Asymmetric Aldol Reactions

DOI: 10.1002/ange.200503791

Highly Diastereo- and Enantioselective Copper-Catalyzed Domino Reduction/Aldol Reaction of Ketones with Methyl Acrylate**

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The development of efficient catalytic asymmetric methodologies for the construction of chiral, nonracemic tertiary alcohols is currently a challenging research area of interest,[1] and a few asymmetric catalytic methods dealing with this demanding task have been described.[2–7] Despite excellent progress in the field of metal-catalyzed enantioselective nucleophilic addition to ketones, only limited success has

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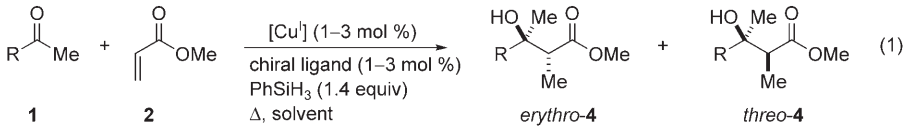
[**] This work was supported by the Université Catholique de Louvain. Dr. B. Pugin (Solvias) and Dr. R. Schmid (Hoffmann–La Roche) are gratefully acknowledged for generous gifts of chiral ligands. Mr. V. Van Tran is also acknowledged for his assistance with the chiral analysis of the new compounds.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

been achieved in catalytic enantioselective aldol reaction to ketones.[7] The reported systems suffer from either moderate enantioselectivity and/or poor substrate scope and practicality. Moreover, they involve silyl enolate derivatives as nucleophilic partners and thus require an additional and stoichiometric step for their preparation. We are interested in developing an efficient catalytic and enantioselective aldol reaction to simple ketones that overcomes these limitations and does not involve preactivation of the nucleophile in an independent step.[8]

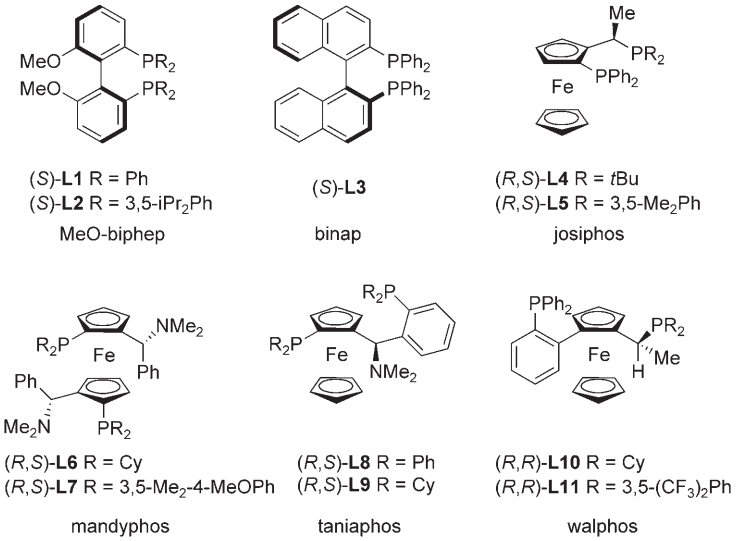


(1)

For this purpose, we turned our intention to the domino conjugate reduction/aldol reaction between α,β-unsaturated carbonyl compounds and ketones with hydrosilane as the reducing agent.[9] This three-component reaction,[10] which allows the preactivation of the nucleophile in situ by generation of a silyl or metal enolate, was successfully employed in the catalytic asymmetric reductive aldol reaction between α,β-unsaturated esters and prochiral aldehydes in the presence of chiral rhodium and iridium complexes.[11,12] Nevertheless, to our knowledge, such a strategy for the development of a catalytic asymmetric aldol process has not been applied to ketones.[13] Herein we disclose our initial studies towards this goal and report the first metal-catalyzed diastereo- and enantioselective intermolecular domino conjugate reduction/aldol reaction between methyl acrylate and simple ketones.[14]

In 1997, pioneer work by Mori et al.[15] suggested that [CuF(PPh$_3$)$_3$]·2 EtOH was an efficient copper(I) source for the generation of copper hydride species by transmetalation of an hydrogen atom from hydrosilane without any additional silane activator.[16,17] The copper hydride species generated under theses conditions reduced α,β-unsaturated carbonyl compounds stoichiometrically[18] in a 1,4-selective manner.[15,19] Later, various enantioselective copper hydride catalyzed protocols for the 1,4-reduction of a variety of prochiral conjugated compounds were successfully developed by using other copper hydride precursors that were also generated from a stoichiometric amount of silane reagent.[20] These reactions are proposed to proceed by formation of a copper enolate that subsequently undergoes metathesis with a silane to form a silyl enolate. The latter can further participate in an alkylation,[21a] arylation,[21b] or Mukaiyama aldol[21c] reaction to give a one-pot sequential process overall. Trapping the copper enolate by the formation of a C–C bond with an electrophilic ketone partner at a rate faster than the metathesis step could be an opportunity for the development of a copper-catalyzed stereoselective domino reaction between α,β-unsaturated carbonyl compounds and ketones. Shibasaki et al. recently reported a general method for the catalytic aldol reaction between ketene trimethylsilyl acetates and ketones by using catalytic [CuF(PPh$_3$)$_3$]·2 EtOH in the presence of a stoichiometric amount of (EtO)$_3$SiF additive.[22] Mechanistic studies showed that the copper enolate intermediate was the reactive nucleophile in this process.[23,24] These observations prompted us to investigate the use of chiral diphosphane-modified copper fluoride as a catalyst for the stereoselective reductive aldol reaction between methyl acrylate and aromatic ketones with hydrosilanes [Eq. (1)].

Our initial experiment was conducted on acetophenone (**1**; R = C$_6$H$_5$) and methyl acrylate (**2**) with a catalytic amount of [CuF(PPh$_3$)$_3$]·2 MeOH[25] (**3**) and Roche chiral ligand (*S*)-**L1** and a stoichiometric quantity of phenylsilane at 0 °C.[26] In



the presence of **3** and (*S*)-**L1** (1.25 mol %) catalyst, the reaction was almost complete in 2 h (95 % conversion) to afford solely a single product, which was identified as adduct **4**.[27]

Despite high chemoselectivity (99 %), **4** was obtained in a low diastereomeric ratio (d.r. = 41:59) but with an encouraging 51 % *ee* for the major *threo* isomer (Table 1, entry 1).[28] To optimize these results, several parameters were changed. Copper(I) salts were first surveyed to assess the effect of the copper hydride precursor on the reaction. No significant changes in chemo-, diastereo-, and enantioselectivity of the domino reaction between **1** (R = C$_6$H$_5$) and **2** were observed when using either PPh$_3$-free CuF–**L1**,[29] CuO*t*Bu–**L1**[30] or CuCl/NaO*t*Bu–**L1** systems under the same conditions.[31] The media effect was then examined by using the easy to handle and air-stable precatalyst **3** and ligand (*S*)-**L1**.

The selectivity of the domino process did not improve by replacing THF with toluene. However, a more polar solvent such as DMF led to poorer conversion and a lower *ee* value of the *threo* isomer. We next investigated the temperature dependence of the reaction. Varying the temperature from 0 to −50 °C raised the *ee* value of *erythro*-**4** from 2 to 25 % (Table 1, entry 1 versus 2), but had hardly any influence on the chemo- and diastereoselectivity of the reaction or on the *ee* value of the *threo* isomer. However, when the reaction was run at −78 °C, chemoselectivity dropped significantly from 99 to 52 % (Table 1, entry 1 versus 3). Diverse chiral ligands were subsequently screened under the optimized conditions (**3**,

Table 1: Asymmetric copper-catalyzed reductive aldol reaction between methyl acrylate (**2**) and acetophenone (**1**; R = C_6H_5) under various reaction conditions with different chiral ligands **L1**–**L11**.[a]

Entry	Ligand	*t* [h]	Conversion [%][b]	Chemoselectivity [%][b, c]	d.r.[b] *erythro* *threo*	*ee*[b] [%] (*erythro*-**4**)	*ee*[b] [%] (*threo*-**4**)
1 [e,f]	**L1**	2	95	99	41:59	2	51
2 [e]	**L1**	2	80	98	41:59	25	55
3 [e][g]	**L1**	2	77	52	45:55	16	38
4	**L2**	1	99	98	78:22	0	2
5	**L3**	1	98	98	54:46	29	52
6	**L4**	1	99	>99	54:46	−73	−63
7	**L5**	1	98	>99	56:44	40	45
8	**L6**	2	96	98	74:26	16	−1
9	**L7**	2	99	>99	77:23	13	35
10	**L8**	1	99	99	76:24	−85	−94
11	**L9**	1	99	>99	92:8	95[d]	72
12[h]	**L9**	4	92	>99	89:11	87	55
13	**L10**	2	99	99	88:12	−22	37
14	**L11**	2	99	>99	64:36	4	46

[a] Reactions were carried out in solution (0.25 M) in toluene at −50 °C under an oxygen-free argon atmosphere containing **1** (R = C_6H_5) (1.0 equiv), **2** (1.2 equiv), **3** (1 mol %), ligand (1 mol %), $PhSiH_3$ (1.4 equiv) unless otherwise stated. [b] Determined by chiral GC analysis. [c] Chemoselectivity = (**4**/(**4**+phenylethanol) × 100). [d] Absolute configuration: 2*R*,3*S* (see Supporting Information). [e] **1** (0.8 equiv), **2** (1.0 equiv), **3** (1 25 mol %), ligand (1.25 mol %), $PhSiH_3$ (1.2 equiv). [f] At 0 °C. [g] At −78 °C. [h] **3** (0.1 mol %), **L9** (0.1 mol %).

toluene, −50 °C). Among them, diphosphane-based ligands were the most promising ligands in terms of activity and selectivity.[32] Various families of chiral diphosphane ligands **L2**–**L11** were tested, and some results are summarized in Table 1, entries 4–14. To our delight, the reactions were highly chemoselective (> 98 %) and almost complete (95–98 % conversion) in less than 2 h (unoptimized reaction time), regardless of the ligand structure. The *erythro*-**4** isomer was favored in all cases. We first investigated axially chiral biaryl ligands **L2** and **L3**. The substitution of (*S*)-**L1** for (*S*)-**L2** led to a remarkable improvement in the diastereoselectivity (d.r. 41:59→78:22) in favor of the *erythro* isomer (Table 1, entry 2 versus 4). Unfortunately, both isomers were obtained as a racemic mixture. The employ of commonly used (*S*)-**L3** restored some enantioselectivity to the reaction with 29 and 52 % *ee* for the major and minor isomers, respectively, despite a decrease in the diastereoselectivity (Table 1, entry 4 versus 5).

We then assessed chiral ferrocenyl-based diphosphane ligands available from the Solvias kit. Among the different ligand families tested, the josiphos[33a] and taniaphos[33b] ligand families were the most efficient in terms of diastereo- and/or enantioselectivities. For example, the combination of C_1-symmetric (*R*,*S*)-**L4** and precatalyst **3** in the presence of **1**, **2**, and phenylsilane afforded almost quantitatively the adduct **4** with a moderate −73 % *ee* for the *erythro* isomer, despite a low 54:46 d.r. (Table 1, entry 6). The use of **L5**, which bears a more acidic phosphane group on the side chain, did not improve the diastereomeric ratio but led to a significantly lower enantioselectivity (Table 1, entry 7). Improved diastereocontrol of the reaction was observed with mandyphos diphosphane ligands (*R*,*S*)-**L6** and (*R*,*S*)-**L7**, which have a C_2-symmetric backbone (Table 1, entries 8 and 9). Unfortunately, both ligands afforded **4** with low enantioselectivities.

We subsequently tested taniaphos ligand (*R*,*S*)-**L8**, which contains a 1,5-diphosphane unit and hence is capable of forming an eight-membered chelate ring with a metal. Taniaphos ligand (*R*,*S*)-**L8** provided a diastereoselectivity (d.r. 76:24) similar to that obtained with mandyphos ligands (*R*,*S*)-**L6** and (*R*,*S*)-**L7**. However, the enantiodifferentiation was drastically enhanced for both isomers of **4**. Under the optimal conditions, the reaction with (*R*,*S*)-**L8** furnished adduct **4** with −85 *ee* and −94 % *ee* for the *erythro* and *threo* isomers, respectively (Table 1, entry 10). The substitution of phenyl groups attached to phosphorus atoms of **L8** by cyclohexyl substituents further improved the diastereo- and enantioselectivity of the reaction.[34] Indeed, the addition of **1**, **2**, and phenylsilane to **3** (1 mol %) and (*R*,*S*)-**L9** (1 mol %)in toluene gave **4** with 92:8 d.r. in favor of the *erythro* isomer and 95 % *ee* for the major isomer (Table 1, entry 11). The catalyst loading can be decreased to 0.1 mol % without significant variation of chemo- and diastereocontrol (Table 1, entry 12). However, under these conditions, a slight decrease in the enantioselectivity was observed for the preponderant isomer. Notably, for both privileged[35] josiphos and taniaphos ligand families, the opposite absolute configuration of the major compound was observed when the groups on the phosphorus atoms were changed from alkyl to aryl substituents (Table 1, entry 6 versus 7 and entry 10 versus 11). Moreover, a change from josiphos ligands (*R*,*S*)-**L4** and (*R*,*S*)-**L5** to taniaphos ligand (*R*,*S*)-**L9** and (*R*,*S*)-**L8**, respectively, which exhibit the same planar chirality, afforded *erythro*-**4** with the opposite configuration (Table 1, entry 6 versus 11 and entry 7 versus 10).[36] The use of other chiral ligands bearing a 1,5-diphosphane unit such as walphos ligands (*R*,*R*)-**L10** and (*R*,*R*)-**L11** afforded adduct **4** with lower diastereo- and enantioselectivity (Table 1, entries 13 and 14).

Next, we analyzed the scope of the copper-catalyzed asymmetric reductive aldol reaction with respect to the ketone substrate by using taniaphos chiral ligand (*R*,*S*)-**L9** under the optimal conditions. A variety of aromatic and heteroaromatic ketones participate successfully in the reac-

Table 2: Asymmetric copper-catalyzed reductive aldol reaction between **2** and various aromatic ketones **1** with (*R*,*S*)-**L9** under the optimal conditions.[a]

Entry	R	*t* [h]	Yield [%][h]	Chemoselectivity [%][b][c]	d.r.[b] *erythro*/*threo*	*ee*[b] [%] (*erythro*-**4**)	*ee*[b] [%] (*threo*-**4**)
1	C_6H_5	1	98	>99	92:8	95[d]	72
2	*p*-FC_6H_5	1	88	94	91:9	92	73
3	*p*-$CF_3C_6H_5$	1	87	89	80:20	83	72
4	*p*$MeOC_6H_5$	1	31[f]	97	92:8	90	56
5	*p*-ClC_6H_5	1	95	95	86:14	90	77
6	*m*-ClC_6H_5	1	70	89	88:12	82	n.d.[e]
7[g]	2-thienyl	2	94	>99	96:4	90	15
8	3-thienyl	2	95	>99	95:5	95	65

[a] Reactions were carried out in solution (0.25 M) in toluene at −50 °C under an oxygen-free argon atmosphere containing **1** (1.0 equiv), **2** (1.2 equiv), **3** (1 mol%), (*R*,*S*)-**L9** (1 mol%), $PhSiH_3$ (1.4 equiv) unless otherwise stated. [b] Determined by chiral GC analysis. [c] Chemoselectivity = (**4**/(**4**+phenylethanol) × 100). [d] Absolute configuration: 2*R*,3*S*. [e] Not determined. [f] Conversion determined by GC analysis and not optimized. [g] **3** (3 mol%), (*R*,*S*)-**L9** (3 mol%). [h] Yield of isolated product.

tion (Table 2). For the range of substrates studied, the diastereo- and enantioselectivity of the reaction were moderate to high (*erythro*-**4**: d.r. 80:20–96:4 and 82–95% *ee*). As a general trend, the introduction of a halogen substituent at the *para* or *meta* position of acetophenone slightly decreased the diastereoselectivity of the reaction and the enantioselectivity of the major isomer (Table 2, entry 1 versus entries 2, 5, and 6). The substitution of an electron-withdrawing group at the *para* position of acetophenone by an electron-donating group increased both the diastereomeric ratio and the *ee* of the *erythro* compound (Table 2, entry 3 versus 4). Heteroaromatic ketones such as 2- and 3-thiophene-substituted ketones also took part efficiently in the domino sequence to give the corresponding *erythro*-**4** compound with very high chemo-, diastereo-, and enantioselectivity (Table 2, entries 7 and 8).

In summary, we have developed a new strategy for the catalytic asymmetric aldol reaction of ketones that relies on a domino reduction/aldol reaction sequence between methyl acrylate and aromatic ketones. The process, catalyzed by a diphosphane-modified copper(I) fluoride complex in the presence of phenylsilane, is highly selective (chemo-, diastereo-, and enantioselectivity) for a range of aromatic ketones. This strategy circumvents the need to preactivate the nucleophile prior to the C–C bond-forming step and affords highly functionalized products with two contiguous stereogenic centers, one of which is a chiral tertiary alcohol. Current efforts are focused on exploring the breadth of this domino reaction.

Received: October 26, 2005
Published online: January 20, 2006

Keywords: aldol reaction · copper · enantioselectivity · enolates · hydrosilylation

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[16] We have reported the use of copper fluoride–phosphine complexes for the catalytic enantioselective hydrosilylation of aromatic ketones with excellent yields and enantioselectivities: a) S. Sirol, J. Courmarcel, N. Mostefai, O. Riant, *Org. Lett.* **2001**, *3*, 4111; b) J. Courmarcel, N. Mostefai, S. Sirol, S. Choppin, O. Riant, *Isr. J. Chem.* **2002**, *42*, 231; for a review on catalytic asymmetric hydrosilylation to ketones and imines, see: c) O. Riant, N. Mostefai, J. Courmarcel, *Synthesis* **2004**, 2943.

[17] For a special topic on copper-mediated conjugate reductions and reductive aldol reactions with organosilanes as the hydride source, see: P. Chiu, *Synthesis* **2004**, 2943.

[18] A catalytic amount of $[CuF(PPh_3)_3]\cdot 2\,EtOH$ was less efficient.[15c]

[19] For a 1,4-reduction mediated by stoichiometric or catalytic amounts of the Stryker reagent, see: a) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291; b) W. S. Mahoney, J. M. Stryker, *J. Am. Chem. Soc.* **1989**, *111*, 8818; c) B. H. Lipshutz, J. Keith, P. Papa, R. Vivian, *Tetrahedron Lett.* **1998**, *39*, 4627.

[20] a) B. H. Lipshutz, J. M. Servesko, *Angew. Chem.* **2003**, *115*, 4937; *Angew. Chem. Int. Ed.* **2003**, *42*, 4789; b) B. H. Lipshutz, J. M. Servesko, T. B. Petersen, P. P. Papa, A. A. Lover, *Org. Lett.* **2004**, *6*, 1273; c) B. H. Lipshutz, J. M. Servesko, B. R. Taft, *J. Am. Chem. Soc.* **2004**, *126*, 8352; d) D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9473; e) Y. Moritani, D. H. Appella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797; f) G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253; g) . P. Rainka, Y. Aye, S. L. Buchwald, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5821; h) C. Czekelius, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 4941; *Angew. Chem. Int. Ed.* **2003**, *42*, 4793; i) C. Czekelius, E. M. Carreira, *Org. Lett.* **2004**, *6*, 4575.

[21] a) B. H. Lipshutz, W. Chrisman, K. Noson, P. Papa, J. A. Sclafani, R. W. Vivian, J. M. Keith, *Tetrahedron* **2000**, *56*, 2779; b) J. Yun, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1129; c) J. Chae, J. Yun, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 4809.

[22] K. Oisaki, Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5644; for complementary work, see reference [7d].

[23] The copper enolate intermediate was proposed to be generated by dynamic ligand exchange between silicon and copper;[22] for pioneering work on a CuF–(*S*)-tolbinap-catalyzed enantioselective aldol reaction between silyl dienolate and aldehyde that involved a metalloenolate intermediate, see: a) J. Krüger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837; b) B. L. Pagenkopf, J. Krüger, A. Stojanovic, E. M. Carreira, *Angew. Chem.* **1998**, *110*, 3312; *Angew. Chem. Int. Ed.* **1998**, *37*, 3124.

[24] For a CuF–tolbinap-catalyzed enantioselective vinylogous Mukaiyama reaction on aliphatic ketones, see reference [7e].

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

[26] $PhSiH_3$ was chosen as hydride source for its tendency not to form stable silyl enol ethers upon transmetalation with copper enolate.[19c]

[27] A minor trace of phenylethanol (<1%), the product of reduction of acetophenone, was observed by GC analysis.

[28] Under the same conditions, without any additional ligand, **3** (1.25 mol%) gave only 20% conversion after a 2-hour reaction.

[29] For the preparation, see: D. Tomita, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4138.

[30] For the preparation of CuO*t*Bu, see: T. Tsuda, T. Hashimoto, T. Saegusa, *J. Am. Chem. Soc.* **1972**, *94*, 658.

[31] Notably, no effect on the reaction rate was observed when using either preprepared CuO*t*Bu or CuO*t*Bu prepared in situ (from CuCl/NaO*t*Bu); for a report on the salt effect on the rate of the enantioselective 1,4-reduction of β,β-disubstituted nitroalkenes when using both methods of CuO*t*Bu preparation, see reference [20 h].

[32] For example, monodentate Feringa phosphonite, tridentate *t*Bu-pybox, and tetradentate Trost ligand gave very low activity and/or no enantioselectivity.

[33] For original work, see: a) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062; b) T. Ireland, G. Grossheimann, C. Wieser-Jeunesse, P. Knochel, *Angew. Chem.* **1999**, *111*, 1560; *Angew. Chem. Int. Ed.* **1999**, *38*, 3212.

[34] These observations are in contrast to those usually made in other processes using taniaphos-derived ligands containing either alkyl or aromatic substituents on phosphorus atoms. Generally, a change from electron-rich aromatic groups to cyclohexyl groups has a negative effect on the enantioselectivity of the process. For some examples, see: a) B. L. Feringa, R. Badorrey, D. Peòa, S. R. Harutyunyan, A. J. Minnaard, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5834; b) F. Spindler, C. Malan, M. Lotz, M. Kesselgruber, U. Pittelkow, A. Rivas-Nass, O. Briel, H.-U. Blaser, *Tetrahedron: Asymmetry* **2004**, *15*, 2299.

[35] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691.

[36] A similar observation was previously made in the copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclic enones.[34a]

