

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

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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 Ru₃(CO)₁₂ and tricyclohexylphosphine, enabling direct conversion of secondary to tertiary alcohols in the absence of premetalated reagents or stoichiometric byproducts. The putative oxaruthenacycle intermediate has been isolated and characterized, and reversible metallacycle formation has been demonstrated.

N itrogen-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 Ru₃(CO)₁₂ and tricyclohexylphosphine, PCy₃, enabling direct conversion of secondary to tertiary alcohols. Further, the putative oxaruthenacycle intermediate has been isolated and characterized by single crystal X-ray diffraction, ¹H and ¹³C NMR and IR spectroscopy, and reversible metallacycle





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 $Ru_3(CO)_{12}$ and PCy₃ 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 PCy₃ with the phosphine oxide contributed to variation in yield, crystallization of commercial PCy₃ 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-

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Table 1. Selected Optimization Experiments in the	
Ruthenium(0) Catalyzed Hydrohydroxyalkylation of	
Isoprene 2a Employing Phenyl-(2-pyridyl)-methanol	1a ⁴

	Ph N Me Me 1a 2a (100 mol %) (200 mol %)	Ru ₃ (CO) ₁₂ Ligand PhMe (2.0 M) T (°C), time (h)	► Me−	Ph OH Me	N 3a
entry	$\operatorname{Ru}_{3}(\operatorname{CO})_{12} \pmod{\%}$	ligand (mol %)	$T(^{\circ}C)$	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%
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"Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

pyridyl)-methanols 1a-11 (Table 2). This includes electroneutral (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-11). 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-11 to Tertiary Alcohols 3a-31 via Ruthenium(0) Catalyzed Hydrohydroxyalkylation of Isoprene $2a^a$



^{*a*}Yields are of material isolated by silica gel chromatography. ^{*b*}Ru₃(CO)₁₂ (2 mol %), PCy₃ (10 mol %), 24 h. ^{*c*}Ru₃(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 $2a^a$



^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 $Ru_3(CO)_{12}$ 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, $Ru_3(CO)_{12}$ (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 PCy₃ (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 Ru₃(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 premetalated 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 structuralinteractional features of the catalytic system, which will accelerate the development of improved catalysts for the hydrohydroxyalkylation of π -unsaturated reactants with alcohols.

ASSOCIATED CONTENT

S 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.

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