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Highly Enantioselective Aldol Reaction Mediated by Mixed Aggregates Derived from a Lithium Ester Enolate and Tetradentate Chiral Lithium Amides

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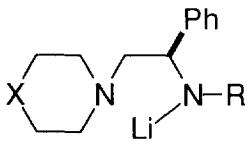
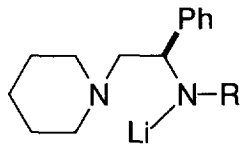
Abstract: A highly enantioselective aldol addition reaction between a lithium ester enolate with aldehydes has been achieved in up to 96% ee for *anti* products by using tetradentate chiral lithium amides (**2c**, **2d**) that are designed to form heterodimeric mixed aggregates with a lithium enolate.

The asymmetric aldol reaction has gained great attention as a useful C-C bond forming method, which is capable of generating two vicinal stereocenters.[1] In recent years, a number of excellent enantioselective aldol reactions have been developed using chiral Lewis acids in combination with silyl enol ethers.[2] As a versatile method using readily accessible lithium enolates, we have reported enantioselective aldol reactions mediated by bidentate chiral lithium amides **1a** or **1b**[3,4] in which the importance of the formation of a mixed aggregate composed of a lithium enolate and a chiral lithium amide for effective asymmetric induction was suggested.[5]

For the purpose of gaining further insights on the structural requirements of the chiral amide, we have carried out a systematic investigation on the enantioselective aldol addition reaction using tri- or tetradentate chiral lithium amides (**2a~2l**) that have one or two additional donor atom(s) in the substituent (R) on nitrogen for intramolecular coordination to lithium. In this paper, we describe highly enantioselective aldol reactions mediated by mixed aggregates derived from a lithium ester enolate and tetradentate chiral lithium amides (**2c** and **2d**).



1a: R=CH(CH$_3$)$_2$, X=CH$_2$
1b: R=cyclohexyl , X=NCH$_3$



2a~l
(see Table 1)

The enantioselective aldol addition reaction of *tert*-butyl propionate with benzaldehyde was carried out as shown in eq. 1.[7,8] The mixed aggregate was formed by adding 1.1 eq of chiral lithium amide to a solution of lithium enolate. The chemical yields and enantiomeric excesses of the *anti* and *syn* aldol products were determined after acetylation. The results are listed in Table 1.

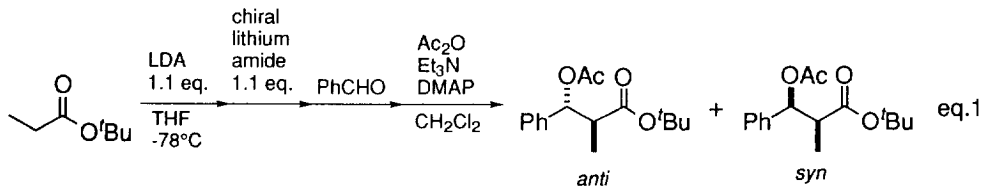


Table 1 The Aldol Reaction of *tert*-Butyl Propionate using Chiral Lithium Amides[a]

run	amide	R	*anti*		*syn*	
			c. y. (%)[b]	ee(%)[c]	c. y. (%)[b]	ee(%)[c]
1	**1b**	-(C_6H_{11})-	70	61	19	25
2	**2a**	$(CH_2)_2OCH_3$	66	75	20	32
3	**2b**	$(CH_2)_2N(CH_3)_2$	70	70	30	7
4	**2c**	$(CH_2)_2O(CH_2)_2N(CH_3)_2$	76	94	7	32
5	**2d**	$(CH_2)_2O(CH_2)_2OCH_3$	80	94	12	43
6	**2e**	$(CH_2)_2N(CH_3)(CH_2)_2N(CH_3)_2$	76	78	19	23
7	**2f**	$(CH_2)_5OCH_3$	73	54	18	18
8	**2g**	$(CH_2)_5N(CH_3)_2$	77	61	19	24
9	**2h**	$(CH_2)_5CH_3$	75	54	18	23
10	**2i**	$(CH_2)_2O(CH_2)_2CH_3$	75	82	21	7
11	**2j**	$(CH_2)_2O(CH_2)_2OPh$	74	86	15	9
12	**2k**	$(CH_2)_2O(CH_2)_2NEt_2$	68	69	20	2
13	**2l**	$(CH_2)_2O(CH_2)_2N^iPr_2$	69	72	23	6

[a] Conditions as in ref 7. [b] Isolated yields. [c] Determined by HPLC using a chiral column (Chiralpak AD).

The introduction of the third donor site to bidentate amide **1b** via an ethylene unit lead to higher enantioselectivities regardless of whether the additional donor is an ether oxygen (**2a**) or a dimethylamino nitrogen (**2b**) (75 or 70 % ee; run 2, 3 vs 1). Further addition of an oxygen or nitrogen donor to **2a** *via* an ethylene unit as the fourth donor site (**2c** and **2d**) lead to a dramatic increase in enantioselectivity (up to 94 % ee; run 4, 5 vs 2). However, a change of the third donor from an ether oxygen (**2c**) to a methylamino nitrogen (**2e**) resulted in a decrease of enantioselectivity (run 4 vs 6).

The lithium amides with an "R" group having a comparable length but lacking the third and/or fourth donor (**2f~2i**) showed rather lower enantioselectivities (run 7~10 vs 4, 5). In particular, the lack of the third donor site (**2f~2h**) resulted in a marked decrease in enantioselectivity (run 7~9 vs 4, 5). The effect of the lack of the fourth (terminal) donor site (**2i**) was rather small (run 10 vs 5). A change of the terminal donor of **2c** or **2d** to the one of poor coodinating ability due to weak basicity (**2j**; run 11) or bulkiness (**2k** and **2l**; runs 12 and 13) also resulted in a decrease in enantioselectivity.

The effectiveness of the present approach has been verified by the high enantioselectivities (93~96% ee) attained by lithium amide **2d** for the *anti* aldol products in the reaction of lithium enolate of *tert*-butyl propionate with aliphatic as well as aromatic aldehydes as shown in Table 2.

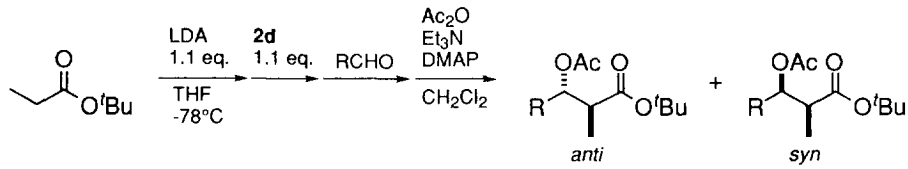


Table 2 The Aldol Reaction of *tert*-Butyl Propionate with Various Aldehydes Promoted by **2d**

run	R	*anti*		*syn*	
		c. y. (%)[b]	ee (%)[c]	c. y. (%)[b]	ee (%)[c]
1	*i*-Pr	76	94	9	45
2	*t*-Bu	66[d]	96[d]	17[d]	47[d]
3	c-Hex	83	93	13	25
4	Ph	80	94	12	43

[a] Conditions as in ref. 7. [b] Isolated yields. [c] Determined by HPLC using a chiral column (Chiralpak AD). [d] Determined without acetylated.

These stereochemical results clearly demonstrate that the formation of a heterodimeric mixed aggregate shown in Figure 1 is indeed an effective approach to achieve high enantioselectivities for the *anti* aldol products. In this regard, the tetradentate chiral lithium amides **2c** and **2d**, having two additional donor atoms that are capable of coordinating to lithium without steric hindrance, can be regarded to have excellent structures. It seems reasonable to assume the formation of a four membered dimer core (two lithiums bridged by an oxygen and a nitrogen) that is rigidly supported by the additional donor atoms (Figure 1). Such an aspect should lead to the generation of an effective chiral environment for a six-membered ring transition state of Zimmerman-Traxler type.[9] Further studies on the detailed mechanisms and application are underway.

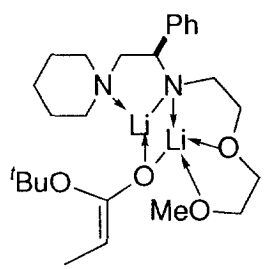


Figure 1

References and Notes

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7. A typical experimental procedure (Table 1, run 4) is as follows: Under argon atmosphere, a solution of LDA was prepared by adding a 1.64 M solution of butyllithium (1.95 mmol) in hexane (1.20 mL) to a solution of diisopropylamine (2.04 mmol) in THF (10 mL) under stirring at -78°C. After 20 min, *tert*-butyl propionate (1.78 mmol) in THF (3 mL) was added and the whole was stirred at -78°C for 20 min. To this reaction mixture was added a solution of chiral lithium amide **2d**, prepared by adding a 1.64 M solution of butyllithium (1.95 mmol) in hexane (1.20 mL) to a solution of the corresponding chiral amine (2.13 mmol) in THF (4 mL). After stirring at -78°C for 30 min, a solution of benzaldehyde (2.13 mmol) in THF (2 mL) was added in one portion and the stirring was continued at -78°C for 1 min. The reaction was quenched by adding satd aq NH_4Cl (10 mL). The crude product obtained after a usual work-up was acetylated with acetic anhydride (0.40 mL, 4.3 mmol), triethylamine (0.74 mL, 5.2 mmol) and DMAP (130 mg, 1.07 mmol) in CH_2Cl_2 (5 mL) at -20°C~r.t. for 1h. After a usual work-up, the acetylated *anti* and *syn* aldol products were purified by column chromatography (silica gel, hexane:ether (30:1~10:1)) to give *anti* product of 94% ee ($[\alpha]_D^{22}$ +43.5 (C 1.508, $CHCl_3$)) in 80% yieled and *syn* product of 43% ee ($[\alpha]_D^{22}$ -11.4 (C 0.296, $CHCl_3$)) in 12% yield. Absolute configuration was determined by transformation to the corresponding methyl ester.[10] The enantiomeric excess was determined by HPLC using a chiral column Chiralpac AD (Daisel Co., Tokyo, Japan) with hexane-isopropyl alcohol (30:1, flow rate = 0.5 mL/min, detected at 254 nm).
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