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Copper(I)-Catalyzed Enantio- and Diastereoselective Tandem Reductive Aldol Reaction

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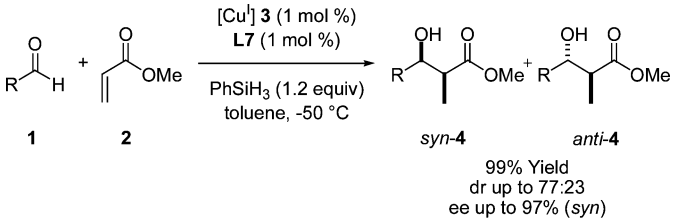
ABSTRACT



An efficient method for the enantioselective tandem reductive aldol reaction of methyl acrylate with aldehydes is reported. By using a copper(I) precursor and a proper diphosphane ligand, high reactivities can be reached, with TOF up to 40 000 h^{-1}. Taniaphos-based ligands lead to enantioselectivities of up to 97% in the case of the major *syn* diastereoisomer.

The aldol reaction is a classical method for the creation of carbon−carbon bonds in organic synthesis.[1] Reductive aldol reaction of α,β-unsatured esters with aldehydes promoted by catalytic amounts of various transition-metal complexes and a silane source is a powerful tool for stereocontrolled C−C bond formation.[2] By using this method, the preactivation of the nucleophile in an independent step is not required as the enolate (the activated form of the nucleophile) is generated in situ through the conjugated addition of a metal hydride onto a Michael acceptor. Previous works in this area has been described, including the obtention of good levels of diastereo- and enantioselectivity variants with rhodium or iridium metal complexes.[3] We were interested in developing a more economic process and selected copper as the transition metal. To our knowledge, copper was only employed in intramolecular reductive aldol cyclization as the Stryker's reagent or as $Cu(OAc)_2 \cdot H_2O$.[4−6] In a preliminary communication, we have recently reported a new catalytic method for the construction of stereogenic quaternary carbon

(1) For reviews on asymmetric aldol reactions, see: (a) Nelson, S. G. *Tetrahedron*: *Asymmetry* **1998**, *9*, 357. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Plaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. III, Chapter 29.1, pp 997−1065. Mahrwald, R., Ed. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (c) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.

(2) For original reports of catalytic reductive aldol reactions, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (c) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *37*, 5331. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 237.

(3) For reductive aldol reactions catalyzed by rhodium and iridium complexes, see: (a) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (b) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (c) Zhao, C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (d) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537. (e) Russell, A. E.; Fuller, N. O.; Taylor, S. J.; Aurriset, P.; Morken, J. P. *Org. Lett.* **2004**, *6*, 2309. (f) Fuller, N. O.; Morken, J. P. *Synlett* **2005**, 1459. (g) Fuller, N. O.; Morken, J. P. *Org. Lett.* **2005**, *7*, 4867. (h) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972. For an indium-catalyzed reductive aldol reaction, see: (i) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711.

(4) For intramolecular reductive aldol reactions with a stoichiometric amount of Stryker reagent, see: (a) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9229. (b) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901. (c) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Tetrahedron Lett.* **2001**, *42*, 4091. For intramolecular reductive aldol reactions with a catalytic amount of Stryker reagent, see: (d) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308. (e) Chiu, P. *Synthesis* **2004**, 2210. For intramolecular reductive aldol reactions catalyzed by $Cu(OAc)_2 \cdot H_2O$, see: (f) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225. (g) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743.

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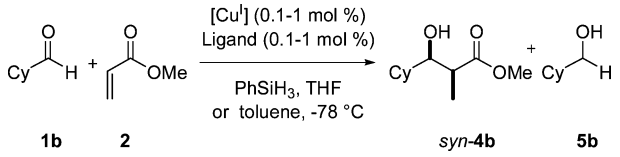
centers through a copper-catalyzed domino conjugated reduction/aldol reaction of methyl acrylate with various alkyl aryl ketones that gave high chemo-, diastereo-, and enantioselectivity.[7] These results prompted us to investigate the use of this system for the construction of small propionate-type compounds.

In our initial experiment we used benzaldehyde **1a** (R = Ph) and methyl acrylate **2** (2.0 equiv), with a catalytic amount of $[CuF(PPh_3)_3]\cdot 2MeOH$ (**3**),[8] (*S*)-BINAP (**L1**), and a stoichiometric quantity of phenylsilane, at room temperature. In the presence of **3** and (*S*)-**L1** (0.01 mol %), a smooth reaction was almost complete within 15 min (94% conversion) affording the aldol adduct **4a** (*syn*:*anti*, 60:40) (ee_{syn} = 45%) and the benzyl alcohol **5a** in a ratio of 86:14. This catalytic system displays a very high activity and the TON was estimated to be 10.000 and the TOF to be 40 000 h^{-1}.

Cyclohexanecarboxaldehyde (**1b**, R = Cy) and **2** were also tested in the presence of **3** and (*S*)-**L1** (0.1 mol %) catalyst. The reaction was completed in 1 h at room temperature leading to **4b** (R = Cy) and **5b** (R = Cy) in a ratio of 89:11, a *syn*:*anti* diastereomeric ratio of 58:42, and an enantiomeric excess for the *syn* adduct of 30% (Table 1, entry 1).[9]

Table 1. Copper-Catalyzed Asymmetric Reductive Aldol Reaction with Various Ligands[a]



1b **2** *syn*-**4b** **5b**

entry	ligand	conversion (%)[b]	**4b**:**5b**	*syn*:*anti*	ee_{syn} (ee_{anti}) (%)[c]
1[c–e]	**L1**	99	89:11	58:42	30
2[f]	**L2**	99	88:12	70:30	60 (12)
3	**L3**	99	30:70	65:35	44
4	**L4**	99	67:33	64:36	57 (30)
5	**L5**	99	34:67	76:24	83
6	**L6**	75	2:98	52:48	38
7[c]	**L7**	99	99:1	77:23	95 (74)
8[g]	**L7**	99	97:3	77:23	94 (74)
9[f]	**L8**	99	15:85	31:69	40 (30)
10	**L9**	39	6:94	63:37	61
11	**L10**	51	5:95	62:38	41

[a] All reactions were carried out in solution (0.25 M) in THF at −78 °C under an oxygen-free argon atmosphere containing **1b** (1.0 equiv), **2** (1.2 equiv), **3** (1 mol %), ligand (1 mol %), and $PhSiH_3$ (1.4 equiv) unless otherwise stated. [b] Determined by chiral GC analysis CHIRALSIL-DEX CB (25 m, 0.25 mm, 25 μm). [c] **3** (0.1 mol %), ligand (0.1 mol %). [d] **1b** (0.8 equiv), **2** (1.0 equiv), **3** (1.25 mol %), ligand (1.25 mol %), $PhSiH_3$ (1.2 equiv). [e] At room temperature. [f] At 0 °C. [g] In toluene.

Despite the high activity of this catalytic system and the rather good chemoselectivity attained, **4a**,**b** (R = Ph or Cy) was obtained only with moderate diastereomeric and enantiomeric excesses. To optimize these results, several parameters were modified. Some chiral ligands were initially screened in THF at lower temperature (−78 °C). Various

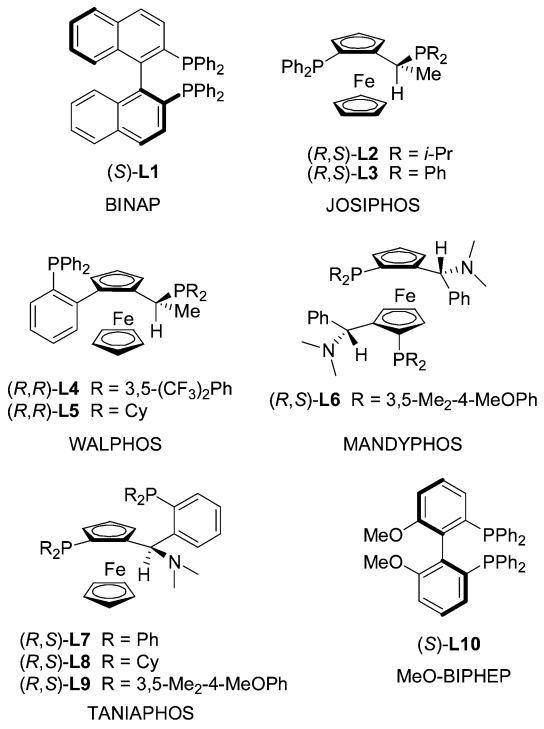


Figure 1. Chiral diphosphane ligands evaluated in asymmetric reductive aldol reaction.

families of chiral diphosphane ligands **L2**−**L10** (Figure 1) were employed and some of the most pertinent results are summarized in Table 1 (entries 2−11), with cyclohexanecarboxaldehyde (**4b**) as the substrate.[10] The reactions were almost complete in less than 2 h, regardless of the ligand's structure (except entries 6, 10, and 11). However, the ratio between **4b** and **5b** fluctuates and depends upon the structure

(5) For intramolecular reductive aldol cyclizations catalyzed by Wilkinson's complex, see: (a) Emiabata-Smith, D.; McKillop, A.; Mills, C.; Motherwell, W. B.; Whitehead, A. J. *Synlett* **2001**, *8*, 1302. (b) Freiria, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron* **2004**, *60*, 2673.

(6) Alternatively, molecular hydrogen may be used as the reducing agent for the reductive aldol cyclization catalyzed by rhodium and cobalt complexes, see: (a) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143. (c) Jang, H. Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653. (d) Jang, H. Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953.

(7) (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292. After our submission, Shibasaki reported a similar catalytic system for the reductive aldol reaction: (b) Zhao, D. B.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403.

(8) The complex was prepared according to a literature procedure, see: Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153. The amount of methanol molecules was determined by single-crystal X-ray crystallographic analysis of the complex (unpublished results).

(9) *Syn* and *anti* diastereoisomers were identified by comparison of chemical shifts obtained by ^1H NMR with those reported by Morken et al.[3a−e] and Nishiyama et al.[3h] Conversion, chemo-, diastereo-, and enantioselectivities were determined by chiral GC. Analytical gas chromatography was performed on a ThermoFinningan Trace GC, using a CHIRALSIL-DEX CB (25 m, 0.25 mm, 25 μm). The ratios are based upon crude integrations which correspond to the corrected integrations by calibration.

(10) For example, monodentate Feringa phosphonite, bidentate Reetz phosphites, and tetradentate Trost ligands gave also good activities but low diastero- and enantioselectivities.

of the ligands. In some cases, the chemoselectivity could almost be completely shifted in favor of the reduction product **5b** (Table 1, entries 6, 9, 10, and 11). Promising results were observed in the case of ligands JOSIPHOS **L2**, WALPHOS **L4 ,**and **L5**. Good enantioselectivities were reached in the case of the *syn* isomer (Table 1, entries 2, 4, and 5). We subsequently tested TANIAPHOS ligands **L7**−**L9,** which contain a 1,5-diphosphane unit and hence are capable of forming an eight-membered chelate ring with the metal. To our delight, **L7** provided a remarkable improvement in the chemoselectivity in favor of **4b** (99:1), with a diastereoselectivity (dr 77:23) (Table 1, entries 7 and 8) similar to that obtained with the **L2** or **L4** ligands, in favor of the *syn* adduct (Table 1, entries 2 and 4). However, the enantiodifferentiation was drastically enhanced for both isomers of **4b**. Under these conditions, the reaction with **L7** furnished adduct **4b** with 95% ee and 74% ee for the *syn* and *anti* isomers, respectively (Table 1, entry 7). The catalyst loading can be decreased to 0.1 mol % without any variation in chemo-, diastereo-, and enantioselectivities (Table 1, entries 1 and 7). Interestingly, TANIAPHOS **L8** and **L9** showed poor results in the reductive aldol reaction compared to **L7** (Table 1, entries 9 and 10).

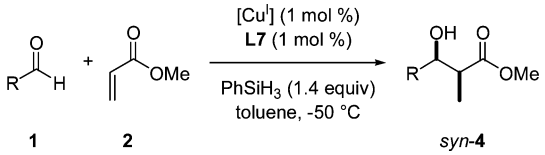
Next, we studied the scope of the copper-catalyzed asymmetric reductive aldol reaction with respect to the aldehyde substrates and the TANIAPHOS chiral ligand **L7**, under optimal conditions. A variety of aliphatic, aromatic, or heteroaromatic aldehydes were tested at −78 °C in THF. However, the low solubility of aromatic substrates at low temperature in THF or toluene forced us to select a compromise in which in toluene, at −50 °C, provided the best results.[11] Remarkably, the selectivity of the domino process did not change when THF was replaced by toluene, and we observed that all substrates participate successfully in the reaction (conversion >99%). The chemoselectivity remains excellent (generally >95:5) with good enantioselectivities but moderate diastereoselectivities (Table 2). The isolated yields for the corresponding adducts after chromatographic purification were all in the range of 74−99%. For acyclic aliphatic aldehydes, good chemoselectivities and moderate diastereoselectivities were observed (entries 1 and 2) and some enantioselectivity was detected in the case of isobutyraldehyde (ee_{syn} = 73%) (entry 1).

Nevertheless, the domino process was more efficient when aromatic and heteroaromatic aldehydes were employed. For the range of substrates studied, the chemoselectivity was good to excellent but the diastereoselectivity remained moderate, favoring either the *syn* or the *anti* isomers (Table 2, entries 6 to 14). In all cases, good to excellent enantiomeric excesses were obtained (up to 86% for the *syn* isomer) at −50 °C. As a general trend, the introduction of a halogen substituent at the *para* position (entries 7 to 9) did not change the selectivity, whereas the replacement of an electron-withdrawing group, at the *para* position of benzaldehyde, by an electron-donating group increased the diastereoselectivity in favor of the *syn* isomer. Unfortunately, the enantiomeric excess on the *syn* isomer was slightly decreased (Table 2, entry 10).

Heteroaromatic aldehydes, such as 2- and 3-thiophene-substituted aldehydes, also took part efficiently in the domino sequence to give the *syn*-**4** adducts with rather good enantioselectivities (Table 2, entries 12 and 13).

We have also investigated the dependence of the structure of the silane on the domino process. Various silanes were tested, such as $(Me_3SiO)_2MeSiH$, $Me_2EtOSiH$, $(Me_2SiH)_2O$, or PMHS, in the reductive asymmetric aldol reaction process, with carboxylaldehyde as the electrophile. Unfortunately, only Ph_2SiH_2 gave excellent results as the diastereomeric ratio and the enantiomeric excesses were both improved at −50 °C in toluene (*syn*:*anti* 88:12, ee_{syn} = 97%) (Table 2, entries 3 and 4 versus 5). Alas, Ph_2SiH_2 did not lead to significantly improved selectivities with the other aldehydes used.

Table 2. Asymmetric Copper-Catalyzed Reductive Aldol Reaction between **2** and Various Aldehydes **1** in the Presence of (*R*,*S*)-**L7** under the Optimal Conditions[a]



entry	R	conversion (%)[b]	4:5	*syn*:*anti*	ee_{syn} (ee_{anti}) (%)[c]
1	*i*-Pr	99	100:0	64:36	73 (26)
2	*t*-Bu	99	77:23	76:24	0 (0)
3	Cy	99	100:0	57:43	86 (70)
4	Cy[d]	99	99:1	77:23	96 (74)
5	Cy[e]	99	100:0	88:12	97 (30)
6	C_6H_5	99	95:5	41:58	nd (72)
7	*p*-FC_6H_4	99	97:3	44:56	86 (76)
8	*p*-$CF_3C_6H_4$	99	74:26	47:53	84 (65)
9	*p*-ClC_6H_4	99	95:5	44:56	85 (69)
10	*p*-$MeOC_6H_4$	99	95:5	60:40	68 (72)
11	*o*-$MeOC_6H_4$	99	95:5	41:59	58 (78)
12	2-thienyl[d−f]	99	95:5	67:33	83 (nd)
13	3-thienyl	99	99:1	51:49	86 (76)
14	2-pyridyl[d]	94	82:18	67:33	34 (44)

[a] All reactions were carried out in toluene (0.25 M) at −50 °C under an oxygen-free argon atmosphere containing **1** (1.0 equiv), **2** (1.2 equiv), **3** (1 mol %), **L7** (1 mol %), and $PhSiH_3$ (1.4 equiv) unless otherwise stated. [b] Determined by chiral GC analysis CHIRALSIL-DEX CB (25 m, 0.25 mm, 25 μm). [c] Configuration determined by comparison with known products. [d] At −78 °C. [e] Ph_2SiH_2 (1.4 equiv) instead of $PhSiH_3$. [f] In THF.

(11) General procedure for catalytic reductive aldol reaction: A 10 mL flame-dried round-bottomed flask, equipped with a magnetic stirrer, was charged with $CuF(PPh_3)_3$·2MeOH (9.0 mg, 0.01 mmol), ligand (0.01 mmol), and toluene (4.8 mL). The catalyst solution was stirred for 30 min at room temperature and phenylsilane (180 μL, 1.40 mmol) was added at the same temperature. After the solution was cooled at −50 °C, methyl acrylate (110 μL, 1.20 mmol) and the corresponding aldehyde (1.00 mmol) were simultaneously added to the solution. The mixture was stirred for 1 h at −50 °C under argon. Conversion, dr and ee were followed by gas chromatography (aliquots were hydrolyzed by 1 mL of aqueous NH_4F solution and filtered through a plug of silica). The reaction mixture was quenched by adding aqueous NH_4F solution (5 mL). The aqueous layer was extracted by diethyl ether (3 × 5 mL). Then, the combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to yield the corresponding adduct.

In summary, we have developed a new catalytic asymmetric system for the reductive/aldol reaction sequence between methyl acrylate and various aldehydes. The process, catalyzed by a chiral diphosphane modified copper(I) fluoride complex, in the presence of phenylsilane or diphenylsilane, is highly chemoselective but gives moderate diastereoselectivity. However, good to excellent enantioselectivities were obtained for a wide range of cyclic aliphatic, aromatic, and heteroaromatic aldehydes when the TANIAPHOS ligand **L7** was employed. This observation clearly reveals that the key parameter in this reaction strongly depends on the choice of the ligand.[12]

(12) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.

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

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