Published in final edited form as:

Org Lett. 2008 March 6; 10(5): 1033–1035. doi:10.1021/ol800159w.

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

John F. Bower, Ryan L. Patman, and Michael J. Krische

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712. USA

Abstract

Under hydrogen auto-transfer conditions employing a catalyst derived from $[\text{Ir}(\text{cod})\text{Cl}]_2$ 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 ($i\text{-PrOH}$).

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

mkrische@mail.utexas.edu .

Supporting Information Available. Experimental procedures and spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge *via* the internet at <http://pubs.acs.org>.

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 auto-transfer processes wherein hydrogen exchange between reactants is used to generate nucleophile-electrophile pairs (Scheme 1).^{2i, 3,4,5,6,7}

Through hydrogen auto-transfer, 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 auto-transfer was explored. Catalytic diene-aldehyde reductive coupling has been accomplished in both intra- and intermolecular settings.^{8,9,10} 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 auto-transfer. 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 $[\text{Ir}(\text{cod})\text{Cl}]_2$ 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 further 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

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 equivalents 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).

In summary, we demonstrate that diene-alcohol hydrogen auto-transfer 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 suggest 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgment is made to the Robert A. Welch Foundation, Johnson & Johnson, Merck, and the NIH-NIGMS (RO1-GM69445) for partial support of this research. Dr. Oliver Briel of Umicore is thanked for the generous donation of [Ir(cod)Cl]₂.

References

- (1). For reviews on hydrogenative C-C coupling, see: (a) Ngai M-Y, Kong J-R, Krische MJ. *J. Org. Chem* 2007;72:1063. [PubMed: 17288361] (b) Iida H, Krische MJ. *Top. Curr. Chem* 2007;279:77. (c) Skucas E, Ngai M-Y, Komanduri V, Krische MJ. *Acc. Chem. Res* 2007;40:1394. [PubMed: 17784728]
- (2). For recent examples, see: (a) C=X Vinylation: Kong J-R, Ngai M-Y, Krische MJ. *J. Am. Chem. Soc* 2006;128:718. [PubMed: 16417351] (b) Skucas E, Kong J-R, Krische MJ. *J. Am. Chem. Soc* 2007;129:7242. [PubMed: 17511459] (c) Barchuk A, Ngai M-Y, Krische MJ. *J. Am. Chem. Soc* 2007;129:8432. [PubMed: 17571894] (d) Barchuk A, Ngai M-Y, Krische MJ. *J. Am. Chem. Soc* 2007;129:12644. [PubMed: 17914825] Aldol and Mannich addition: Jung C-K, Garner SA, Krische MJ. *Org. Lett* 2006;8:519. [PubMed: 16435874] (e) Jung C-K, Krische MJ. *J. Am. Chem. Soc* 2006;128:17051. [PubMed: 17177457] (f) Garner SA, Krische MJ. *J. Org. Chem* 2007;72:5843. [PubMed: 17583961] (g) Bee C, Iida H, Han SB, Hassan A, Krische MJ. *J. Am. Chem. Soc* 2008;130 In Press. (h) C=O Allylation: Skucas E, Bower JF, Krische MJ. *J. Am. Chem. Soc* 2007;129:12678. [PubMed: 17900123] (i) Bower JF, Skucas E, Patman RL, Krische MJ. *J. Am. Chem. Soc* 2007;129:15134. [PubMed: 18020342]
- (3). For reviews on hydrogen auto-transfer, see: (a) Guillena G, Ramón DJ, Yus M. *Angew. Chem. Int. Ed* 2007;46:2358. (b) Hamid MHSA, Slatford PA, Williams JMJ. *Adv. Synth. Catal* 2007;349:1555.
- (4). Withstanding work cited in reference 2i and ⁵, reported hydrogen auto-transfer processes involve three fundamental steps: (i) alcohol oxidation, (ii) carbonyl condensation/olefination, (iii) olefin reduction to deliver saturated products.
- (5). Aryl amine-olefin hydrogen auto-transfer provide products of imine addition from the amine oxidation level, see: Herzon SB, Hartwig JF. *J. Am. Chem. Soc* 2007;129:6690. [PubMed: 17474747] 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. [PubMed: 18081296]

- (7). For an example of catalytic metal-hydride mediated C-C coupling using isopropanol as a hydride donor, see: Gligorich KM, Cummings SA, Sigman MS. *J. Am. Chem. Soc* 2007;129:14193. [PubMed: 17963397]
- (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. [PubMed: 11440574] (g) Sato Y, Saito N, Mori M. *J. Org. Chem* 2002;67:9310. [PubMed: 12492333] (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. [PubMed: 16178570]
- (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. [PubMed: 12153217] (g) Sato Y, Sawaki R, Saito N, Mori M. *J. Org. Chem* 2002;67:656. [PubMed: 11856003] (h) Jang H-Y, Huddleston RR, Krische MJ. *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. [PubMed: 16802822] (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. [PubMed: 17269780] (l) Sato Y, Hinata Y, Seki R, Oonishi Y, Saito N. *Org. Lett* 2007;9:5597. [PubMed: 18020355]
- (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., editor. *Modern Organonickel Chemistry*. Wiley-VCH; Weinheim, Germany: 2005. (e) Kimura 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 Bu₄Ni, a 7:1 ratio of **1c** and **1d** was formed along with significant amounts (*ca.* 10 %) of *anti*-**1c**. Other halide sources, such as Bu₄NBr and Bu₄NCl, were less effective and the use of NaI resulted in minimal consumption of starting material. At present, the precise role of the Bu₄Ni 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.

Scheme 1.

Carbonyl & Imine Addition *via* Hydrogen Auto-Transfer.

Scheme 2.
Isotopic labeling experiments.

Table 1

7b, R₁ = 5-piperonyl
 8b, R₁ = 2-Thienyl
 9b, R₁ = 2-indolyl

4b, R₁ = *p*-CO₂Me
 5b, R₁ = *m*-MeOPh
 6b, R₁ = 3-NO₂-4-BrPh

96% Yield
 11:1, **2c:2d**

66% Yield
 25:1, **3c:3d**

7b, R₁ = 5-piperonyl
 8b, R₁ = 2-Thienyl
 9b, R₁ = 2-indolyl

4b, R₁ = *p*-CO₂Me
 5b, R₁ = *m*-MeOPh
 6b, R₁ = 3-NO₂-4-BrPh

88% Yield
 17:1, **5c:5d**

73% Yield
 33:1, **6c:6d**

7b, R_1 = 5-piperonyl
 8b, R_1 = 2-Thienyl
 9b, R_1 = 2-indolyl

4b, R_1 = $p\text{-CO}_2\text{Me}$
 5b, R_1 = $m\text{-MeOPh}$
 6b, R_1 = 3- NO_2 -4-Br-Ph

^a Cited yields are of isolated material. Standard conditions employ 1 equiv. of alcohol and 12 equiv. 1,3-cyclohexadiene.

^b Cited yields are of isolated material. Standard conditions employ 1 equiv. of aldehyde and 4 equiv. 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.