1, entry 1). We also observed the formation of enone **4a**, which is consistent with our initial proposal. Notably, SIPr was found to be superior to other NHC ligands furnishing **3a** in 84% yield with a high ratio of **3a**/**4a** (88:12, entry 2). The use of IPr provided the product in the same ratio of **3a**/**4a** but with other byproducts mainly derived from the trimerization of 4-octyne (entry 3)[10]. Other NHC ligands such as IMes and IPr*^{OMe}, as well as phosphine ligands (see SI), gave both lower reactivity and selectivity (entries 4-5). Using SIPr as the optimized ligand, we then focused on lowering the amount of enone **4a**. As we had proposed that **4a** might be selectively reduced to **3a** by using alcohol as a reductant in the presence of the nickel catalyst, we gradually increased the equivalent of alcohol. As expected, the amount of enone decreased dramatically (entries 6-8). When 1.5 equivalent of alcohol (**1a**) was employed, the enone (**4a**) was undetectable, and the ketone product (**3a**) could be isolated in 90% yield (entry 8).



With the optimized conditions in hand, we next examined the generality of this nickel-catalyzed coupling reaction using an array of benzyl alcohols and alkynes. As shown in Table 2, various benzylic alcohols with electron-donating substituents such as methyl or alkoxyl groups at *ortho*-, *meta*-, and *para*-position efficiently coupled with 4-octyne (**2a**) to give the corresponding ketones in high yields (86-94%, **3a–3h**). As for benzylic alcohols with electron-withdrawing substituents such as fluoro and trifluoromethyl groups, bulkier ligand IPr*^{OMe} was used instead of SIPr, and ketone products were obtained in high yields (84-90%, **3i** and **3j**). In addition to 4-octyne, symmetric internal alkynes including 3-hexyne, 5-decyne, 7-tetradecyne, and a cyclic alkyne (cyclododecyne), were all competent substrates for this redox-economical transformation (**3k–3n**). Moreover, unsymmetric internal alkynes also served as viable substrates, and the products were generated in high yields (77-87%, **3o–3r**) as regioisomeric mixtures. Given that the similar size of alkyl substituents on the alkynes, the reactions using 3-octyne or 2-hexyne gave products in reasonable levels of regioselectivity (1.9-3.5:1, **3o**, **3p**). In the case of 4-methyl-2-pentyne, the catalyst could effectively differentiate the isopropyl and methyl group substituents furnishing the product in regioselectivity of 6.7:1 (**3q**), while the use of an aryl-alkyl internal alkyne (1-phenyl-1-hexyne) afforded the product in excellent regioselectivity (12.5:1, **3r**). Importantly, a gram-scale (8 mmol) was successfully performed to deliver products in high yields (84%, **3a**). It bears mentioning that in all these cases, enones **4** were not observed in the reaction mixture(**3**/**4** > 20/1), further highlight the efficiency and robustness of the transformation.

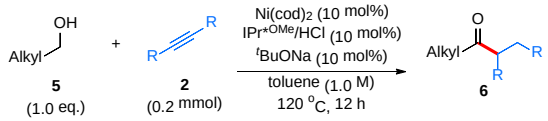
Next, we surveyed the possibility of expanding the reaction to simple aliphatic alcohol substrates. Due to the more challenging dehydrogenation of aliphatic alcohols compared to that of benzylic alcohols, and more labile of the transiently formed aliphatic aldehydes to undergo aldol reaction and Tishchenko reaction, the application of simple aliphatic alcohols to this novel coupling reaction was non-trivial. Fortunately, we identified IPr*^{OMe} as a suitable ligand to efficiently couple aliphatic alcohols and alkynes for the synthesis of alkyl-alkyl ketones. As shown in Table 3, aliphatic alcohols, including long linear alcohols (**6a**-**6e**), α- or β-branched alcohols (**6g** and **6h**), β-amino alcohols (**6i**), and ethanol (**6j**), were all viable substrates for this protocol affording products in moderate to high yields (45-89%). Functional groups such as esters (**6k** and **6l**), silyl-ethers (**6m**), fluoride (**6k**), trifluoromethoxy (**6l**) group, and aniline (**6i**), are well tolerated under the catalytic conditions. Alcohols bearing pyridine or thiophene heterocycles were compatible, giving products in moderate yields (**6n** and **6o**). In the case of α-branched alcohol, ester byproduct was observed, which is formed by the Tishchenko reaction of a transient aldehyde; and the desired ketone product was obtained in moderate yield (**6g**). Notably, coupling reactions involving both labile aldehydes (phenylacetaldehyde (**6f**), amino acetaldehyde (**6i**), and acetaldehyde (**6j**)) and the corresponding ketone products with acidic α-protons, which are more inclined to go aldol reaction, were performed smoothly to give products in synthetically useful yields.

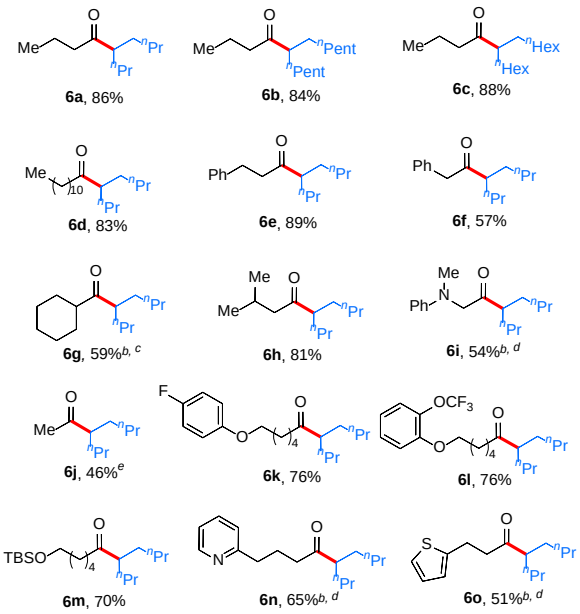
Table 2. Nickel-catalyzed coupling of benzylic alcohols with alkynes[a]



[a] Isolated yields on 0.2 mmol scale reactions. [b] Using IPr*^{OMe} instead of SIPr as the ligand. [c] Ratio of regioisomers.

Table 3. Nickel-catalyzed coupling of aliphatic alcohols and alkynes [a]





[a] Isolated yield on 0.2 mmol scale reactions; the ratio of ketone: enone is all > 20:1 unless otherwise indicated. [b] Using 15 mol% of catalyst and base. [c] Reaction runs at 40 ℃. [d] Reaction runs at 80 ℃. [e] Reaction runs at 25 ℃, the ratio of ketone: enone is 12:1.

To get insight into the reaction mechanism, we performed additional experiments. We first examined the coupling of benzyl alcohol (**1a**) and 4-octyne (**2a**) under the standard conditions. When the reaction was heated for just 5 minutes, we obtained the ketone (**3a**) in a 60% NMR yield, alone with enone **4a**, allylic alcohol **7a**, and benzaldehyde in 15%, 6%, and 4% NMR yield, respectively (Figure 2a). When heating the reaction mixture for 1 hour, the enone **4a** and allylic alcohol **7a** were not detected. These results suggest that enone and allylic alcohol may be the intermediates

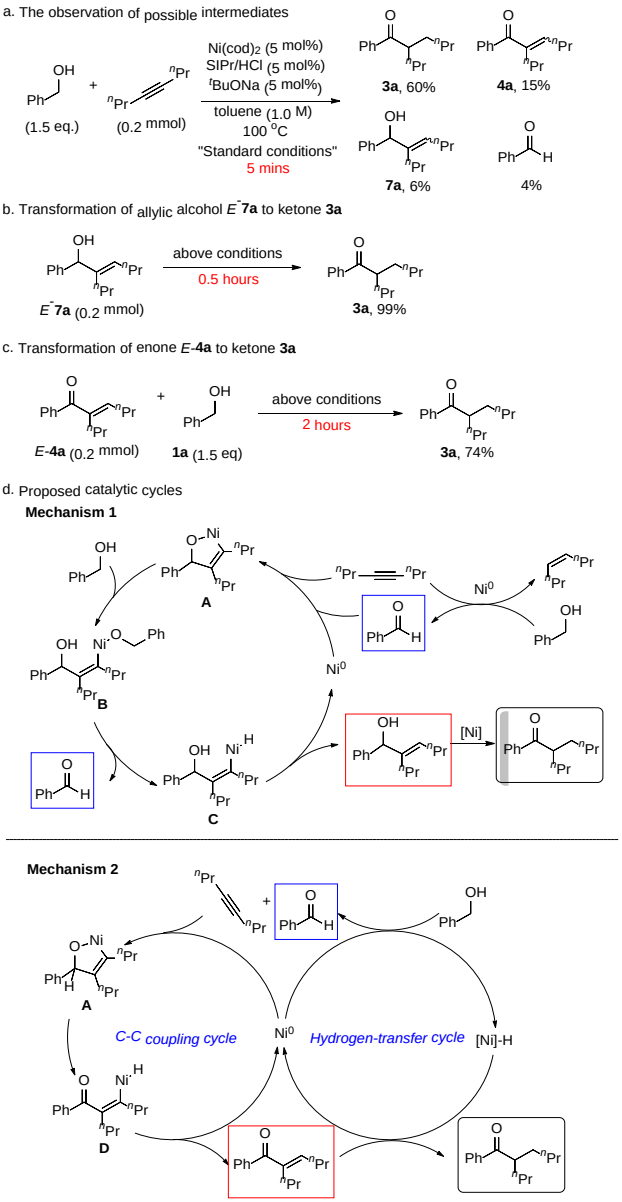


Figure 2. Mechanism investigation

the reaction. Then we performed transformations of enone and allylic alcohol to ketone products under standard conditions. The reaction of allylic alcohol (**7a**) can give ketone (**3a**) quantitively in just 0.5 hours (Figure 2b), suggesting that the isomerization of allylic alcohol to the ketone[18] is a facile reaction under the standard conditions. When treated enone **4a** with benzyl alcohol (**1a**) under standard conditions for 2 hours, we obtained the ketone product (**3a**) in 74% yield, which suggests that **4a** can be reduced to a ketone with alcohol as a reductant in this reaction (Figure 2c). These results proved that enone and allylic alcohol both could be the intermediate of ketone in this reaction.

It has been reported the nickel-catalyzed coupling of alcohols and alkynes to furnish allylic alcohols by our group[6a,c], and the nickel-catalyzed coupling of aldehydes and alkynes to form enones.[7b,9] Based on these works and our observations in this reaction, we proposed two possible mechanisms, as shown in Figure 2d. In the mechanism 1, the alkyne and in-situ formed aldehyde first go cyclometallation with Ni(0) catalyst to afford an oxanickelacycle **A**. Then the protonation of **A** by alcohol delivers acyclic nickel intermediate **B**, which subsequently goes β-H elimination to provide nickel hydride intermediate **C**, meanwhile regenerates an aldehyde. Then reductive elimination of **C** gives

allylic alcohol, which isomerizes to afford the ketone. Alternatively, the oxanickelacycle **A** can undergo β-H elimination to give an enone, which is shown in the mechanism 2, and then the conjugate reduction by nickel hydride species affords the ketone product. Although both mechanisms are possible, we think the mechanism 1 is the major pathway because the isomerization of allylic alcohol **7a** to the ketone is faster than the conjugate reduction of enone.

In conclusion, we have developed a novel NHC/nickel-catalyzed coupling of alcohols and alkynes for the expedient synthesis of ketones. A variety of α-branched aryl alkyl ketones and dialkyl ketones, which are difficult to access through a metal-catalyzed hydroacylation of simple internal alkenes with aldehydes, were readily prepared in one chemical step. This hydrogenative transfer protocol is free from any oxidative or reductive additives, rendering this reaction atom-, step- and redox-economical. Further expanding the scope of this type of reaction is underway in our laboratory.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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Expedient Synthesis of Ketones via NHC/Nickel-Catalyzed Redox-Economical Coupling of Alcohols and Alkynes

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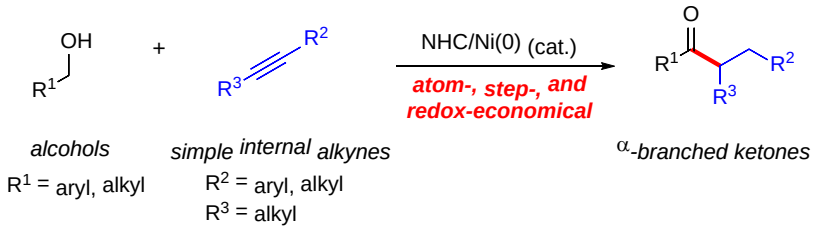

alcohols R^1 = aryl, alkyl

simple internal alkynes R^2 = aryl, alkyl; R^3 = alkyl

α-branched ketones

An NHC/Ni-catalyzed direct coupling of alcohols and internal alkynes for a convenient synthesis of α-branched ketones is reported. This novel hydrogenative transfer protocol provides an atom-, and redox-economical approach to α-branched ketones, products that are difficult to access through the hydroacylation of unactivated internal alkenes with aldehydes, in one chemical step.

Yu-Qing Li, # Feng Li, # and Shi-Liang Shi *

