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α-Hydroxy Esters via Enantioselective Hydrogen-Mediated C–C Coupling: Regiocontrolled Reactions of Silyl-Substituted 1,3-Diynes

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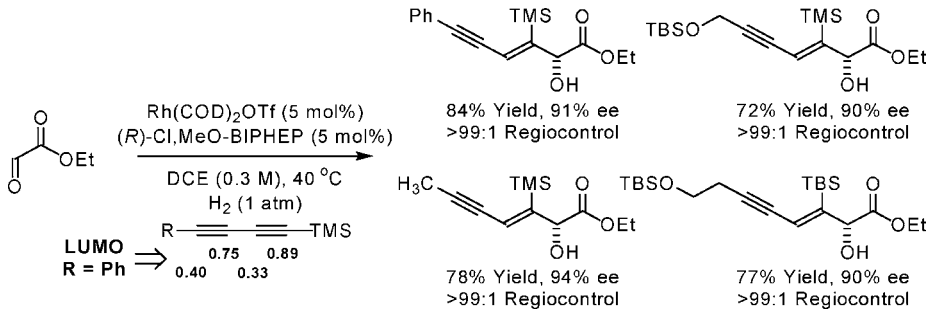
ABSTRACT



Catalytic hydrogenation of ethyl glyoxalate in the presence of 1,3-diynes 4a–9a using chirally modified rhodium catalysts enables formation of α-hydroxy esters 4c–9c in highly optically enriched form. Notably, for such trialkylsilyl-substituted 1,3-diynes, C–C coupling occurs exclusively at the carbon atom bearing silicon. π-Back-bonding from low valent rhodium as described by the Dewar–Chatt–Duncanson model appears to direct the regiochemistry of C–C coupling, as corroborated by calculations of the diyne LUMO coefficients.

Recent studies from our laboratory reveal that cationic rhodium complexes catalyze the hydrogen-mediated reductive coupling of diverse π-unsaturated substrates.[1−3] Specifically, catalytic hydrogenation of enones in the presence of aldehydes provides products of reductive aldol coupling,[1] and catalytic hydrogenation of 1,3-cyclohexadiene[2a] or conjugated alkynes (1,3-enynes, 1,3-diynes)[2b−f] in the presence of vicinal dicarbonyl compounds or iminoacetates provides α-hydroxy ketones,[2a−c,f] α-hydroxy esters,[2e] and α-amino esters.[2d] In addition, hydrogenation of 1,6-enynes and 1,6-diynes provides products of reductive cyclization.[3] Finally, through use of chirally modified catalysts, enantioselective hydrogen-mediated couplings have been devised.[2b,e,f,3b] These studies are among the first examples of hydrogen-mediated C−C coupling that extend beyond alkene hydroformylation.[4]

In our preliminary studies of the hydrogen-mediated coupling of alkynes to carbonyl compounds, coupling

(1) For hydrogen-mediated reductive aldol coupling, see: (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143. (c) Koech, P. K.; Krische, M. J. *Org. Lett.* **2004**, *6*, 691. (d) Marriner, G. A.; Garner, S. A.; Jang, H.-Y.; Krische, M. J. *J. Org. Chem.* **2004**, *69*, 1380. (e) Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519.

(2) For hydrogen-mediated reductive coupling of conjugated alkenes and alkynes to vicinal dicarbonyl compounds and iminoacetates, see: (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4074. (b) Huddleston, R. R.; Jang, H.-Y. Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488. (c) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664. (d) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269. (e) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718. (f) Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 891.

(3) For hydrogen-mediated reductive carbocyclization, see: (a) Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 7875. (b) Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. *J. Am. Chem. Soc.* **2005**, *127*, 6174.

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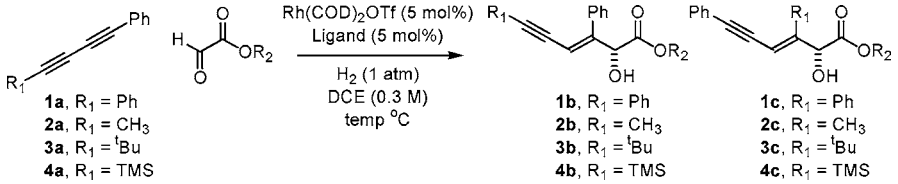
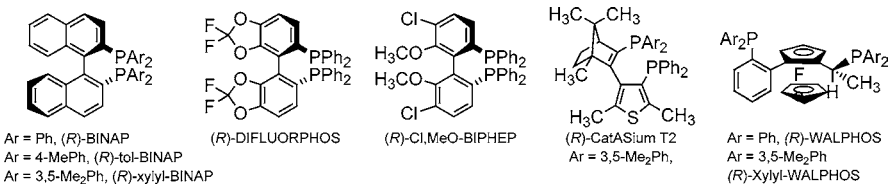
Table 1. Enantioselective Hydrogen-Mediated Reductive Coupling of Trialkylsilyl-Substituted 1,3-Diynes to Ethyl Glyoxalate[a]



entry	ligand	R_1	R_2	temp (°C)	**b**:**c**	ee%, b/c	yield (%)
1	(*S*)-BINAP	Ph	Et	25	**1b** = **1c**	+ 69, **1b**	51
2	(*R*)-tol-BINAP	Ph	Et	25	**1b** = **1c**	− 57, **1b**	50
3	(*S*)-3,5-xylyl-BINAP	Ph	Et	25	**1b** = **1c**	+ 49, **1b**	73
4	(*R*)-DIFLUORPHOS	Ph	Et	25	**1b** = **1c**	− 79, **1b**	76
5	(*R*,*R*)-Walphos	Ph	Et	25	**1b** = **1c**	− 68, **1b**	21
6	(*R*,*R*)-xylyl-Walphos	Ph	Et	25	**1b** = **1c**	− 72, **1b**	17
7	(*R*)-CatASium T2	Ph	Et	25	**1b** = **1c**	+ 8, **1b**	74
8	(*R*)-Cl,MeO-BIPHEP	Ph	Et	25	**1b** = **1c**	− 82, **1b**	78
9	(*R*)-Cl,MeO-BIPHEP	Ph	Et	45	**1b** = **1c**	− 78, **1b**	83
10	(*R*)-Cl,MeO-BIPHEP	CH_3	Et	25	3.3:1	− 89, **2b**	78
11	(*R*)-Cl,MeO-BIPHEP	CH_3	Bu^t	25	3.0:1	− 87, **2b**	52
12	(*R*)-Cl,MeO-BIPHEP	Bu^t	Et	40	>99:1	+ 88, **3b**	78
13	(*R*)-Cl,MeO-BIPHEP	TMS	Et	25	1:>99	+ 93, **4c**	74
⇒ 14	(*R*)-Cl,MeO-BIPHEP	TMS	Et	40	1:>99	+ 91, **4c**	84



[a] Cited yields are of isolated material. Enantiomeric excess was determined via chiral stationary phase HPLC analysis using a Chiracel OJ-H column. The designation of "+" indicates that the first enantiomer to appear in the HPLC trace is the major enantiomer. Conversely, the designation of "−" indicates that the second enantiomer to appear in the HPLC trace is the major enantiomer. See Supporting Information for further details.

partners in the form of conjugated diynes and α-keto aldehydes were employed.[2b] Using cationic rhodium catalysts ligated by (*R*)-Cl,MeO-BIPHEP, the corresponding α-hydroxy ketones were produced in highly optically enriched form. However, for nonsymmetric diynes possessing alkyl or aryl substitution, incomplete levels of regiocontrol were observed. The present study embodies two important advances that significantly extend the scope of the parent transformation. First, conditions applicable to use of commercially available ethyl glyoxalate are disclosed, which allows access to novel α-hydroxy esters. Second, nonsymmetric diynes possessing trialkylsilyl termini are revealed to engage in completely regioselective coupling, wherein C−C bond formation occurs proximal to the trialkylsilyl residue.

To assess whether optically enriched α-hydroxy esters may be prepared through the coupling of 1,3-diynes and glyoxalate esters, solutions of diphenylbutadiyne **1a** (200 mol %) and ethyl glyoxalate (100 mol %) in dichloroethane (0.3 M) were exposed to gaseous hydrogen (1 atm) in the presence of $Rh(COD)_2OTf$ (5 mol %) and various chiral nonracemic chelating phosphine ligands (5 mol %) at ambient temperature (Table 1). Through a survey of eight commercially available ligands (Table 1, entries 1−8), (*R*)-Cl,MeO-BIPHEP was again found to be unique in terms of conferring high reactivity and selectivity (Table 1, entry 8). This result set the stage for an examination of nonsymmetric diyne partners. Coupling of 1-phenyl-1,3-pentadiyne **2a** with ethyl glyoxalate proceeds in good yield, but with only modest levels of regiocontrol (Table 1, entry 10). It was reasoned that higher levels of regioselection could be achieved if the steric demand of the coupling partners were increased. In the event, coupling of diyne **2a** and *tert*-butyl glyoxalate actually led to slightly decreased levels of regiocontrol (Table 1, entry 11). In contrast, the *tert*-butyl-substituted diyne **3a** couples to ethyl glyoxalate at the diyne carbon proximal to the phenyl residue in a completely regioselective fashion (Table 1, entry 12). The coupling of the synthetically more versatile TMS-substituted diyne **4a** was examined next. Remarkably, coupling occurred with complete inversion of regiochemistry. Coupling product **4c** was obtained in 74% yield, 93% enantiomeric excess, and with >99:1 regioselectivity (Table 1, entry 13). By conducting the reaction at slightly elevated temperature (40 °C), the yield of coupling product **4c** was increased to 84% yield, with little erosion

(4) Prior to our work, the following hydrogen-mediated "CO-free" C−C bond formations were reported: (a) Molander, G. A.; Hoberg, J. O *J. Am. Chem. Soc.* **1992**, *114*, 3123. (b) Kokubo, K.; Miura, M.; Nomura, M. *Organometallics* **1995**, *14*, 4521.

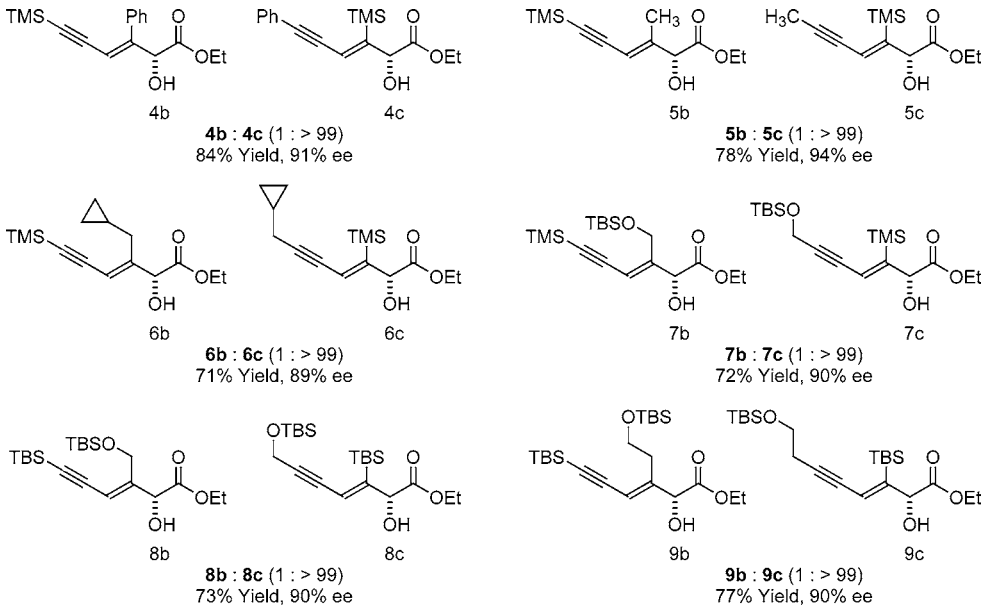


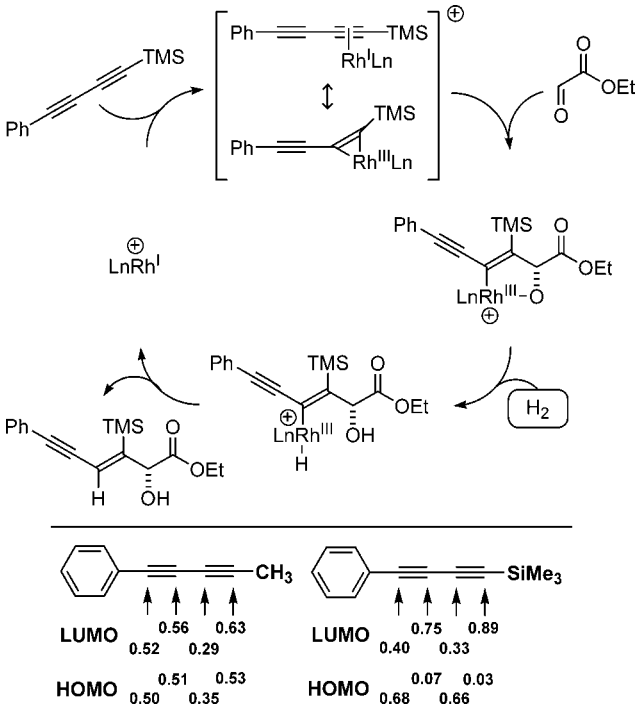
Figure 1. Regio- and enantioselective reductive coupling of trialkylsilyl-substituted diynes to ethyl glyoxalate mediated by hydrogen. Cited yields are of isolated material. Reactions were run at 40 °C for TMS-substituted diynes and 45 °C for TBS-substituted diynes. The reaction conditions are otherwise identical to those employed in Table 1, entry 14. See Supporting Information for detailed experimental procedures.

in enantioselectivity (91% ee) and complete regiocontrol (>99:1) (Table 1, entry 14).

The optimized conditions determined for the reductive coupling of TMS-substituted diyne **4a** were applied to a range of trialkylsilyl-substituted diynes **4a**−**9a** (Figure 1). In all cases, C−C coupling occurs exclusively at the diyne terminus directly adjacent to the trialkylsilyl moiety to afford regioisomers **4c**−**9c**, with enantiomeric excesses ranging between 89% and 94%. Both TMS- and TBS-substituted diynes couple with equal facility, as demonstrated by the formation of coupling products **7c** and **8c**. The absolute stereochemical assignment of all coupling products is based upon single crystal X-ray diffraction analysis of the amide derived from **4c** and (*R*)-(+)-1-(2-naphthyl)ethylamine.

The unusual regiochemistry observed in these couplings may be reconciled with the catalytic mechanism previously proposed (Scheme 1).[2d] Oxarhodacycle formation is the regio-determining step of the coupling process. Formation of this metallacyclic intermediate should be preceded by alkyne coordination in accordance with the Dewar−Chatt−Duncanson model.[5] Alkyne coordination by low valent rhodium should be driven by π-back-bonding and, hence, should occur preferentially at the most π-acidic position of the conjugated diyne. In this way, selective formation of the metallacyclic intermediate is linked to the LUMO of the π-unsaturated coupling partners, as explained by Hoffman.[6] In Hoffman's studies, formation of the metallacyclic intermediate occurs such that the alkyne carbon bearing the largest LUMO coefficient appears β to the metal. The veracity of this hypothesis is supported by the elegant studies of Saá and co-workers on the cobalt(I)-catalyzed [2 + 2 + 2] cycloaddition reaction, wherein selectivities presumed to arise via competitive formation of isomeric metallacyclic inter-

Scheme 1. A Plausible Catalytic Mechanism Accounting for π-Back-Bonding-Directed Regiocontrol



(5) (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939. (c) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1979**, *101*, 783.

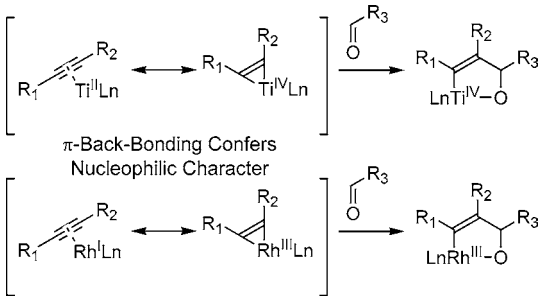
(6) Stockis, A.; Hoffman, R. *J. Am. Chem. Soc.* **1980**, *102*, 2952.

mediates are correlated to LUMO coefficients of conjugated diyne substrates.[7]

Calculation of the LUMO coefficients for diynes **2a** and **4a** at the HF (Hartree−Fock)//6-311G* level of theory reveals a substantial increase in LUMO coefficient upon introduction of the trialkylsilyl substituent. Hence, complexation proximal to the TMS moiety should be strongest by virtue of π-back-bonding. Further, the rhodacyclopropene formed adjacent to the silyl residue should be more nucleophilic than the regioisomeric metallacycle. The ability of low valent *early* transition metals to confer nucleophilic character to bound organic fragments is well established, as exemplified by the Kulinkovich reaction.[8] For example, olefin complexation by Ti(II) confers vicinal dianion character due to π-back-bonding: Ti(II)(olefin) ↔ Ti(IV)(metallocyclopropane).[9] For low valent early transition metals, π-back-bonding is driven by the stability conferred by a d^0-electronic configuration. In the case of low valent rhodium, the d^6-electronic configuration of the metallacyclopropene resonance structure corresponds to a filled subshell, which may confer only weak nucleophilic character to the bound alkyne, thus accounting for the requirement of highly electrophilic coupling partners in the form of vicinal dicarbonyl compounds (Scheme 2).

In summary, we report a highly regio- and enantioselective hydrogen-mediated reductive coupling of trialkylsilyl-substituted 1,3-diynes to ethyl glyoxalate catalyzed by rhodium. The collective data are consistent with a catalytic mechanism wherein π-back-bonding plays a crucial role in directing regiochemistry and conferring reactivity. This study provides important insight into the structural and interactional features of both catalyst and substrate and should facilitate the design of second generation catalytic systems for hydrogen-mediated C−C coupling.

Scheme 2. Nucleophilic Character Is Conferred to Bound Alkynes via π-Back-Bonding from Low Valent Metal Centers



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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 **4c** 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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(7) (a) Varela, J. A.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **1998**, *120*, 12147. (b) Varela, J. A.; Castedo, L.; Maestro, M.; Hahia, J.; Saá, C. *Chem. Eur. J.* **2001**, *7*, 5203.

(8) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291.

(9) For a review, see: Sato, F.; Urable, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.