Communication

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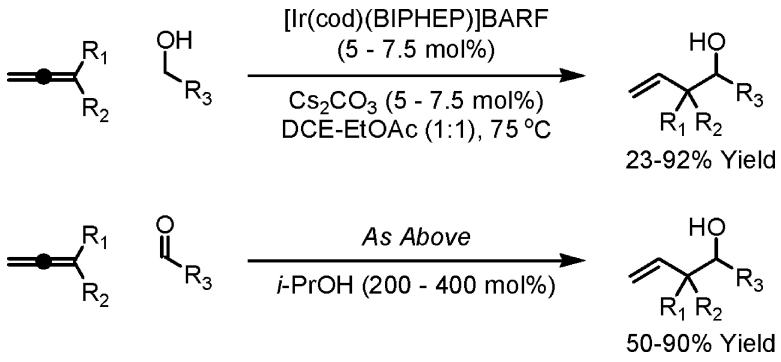

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Catalytic C−C Coupling via Transfer Hydrogenation: Reverse Prenylation, Crotylation, and Allylation from the Alcohol or Aldehyde Oxidation Level

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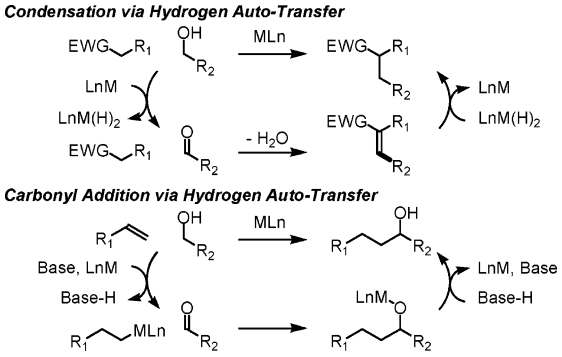
As first demonstrated by Guerbet (1908),[1,2] hydrogen autotransfer processes[3] allow diverse nucleophiles (ketones,[4] nitriles,[5] activated methylene compounds,[6] and stabilized Wittig reagents)[7] to be alkylated by alcohols. To date, all reported hydrogen autotransfer processes involve three fundamental steps: (a) alcohol dehydrogenation provides an aldehyde, which (b) undergoes condensation or olefination to furnish an unsaturated adduct, which (c) hydrogenates to deliver the saturated product. Such oxidation−condensation−reduction processes do not produce alcohol containing products of carbonyl addition. A related class of hydrogen autotransfer processes potentially involves hydrogen exchange between alcohols and π-unsaturated reactants to generate nucleophile−electrophile pairs. This approach would enable byproduct-free carbonyl addition from the alcohol oxidation state.

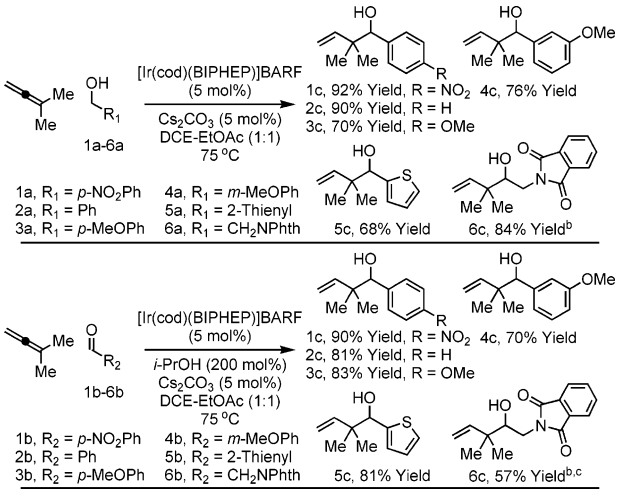


We have developed a class of reductive C−C couplings that employ elemental hydrogen as the terminal reductant.[8] These transformations offer a byproduct-free alternative to stoichiometrically preformed organometallic reagents in a diverse assortment of C=X (X = O, NR) addition processes.[9] Most recently, we found that hydrogenation of 1,1-dimethylallene in the presence of carbonyl electrophiles delivers products of carbonyl allylation, specifically, products of reverse prenylation.[10,11] However, attempted crotylation and allylation under conditions employing gaseous hydrogen as the terminal reductant were foiled by over-reduction of the olefinic adduct.

Here, we report that carbonyl allylation can be achieved directly from the alcohol oxidation state through alcohol−allene hydrogen autotransfer. This method represents a direct, byproduct-free protocol for carbonyl allylation and, to our knowledge, is the first metal-catalyzed transfer hydrogenation to furnish products of carbonyl addition. Additionally, we disclose that isopropanol may be used as a terminal reductant in aldehyde−allene reductive C−C couplings under transfer hydrogenation conditions. Both protocols circumvent over-reduction of the product, allowing reverse prenylation, crotylation, and allylation to be achieved from the alcohol or aldehyde oxidation state in the absence of preformed allyl metal reagents.[11−14]

To probe the feasibility of allylation by way of alcohol−allene hydrogen autotransfer, a solution of dimethylallene and *p*-nitrobenzyl alcohol **1a** was exposed to our initially disclosed conditions for iridium catalyzed hydrogenative carbonyl allylation, but in the absence of gaseous hydrogen. Gratifyingly, the desired allylation product **1c** was observed and, upon further optimization, could be obtained in excellent yield. These conditions were applied to alcohols **1a**−**6a**. Good to excellent yields of the reverse prenylation products **1c**−**6c** were obtained (Table 1, top). The efficiency of these hydrogen autotransfer processes suggested the feasibility of related C−C couplings under the conditions of transfer hydrogenation. Accordingly, solutions of dimethylallene and aldehydes **1b**−**6b** were exposed to standard reaction conditions, but in the presence of isopropanol (200 mol %). Remarkably, the very same adducts **1c**−**6c** were obtained in comparable yield (Table 1, bottom). Notably, adducts **1c**−**6c** also were prepared previously via hydrogenative coupling, meaning that reverse prenylation can be achieved under three alternate conditions: hydrogenative coupling, hydrogen autotransfer, and transfer hydrogenation. Unactivated aliphatic alcohols or aldehydes do not couple efficiently under these conditions.

Table 1. Reverse Prenylation via Iridium-Catalyzed Hydrogen Autotransfer and Transfer Hydrogenation[a]



[a] Cited yields are of isolated material. Standard conditions employ 1 equiv of alcohol/aldehyde and 4 equiv of allene. See Supporting Information for detailed experimental procedures. [b] For **6a** and **6b**, 10 mol % of precatalyst and base were used. [c] Reaction run using 4 equiv IPA and 8 equiv of allene.

To assess scope, methylallene was exposed to alcohols **1a**, **2a**, and **3a** under standard conditions for C−C coupling via hydrogen autotransfer. The products of crotylation **1d**, **2d**, and **3d** were obtained in 82%, 69%, and 72% yields, respectively (Table 2). Similarly, using methylallene, aldehydes **1b**, **2b**, and **3b** are converted to the very same products of crotylation **1d**, **2d**, and **3d** in 83%, 77%, and 79% yields, respectively, under standard conditions for isopropanol-mediated transfer hydrogenation. Finally, allylations of alcohol **1a** or aldehyde **1b** are achieved using allene to provide **1e** in 23% and 50% yields under autotransfer of transfer hydrogenation conditions, respectively. Diminished efficiency may be due the presence of propyne, an impurity found in commercial allene gas.

A series of experiments reveal key features of the catalytic mechanism. Coupling of dimethylallene to *deuterio*-**2a** under

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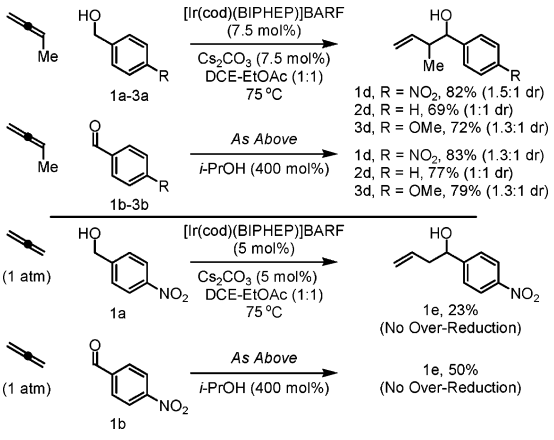
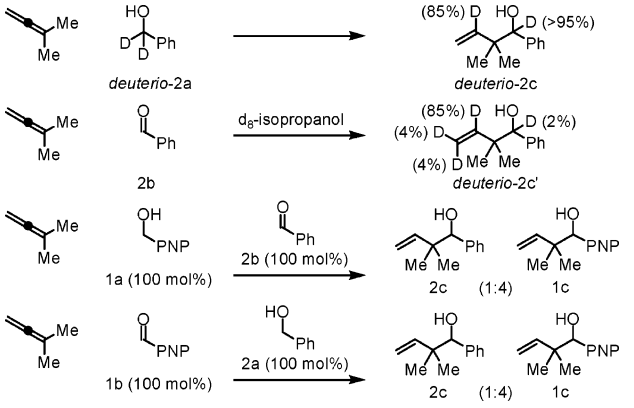
Table 2. Crotylation and Allylation via Iridium-Catalyzed Hydrogen Autotransfer and Transfer Hydrogenation[a]



[a] Cited yields are of isolated material; 1 equiv of alcohol or aldehyde and 4 equiv of methylallene were used.

Table 3. Isotopic Labeling Studies and Competition Experiments[a]



[a] All reactions were performed under standard conditions cited in Table 1. PNP = *p*-nitrophenyl.

standard conditions provides *deuterio*-**2c**, which incorporates deuterium at the benzylic (>95%) and internal vinylic positions (85%) (Table 3). Coupling of dimethylallene to aldehyde **2b** under standard conditions using d_8-isopropanol as terminal reductant provides *deuterio*-**2c′**, which incorporates deuterium primarily at the internal vinylic position (85%). In this case, deuterium at the hydroxylic position exchanges out during chromatographic isolation of the product. Competition experiments involving exposure of dimethylallene to equimolar quantities of **1a** and **2b** under standard conditions provide **2c** and **1c** in 94% yield in a 1:4 ratio, respectively. An identical product distribution and yield is observed upon exposure of dimethylallene to equimolar quantities of **1b** and **2a** under standard conditions, suggesting rapid redox equilibration of alcohol and aldehyde partners in advance of C−C coupling. *Indeed, upon exposure of equimolar quantities of **1a** and **2b** or **1b** and **2a** to standard conditions in the absence of allene, an identical 4:1:1:4 mixture of **1a**, **1b**, **2a**, and **2b**, respectively, is formed.*

The ability to achieve carbonyl addition directly from the alcohol oxidation level circumvents the redox manipulations so often required to convert alcohols to aldehydes. Further, through hydrogen autotransfer, there resides the potential to develop myriad byproduct-free carbonyl additions, wherein alcohols and π-unsaturated compounds are exploited as coupling partners.

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

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