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Regio- and Diastereoselective C-C Coupling of α -Olefins and Styrenes to 3-Hydroxy-2-oxindoles via Ruthenium Catalyzed Hydrohydroxyalkylation**

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Keywords

hydrohydroxyalkylation; α -olefins; styrenes; diastereoselectivity; transfer hydrogenation

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 α -olefins to carbonyl compounds are unknown, withstanding the special case of hydroformylation.^[2,3,4] Motivated in part by the prospect of addressing this deficiency, our laboratory 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 α -unsaturated reactants are hydrogenated to form a single, more complex product.^[5] Such transformations typically proceed through pathways involving metallacycle formation and hydrogenolysis (Figure 1, top). Based on these studies, related C-C bond forming transfer hydrogenations were developed, in which hydrogen transfer from alcohols to α -unsaturated reactants via hydrometallation triggers generation of organometal-carbonyl pairs that combine to form products of addition (Figure 1, middle).^[5] In a more recent advance, a third pathway involving alcohol mediated transfer hydrogenolysis of metallacycles was uncovered, as illustrated in couplings of α -hydroxy esters to isoprene or myrcene to form products of prenylation or geranylation, respectively, and related couplings dienes of 3-hydroxy-2-oxindoles (Figure 1, bottom).^[6] The availability of this novel mechanistic pathway prompted a reinvestigation of the coupling of α -olefins. Here, we report that the ruthenium(0) catalyst generated from $\text{Ru}_3(\text{CO})_{12}$ and tricyclohexylphosphine, PCy_3 , 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 conditions used to promote C-C coupling of substituted mandelic esters to dienes.^[6] However, only trace quantities of the isopropyl-substituted oxindole **3b** was observed. Nevertheless, the branch-regioselectivity suggested the predicted mechanism involving carbonylalkene oxidative coupling was operative but inefficient. As it was previously observed 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

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aforementioned 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 (eqn. 1).

(eqn. 1)

These optimal conditions were applied to the C-C coupling of **1a** to α -olefins **2a-2f** (Table 1). The corresponding adducts **3a-3f** were obtained in excellent yield with complete levels of branched regioselectivity. As illustrated in the formation of the 3-hydroxy-2-oxindoles **3c-3f**, exceptional levels of diastereoselectivity are observed in couplings that generate 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 $\text{Ru}_3(\text{CO})_{12}$ derived catalysts are known to promote olefin isomerization,^[8] the coupling of **1a** to allylbenzene **2d** occurs efficiently. This result is significant as α -methylstyrene and other 1,2-disubstituted olefins do not participate in C-C coupling under these conditions.

These conditions for ruthenium(0) catalyzed hydrohydroxyalkylation were applied to the coupling of 3-hydroxy-2-oxindole **1a** to substituted styrenes **2g-2r** (Table 2). With the exception of 2-methoxy styrene **2k**, the coupling of electron neutral and electron rich styrene derivatives **2g-2m** occurs efficiently with complete levels of branched regio- and diastereoselectivity. 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 styrenes **2n-2q**, increasing electron deficiency is accompanied by erosion in regioselectivity, which is attributed to a non-metal 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 (eqn. 2).

(eqn. 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 an *N*-protecting group, was exposed to styrene **2g** under slightly modified conditions for hydrohydroxyalkylation. Due to the poor solubility of

1b in *m*-xylene, the reaction was conducted in chlorobenzene for 72 hours. The anticipated adduct **3g-NH** was formed in 72% yield as a single regio- and diastereomer (eqn. 3).

(eqn. 3)

A plausible catalytic mechanism accounting for the effect of 1-adamantanecarboxylic acid begins with the combination of $\text{Ru}_3(\text{CO})_{12}$ and tricyclohexylphosphine, PCy_3 , to form a discrete mono-metallic ruthenium(0) complex.^[9] Oxidative coupling necessitates initial dehydrogenation of 3-hydroxy-2-oxindole **1a** to form isatin **1c**, which finds precedent in the $\text{Ru}_3(\text{CO})_{12}$ catalyzed oxidation of alcohols employing olefins and alkynes as hydrogen acceptors,^[10,11] as well as $\text{Ru}_3(\text{CO})_{12}$ catalyzed aminations of secondary alcohols, which involves dehydrogenation of α -hydroxy esters.^[12c] Indeed, for couplings of styrene **2g**, small quantities of ethylbenzene are detected in the ^1H NMR spectrum of crude reaction mixtures. Oxidative coupling of isatin **1c** and styrene **2g** to form oxametallacycle **I** finds precedent in the work of Chatani and Murai on Pauson-Khand type reactions of 1,2-diones,^[13] and studies from our own laboratory on the prenylation of substituted mandelic esters.^[6] We postulate that direct transfer hydrogenolytic cleavage of the oxaruthenacycle **I**, which would involve 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 1).

In summary, we report the first examples of the metal catalyzed hydrohydroxyalkylation of unactivated olefins, as illustrated by their C-C coupling to *N*-benzyl-3-hydroxy-2-oxindole **1a**. This process was enabled by the recent discovery of a novel reactivity pattern wherein the metallacyclic intermediates obtained upon carbonyl-olefin oxidative coupling suffer transfer hydrogenolysis mediated by a secondary alcohol reactant to liberate the product of hydrohydroxyalkylation and regenerate the carbonyl partner for oxidative coupling (Figure 1, bottom).^[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 byproducts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Three distinct catalytic mechanisms enable C-C bond forming hydrogenation and transfer hydrogenation.

Scheme 1.

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

Table 1

Ruthenium catalyzed hydrohydroxyalkylation of α -olefins **2a-2f** and 3-hydroxy-2-oxindole **1a**.^a

^aYields are of material isolated by silica gel chromatography. $\text{C}_{10}\text{H}_{15}\text{CO}_2\text{H}$ refers to 1-adamantanecarboxylic acid. See Supporting Information for further details.

^bolefin (1 atm).

Table 2

Ruthenium catalyzed hydrohydroxyalkylation of styrenes **2g-2r** and 3-hydroxy-2-oxindole **1a**.^a

entry	olefin	product	Ar moiety	branched:linear	yield (dr)
1	2g	3g (x-ray)	Ph	>20:1	94% (>20:1)
2	2h	3h	2-naphthyl	13:1	81% (>20:1)
3	2i	3i	4-Me-Ph	>20:1	83% (>20:1)
4	2j	3j	4-OMe-Ph	>20:1	77% (>20:1)
5	2k	3k	2-OMe-Ph	1.3:1	91% (>20:1)
6	2l	3l	4-NMe ₂ -Ph	>20:1	65% (>20:1)
7	2m	3m	1,3-benzodioxole	>20:1	81% (>20:1)
8	2n	3n	4-Cl-Ph	>20:1	82% (>20:1)
9	2o	3o	4-CF ₃ -Ph	>20:1	81% (>20:1)
10	2p	3p	4-CN-Ph	8.5:1	76% (>20:1)
11	2q	3q	4-CO ₂ Me-Ph	4:1	87% (>20:1)
12	2r	3r	2-Thienyl	>20:1	87% (>20:1)

^aYields are of material isolated by silica gel chromatography. $\text{C}_{10}\text{H}_{15}\text{CO}_2\text{H}$ refers to 1-adamantanecarboxylic acid. See Supporting Information for further details.