Communications



Transfer Hydrogenation

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Regio- and Diastereoselective C–C Coupling of α -Olefins and Styrenes to 3-Hydroxy-2-oxindoles by Ru-Catalyzed Hydrohydroxyalkylation



The direct approach: Ruthenium(0)-catalyzed hydrohydroxyalkylation of α -olefins and styrenes with 3-hydroxy-2-oxindoles forms branched products of C–C coupling with high levels of diastereocontrol. A mechanism involving diene–olefin oxidative coupling and a subsequent carboxylic acid co-catalyzed transfer hydrogenolysis of the resulting oxaruthenacycle intermediate is postulated.

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Eiji Yamaguchi, Jeffrey Mowat, Tom Luong, and Michael J. Krische*

 α -Olefins are abundant petrochemical feedstocks used in the manufacture of diverse chemical products.^[1] Despite their commercial significance, intermolecular catalytic reductive C-C couplings of a-olefins to carbonyl compounds are unknown, withstanding the special case of hydroformylation.^[2-4] Motivated in part by the prospect of addressing this deficiency, our research group embarked upon a systematic exploration of hydrogen-mediated reductive couplings beyond hydroformylation.^[5] These efforts led to a broad family of catalytic C–C couplings wherein two or more π unsaturated reactants are hydrogenated to form a single, more complex product.^[5] Such transformations typically proceed through pathways involving metallacycle formation and hydrogenolysis (Scheme 1 a, top). Based on these studies, related C-C bond-forming transfer hydrogenations were developed, in which hydrogen transfer from alcohols to π unsaturated reactants through hydrometallation triggers generation of organometal-carbonyl pairs that combine to form products of addition (Scheme 1 a, bottom).^[5] In a more recent advance, a third pathway involving alcohol-mediated transfer hydrogenolysis of metallacycles was uncovered, as illustrated in couplings of a-hydroxy esters to isoprene or myrcene to form products of prenylation or geranylation, respectively, and related couplings of dienes to 3-hydroxy-2oxindoles (Scheme 1 b).^[6] The availability of this novel mechanistic pathway prompted a reinvestigation of the coupling of α -olefins. Herein, we report that the ruthenium(0) catalyst generated from [Ru₃(CO)₁₂] and tricyclohexylphosphine, PCy₃, promotes direct C-C coupling of α-olefins and styrenes to 3-hydroxy-2-oxindoles to form branched products of hydrohydroxyalkylation as single diastereomers. To our knowledge, this work represents the first example of the metal-catalyzed hydrohydroxyalkylation of unactivated olefins.

In an initial experiment, *N*-benzyl-3-hydroxy-2-oxindole **1a** was exposed to propylene **2b** under reaction conditions used to promote C–C coupling of substituted mandelic esters to dienes.^[6] However, only trace quantities of the isopropylsubstituted oxindole **3b** was observed. Nevertheless, the

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a) Previously established mechanistic pathways



b) This work: Applicable to α -olefins





Scheme 1. Three distinct catalytic mechanisms enable C–C bond-forming hydrogenation and transfer hydrogenation. EWG = electron-withdrawing group, L=ligand.

regioselectivity for the branched product suggested that the predicted mechanism involving carbonyl–alkene oxidative coupling was operative but inefficient. As it was previously shown that carboxylic acids co-catalyze hydrogenolysis of oxa- and azametallacycles to enhance rate and conversion,^[7] a range of carboxylic acids were screened under the aforementioned reaction conditions. Remarkably, upon use of 1-adamantanecarboxylic acid (10 mol%) as co-catalyst, the isopropyl-substituted oxindole **3b** was isolated in 90% yield as a single regioisomer [Eq. (1); Bn = benzyl].

These optimized reaction conditions were applied to the C–C coupling of **1a** to α -olefins **2a–2f** (Scheme 2). The corresponding adducts **3a–3f** were obtained in excellent yield with complete regioselectivity for the branched products. As

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illustrated in the formation of the 3-hydroxy-2-oxindoles 3c-3f, exceptional levels of diastereoselectivity are observed in couplings that generate two stereogenic centers. The assignment of relative stereochemistry was corroborated by single crystal X-ray diffraction analysis of adduct 3c. In terms of functional group compatibility, the efficient coupling of olefins 2e and 2f, which incorporate alkoxy and silyl groups at the allylic position, is noteworthy. Finally, although $[Ru_3(CO)_{12}]$ -derived catalysts are known to promote olefin isomerization,^[8] the coupling of 1a to allylbenzene 2d occurs efficiently. This result is significant as β -methylstyrene and other 1,2-disubstituted olefins do not participate in C–C coupling under these reaction conditions.



Scheme 2. Ruthenium-catalyzed hydrohydroxyalkylation of α -olefins **2a–2f** and 3-hydroxy-2-oxindole **1a**. Yields are of material isolated by silica gel chromatography. C₁₀H₁₅CO₂H refers to 1-adamantanecarboxylic acid. See the Supporting Information for further details. [a] Olefin (1 atm). Cy = cyclohexyl.

These reaction conditions for ruthenium(0)-catalyzed hydrohydroxyalkylation were applied to the coupling of 3hydroxy-2-oxindole **1a** to substituted styrenes **2g-2r** (Table 1). With the exception of 2-methoxy styrene **2k**, the coupling of electron-neutral and electron-rich styrene derivatives **2g-2m** occurs efficiently with complete regio- and diastereoselectivity for the branched products. The assignment of relative stereochemistry was corroborated by single crystal X-ray diffraction analysis of adduct **3g**. Formation of the 3-hydroxy-2-oxindole **3r**, which incorporates a thiophene moiety, further illustrates functional-group compatibility. For **Table 1:** Ruthenium-catalyzed hydrohydroxyalkylation of styrenes 2g-2r and 3-hydroxy-2-oxindole 1a.^[a]



Entry	Olefin	Product	Ar moiety	Branched/ Linear	Yield [%] (d.r.)
1	2g	3 g ^[b]	Ph	> 20:1	94 (>20:1)
2	2ĥ	3 h	2-napthyl	13:1	81 (>20:1)
3	2 i	3 i	4-MeC ₆ H ₄	> 20:1	83 (>20:1)
4	2 j	3 j	4-MeOC ₆ H₄	> 20:1	77 (>20:1)
5	2k	3 k	2-MeOC ₆ H₄	1.3:1	91 (>20:1)
6	21	31	4-Me ₂ NC ₆ H ₄	> 20:1	65 (>20:1)
7	2 m	3 m	1,3-benzodioxole	> 20:1	81 (>20:1)
8	2 n	3 n	4-CIC ₆ H ₄	> 20:1	82 (>20:1)
9	2 o	3 o	$4-CF_3C_6H_4$	> 20:1	81 (>20:1)
10	2р	3 p	4-CNC ₆ H ₄	8.5:1	76 (>20:1)
11	2 q	3 q	$4-CO_2MeC_6H_4$	4:1	87 (>20:1)
12	2r	3 r	2-thienyl	>20:1	87 (>20:1)

[a] Yields are of material isolated by silica gel chromatography. $C_{10}H_{15}CO_2H$ refers to 1-adamantanecarboxylic acid. See the Supporting Information for further details. [b] The structure was determined by single crystal X-ray diffraction analysis.

styrenes 2n-2q, increasing electron deficiency is accompanied by erosion in regioselectivity; this erosion is attributed to a nonmetal-catalyzed background reaction involving classical conjugate addition. The veracity of this hypothesis is corroborated by the fact that *N*-benzyl-3-hydroxy-2-oxindole **1a** spontaneously reacts with 2-vinylpyridine **2s** in the absence of a metal catalyst to form the linear product exclusively [Eq. (2)].



The use of 1-adamantanecarboxylic acid as a co-catalyst suggests substrates that possess acidic functional groups should be tolerated in the C–C coupling. To probe this question, the 3-hydroxy-2-oxindole **1b**, which lacks a protecting group on the nitrogen atom, was exposed to styrene **2g** under slightly modified conditions for hydrohydroxyalkylation. Owing to the poor solubility of **1b** in *m*-xylene, the reaction was conducted in chlorobenzene for 72 h. The anticipated adduct **3g**-NH was formed in 72% yield as a single regio- and diastereomer [Eq. (3)].



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A plausible catalytic mechanism accounting for the influence of 1-adamantanecarboxylic acid begins with the combination of [Ru₃(CO)₁₂] and tricyclohexylphosphine, PCy₃, to form a discrete monometallic ruthenium(0) complex.^[9] Oxidative coupling necessitates initial dehydrogenation of 3-hydroxy-2-oxindole 1a to form isatin 1c. There is precedence for this dehydrogenation in the $[Ru_3(CO)_{12}]$ catalyzed oxidation of alcohols employing olefins and alkynes as hydrogen acceptors,^[10,11] as well as in [Ru₃(CO)₁₂]-catalyzed aminations of secondary alcohols,^[12] which involves dehydrogenation of a-hydroxy esters.^[12c] Indeed, for couplings of styrene 2g, small quantities of ethylbenzene are detected in the ¹H NMR spectrum of the reaction mixtures. Oxidative coupling of isatin 1c and styrene 2g to form oxametallacycle I finds precedent in the work of Chatani, Murai, and co-workers on Pauson-Khand type reactions of 1,2-diones,^[13] and studies by our own research group on the prenylation of substituted mandelic esters.^[6] We postulate that direct transfer hydrogenolytic cleavage of the oxaruthenacycle I, involving initial protonation of oxaruthenacycle I to form ruthenium alkoxide III, may be prohibitively slow, whereas protonolysis of oxaruthenacycle I by 1-adamantanecarboxylic acid to form ruthenium carboxylate II and subsequent exchange of the carboxylate to form ruthenium alkoxide III are relatively rapid. The ruthenium alkoxide III suffers β -hydride elimination to concomitantly generate ruthenium hydride IV and isatin 1c. Finally, C-H reductive elimination produces the product 3g and the initial ruthenium(0) complex to close the catalytic cycle. As depicted in the proposed stereochemical model, oxidative coupling should occur so as to avoid steric interactions between the olefin substituent and the arene moiety (Scheme 3).

In summary, we report the first examples of the metalcatalyzed hydrohydroxyalkylation of unactivated olefins, as illustrated by their C–C coupling to *N*-benzyl-3-hydroxy-2oxindole **1a**. This process was enabled by the recent discovery of a novel reactivity pattern wherein the metallacyclic intermediates obtained upon carbonyl–olefin oxidative coupling undergo transfer hydrogenolysis mediated by a secondary alcohol reactant to liberate the product of hydrohydroxyalkylation and regenerate the carbonyl partner for oxidative coupling (Scheme 1b).^[6] Future studies will focus on the development of related catalysts for the direct conversion of α -olefins and aliphatic primary and secondary alcohols to form higher alcohols in the absence of stoichiometric by-products.

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Scheme 3. Proposed catalytic mechanism illustrating the effect of the carboxylic acid co-catalyst and stereochemical model.

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