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Iridium-Catalyzed C–C Coupling via Transfer Hydrogenation: Carbonyl Addition from the Alcohol or Aldehyde Oxidation Level Employing 1,3-Cyclohexadiene

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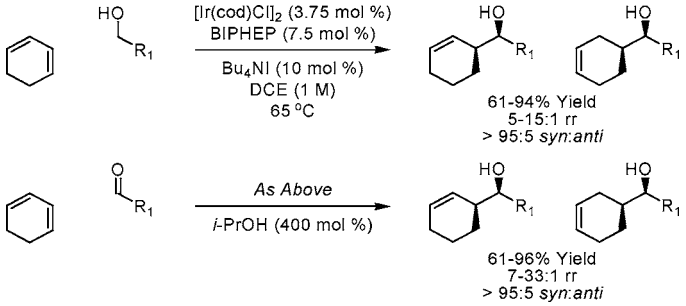
ABSTRACT



Under hydrogen autotransfer conditions employing a catalyst derived from [Ir(cod)Cl]$_2$ and BIPHEP, 1,3-cyclohexadiene (CHD) couples to benzylic alcohols 1a–9a to furnish carbonyl addition products 1c–9c, which appear as single diastereomers with variable quantities of regioisomeric adducts 1d–9d. Under related transfer hydrogenation conditions employing isopropanol as terminal reductant, identical carbonyl adducts 1c–9c are obtained from the aldehyde oxidation level. Isotopic labeling studies corroborate a mechanism involving hydrogen donation from the reactant alcohol or sacrificial alcohol (*i*-PrOH).

As part of a broad program aimed at the development of methods for byproduct-free carbonyl and imine addition,[1,2] we recently reported that carbonyl allylation may be achieved by simply hydrogenating allenes in the presence of aldehydes.[2h] Though effective for reverse prenylation, attempted crotylations and allylations using gaseous hydrogen as the terminal reductant suffered from over-reduction of the olefinic adduct. To address this limitation, allene−aldehyde reductive coupling was performed under the conditions of transfer hydrogenation using isopropanol as the terminal reductant.[2i] In the course of these studies, it was found that carbonyl allylation could be achieved directly *from the alcohol oxidation level* by way of allene−alcohol transfer hydrogenation,[2i] constituting a novel variant of hydrogen autotransfer processes wherein hydrogen exchange between reactants is used to generate nucleophile−electrophile pairs (Scheme 1).[2i,3−7]

(1) For reviews on hydrogenative C−C coupling, see: (a) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007**, *279*, 77. (c) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394.

(2) For recent examples, see: (a) *C═X Vinylation*: Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718 (b) Skucas, E.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242. (c) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432. (d) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644. *Aldol and Mannich addition*: Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519. (e) Jung, C.-K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051. (f) Garner, S. A.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 5843. (g) Bee, C.; Iida, H.; Han, S. B.; Hassan, A.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*. In Press. (h) *C═O Allylation*: Skucas, E.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678. (i) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134.

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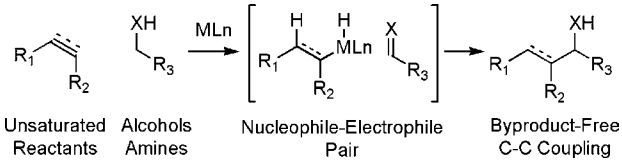
Scheme 1. Carbonyl and Imine Addition via Hydrogen Autotransfer



Through hydrogen autotransfer, there exists the potential to develop a broad new family of byproduct-free catalytic C−C bond formations wherein alcohols and diverse π-unsaturated compounds are exploited as coupling partners. Motivated by this prospect, diene−aldehyde hydrogen autotransfer was explored. Catalytic diene−aldehyde reductive coupling has been accomplished in both intra- and intermolecular settings.[8−10] Recently, the first examples of asymmetric diene−aldehyde intermolecular coupling were reported.[9k,l] Here, we disclose that 1,3-cyclohexadiene and aromatic alcohols **1a**−**9a** engage in C−C coupling under the conditions of iridium-catalyzed hydrogen autotransfer. Additionally, we report the coupling of 1,3-cyclohexadiene to an analogous set of aldehydes **1b**−**9b** under related transfer hydrogenation conditions employing isopropanol as the terminal reductant.

Initial studies focused upon the coupling of benzyl alcohol **1a** to 1,3-cyclohexadiene (CHD) under the conditions of iridium catalysis. It was found that a catalyst derived from commercially available $[Ir(cod)Cl]_2$ and BIPHEP delivers homoallylic alcohol **1c** as a mixture of diastereomers, along with significant amounts of the regioisomeric product **1d**.[11] Notably, cationic iridium salts were almost completely ineffective for this process, and basic additives were unnecessary. With the aim of minimizing isomer formation, a screen of additives was undertaken, leading to the discovery that Bu_4NI had a small but significant effect on diastereoselectivity and the suppression of the regioisomeric product **1d**.[12] Finally, formation of adduct **1c** as a *single* diastereomer (>95:5 *syn*:*anti*) is enabled using excess CHD (12 equiv), which also suppresses the formation of regioisomer **1d**. Under these conditions, CHD couples to diverse benzylic alcohols **2a**−**9a**, providing adducts **2c**−**9c** in good to excellent yields as single diastereomers (Table 1, left).

The very same products **1c**−**9c** are accessible through the coupling of CHD to aldehydes **1b**−**9b** under the conditions of iridium-catalyzed transfer hydrogenation employing isopropanol as the terminal reductant. Conditions similar to those described in Table 1 are used, but with lower loadings of 1,3-cyclohexadiene (4 equiv). Thus, carbonyl addition products **1c**−**9c** are accessible from the alcohol or aldehyde oxidation level (Table 1, right).

In light of previous results,[2i] a plausible general mechanism for catalytic C−C coupling under hydrogen autotransfer conditions is proposed in Scheme 1. Iridium-catalyzed dehydrogenation of the alcohol followed by hydrometallation of 1,3-cyclohexadiene results in the generation of a nucleophile−electrophile pair. The iridium σ-allyl species engages the aldehyde in a closed six-centered transition state, to furnish the *syn*-adduct. Cleavage of the iridium−alkoxide delivers the alcohol product and releases the catalyst to close the cycle. Formation of regioisomers **1d**−**9d** is attributed to metal−hydride-mediated olefin isomerization subsequent to C−C coupling. This interpretation is supported by the fact that decreased levels of this component are observed at lower conversion. Under the conditions of transfer hydrogenation, iridium−monohydride generation is accomplished by employing isopropanol as a sacrificial alcohol.[13]

(3) For reviews on hydrogen autotransfer, see: (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.

(4) Withstanding work cited in refs 2i and 5, reported hydrogen autotransfer processes involve three fundamental steps: (i) alcohol oxidation, (ii) carbonyl condensation/olefination, (iii) olefin reduction to deliver saturated products.

(5) Aryl amine−olefin hydrogen autotransfer provides products of imine addition from the amine oxidation level, see: Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690 and references cited therein.

(6) For a three-component Ni-catalyzed C−C coupling involving internal redox, see: Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469.

(7) For an example of catalytic metal−hydride mediated C−C coupling using isopropanol as a hydride donor, see: Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 14193.

(8) Catalytic intramolecular diene−aldehyde reductive coupling: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887. (c) Sato, Y.; Takanashi, T.; Hoshiba, M.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 5579. (d) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (e) Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371. (f) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181. (g) Sato, Y.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 9310. (h) Sato, Y.; Takanashi, T.; Hoshiba, M.; Mori, M. *J. Organomet. Chem.* **2003**, *688*, 36. (i) Yu, C.-M.; Youn, J.; Yoon, S.-K.; Hong, Y.-T. *Org. Lett.* **2005**, *7*, 4507.

(9) Catalytic intermolecular diene−aldehyde reductive coupling: (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (b) Takai, K.; Toratsu, C. *J. Org. Chem.* **1998**, *63*, 6450. (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) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4074. (i) Bareille, L.; Le Gendre, P.; Moïse, C. *Chem. Commun.* **2005**, 775. (j) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559. (k) Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248. (l) Sato, Y.; Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. *Org. Lett.* **2007**, *9*, 5597.

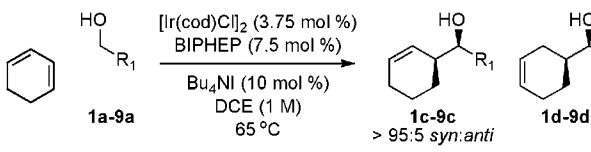
(10) For reviews encompassing nickel-catalyzed diene−aldehyde reductive coupling, see: (a) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576*, 215. (b) Ikeda, S.-i. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120. (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (d) Tamaru, Y., Ed. *Modern Organo Nickel Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (e) Kimuara, M.; Tamaru, Y. *Top. Curr. Chem.* **2007**, *279*, 173.

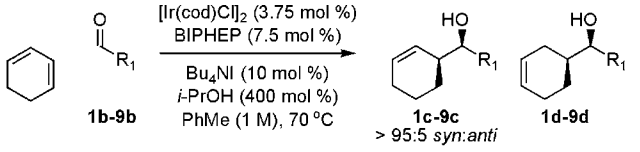
(11) The stereochemical assignment of **1c** was made by comparison with the corresponding literature NMR data.[9j] The stereochemical assignment of products **2c**−**9c** was made in analogy to **1c**. That **1c** and **1d** are regioisomers (and not diastereomers) was confirmed by oxidation (Dess−Martin periodinane) to the corresponding mixture of ketones and comparison with relevant literature NMR data. See Supporting Information for details.

(12) For example, when **1a** was exposed to the reaction conditions described in Table 1, but in the absence of Bu_4NI, a 7:1 ratio of **1c** and **1d** was formed along with significant amounts (ca. 10%) of *anti*-**1c**. Other halide sources, such as Bu_4NBr and Bu_4NCl, were less effective, and the use of NaI resulted in minimal consumption of starting material. At present, the precise role of the Bu_4NI additive is unclear. For a review on the effect of halide additives in metal-catalyzed reactions, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(13) In the absence of isopropanol, benzaldehyde **1b** is converted to **1c** in 5% yield.

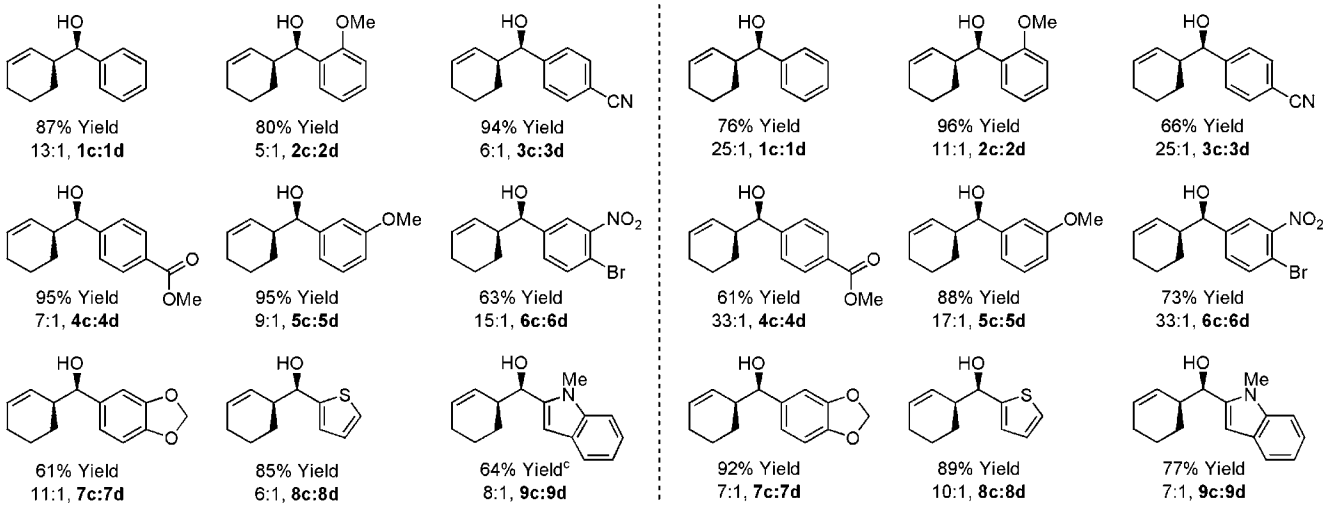
Table 1. (Left) Iridium-Catalyzed Coupling of 1,3-Cyclohexadiene to Alcohols **1a**−**9a** via Hydrogen Autotransfer;[a] (Right) Iridium-Catalyzed Coupling of 1,3-Cyclohexadiene to Aldehydes **1b**−**9b** via Transfer Hydrogenation[b]





1a, R_1 = Ph	**4a**, R_1 = *p*-CO_2MePh	**7a**, R_1 = 5-piperonyl
2a, R_1 = *o*-MeOPh	**5a**, R_1 = *m*-MeOPh	**8a**, R_1 = 2-Thienyl
3a, R_1 = *p*-CNPh	**6a**, R_1 = 3-NO_2-4-BrPh	**9a**, R_1 = 2-indolyl

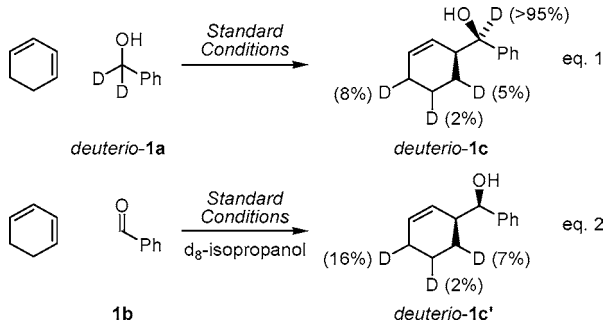
1b, R_1 = Ph	**4b**, R_1 = *p*-CO_2MePh	**7b**, R_1 = 5-piperonyl
2b, R_1 = *o*-MeOPh	**5b**, R_1 = *m*-MeOPh	**8b**, R_1 = 2-Thienyl
3b, R_1 = *p*-CNPh	**6b**, R_1 = 3-NO_2-4-BrPh	**9b**, R_1 = 2-indolyl



[a] Cited yields are of isolated material. Standard conditions employ 1 equiv of alcohol and 12 equiv of 1,3-cyclohexadiene. [b] Cited yields are of isolated material. Standard conditions employ 1 equiv of aldehyde and 4 equiv of 1,3-cyclohexadiene. [c] Run at 75 °C with 5 mol % $[Ir(cod)Cl]_2$ and 10 mol % BIPHEP. See Supporting Information for detailed experimental procedures.

To gain further insight into the catalytic mechanism, isotopic labeling studies were performed. Thus, exposure of *deuterio*-**1a** to standard conditions results in the formation of *deuterio*-**1c** which incorporates deuterium in the benzylic position (95%) and, to a limited extent (ca. 15%), in the cyclohexene ring (eq 1). Incomplete deuterium incorporation is possibly a result of deuterium−hydrogen exchange with cyclohexadiene (12 equiv) in advance of C−C coupling. Indeed, when the reaction is run using only 2 equiv of 1,3-cyclohexadiene, an increase in deuterium incorporation in the cyclohexene ring (ca. 40%) is observed. Here, positional analysis by NMR is complicated by the presence of significant amounts of **1d** and *anti*-**1c**/**1d**. Similarly, coupling of **1b** using d_8-isopropanol, results in the formation of *deuterio*-**1c′**, where deuterium incorporation (ca. 25%) is observed solely in the cyclohexene ring (eq 2). These data do not preclude alternative mechanisms involving diene−aldehyde oxidative coupling (Scheme 2).

Scheme 2. Isotopic Labeling Experiments



In summary, we demonstrate that diene−alcohol hydrogen autotransfer enables byproduct-free carbonyl addition *from the alcohol oxidation level*. Under related transfer hydrogenation conditions employing isopropanol as terminal reductant, identical carbonyl adducts are obtained from the aldehyde oxidation level. These studies further support the feasibility of developing a broad new class of catalytic C−C bond formations, wherein alcohols and π-unsaturated reactants are exploited as coupling partners.

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Supporting Information Available: Experimental procedures and 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.

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