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Enantioselective Reductive Coupling of 1,3-Enynes to Glyoxalates Mediated by Hydrogen: Asymmetric Synthesis of β,γ-Unsaturated α-Hydroxy Esters

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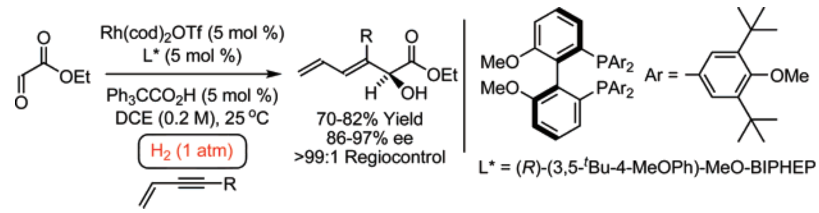
ABSTRACT



Catalytic hydrogenation of 1,3-enynes 1a–8a in the presence of ethyl glyoxalate at ambient pressure and temperature using a rhodium catalyst modified by (*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP results in highly regio- and enantioselective reductive coupling to furnish the corresponding α-hydroxy esters 1b–8b. As demonstrated by the elaboration of α-hydroxy ester 1b, the terminal and internal olefin moieties embodied by the diene side chain are subject to selective manipulation, one over the other.

The Fischer−Tropsch reaction[1a,b] and alkene hydroformylation[1c] are practiced on enormous scale and may be viewed as prototypical hydrogen-mediated C−C bond formations. Whereas these processes rely upon the use of carbon monoxide as a coupling partner, only recently has it been shown that catalytic hydrogenation may induce C−C coupling between π-unsaturated reactants and conventional electrophilic partners in the form of carbonyl compounds and imines.[2−7] Through the use of cationic rhodium and iridium precatalysts, the hydrogenative coupling of conjugated enones,[3] conjugated alkenes,[4] and both conjugated[5a−g] and nonconjugated alkynes[5h,i,j,k] to carbonyl and imine[3h,5c,j,k] partners have been devised. In addition, hydrogenation of 1,6-diynes, 1,6-enynes, and 1,6-alkynals is found to provide products of reductive carbocyclization.[6]

In the course of studies aimed at the development of methods for alkyne−carbonyl reductive coupling,[8−10] highly enantioselective direct hydrogen-mediated couplings of 1,3-enynes to pyruvates and α-ketoesters using cationic rhodium catalysts modified by (*R*)-xylyl-WALPHOS were developed.[5e] More recently, related couplings of trialkylsilyl-substituted 1,3-diynes to glyoxalates using cationic rhodium catalysts modified by (*R*)-Cl,MeO-BIPHEP were devised.[5f] Parallel efforts toward the enantioselective reductive coupling of 1,3-enynes to glyoxalates were impeded by the fact that commercially available chelating chiral phosphine ligands

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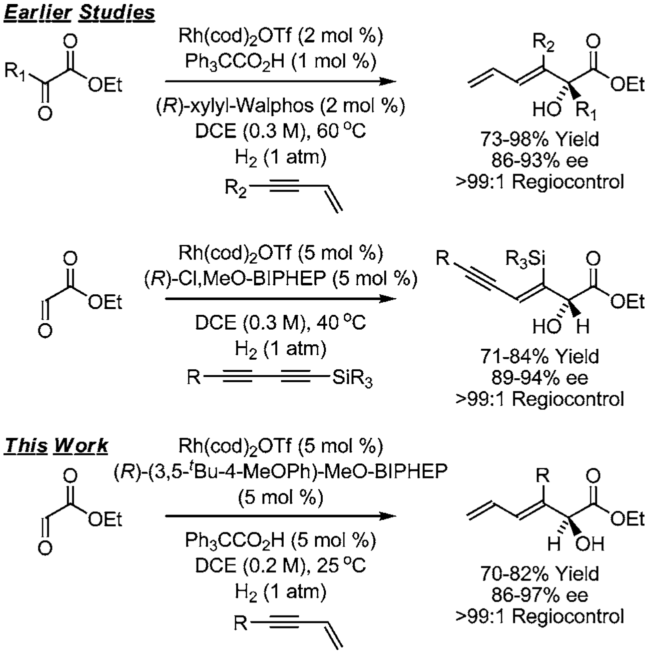
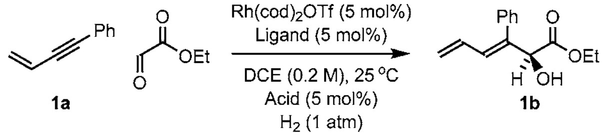
Scheme 1. α-Hydroxy Esters via Direct Enantioselective Reductive Coupling of Conjugated Alkynes to Pyruvates and Glyoxalates Mediated by Hydrogen



uniformly failed to promote high levels of asymmetric induction. Here, we report that cationic rhodium complexes modified by (*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP catalyze the reductive coupling of 1,3-enynes **1a**−**8a** to ethyl glyoxalate under hydrogenation conditions to furnish the corresponding α-hydroxy esters **1b**−**8b** in good to excellent yield and with high levels of asymmetric induction (Scheme 1).

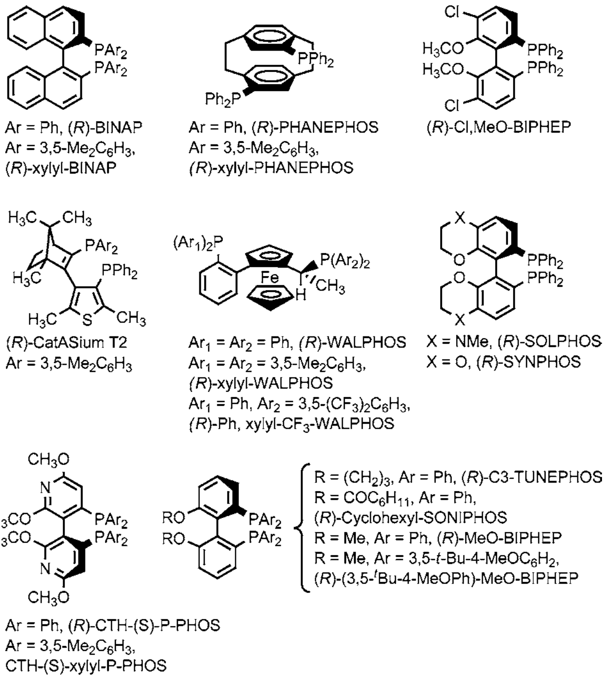
Preliminary studies involved a ligand assay, wherein 1,3-enyne **1a** (200 mol %) was hydrogenated in the presence of ethyl glyoxalate (100 mol %) at ambient temperature and pressure in dichloroethane (0.2 M) using a catalyst derived from $Rh(cod)_2OTf$ (5 mol %) and a chiral bidentate phosphine ligand (5 mol %). Using (*R*)-BINAP as the ligand, the desired product of reductive coupling **1b** was obtained in 84% yield and 63% enantiomeric excess as a single regioisomer and with complete control of olefin geometry. This promising result stimulated further efforts toward the identification of highly enantioselective catalysts for the reductive coupling of enyne **1a** to ethyl glyoxalate. Numerous commercially available chiral bidentate phosphine ligands were assayed under the standard coupling conditions specified above, which enabled a rough correlation between ligand structural features vis-à-vis conversion and enantioselection (Table 1). In general, aryl substitution at phosphorus is required for high levels of conversion. A single alkyl substituent at phosphorus, as in the case of WALPHOS type ligands, significantly decreases the isolated yield (Table 1, entries 7−9). In the BINAP, PHANEPHOS and WALPHOS series of ligands, the xylyl derivatives were slightly better at enforcing asymmetric induction than the corresponding phenyl derivatives (Table 1, entries 1−2, 3−4, and 7−9, respectively). Among the phenyl-substituted chiral chelating phosphine ligands assayed, (*R*)-MeO-BIPHEP enforced the highest levels of asymmetric induction (Table 1, entry 16). Stimulated by this result and the aforementioned trends, (*R*)-

Table 1. Enantioselective Hydrogen-Mediated Reductive Coupling of Conjugated Enyne **1a** to Ethyl Glyoxalate[a]



1a **1b**

Entry	Rh-Catalyst	Chiral Ligand	Acid	Yield%	ee%
1	$Rh(cod)_2OTf$	(*R*)-BINAP	---	84	63
2	$Rh(cod)_2OTf$	(*R*)-3,5-xylyl-BINAP	---	69	69
3	$Rh(cod)_2OTf$	(*R*)-PHANEPHOS	---	62	48
4	$Rh(cod)_2OTf$	(*R*)-3,5-xylyl-PHANEPHOS	---	51	56
5	$Rh(cod)_2OTf$	(*R*)-Cl,MeO-BIPHEP	---	70	81
6	$Rh(cod)_2OTf$	(*R*)-CatASium T2	---	28	32
7	$Rh(cod)_2OTf$	(*R,R*)-WALPHOS	---	24	15
8	$Rh(cod)_2OTf$	(*R,R*)-xylyl-WALPHOS	---	29	21
9	$Rh(cod)_2OTf$	(*R*)-Ph, xylyl-CF_3-WALPHOS	---	10	28
10	$Rh(cod)_2OTf$	(*R*)-SOLPHOS	---	70	36
11	$Rh(cod)_2OTf$	(*R*)-SYNPHOS	---	77	64
12	$Rh(cod)_2OTf$	CTH-(*R*)-P-PHOS	---	75	-74
13	$Rh(cod)_2OTf$	CTH-(*R*)-xylyl-P-PHOS	---	74	-69
14	$Rh(cod)_2OTf$	(*R*)-C3-TUNEPHOS	---	68	46
15	$Rh(cod)_2OTf$	(*R*)-*c*-Hex-SONIPHOS	---	76	71
16	$Rh(cod)_2OTf$	(*R*)-MeO-BIPHEP	---	71	75
17	$Rh(cod)_2OTf$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	---	65	91
18	$Rh(cod)_2BF_4$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	---	65	90
19	$Rh(cod)_2BARF$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	---	66	93
20	$Rh(cod)_2OTf$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	NPOH	78	25
21	$Rh(cod)_2OTf$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	TPAA	82	95



[a] Cited yields are of isolated material. Enantiomeric excess was determined via chiral stationary-phase HPLC analysis using a Chiralcel OD-H column. Eluant: 2% *i*-PrOH in hexane. Flow rate: 0.5 mL/min. Detection wavelength: 254 nm. Retention times: t_{major} = 16.7 min, t_{minor} = 18.6 min. NPOH = 2-naphthoic acid. TPPA = triphenylacetic acid. See the Supporting Information for further details.

(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP was investigated. Gratifyingly, α-hydroxy ester **1b** was obtained in 65% isolated yield and 91% enantiomeric excess (Table 1, entry 17). Further assay of the rhodium counterion, [Rh(cod)$_2$]X, where X = OTf, BF$_4$, and "BARF" (BARF = B(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_4$), revealed no significant change in isolated yield or enantioselection in response to variation of counterion (Table 1, entries 17−19). In contrast, Brønsted acid additives were found to have a profound effect on both isolated yield and enantioselection. Brønsted acid additives are believed to facilitate the catalytic process by circumventing highly energetic 4-centered transition structures for σ-bond metathesis, as required for direct hydrogenolysis of metallacyclic intermediates, with 6-centered transition structures for hydrogenolysis of rhodium carboxylates derived upon protonolytic cleavage of the metallacycle.[2] Whereas 2-naphthoic acid (5 mol %) significantly increases the isolated yield of **1b**, a dramatic decrease in enantioselection is observed (Table 1, entry 20). For couplings conducted in the presence of triphenylacetic acid, which provide α-hydroxy ester **1b** in 78% isolated yield and 95% enantiomeric excess, an increase in both isolated yield and enantioselection was observed (Table 1, entry 20). Accordingly, these latter conditions were adopted as standard conditions.

To assess scope, conjugated enynes **1a−8a** possessing structurally diverse acetylenic termini were coupled to ethyl glyoxalate under standard conditions (Figure 1). In all cases, C−C coupling occurs at the acetylenic terminus of the conjugated enyne to furnish α-hydroxy esters **1b-8b** as single constitutional isomers with complete control of alkene geometry. The coupling was applicable to conjugated enynes possessing aryl (**1a**, **2a**, **3a**), heteroaryl (**4a**, **8a**), primary alkyl (**6a**, **7a**), and secondary alkyl (**5a**) substituents at the acetylenic terminus. Isolated yields of the α-hydroxy esters **1b−8b** ranged from 70 to 82%, and the levels of enantioselection ranged from 86 to 97% ee (Figure 1). Notably, overreduction of the diene side chain of adducts **1b−8b** was not observed under the conditions of hydrogen-mediated coupling. Absolute stereochemical assignment of α-hydroxy esters **1b−8b** is based upon X-ray diffraction analysis of the amide derived from **1b** and (*R*)-1-(2-naphthyl)ethylamine.

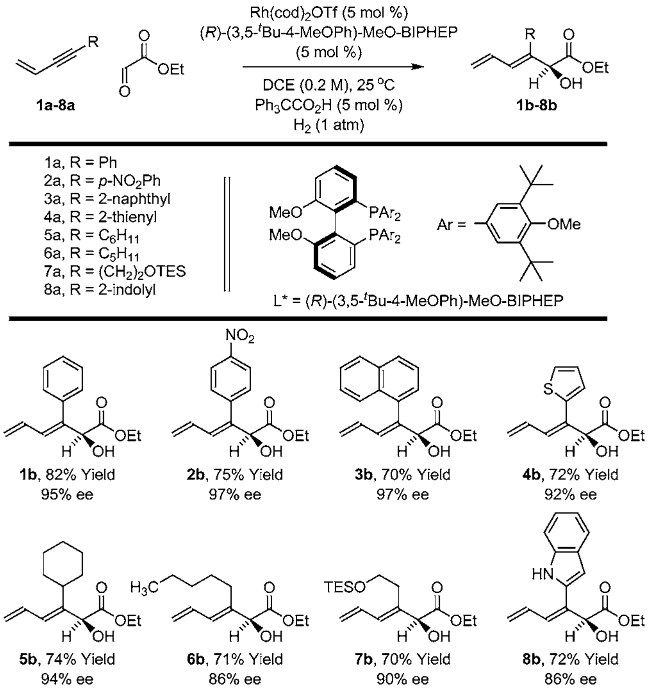


Figure 1. Enantioselective catalytic reductive coupling of substituted 1,3-enynes to ethyl glyoxalate mediated by hydrogen. Cited yields are of isolated material. See the Supporting Information for detailed experimental procedures. Enantiomeric excess was determined via chiral stationary phase HPLC analysis.

Each olefin of the diene side chain of the reductive coupling products **1b−8b** is subject to selective manipulation. To illustrate, α-hydroxy ester **1b** was subjected to the

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following transformations. Hydroxy-directed epoxidation of **1b** catalyzed by OV(acac)$_2$[11] stereoselectively delivers vinyl epoxide **1c**. Oxidative cleavage of the diene terminus using the Lemieux−Johnson protocol furnishes the conjugated enal **1e**[12] Exhaustive reduction of the diene side chain to form the saturated α-hydroxy ester **1d** is achieved upon hydrogenation of **1b** using Crabtree's catalyst.[13] Finally, exposure of diene **1b** to conditions for ruthenium catalyzed cross metathesis with 1,4-diacetoxy-2-butene[14] enables formation of allylic acetate **1f**. The structural assignment of **1c**-**1f** is made in analogy to the corresponding pyruvate coupling products (Figure 2).[5e]

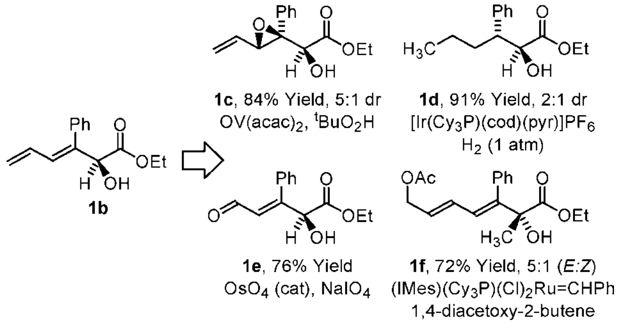

Figure 2. Elaboration of coupling product **1b**.

In summary, we report a regio- and enantioselective hydrogenative coupling of substituted 1,3-enynes to ethyl glyoxalate catalyzed by rhodium. Good to excellent levels of asymmetric induction are achieved using (*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP as chiral ligand with triphenylacetic acid as a Brønsted acid cocatalyst. A stereochemical model accounting for the high levels of enantioselection enforced by (*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP will be disclosed in due course. These studies serve as a prelude to our long-term goal of developing hydrogenation catalysts enabling reductive C−C coupling of simple, commercially available nonconjugated alkynes to diverse aldehydes en route to optically enriched allylic alcohols.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). Single-crystal X-ray diffraction data corresponding to the amide derived from **1b** and (*R*)-(+)-1-(2-naphthyl)ethylamine. This material is available free of charge via the Internet at http://pubs.acs.org.

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