1,2-Asymmetric induction in the aldol addition reaction of malonate ester enolate to α-alkoxy aldehyde

Shinji Marumoto, Hiroshi Kogen*† and Shunji Naruto

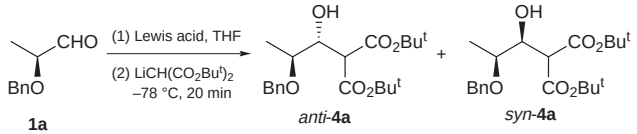
Exploratory Chemistry Research Laboratories, Sankyo Co., Ltd., 2-58, Hiromachi 1-chome, Shinagawa-ku Tokyo, 140-8710 Japan

Stereoselective aldol reactions between the lithium enolate of *tert*-butyl malonate and various α-alkoxy aldehydes in the presence of zinc chloride gave *anti*-1,2-diols in high yields; 2-trityloxypropanal yielded the *syn*-1,2-diol under the same conditions.

The stereoselective aldol reaction represents one of the major challenges of modern synthetic organic chemistry.[1] Many useful methodologies have been reported during the last few decades. For instance, 1,2-asymmetric induction in the aldol reaction of α-alkoxy aldehydes with silyl enol ethers or ketene silyl acetals is well-established.[2] The aldol reaction between α-alkoxy aldehydes and a malonate ester is especially useful for the synthesis of biologically active compounds.[3] For example, our recent synthesis of the neuritogenic agent epolactaene[4] relied exclusively on this operation for the formation of the 1,2-diol. However, Saba *et al*.[5] have been the only ones to report this type of aldol reaction, and the examples are limited. According to their report, when optically active dimenthyl malonate was added to chiral α-alkoxy aldehydes, the *anti* aldol adduct was obtained in ratios from 3:1 to 5:1, even in matched cases. Here we demonstrate simpler and more general methodologies for these aldol reactions which give higher *anti* product stereoselectively.

Initially, we attempted an 1,2-asymmetric aldol reaction between the lithium enolate of *tert*-butyl malonate and 2-benzyloxypropanal **1a**,[6] derived from methyl lactate, at −78 °C (Table 1). When this reaction was carried out without Lewis acid, aldol adduct **4a** was obtained with low diastereoselectivity (60:40, entry 1). However, when we added $MgBr_2$ to coordinate to the carbonyl group, the diastereoselectivity was slightly increased (68:32, entry 2). The reaction was further examined in the presence of various Lewis acids under various conditions.‡ The results are shown in Table 1. High *anti*-selectivity was observed using $ZnCl_2$ (82:18) or $BF_3{\cdot}OEt_2$ (91:9) (entries 4, 5). Moreover, when the reaction was carried out at −98 °C in the presence of $ZnCl_2$, the *anti* aldol adduct was obtained in excellent yield with high stereoselectivity (87:13).

Table 1 Aldol addition reaction of malonate ester enolate to 2-benzyloxypropanal



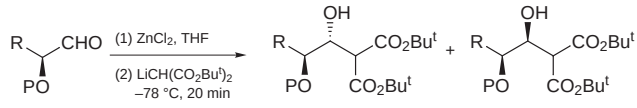
1a *anti*-**4a** *syn*-**4a**

Entry	Lewis acid	Yield (%)	*anti*:*syn*[a,b]
1	None	71[c]	60:40
2	$MgBr_2$	80	68:32
3	$ZnBr_2$	68	73:27
4	$ZnCl_2$	81	82:18
5	$ZnCl_2$	89[d]	87:13
6	$BF_3{\cdot}Et_2O$	52	91:9

[a] Ratios were determined by HPLC analysis of the crude mixture. [b] Stereochemical assignments were secured through deprotection to diol (see note §). [c] Reaction was carried out for 2 h. [d] Reaction was carried out at −98 °C.

In order to further evaluate the effect of the addition process on stereoselectivity, various α-alkoxy aldehydes were examined in this aldol reaction in the presence of $ZnCl_2$ at −78 °C. The results are summarized in Table 2. The stereoselectivity decreased somewhat when a bulky silyl group was used in place of the benzyl group as the protective group (entries 1–3). In contrast, when the alkyl group was changed from methyl to a more bulky isopropyl group (**2a**–**d**) high *anti*-selectivity was obtained using any aldehyde, although the chemical yield was affected by the size of the protective group (entries 4–7). The aldehyde **3a**, derived from mandelic acid, also gave a good result (entry 8).

Table 2 Influence of the substitution of the aldehyde in the aldol reaction in the presence of $ZnCl_2$

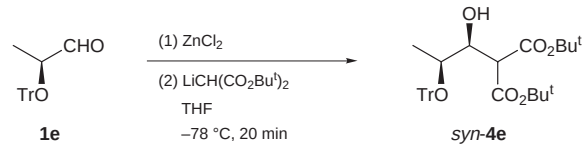


1 R = Me, **2** R = Pr^i, **3** R = Ph — **4** R = Me, **5** R = Pr^i, **6** R = Ph

Entry	Aldehyde	R	P	Yield (%)	*anti*:*syn*[a]
1	**1a**[b]	Me	Bn	81	82:18[c]
2	**1c**[d]	Me	Bu^{t}Ph$_2$Si	92	76:24[e]
3	**1d**[f]	Me	Ph$_3$Si	94	58:42[e]
4	**2a**[g]	Pr^i	Bn	75	97:3[c]
5	**2b**[f]	Pr^i	Bu^{t}Me$_2$Si	(90)[h]	98:2[e]
6	**2c**[i]	Pr^i	Bu^{t}Ph$_2$Si	(39)[h]	97:3[e]
7	**2d**[f]	Pr^i	Ph$_3$Si	(52)[h]	97:3[e]
8	**3a**[j]	Ph	Bn	83	94:6[c]

[a] Stereochemical assignments were secured through deprotection to the diol (see note §). [b] Ref. 6. [c] Ratios were determined by HPLC analysis of the crude mixture. [d] Ref. 7. [e] Ratios were determined by ^{1}H NMR analysis of the crude mixture. [f] Ref. 8. [g] Ref. 9. [h] Figures in parenthesis are the NMR yield. [i] Ref. 10. [j] Ref. 11.

To determine the extent to which the ratio of stereoisomers is affected by the protecting groups on the α-oxygen, we examined 2-trityloxypropanal **1e**[12] under the same conditions (Scheme 1). Surprisingly, the stereoselectivity was reversed and the *syn*-aldol product **4e** was preferred with high selectivity (90:10) in 53% yield (85% yield based on 62% conversion of the aldehyde **5** by ^{1}H NMR analysis). In this case, no aldol product was obtained in the absence of Lewis acid.



1e *syn*-**4e**

53% (85% conv. yield)

syn : *anti* = 90 : 10

Scheme 1

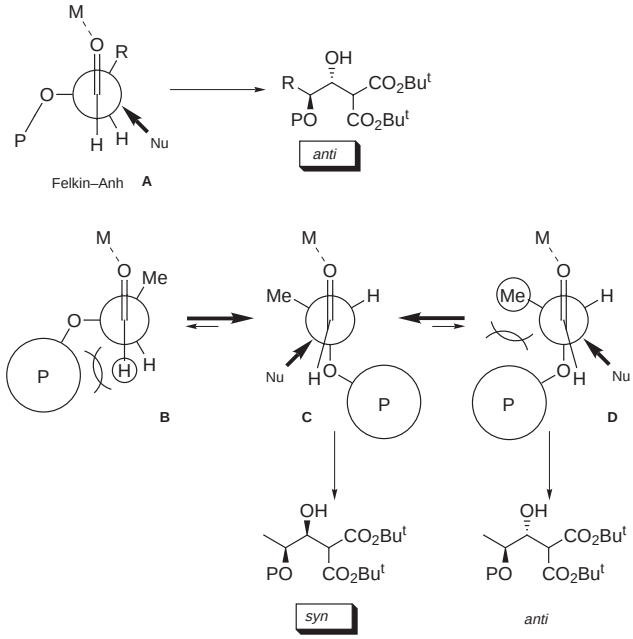


Fig. 1

To explain the reaction mechanism responsible for the observed stereoselectivity, we considered the following. The preferential formation of the *anti*- rather than *syn*-aldol product may be rationalized in terms of the normal Felkin–Anh transition state model[13] **A** described in Fig. 1. On the other hand, the remarkable *syn*-selectivity observed in Scheme 1 could not be explained by this Felkin–Anh transition state model. In this case, we postulate dipolar models **C** and **D**, avoiding steric interaction between the extremely bulky trityl group and aldehyde in model **B**. Because of the steric interaction between the trityl group and the methyl group in model **D**, model **C**, which provides a *syn*-aldol product, is favored over model **D**.

In conclusion, we have demonstrated 1,2-asymmetric induction in the aldol reaction between the lithium enolate of *tert*-butyl malonate and α-alkoxy aldehydes in the presence of a Lewis acid. *Anti*- or *syn*-aldol products were obtained in high yield with high stereoselectivity.

Dedicated to Professor Kenji Koga on the occasion of his 60th birthday.

Notes and References

† E-mail: hkogen@shina.sankyo.co.jp

‡ *General procedure*: To a solution of aldehyde (0.10 mmol) in THF (1 mL) was added zinc chloride (0.5 M in THF, 0.24 ml, 0.12 mmol) at room temperature. The reaction mixture was stirred for 1.5 h and then cooled to −78 °C. A solution of di-*tert*-butyl malonate (34 μl, 0.15 mmol) in THF (1 ml), which was treated with LHMDS (1.0 M in THF, 0.14 ml, 0.14 mmol) at −78 °C for 20 min, was added to the reaction mixture through a cannula. The stirring was continued for another 20 min at this temperature. To the mixture was added saturated aq. NH_4Cl, and the organic material was extracted with Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography provided the aldol adduct. In the case of entry 7 in Table 2, the reaction was repeated on a 10 mmol scale. The same result was obtained.

§ The relative stereochemistry of the aldol adducts was determined by deprotection of the major and minor isomers of **1a**, **2a** and **3a** to give the diol and conversion to the corresponding acetonide followed by NOE observations.

1 For a review of stereoselective aldol reactions, see: A. S. Franklin and I. Paterson, *Contemp. Org. Synth.*, 1994, **1**, 317; C. H. Heathcock, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 2, p. 181; C. H. Heathcock, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 111; D. A. Evans, J. V. Nelson and T. R. Taber, *Top. Stereochem.*, 1982, **13**, 1.
2 C. Gennari, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 2, p. 629.
3 J. Yoshimura, *Adv. Carbohydr. Chem. Biochem.*, 1984, **42**, 69.
4 S. Marumoto, H. Kogen and S. Naruto, *J. Org. Chem.*, 1998, **63**, 2068.
5 A. Saba, *Tetrahedron*: *Asymmetry*, 1992, **3**, 371; A. Saba, V. Adovasio and M. Nardelli, *Tetrahedron*: *Asymmetry*, 1992, **3**, 1573.
6 R. E. Ireland, S. Thaisrivongs and P. H. Dussault, *J. Am. Chem. Soc.*, 1988, **110**, 5768.
7 S. K. Massad, L. D. Hawkins and D. C. Baker, *J. Org. Chem.*, 1983, **48**, 5180.
8 Synthesized using the method described in ref. 7.
9 W-R. Li, W. R. Ewing, B. D. Harris and M. M. Joullie, *J. Am. Chem. Soc.*, 1990, **112**, 7659.
10 H. Ina, M. Ito and C. Kibayashi, *J. Org. Chem.*, 1996, **61**, 1023.
11 F. Effenberger, M. Hopf, T. Ziegler and J. Hudelmaeyer, *Chem. Ber.*, 1991, **124**, 1651.
12 K. Mori and H. Kikuchi, *Liebigs. Ann. Chem.*, 1989, 963.
13 N. T. Anh, *Top. Curr. Chem.*, 1980, **88**, 145.

Received in Cambridge, UK, 10th August 1998; 8/06290K