Diastereoselective Aldol Reaction of Tin Enolate of Cyclohexanone Catalyzed by Metal Triflates

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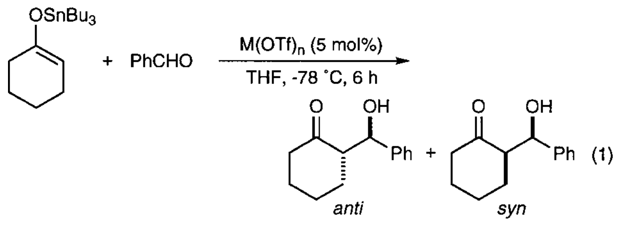
Abstract: The diastereoselective aldol reaction of tributyltin enolate of cyclohexanone with benzaldehyde was studied in the presence of a catalytic amount of various metal triflates. The highest *anti* selectivity was observed with Pd(OTf)$_2$, while Zn(OTf)$_2$ in THF showed moderate *syn* selectivity. The use of (*S*,*S*)-^{i}Pr-pybox **3**·Cu(OTf)$_2$ complex as a catalyst preferentially produced the optically active *syn* aldol adduct with 84% ee.

The Mukaiyama aldol reaction is a popular method for preparing β-hydroxy carbonyl compounds, and has been widely applied to the synthesis of natural products.[1] A variety of achiral and chiral Lewis acid catalysts have been developed for the stereoselective reaction of silyl enol ethers or ketene silyl acetals with carbonyl compounds.[1,2] In contrast, the use of organotin(IV) enolates for aldol reactions has so far received little attention.[3] We report here the diastereoselective aldol reaction of tributyltin enolate of cyclohexanone with benzaldehyde in the presence of a catalytic amount of various metal triflates and the asymmetric version of this process using chiral ligands (eq 1).



The tributyltin enolate of cyclohexanone is easily prepared from the corresponding enol acetate and tributyltin methoxide.[4] The tin enolate itself can react with benzaldehyde in THF even at -78° C,[5] although the chemical yield of the products is low (entry 1 in Table 1). In the presence of 5 mol% of metal triflates, however, the yield was significantly increased, as shown in Table 1. In addition, high diastereoselectivity was observed using these metal triflates. Among them, TMSOTf and Pd(OTf)$_2$[6] provided the *anti* aldol adduct with high selectivity in THF (entries 13 and 17). In contrast, moderate *syn* selectivity was seen for Cu(OTf)$_2$ and Zn(OTf)$_2$ (entries 8 and 10). The *anti/syn* ratio of the aldol reaction is dependent on the solvent, and higher *anti* selectivity was generally obtained in less-polar solvent. The highest *anti/syn* selectivity (96/4) was attained using Pd(OTf)$_2$ in toluene (entry 18). At present, the origin of the solvent effect is not clear.

Next, we investigated the possibility of an enantioselective version of the present diastereoselective aldol reaction, which is a significant challenge from the viewpoint of asymmetric synthesis (Table 2). Using (*R*)-BINAP **1**, (*S*,*S*)-^{t}Bu-box **2**,[7] or (*S*,*S*)-^{i}Pr-pybox **3**[8] as a chiral ligand, we studied the enantioselectivity of the *anti*-selective reaction, however, only very poor results were obtained with chiral ligand·Pd(OTf)$_2$ complexes, while the minor *syn* product showed 53% ee in the case of **1**·Pd(OTf)$_2$[6,9] (entries 1, 3, and 6). In contrast, for the *syn* selective reaction, highly asymmetric induction took place when **3**·Cu(OTf)$_2$[10] was used as a catalyst, and 84% ee of the *syn* product was formed diastereoselectively (entry 8).[11,12] Several different solvents were tested for the reaction and THF was found to give the highest enantioselectivity (entries 8-10). A complex of CuOTf with **3** also provided moderate ee with *syn* selectivity (entry 7), in contrast to the *anti* selectivity shown with CuOTf without a ligand (entries 5-7 in Table 1).

Table 1. Diastereoselective Aldol Reaction of Tin Enolate of Cyclohexanone with Benzaldehyde in the Presence of Various Metal Triflates[a]

entry	M(OTf)$_n$	solvent	yield, %[b]	*anti/syn*[c]
1	—	THF	16	57/43
2	AgOTf	THF	30	73/27
3		toluene	67	82/18
4		hexane	46	62/38
5	CuOTf	THF	69	64/36
6		toluene	75	89/11
7		hexane	72	82/18
8[d]	Cu(OTf)$_2$	THF	72	43/57
9		toluene	77	47/53
10	Zn(OTf)$_2$	THF	59	35/65
11		toluene	78	57/43
12	Sn(OTf)$_2$	THF	69	74/26
13	TMSOTf	THF	72	87/13
14		toluene	81	85/15
15	Y(OTf)$_3$	THF	64	66/34
16	Sc(OTf)$_3$	THF	53	48/52
17	Pd(OTf)$_2$	THF	77	92/8
18		toluene	76	96/4
19		hexane	64	76/24

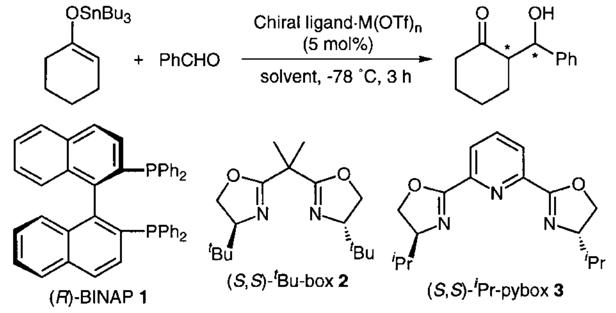
[a] Unless otherwise noted, the reaction was carried out using metal triflate (5 mol%), tin enolate (1 equiv), and benzaldehyde (1 equiv) in the specified solvent at -78 °C for 6 h. The O-Sn/C-Sn ratio of tin enolate of cyclohexanone was >99/1. The concentration of the metal triflate was 8.3×10^{-3} mol/L. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] 10 mol % of the catalyst was used

1,2-Addition of the cyclohexanone-derived enol tributylstannane to α,β-unsaturated aldehydes can also be achieved enantio- and diastereoselectively by this method. For example, the reaction of cinnamaldehyde with 5 mol% of **3**·Cu(OTf)$_2$ in THF at -78 °C for 3 h preferentially gave the optically active *syn* aldol adduct with an *anti/syn* ratio of 33/67. The *syn* isomer indicated 88% ee (eq 2).[13]

A new catalytic enantio- and diastereoselective aldol reaction using a tributyltin enolate is described which is significant for the addition of an enolate of cyclohexanone with aldehydes, since the corresponding trimethylsilyl enol ether did not react with benzaldehyde under the influence of 5 mol% of **3**·Cu(OTf)$_2$ even at room temperature (eq 3).[14] Further work on the catalytic asymmetric aldol addition is now in progress.

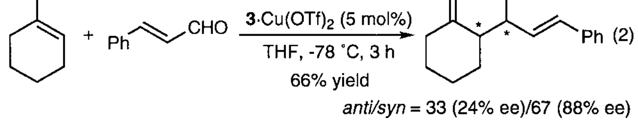
A representative experimental procedure is given by the reaction of tributyltin enolate of cyclohexanone with benzaldehyde catalyzed by **3**·Cu(OTf)$_2$ (entry 8 in Table 2). A mixture of Cu(OTf)$_2$ (18 mg, 0.050

Table 2. Diastereo- and Enantioselective Aldol Reaction of Tin Enolate of Cyclohexanone with Benzaldehyde Catalyzed by Chiral Ligand·M(OTf)$_n$ Complex[a]

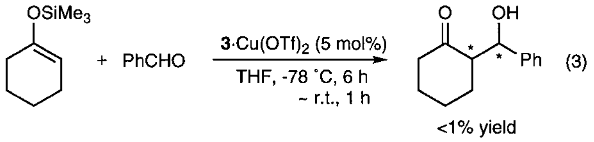


entry	chiral ligand·M(OTf)$_n$	solvent	yield, %[b]	anti/syn[c]	% ee[d]
1[e]	**1**·Pd(OTf)$_2$	THF	73	92/8	2[f]
2[e]	**1**·CuOTf	toluene	55	79/21	14[g]
3	**2**·Pd(OTf)$_2$	THF	75	90/10	2[h]
4	**2**·CuOTf	toluene	79	36/64	3[i]
5	**2**·Zn(OTf)$_2$	THF	77	46/54	12[j]
6	**3**·Pd(OTf)$_2$	THF	8	64/36	5[k]
7	**3**·CuOTf	THF	72	39/61	43[l]
8	**3**·Cu(OTf)$_2$	THF	74	36/64	84[m]
9		toluene	78	29/71	17[n]
10		CH_2Cl_2	69	42/58	69[o]

[a] Unless otherwise specified, the reaction was carried out using chiral ligand·M(OTf)$_n$ (5 mol%), tin enolate (1 equiv), and benzaldehyde (1 equiv) in the specified solvent at -78 °C for 3 h. The concentration of the chiral catalyst was 8.3×10^{-3} mol/L. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The value corresponds to the major diastereomer. Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [e] 10 mol % of the catalyst was used. [f] The *syn*-isomer: 53% ee. [g] The *syn*-isomer: <1% ee. [h] The *syn*-isomer: 7% ee. [i] The *anti*-isomer: 7% ee. [j] The *anti*-isomer: 16% ee. [k] The *syn*-isomer: 7% ee. [l] The *anti*-isomer: 2% ee. [m] The *anti*-isomer: 16% ee. [n] The *anti*-isomer: 5% ee. [o] The *anti*-isomer: 33% ee



mmol) and (*S*,*S*)-^{i}Pr-pybox **3** (15 mg, 0.050 mmol) was dissolved in dry THF (6 mL) under an argon atmosphere, and stirred at 20° C for 10 min. To the resulting solution was added dropwise benzaldehyde (100 µL, 0.98 mmol), and (1-cyclohexenyloxy)tributyltin (342 mg, 1.0 mmol) was then added over a period of 10 min at -78° C. After being stirred for 3 h at this temperature, the mixture was treated with MeOH (2 mL). After warming to room temperature, the mixture was treated with solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting precipitate was filtered off by a glass filter funnel filled with Celite® and silica gel. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* after filtration. The residual crude product was purified by column chromatography on silica gel to afford a mixture of aldol adducts (148 mg, 74% yield) as a white solid which showed the appropriate spectral data.[11] The *anti/syn* ratio was determined to be 36/64 by ^{1}H NMR analysis. The enantioselectivities of the *anti* and *syn* isomers were determined to be 16% ee and 84% ee, respectively, by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd., hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min): $t_{syn\text{-}minor}$ = 14.1 min, $t_{syn\text{-}major}$ = 15.4 min, $t_{anti\text{-}minor}$ = 17.2 min (2*S*,1'*R*), $t_{anti\text{-}major}$ = 23.8 min (2*R*,1'*S*). The absolute configurations of the *syn* isomers are not known.



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(11) Spectral data of the *syn* isomer: TLC R_f 0.13 (1:5 ethyl acetate/hexane); IR (KBr) 3600-3125, 2940, 2855, 1701, 1603, 1495, 1449, 1406, 1320, 1132, 1063, 986, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47-1.80 (m, 4 H, 2 CH_2), 1.81-1.91 (m, 1 H, one proton of CH_2), 2.04-2.15 (m, 1 H, one proton of CH_2), 2.32-2.51 (m, 2 H, CH_2), 2.56-2.65 (m, 1 H, CH), 3.01 (d, 1 H, *J* = 3.2 Hz, OH), 5.40 (d, 1 H, *J* = 2.4, 3.2 Hz, C$\underline{H}$(OH)), 7.25-7.37 (m, 5 H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.9, 27.8, 42.5, 57.1, 70.5, 125.7 (2 C), 126.8, 128.0 (2 C), 141.5, 214.5; $[\alpha]^{28.5}_D$ +132.0 (*c* 1.1, $CHCl_3$). Selected spectral data of the *anti* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (d, 1 H, *J* = 2.8 Hz, OH), 4.79 (dd, 1 H, *J* = 2.8, 8.8 Hz, C$\underline{H}$(OH)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 27.6, 30.6, 42.4, 57.3, 74.5, 126.9 (2 C), 127.7, 128.3 (2 C), 140.9, 215.3.

(12) The corresponding *anti* isomer can be selectively obtained with high enantioselectivity by a BINAP·silver(I)-catalyzed aldol reaction.[3c]

(13) Spectral data of the *syn* isomer: TLC R_f 0.11 (1:5 ethyl acetate/hexane); IR (KBr) 3580-3250, 2934, 2857, 1698, 1599, 1495, 1451, 1424, 1314, 1130, 1123, 970, 760, 739, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.78 (m, 3 H, CH_2 and one proton of CH_2), 1.86-1.96 (m, 1 H, one proton of CH_2), 2.05-2.17 (m, 2 H, CH_2), 2.30-2.49 (m, 2 H, CH_2), 2.53-2.62 (m, 1 H, CH), 2.96 (d, 1 H, *J* = 5.0 Hz, OH), 4.77 (ddt, *J* = 1.8, 5.0, 6.0 Hz, 1 H, C$\underline{H}$(OH)), 6.22 (dd, 1 H, *J* = 6.0, 16.0 Hz, CH), 6.64 (dd, 1 H, *J* = 1.3, 16.0 Hz, CH), 7.21-7.40 (m, 5 H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 27.3, 27.5, 42.5, 55.5, 70.5, 126.3 (2 C), 127.5, 128.5 (2 C), 129.0, 130.8, 136.7, 214.2; $[\alpha]^{31}_D$ +35.5 (*c* 1.0, $CHCl_3$). Selected spectral data of the *anti* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (d, 1 H, *J* = 3.4 Hz, OH), 4.44 (ddd, 1 H, *J* = 3.4, 7.4, 7.9 Hz, C$\underline{H}$(OH)) , 6.19 (dd, 1 H, *J* = 7.4, 15.9 Hz, CH), 6.62 (d, 1 H, *J* = 15.9 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 27.5, 30.4, 42.4, 56.0, 72.8, 126.3 (2 C), 127.5, 128.3 (2 C), 128.8, 131.8, 136.4, 214.7.

(14) **3**·Cu(OTf)2 and related complexes are effective chiral catalysts for enantioselective aldol additions of silylketene acetals to α-(benzyloxy)acetaldehyde or pyruvate esters, see ref. 10.