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Iridium-Catalyzed C−C Bond Forming Hydrogenation: Direct Regioselective Reductive Coupling of Alkyl-Substituted Alkynes to Activated Ketones

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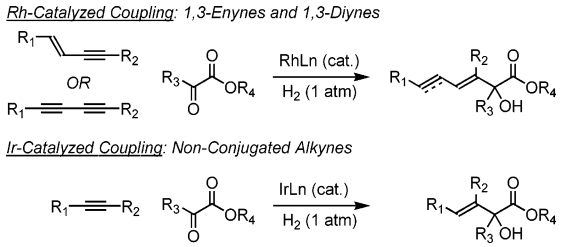
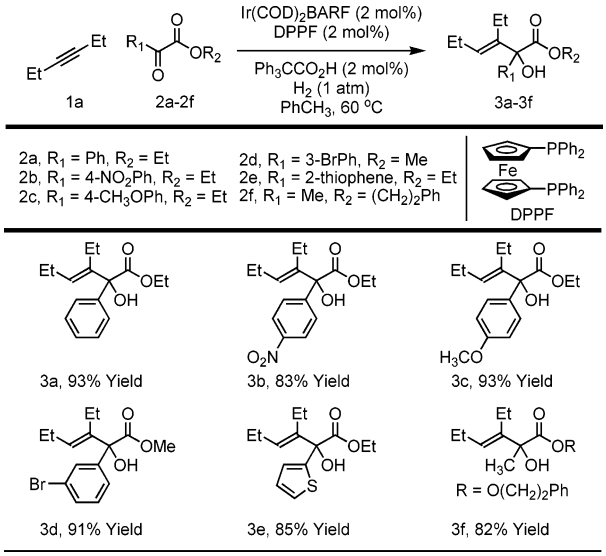
Clean, cost-effective and powerful, catalytic hydrogenation is the foremost method utilized for the reduction of organic compounds. Studies from our laboratory reveal that hydrogenation also may be exploited as a means of reductive C−C coupling, constituting a novel adjunct to cross-coupling chemistry.[1] Specifically, hydrogen-mediated couplings of conjugated enones,[1a−d,k] dienes,[1e] enynes,[1f,l] and diynes[1g,n] to carbonyl and imine[1j] partners have been developed. Further, hydrogenation of 1,6-diynes, 1,6-enynes,[1h,l] and 1,6-alkynals[1m] furnish products of reductive carbocyclization. These studies are among the first hydrogenative C−C couplings beyond hydroformylation.[2]

To date, all hydrogenative couplings developed in our laboratory have employed cationic rhodium precatalysts.[1] Here, the first iridium-catalyzed hydrogenative couplings are disclosed, which significantly extend the scope of hydrogenative alkyne−carbonyl coupling.[1,3,4] Whereas rhodium-catalyzed couplings of this type are restricted to conjugated alkynes (1,3-enynes[1f,l] and 1,3-diynes[1g,n]), corresponding iridium-catalyzed couplings are applicable to commercially available nonconjugated, alkyl-substituted alkynes. Further, in most cases, nonsymmetric alkyl-substituted alkynes couple in a highly regioselective fashion.



In hydrogenative alkyne−carbonyl coupling, our collective studies suggest that a key feature of the catalytic mechanism involves oxidative coupling of the π-unsaturated reactants to afford an oxametallacyclic intermediate.[1l] Hydrogenolytic cleavage of this species via σ-bond metathesis furnishes the coupling product with concomitant regeneration of the catalyst. We speculate that π-backbonding in the metal−alkyne complex[5] facilitates this oxidative coupling event. For rhodium, a relatively weak π-donor, conjugated alkynes, which embody lower lying LUMOs, more readily engage in carbonyl coupling than their nonconjugated counterparts. Iridium is a stronger π-donor than rhodium[6] due to relativistic effects.[7] These data suggest that iridium complexes may catalyze the hydrogenative coupling of nonconjugated alkynes that embody higher lying LUMOs. The veracity of this analysis is supported by the following results. Upon exposure of 3-hexyne **1a** (300 mol %) to α-ketoesters **2a**−**2f** (100 mol %) under 1 atm of hydrogen in the presence of Ir(COD)$_2$BARF (BARF = {3,5-(CF$_3$)$_2$C$_6$H$_3$}$_4$B$^{\ominus}$) (2 mol %), DPPF (2 mol %), and triphenylacetic acid (2 mol %), α-hydroxyesters **3a**−**3f** are obtained in excellent yield as single alkene geometrical isomers (Table 1). Similarly, 1-phenylpropyne **1b** (300 mol%) couples to α-ketoesters **2a**−**2e** and **2g** (100 mol %).

Table 1. Hydrogen-Mediated Reductive Coupling of Alkyl-Substituted 3-Hexyne **1a** to α-Ketoesters **2a**−**2f**[a]



[a] Cited yields are of isolated material. See Supporting Information for further details.

under nearly identical conditions to afford α-hydroxyesters **4a**−**4f**. With the exception of adduct **4f**, coupling occurs in a highly regioselective fashion, proximal to the methyl terminus of alkyne **1b** (Table 2). Notably, as demonstrated by the formation of adducts **3b**, **4b**, **3d**, and **4d**, nitroarene and bromoarene moieties remain intact under the conditions of hydrogen-mediated coupling. Finally, the coupling of alkynes **1c**−**h** to α-ketoester **2c** was explored. Despite its volatility, 2-butyne **1c** couples in excellent yield. The nonsymmetric alkyl-substituted alkyne, 4-methyl-2-pentyne **1d**, couples regioselectively proximal to the methyl terminus. Fluorophenyl (**1e**, **1f**), methoxyphenyl (**1g**), and heteroaryl-substituted alkynes all couple in excellent yield with complete control of regioselectivity and olefin geometry.

Reductive coupling of 3-hexyne **1a** to α-ketoester **2a** under an atmosphere of elemental deuterium provides, after chromatographic isolation, *deuterio*-**3a** (95% ^{2}H incorporation). Direct analysis of the reaction mixture by electron impact mass spectrometric (EI-MS) analysis reveals the presence of the product incorporating deuterium at both carbon and oxygen. Upon chromatographic isolation, the deuterium at oxygen is lost through exchange. These data are consistent with a catalytic mechanism involving alkyne−carbonyl oxidative coupling to furnish an oxametallacyclic intermediate, which is protonolytically cleaved by the Brønsted acid cocatalyst to furnish a cationic iridium carboxylate. Hydrogenolysis of the Ir−O bond followed by C−D reductive elimination delivers *deuterio*-**3a**, along with the starting cationic iridium complex to close the catalytic cycle (Scheme 1). In the absence of the Brønsted acid cocatalyst, the couplings proceed more slowly and are accom-

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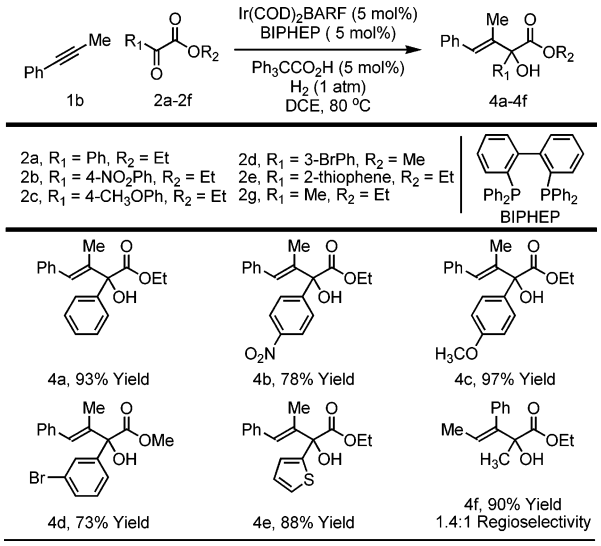
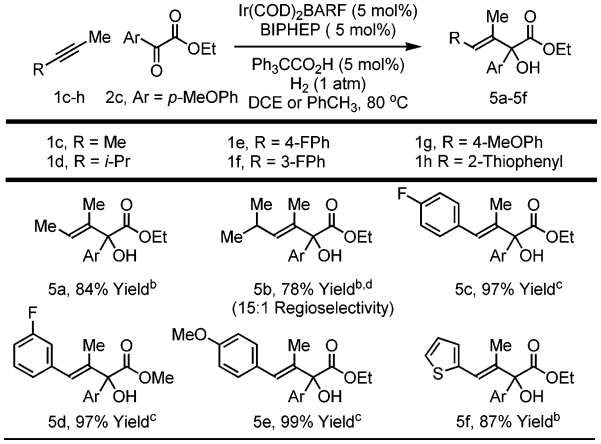
Table 2. Hydrogen-Mediated Reductive Coupling of 1-Phenylpropyne **1b** to α-Ketoesters **2a**−**2e**, **2g**[a]



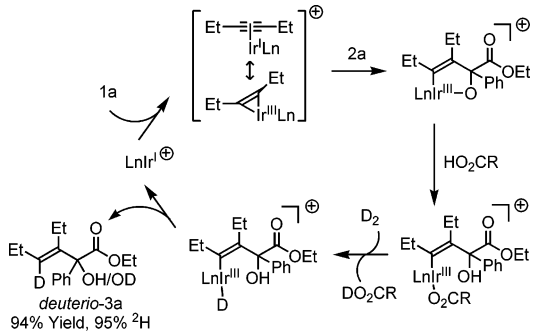
[a] Cited yields are of isolated material. See Supporting Information for further details.

Table 3. Hydrogen-Mediated Reductive Coupling of Alkynes **1c**−**h** to α-Ketoesters **2c**[a]

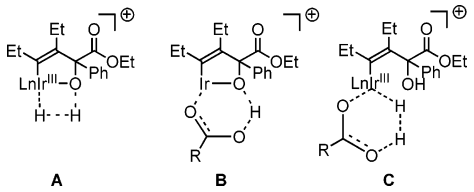


[a] Cited yields are of isolated material. See Supporting Information for further details. [b] Toluene was used as solvent. [c] 1,2-Dichloroethane was used as solvent. [d] The reaction was performed at 35 °C using DPPF as ligand.

Scheme 1. Plausible Catalytic Cycle as Supported by ^{2}H-Labeling



panied by over-reduction of the olefinic product. Excess Brønsted acid does not diminish the extent of deuterium incorporation. Recent studies by Musashi and Sakaki[8] suggest that Brønsted acid cocatalysts may accelerate coupling by circumventing four-centered transition structures for σ-bond metathesis (**A**), as required for direct hydrogenolysis of the putative oxametallacyclic intermediate, with six-centered transition structures (**C**) for hydrogenolysis of iridium carboxylates derived upon protonolysis of the oxametallacycle. Protonolysis itself may occur through a six-centered transition structure (**B**). Studies aimed at elucidating the precise role of Brønsted acid cocatalysts in hydrogenative couplings are currently underway.



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Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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