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Cu(I)-Catalyzed Direct Enantioselective Cross Aldol-Type Reaction of Acetonitrile

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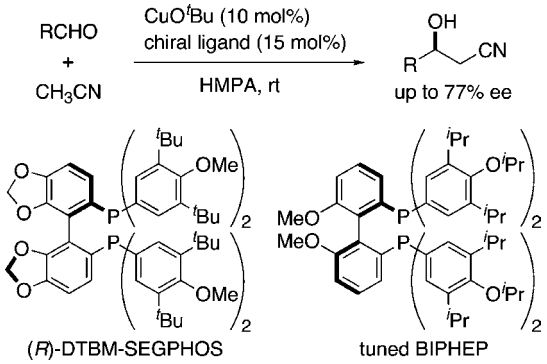
ABSTRACT



Direct catalytic enantioselective cross aldol-type reaction of an acetate surrogate was developed using Cu alkoxide−chiral phosphine complexes as catalysts. Chemoselective activation and deprotonation of the donor substrate (acetonitrile) by the soft metal alkoxide in a strongly donating solvent (HMPA) are key to success in this reaction. Useful chemical yields and promising enantioselectivities are produced using either DTBM-SEGPHOS or a tuned BIPHEP as a chiral ligand.

Catalytic enantioselective carbon−carbon bond-forming reactions through proton transfer are advantageous compared to reactions using *preactivated* nucleophiles with stoichiometric amounts of metals, because minimum waste is generated. Catalytic enantioselective aldol reactions, one of the most important synthetic methodologies in organic chemistry,[1] are intrinsically atom-economical reactions. For successful direct catalytic enantioselective aldol reactions that produce synthetically useful enantioselectivity, chemoselective deprotonation of donor substrates to generate active nucleophiles in the presence of acceptor aldehydes is essential. Our group reported the first example in this category using lanthanum−lithium−chiral binaphthoxide (LLB) complex as a catalyst and ketones as donor substrates.[2] Since then, there has been a very active research effort toward developing direct catalytic enantioselective aldol reactions.[3] The current aim is to utilize more synthetically useful carboxylic acid analogues as the donor.

There are three main approaches. First, MacMillan reported a direct proline-catalyzed enantioselective anti cross-aldol reaction using aldehydes as donors.[4,5] Chemoselective deprotonation is possible through slow addition of an acceptor aldehyde to a mixture of the catalyst and a donor

(1) For reviews, see: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, pp 997−1065. (b) Carreira, E. M. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: 2000; pp 513−541.

(2) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178.

(3) For a review on direct catalytic enantioselective aldol reactions, see: (a) Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 197−227. (b) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570−579. (c) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591.

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aldehyde. The synthetic utility of this method is demonstrated by extension to a two-step synthesis of carbohydrates, directly subjecting the resulting chiral β-hydroxy aldehyde to a second diastereoselective aldol reaction. Second, Evans reported a Ni(II)−bis(oxazoline)-catalyzed enantioselective syn aldol reaction using *N*-propionylthiazolidinethiones as the donor.[6] Chemoselective deprotonation of the donor is possible through chelate coordination to the cationic Ni. Although the reaction proceeds via in situ-generated nickel enolate, stoichiometric amounts of TMSOTf and 2,6-lutidine are necessary for dissociation of the intermediate aldolate from the catalyst. Third, Shair reported a Cu(II)−bis(oxazoline)-catalyzed enantioselective syn aldol reaction using a malonic acid half ester as the donor.[7] Higher acidity of the donor than the acceptor aldehydes and irreversible CO_2 emission after aldol-type addition are key to the success of the cross-aldol reaction under mild conditions. Indeed, protic functional groups are tolerated in Shair's reaction. Although excellent enantioselectivity and chemical yields are obtained in these three reactions, even from enolizable aldehydes, all of these examples utilize α-substituted carbonyl compounds (such as propionaldehyde or propionate derivatives) as donors. In contrast, there is no catalytic enantioselective direct aldol-type reaction of simple acetate analogues that is applicable to enolizable aldehydes.

Our approach for developing a direct catalytic enantioselective aldol-type reaction of carboxylic acid analogues is to use a chiral soft metal alkoxide as a catalytic Brönsted base and alkylnitriles as the donor (Scheme 1).[8,9] Due to the strong coordination ability of nitriles to soft metals, alkylnitriles are selectively activated and deprotonated by a soft metal alkoxide to generate the active nucleophile **3** through a possible complex **2**. Once the nitrile aldol reaction proceeds (from **3** to **1**), the intermediate soft metal aldolate **1** again works as a chiral Brönsted base catalyst for the second cycle. On the basis of these considerations, we reported preliminary examples of the catalytic enantioselective direct nitrile aldol reaction; using CuO^{t}Bu[10]−DTBM−SEGPHOS complex as a catalyst, nitrile aldol product was produced with up to 53% ee from aldehydes without enolizable protons. When easily enolizable linear aldehydes were used, however, chemoselective deprotonation of alkylnitriles was difficult and aldehyde self-condensation was a serious side reaction. In this communication, we report improved reaction conditions applicable to linear aldehydes, giving products with up to 77% ee. Specifically, this is the first catalytic enantioselective direct aldol-type reaction of an acetic acid surrogate that demonstrates significant enantioselectivity from easily enolizable linear aldehydes.

Scheme 1. General Concept of Direct Enantioselective Nitrile Aldol Reaction Catalyzed by Soft Metal Alkoxide

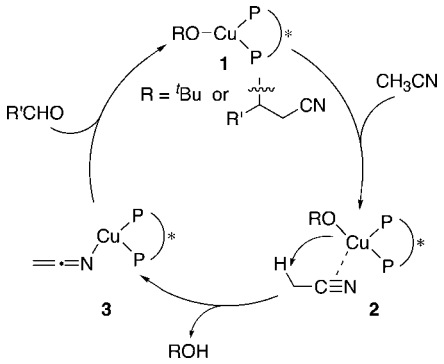
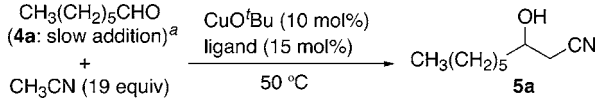


Table 1. Optimization of Direct Catalytic Nitrile Aldol Reaction to Linear Aldehyde



entry	ligand	solvent	yield % (ee %)
1[b]	dppe	DMSO	12 (−)
2	dppe	DMSO	33 (−)
3	dppe	HMPA	79 (−)
4	Ph_3P	HMPA	23 (−)
5	$(Me_2N)_3P$	HMPA	9 (−)
6	(*S*)-tol-BINAP	HMPA	21 (16)
7	(*R*,*R*)-Ph-BPE	HMPA	32 (0)
8	(*R*,*S*)-Josiphos	HMPA	18 (6)
9	(*R*)-SEGPHOS	HMPA	18 (8)
10	(*R*)-DTBM−SEGPHOS	HMPA	84 (58)
11[c]	(*R*)-DTBM−SEGPHOS	HMPA	72 (74)
12[c]	(*R*)-DTBM−SEGPHOS	DMPU	60 (71)

[a] Aldehyde was added slowly over 2.5 h using a syringe pump unless otherwise noted. Reaction time = 2.7 h (including the slow addition time). [b] Aldehyde was added in one portion. Reaction time = 30 min. [c] Reaction was conducted at room temperature. The aldehyde was added slowly over 5 h with a syringe pump. Reaction time = 5.2 h.

Basic reaction conditions were first optimized using heptanal (**4a**) as an acceptor, acetonitrile as a donor, and CuO^{t}Bu−achiral phosphine ligand complex as a catalyst (Table 1, entries 1−5). When previously optimized reaction conditions[8] were applied to **4a** at 50 °C (entry 1), the nitrile aldol product was obtained in only 12% yield. The main reaction pathway was self-condensation of the aldehyde. Even with slow addition of **4a** to a mixture of the catalyst

(4) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799. (b) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152−2154. (c) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752−1755.

(5) For other examples of direct catalytic enantioselective aldol reactions using aldehydes as donors, see: (a) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun*. **2002**, 620−621. (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed*. **2004**, *43*, 2420−2423. (c) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed*. **2003**, *42*, 858−860.

(6) Enans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc*. **2003**, *125*, 8706−8707.

(7) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc*. **2005**, *127*, 7284−7285.

(8) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett*. **2003**, *5*, 3147−3150.

(9) For catalytic nitrile aldol reaction without enantiocontrol, see: (a) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem*. **1999**, *64*, 3090−3094. (b) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc*. **2004**, *126*, 13632−13633. (c) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Chem. Commun*. **2005**, 3600−3602.

and acetonitrile, the yield of **5a** improved very little (entry 2). This aldehyde self-condensation is due to the undesired deprotonation of an easily enolizable linear aldehyde by the Cu alkoxide catalyst, even in the presence of excess soft acetonitrile. Because aldehyde deprotonation proceeds through coordination of the carbonyl oxygen to Cu, the difference in coordination affinity of the soft nitrile and the hard aldehyde oxygen to Cu is not sufficient in the case of easily enolizable linear aldehydes.

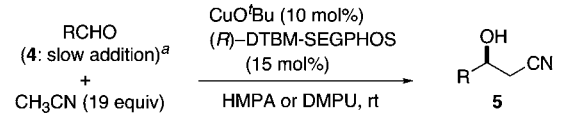
To more effectively differentiate between the coordination of acetonitrile and aldehyde oxygen to Cu, reactions in a highly donating solvent such as HMPA were investigated. We expected that HMPA would competitively inhibit the coordination of aldehydes to Cu, because the coordination mode is similar to that of HMPA (σ-donation of the oxygen lone pair to the vacant Cu sp^3 orbital). On the other hand, nitrile coordination to Cu might not be affected much by the σ-donor solvent, because back-donation from the filled 3d orbital of Cu to the nitrile π^* orbital significantly contributes to the stability of the nitrile coordination to Cu. As expected, the yield of the desired **5a** was greatly improved to a synthetically useful range (79%) when HMPA was used as a solvent and **4a** was slowly added with a syringe pump (Table 1, entry 3).

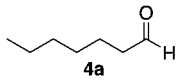
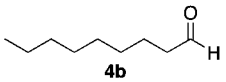
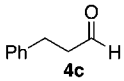
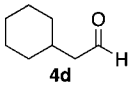
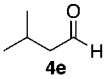
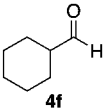
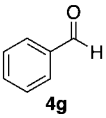
Next, the optimized conditions were extended to a catalytic enantioselective reaction (Table 1, entries 6−12). The product yield was strongly dependent on the chiral ligand structure. DTBM−SEGPHOS was the only chiral ligand that produced high chemical yield and enantioselectivity (entry 10). Optimization of the reaction temperature and the slow addition time of **4a** improved the enantioselectivity to 74% ee without significantly affecting the chemical yield (entry 11). Use of the noncarcinogenic donating solvent DMPU produced slightly less successful results (entry 12).

The substrate generality of the direct catalytic enantioselective nitrile aldol reaction was then investigated under the optimized conditions described above (Table 2). Enantioselectivity was almost constant (up to 76% ee) with a range of enolizable aldehydes (entries 1−6). For nonenolizable aldehydes, enantioselectivity was slightly improved under the present reaction conditions (entry 8) compared to the previous reactions in DMF or DMSO (entry 9). Because the products can be easily hydrolyzed to the corresponding carboxylic acids without racemization,[8] this reaction is a surrogate for a direct catalytic enantioselective aldol reaction of an acetate derivative.

There are several noteworthy points in this reaction. First, positive nonlinear effects[11] were observed (Figure 1). Thus, despite the large steric hindrance of the DTBM−SEGPHOS ligand, there exists aggregated chiral copper alkoxide complexes in the reaction mixture. Second, the chirality and electronic characteristics of the initial alkoxide ligand of the copper atom had very little effect on the enantioselectivity and catalyst activity: Cu−binaphthoxide−(*R*)-DTBM−SEGPHOS complex (10 mol %) produced **5g** in 81% yield with 52% ee when the catalyst was derived from (*R*)-BINOL and

Table 2. Catalytic Enantioselective Nitrile Aldol Reaction



entry	aldehyde	yield (%)[b]	ee (%)[c]
1	 **4a**	72	74
2	 **4b**	62	73
3	 **4c**	67	68
4	 **4d**	88	76
5	 **4e**	86	75
6 7[d]	 **4f**	91 88	75 72
8 9	 **4g**	85 70	51 47[e]

[a] Aldehyde was added slowly over 5 h using a syringe pump. Reaction time = 5.2 h (including the slow addition time). [b] Isolated yield. [c] Determined by chiral HPLC. [d] Solvent = DMPU. [e] Previous results in DMF at 0 °C with one-portion addition of the aldehyde (see ref 8).

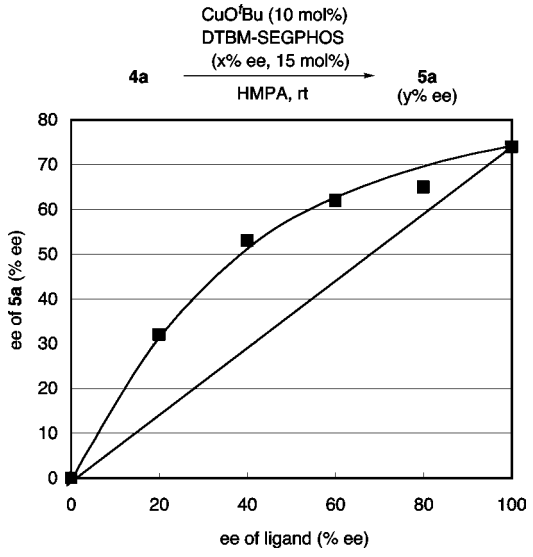


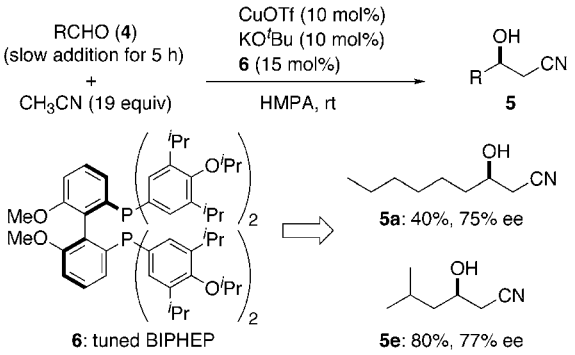
Figure 1. Nonlinear effects.

(10) CuO^{t}Bu was prepared by adding 1 equiv of ^{t}BuOH to mesitylcopper generated using Saegusa's method: Tsuda, T.; Watanabe, K.; Miyata, K.; Yamamoto, H.; Saegusa, T. *Inorg. Chem.* **1981**, *20*, 2728−2730.

(11) (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959. (b) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402−411.

in 93% yield with 47% ee in the same configuration when the catalyst was derived from (*S*)-BINOL (also compare with the results in Table 2, entry 8). Therefore, the alcohol (or phenol) generated after deprotonation of acetonitrile (Scheme 1, from **2** to **3**) might not be involved in the addition step of the chiral copper ketene imide to an aldehyde. Third, a more convenient catalyst generation method was developed: using in situ-prepared CuO^{t}Bu−chiral diphosphine complex from CuOTf·1/2benzene complex and KO^{t}Bu, **5e** was produced in 90% yield with 75% ee (86% yield with 75% ee when using pure CuO^{t}Bu: Table 2, entry 5).[12] Fourth, the enantioselectivity can be improved through optimization of the chiral ligand structure (Scheme 2). Thus, a tuned BIPHEP[13] ligand **6** containing bulky substituents on the phosphorus atoms produced higher enantioselectivity than DTBM−SEGPHOS, and products with up to 77% ee were obtained.[14]

Scheme 2. Improvement by Ligand Structure Tuning



In conclusion, we developed a catalytic enantioselective nitrile aldol reaction that can be applied to easily enolizable linear aldehydes. The basic concept is the chemoselective activation of acetonitrile by a soft metal alkoxide in the presence of an acceptor aldehyde in a strongly donating solvent. On the basis of these findings, further studies to improve the enantioselectivity are currently ongoing.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Other combinations such as CuOTf−NaO^{t}Bu, CuOTf−LiO^{t}Bu, CuBr−KO^{t}Bu, or CuOAc−KO^{t}Bu for the in situ catalyst preparation gave less satisfactory results.

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

(14) **General Procedure.** HMPA (0.54 mL) and CH_3CN (0.27 mL) were added to a mixture of chiral ligand **6** (46.6 mg, 0.0405 mmol), CuOTf·1/2benzene complex (6.8 mg, 0.027 mmol), and KO^{t}Bu (3.0 mg, 0.027 mmol). After stirring for 10 min at room temperature, aldehyde **4e** was added slowly over 5 h using a syringe pump. After the addition was completed, the mixture was stirred further for 10 min to complete the reaction.