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Tandem Catalysis: Transforming Alcohols to Alkenes by Oxidative Dehydroxymethylation

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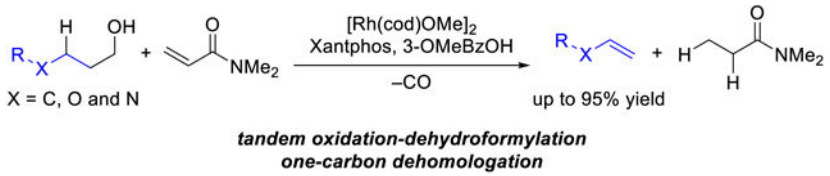
Abstract

We report a Rh-catalyst for accessing olefins from primary alcohols by a C–C bond cleavage that results in dehomologation. This functional group interconversion proceeds by an oxidation-dehydroformylation enabled by *N,N*-dimethylacrylamide as a sacrificial acceptor of hydrogen gas. Alcohols with diverse functionality and structure undergo oxidative dehydroxymethylation to access the corresponding olefins. Our catalyst protocol enables a two-step semisynthesis of (+)-yohimbenone and dehomologation of feedstock olefins.

Graphical Abstract



Enzymes perform one-carbon dehomologations of alcohols via the intermediacy of an aldehyde. For example, DNA demethylases oxidize alcohols to aldehyde intermediates that are decarbonylated to generate alkanes and arenes.[1] Lanosterol demethylase performs a tandem oxidation and dehydroformylation to generate alkenes (Figure 1a). In contrast, while dehomologation of alcohols to generate alkanes has been achieved with various homogeneous catalysts,[2] initial efforts to convert alcohols into olefins used heterogeneous catalysis and resulted in side reactions, including dehydration, olefin isomerization, and cracking, due to high reaction temperatures (>380 °C).[3c] Inventing ways to access olefins remains a primary focus due to their versatility as building blocks for materials and medicines.[4] To achieve a mild, selective, and more general alcohol to alkene transformation, we thus focused on developing a bioinspired cascade.

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The authors declare no competing financial interests.

Supporting Information

Detailed experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

Our laboratory reported a dehomologation that transforms aldehydes into olefins via transfer of the formyl group and hydride onto a strained olefin acceptor, such as norbornadiene.[5a] Morandi coined such processes *shuttle catalysis*.[6] Nozaki and Sorensen reported complementary dehydroformylations, through Ir-catalysis or photocatalysis, respectively (Figure 1b).[5b, 3d] In Sorensen's study, he illustrated one oxidative dehydroxymethylation of a neopentylic alcohol, although a mixture of products was observed.[3d] Given precedence for both transfer hydrogenation[7,8] and transfer dehydroformylation,[5a] we focused on the use of tandem Rh-catalysis to achieve a more general alcohol dehomologation to alkenes (Figure 1c).[9]

We set out to identify one catalyst capable of both transfer hydrogenation and transfer hydroformylation.[10] Using 1-dodecanol **1a** as a model substrate, we began our studies with a catalyst known to activate aldehyde C–H bonds ($[Rh(cod)OMe]_2$, 3-OMeBzOH, and Xantphos, Table 1).[5a] Upon successful oxidation of alcohol **1a**, we imagined the resulting aldehyde could undergo dehydroformylation to the alkene **2a** or decarbonylation to the alkane **3a**. From an initial survey, we discovered that selectivity for alkene vs alkane was influenced by the acceptor. In the absence of an acceptor, we observed undecane **3a** as the only product (10% yield). In stark contrast, by using strained olefin acceptors **A1** and **A2**, we observed 1-undecene (**2a**, 32% and 18% respectively), along with undecene isomers (*iso*-**2a**, 16:1 and 2.3:1, **2a**:*iso*-**2a**). Using ketones as acceptors (**A3**–**4**) resulted in decarbonylation to undecane **3a**. While using electron-deficient olefin acceptors, such as enone **A5** or acrylonitrile **A6**, a mixture of 1-undecene **2a** and undecane **3a** was observed (1.4:1 and 1:3, **2a**:**3a**). Using unsaturated ester or amide acceptors provided a major breakthrough in selectivity for the desired alkene **2a**.

Unsaturated ester and amide acceptors (**A7**–**A8**) enabled selective formation of 1-undecene (**2a**, 33–35%, >20–17.5:1, **2a**:**3a**). Use of *N*,*N*-dimethylacrylamide (DMAA) as an acceptor gave 1-undecene **2a** in 95% yield and >20:1 selectivity.[11] We reason DMAA affords improved reactivity because it can bind more effectively to the Rh-catalyst in comparison to other Michael acceptors (**A5**–**A8, A10**). We found that the byproduct was *N*,*N*-dimethylpropionamide, which arises from the hydrogenation of DMAA. The use of *N*-vinylpyrrolidone (**A9**) or the α-methyl substituted acrylamide **A10** resulted in diminished reactivity (3–5%). Previously, we found that both CO and H_2 were transferred to our strained olefin acceptor, norbornadiene **A1**.[5a] In contrast, we do not observe transfer hydroformylation, yet catalyst turnover still proceeds in the presence of CO generation, as quantified by GC-thermal conductivity detection (see SI).[12]

With this catalyst-acceptor combination, we performed the dehomologation of primary alcohols (Table 2a). Allylbenzene **2b** was obtained (93% yield) from 4-phenyl-1-butanol, without isomerization to a conjugated olefin. 3-Phenyl-1-propanol and derivatives with electron-donating and electron-withdrawing groups gave styrenes (**2c–e)** in 85–93% yields. Heterocyclic alcohols, such as those with pyridine and indole, were tolerated (**2f**, 85%; **2g**, 77%). A primary diol gave diene **2h** in 88% yield, in the presence of double the amount of DMAA (6 equivalents). A β,β-disubstituted alcohol transformed to internal olefin **2i** in 91% yield. Alcohols bearing alkenes and tertiary alcohols underwent dehomologation (**2j**, 82%;

2k, 87%). Next, we explored 1,3- or 1,4-diols and 2-, 3- or 4-amino derived alcohols (**2l**–**s**). Allylic ether **2l** and amine **2o** were obtained in 81% and 92% yields respectively, without allylic C–O or C–N bond cleavage or debenzylation. Enol and enamine derivatives (**2m**, **2n**, **2p**–**s**) can be accessed (75–83% yields). Enamine formation occurred preferentially over allyl amine formation to afford **2q** (80% yield). We obtained tri-substituted enamide **2r** in 75% yield from alcohol **1r**. With most alcohols, excellent chemoselectivities (>20:1) were observed. In contrast, use of 3-phthalimido-1-propanol gave a 4:1 mixture of oxidation-dehydroformylation (**2s**) and oxidation-decarbonylation (**3s**). When *cis*- or *trans*-**1t** was used, β-hydride elimination occurred preferentially at the less substituted position to give **2t1**. In addition, we found that allylic alcohols (**4a-c**) underwent oxidative dehydroxymethylation (75–95% yields), with only 1.5 equivalents of DMAA needed (Table 2b).[13]

Next, we explored applications (Scheme 1). By combining hydroboration-oxidation with oxidative dehydroxymethylation, a one-carbon dehomologation of 1-dodecene **6** was achieved on gram scale to give 1-undecene **2a** (82% yield, Scheme 1a). This two-step process provides valuable odd-numbered carbon olefins from readily available deven-numbered carbon olefins.[14c] A two-carbon dehomologation of olefins can be achieved by combining olefin dihydroxylation and oxidative dehydroxymethylation. For example, we found that 1-dodecene **6** could be transformed to 1-decene **2v** (Scheme 1a).[15] The transformation occurs efficiently with molecules that are more structurally complex (Scheme 1b). Benzyl protected deoxycholic acid derivative **8a** gave olefin **9a** (81% yield), with no debenzylation. We probed chemoselectivity by using triol **8b**, with alcohols bearing different steric bulk. We observed oxidation-dehydroformylation of the primary alcohol and selective oxidation of the less hindered secondary alcohol to afford **9b** (66% yield). Diol **8c** underwent oxidative dehydroxymethylation and secondary alcohol oxidation to access (+)-yohimbenone **9c**. Based on this result, we improved our previous synthesis of (+)-yohimbenone **9c** by shortening the sequence to two steps.[5a, 16]

While further studies are warranted, on the basis of literature reports[2,5,6,11,17] and our own observations, we propose the following pathway (Scheme 3). Exchange between the benzoate counterion in Rh-complex **A** and an alcohol affords **B**. Intermediate **B** undergoes β-hydride elimination to give Rh-hydride **C**. Coordination of DMAA to **C** generates intermediate **D**. Hydrometallation of DMAA followed by protodemetalation provides the aldehyde and regenerates complex **A**. Oxidative addition into the aldehyde C–H bond by **A** generates acyl-Rh-hydride **F**. Reductive elimination of 3-methoxybenzoic acid generates acyl-Rh **G**. CO deinsertion to **H**, followed by β-hydride elimination, yields Rh-hydrido-carbonyl **I**. Olefin exchange with DMAA generates Rh-hydride **J**. Hydrometallation of DMAA gives complex **K**, and CO is extruded to make **L**. Finally, protodemetalation regenerates complex **A**.

To support the proposed mechanism, control experiments and deuterium-labeling experiments were carried out. Under standard conditions, neopentylic alcohol **1w** oxidizes to aldehyde **10** in 90% yield (Scheme 4a). Incorporation of a quaternary carbon alpha to the carbonyl suppressed dehydroformylation. These results support the intermediacy of an

aldehyde in the catalytic cycle. Of note, aldehyde **11** undergoes dehydroformylation under standard conditions (Scheme 4b), showing similar reactivity to our previous report,[5a] but with a more economical acceptor (i.e., norbornadiene vs DMAA). Replacing the benzoate counterion with chloride suppressed both oxidation and dehydroformylation (Scheme 4a and b). In the absence of DMAA, dehydrogenation of alcohol **1w** was not observed (Scheme 4a). In contrast, decarbonylation of aldehyde **11** gave ethyl benzene **3c** (78% yield, 5.5:1 **3c**:**2c**, Scheme 4b). These observations highlight the importance of both the benzoate counterion and DMAA. In support of the protonation of intermediate **E** (Scheme 3), we observed deuterium incorporation at the β-position of DMAA when using deuterated isopropanol **D-12** (Scheme 4c). Hydrogen-deuterium exchange is possible during dehydroformylation via the benzoate counterion acting as a proton shuttle (Scheme 4c and d).[5a]

Using competition experiments, we studied the chemoselectivity of this cascade (Scheme 2, see SI for details). Aldehydes undergo dehydroformylation in preference to primary alcohols undergoing oxidative dehydroxymethylation, with 60:1 selectivity. Primary alcohols oxidize faster than secondary and benzylic alcohols faster than aliphatic. These observations support that alcohol oxidation is the turnover limiting cycle in this novel cascade.

Established strategies for constructing olefins, including the Wittig olefination,[18] the Heck reaction,[19] and olefin metathesis,[20] generate carbon-carbon bonds. In contrast, our strategy contributes to emerging routes to olefins that involve C–C bond cleavage.[21] These methods represent examples of a one-carbon dehomologation of carbon frameworks and thus hold promise for various applications, including the conversion of biomass into feedstocks.[22] Moreover, such transformations increase retrosynthetic flexibility by allowing the interconversion of two common functional groups.[14]

ACKNOWLEDGMENT

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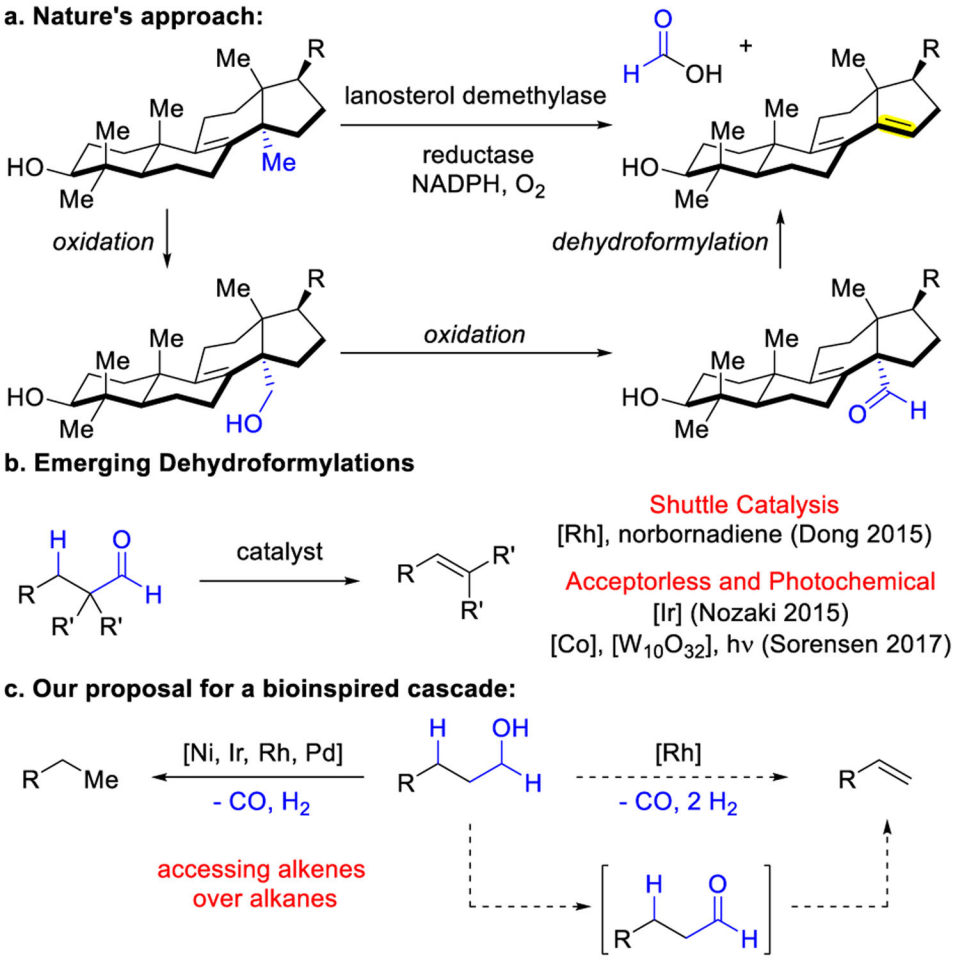
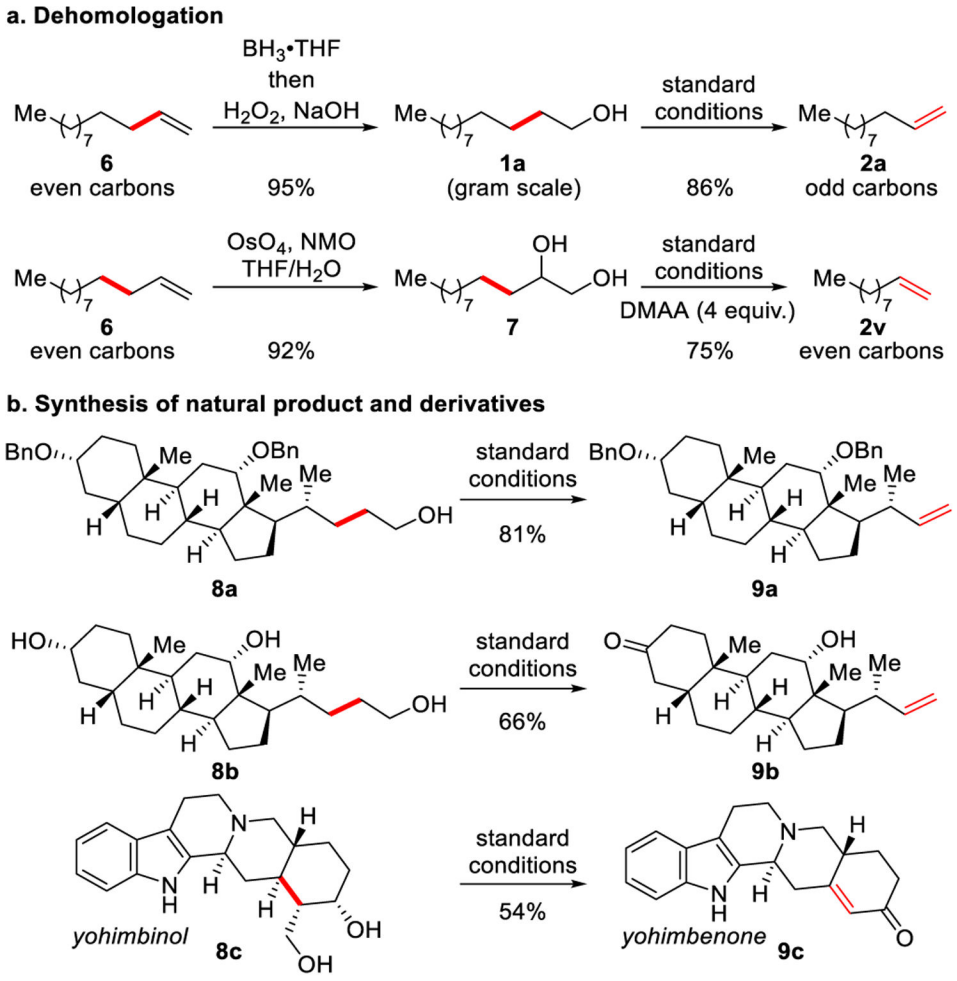
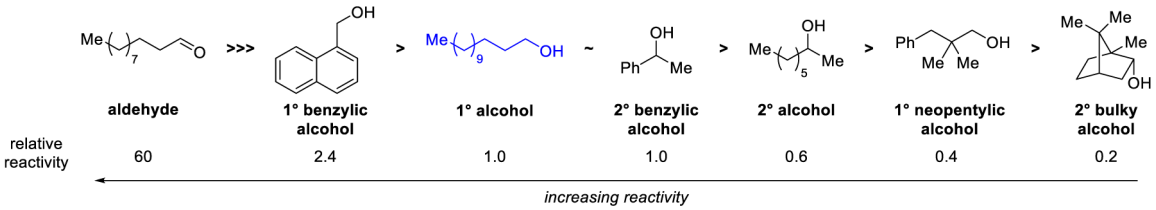


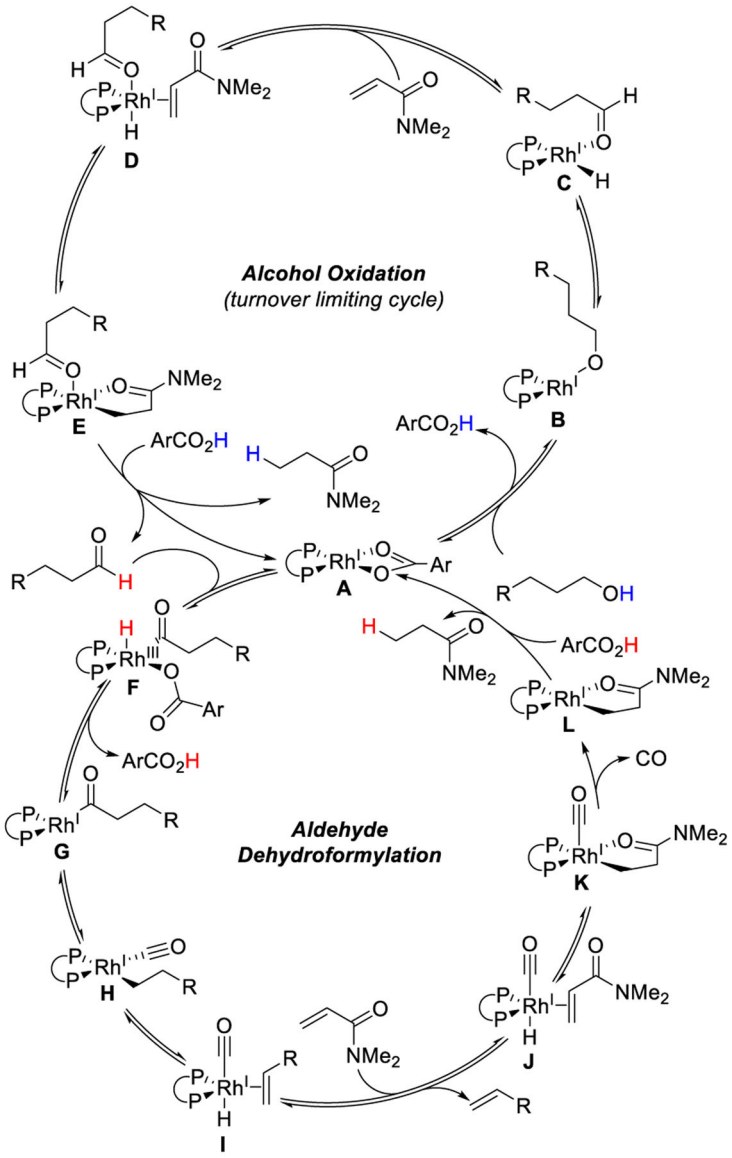
Figure 1.
Inspiration for proposed alcohol oxidative dehydroxymethylation.



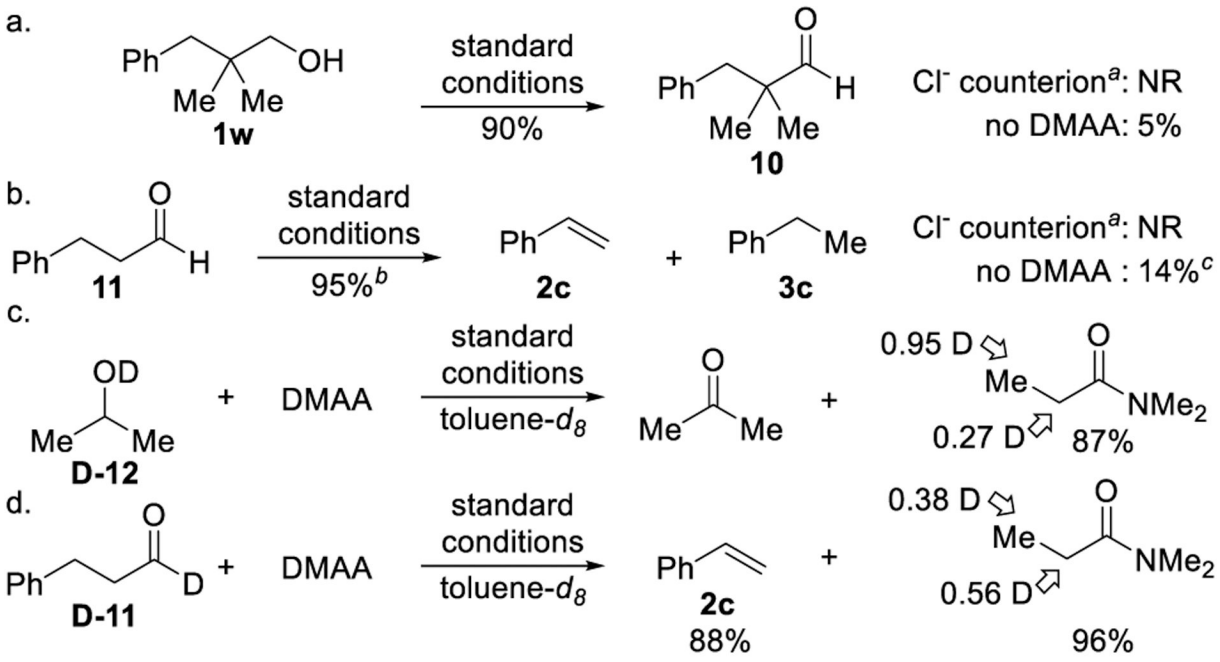
Scheme 1.
Synthetic Applications



Scheme 2.
Competition Experiments



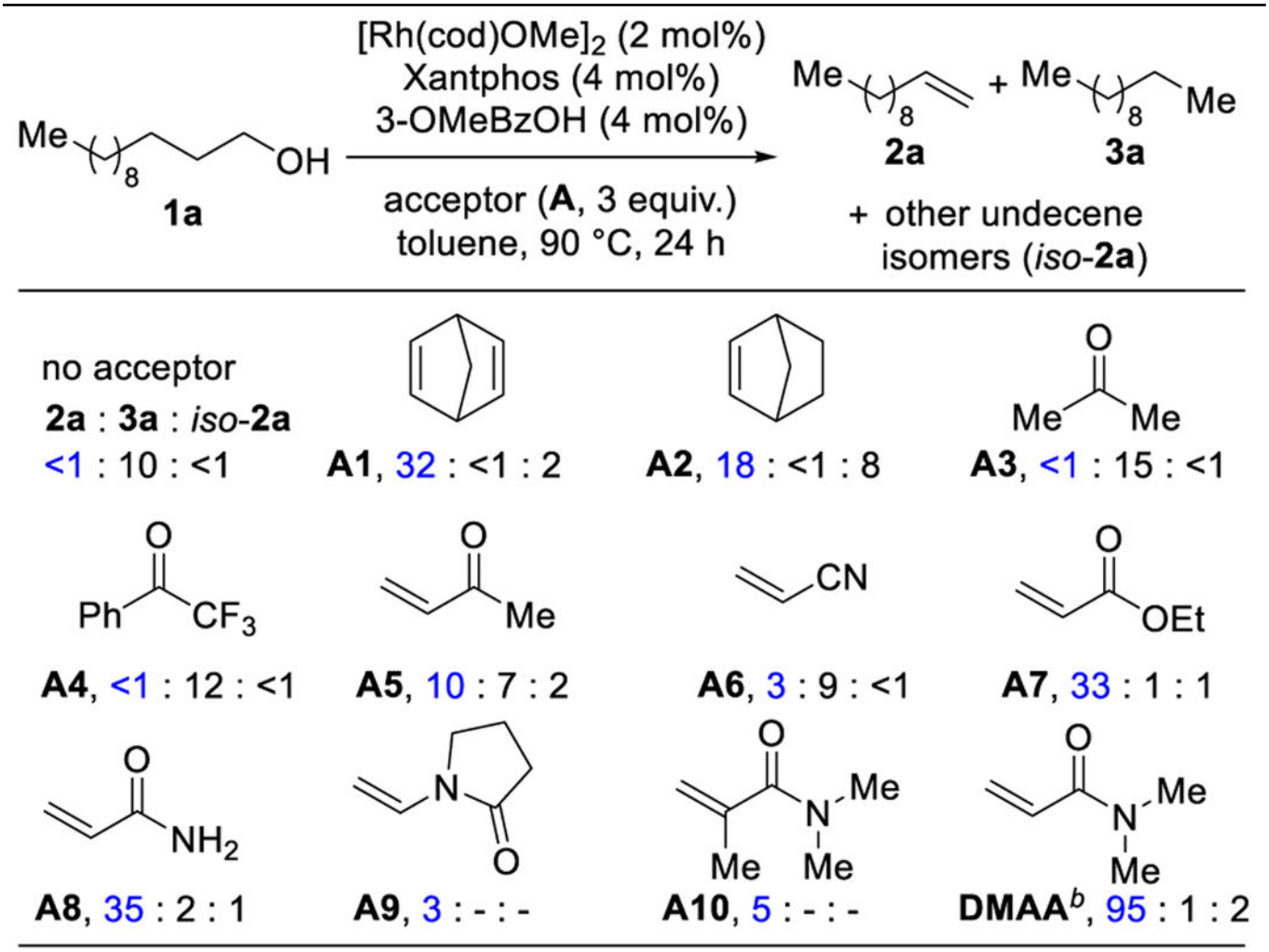
Scheme 3.
Proposed Mechanism



Scheme 4.
Probing the Mechanism.

Table 1.

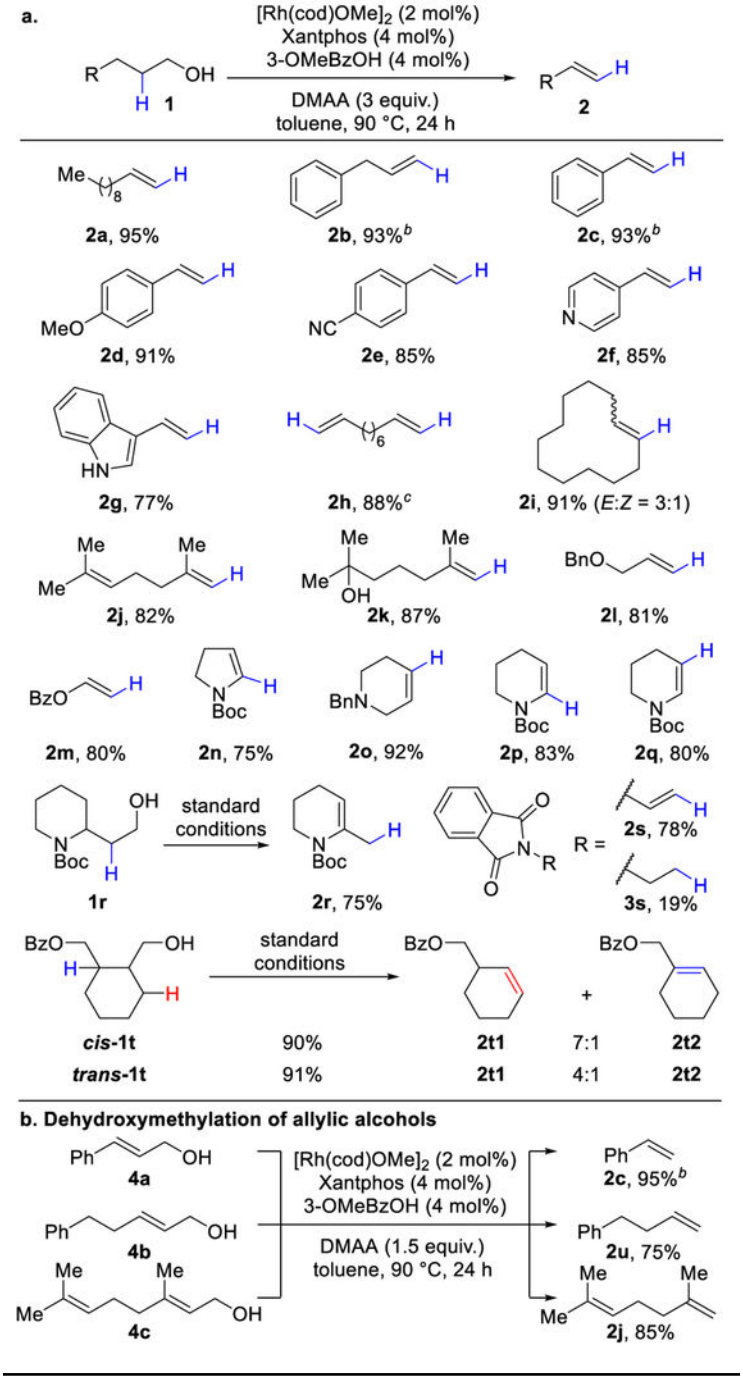
Effect of Acceptor on Selectivity for Oxidative Dehydroxymethylation[a]



[a]Conditions: **1a** (0.2 mmol), $[Rh(cod)OMe]_2$ (2 mol%), 3-OMeBzOH (4 mol%), Xantphos (4 mol%) and acceptor (3 equiv.) in toluene (0.4 mL), 90 °C, 24 h. Yields were determined by GC using durene as an internal standard. [b]92% yield of CO by GC-TCD.

Table 2.

Oxidative Dehydroxymethylation of Alcohols[a]



[a]Conditions: **1** (0.2 mmol), [Rh(cod)OMe]2 (2 mol%), 3-OMeBzOH (4 mol%), Xantphos (4 mol%) and DMAA (3 equiv.) in toluene (0.4 mL), 90 °C, 24 h. Isolated yields. [b]GC yields using durene as an internal standard. [c]DMAA (6 equiv.) used.