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Enantioselective Reductive Coupling of 1,3-Enynes to Heterocyclic Aromatic Aldehydes and Ketones via Rhodium-Catalyzed Asymmetric Hydrogenation: Mechanistic Insight into the Role of Brønsted Acid Additives

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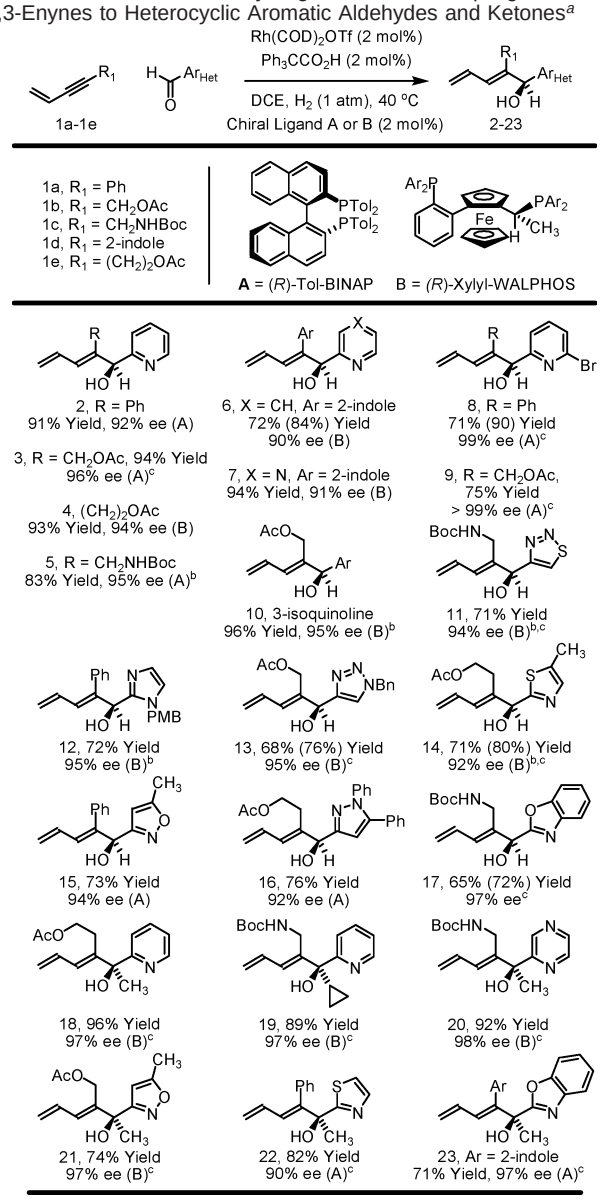
Although alkene hydroformylation represents the largest volume application of homogeneous metal catalysis,[1] systematic efforts toward the development of hydrogen-mediated C−C bond formations that extend beyond couplings to carbon monoxide have been absent from the literature, withstanding recent work from our laboratory.[2,3] Through the use of cationic rhodium precatalysts, the hydrogen-mediated reductive coupling of conjugated enones,[2a−d,k] dienes,[2e] enynes,[2f,j,l,n] and diynes[2g,o] to carbonyl and imine[2j] partners has been devised. Further, hydrogenation of 1,6-diynes, 1,6-enynes,[2h,i] and 1,6-alkynals[2m] was found to provide products of reductive carbocyclization. These studies rank among the first examples of hydrogen-mediated C−C bond formation that proceed in the absence of carbon monoxide.[3]

Recently, we found that Brønsted acid co-catalysts greatly enhance both rate and conversion in hydrogen-mediated alkyne−carbonyl coupling reactions.[2l] However, all hydrogen-mediated alkyne couplings developed to date require vicinal dicarbonyl partners. It was postulated that heterocyclic aromatic aldehydes and ketones that are isoelectronic with respect to the vicinal dicarbonyl motif might be viable electrophilic partners. Here, we disclose that hydrogenation of conjugated enynes in the presence of such heterocyclic aromatic aldehydes and ketones using chirally modified rhodium catalysts enables direct formation of carbonyl addition products with exceptional levels of asymmetric induction and regiocontrol.[4−6] Further, upon use of the Akiyama−Terada-type phosphoric acid derived from BINOL as the Brønsted acid co-catalyst,[7,8] highly optically enriched products of C−C coupling are obtained using an achiral rhodium catalyst.

Our initial studies focused on the reductive coupling of enyne **1a** to 2-pyridinecarboxaldehyde (100 mol %). Gratifyingly, hydrogenation of these two compounds at 40 °C using a cationic rhodium catalyst modified by (*R*)-Tol-BINAP provides the reductive coupling product **2** in 91% isolated yield and 92% ee. Isomeric 3- and 4-pyridinecarboxaldehydes do not participate in the coupling. These conditions were applied to the reductive coupling of diverse heterocyclic aromatic aldehydes to enynes **1a**−**e** (Table 1). In cases where the (*R*)-Tol-BINAP-modified catalyst provides insufficient levels of asymmetric induction, catalysts ligated by (*R*)-xylyl-WALPHOS were found to confer high levels of optical enrichment. Notably, coupling proceeds efficiently in the presence of multiple Lewis basic nitrogen atoms (**7**, **13**) and sulfur atoms (**11**, **14**). Further, as demonstrated by the formation of **18**−**23**, heterocyclic aromatic ketones are efficient coupling partners (Table 1). Absolute stereochemical assignments are based upon single-crystal X-ray diffraction analysis of the carbamate derived upon reaction of coupling product **2** with the isocyanate derived from phenylalanine methyl ester. Finally, the diene side chain of the coupling products may be selectively transformed, providing access to a variety of functional group arrays (Table 2). To gain further insight into the catalytic mechanism and, in particular, the role of the Brønsted acid co-catalyst, the reductive coupling of enyne **1a** to 2-pyridinecarboxaldehyde was performed using an achiral rhodium catalyst in the presence of substoichiometric quantities of the Akiyama−

Table 1. Enantioselective Hydrogen-Mediated Coupling of 1,3-Enynes to Heterocyclic Aromatic Aldehydes and Ketones[a]



[a] Cited yields are of isolated material and represent the average of two runs. Yields indicated parenthetically are based upon recovered starting material. All reactions simply employ hydrogen balloons and typically require less than 3 h to reach completion. See Supporting Information for detailed experimental procedures. [b] Reaction was run at 65 °C. [c] Reaction was performed at 4 mol % catalyst loadings. [d] The opposite sense of asymmetric induction is observed upon use of (*R*)-Tol-BINAP and (*R*)-xylyl-WALPHOS. The indicated enantiomers represent the major enantiomers obtained using (*R*)-Tol-BINAP as ligand.[9]

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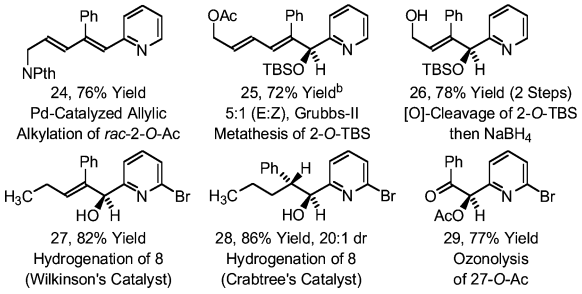
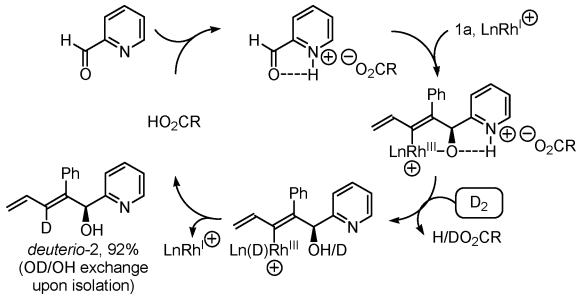
Table 2. Elaboration of Coupling Products **2** and **8**[a]

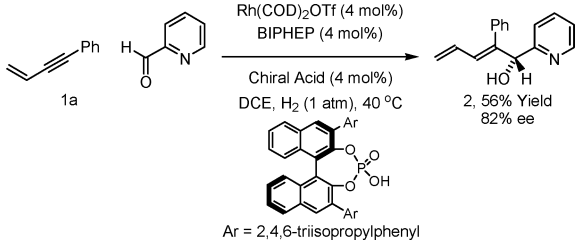


[a] Cited yields are of pure isolated material and represent the average of two runs. See Supporting Information for detailed experimental procedures. [b] Yield based on recovered starting material.

Scheme 1. Plausible Catalytic Mechanism as Supported by the Effect of Chiral Brønsted Acid Catalyst and ^{2}H-Labeling



Terada-type phosphoric acid derived from BINOL.[7,8] Remarkably, the coupling product **2** exhibits substantial levels of optical enrichment (82% ee). These data are consistent with a catalytic mechanism in which the Brønsted acid co-catalyst protonates and/or forms a strong hydrogen bond to 2-pyridinecarboxaldehyde in advance of the stereogenic C−C bond forming event. Further, the high levels of optical enrichment suggest that the LUMO lowering effects of protonation and/or hydrogen bonding dramatically accelerate the rate of C−C coupling. In analogous experiments involving pyruvates and glyoxalates,[2l] chiral Brønsted acid co-catalysts do not provide optically enriched product, suggesting that protonation of **1a** is responsible for asymmetric induction and not ion-pairing to rhodium.



Reductive coupling of enyne **1a** to 2-pyridinecarboxaldehyde under a deuterium atmosphere provides, after isolation by silica gel chromatography, *deuterio*-**2**. The collective data suggest a catalytic mechanism in which association of the Brønsted acid to 2-pyridinecarboxaldehyde precedes oxidative coupling with the conjugated enyne to form an oxarhodacyclic intermediate. Deuteriolytic cleavage of the metallacycle via σ bond metathesis, which likely occurs through a six-centered transition structure,[9] releases the Brønsted acid co-catalyst and delivers a cationic Rh(III)(vinyl)(deuteride), which reductively eliminates to form the *deuterio*-**2**, along with the starting cationic rhodium complex to complete the catalytic cycle.

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Supporting Information Available: Spectral data for all new compounds, along with HPLC traces of racemic and optically enriched coupling products. Single-crystal X-ray diffraction data for of the carbamate derived upon reaction of coupling product **2** with the isocyanate derived from phenylalanine methyl ester. This material is available free of charge via the Internet at http://pubs.acs.org.

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