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Highly Enantioselective Direct Reductive Coupling of Conjugated Alkynes and α-Ketoesters via Rhodium-Catalyzed Asymmetric Hydrogenation

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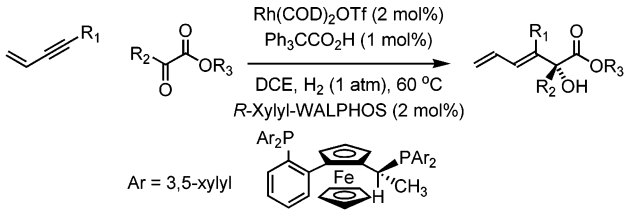
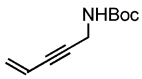
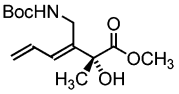
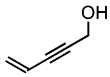
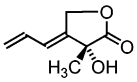
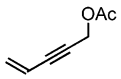
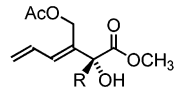
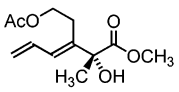
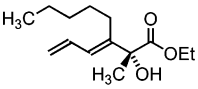
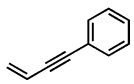
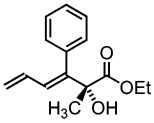
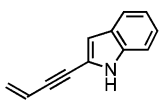
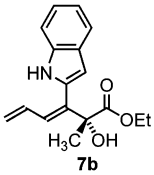
Asymmetric hydrogenation is the most broadly utilized catalytic enantioselective process employed industrially and accounts for over half the chiral compounds made by man not produced via resolution.[1] The enormous impact of asymmetric hydrogenation portends an equally powerful approach to enantioselective reductive C−C bond formation mediated by elemental hydrogen. However, since the discovery of the Fischer−Tropsch reaction and alkene hydroformylation, which are restricted to the migratory insertion of carbon monoxide, the field of hydrogen-mediated C−C bond formation has lain fallow. Recognizing the potential of catalytic hydrogenation to serve as a fully atom economical means of reductive C−C bond formation, this topic has become the focus of research in our lab.[2] To date, the hydrogen-mediated reductive coupling of conjugated enones,[2a−d] dienes,[2e] enynes,[2f] and diynes[2g] to carbonyl and imine[2j] partners has been devised, as well as the reductive carbocyclization of 1,6-diynes and 1,6-enynes.[2h,i] These studies are among the first examples of hydrogen-mediated C−C bond formation that proceed in the absence of carbon monoxide.[3] As part of a continuing effort to broaden this emergent class of C−C bond formations, the use of activated ketones as electrophilic partners in hydrogen-mediated C−C bond formation was explored. Here, we disclose that hydrogenation of conjugated enynes in the presence of α-ketoesters using chirally modified rhodium catalysts enables formation of α-hydroxy esters with high levels of asymmetric induction and complete regiocontrol. Further, we find that reaction rate and chemical yield are dramatically enhanced through use of Brønsted acid additives. These studies, which enable concise access to optically enriched α-hydroxy esters, represent the first highly enantioselective direct catalytic reductive couplings of alkynes to activated ketones.[14b]

Catalytic enantioselective additions of preformed organometallics to aldehydes have reached a sophisticated level.[4] Corresponding *ketone* additions remain a challenge.[5] In the case of carbonyl vinylation, an effective strategy involves tandem hydrometalation−transmetalation of alkynes to afford organozinc reagents, which participate in catalyzed additions to aldehydes[6,7] and ketones.[8,9] This approach necessitates stoichiometric use of two metallic reagents. An alternate strategy involves the direct reductive coupling of π-unsaturated substrates to carbonyl compounds[10−14] or imines,[2j,15] which presently encompasses the use of alkenes,[10] alkynes,[11] allenes,[12] enones,[2a−d,13] 1,3-dienes,[2e,11,] 1,3-enynes,[2f,14] and 1,3-diynes[2g] as pronucleophiles.

Our initial efforts on hydrogen-mediated reductive couplings to ketones involved the hydrogenation of 1,3-enyne **1a** in the presence of methyl pyruvate. Gratifyingly, formation of α-hydroxy ester **1b** was observed. Through an assay of chiral ligands, it was revealed that (*R*)-xylyl-Walphos provides excellent levels of asymmetric induction. However, chemical yields varied dramatically in response to aging of the solvent 1,2-dichloroethane (DCE), with older batches of solvent providing better results. It was reasoned that adventitious HCl may promote reductive coupling. Indeed, an assay of Brønsted acid additives reveals that reactions performed with substoichiometric quantities of triphenylacetic acid (1 mol %) in freshly distilled DCE reproducibly gave the coupling product **1b** in 88% isolated yield and 90% ee. In the absence of the Brønsted acid additive, but under otherwise identical conditions, **1b** is produced in only 42% yield and 87% ee.

Table 1. Enantioselective Hydrogen-Mediated Reductive Coupling of Conjugated Enynes **1a**−**7a** to α-Ketoesters[a]

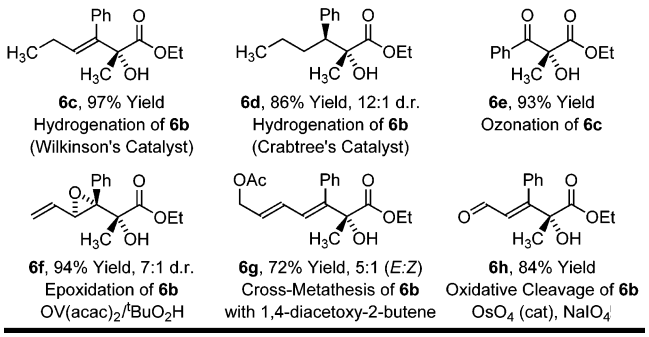


Entry	Substrate	Coupling Product	Yield	ee %
1				
	1a	**1b**	**88%**	**90%**
2				
	2a	**2b**	**80%**	**91%**
3				
	3a	**3b, R = methyl**	**98%**	**90%**
		3c, R = cyclopropyl	**85%**	**88%**
		3d, R = phenyl	**73%**	**91%**
		3e, R = *m*-bromophenyl	**93%**	**90%**
		3f, R = ethyl	**97%**	**86%**
4				
	4a	**4b**	**87%**	**92%**
5				
	5a	**5b**	**96%**	**91%**
6				
	6a	**6b**	**92%**	**92%**
7				
	7a	**7b**	**92%**	**93%**

[a] Cited yields are of pure isolated material and represent the average of two runs. Reaction times are typically less than 3 h. See Supporting Information for detailed experimental procedures.

10.1021/ja056474l CCC: $33.50

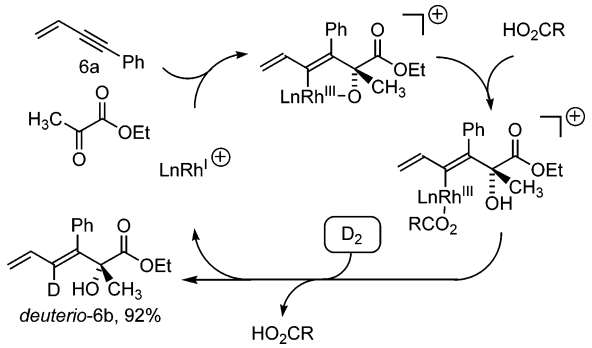
Table 2. Elaboration of Coupling Product **6b**[a]



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

These conditions are applicable to the reductive coupling of conjugated enynes **1a**−**7a** to methyl and ethyl pyruvate.[16] Other α-ketoesters also participate, as demonstrated by the coupling of enyne **3a** to afford products **3c**−**3f**, which are obtained in high yield and good to excellent enantiomeric excess. In all cases, the diene containing coupling products are not subject to over-reduction under the conditions of hydrogen-mediated coupling, and the trisubstituted alkene forms as a single geometrical isomer (Table 1). The functional group array presented by the reductive coupling products offers numerous prospects for further elaboration. For example, the diene containing side chain of **6b** is subject to selective reduction (**6c**, **6d**), selective oxidation (**6e**, **6f**, **6h**), and alkene cross-metathesis (**6g**) (Table 2). The absolute and relative stereochemical assignments of all new compounds are based upon X-ray diffraction analysis of the amides derived from compounds **6d** and **6f** with (*R*)-1-(2-naphthyl)ethylamine.

Reductive coupling of enyne **6a** and ethyl pyruvate under a deuterium atmosphere provides *deuterio*-**6b**. This result is consistent with a catalytic mechanism involving oxidative coupling followed by hydrogenolytic cleavage of the resulting metallacycle via σ-bond metathesis. Even when using 50 mol % loadings of Brønsted acid under otherwise standard conditions that involve 2 mol % loadings of the rhodium catalyst, clean monodeuteration persists. This result excludes mechanisms involving protonolytic cleavage of the rhodium−carbon bond of the oxametallacycle and suggests a plausible role for the acidic additive might involve protonolytic cleavage of the rhodium−oxygen bond. Alternatively, protonation of the pyruvate may facilitate oxidative coupling by lowering the LUMO of the ketone partner. Oxidative coupling is suggested further by ESI−MS analysis of the coupling reaction of Boc-protected enyne **1a** and phenyl glyoxal using a $Rh(COD)_2OTf$−BIPHEP catalyst.[17] Here, the mass of the most abundant ion observed matches that of Rh(BIHPEP)(**1a**)(phenylglyoxal) or Rh-(BIPHEP)(metallacycle). Hydride intermediates are not observed.



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Supporting Information Available: Single crystal X-ray diffraction data for derivatives of **6d** and **6f**, and ESI−MS data. 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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(16) Exposure of ethyl pyruvate to cyclohexadiene or diphenylbutadiyne under these precise conditions provides only trace quantities of reductive coupling product.

(17) See Supporting Information for ESI−MS data.

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