Nickel-Catalyzed Redox-Economical Coupling of Alcohols and Alkynes to Form Allylic Alcohols

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S *Supporting Information*

ABSTRACT: We have developed a redox-economical coupling reaction of alcohols and alkynes to form allylic alcohols under mild conditions. The reaction is redox-neutral as well as redox-economical and thus free from any additives such as a reductant or an oxidant. This atom-economical coupling can be applied for the conversion of both aliphatic and benzylic alcohols to the corresponding substituted allylic alcohols in a single synthetic operation.

Allylic alcohols are among the most fundamental organic compounds and are versatile building blocks for organic synthesis. In the past decade, transition-metal-catalyzed direct coupling of alkynes and aldehydes was identified as a significant methodology for the divergent synthesis of allylic alcohols.[1−3] Nickel-catalyzed reductive coupling of alkynes and aldehydes in the presence of organometallic reagents (e.g., organozincs and organoboranes) is an example of seminal work on such a transformation (Scheme 1).[4] The
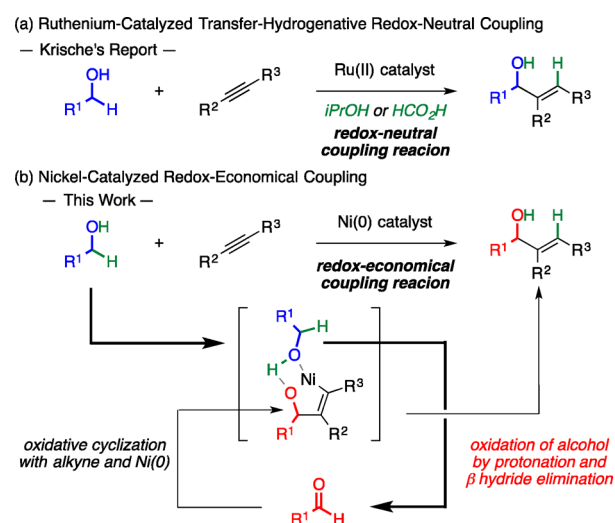
Scheme 1. Nickel-Catalyzed Alkyne-Aldehyde Reductive Coupling Reactions
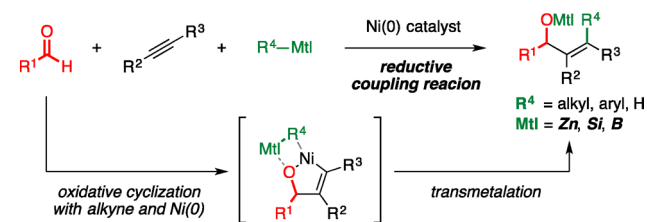
more recent ruthenium-catalyzed "redox-neutral" coupling reaction of alkynes and alcohols in the presence of an external hydrogen source (e.g., iPrOH and HCO$_2$H) is another straightforward route to diverse allylic alcohols. (Scheme 2a).[5,6] However, to the best of our knowledge, there is only one report on the use of transition-metal catalysts for the "redox-neutral as well as redox-economical" coupling of alcohols and alkynes to form allylic alcohols.[7] Herein, we demonstrate the feasibility of the aforementioned process—direct coupling of alcohols and alkynes—to form allylic alcohols without using any reductant or oxidant (Scheme 2b).

Oxidative cyclization of an aldehyde and an alkyne with Ni(0) to afford the corresponding oxa-nickelacycle, a key intermediate, is a well-known step in various catalytic

Scheme 2. Transition-Metal-Catalyzed Alkyne-Alcohol Coupling Reactions[a]
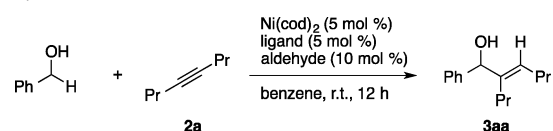

[a](a) Ruthenium-catalyzed transfer hydrogenative redox-neutral coupling and (b) nickel-catalyzed redox-economical coupling.

reactions involving the aforementioned reductive coupling with an organometallic reagent (Scheme 1). The formation of such oxa-nickelacycles has been well investigated by a stoichiometric reaction and confirmed by X-ray single-crystal structural analysis in some cases.[8−10] Therefore, we hypothesized that (1) if the oxa-nickelacycle is reduced by an alcohol via hydrogen transfer (oxidation of an alcohol by protonation of the oxa-nickelacycle and subsequent β-hydride elimination to provide an aldehyde),[11] an allylic alcohol would be obtained (Scheme 2b); and (2) if the newly produced aldehyde could participate in the oxidative cyclization with an alkyne and Ni(0) to regenerate the initial oxa-nickelacycle, redox-economical coupling of an alcohol and an alkyne would be achieved.

To prove our hypothesis, we first examined the coupling of benzyl alcohol **1a** and alkyne **2a** in the presence of a catalytic amount of benzaldehyde to facilitate the initial oxa-nickelacycle formation (Table 1). Allylic alcohol **3aa** was obtained in 78% yield when nickel bis(1,5-cyclooctadiene) (Ni(cod)$_2$) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) were

Table 1. Effects of Ligand and Additive on the Formation of Allylic Alcohol[a]
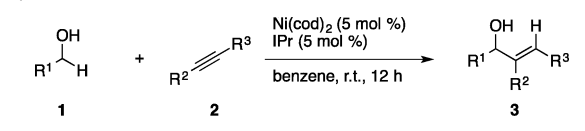
entry	ligand	aldehyde	yield (%)[b]
1	IPr[c]	PhCHO	78
2	SIPr[d]	PhCHO	64
3	IMes[e]	PhCHO	12
4	PCy$_3$	PhCHO	5
5	PPh$_3$	PhCHO	<1
6	PPr$_3$	PhCHO	<1
7	IPr	–	80 (77)[f]

[a]Reactions were carried out using Ni(cod)$_2$ (5 mol %), ligand (5 mol %), **1a** (0.2 mmol), and **2a** (0.24 mmol) in 2 mL of benzene for 12 h. [b]Determined by ^{1}H NMR analysis using CHBr$_3$ as the internal standard. [c]IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [d]SIPr: 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene. [e]IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. [f]Isolated yield.

employed as the catalysts, in benzene at ambient temperature (entry 1). Other N-heterocyclic carbene ligands such as 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr) and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) were less effective for the reaction and afforded lower yields of **3aa** (entries 2–3). The reaction in which phosphine ligands were used in place of the IPr ligand afforded only a trace amount of **3aa**, regardless of their steric or electronic properties (entries 4–6). Further examination revealed that the redox-economical coupling proceeded in the absence of a catalytic amount of aldehyde (additive) to furnish **3aa** in 80% yield (entry 7).

Next, we carried out the nickel-catalyzed redox-economical coupling of various substituted benzylic and aliphatic alcohols with alkynes to obtain the corresponding allylic alcohols (Table 2). Benzylic alcohols having electron-donating groups such as methyl and methoxy groups reacted with 4-octyne **2a** to give the corresponding allylic alcohols (**3ba**, **3ca**, **3da**) in high yields. The reactions of benzylic alcohols with electron-withdrawing groups also afforded the desired products, albeit in moderate yields (**3ea**, **3fa**, **3ga**). Of note, benzylic alcohol **1h** possessing an acetyl group also participated in the reaction to give **3ha** in 70% yield; clearly, the acetyl group was tolerated under the reaction conditions, and the coupling reaction proceeded chemoselectively. Aliphatic alcohols such as cyclohexanemethanol and cyclopropanemethanol, too, were successfully coupled with alkyne **2a** under the same reaction conditions to afford the corresponding substituted allylic alcohols (**3ja**, **3ka**) in good yields. Various functional groups were tolerated in the coupling reaction of benzyl alcohol **1a** with alkynes: alkynes possessing an alkoxy group participated in the reaction to provide allylic alcohols **3ad** and **3ae** in 71% and 74% yields, respectively. Both acyclic and cyclic alkynes participated in the reaction; cyclopentadecyne **2f** coupled with benzyl alcohol **1a** to furnish allylic alcohol **3af**.

We next carried out a deuterium-labeling experiment to address the following questions: (1) which of the hydrogen atoms on alcohol **1** acts as a proton or hydride source to reduce the oxa-nickelacycle to afford the final product **3**? and (2) how is the initial oxa-nickelacycle key intermediate

Table 2. Nickel-Catalyzed Coupling Reaction between Alkyne 1 and Alcohol 2[a]

[a]Reactions were carried out using Ni(cod)$_2$ (5 mol %), IPr (5 mol %), **1** (0.2 mmol), and **2** (0.24 mmol) in 2 mL of benzene for 12 h. [b]Isolated yields are given. [c]Ratio of regioisomers.

Scheme 3. Deuterium-Labeling Experiment
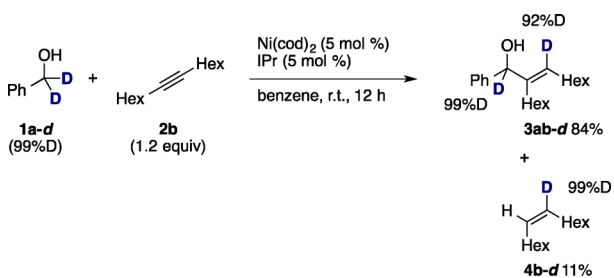
generated in situ? Accordingly, we performed the coupling of α,α-dideuteriobenzyl alcohol **1a–d** with 7-tetradecyne **2b** under the standard reaction conditions, as shown in Scheme 3, and obtained allylic alcohol **3ba–d** with 92% deuterium labeling at the olefinic position. This result indicated that the coupling reaction proceeds via the formation of an oxa-nickelacycle, which undergoes reduction by proton transfer from the hydroxy hydrogen and hydride transfer from the benzylic hydrogen. Detailed observation of the deuterium-labeling reaction revealed the formation of cis-7-tetradecene **4b–d** in 11% yield, with 99% deuterium labeling at the olefinic position, as a minor product along with the main coupling product **3ab–d**. This result indicated that the alkyne, which exists in a slightly excess amount as compared to the alcohol (1.2 equiv), acts as the oxidant for the alcohol to

generate a catalytic amount of the aldehyde, which then participates in the formation of the initial reactive oxa-nickelacycle through oxidative cyclization of an aldehyde and an alkyne with Ni(0).
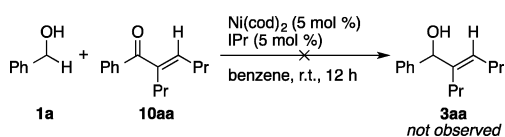
Scheme 4. Plausible Reaction Pathway
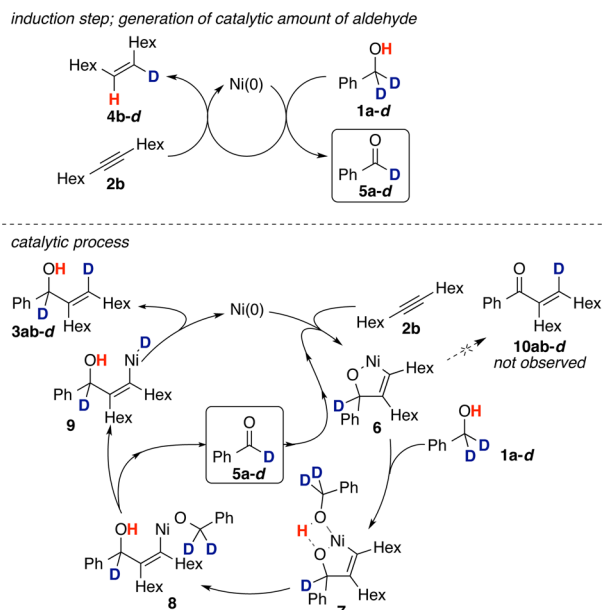
On the basis of our observations, we proposed a plausible mechanism for the redox-economical coupling of α,α-dideuteriobenzyl alcohol **1a−d** and 7-tetradecyne **2b** (Scheme 4). As the first step toward the generation of the reactive oxa-nickelacycle intermediate, **1a−d** is oxidized to benzaldehyde **5a−d** via hydrogen transfer with alkyne **2b** as the reductant (hydrogen scavenger) to yield alkene **4b−d** (induction step). Then, **5a−d** and **2b** participate in the formation of oxa-nickelacycle **6** by oxidative cyclization with Ni(0) (catalytic process). Another alcohol **1a−d** would then protonate **6** with its hydroxy hydrogen atom to afford acyclic intermediate **8**. Subsequent β-hydride elimination affords nickel hydride complex **9** along with aldehyde **5a−d**, followed by reductive elimination to provide allylic alcohol **3ab−d** and regenerate Ni(0).[12] An alternative reaction pathway would involve β-hydride elimination of enone **10ab−d** on oxa-nickelacycle **6** and reduction of the resulting **10ab−d** with alcohol **1a** by hydrogen transfer under the reaction conditions. However, the attempted reduction of enone **10aa** with alcohol **1a** under the standard reaction conditions did not afford allylic alcohol **3aa** (Scheme 5), thus ruling out this alternative pathway.

In summary, we have developed a transition-metal-catalyzed "redox-economical" coupling of alcohols and alkynes to form allylic alcohols. The transition-metal-catalyzed reaction of alkynes, which involves isomerization of the π bond for constructing more thermodynamically stable σ bonds, is widely used to form molecular frameworks in an atom-economical manner. In this context, the aforesaid coupling of alkynes and alcohols represents a rare example of the isomerization of the π bond of an alkyne to construct a new C−C σ bond with an alcohol. Efforts to expand the scope of the reaction and develop an asymmetric variant of this reaction are underway; the results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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Scheme 5. Reduction of Enone with Alcohol

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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 4 contained errors in the version published ASAP May 20, 2014; the correct version reposted May 22, 2014.

7800

dx.doi.org/10.1021/ja500666h | *J. Am. Chem. Soc.* 2014, 136, 7797−7800