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Cu(I)-Catalyzed Reductive Aldol Cyclizations: Diastereo- and Enantioselective Synthesis of β-Hydroxylactones†

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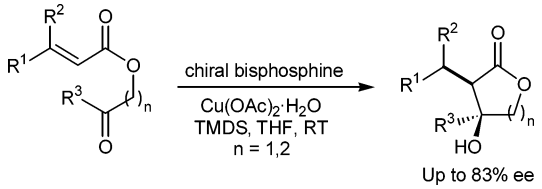
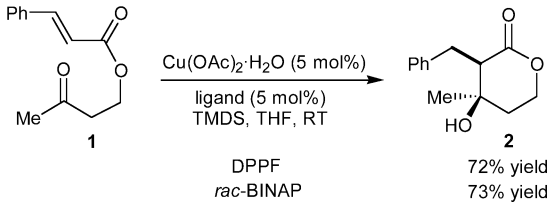
ABSTRACT



Copper bisphosphine complexes catalyze the intramolecular reductive aldol reaction of α,β-unsaturated esters with ketones, affording five- and six-membered β-hydroxylactones in high stereoselectivities. Utilization of chiral nonracemic bisphosphines render the cyclizations enantioselective.

The hydrometalation of α,β-unsaturated carbonyl compounds has proven to be a mild and versatile method of enolate generation, one that is amenable to catalysis and that may be applied to a range of reductive carbon−carbon bond constructions.[1−3] Since the seminal report of the rhodium-catalyzed intermolecular reductive aldol reaction by Revis and Hilty,[1a] a number of related processes have been described,[1b−h] including enantioselective variants.[2] Intramolecular versions of these processes have also been utilized by a number of groups to prepare a range of carbocyclic products, often in high diastereomeric purities.[1f,h,3] During the course of a natural product synthesis program, we became interested in the possibility of applying reductive aldol cyclizations to the preparation of heterocyclic products.[4] Herein we wish to report a highly diastereoselective synthesis of β-hydroxylactones and our preliminary attempts at rendering the cyclizations enantioselective.

Our initial studies focused upon the cyclization of substrate **1**, containing an α,β-unsaturated carbonyl moiety tethered to a ketone through an ester linkage (eq 1). Reductive aldol



(1)

cyclizations of this type would allow the stereoselective synthesis of tertiary-alcohol-containing lactones, which could serve as potentially versatile chemical building blocks. Although reductive aldol reactions have been mediated by a variety of metal catalysts,[1−3] phosphine-stabilized copper hydride complexes appeared to be a good choice for

† Dedicated to Prof. Gerald Pattenden on the occasion of his 65th birthday.

(1) For reports of catalytic intermolecular reductive aldol reactions, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809−4812. (b) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005−2008. (c) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *37*, 5331−5334. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237−5238. (e) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133-2136. (f) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156−15157. (g) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711−714. (h) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985−1989.

(2) (a) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972−6973. (b) Russell, A. E.; Fuller, N. O.; Taylor, S. J.; Aurriset, S.; Morken, J. P. *Org. Lett.* **2004**, *6*, 2309−2312. (c) Zhao, C.-X.; Duffey, M. O.; Taylor, S. O.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829−1831. (d) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528−4529.

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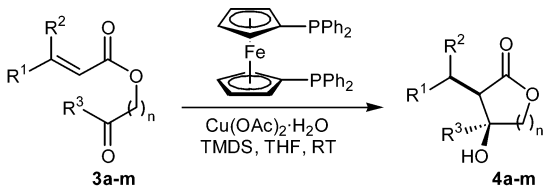
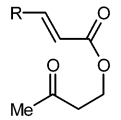
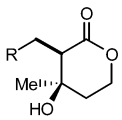
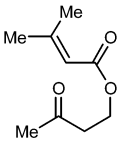
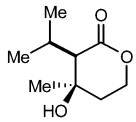
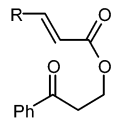
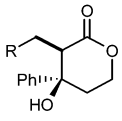
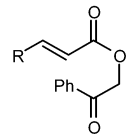
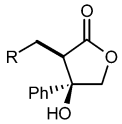
evaluation in the present reaction for a number of reasons. First, Chiu and co-workers have demonstrated the ability of $[(Ph_3P)CuH]_6$ (commonly known as Stryker's reagent[5]), used either in stoichiometric fashion or catalytically in the presence of stoichiometric siloxane, to promote reductive aldol cyclizations in carbocycle synthesis.[3d,f] Second, recent developments in asymmetric reduction reactions catalyzed by chiral copper(I)-bisphosphine complexes[6] suggested that in principle a highly enantioselective process might also be realized in the present case through identification of an appropriate ligand.

We began our investigation by surveying a number of copper salts,[7] siloxanes,[8] and bisphosphine ligands[9] in order to identify a suitable catalyst system. From these studies, $Cu(OAc)_2 \cdot H_2O$,[10] 1,1,3,3-tetramethylhydrosiloxane (TMDS), and either 1,1′-bis(diphenylphosphino)ferrocene (DPPF) or racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (*rac*-BINAP) in THF emerged as suitable reagent combinations to promote the desired cyclization, giving lactone **2** in good yields (eq 1).[11] DPPF was arbitrarily chosen for subsequent experiments.

Under these conditions, a range of substrates underwent cyclization to give β-hydroxy-δ-valerolactone products (Table 1, entries 1−9). α,β-Unsaturated ester components containing aromatic (entries 1 and 2), heteroaromatic (entry 3), and alkyl (entries 4 and 5) substituents were tolerated in the reaction, as was the trisubstituted enoate **3f** (entry 6). Replacement of the methyl ketone with a phenyl ketone also permitted cyclization to take place (entries 7−9), though in the case of substrates **3h** and **3i** the reactions did not proceed to completion (entries 8 and 9). Surprisingly, the process could also be applied to the formation of five-membered lactones (entries 10−13), despite these cyclizations formally being disfavored 5-(enolendo)-*exo*-*trig* ring closures according to Baldwin's rules.[12]

Table 1. Catalytic Reductive Aldol Cyclizations To Form β-Hydroxylactones[a]



entry	substrate		product[b]		yield (%)[c]
1		R = PMP **3a**		**4a**	61
2		R = 4-ClC_6H_4 **3b**		**4b**	65
3		R = 2-furyl **3c**		**4c**	63
4		R = *i*-Bu **3d**		**4d**	73
5		R = $PhCH_2CH_2$ **3e**		**4e**	61
6		**3f**		**4f**	62
7		R = H **3g**		**4g**	71
8		R = Me **3h**		**4h**	50[d]
9		R = Ph **3i**		**4i**	47[e]
10		R = H **3j**		**4j**	69
11		R = Me **3k**		**4k**	72
12		R = *i*-Bu **3l**		**4l**	65
13		R = $PhCH_2CH_2$ **3m**		**4m**	60

[a] Reactions were conducted using 1.0 mmol of substrate, 5 mol % Cu, 5 mol % ligand, and 1.0 mmol TMDS in 5 mL THF for 13−30 h. [b] Unless otherwise stated, only one diastereoisomer of product was observed by ^1H NMR spectroscopy. [c] Isolated yield of diastereomerically pure material. [d] Product formed as an 8:1 mixture of diastereoisomers. [e] Product isolated as an inseparable 10:1 mixture of diastereoisomers. PMP = *p*-methoxyphenyl.

The reactions proceeded at room temperature and except in the cases of substrates **3h** and **3i** were highly diastereoselective (>95:5 by ^1H NMR analysis of the unpurified reaction mixtures).[13] However, the desired β-hydroxylactones were often accompanied by small quantities of uncyclized side products that had undergone reduction at the enoate and

(3) (a) Koech, P. K.; Krische, M. J. *Org. Lett.* **2004**, *6*, 691−694. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143−1146. (c) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448−9453. (d) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308−2309. (e) Freiría, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron* **2004**, *60*, 2673−2692. For an example of a stoichiometric reductive aldol reaction, see: (f) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901−1903. For an example of a stoichiometric reductive Michael reaction, see: (g) Kamenecka, T. M.; Overman, L. E.; Ly Sykata, S. K. *Org. Lett.* **2002**, *4*, 79−82.

(4) For the formation of a tetrahydropyran from a reductive aldol cyclization, see ref 3b.

(5) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−295.

(6) For examples of enantioselective conjugate reductions, see: (a) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352−8353. (b) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821−5823. (c) Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575−4577. For examples of enantioselective ketone reductions, see: (d) Wu, J.; Ji, J.-X.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 3570−3575. (e) Lee, D.-w.; Yun, J. *Tetrahedron Lett.* **2004**, *45*, 5415−5417. (f) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779−8789. (g) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111−4113. For an example of enantioselective imine reduction, see: (h) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228−2230.

(7) Copper salts examined included $CuCl_2 \cdot 2H_2O$, CuF_2, $Cu(OAc)_2 \cdot H_2O$, Cu(2-ethylhexanoate)$_2$, Cu(OBz)$_2$, and Cu(acac)$_2$.

(8) The inexpensive siloxanes polymethylhydrosiloxane (PMHS) and 1,1,3,3-tetramethylhydrosiloxane (TMDS) were evaluated.

(9) The following bisphosphine ligands were studied: 1,2-bis(diphenylphosphino)ethane (DPPE), 1,2-bis(diphenyl-phosphino)butane (DPPB), 1,1′-bis(diphenylphosphino)ferrocene (DPPF), racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (*rac*-BINAP), and (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene ((*S*,*S*)-Et-DuPhos).

(10) $Cu(OAc)_2 \cdot H_2O$ has shown to be a particularly convenient copper source for copper hydride generation. See refs 6b and 6e.

(11) Preliminary experiments were conducted in THF using PMHS as the siloxane. Of the copper salts examined, only $Cu(OAc)_2 \cdot H_2O$ and Cu(2-ethylhexanoate)$_2$ resulted in high conversions, with $Cu(OAc)_2 \cdot H_2O$ being preferred for economic considerations. *rac*-BINAP and DPPF performed with similar efficacy, with very low conversions being observed with DPPE, DPPB, and (*S*,*S*)-Et-DuPhos. For substrate **1**, PMHS and TMDS were found to be equally effective. However, subsequent studies showed TMDS to give slightly cleaner reactions for a wider range of substrates. Toluene, CH_2Cl_2, and MeCN proved to be inferior solvents, although DME was similar to THF.

(12) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939−2947. A possible explanation for the ready cyclization of substrates **3j**−**m** is that the copper enolate intermediate (depicted as an oxa-π-allylcopper species in Scheme 1) has significant C-bound character, which reduces its planarity and better enables ring closure.

in some cases at the ketone, resulting in moderate yields. This observation indicates that the rate of σ-bond metathesis[14] of the intermediate copper enolate with the siloxane is competitive with the rate of aldol cyclization (see Scheme 1, vide infra).

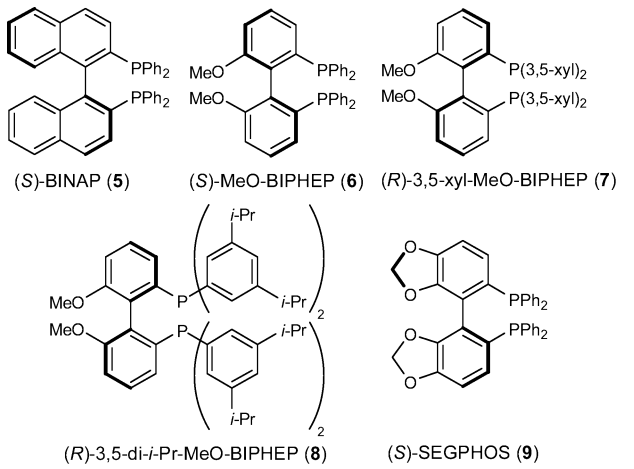
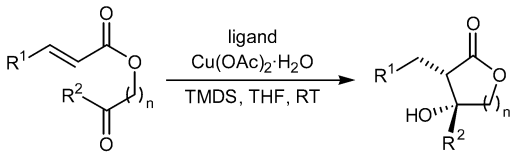


Figure 1. Bisphosphine ligands evaluated in asymmetric cyclizations.

Having established the viability of the basic process, we next turned our attention to the use of nonracemic chiral bisphosphine ligands to generate enantiomerically enriched products. A selection of bisphosphines **5**−**9** incorporating a biaryl backbone[15] (Figure 1) were evaluated in the asymmetric cyclizations of substrates **1**, **3b**, **3e**, and **3m**, and the results are presented in Table 2.

In general, the chiral ligands performed with efficiency comparable to that of the achiral ligand DPPF, affording the products in similar yields. However, at our current level of optimization, the enantioselectivies obtained remain modest. While (*S*)-BINAP (**5**) gave the lactone **2** in 62% ee (entry 1), the Roche MeO-BIPHEP ligands **6**−**8**[16] and Takasago's SEGPHOS ligand **9**[17] led to slight improvements in enantioselectivity (entries 2−5). Similar patterns were observed for two other substrates (entries 6−13), with the best result of 83% ee being obtained using ligand **7** in the cyclization of **3b** (entry 8). In the case of the formation of the five-membered lactone **4m** using ligand **7**, the enantiomeric excess was only 49% (entry 14). The absolute sense of asymmetric induction in these reactions was determined by X-ray crystallography of the chlorine-containing lactone **4b**.[18]

Table 2. Catalytic Asymmetric Reductive Aldol Cyclizations[a]

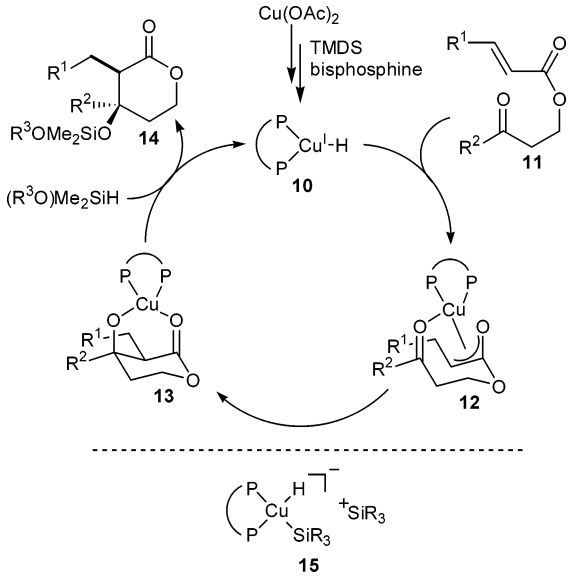


1	n = 2, R^1 = Ph, R^2 = Me	**2**
3b	n = 2, R^1 = 4-ClC_6H_4, R^2 = Me	**4b**
3e	n = 2, R^1 = $PhCH_2CH_2$, R^2 = Me	**4e**
3m	n = 1, R^1 = $PhCH_2CH_2$, R^2 = Ph	**4m**

entry	substrate	ligand	yield (%)	ee (%)
1	**1**	**5**	72	62
2	**1**	**6**	73	73
3	**1**	**7**	69	70[b]
4	**1**	**8**	64	77[b]
5	**1**	**9**	62	74
6	**3b**	**5**	79	73
7	**3b**	**6**	71	76
8	**3b**	**7**	71	83[b]
9	**3b**	**9**	73	82
10	**3e**	**5**	60	72
11	**3e**	**6**	60	73
12	**3e**	**7**	61	80[b]
13	**3e**	**9**	68	80
14	**3m**	**7**	51	49[b]

[a] Reactions were conducted using 0.2 mmol of substrate, 5 mol % Cu, 5 mol % ligand, and 0.2 mmol TMDS in 2 mL THF for 24 h. [b] The enantiomer opposite to that depicted was obtained.

Scheme 1. Proposed Catalytic Cycle



A plausible catalytic cycle for the process is presented in Scheme 1. Presumably, in the presence of bisphosphine and TMDS, reduction of copper(II) occurs[19] to generate a copper(I)-bisphosphine hydride complex **10**, which then engages

(13) The relative configurations of lactones **4b**, **4e**, and **4f** were confirmed by X-ray crystallography, and the relative configurations of **2**, **4j** and **4l** were confirmed by NOESY experiments. The stereochemistries of the remaining products were assigned by analogy. See Supporting Information for details.

(14) Lipshutz, B. H.; Chrisman, W.; Noson, K. *J. Organomet. Chem.* **2001**, *624*, 367−371.

(15) For a recent review of biaryl-type bisphosphine ligands, see: Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405−5432.

(16) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131−138.

(17) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264−267.

(18) See Supporting Information for details.

in hydrometalation with the substrate **11** to generate the copper enolate **12**. Carbonyl addition results in the copper aldolate **13**, which then undergoes σ-bond metathesis[14] with the siloxane to liberate the silylated product **14** (which is deprotected upon workup), regenerating the copper(I) complex **10**. However, we do not rule out alternative mechanisms that invoke the participation of copper species such as silyl hydrido cuprates **15**.[6f] Furthermore, the role played by the acetate counterions is unclear. The observed stereochemistry of the products[13] presumably arises from preferential formation of the *Z*-copper enolate, coupled with chelation in the carbonyl addition step (as in **12**).

In summary, we have developed diastereo- and enantioselective copper-catalyzed reductive aldol cyclizations that afford five- and six-membered β-hydroxylactones. Efforts are underway in our laboratory to discover further applications of the general process and to identify other catalyst systems that deliver improved activities, higher yields, and higher levels of enantioselection.

(19) Consistent with this hypothesis is the observation of the characteristic emerald green color of a solution of $Cu(OAc)_2 \cdot H_2O$ (blue) and DPPF (yellow) in THF being quickly converted into a yellow solution upon addition of TMDS, which is indicative of the reduction of copper(II) and the disappearance of the associated blue color.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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