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First Catalytic Reductive Coupling of 1,3-Diynes to Carbonyl Partners: A New Regio- and Enantioselective C−C Bond Forming Hydrogenation

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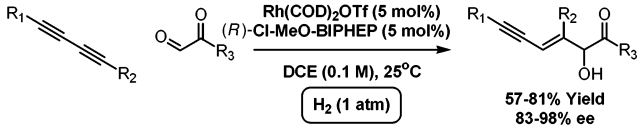
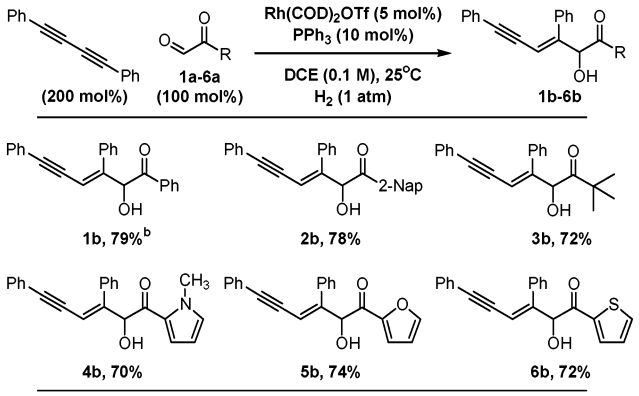
Since the discovery of catalytic hydrogenation over a century ago,[1,2] C−C bond formation has only been observed under hydrogenation conditions in the case of alkene hydroformylation and Fischer−Tropsch type processes, that is, catalytic processes involving migratory insertion of carbon monoxide.[3,4] Recently, a catalytic reductive coupling of enones with aldehyde or ketone partners under hydrogenation conditions was disclosed from our lab.[5] A reductive coupling of 1,3-cyclohexadiene and glyoxals under hydrogenation conditions was subsequently developed.[6] For such reductive C−C bond formations, a key feature relates to the heterolytic activation of elemental hydrogen by cationic rhodium catalysts, that is, $H_2 + Rh^+X^- \rightarrow Rh{-}H + HX$.[7,8] Heterolytic activation of hydrogen promotes monohydride based catalytic cycles, which attenuate simple hydrogenation pathways by disabling alkyl-hydrogen reductive elimination manifolds.[5,6]

The catalytic reductive coupling of enones and dienes to carbonyl partners under hydrogenation conditions suggests the feasibility of activating other π-unsaturated systems as nucleophiles, thereby enabling a family of catalytic C−C bond forming hydrogenations. Here, we disclose a new example of this uncommon reaction type. Upon exposure of diynes and glyoxals to cationic Rh(I) catalysts under 1 atm of hydrogen gas, regioselective condensation occurs to afford highly unsaturated enyne products without over-reduction.[9] Moreover, in the presence of chiral phosphine ligands, reductive coupling products are obtained in high enantiomeric excess at ambient temperature and pressure.



Given the elegant studies of Osborn, who reports the selective hydrogenation of alkynes to *cis*-olefins using cationic rhodium catalysts,[10] it became of interest to determine whether the organometallic intermediates derived upon alkyne hydrogenation are subject to electrophilic trapping by exogenous carbonyl partners. Accordingly, a range of alkyne and aldehyde partners were hydrogenated using $Rh(COD)_2OTf$ (5 mol %) with Ph_3P (10 mol %) as ligand at ambient temperature and pressure in dichloroethane solvent (0.1 M). Through this assay, it was found that diphenylbutadiyne readily condenses with phenyl glyoxal **1a** to afford the conjugated enyne **1b** in 79% yield as a single regio- and alkene stereoisomer. The structure assignment of **1b** is corroborated by single-crystal X-ray diffraction analysis. Under these conditions, the catalytic reductive coupling of diphenylbutadiyne with diverse glyoxal partners was examined. Both aromatic and aliphatic glyoxals provide reductive coupling products **1b**−**3b** in good yield. Heteroaromatic glyoxal partners also participate in the reaction, as evidenced by the formation of coupling products **4b**−**6b**. Reductive condensation of diphenylbutadiyne with ethyl glyoxalate or simple aldehydes does not occur under these conditions. Additionally, simple alkynes are not viable reacting partners. In accordance with the requirement of cationic rhodium catalysts, an 80% yield of **1b** is obtained using $Rh(COD)_2BF_4$ as precatalyst, whereas no reductive coupling product is obtained using Wilkinson's catalyst (Table 1).

Table 1. Catalytic Reductive Condensation of Diphenylbutadiyne with Assorted Glyoxals under Hydrogenation Conditions[a]



[a] Procedure: To a solution of glyoxal (100 mol %) and diphenylbutadiyne (200 mol %) in DCE (0.1 M) at ambient temperature were added $Rh(COD)_2OTf$ (5 mol %) and Ph_3P (10 mol %). The system was purged with hydrogen gas, and the reaction was allowed to stir at 25 °C under 1 atm of hydrogen until complete consumption of substrate, at which point the reaction mixture was evaporated onto silica gel and the product purified by silica gel chromatography. [b] Using $Rh(COD)_2BF_4$ as precatalyst, **1b** is obtained in 80% yield.

To explore the feasibility of an enantioselective variant, the reductive condensation of diphenylbutadiyne with phenyl glyoxal **1a** was performed in the presence of assorted chiral ligands. Whereas ligands incorporating *N*-donors inhibit the reaction, triarylphosphines give good chemical conversion. Among the chiral triarylphosphines assayed, (*R*)-Cl-MeO-BIPHEP proved superior, providing a 74% yield of **1b** in 76% enantiomeric excess in dichloroethane solvent. Through variation of the reaction medium, benzene was identified as the ideal solvent, affording a 74% yield of **1b** in 91% enantiomeric excess. These conditions proved general for the enantioselective condensation of diphenylbutadiyne with glyoxals **1a**−**6a**. Condensation products **1b**−**6b** are produced in yields and enantiomeric excesses ranging from 71−77% and 86−95%, respectively. Notably, highly enantioselective C−C bond formation is achieved at ambient temperature.

The regioselectivity of the catalytic enantioselective reductive coupling was further examined through couplings to nonsymmetric alkyl-terminated 1-phenylbutadiynes to phenyl glyoxal **1a** and *tert*-butyl glyoxal **3a**. In all cases, coupling occurs proximal to the phenyl moiety, as supported by two-dimensional ^1H NMR analysis. Condensation products **7b**−**10b** are produced in yields and enantiomeric excesses ranging from 57%−80% and 83−98%, respectively (Table 3).

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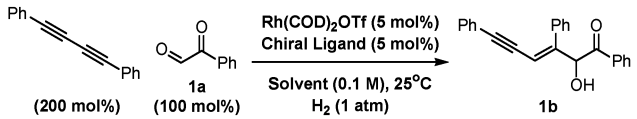
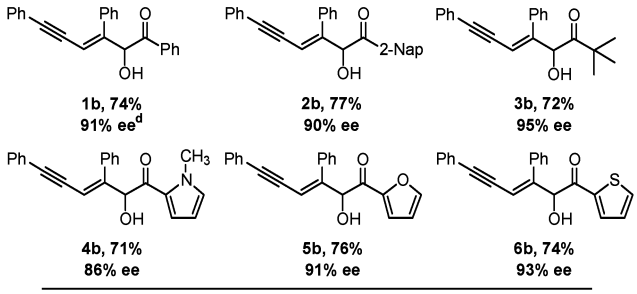
Table 2. Enantioselective Catalytic Reductive Condensation of Diphenylbutadiyne with Assorted Glyoxals under Hydrogenation Conditions[a]

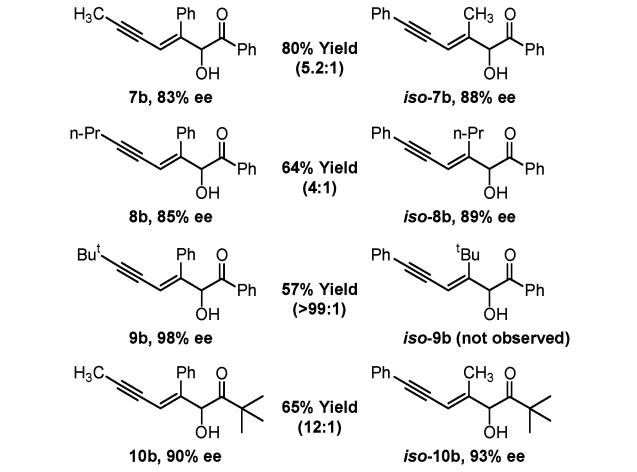


Entry	Ligand	Solvent	Yield[b]	e.e.[c]
1	(*R*)-BINAP	DCE	72%	47%
2	(*R*)-Phanephos	DCE	79%	67%
3	(*R*)-Cl-OMe-BIPHEP	DCE	74%	76%
4	(*R*)-Cl-OMe-BIPHEP	EtOH	69%	80%
5	(*R*)-Cl-OMe-BIPHEP	THF	67%	82%
6	**(*R*)-Cl-OMe-BIPHEP**	**PhH**	**74%**	**91%**



[a] Procedure: As described in Table 1, but substituting (*R*)-Cl-MeO-BIPHEP for Ph_3P. [b] Isolated yields after purification by silica gel chromatography. [c] Enantiomeric excess determined by chiral stationary phase HPLC analysis. [d] Using $Rh(COD)_2BF_4$ as precatalyst, **1b** is obtained in 77% yield and 90% enantiomeric excess.

Table 3. Enantioselective Catalytic Reductive Condensation of Nonsymmetric Butadiynes with Phenylglyoxal and *tert*-Butylglyoxal under Hydrogenation Conditions[a]

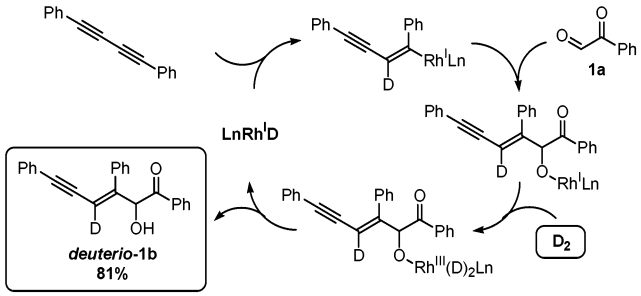


[a] Procedure: As described in Table 2, but with 10 mol % catalyst loading.

Reductive condensation of diphenylbutadiyne with phenyl glyoxal **1a** performed under 1 atm of D_2 provides the monodeuterated product *deuterio*-**1b** in 81% yield. These results are consistent with the catalytic mechanism proposed in Scheme 1. This result clearly excludes pathways involving tandem alkyne hydroacylation-carbonyl reduction.

In summation, the present studies are among the first examples of the electrophilic trapping of organometallic intermediates derived

Scheme 1. Proposed Mechanism as Corroborated by Catalytic Reductive Coupling of Diphenylbutadiyne with **1a** under 1 atm of D_2[a]



[a] Procedure: As described in Table 1, but substituting D_2(g) for H_2(g).

transiently under the conditions of catalytic hydrogenation.[5,6] Future studies will be devoted to expanding the scope of this new reaction type through the development of improved second generation catalyst systems with the goal of achieving related catalytic couplings to simple alkyne and alkene partners.

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Supporting Information Available: Spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS). X-ray crystallographic data for compound **1b**. Chiral stationary phase HPLC traces for optically enriched products **1b**−**7b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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