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Enantioselective Copper-Catalyzed Reductive Michael Cyclizations

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ABSTRACT

In the presence of siloxanes as stoichiometric reductants, chiral copper-bisphosphine complexes catalyze highly enantioselective reductive Michael cyclizations of substrates containing two α,β-unsaturated carbonyl moieties. The diastereochemical outcome of these reactions is dependent upon whether biaryl- or ferrocene-based chiral bisphosphines are employed.

Catalytic hydrometalation of α,β-unsaturated carbonyl compounds represents a powerful method for accessing metal enolates, allowing chemo- and regioselective enolization of substrates possessing multiple acidic sites.[1] In situ trapping of enolates generated in this fashion in aldol,[2] Mannich,[2d,3] and Michael reactions[2d,4,5] enables the formation of a wide range of valuable chemical building blocks. Although the utilization of chiral metal−ligand complexes in these reactions provides an obvious entry to enantiomerically enriched products, catalytic asymmetric variants have thus far been restricted to reductive aldol[6] and Mannich reactions.[3f,7] To our knowledge, the only reports of catalytic enantioselective reductive Michael reactions employ a chiral secondary amine as the catalyst.[8a,b]

Our recent studies into the development of enantioselective reductive aldol cyclizations revealed that in the presence of 1,1,3,3-tetramethyldisiloxane (TMDS) as a terminal reductant, chiral copper-bisphosphine complexes catalyze the formation of β-hydroxylactones with modest levels of enantioselection (up to 83% ee).[6j,9] Herein, we demonstrate that these complexes are also effective in reductive Michael reactions to afford cyclic products with high enantioselectivities.

Our investigations began with a survey of biaryl-based chiral bisphosphines **L1**−**L6** using bis-enoate **1a** as a test substrate (Table 1). Using 5 mol % of $Cu(OAc)_2 \cdot H_2O$, 5 mol

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(1) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12–21.
(2) For a seminal reference, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809–4812. For relevant reviews of catalytic reductive aldol reactions, see: (b) Han, S. B.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, 2669–2679. (c) Garner, S.; Han, S. B.; Krische, M. J. In *Modern Reductions*; Andersson, P., Munslow, I., Eds.; Wiley-VCH: Weinheim, 2008; pp 387−408. (d) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105–137. (e) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953–3958. (f) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653–661. (g) Chiu, P. *Synthesis* **2004**, 2210–2215. (h) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135–142. Also, see ref 1.
(3) (a) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. A. *Org. Lett.* **2002**, *4*, 2537–2540. (b) Muraoka, T.; Kamiya, S.-i.; Matsuda, I.; Itoh, K. *Chem. Commun.* **2002**, 1284–1285. (c) Garner, S. A.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 5843–5846. (d) Nishiyama, H.; Ishikawa, J.; Shiomi, T. *Tetrahedron Lett.* **2007**, *48*, 7841–7844. (e) Prieto, O.; Lam, H. W. *Org. Biomol. Chem.* **2008**, *6*, 55–57. (f) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146–16147.
(4) (a) Baik, T.-G.; Luiz, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112–5113. (b) 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. (c) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985–1989. (d) Lee, H.; Jang, M.-S.; Hong, J.-T.; Jang, H.-Y. *Tetrahedron Lett.* **2008**, *49*, 5785–5788. (e) Lee, H.; Jang, M.-S.; Song, Y.-J.; Jang, H.-Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 327–333.

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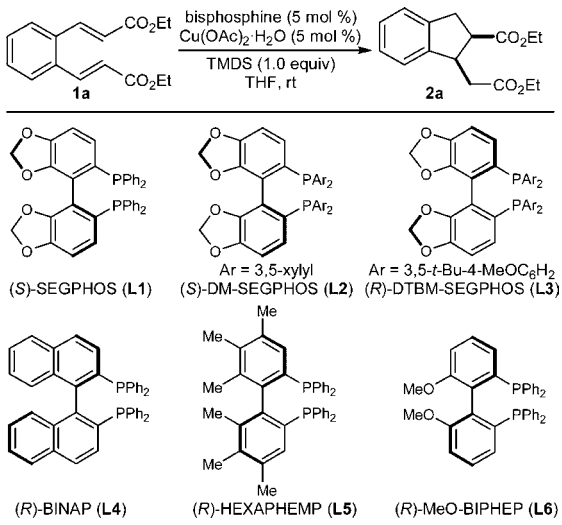
Table 1. Survey of Chiral Ligands for Reductive Michael Cyclization of **1a**[a]



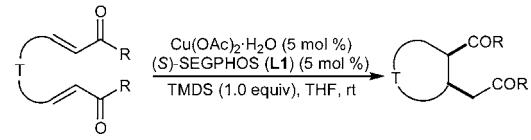
entry	ligand	dr[b]	ee (%)[c]
1	**L1**	10:1	94(+)
2	**L2**	9:1	84(+)
3	**L3**	6:1	81(−)
4	**L4**	6:1	87(−)
5[d]	**L5**	5:1	84(−)
6	**L6**	6:1	92(−)

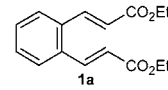
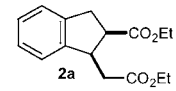
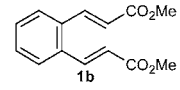
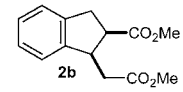
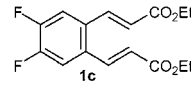
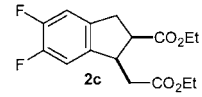
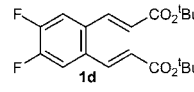
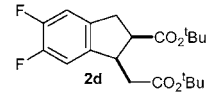
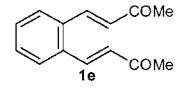
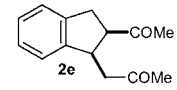
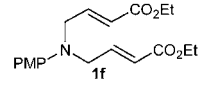
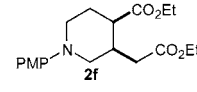
[a] Reactions were conducted using 0.065 mmol of **1a** in THF (0.2 mL). Unless otherwise stated, complete consumption of **1a** was observed. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Determined by chiral HPLC analysis of the unpurified reaction mixtures. The absolute stereochemistry of **2a** was not determined. The sign of optical rotation is provided in parentheses. [d] Reaction proceeded to 80% conversion as determined by ^{1}H NMR analysis.

% of ligand, and 1.0 equiv of TMDS in THF at room temperature, cyclization to the indane derivative **2a** was successful in all cases, and except when (*R*)-HEXAPHEMP (**L5**) was employed (entry 5), complete consumption of starting material was observed.[10] Bisphosphines **L1**−**L6** generally provided comparable levels of diastereo- and enantioselection, but marginally superior results were obtained using (*S*)-SEGPHOS (**L1**) (entry 1).

Next, the scope of this process was explored (Table 2), and a number of aromatic-tethered bis-α,β-unsaturated carbonyl compounds were found to undergo cyclization with modest yields,[11] but with reasonable to high diastereoselectivities[12] and high enantioselectivites. Using (*S*)-SEGPHOS

Table 2. Scope of Enantioselective Copper-Catalyzed Reductive Michael Cyclizations



entry	substrate	product	yield (%)[a]	dr[b]	ee (%)[c]
1			57[d]	12:1	94(+)
2			41[d]	6:1	93(+)
3			53	7:1	92(+)
4[e]			54	8:1	90(−)
5			41	6:1	97(+)
6[f]			41	4:1	91(−)

[a] Isolated yields of pure major diastereomers unless otherwise specified. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Enantiomeric excess of major diastereomer as determined by chiral HPLC analysis. The absolute stereochemistry was not determined. The sign of optical rotation is provided in parentheses. [d] Yield of a mixture of inseparable diastereomers. [e] Reaction conducted using (*R*)-BINAP (**L4**). [f] Reaction conducted using (*S*)-DM-SEGPHOS (**L2**).

(5) For stoichiometric reductive Michael cyclizations using Stryker's reagent, see: Kamenecka, T. M.; Overman, L. E.; Ly Sakata, S. K. *Org. Lett.* **2002**, *4*, 79–82.

(6) For catalytic enantioselective reductive aldol reactions with aldehydes, see: (a) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528–4529. (b) Zhao, C.-X.; Duffey, M. O.; Taylor, S. O.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829–1831. (c) Russell, A. E.; Fuller, N. O.; Taylor, S. J.; Aurriset, S.; Morken, J. P. *Org. Lett.* **2004**, *6*, 2309–2312. (d) Fuller, N. O.; Morken, J. P. *Synlett* **2005**, 1459–1461. (e) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972–6973. (f) Shiomi, T.; Ito, J.-i.; Yamamoto, Y.; Nishiyama, H. *Eur. J. Org. Chem.* **2006**, 5994–5600. (g) Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O. *Org. Lett.* **2006**, *8*, 5943–5946. (h) Bee, C.; Han, A.; Hassan, S. B.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746–2747. (i) Shiomi, T.; Adachi, T.; Ito, J.; Nishiyama, H. *Org. Lett.* **2009**, *11*, 1011–1014. For catalytic enantioselective reductive aldol reactions with ketones, see: (j) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225–4228. (k) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292–1297. (l) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403–1407. (m) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441. (n) Shiomi, T.; Nishiyama, H. *Org. Lett.* **2007**, *9*, 1651–1654. (o) Lipshutz, B. H.; Amorelli, B.; Unger, J. B. *J. Am. Chem. Soc.* **2008**, *130*, 14378–14379. (p) Deschamp, J.; Riant, O. *Org. Lett.* **2009**, *11*, 1217–1220.

(7) A sequential organocatalytic asymmetric conjugate reduction-Mannich reaction of β,β′-disubstituted α,β-unsaturated aldehydes has been reported: Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 7417–7421.

(8) Organocatalytic asymmetric reductive Michael cyclizations: (a) Wang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037. (b) Michrowska, A.; List, B. *Nature Chem.* **2009**, *1*, 225–228. For related *N*-heterocyclic carbene-catalyzed Michael cyclizations, see: (c) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107–3110. (d) Li, Y.; Wang, X.-Q.; Zheng, C.; You, S.-L. *Chem. Commun.* **2009**; DOI: 10.1039/b914805a.

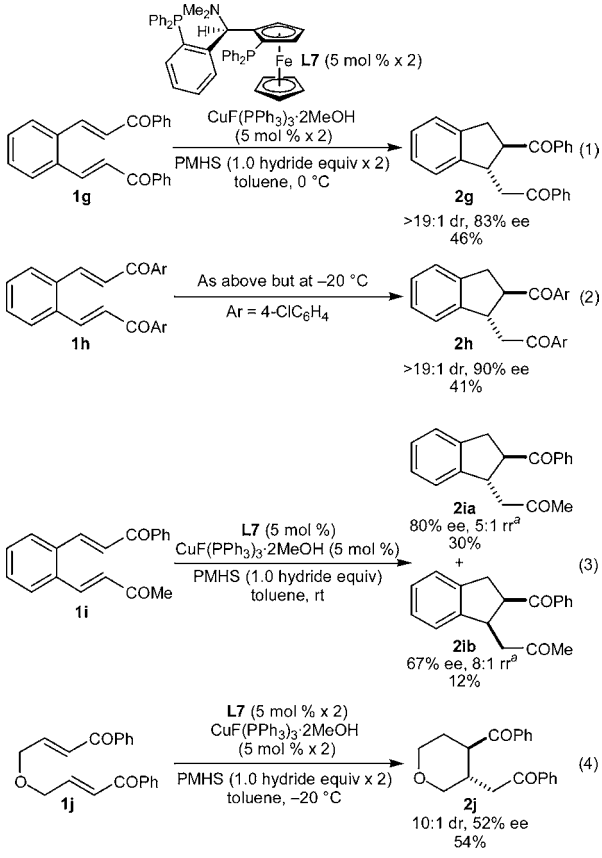
(9) For reviews of copper hydride-catalyzed reactions, see: (a) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2926. (b) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 498–504. (c) Lipshutz, B. H. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 167−187.

(10) No discernible differences in reaction efficiency were observed between ligands **L1**−**L4** and **L6**, which provided comparable conversions (*ca.* ≥ 85%) into indane **2a**.

(**L1**), cyclization of **1a** provided **2a** as a 12:1 mixture of diastereomers with 94% ee for the major isomer (entry 1), while the bis-methyl ester analogue **1b** resulted in diminished diastereoselectivity but comparable enantioselectivity (entry 2). Fluorine substitution on the benzene ring was tolerated (entry 3), as was the use of methyl ketones (entry 5). With (*R*)-BINAP (**L4**) as the ligand, bis-*tert*-butyl ester **1d** containing fluorine substitution on the benzene ring successfully provided **2d** in 90% ee (entry 4). Finally, aniline-tethered substrate **1f** underwent cyclization to provide piperidine **2f** with 4:1 dr[13] and 91% ee using (*S*)-DM-SEGPHOS (**L2**) (entry 6).

Efforts to apply similar reaction conditions to substrates containing aromatic ketones were unsuccessful. For example, attempted cyclization of bis-phenyl ketone **1g** (see Scheme 1) resulted in a complex mixture of unidentified products.

Scheme 1. Enantioselective Reductive Michael Cyclizations of Substrates Containing Aromatic Ketones[a]



[a] rr = Regioisomeric ratio as determined by ^{1}H NMR analysis. Product isolated as an inseparable regioiosmeric mixture.

Therefore, investigations to identify workable conditions for this substrate were undertaken.

After extensive experimentation, it was discovered that $CuF(PPh_3)_3$•2MeOH in conjunction with the commercially available Taniaphos ligand **L7**[14,15] was effective in toluene when polymethylhydrosiloxane (PMHS) was used as the reductant. To ensure high conversions, the optimized procedure involved reaction of **1g** with PMHS (one hydride equivalent) in the presence of 5 mol % of the copper-ligand complex for 24 h, followed by addition of a solution of a second batch of catalyst and reductant (5 mol % and one hydride equivalent, respectively), and reaction for a further 24 h.

Using these conditions, **1g** gave indane **2g** as one observable diastereomer (>19:1 dr) in 83% ee and 46% yield (Scheme 1, eq 1). Importantly, the diastereochemical outcome in this reaction, where the two substituents on the five-membered ring possess a *trans*-relationship,[16] is opposite to that shown in Table 2. In similar fashion, substrate **1h** containing *p*-chlorophenyl ketones underwent cyclization to provide **2h** as the only observable diastereomer (>19:1 dr) in 90% ee at −20 °C (Scheme 1, eq 2).[17] In this case, the relative and absolute stereochemistries of **2h** were confirmed by X-ray crystallography (Figure 1). It was also of interest

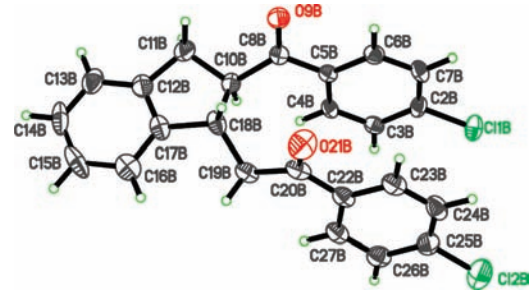


Figure 1. X-ray structure of reductive Michael product **2h**.

to evaluate the regioselectivity in the cyclization of the unsymmetrical substrate **1i**. In the event, this reaction did not require two portionwise additions of the copper-ligand complex and reductant, and provided two diastereomeric products **2ia** and **2ib** in 80% ee and 67% ee, respectively, where the major regioisomers are the result of initial

(11) Complete consumption of the starting material was observed in these reactions, and ^{1}H NMR spectroscopy of unpurified material (obtained with good mass recovery) indicated relatively clean (*ca.* ≥ 85%) conversion into cyclized products. However, isolated yields after purification by column chromatography were consistently lower than expected, and the fate of the remaining mass balance is not clear at this time.

(12) The diastereochemical outcome of cyclization of **1e** was assigned on the basis of NOE experiments conducted on both the major diastereomer **2e** and the corresponding minor diastereomer. See Supporting Information for details. The diastereochemical outcomes of the remaining reactions in Table 2 (except for entry 6) were assigned by analogy.

(13) The relative stereochemistry of **2f** was determined by X-ray crystallography of a derivative. See Supporting Information for details.

(14) For references describing Taniaphos-type ligands, see: (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212–3215. (b) Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem.—Eur. J.* **2002**, *8*, 843–852. (c) Tappe, K.; Knochel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 91–102.

(15) Other ferrocene-based ligands such as Josiphos, Mandyphos, and Walphos were also evaluated, but gave inferior enantioselectivities.

(16) The stereochemistry of **2g** was assigned by comparison with literature data and by analogy with the stereochemistry of **2h**, which was secured by X-ray crystallography (see Figure 1). See Supporting Information for details.

(17) Conducting the cyclization of **1g** at −20 °C led to only low conversions.

conjugate reduction at the phenyl-substituted enone followed by addition of the resulting enolate to the methyl-substituted enone (Scheme 1, eq 3).[18] Finally, cyclization of the oxygen-tethered substrate **1j** led to tetrahydropyran **2j**[19] in 54% yield but in only 52% ee (Scheme 1, eq 4).

In summary, asymmetric copper-catalyzed reductive Michael cyclizations have been reported. Although the yields of these reactions are modest, various indanes and heterocycles are generated with generally good to high levels of diastereoselection and high enantioselectivities. These results further add to the increasing repertoire of reactions catalyzed by copper hydride complexes.[9]

(18) The regioselectivity of this reaction is consistent with other (racemic) reports of reductive Michael cyclizations involving unsymmetrical substrates. See refs 4a,d and 4e.

(19) The relative stereochemistry of **2j** was assigned by comparison with literature data. See ref 4a.

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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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