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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4325–4329

New chiral bis(diphenylphospholane) ligands: design, synthesis, and application to catalytic enantioselective aldol reaction to ketones

Kounosuke Oisaki,[a] Dongbo Zhao,[a] Yutaka Suto,[a] Motomu Kanai[a,b,*] and Masakatsu Shibasaki[a,*]

[a]*Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113–0033, Japan*
[b]*PRESTO, Japan Science and Technology Corporation, Japan*

Received 21 March 2005; revised 22 April 2005; accepted 25 April 2005
Available online 10 May 2005

Abstract—New chiral bidentate diphenylphospholanes were designed targeting a catalytic enantioselective aldol reaction to ketones. Ligands **5l** and **5m** having *cis*-2-butenyl and cyclopropyl groups at the linker part, respectively, were identified as effective chiral ligands for a CuF-catalyzed enantioselective aldol reaction to ketones. Catalysts prepared from $CuF{\cdot}3PPh_3{\cdot}2EtOH$ and these ligands produced ketone aldol products with up to 66% ee, which is promising particularly for this extremely difficult and important catalytic enantioselective carbon–carbon bond forming reaction. The enantioselectivity was strongly dependent on the linker structure. Construction of a deep chiral pocket around the copper metal with stable bidentate chelation is the key to meaningful enantioinduction.

Catalytic enantioselective construction of chiral tertiary alcohols through carbon–carbon bond formation is one of the most important and challenging research targets in current organic synthesis.[1] Although there are many biologically active naturally occurring compounds and artificial pharmaceuticals containing chiral tertiary alcohols, there are only few reliable and practical synthetic methods for these chiral building blocks. Catalytic enantioselective cyanosilylation,[2] organozinc addition,[3] and allylation[4] of simple ketones are recent entries in this category. One extremely important piece, however, is missing; that is, the catalytic enantioselective aldol reaction to ketones. The first and only example of a catalytic enantioselective aldol reaction to simple ketones was reported by Denmark and Fan.[5] The use of very unstable trichlorosilyl enolate as a nucleophile, narrow substrate generality in terms of both nucleophiles (only acetate-derived enolate can be used) and electrophiles, and moderate enantioselectivity are the main drawbacks of this pioneering reaction. The difficulty in developing this reaction is partly due to the attenuated reactivity of ketones and the intrinsic facile reversibility of an aldol reaction to ketones. Thus, development of a catalytic enantioselective aldol reaction to ketones is among the most difficult tasks for producing a practical range of enantioselectivity and substrate generality.

We reported a new general method for catalytic aldol reaction to ketones using CuF as a catalyst and relatively stable and commonly used ketene trimethylsilyl acetals as nucleophiles.[6,7] In this method, the addition of a stoichiometric amount of $(EtO)_3SiF$ was critical. Mechanistic studies indicated that a copper enolate generated through transmetalation between silicon and copper atoms is the actual nucleophile, and $(EtO)_3SiF$ facilitates the rate-determining catalyst turnover step.[8] This method has almost completely overcome the reactivity problem of ketones in the aldol reaction, producing a high chemical yield and reaction rate from a wide range of ketones and silyl enolates. Thus, this reaction can be a valuable base for developing a general and practical catalytic enantioselective aldol reaction to ketones. In this letter, we describe our preliminary results of this venue by developing a series of new chiral bidentate phosphine ligands.

Keywords: Asymmetric catalysis; Aldol reaction; Ketones; Chiral tertiary alcohol; Chiral phospholane.
* Corresponding authors. Tel.: +81 358414830; fax: +81 356845206 (M.S.); e-mail: mshibasa@mol.f.u-tokyo.ac.jp

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doi:10.1016/j.tetlet.2005.04.084

Various available chiral diphosphine ligands were first screened in the reaction between acetophenone (**1a**) and ketene silyl acetal **2** in the presence of 2.5 mol % CuF·3PPh$_3$·2EtOH and 5 mol % chiral ligands (Scheme 1).[9] Although high chemical yields were obtained in each case, the maximum enantiomeric excess was only 33%, even when using privileged chiral bidentate phosphines. Unexpectedly low enantioselectivity was partly rationalized from the reaction mechanism of this CuF-catalyzed aldol reaction. Previous studies suggested that the reaction proceeds through a linear transition state from a copper enolate (Fig. 1).[10] Thus, a substrate ketone should approach the copper enolate from an outside space far from the chiral environment constructed by chiral bidentate phosphine ligands. As a result, shielding one specific enantioface of the ketone by steric hindrance of chiral ligands might be inefficient.

These considerations led us to design new chiral bidentate phosphines containing a deeper chiral pocket, which can control the orientation of the substrate ketone at a position far from the metal center in the transition state. Molecular modeling studies suggested that a diphenylphospholane is a suitable chiral module to construct chiral bidentate phosphines for this purpose. The fact that low but meaningful enantioselectivity (24% ee) was obtained using Ph-BPE in the preliminary ligand screening (Scheme 1) supports this idea. We anticipated that if an appropriate linker to connect the two chiral diphenylphospholanes was identified, the phenyl groups of the phospholane would act far from the metal center to where a ketone exists in the transition state, and enantioselectivity could be expected to improve. The diphenylphospholane module can be synthesized on a multigram-scale according to the reported procedure.[11] Linking the two phospholanes was accomplished through a substitution reaction by the BH$_3$-protected phospholane followed by deprotection using DABCO (Scheme 2). Following this general scheme, we synthesized 12 new bidentate chiral phosphines as shown in Table 1.

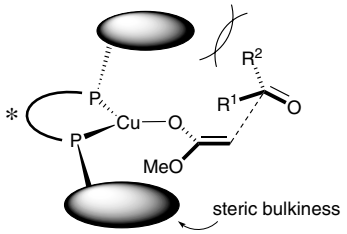
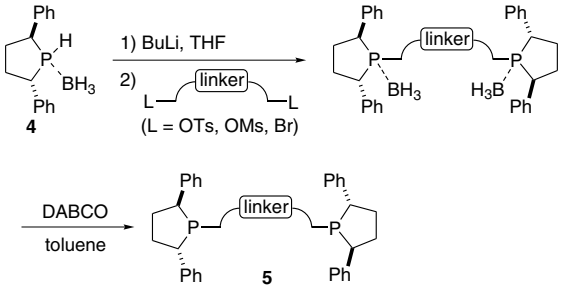
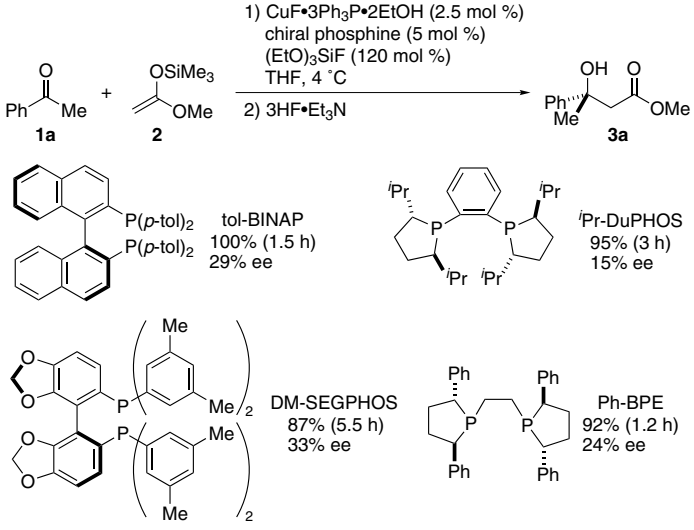


Figure 1. Proposed transition state model.



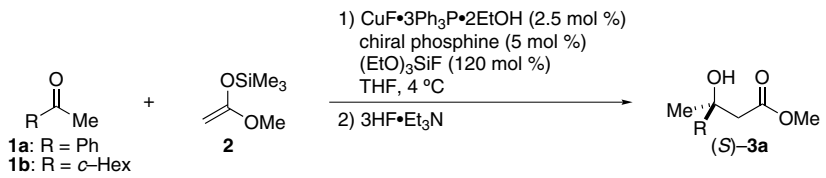
Scheme 2. General scheme of bis(diphenylphospholane) synthesis.

The enantioselectivity of these ligands was assessed in the catalytic aldol reaction of ketone **1a**. As expected, the linker had a profound effect on enantioselectivity (Table 1). Ligand **5b**, which has a propyl linker, produced higher enantioselectivity than **5a** and **5d** which have either an ethyl or a butyl linker (entries 1–4). Constraining the propyl linker flexibility by introducing a methyl substituent (ligand **5c**) improved the enantioselectivity (entry 2 vs entry 3). Molecular modeling studies suggested that ligands **5b** and **5c** would produce a more obtuse bite angle than Ph-BPE (**5a**) when the chelate was formed with copper metal. Therefore, the phenyl group of the phospholane should work more efficiently to produce steric bulkiness at the far position from the copper center, thus giving higher enantioselectivity using **5b** and **5c** than **5a**. On the other hand, if the linker is longer

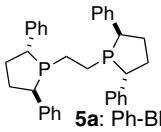
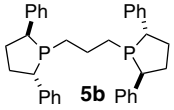
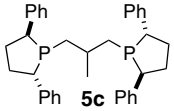
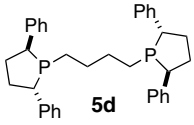
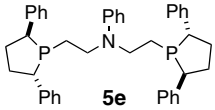
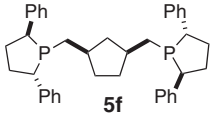
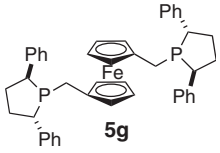
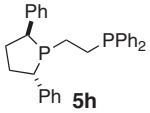
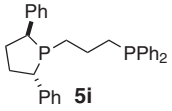
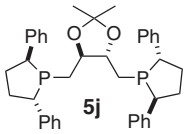
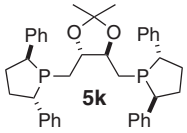


Scheme 1. Preliminary screening of privileged bidentate phosphines.

Table 1. Catalytic enantioselective aldol reaction to ketones[a]

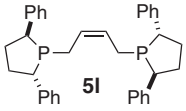
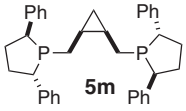


1a: R = Ph
1b: R = *c*–Hex

Entry	Chiral ligand	Time (h)	Yield (%)[b]	ee (%)[c]	*R*/*S*
1	 **5a**: Ph-BPE	1.2	92	24	*R*
2	 **5b**	24	86	41	*S*
3	 **5c**	24	53	50	*S*
4	 **5d**	18	86	29	*S*
5	 **5e**	24	65	8	*R*
6[d]	 **5f**	24	73	4	*S*
7[d]	 **5g**	24	83	3	*R*
8	 **5h**	20	87	0	—
9	 **5i**	13	86	0	—
10	 **5j**	18	100	18	*S*
11	 **5k**	18	95	14	*R*

(*continued on next page*)

Table 1 (*continued*)

Entry	Chiral ligand	Time (h)	Yield (%)[b]	ee (%)[c]	*R*/*S*
12[d]	 **5l**	8	95	62	*S*
13[d,e]		43	78	66	—
14[d]	 **5m**	13	91	60	*S*

[a] Substrate **1a** was used unless otherwise mentioned.
[b] Isolated yield.
[c] Determined by chiral HPLC after conversion to the corresponding 3,5-dinitrobenzoate.
[d] DME was used as solvent. Reactions in DME generally gave 3–4% higher ee than in THF.
[e] Substrate **1b** was used.

than propyl without any constraining group (ligand **5d**), the chelation should become less stable due to entropy factor. As a result, a less enantioselective pathway catalyzed by monodentate coordinated copper should compete with the desired pathway catalyzed by the bidentate coordinated copper, thus giving the product with lower enantioselectivity in the case of **5d** than **5b**.[12] Consistent with these considerations, ligands with more flexible linkers (entries 5–7) produced only very low enantioselectivity. In addition, no enantioselectivity was observed using C_1-symmetric bidentate phosphines (entries 8 and 9), which indicated that both of the chiral phospholanes are essential for enantioinduction.

The rational design concept based on these investigations is to construct a C_2-symmetric bidentate chiral phosphine with a wide bite angle and stable chelation ability. Thus, ligands **5j–m** were synthesized and their enantioselectivity was assessed (Table 1, entries 10–14). Gratifyingly, the best enantioselectivity (62% ee) was obtained using ligand **5l** having *cis*-2-butene linker (entry 12).[13,14] A comparable result was also obtained using ligand **5m** having cyclopropyl linker (entry 14). These linkers should define the positions of the steric hindrance (the phenyl groups of the phospholane) far from the metal center while maintaining stable bidentate coordination to the copper atom. The predominant effect of the linker structure on the enantioselectivity was also demonstrated using ligands **5j** and **5k**. Although enantioselectivity was much lower than when using **5l** and **5m**, the absolute configuration of the aldol product depended on the chirality at the linker part, and not on the chirality of the phospholane (entries 10 and 11).

Finally, the best ligand **5l** also produced appreciable enantioselectivity (66% ee) from an aliphatic ketone **1b** (Table 1, entry 13).[15] Although enantioselectivity is still in the moderate range, this result is significant if compared with the results obtained under the following representative conditions; the aldol product was obtained with only 32% ee under Denmark's conditions,[5] and with 12% ee using tol-BINAP as a ligand under CuF-catalyzed reactions. Thus, this is the most enantioselective catalytic aldol reaction reported to date using aliphatic ketones.[16]

To summarize, we established a new ligand design concept for a CuF-catalyzed enantioselective aldol reaction to ketones. A modular approach was used to identify new chiral bidentate diphenylphospholane ligands **5l** and **5m**, which produced up to 66% ee. The linker moiety connecting the two diphenylphospholane modules had a profound effect on enantioselectivity. This linker effect was rationalized by the generation of a deep chiral pocket around the catalytically active copper metal, as well as the formation of a stable chelation to copper. These factors are essential for constructing an effective chiral environment to control the orientation of the substrate ketone in the linear transition state of this catalytic enantioselective aldol reaction. Although enantioselectivity is still moderate, the applicability to both aromatic and aliphatic ketones and the use of a relatively stable ketene trimethylsilyl acetal are significant advantages to the previous example, considering the formidable difficulty and high importance of the target reaction.[17] The results described here demonstrated that a rational design of chiral bidentate phosphine ligands is possible toward a general and practical catalytic enantioselective aldol reaction to ketones. Studies toward this goal are ongoing. In addition, the unique chiral environment constructed by the newly developed ligands **5l** and **5m** should be useful for other transition metal-catalyzed organic reactions.

Acknowledgements

Financial support was provided by PRESTO of Japan Science and Technology Agency (JST) and Grant-in-Aid for Specially Promoted Research of MEXT. K.O. and Y.S. thank JSPS for research fellowships.

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8. The following experimental results support these ideas. (1) The enantioselectivity was independent of the alkoxide substituents of the silicon atom. Both ketene triethoxysilyl acetal and ketene trimethoxysilyl acetal produced the same enantioselectivity, which suggested that the silicon is not relevant to the enantio-differentiation step (aldol addition to substrate ketones). (2) The order dependencies of the initial reaction rate on [ketone], [catalyst], and [silyl enolate] were determined to be 0, 1.5, and –0.8, respectively, which indicated that the addition step is not the rate-determining step (see Ref. 6).
9. Chiral amine ligands such as pybox and salen, and monophosphines such as MOP and Feringa's phosphoramidite produced only very low reactivity and/or no enantioselectivity.
10. Both *E*- and *Z*-silyl enolates produced the *syn*-isomer with low diastereoselectivity (*syn:anti* = 1.6:1), which suggested a linear transition state (see Ref. 6).
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12. There was no significant difference in reactivity between catalysts coordinated by a monodentate phosphine and a bidentate phosphine.
13. A triphenylphosphine-free catalyst generated via in situ reduction of $CuF_2{\cdot}2H_2O$ with the chiral bidentate phosphine (see Ref. 4) produced the same enantioselectivity as the catalyst prepared by simply mixing $CuF{\cdot}3PPh_3{\cdot}2EtOH$ and **5l**. Therefore, the competitive coordination of triphenylphosphine to generate achiral CuF was negligible when **5l** was used as a chiral ligand.
14. Representative spectroscopic data of **5l**: ^1H NMR (500 MHz, $CDCl_3$) δ: 1.46–1.54 (m, 2H), 1.85–1.95 (m, 2H), 2.00–2.08 (m, 2H), 2.18–2.28 (m, 2H), 2.35–2.45 (m, 2H), 2.50–2.60 (m, 2H), 3.23–3.31 (m, 2H), 3.65–3.75 (m, 2H), 5.15–5.21 (m, 2H), 7.14–7.34 (m, 20H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 23.93, 24.13, 31.63, 37.50, 46.39, 46.49, 48.46, 48.57, 125.55, 125.63, 125.67, 127.27, 127.81, 127.85, 127.88, 128.30, 128.32, 138.88, 144.83; ^{31}P NMR (202 MHz, $CDCl_3$) δ: 12.0 (s).
15. General procedure for catalytic enantioselective aldol reaction to ketones: A solution of $CuF{\cdot}3PPh_3{\cdot}2EtOH$ (9.6 mg, 0.010 mmol, 2.5 mol %) and chiral phosphine ligand (0.020 mmol, 5 mol %) in degassed DME (0.6 mL) was stirred at room temperature for 30 min. To this solution, ketone (0.40 mmol) and $(EtO)_3SiF$ (0.48 mmol, 1.2 equiv) were added at room temperature and stirred for 15 min. Ketene silyl acetal **2** (0.80 mmol, 2 equiv) was then added at 0–4 °C, and the mixture was stirred for the indicated period shown in Table 1. $3HF{\cdot}Et_3N$ (0.3 mL) was added to quench the reaction, and the mixture was stirred at room temperature for 30 min. After the addition of satd NaCl, the product was extracted with AcOEt, and the combined organic layer was washed with brine. Drying with Na_2SO_4, filtration, concentration, and purification by silica gel column chromatography (AcOEt/hexane) gave the aldol product.
16. The previous best result for aliphatic ketones was only 35% ee from 4-phenylbutan-2-one in Denmark's catalysis.
17. Other ketene silyl acetals than **2** can be utilized for the present catalytic enantioselective aldol reaction to ketones. The enantio-induction at the α-position was much more efficient (up to 90% ee was obtained using tol-BINAP; unpublished result) than the tertiary alcohol construction at the β-position. See Ref. 6 for preliminary results of this type of asymmetric reaction.