

Ruthenium Catalyzed Hydrohydroxyalkylation of Isoprene with Heteroaromatic Secondary Alcohols: Isolation and Reversible Formation of the Putative Metallacycle Intermediate

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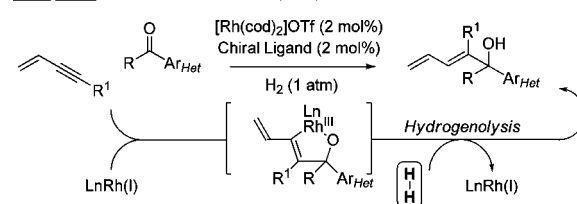
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S Supporting Information

ABSTRACT: Heteroaromatic secondary alcohols react with isoprene to form products of hydrohydroxyalkylation in the presence of ruthenium(0) catalysts generated from $\text{Ru}_3(\text{CO})_{12}$ and tricyclohexylphosphine, enabling direct conversion of secondary to tertiary alcohols in the absence of premetallated reagents or stoichiometric byproducts. The putative oxaruthenacycle intermediate has been isolated and characterized, and reversible metallacycle formation has been demonstrated.

Nitrogen-bearing heterocycles are ubiquitous substructures in active pharmaceutical ingredients,¹ with pyridines appearing most frequently.² While numerous methods exist for functionalization of the heteroaromatic nucleus through metal catalyzed cross-coupling or related C-H activation initiated processes,³ metal catalyzed C-C couplings that exploit the LUMO-lowering effect of pyridines and higher azines to enable functionalization of extranuclear substituents are less common. Selected examples include the rhodium catalyzed addition of organoboron reagents to 2-vinyl azines⁴ and 2-alkynyl azines⁵ as well as reductive aldol and Mannich type couplings of 2-vinyl azines.⁶ In rhodium(I) catalyzed hydrogenative C-C couplings developed in our laboratory,⁷ the LUMO-lowering effect of pyridines, which is amplified by their capacity for chelation, was essential in promoting alkyne-carbonyl oxidative coupling pathways. Indeed, formation of the transient oxarhodacyclopentene may be viewed as a rhodium(I) mediated reduction across the alkyne and carbonyl functional groups (Figure 1, top). In more recent work from our laboratory, a ruthenium(0) catalyst was identified that promotes analogous transfer hydrogenative C-C couplings, in which α -hydroxy esters or 1,2-diols engage in oxidative coupling to dienes by way of transient α -ketoesters or 1,2-diones, respectively.^{8,9} The structural homology between vicinal dicarbonyl compounds and certain heteroaromatic ketones suggested the feasibility of engaging heteroaromatic secondary alcohols in ruthenium(0) catalyzed diene hydrohydroxyalkylation. Here, we report that diverse heteroaromatic secondary alcohols engage in C-C coupling to dienes in the presence of the ruthenium(0) catalyst generated from $\text{Ru}_3(\text{CO})_{12}$ and tricyclohexylphosphine, PCy_3 , enabling direct conversion of secondary to tertiary alcohols. Further, the putative oxaruthenacycle intermediate has been isolated and characterized by single crystal X-ray diffraction,¹ ^1H and ^{13}C NMR and IR spectroscopy, and reversible metallacycle

Prior Work: *J. Am. Chem. Soc.* **2006**, *128*, 16448



This Work

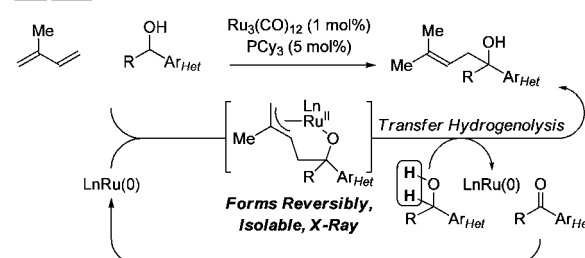


Figure 1. LUMO-lowering effect of aromatic heterocycles promotes oxidative coupling pathways in catalytic hydrogenative and transfer hydrogenative C-C coupling.

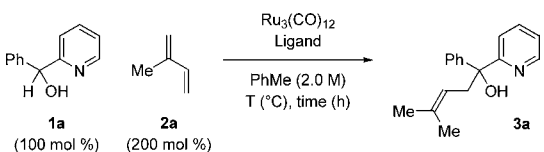
formation has been demonstrated through exchange experiments (Figure 1, bottom).

The prospect of adapting conditions previously developed for diene hydrohydroxyalkylation employing aryl substituted α -hydroxy esters⁸ to corresponding reactions of heteroaryl substituted secondary alcohols was rendered uncertain by the typically strong chelation of pyridyl ligands to ruthenium. That is, the catalytic intermediates or reaction products may bind ruthenium so strongly as to inhibit turnover. Despite this concern, conditions for highly efficient hydrohydroxyalkylation were eventually identified (Table 1). Specifically, exposure of phenyl-(2-pyridyl)-methanol **1a** to isoprene **2a** in the presence of $\text{Ru}_3(\text{CO})_{12}$ and PCy_3 in toluene solvent at 130 °C provided the product of diene hydrohydroxyalkylation **3a** in 90% isolated yield as a single regioisomer (Table 1, entry 13). As contamination of PCy_3 with the phosphine oxide contributed to variation in yield, crystallization of commercial PCy_3 from ethanol under an atmosphere of argon was necessary to ensure for consistent results. Notwithstanding this caveat, these conditions for ruthenium(0) catalyzed hydrohydroxyalkylation could be applied across a diverse range of substituted-(2-

Received: August 29, 2013

Published: October 24, 2013

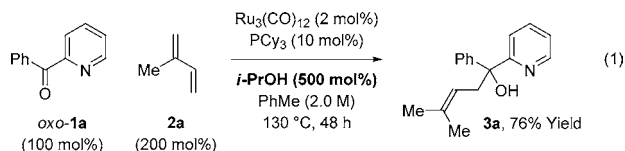
Table 1. Selected Optimization Experiments in the Ruthenium(0) Catalyzed Hydrohydroxyalkylation of Isoprene 2a Employing Phenyl-(2-pyridyl)-methanol 1a^a



entry	Ru ₃ (CO) ₁₂ (mol %)	ligand (mol %)	T (°C)	time (h)	yield 3a
1	2.0	—	130	24	49%
2	2.0	bipy (6.0)	130	24	52%
3	2.0	terpy (6.0)	130	24	50%
4	2.0	phen (6.0)	130	24	45%
5	2.0	PCy ₃ (12.0)	130	24	85%
6	2.0	PCy ₃ (12.0)	140	24	75%
7	2.0	PCy ₃ (12.0)	120	24	50%
8	2.0	PCy ₃ (10.0)	130	24	90%
9	2.0	PCy ₃ (8.0)	130	24	87%
10	2.0	PCy ₃ (6.0)	130	24	76%
11	2.0	PCy ₃ (4.0)	130	24	72%
12	1.0	PCy ₃ (5.0)	130	24	91%
13	1.0	PCy ₃ (5.0)	130	18	90%
14	1.0	PCy ₃ (5.0)	130	12	81%
15	0.5	PCy ₃ (2.5)	130	24	75%
16	0.5	PCy ₃ (2.5)	130	48	88%
17	0.25	PCy ₃ (1.25)	130	24	42%
18	0.25	PCy ₃ (1.25)	130	48	84%

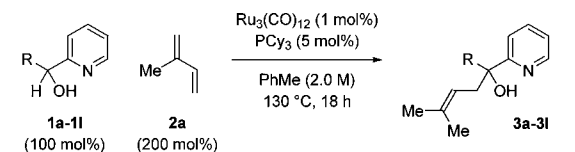
^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

pyridyl)-methanols **1a–1l** (Table 2). This includes electro-neutral (**1a**), electron-deficient (**1b–1e**) and electron-rich (**1f**, **1g**) aryl-(2-pyridyl)-methanols as well as heteroaryl-(2-pyridyl)-methanols (**1h**, **1i**) and alkyl-(2-pyridyl)-methanols (**1j–1l**). Beyond the 2-pyridyl group, it was found that other heteroaryl substituted benzyl alcohols engage in efficient diene hydrohydroxyalkylation, as illustrated in reactions of the indicated pyrimidine, benzoxazole, and thiazole containing secondary alcohols **1m–1o**, respectively (Table 3). It was also found that the products of C-C coupling are accessible via ketone-diene reductive coupling employing isopropanol as terminal reductant, as demonstrated in the conversion of *oxo-1a* to tertiary alcohol **3a** (eq 1).

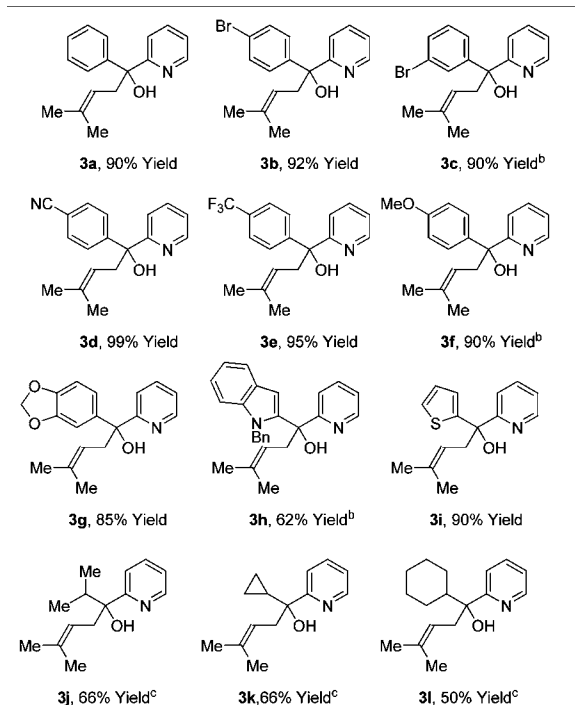


Based on our prior studies of the ruthenium(0) catalyzed hydrohydroxyalkylation of dienes employing α -hydroxy esters,⁸ a catalytic mechanism involving diene-carbonyl oxidative coupling was proposed (Scheme 1). A discrete monometallic ruthenium(0) complex should be formed from the combination of Ru₃(CO)₁₂ and tricyclohexylphosphine.¹⁰ To initiate oxidative coupling pathways, phenyl-(2-pyridyl)-methanol **1a** must oxidize to form 2-benzoylpyridine *oxo-1a*. Such Ru₃(CO)₁₂ catalyzed alcohol oxidations employing olefins and alkynes as hydrogen acceptors are known,¹¹ as are related Ru₃(CO)₁₂ catalyzed transfer hydrogenations of ketones¹² and aminations of secondary alcohols, which proceed by way of

Table 2. Direct Conversion of Secondary Alcohols 1a–1l to Tertiary Alcohols 3a–3l via Ruthenium(0) Catalyzed Hydrohydroxyalkylation of Isoprene 2a^a

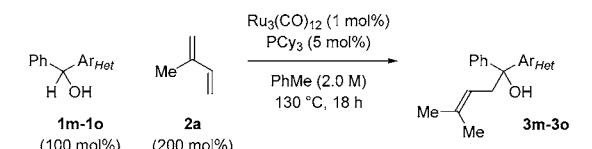


1a, R = Ph	1b, R = 4-Br-Ph	1c, R = 3-Br-Ph
1d, R = 4-CN-Ph	1e, R = 4-CF ₃ -Ph	1f, R = 4-OMe-Ph
1g, R = 1,3-benzodioxole	1h, R = 2-(N-Bn-indolyl)	1i, R = 2-thienyl
1j, R = <i>i</i> -propyl	1k, R = <i>c</i> -propyl	1l, R = <i>c</i> -hexyl



^aYields are of material isolated by silica gel chromatography. ^bRu₃(CO)₁₂ (2 mol %), PCy₃ (10 mol %), 24 h. ^cRu₃(CO)₁₂ (2 mol %), PCy₃ (10 mol %), 48 h. See Supporting Information for further details.

Table 3. Direct Conversion of Secondary Alcohols 1m–1o to Tertiary Alcohols 3m–3o via Ruthenium(0) Catalyzed Hydrohydroxyalkylation of Isoprene 2a^a

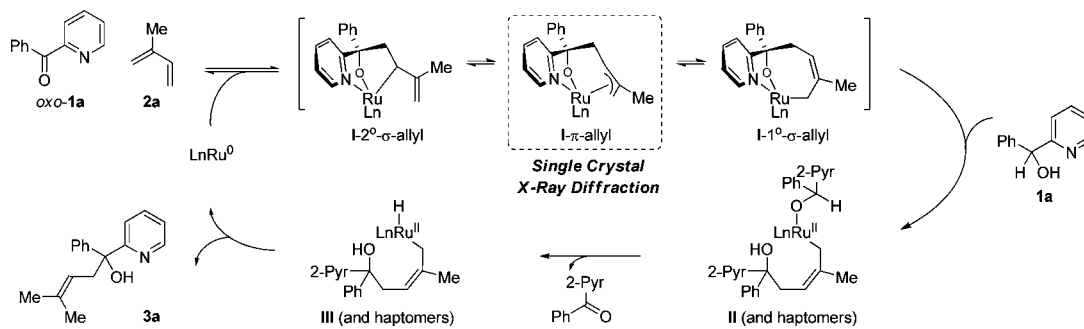


1m, R = 2-pyrimidyl	1n, R = 2-benzoxazolyl	1o, R = 2-thiazolyl
91% Yield, 3m ^b	88% Yield, 3n ^c	86% Yield, 3o

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details. ^b120 °C. ^cRu₃(CO)₁₂ (2 mol %), PCy₃ (10 mol %), 24 h.

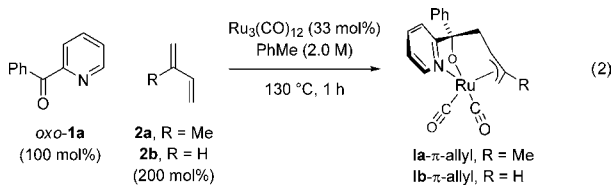
transient ketones.¹³ Diene-carbonyl oxidative coupling¹⁴ involving 2-benzoylpyridine *oxo-1a* and isoprene **2a** delivers

Scheme 1. Postulated Catalytic Mechanism Involving Diene-Carbonyl Oxidative Coupling



secondary σ -allyl oxaruthenacycle **I**, which exists in equilibrium with the indicated haptomers. Related oxidative couplings mediated by ruthenium(0) complexes derived from $\text{Ru}_3(\text{CO})_{12}$ find precedent in Pauson-Khand-type reactions of 1,2-diones and alkenes, as described by Chatani and Murai.¹⁵ The proposed diene-carbonyl oxidative coupling pathway also finds precedent in our prior studies on the prenylation of α -hydroxy esters.^{8a} Protonation of the primary σ -allyl oxaruthenacycle **I** by phenyl-(2-pyridyl)-methanol **1a** delivers the ruthenium alkoxide **II**, which suffers β -hydride elimination to generate the ruthenium hydride **III** and 2-benzoylpyridine *oxo-1a*. Finally, C-H reductive elimination delivers the product of hydrohydroxyalkylation **3a** and the starting ruthenium(0) complex to complete the catalytic cycle. Reversible pyridine coordination is probable at the stage of each catalytic intermediate.¹⁶

To corroborate the proposed mechanism, an attempt to isolate the allyl-oxaruthenacycle **I** was made. Toward this end, $\text{Ru}_3(\text{CO})_{12}$ (33 mol %), 2-benzoylpyridine *oxo-1a* (100 mol %), and isoprene **2a** (200 mol %) were combined in toluene and heated to 130 °C for 1 h (eq 2). After cooling, vapor-vapor



diffusion with pentane induced crystallization. To our delight, single crystal X-ray diffraction revealed the oxaruthenacycle **Ia- π -allyl** (Figure 2).¹⁴ In the crystal structure, there is a water molecule hydrogen-bonded to the alkoxide, suggestive of the protonation of **I-1°- σ -allyl** to form **II** (Scheme 1). This complex was relatively stable and could be isolated from the crude reaction by conventional silica gel chromatography, albeit with significant loss of material. In contrast, the oxaruthenacycle **Ib- π -allyl**, prepared from butadiene **2b**, was significantly more robust and could be isolated by silica gel chromatography in 42% yield. To corroborate the catalytic competence of these oxaruthenacycles, phenyl-(2-pyridyl)-methanol **1a** was exposed to isoprene **2a** in the presence of **Ib- π -allyl** (6 mol %) and PCy_3 (10 mol %). The product of hydrohydroxyalkylation **3a** was isolated in 77% yield (eq 3).

Although complexes **Ia- π -allyl** and **Ib- π -allyl** could exist as diastereomeric mixtures, especially given the fluxional nature of such π -allyls, a single stereoisomer is observed by ¹H and ¹³C NMR. This fact facilitated exchange experiments aimed at probing the reversibility of oxaruthenacycle formation.¹⁴ Upon

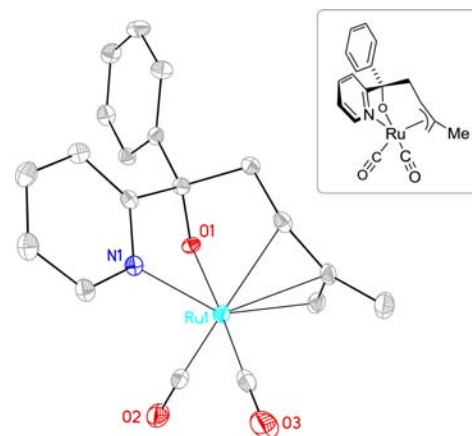


Figure 2. Single crystal X-ray diffraction data of the oxaruthenacycle **Ia- π -allyl** derived from $\text{Ru}_3(\text{CO})_{12}$, 2-benzoylpyridine *oxo-1a*, and isoprene **2a**. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms have been omitted for clarity.

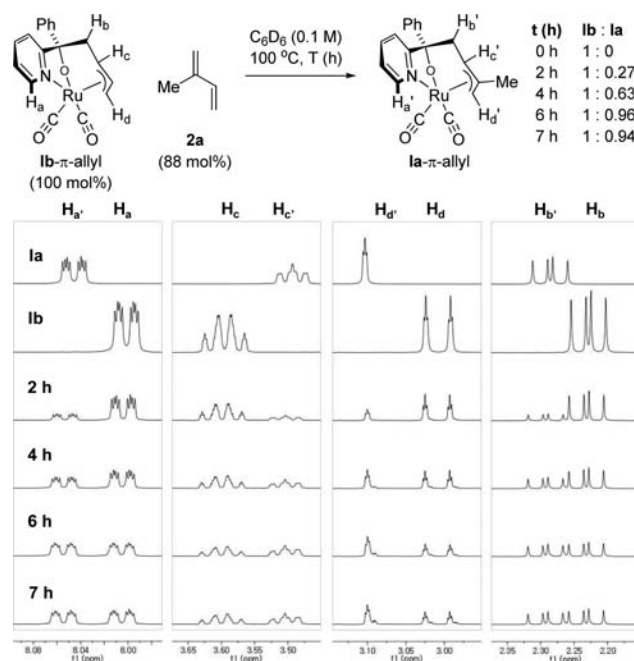
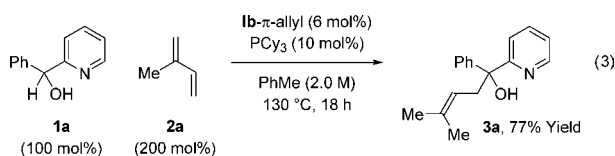


Figure 3. Conversion of **Ib- π -allyl** to **Ia- π -allyl** corroborates reversible formation of the oxaruthenacycle intermediate.

exposure of **Ib- π -allyl** (100 mol %) to isoprene **2a** (88 mol %) in benzene-*d*₆ at 100 °C, the gradual formation of **Ia- π -allyl** could clearly be observed by ¹H NMR (Figure 3). After 6 h, no



further conversion was observed suggesting equilibrium was established. These data suggest that the development of enantioselective variants of this process may require especially high kinetic stereoselectivities to offset erosion of enantiomeric excess stemming from reversible C-C bond formation. Studies aimed at probing this question are ongoing and will be reported in due course.

In summary, we report the ruthenium(0) catalyzed hydrohydroxyalkylation of dienes with heteroaryl substituted secondary alcohols. This process enables direct conversion of secondary to tertiary alcohols in the absence of stoichiometric byproducts or premetallated reagents. The oxaruthenacycle postulated as a key intermediate has, for the first time, been isolated and characterized. Furthermore, its reversible formation has been demonstrated through exchange experiments. These studies provide deeper insight into the structural-interactive features of the catalytic system, which will accelerate the development of improved catalysts for the hydrohydroxyalkylation of π -unsaturated reactants with alcohols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and 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 interest.

■ ACKNOWLEDGMENTS

The Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) are acknowledged for partial support of this research.

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(16) Under standard conditions, the 3- and 4-substituted constitutional isomers of phenyl-(2-pyridyl)-methanol **1a** dehydrogenate but do not participate in C-C coupling, suggesting that chelation, which amplifies the LUMO lowering effect of the pyridine, is a prerequisite to C-C coupling in transformations of this type.