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Regioselective Ruthenium Catalyzed Hydrohydroxyalkylation of Dienes with 3-Hydroxy-2-oxindoles: Prenylation, Geranylation, and Beyond

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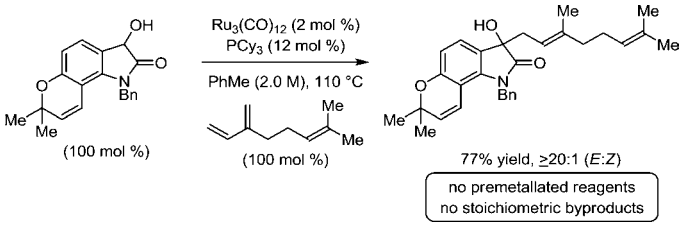
ABSTRACT



The direct conversion of secondary to tertiary alcohols *via* ruthenium(0) catalyzed C−C coupling of substituted 3-hydroxy-2-oxindoles with various dienes is described. Coupling occurs in a completely regioselective manner in the absence of stoichiometric byproducts.

In the course of exploring hydrogen-mediated C−C couplings outside of hydroformylation,[1] our laboratory has developed metal catalysts that promote the transfer of hydrogen from primary alcohols to various π-unsaturated compounds resulting in generation of aldehyde−organometallic nucleophile−electrophile pairs that combine to form products of aldehyde addition. These processes merge redox and C−C bond construction events,[2] bypassing both discrete alcohol-to-aldehyde oxidation and the stoichiometric use of premetalated reagents. Although conditions for the C−C coupling of primary alcohols to dienes[3−5] and other π-unsaturated reactants (allenes, enynes, alkynes and allylic acetates)[1] have been developed, corresponding couplings of secondary alcohols have proven more challenging.

(1) For selected reviews on C-C bond forming hydrogenation and transfer hydrogenation, see: (a) Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011**, *43*, 107. (b) Hassan, A.; Krische, M. J. *Org. Proc. Res. Devel.* **2011**, *15*, 1236. (c) Moran, J.; Krische, M. J. *Pure Appl. Chem.* **2012**, *84*, 1729.

(2) For a review on the topic of redox economy, see: Baran, P. S.; Hoffmann, R. W.; Burns, N. Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(3) For iridium catalyzed transfer hydrogenative coupling of alcohols to dienes, see: (a) Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, *10*, 1033. (b) Zbieg, J. R.; Fukuzumi, T.; Krische, M. J. *Adv. Synth. Catal.* **2010**, *352*, 2416.

(4) For ruthenium catalyzed transfer hydrogenative coupling of alcohols to dienes, see : (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. (b) Han, H.; Krische, M. J. *Org. Lett.* **2010**, *12*, 2844. (c) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582. (d) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. (e) Leung, J. C.; Geary, L. M.; Chen, T.-Y.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 15700. (f) Geary, L. M.; Glasspoole, B. W.; Kim, M. M.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *134*, 3796Also, see reference 5.

(5) For ruthenium catalyzed transfer hydrogenative reductive coupling of dienes to paraformaldehyde, see: Smejkal, T.; Han, H.; Breit, B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 10366.

(6) A related oxidative coupling pathway is observed in ruthenium(0) catalyzed Pauson−Khand type reactions of 1,2-diones: (a) Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160. (b) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663.

(7) For nickel catalyzed intermolecular diene-aldehyde reductive coupling, see: (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (b) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543. (c) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397. (d) Kimura, M.; Shibata, K.; Koudahashi, Y.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 6789. (e) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3600. (f) Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* **2002**, *4*, 2715. (g) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 656. (h) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559. (i) Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248. (j) Sato, Y.; Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. *Org. Lett.* **2007**, *9*, 5597. (k) Köpfer, A.; Sam, B.; Breit, B.; Krische, M. J. *Chem. Sci.* **2013**, *4*, 1876.

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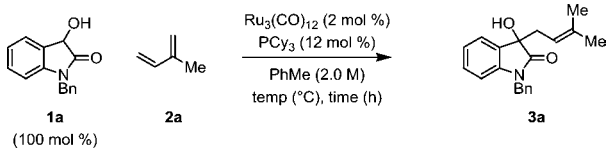
Recently, it was found that ruthenium(0) complexes derived from $Ru_3(CO)_{12}$ and phosphine ligands catalyze C−C coupling of mandelic esters with 2-substituted dienes at the C4-position to form prenylated and geranylated compounds from isoprene and myrcene, respectively.[4e] As corroborated by mechanistic studies, this regioselectivity is a consequence of a catalytic mechanism wherein alcohol dehydrogenation drives oxidative coupling between the diene and a transient α-oxoester.[6] To our knowledge, such C4 regioselectivity is unique for intermolecular reductive couplings of 2-substituted dienes to carbonyl partners.[7−9] Given the structural homology of substituted mandelic esters and 3-hydroxy-2-oxindoles, which represent important natural product substructures, the latter compounds were explored as partners for redox triggered C−C coupling with dienes.[10] Here, we report that exposure of 3-hydroxy-2-oxindoles to isoprene or myrcene and the ruthenium(0) catalyst derived from $Ru_3(CO)_{12}$ and tricyclohexylphosphine, PCy_3, results in direct, secondary carbinol C−H prenylation and geranylation, respectively, in the absence of stoichiometric byproducts. Further, we find that dienes beyond isoprene or myrcene participate in such secondary alcohol C−C couplings.

Table 1. Selected Optimization Experiments in the Ruthenium Catalyzed C−C Coupling of 3-Hydroxy-2-oxindole **1a** and Isoprene **2a**[a]



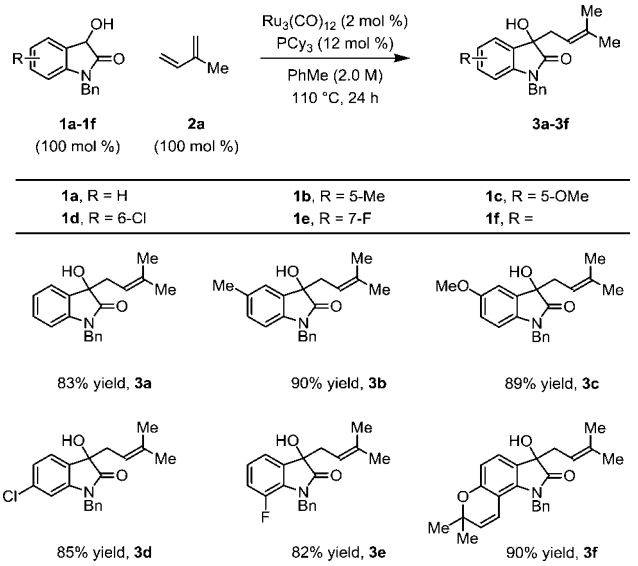
1a (100 mol %) **2a** **3a**

entry	**2a** (mol %)	temp	time (h)	yield %
1	500	130	72	71
2	500	130	48	76
3	500	130	24	73
4	300	130	24	74
5	100	130	24	76
⇨ **6**	**100**	**110**	**24**	**83**
7	100	90	24	57

[a] Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

To probe the feasibility of isatin prenylation from the alcohol oxidation level, 3-hydroxy-2-oxindole **1a** was exposed to conditions optimized for the prenylation of ethyl mandelate.[4e] Gratifyingly, upon exposure of **1a** (100 mol %) to isoprene **2a** (500 mol %), $Ru_3(CO)_{12}$ (2 mol %) and PCy_3 (12 mol %) at 130 °C in toluene (2.0 M) for 48 h, the product of prenylation **3a** was generated in 76% isolated yield (Table 1, entry 2). Extended reaction times (72 h) did not enhance the isolated yield of **3a** (Table 1, entry 1), and for reactions conducted over a 24 h period comparable isolated yields of **3a** were obtained (Table 1, entry 3). The isolated yield of **3a** was not adversely effected at lower loadings of isoprene (300 mol %) (Table 1, entry 4) even when equimolar quantities of 3-hydroxy-2-oxindole **1a** and isoprene **2a** were employed (Table 1, entry 5). When the reaction was conducted at 110 °C the isolated yield of **3a** improved (Table 1, entry 6); however, any further decrease in reaction temperature led to a significant decrease in conversion (Table 1, entry 7).

Table 2. Ruthenium Catalyzed C−C Coupling of 3-Hydroxy-2-oxindoles **1a**−**1f** and Isoprene **2a** To Form Products of Prenylation **3a**−**3f**[a]



[a] Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

Optimal conditions identified for the *n*-prenylation of 3-hydroxy-2-oxindole **1a** (Table 1, entry 6) were applied to substituted 3-hydroxy-2-oxindoles **1b**−**1f**. The desired products of prenylation **3b**-**3f** were obtained in excellent isolated yields and in each case single regioisomers were obtained (Table 2). Similarly, exposure of 3-hydroxy-2-oxindoles **1a**−**1f** to myrcene **2b** provides the products of *n*-geranylation as single regioisomers with complete control of olefin geometry (Table 3). Thus, direct prenylation and geranylation of secondary carbinol C−H bonds is achieved in the absence of stoichiometric byproducts or premetalated reagents.

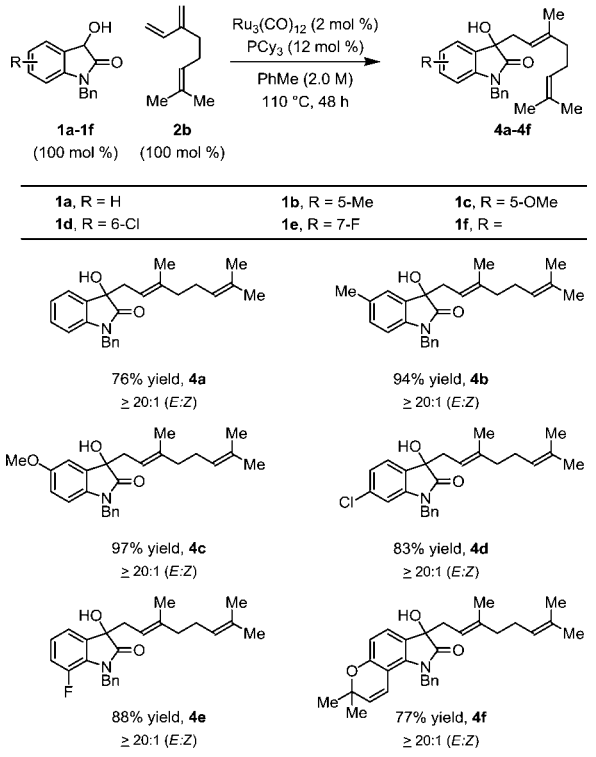
To further evaluate scope, the redox triggered C−C coupling of *N*-benzyl 3-hydroxy-2-oxindole **1a** with dienes **2c**−**2f** was investigated. The coupling of **1a** with butadiene **2c** provided the product of (*Z*)-2-butenylation **5a** as a single geometrical isomer. As will be discussed, the (*Z*)-olefin geometry of **5a** is indicative of a catalytic mechanism involving diene-carbonyl oxidative coupling.[4e] As illustrated in the conversion of 1,3-cyclohexadiene **2d** to

(8) For rhodium catalyzed intermolecular diene-aldehyde reductive coupling, see: (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4074. (b) Kimura, M.; Nojiri, D.; Fukushima, M.; Oi, S.; Sonoda, Y.; Inoue, Y. *Org. Lett.* **2009**, *11*, 3794.

(9) For titanium catalyzed intermolecular diene-aldehyde reductive coupling, see: Bareille, L.; Le Gendre, P.; Moïse, C. *Chem. Commun.* **2005**, 775.

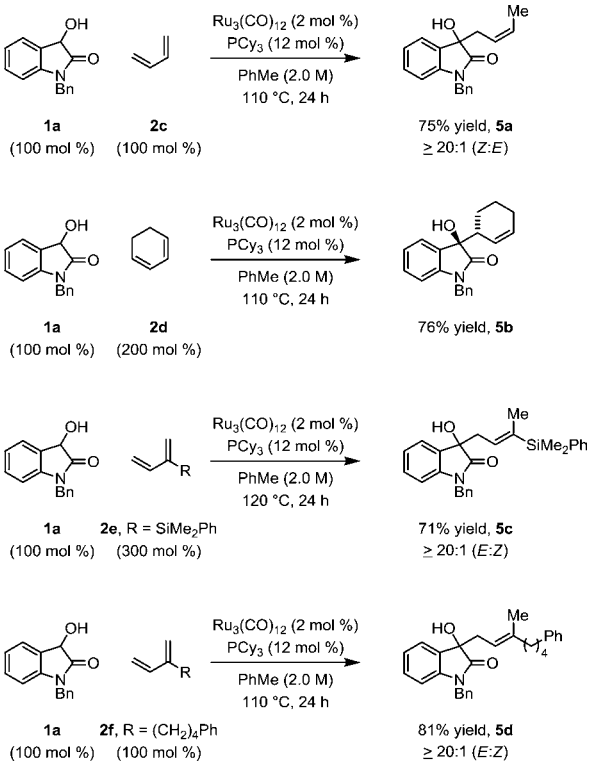
(10) For related allylations of isatins under the conditions of iridium catalyzed transfer hydrogenation, see: Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313.

Table 3. Ruthenium Catalyzed Coupling of 3-Hydroxy-2-oxindoles **1a**–**1f** and Myrcene **2b** To Form Products of Geranylation **4a**–**4f**[a]



[a] Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

Scheme 1. Ruthenium Catalyzed C–C Coupling of 2-Hydroxy-3-oxindoles **1a** and Dienes **2c**–**2f**[a]



[a] Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

the product of 2-cyclohexenylation **5b**, cyclic dienes also participate in efficient coupling. In a similar manner, the 2-silyl substituted butadiene **2e** and pentadiene **2f** are converted to adducts **5c** and **5d**, respectively, as single olefin geometrical isomers (Scheme 1).

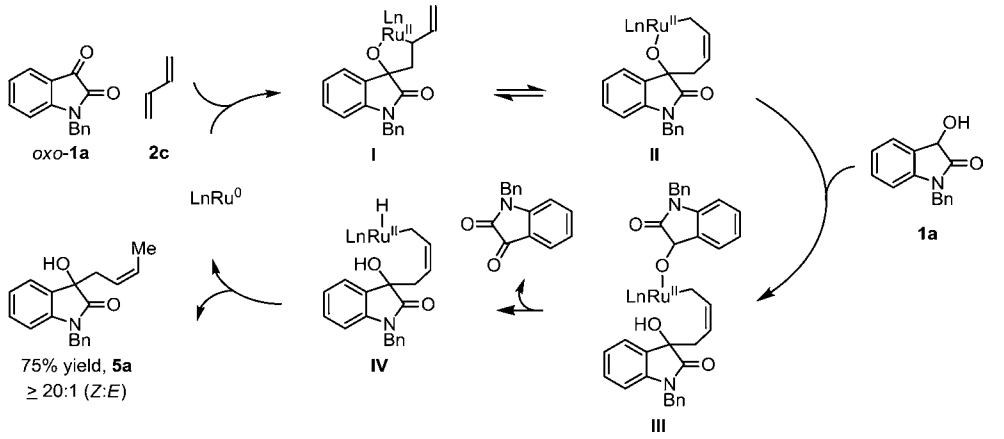
A plausible catalytic mechanism accounting for the linear regioselectivity of diene C–C coupling and (*Z*)-stereoselectivity observed in the formation of the butadiene adduct **5a** is as follows (Scheme 2). Exposure of $Ru_3(CO)_{12}$ to chelating phosphine ligands provides complexes of the type $Ru(CO)_3$(diphosphine).[11] Although the present catalytic system employs a nonchelating monophosphine ligand, intervention of a discrete, monometallic catalyst is anticipated based on this precedent. As implicated in related Pauson–Khand type reactions of 1,2-diones,[6] along with subsequent studies from our laboratory,[4e] ruthenium(0) mediated diene-carbonyl oxidative coupling delivers the ruthenium(II) oxametallacycle **I**, which isomerizes to oxametallacycle **II**, the presumably more stable primary σ-allyl haptomer. The (*Z*)-stereoselectivity observed in the formation of adduct **5a** ultimately is defined by the olefin geometry evident in oxametallacycle **II**. Oxindole **1a** protonates oxametallacycle **II** to form the ruthenium(II) alkoxide **III**, which upon β-hydride elimination delivers the isatin *oxo*-**1a** and the allylruthenium(II) hydride **IV**. Related β-hydride eliminations of σ-hydroxy amides employing catalysts derived from $Ru_3(CO)_{12}$ have been reported.[12] Reductive elimination of the allylruthenium hydride **IV** delivers the pro duct **5a** and returns ruthenium to its zerovalent form. The reductive elimination event must occur at a faster rate than π-facial interconversion of the allyl moiety, which would otherwise erode the control of olefin geometry (Scheme 2).

In summary, the present ruthenium(0) catalyst system has proven unique in its ability to mechanistically link alcohol dehydrogenation to diene–carbonyl oxidative C–C coupling. On the basis of this novel pattern of reactivity, a new transformation of the ubiquitous hydroxyl functional group has been availed: the direct prenylation and geranylation of secondary carbinol C–H bonds in the absence of stoichiometric byproducts employing isoprene **2a** and myrcene **2b** as prenyl and geranyl donors, respectively. Whereas in prior work, secondary alcohols in the form of mandelic esters were shown to participate in such C–C bond

(11) For example, exposure of $Ru_3(CO)_{12}$ to dppe in benzene solvent provides $Ru(CO)_3$(dppe): Sanchez-Delgado, R. A.; Bradley, J. S.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1976**, 399.

(12) For mechanistically related $Ru_3(CO)_{12}$ catalyzed secondary alcohol amination *via* alcohol mediated hydrogen transfer, see: (a) Baehn, S.; Tillack, A.; Imm, S.; Mevius, K.; Michalik, D.; Hollmann, D.; Neubert, L.; Beller, M. *ChemSusChem* **2009**, *2*, 551. (b) Pingen, D.; Müller, C.; Vogt, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8130. (c) Zhang, M.; Imm, S.; Bahn, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11197.

Scheme 2. Plausible Catalytic Mechanism for the Redox Triggered C−C Coupling of Oxindole-**1a** and Butadiene **2c** Accounting for the Observed Olefin (*Z*)-Stereoselectivity



forming transfer hydrogenations,[4e] the present study demonstrates that oxindoles **1a**−**1f** readily engage in analogous transformations. These studies contribute to a departure from the stoichiometric use of premetalated reagents in organic synthesis.

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Supporting Information Available. Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.