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Direct Asymmetric Aldol Reaction of Aryl Ketones with Aryl Aldehydes Catalyzed by Chiral BINOL-Derived Zincate Catalyst

Hong Li, Chao-Shan Da,* Yu-Hua Xiao, Xiao Li, and Ya-Ning Su

Institute of Biochemistry & Molecular Biology, School of Life Sciences, Lanzhou University, Lanzhou 730000, China

dachaoshan@lzu.edu.cn

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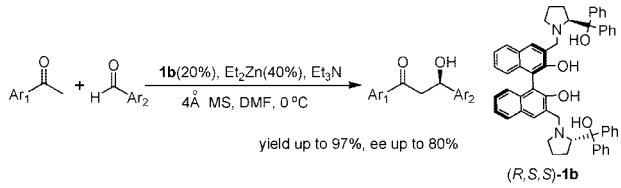

Direct asymmetric aldol reaction of aryl ketones with aryl aldehydes catalyzed by chiral metal complex is reported for the first time herein. Two novel semicrown chiral ligands **1a** and **1b** were synthesized from (*S*)- and (*R*)-BINOL, respectively, and then employed to catalyze the direct asymmetric aldol addition of aryl ketones to aryl aldehydes. Introduced with 2.0 equiv of diethylzinc, **1b** had higher enantioselectivity than **1a**. Up to 97% yield and up to 80% enantioselectivity were achieved.

The aldol reaction is one of the most important and useful carbon−carbon bond formation reactions in organic chemistry,[1] because it can produce versatile β-hydroxyl carbonyl compounds, which are key intermediates or synthetic building blocks of biologically active compounds.[2] Therefore, many groups are now focusing on catalytic asymmetric direct aldol addition reactions.[1a,b] There are three processes that have emerged. The most developed methods are asymmetric organocatalytic direct aldol reactions[3] which have been fruitful since List, Lerner, and Barbas[4] reported the first remarkably successful case of direct reaction of acetone with aryl aldehydes catalyzed by L-proline. Another protocol is based on biological catalysts, i.e., enzymes or abzymes.[5] The third method is the protocol catalyzed by chiral metal complexes.[6−8] Among the chiral metal catalysts, Trost's dinuclear Zn catalysts[8] and Shibasaki's (*S*,*S*)-zinc−zinc-linked-BINOL complex[7c,d] are especially efficient, which were broadly applied to catalyze simple aldol addition of arylketones,[7c,8a] methyl vinyl ketone,[8f] acetone,[8c] α-hydroxyl aryl ketones,[8b,d] and methyl ynones[8e] to aldehydes as well as nitro aldol reactions (the Henry reaction).[8g−i] These facts make zinc-containing chiral catalysts more promising for various direct aldol additions. To the best of our knowledge, however, direct asymmetric aldol reaction between aryl ketones and aryl aldehydes catalyzed by chiral organometallic complexes has not been reported to date.[9] This reaction can generate versatile biologically active diaryl β-hydroxyl ketones. Traditionally, these compounds are synthesized by Mukaiyama-type aldol reactions,[10] in which preconversion of aryl ketones to more reactive intermediates is indispensable.[11] This situation makes it very interesting to develop zinc-containing chiral ligands for direct aldol addition of aryl ketones to aryl aldehydes today. Herein we report our results on the design and synthesis of novel C_2-symmetric

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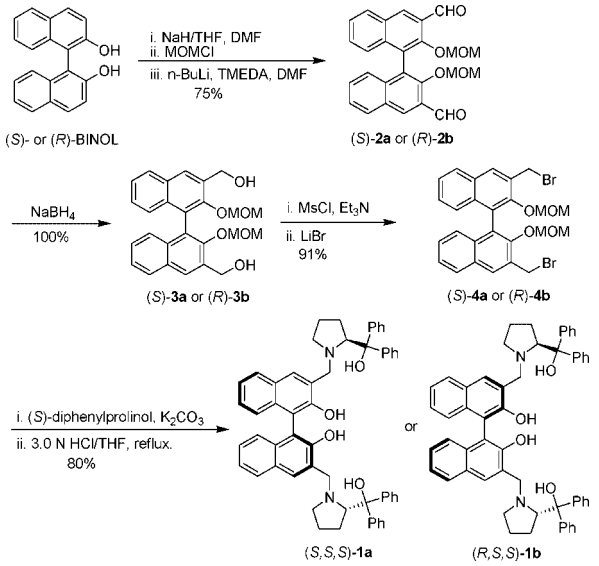
SCHEME 1. Synthesis of Ligands 1



semicrown zinc-containing catalysts derived from commercially available chiral BINOL and their application in this challenging asymmetric reaction.

Ligands **1a** and **1b** were designed and synthesized from chiral BINOL and (*S*)-diphenylprolinol. The preparative course was depicted in Scheme 1. Initially, (*S*)- or (*R*)-BINOL was routinely protected with the MOM group according to the reported processes.[12] The dialdehyde derivatives **2a**,**b** were achieved by lithiation of the MOM-protected (*S*)- and (*R*)-BINOL with *n*-BuLi and successive reaction with DMF. Dialdehydes **2a**,**b** were then reduced with $NaBH_4$ to yield dialcohols **3a**,**b**, which were brominated in succession to give dibromo derivatives **4a**,**b**. Amination of **4a**,**b** with (*S*)-diphenylprolinol and deprotection of the MOM group afforded C_2-symmetric semicrown ligands (*S*,*S*,*S*)-**1a** and (*R*,*S*,*S*)-**1b**.

Activities of ligands **1a** and **1b** were evaluated by catalyzing direct aldol addition of acetophenone to benzaldehyde (Table 1). (*S*,*S*,*S*)-**1a** yielded (*S*)-product whereas (*R*,*S*,*S*)-**1b** afforded (*R*)-diaryl β-hydroxyl ketone. These phenomena implied that the configuration of the aldol product should be determined by the BINOL moiety rather than the amino alcohols' parts. The results showed that **1b** was superior to **1a** in enantioselectivity. As for solvent, DMF gave the highest ee and yield among the six screened solvents. The ratio of ligand to diethyl zinc was crucial to the enantioselectivity. **1b**/Et_2Zn = 1/2 gave the optimal result. When the ratio was higher than 1:2, the enantioselectivity dropped. Although the ratio of 1:1.6 yielded the same ee as 1:2 achieved, less Et_2Zn made the reaction quite sluggish. And further lowering this ratio also afforded the decreased enantioselectivity. So **1b**:Et_2Zn = 1:2 should be the optimal ratio. This was consistent with results reported by Trost[8a] and Shibasaki.[7c] When DMF was selected as solvent, we occasionally found that organic amines could be beneficial to the stereoseletion.[13] Three amines were checked. It was shown that tertiary amine could heighten the enantioselectivity whereas secondary amine gave a sharply decreased ee. Triethylamine was the best additive among them; it gave the obviously heightened ee value. Enantioselectivity could be further improved by lowering the temperature at the accompanying expense of increasing the reaction time. When the amount of **1b** was increased, no effect on the enantioselectivity was observed, but a higher yield was achieved.

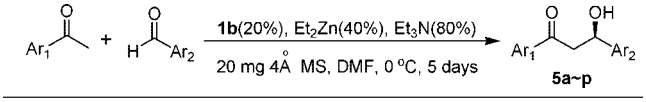
Under the optimized reaction conditions (20% **1b**, 40% Et_2Zn, 4Å MS, DMF as solvent and triethylamine as an additive at 0 °C) direct aldol reactions of a brand of aryl aldehydes with aryl

TABLE 1. Direct Aldol Reaction of Acetophenone and Benzaldehyde Catalyzed by Chiral Zinc Catalysts[a]

ligand (%)	Et_2Zn[b]	solvent	additive	ee (%)[c]
1a (5)	1/2.0	DMF	no	14[d]
1a(20)	1/2.0	THF	no	13[d]
1b (5)	1/2.0	THF	no	30
1b (5)	1/2.0	DMSO	no	26
1b (5)	1/2.0	CH_2Cl_2	no	27
1b (5)	1/2.0	Tol.	no	38
1b (5)	1/2.0	Et_2O	no	8
1b (5)	1/2.0	DMF	no	48
1b (5)	1/1.3	DMF	no	42
1b (5)	1/1.6	DMF	no	48
1b (5)	1/2.3	DMF	no	38
1b(10)	1/2.0	DMF	No	46 (45)
1b(10)	1/2.0	DMF	Et_2N[e]	19
1b(10)	1/2.0	DMF	Et_3N[e]	58 (43)
1b(10)	1/2.0	DMF	DIPEA[e]	40
1b(10)	1/2.0	DMF	DIPEA[e]	56[f]
1b(20)	1/2.0	DMF	Et_3N[e]	58 (76)
1b(20)	1/2.0	DMF	Et_3N[e]	70 (61)[f]

[a] The reaction was performed at room temperature under an argon atmosphere, and 20 mg 4Å molecular sieves were added. [b] Data was the ratio of ligand **1a** or **1b** to Et_2Zn. [c] The ee was determined by the chiral HPLC. Data in parentheses are yields. The configuration is *R* except for entries 1 and 2, which was determined by the optical direction and retention time on HPLC compared to the reported data.[14] [d] Configuration of the product is *S*. [e] 80% additive equiv to benzaldehyde was used. [f] The reaction was performed under 0 °C.

TABLE 2. Direct Asymmetric Aldol Addition of Aryl Ketones to Aryl Aldehydes



entry	Ar_1	Ar_2	yield (%)	ee (%)[a]
1	Ph	Ph	61	70
2	Ph	1-naphthyl	63	73
3	Ph	2-naphthyl	70	72
4	Ph	2-MeO-Ph	65	59
5	Ph	3-MeO-Ph	70	62
6	Ph	4-MeO-Ph	22	32
7	Ph	2-Cl-Ph	97	54
8	Ph	3-Cl-Ph	95	74
9	Ph	4-Cl-Ph	70	64
10	Ph	3-NO_2-Ph	74	57
11	Ph	4-NO_2-Ph	75	46
12	Ph	3-Me-Ph	43	50
13	Ph	furan-2-	45	80
14	Ph	thiophene-2-	36	69
15	1-naphthyl	Ph	65	54
16	2-naphthyl	Ph	59	57

[a] Determined by chiral HPLC.

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(13) The solvent DMF usually contains some little amines. When we initially used simply dried DMF as solvent, we got varied results which could not be easily duplicated. After carefully preparing dry DMF, however, a decreased ee value was achieved. So we speculated that amines might be beneficial to higher enantioselectivity.

(14) Mandal, S. K.; Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 4600.

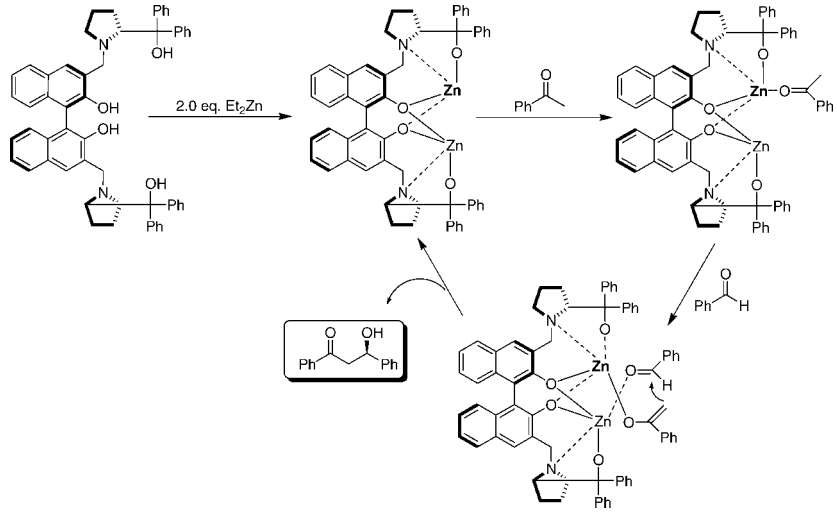

FIGURE 1. The proposed mechanism elucidates that the attack will occur from the *Re*-face of the benzaldehyde.

ketones were observed. The results were included in Table 2. It could be found that this dinuclear zincate catalyst was effective in this reaction. Up to 97% yield could be obtained. As for enantioselectivity, moderate to high ee was achieved. Acetophenone yielded higher enantioselectivity than two acetonaphthones. The catalyst could be employed to catalyze many sorts of aryl aldehydes in this reaction. The sites of the substituent groups on the phenyl ring could have great effects on the stereoselection. The meta-substituted substrates generated higher ee than ortho- and para-substituted aldehydes. Big aryl rings such as 1-naphthyl and 2-naphthyl aldehydes both gave higher enantioselectivity. Strong electron-withdrawing groups impaired the enantioselectivity such as nitro, as did electron-donating groups such as the methoxy group. When furan-2-carbaldehyde was used as the substrate, the highest enantioselectivity up to 80% was achieved. All products were *R* configuration, which was determined by comparing their optical direction or retention time on HPLC to the reported data.[14,15]

According to the mechanisms of Trost's semicrown zincate catalysts,[7a] Shibasaki's zinc−zinc-linked BINOL catalyst,[7c] and Pu's speculation on their research,[16] we envisioned that zincate-**1b** should mainly adopt the steady transition state as depicted in Figure 1. Thus the attack of zincate enol to benzaldehyde should chiefly occur from the *Re*-face of benzaldehyde and yield diaryl β-hydroxyl carbonyl compound **5a** with *R* configuration.

In conclusion, we have successfully performed the first case of direct enantioselective aldol reaction of aryl ketones with aryl aldehydes catalyzed by chiral metal-containing complex. Two novel C_2-symmetric semicrown ligands **1a** and **1b** were effectively synthesized from chiral BINOL and (*S*)-diphenylprolinol. The zincate of **1b** was found to be a more effective catalyst, which could highly catalyze this topic reaction. Up to 97% yield and up to 80% enantioselectivity were achieved.

Experimental Section

3b was routinely synthesized from (*R*)-BINOL according to the reported procedures.[12]

Preparation of (*R*)-3,3′-Bis(bromomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthol (4b). To an ice-cooled solution of crude **3b** (1.96 g, 4.5 mmol) in toluene (30 mL)/ethyl acetate (30 mL) were successively added Et_3N (5 mL, 36mmol) and MsCl (1.4 mL, 18 mmol). The mixture was stirred at 0 °C for 90 min. The resulting suspension was filtered to remove solid salt $Et_3NH^+Cl^-$ and the solid was washed with ethyl acetate (30 mL). The combined filtrate and washings were cooled to 0 °C and then LiBr (7.82 g, 90 mmol) in 75 mL of DMF was added. The mixture was stirred at room temperature for a further 10 min. It was then diluted with ether (120 mL) and washed with water (60 mL × 2), 1 mmol/L aqueous HCl (30 mL × 2), saturated aqueous $NaHCO_3$ (30 mL), and saturated brine in succession, and finally dried over $MgSO_4$ and evaporated in vacuo to give **4b** as yellow oil (5.568 g, 11.9 mmol, and yield 91%) which was pure enough to be used in the next step without further purification. $[\alpha]^{20}_D$ −36 (*c* 0.84, THF); IR (KBr) 2924, 2854, 1745, 1460, 1157, 968, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.28−7.24 (m, 2H), 7.18−7.15 (m, 2H), 4.89 (d, J = 9.6 Hz, 2H), 4.85 (d, J = 10 Hz, 2H), 4.67 (d, J = 6.0 Hz, 2H), 4.56 (d, J = 5.2 Hz, 2H), 2.99 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.3, 134.2, 131.5, 130.6, 129.0, 128.2, 127.3, 126.0, 125.6, 125.3, 99.3, 56.9, 29.3; HRMS calcd for $C_{26}H_{28}Br_2NO_4$ ($[M + NH_4]^+$) 576.0380, found 576.0382.

Preparation of (*R*,*S*,*S*)-3,3′-Bis[(*N*-diphenylprolinol)methyl]-2,2′-bis(methoxymethyl)-1,1′-binaphthol (1b). To a mixture of 0.84 g of (*R*)-**4b** (1.5 mmol) and 2.1 g of anhydrous K_2CO_3 (15 mmol) in 15 mL of dry DMF was introduced in one portion at room temperature 0.84 g of solid (*S*)-diphenylprolinol (3.3 mmol). The reaction was stirred for 24 h, and it was then quenched with 30 mL of water, extracted with ethyl acetate three times, combined the organic layers, washed with water two times and a little saturated brine, and condensed in vacuo to give yellow thick oil. This oil was redissolved with 3.0 N HCl (5 mL) in 20 mL of THF. This solution was refluxed for 6 h, and then the organic solvents were removed by condensation in vacuo. Next 5 mL of water was added, the solution pH was adjusted to 10.0 or so with concentrated hydrous ammonia, and the solution was extracted with ethyl acetate three times. The combined ethyl acetate layers were washed successively with water and a little saturated brine, dried with anhydrous Na_2SO_4, and condensed in vacuo to give a yellow solid. Purification by a silica column afforded the product (*R*,*S*,*S*)-**1b** as a white solid (0.98 g, yield 80%). $[\alpha]^{20}_D$ +82 (*c* 5.0, $CHCl_3$); mp 119−124 °C; IR (KBr) 3509, 2964, 1729, 1446, 1248, 1108, 748, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.2 Hz, 1H), 7.58−7.51 (m, 5H), 7.37−7.07 (m, 9H), 4.14−4.09 (m, 1H), 3.98 (br, 1H), 3.52 (br, 2H), 3.13−3.10 (m, 1H), 2.54−2.52 (m,

(15) Two alkyl aldehydes, isovaleraldehyde and butyraldehyde, were also used to replace aryl aldehydes as electrophilic acceptors, and both of them afforded *R*-configurational products with moderate enantioselectivities of 44% (**5q**) and 39% (**5r**), but with low yields of 22% (**5q**) and 21% (**5r**).

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1H), 2.08−2.04 (m, 2H), 1.85 (br, 1H), 1.71 (br, 2H), 1.27−1.23 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.3, 128.5, 128.3, 128.1, 127.8, 127.0, 126.6, 125.9, 124.7, 123.3, 114.2, 79.0, 55.5, 29.5, 24.0, 14.2; HRMS calcd for $C_{56}H_{53}N_2O_4$ ([M + H]$^+$) 817.4000, found 817.3999.

Typical Procedure of Direct Aldol Addition of Aryl Ketone to Aryl Aldehyde (5a). Diethyl zinc (0.04 mmol, 1.123 mmol/mL in *n*-hexane) was added dropwise into a solution of **1b** (0.02 mmol, 16.35 mg) in 1.0 mL of DMF at 0 °C under an argon atmosphere. The mixture was stirred for 40 min, and then 20 mg of 4Å molecular seives and triethylamine (0.08 mmol, 11.2 μL) were successively introduced. After 10 min, 0.1 mmol of aldehyde and 1.0 mmol of ketone were successively added. The reaction was continued for 5 days. Cold diluted hydrous HCl was added dropwise and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed successively with water and a little brine, and dried with anhydrous Na_2SO_4. The salt was filtered out and the solution was condensed under reduced pressure. Purification by column chromatography afforded the desired product **5a** in 61% yield: mp 50−52 °C; $[\alpha]^{20}_D$ +60 (*c* 0.83, $CHCl_3$) (lit.[14] $[\alpha]^{20}_D$ −85.3 (*c* 1.3, $CHCl_3$) for the *S* enantiomer); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, J = 7.0 Hz, 2H), 7.59−7.25 (m, 8H), 5.35 (t, J = 6.0 Hz, 1H), 3.37 (d, J = 6.0 Hz, 2H); ee was determined by HPLC with a OD-H column (hexane:2-propanol = 85:15, 0.8 mL/min), major enantiomer t_R = 13.1 min, minor enantiomer t_S = 11.8 min.

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Supporting Information Available: Detailed preparation of ligands **1a**,**b** from (*S*)- and (*R*)-BINOL and data for the aldol products **5a**−**r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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