Letter

# Catalytic Tandem and One-pot Dehydrogenation-alkylation and -insertion Reac-tions of Saturated Hydrocarbons with Alcohols and Alkenes

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# Catalytic Tandem and One-pot Dehydrogenation-alkylation and -insertion Reactions of Saturated Hydrocarbons with Alcohols and Alkenes

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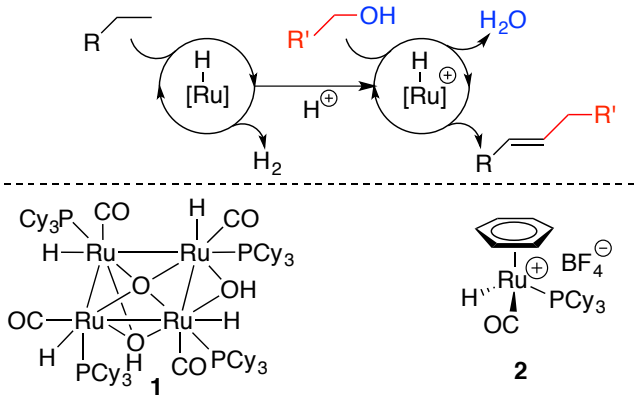
**ABSTRACT:** The ruthenium-hydride catalyst has been successfully used for the tandem *sp*³ C–H dehydrogenation-alkylation reaction of saturated hydrocarbon substrates with alcohols to form the alkyl-substituted alkene and arene products. The analogous one-pot dehydrogenation-insertion of saturated ketones with alkenes and dienes directly yielded synthetically useful 2-alkylphenol and benzopyran products in a highly regio- and stereoselective manner without forming any wasteful byproducts.

Keywords: tandem catalysis, dehydrogenation, alkylation, saturated hydrocarbon, ruthenium catalyst

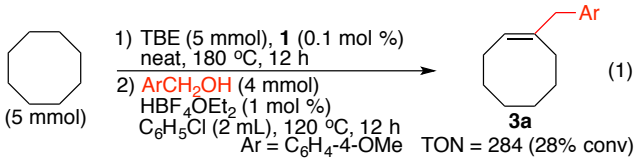
Transition metal catalyzed *sp*³ C–H bond activation and functionalization reactions of saturated hydrocarbon compounds have been regarded as one of the frontier topics in the field of homogeneous catalysis.[1] During the last decades, concerted research efforts have led to the development of many catalytic *sp*³ C–H coupling methods, and of these, heteroatom assisted *sp*³ C–H activation methods have been shown to be one the most effective strategy in promoting regioselective C–C coupling reactions for saturated hydrocarbons.[2] Soluble transition metal catalysts have also been successfully employed for the *sp*³ C–H oxidative cross coupling reactions of saturated hydrocarbons with heteroatom neighboring group.[3] Chiral Rh catalysts have been extensively used for highly asymmetric *sp*² and *sp*³ C–H carbene insertion reactions,[4] and its synthetic power has been recently demonstrated for a remarkably enantioselective carbene insertion of simple linear alkanes.[5] Bidentate sulfoxide ligands have been found to be particularly effective for late transition metal catalysts in promoting *sp*³ C–H coupling of biologically active complex organic molecules.[6]

Tandem dehydrogenation and functionalization protocol has emerged as an attractive strategy for the C–H coupling reactions.[7] Over the years, a number of different tandem *sp*² C–H coupling methods have been utilized for the construction of nitrogen and oxygen heterocycles.[8] In a pioneering report, Brookhart and Goldman devised an elegant "alkane metathesis" method, where Ir-hydride and Mo-carbene catalysts were used to promote tandem *sp*³ C–H dehydrogenation and olefin metathesis of alkanes.[9] More recently, Jones and Stahl independently reported the dehydrogenation of nitrogen heterocycles by using earthly abundant Fe and Co catalysts.[10] Compared to the *sp*² C–H coupling methods, however, a relatively few tandem *sp*³ C–H coupling methods have been implemented for the synthesis of complex organic molecules.[11]



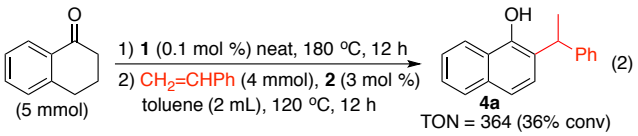

**Scheme 1. General Tandem Dehydrogenation-Alkylation Reaction Scheme and the Structure of Ruthenium Catalysts.**

We previously discovered that the tetranuclear ruthenium-hydride complex {[(PCy₃)(CO)RuH]₄(μ-O)(μ-OH)₂} (**1**) is a uniquely effective catalyst precursor for the dehydrogenation of saturated hydrocarbon substrates having a variety of oxygen and nitrogen functional groups.[12] We subsequently disclosed a number of dehydrative *sp*² C–H coupling reactions of alkenes and arenes with alcohols by using the cationic ruthenium-hydride complex [(C₆H₆)(PCy₃)(CO)RuH]⁺BF₄⁻ (**2**) as the catalyst precursor.[13] Since both dehydrogenation and dehydrative alkylation reactions are mediated by the similar ruthenium-hydride catalysts as the complex **2** is synthesized from the protonation of **1**, we reasoned that a direct *sp*³ C–H coupling of saturated hydrocarbon compounds might be achievable if we combine these two reactions in tandem as depicted in Scheme 1 to form elaborate olefins. Herein, we report an efficient tandem catalytic dehydrogenation-alkylation and –insertion protocol, which promotes the C–C coupling reactions on saturated hydrocarbon substrates.



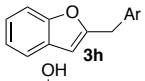
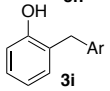
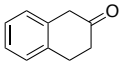
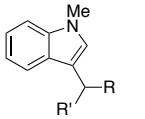
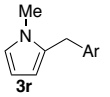
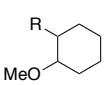
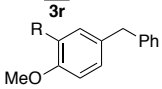

We initially tested the feasibility of tandem dehydrogenation-alkylation reaction of cyclooctane by using the tetranuclear ruthenium catalyst **1** (eq 1). The dehydrogenation of cyclooctane (5 mmol) was performed in the presence of **1** (0.1 mol %) under neat conditions at 180 °C for 12 h by following the previously reported procedure using *t*-butylethylene (TBE) (5 mmol) as the hydrogen scavenger.[12] For the second alkylation step, $HBF_4{\cdot}OEt_2$ (1 mol %) in chlorobenzene (2 mL) was added to the reaction mixture to generate a cationic Ru-H complex *in-situ*. After stirring at room temperature for 15 min, 4-methoxybenzyl alcohol (4 mmol) was added, and the reaction mixture was stirred at 120 °C for 12 h. The overall turnover number (TON) of product **3a** was determined to be 284 based on the consumption of cyclooctane substrate (28% conversion, >95% selectivity), as analyzed by both GC and NMR spectroscopic methods.

To demonstrate synthetic utility of the tandem catalytic dehydrogenation-alkylation reaction, we explored the scope of hydrocarbon substrates by using the catalyst **1** (Table 1). Aryl-substituted hydrocarbons such as indan and tetrahydronaphthalene readily reacted with both aliphatic and benzyl alcohols to form the alkylation products **3c-3g** (entries 3-7). The tandem dehydrogenation-alkylation of saturated cyclic ketones occurred predictively to give the *ortho*-alkylated phenol products **3i-3m** (entries 9-13). The tandem coupling of 2,3-dihydrobenzofuran led to the C2-alkylation product **3h** (entry 8), while the formation of exclusive C3-alkylation products **3n-3q** was obtained from the coupling with *N*-methylindole (entries 14-17). The tandem dehydrogenation-alkylation of *N*-methylpyrrolidine with benzyl alcohol afforded the 2-benzylpyrrole product **3r** (entry 18), and methoxy-substituted cyclohexane with benzyl alcohol gave 4-benzylanisole products **3s** and **3t** (entries 19, 20). The salient features for the tandem catalytic method from a synthetic point of view are: the C–C coupling products are directly formed from the dehydrogenation-alkylation of oxygen and nitrogen-containing saturated hydrocarbon substrates, a single Ru precatalyst is used to carry out both reaction steps, and the catalytic method does not generate any toxic byproducts as it employs inexpensive and widely available alcohols as the alkylating reagent.




To further extend its synthetic versatility, we next surveyed the tandem dehydrogenation-alkene insertion reaction of saturated hydrocarbon compounds. In this case, the choice of hydrocarbon substrates is limited to the ones that can undergo the dehydrogenation under the acceptorless conditions because TBE was found to react with the resulting naphthol during the insertion step. Initially, we have chosen 1-tetralone and styrene to optimize the reaction conditions (eq 2). Thus, the treatment of 1-tetralone (5 mmol) with **1** (0.1 mol %) at 180 °C under acceptorless conditions for 12 h led to the clean formation of 1-naphthol (TON = 640). For the second step, styrene (4 mmol) and the cationic Ru–H catalyst **2** (3 mol %) in toluene (2 mL) were added, and the reaction tube was stirred at 120 °C for 12 h. The insertion product **4a** was formed with an overall TON = 364 as analyzed by both GC and NMR spectroscopic methods. It should be noted that adding the Ru–H catalyst **2** for the insertion reaction was found to be essential in this case because the *in-situ* generation method of the cationic Ru–H catalyst by the addition of $HBF_4{\cdot}OEt_2$ was found to give a mixture of the styrene dimer $PhCH(CH_3)CH{=}CHPh$ and the coupling products.

**Table 1. Tandem Dehydrogenation-Alkylation of Saturated Hydrocarbons with Alcohols[a]**

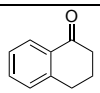
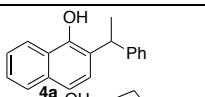
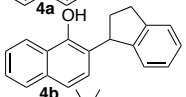
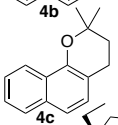
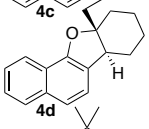
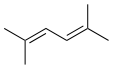
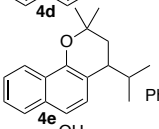
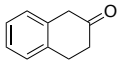
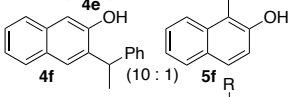
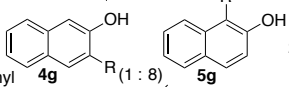
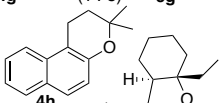
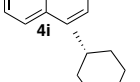
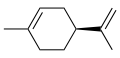
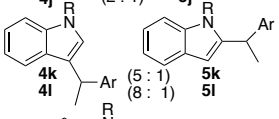
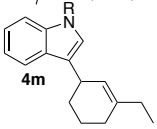
| entry | hydrocarbon | alcohol | product(s) | TON |
|---|---|---|---|---|
| 1 |  | Ar-$CH_2$OH | **3a** R = Ar | 284 |
| 2 | | $ArCH_2CH_2CH_2OH$ | **3b** R = $CH_2CH_2Ar$ | 182 |
| 3 |  | 1-hexanol | **3c** R = *n*-pentyl | 64 |
| 4 | | $PhCH_2OH$ | **3d** R = Ph | 98 |
| 5 | | Ar$CH_2$OH | **3e** R = Ar | 84 |
| 6 |  | $PhCH_2OH$ | **3f** R = Ph | 154 |
| 7 | | Ar$CH_2$OH | **3g** R = Ar | 86 |
| 8 |  | Ar$CH_2$OH |  **3h** | 280 |
| 9 |  | Ar-$CH_2$OH |  **3i** | 153[b] |
| 10 |  | 1-hexanol | **3j** R = *n*-pentyl, R' = H | 418[b,c] |
| 11 | | $PhCH(OH)CH_2CH_3$ | **3k** R = Ph, R' = Et | 439[c] |
| 12 |  | 1-pentanol | **3l** R = *n*-butyl | 142[b,c] |
| 13 | | $PhCH_2OH$ | **3m** R = Ph | 130[c] |
| 14 |  | Ar$CH_2$OH |  **3n** R = Ar, R' = H | 1410[b,d] |
| 15 | | 1-hexanol | **3o** R = *n*-pentyl, R' = H | 1080[b,d] |
| 16 | | $PhCH(OH)CH_2CH_3$ | **3p** R = Ph, R' = Et | 380[d] |
| 17 | | (-)-$PhCHMeCH_2OH$ | (-)-**3q** R = CHMePh, R' = H | 560[b,d] |
| 18 |  | Ar$CH_2$OH |  **3r** | 82 |
| 19 |  | $PhCH_2OH$ |  **3s** R = OMe | 84 |
| 20 | | | **3t** R = H | 78 |

[a] Reaction conditions. Dehydrogenation: hydrocarbon compound (5 mmol), TBE (5 mmol), **1** (0.1 mol %), 180 °C, 12 h. Alkylation: alcohol (4 mmol), $HBF_4{\cdot}OEt_2$ (1 mol %), $C_6H_5Cl$ (2 mL), 120 °C, 12 h. TON was

determined by GC. [b] **2** (3 mol %) was used for the alkylation step. [c] 200 °C. [d] **1** (0.05 mol %), 160 °C. Ar = $C_6H_4$-4-OMe

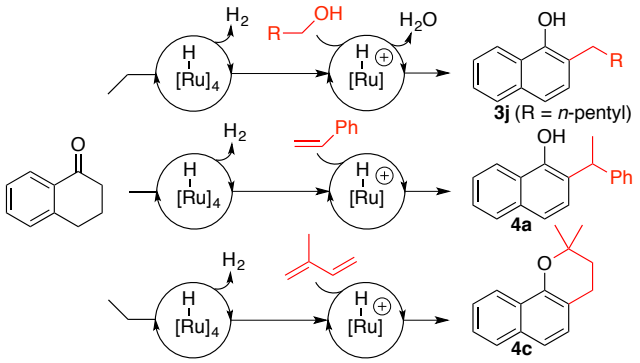
The one-pot dehydrogenation-insertion reaction scope was explored by using different alkenes and dienes under these optimized conditions (Table 2).[14] In general, both 1- and 2-tetralone substrates readily reacted with aryl-substituted alkenes to form the corresponding alkylation products **4a**, **4b**, **4f** and **4g** (entries 1, 2, 6, 7). In case of indoline, a preferential formation of C3-alkylation products **4k** and **4l** was observed over the C2-alkylation products **5k** and **5l** (entries 11, 12). The dehydrogenation-insertion of 1- and 2-tetralone with 1,3-dienes also proceeded smoothly to give the corresponding benzopyran products **4c**, **4e** and **4h** (entries 3, 5, 8).

**Table 2. Tandem Dehydrogenation-Alkylation and Annulation of Saturated Hydrocarbons with Alkenes and Dienes[a]**

| entry | hydrocarbon | alkene/diene | product(s) | TON |
|---|---|---|---|---|
| 1 |  |  |  | 364 |
| 2 | |  |  | 328 |
| 3 | |  |  | 310 |
| 4 | |  |  | 284 |
| 5 | |  |  | 266 |
| 6 |  |  |  | 308 |
| 7 | |  R = 1-indanyl |  | 288 |
| 8 | |  |  | 260 |
| 9 | |  |  | 282 |
| 10 | |  |  | 242[b] |
| 11<br>12 |  R = H<br>R = Me |  Ar = Ph<br>Ar = *p*-Tol |  | 244[b]<br>210[b] |
| 13 | R = H |  |  | 430 |

[a] Reaction conditions. Dehydrogenation: hydrocarbon compound (5 mmol), **1** (0.1 mol %), 200 °C, 12 h. Insertion: alkene (4 mmol), **2** (3 mol %), toluene (2 mL), 120 °C, 12 h. TON was determined by GC. [b] At 180 °C.

The one-pot treatment of 1-teralone with vinylcyclohexene led to the stereoselective formation of a *trans*-fused benzofuran product **4d** (entry 4). The relative stereochemistry of **4d** has been tentatively assigned from the NMR spectroscopic analysis. The methine proton peak at δ 3.16 (pseudo quintet, $J$ = 3.2 Hz), which exhibited vicinal couplings with both neighboring $CH_2$ groups, is a diagnostic feature for the assigned *anti*-stereochemistry. We compared the $^1$H NMR of the methine peak of the previously reported *cis*-fused stereoisomer of benzofuran analog, which showed a simple triplet δ 3.09 (t, $J$ = 5.1 Hz), devoid of the coupling with the neighboring $CH_3$ group (p. S3, Supporting Information).[15] Since we have not been able to obtain the *cis*-stereoisomer of **4d** independently, we could not unambiguously determine the stereochemistry of **4d**. The coupling reaction of 2-tetralone with vinylcyclohexene and 1-methyl-4-(1-methylethenyl)cyclohexene also resulted in the coupling products **4i** and **4j** with the same relative stereochemistry (entries 9, 10). In contrast, the analogous reaction of indoline with vinylcyclohexene selectively gave the C3-alkylation product **4m** (entry 13). Traditional synthetic methods to hydrobenzofuran structures typically involve multiple manipulation steps,[16] but our catalytic method expediently assembles the structure in a stereoselective manner without using any reactive reagents.




**Scheme 2. Synthesis of Naphthol Derivatives from the One-Pot Dehydrogenation-Alkylation of 1-Tetralone with an Alcohol, Styrene and a 1,3-Diene.**

In summary, we successfully developed a highly regio- and stereoselective catalytic tandem and one-pot dehydrogenation-alkylation and -insertion protocol to achieve $sp^3$ C–H couplings of oxygen and nitrogen containing saturated hydrocarbons.[16] As illustrated in Scheme 2, the one-pot dehydrogenation-alkylation reaction of tetralones with alcohols and styrene furnishes a number of synthetically useful naphthol derivatives with a high degree of efficiency. The dehydrogenation-insertion of tetralones with 1,3-dienes directly led to the formation of benzopyran and benzofuran products. The tandem catalytic method also validates a number of environmentally attractive features in that it does not employ any reactive reagents or forms any toxic byproducts. Efforts to extend the scope and synthetic utility of the catalytic method are continuing in our laboratory.

## ASSOCIATED CONTENT

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedure and NMR spectral data (PDF)

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**Notes**

The authors declare no competing financial interest.

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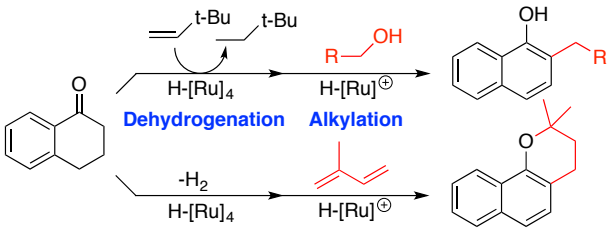


* Exhibit high efficiency and selectivity for direct $sp^3$ C-H coupling
* Tolerate oxygen and nitrogen functional groups
* Do not form any toxic byproducts