Communication

Catalytic Coupling between Unactivated Aliphatic C-H Bonds and Alkynes via a Metal-Hydride Pathway

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 07 Apr 2017

Catalytic Coupling between Unactivated Aliphatic C−H Bonds and Alkynes *via* a Metal−Hydride Pathway

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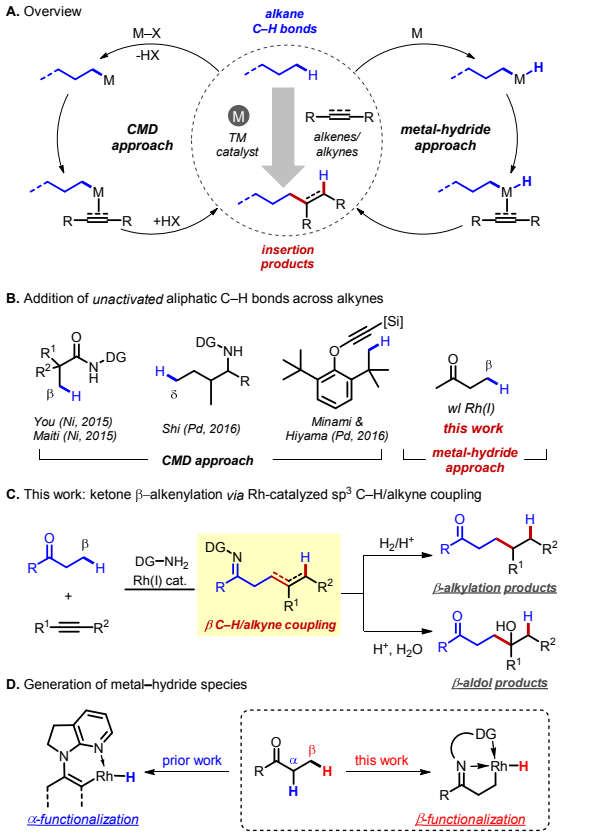
Supporting Information Placeholder

ABSTRACT: We report a Rh(I)-catalyzed site-selective coupling between ketone β C(sp^3)−H bonds and aliphatic alkynes using an *in-situ*-installed directing group (DG). Upon hydrogenation or hydration, various β-alkylation or β-aldol products of the ketones are obtained with broad functional group tolerance. Mechanistic investigations support the involvement of a Rh−H intermediate through oxidative addition of Rh(I) into the β C−H bonds. Thus, to the best of our knowledge, this transformation represents the first example of catalytic couplings between unsaturated hydrocarbons and unactivated aliphatic C−H bonds via a metal−hydride pathway.

Direct addition of unactivated C−H bonds across unsaturated hydrocarbons, e.g. alkenes and alkynes, offers a *byproduct-free* and *redox-neutral* method to form carbon−carbon bonds.[1] This transformation can be possibly realized by two approaches (Scheme 1A).[2] In the first case, the C–H bond is cleaved through a concerted metallation-deprotonation (CMD) pathway,[3] which is followed by migratory insertion of the alkene or alkyne and then protodemetallation to afford the coupling product (left cycle). Alternatively, a metal−hydride species can be formed through oxidative addition of a low-valent metal catalyst into a C–H bond.[4] Upon coordination of an unsaturate, the product is formed *via* a sequence involving migratory insertion and reductive elimination (right cycle). To date, addition of sp^2 C–H bonds across alkenes or alkynes has been extensively developed with both approaches,[5] often resulting in complementary regioselectivity. In contrast, much fewer examples are known for sp^3 C–H bonds,[6,7] of which the majority are at activated positions (benzylic,[7a-c] allylic,[7d] α-to-heteroatoms[7e-h] or at activated methylenes[7i]). It was not until recently that alkenylations of unactivated aliphatic C–H bonds with alkynes were achieved with amide,[8] amine[9,10] and 2,6-(tBu)$_2$phenyl ether substrates,[11] exclusively *via* a *CMD pathway* (Scheme 1B). The direct coupling of unactivated aliphatic C–H bonds with unsaturated hydrocarbons *via* a *metal−hydride approach* remained unknown.[12] The challenge is three-fold: 1) oxidative addition into unactivated sp^3 C–H bonds is often significantly slower than sp^2 C–H bonds;[13] 2) reductive elimination involving an alkyl moiety is generally difficult;[14] and 3) low-valent metals often catalyze oligomerization of unsaturated hydrocarbons as a competitive reaction pathway.[15] As part of our long-term interest in site-selective C−H functionalization of ketones,[16,17] we herein describe the development of a Rh-catalyzed ketone β-alkenylation method with aliphatic alkynes using an *in-situ*-installed directing group (DG) (Scheme 1C). Our mechanistic study demonstrates that this C−H/alkyne coupling reaction proceeds through a metal−hydride reaction pathway.

Scheme 1. Transition metal-catalyzed addition of C−H bonds across alkenes/alkynes

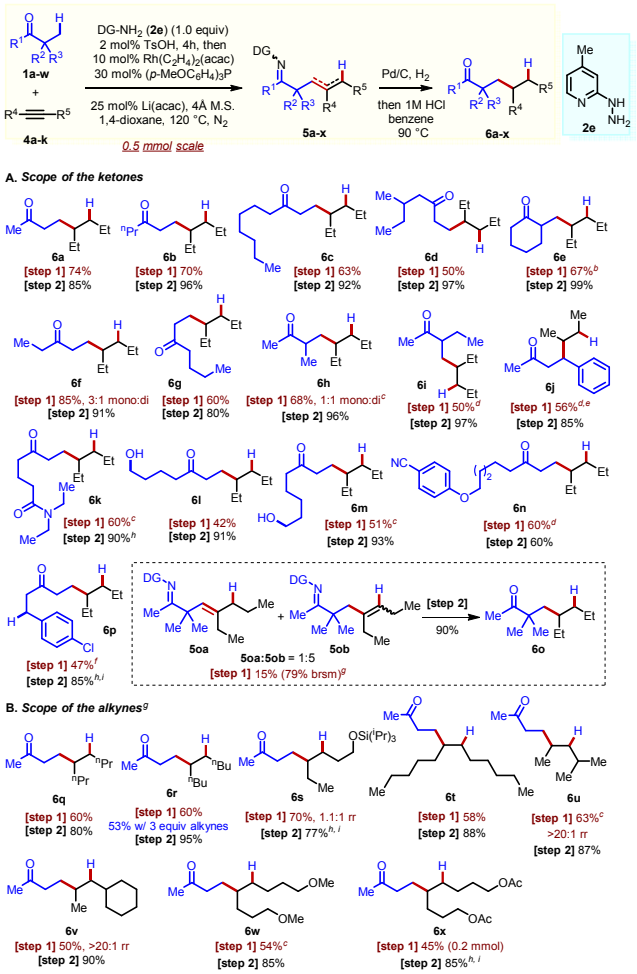


Our prior work involves introducing an *enamine* DG to generate a metal−hydride species at ketone α positions, which leads to α−alkylation or alkenylation with olefins or alkynes (Scheme 1D, left).[16a,c-f] To form a metal−hydride species at ketone β positions, it was hypothesized that a properly selected *imine-type* DG would promote C−H oxidative addition through forming a five-membered metallocycle.[18,19] In addition, we envision that the direct coupling of β C–H bonds with alkynes should introduce one degree of unsaturation, which can serve as a convenient handle to access other valuable derivatives, such as the *β-alkylation* and *β-aldol* products (Scheme 1C).

Our study initiated with 2-butanone (**1a**) as a model substrate to couple with 3-hexyne (Table S1). We foresaw the advantage of using an *in situ*-generated hydrazone intermediate (i.e. **3a**)[20] that

contains an additional coordinative motif. First, hydrazones should exhibit enhanced stability over regular imines; and second, the chelation effect would assist oxidative addition of Rh(I) into the β C−H bond. After a survey of various DGs, metal precatalysts, ligands and other reaction parameters, ultimately the desired product (**5a**) was isolated in 74% yield using $Rh(C_2H_4)_2(acac)$/$(p\text{-}MeOC_6H_4)_3P$ as the metal/ligand combination, hydrazine **2e** to form the optimal DG, and Li(acac) as the additive at 120 °C in 1,4-dioxane. Unsurprisingly, the alkene migrated under the reaction conditions, leading to a mixture of γ,δ- and β,γ-unsaturated products.[21] In general, the pyridine-derived hydrazone DGs are more effective than the corresponding hydrazide or quinoline-derived DG (entries 2 and 3). A series of control experiments were also conducted to understand the role of each reactant. No product was observed in the absence of either the DG or the Rh pre-catalyst (entries 7-8). The counter anion of the catalyst appears to be important, as replacing the $Rh(C_2H_4)_2(acac)$ with $[Rh(C_2H_4)_2Cl]_2$ (without Li(acac)) provided the desired product in a much lower yield (entry 9). $(p\text{-}MeOC_6H_4)_3P$ proved to be an optimal ligand for this transformation, while using bidentate ligands generally gave no conversion of the starting material, and other mono-dentate phosphines were less effective.[22] A diminished yield was observed when less phosphine was used (entry 11). The excess phosphine ligand is likely beneficial for the catalyst dissociation from the product. The use of a lower catalyst loading, e.g. 5 mol% Rh, still afforded 70% yield (entry 12). Finally, the addition of Li(acac) improved the yield to some extent (entry 13), while the addition of water reduced the reaction efficiency (entry 14).

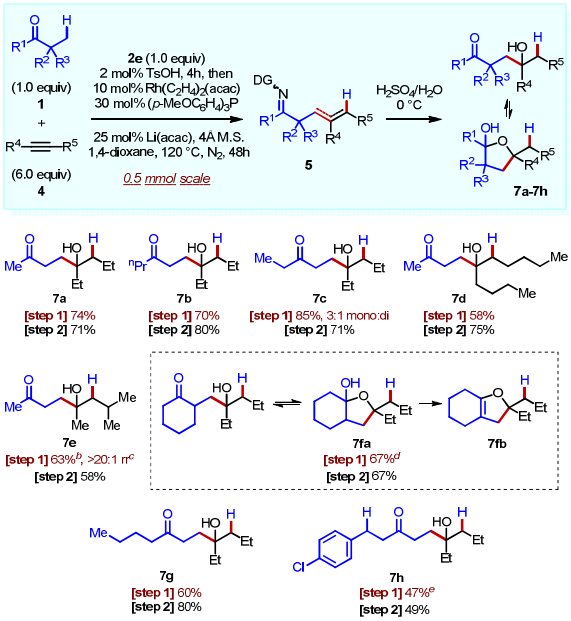
Scheme 2. Substrate scope with various ketones and alkynes[a]



[a] Run with 0.5 mmol **1a** and 3.0 mmol **4a** in 48h. All yields are isolated yields. [b] 15 mol% [Rh]. [c] 72h. [d] 72h, 130 °C. [e] 2.5 ml 1,4-dioxane, 20 equiv alkyne. [f] The benzylic alkenylated product and the di-alkenylated product were observed in <5% yield. [g] Use the pre-condensed substrate. [h] no HCl was added in the hydrogenation step. [i] In step 2, the hydrolysis was conducted before the hydrogenation. brsm = based on recovered starting material. rr: regioisomer ratio.

The scope of the ketone-alkyne coupling was then explored (Scheme 2). Both linear and cyclic ketones can couple with aliphatic internal alkynes efficiently.[23] Simple treatment of the alkenylation products with Pd/C and H_2, followed by addition of aqueous HCl afforded the corresponding β-alkylated ketones in one pot. When unsymmetrical ketones were employed as the substrates, alkenylation occurred predominately at the primary C–H bonds. However, in the absence of β methyl groups, the benzylic methylenes can also be activated (**6j**). A range of functional groups were compatible, including aryl chlorides (**6p**), free alcohols (**6l**, **6m**), ethers (**6n**, **6w**), amides (**6k**), nitriles (**6n**) and esters (**6x**). While bulky pinacolone gave a low conversion (**6o**),[24] α-branches (**6e**, **6h**, **6i**) were well tolerated. In addition, various symmetrical and unsymmetrical aliphatic alkynes can be used as coupling partners (**6q-v**), including a protected homopropargyl alcohol moiety (**6s**) that is often used as a synthetic handle. Note that when a heavier alkyne (e.g. 5-decyne) was employed, the alkyne loading can be reduced to 3 equiv without significantly affecting the yield (**6r**). Excellent regioselectivity was achieved when the two substituents of alkynes are differentiated by size (**6u**, **6v**), favoring C–C bond formation at the less hindered side of the alkynes.

Scheme 3. Synthesis of β-aldol adducts through the Rh-catalyzed C–H alkenylation/hydration sequence[a]



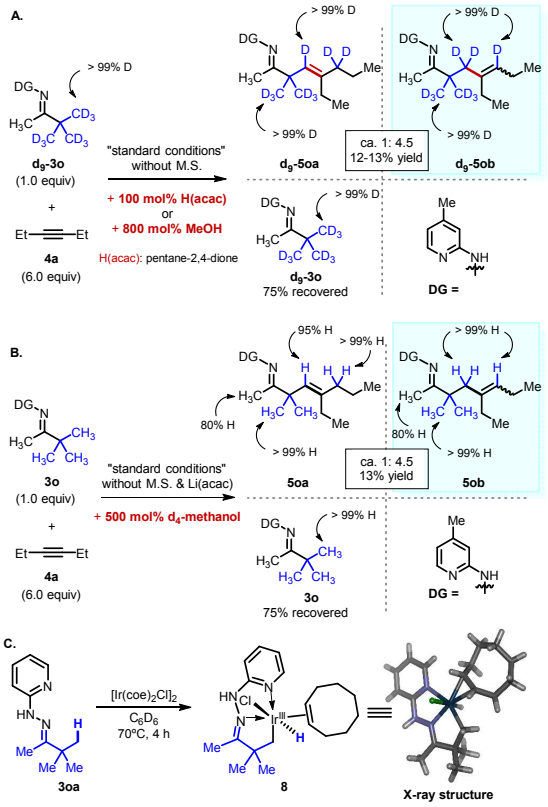
[a] All yields are isolated yields. [b] 72h. [c] from > 20:1 rr. [d] 15 mol% [Rh]. [e] The benzylic alkenylated product and the di-alkenylated product were observed in <5% yield.

While the initial alkenylation products contain olefin isomers, the olefins generally share the same tertiary carbon at the γ-position. Thus, a Markovnikov hydration is expected to yield a γ-ketol, formally a *β-aldol adduct*, as a unified product. Indeed, after simply treating the alkenylation products in aqueous H_2SO_4

at 0 °C for 1h, the hydration products (in equilibrium between γ-ketol and hemiketal forms) were readily obtained in moderate to good yields, and gratifyingly, the DG was removed at the same time (Scheme 3). Interestingly, when 2-methylcyclohexanone was used as the substrate, the final hydration product underwent simultaneous cyclization and dehydration to afford dihydrofuran **7fb**.

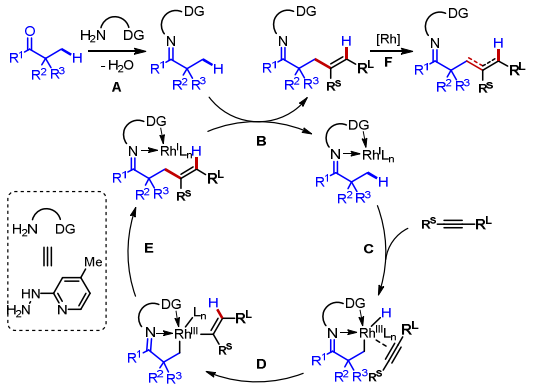
Regarding the reaction mechanism, the key question is whether the C–H activation occurs through a metal−hydride pathway or a CMD pathway. To address this question, first, the deuterium-labeling experiments were carried out with a β-d_9-pinacolone derivative (Scheme 4A). A tertiary alkyl ketone substrate was specifically chosen to avoid potential H/D scrambling between the α and β positions through a β-H elimination and re-insertion pathway. If the reaction follows a metal−hydride pathway, the deuterium at the original β position should be transferred to the δ position of the product (the vinyl hydrogen in major product **5ob**).[7g] However, in the case of a CMD pathway, the reaction should end with a protodemetalation step, thus it is expected that significant deuterium erosion at the δ position would occur in the presence of external proton sources.[9] Our experiments showed that complete deuterium incorporation was found at the vinyl position of product **5ob** with either acetylacetone (100 mol%) or MeOH (800 mol%). In addition, almost no deuterium loss was found at either the unreacted methyl groups or the recycled starting material. All of these observations support a metal−hydride pathway and disfavor a CMD pathway.[25] Second, as a control experiment, when non-deuterated substrate **3o** was subjected to the reaction with excess d_4-methanol, nearly no deuterium incorporation was observed at either the β or vinyl position of the products or the recycled starting material (Scheme 4B). This result further ruled out a CMD pathway.

Scheme 4. Preliminary mechanistic studies



Attempts to capture the Rh–H intermediate via NMR experiments were unfruitful; however, the corresponding Ir–H complex was successfully isolated and characterized, which is likely driven by forming a stronger Ir–H bond (Scheme 4C). While this specific Ir complex was found catalytically inactive, this result nevertheless demonstrates the feasibility of oxidative addition of a low-valent group-9 metal into unactivated β C–H bonds with this specific hydrazone type of DG. Finally, the observed regioselectivity for insertion of unsymmetrical alkynes (**6u**, **6v** and **7e**) is consistent with a hydride-migratory insertion pathway instead of an alkyl-migratory insertion pathway.[26] Altogether, our mechanistic investigations strongly support a metal−hydride reaction pathway.

Scheme 5. Proposed catalytic cycle



Accordingly, a plausible catalytic cycle is proposed (Scheme 5). First, upon hydrazone formation (step A), coordination with Rh(I) through chelation with the DG facilitates oxidative addition into the β-C(sp^3)–H bond to generate a Rh(III)−hydride species (step C). The hydride intermediate then undergoes alkyne migratory insertion (step D), sp^2-sp^3 reductive elimination (step E), and ligand exchange with a new substrate (step B) to yield the alkenylation product and resume the catalytic cycle. Further olefin migration of the product may take place, which can also be catalyzed by Rh (step F).[21] Efforts toward enabling use of catalytic DGs as well as coupling with alkenes are ongoing.

ASSOCIATED CONTENT

Supporting Information Experimental procedures; spectral data. 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 interests.

ACKNOWLEDGMENT

We thank the Frasch Foundation and NSF (CAREER: CHE-1254935) for funding. G.D. is a Searle Scholar and Sloan Fellow.

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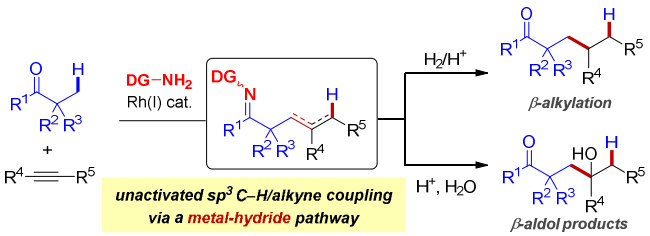
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Rh(I) cat.
H2/H+
H+, H2O
β-alkylation
β-aldol products
unactivated sp3 C–H/alkyne coupling
via a metal-hydride pathway