Asymmetric aldol reactions under normal and inverse addition modes of the reagents†

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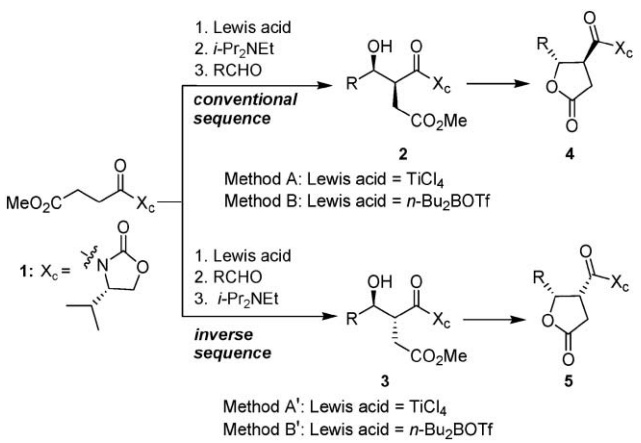
Both *syn*- and *anti*-aldol products can be obtained from common reactants by simply changing their addition sequence.

The asymmetric aldol reaction based on chiral auxiliaries is one of the most important stereoselective C–C bond forming reactions in synthetic organic chemistry. Several methods[1–9] have been reported for the synthesis of *syn*-aldol products. Asymmetric *anti*-aldol reactions have been achieved by varying either the chiral auxiliaries or reagents.[10–13] The synthesis of both *syn*- and *anti*-aldol products from the same acyl substrate using similar protocols remains an active area of research. Herein, we report the formation of both *syn*- and *anti*-aldol products from the same set of reactants by simply *inverting* the addition sequence of the base and aldehyde when chiral *N*-acyl-2-oxazolidinones, containing γ/δ-chelating functional groups, are used. This method also results in direct access to *trans*- and *cis*-4,5-disubstituted-γ-butyrolactones when *N*-succinyl-2-oxazolidinone (**1**) is used as the acyl substrate (Scheme 1).

Recent discoveries of asymmetric aldol reactions[8–13] led us to think that the presence of an additional chelating functionality in the acyl substrate might have an impact on their stereoselectivity. Initially, aldol reactions of **1**, having an additional ester functionality, were investigated, in view of the importance of functionalized succinyl substrates for the synthesis of many biologically active compounds.[14–16]



Scheme 1

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† Electronic supplementary information (ESI) available: Spectral and physical data of compounds **2**, **3**, **4**, **5**, **7** and **8**, and the details of the X-ray crystallography study of compound **3a**. See DOI: 10.1039/b618699h

Table 1 *syn*-Aldol reaction of **1** under conventional methods

Entry	Aldehyde	Method[a]	Product	dr[b]	Yield[c] (%)
1	3,4-$MeOC_6H_3CHO$	A	**4a**	>95 : 5	65
2	3,4-$MeOC_6H_3CHO$	B	**4a**	>95 : 5	81
3	4-$NO_2C_6H_4CHO$	A	**4b**	>95 : 5	62
4	4-$NO_2C_6H_4CHO$	B	**4b**	>95 : 5	78
5	2-$NO_2C_6H_4CHO$	A	**4c**	>95 : 5	65
6	2-$NO_2C_6H_4CHO$	B	**4c**	>95 : 5	70
7	*n*-$C_5H_{11}CHO$	A	**4d**	>95 : 5	60
8	*n*-$C_5H_{11}CHO$	B	**4d**	>95 : 5	80

[a] Method A: 1.1 equiv. $TiCl_4$, 1.2 equiv. *i*-Pr_2NEt and 1.4 equiv. aldehyde following the normal aldol sequence (base followed by aldehyde). Method B: 1.1 equiv. *n*-Bu_2BOTf instead of $TiCl_4$, otherwise the same as Method A. For details, see the supplementary information. [b] Ratios were determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield of the major diastereoisomer **4** after column chromatography.

Under the conventional method (Method A: $TiCl_4$, base followed by aldehyde, −78 → −15 °C), the $TiCl_4$-mediated aldol reaction of **1**[17] with 3,4-dimethoxybenzaldehyde (veratraldehyde) at −78 °C provided *trans*-4,5-disubstituted-γ-butyrolactone **4a** in 65% yield (Table 1, entry 1).[18] Under the inverse method (Method A′: $TiCl_4$, aldehyde followed by base), the aldol reaction of **1** with veratraldehyde led to *anti*-aldol product **3a** in high selectivity, unlike the former case. Thus, the treatment of a solution of substrate **1** (1.0 equiv.), $TiCl_4$ (1.2 equiv.) and veratraldehyde (1.4 equiv.) in CH_2Cl_2 with *i*-Pr_2NEt (1.4 equiv.) at −78 °C furnished *anti*-aldol product **3a** in high diastereoselectivity and with a 76% yield.[19] The relative stereochemistry of **3a** was established by a single crystal X-ray diffraction analysis (Fig. 1).[20]

The Bu_2BOTf-mediated aldol reaction of **1** also showed the same trend of selectivity on inverting the addition sequence of base and aldehyde (Method B′), and it provided the *anti*-aldol **3a** with a high diastereoselectivity in 48% yield (39% of starting **1** was recovered). The yield of *anti*-aldol **3a** increased to 65 and 92%,

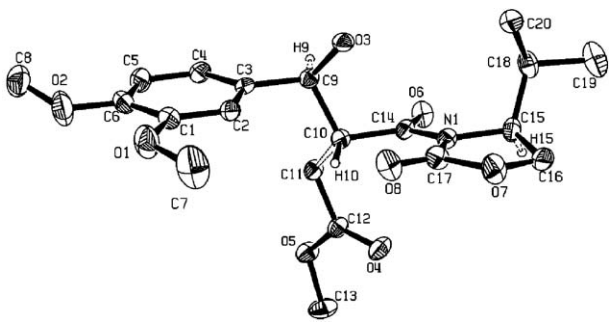


Fig. 1 ORTEP plot of **3a** with 30% thermal ellipsoid probability.

Table 2 *anti*-Aldol reaction of **1** under inverse methods

Entry	Aldehyde	Method[a]	Product	dr[b]	Yield[c](%)
1	3,4-$MeOC_6H_3CHO$	A′	**3a**	>95 : 5	76
2	3,4-$MeOC_6H_3CHO$	B′	**3a**	>95 : 5	92 (48, 65)
3	4-$NO_2C_6H_4CHO$	A′	**3b**	>95 : 5	88
4	4-$NO_2C_6H_4CHO$	B′	**3b**	>95 : 5	85 (42, 62)
5	2-$NO_2C_6H_4CHO$	A′	**3c**	>95 : 5	62
6	2-$NO_2C_6H_4CHO$	B′	**3c**	>95 : 5	74
7	*n*-$C_5H_{11}CHO$	A′	Mixture of products		
8	*n*-$C_5H_{11}CHO$	B′	Mixture of products		
9	CH_3CH=$CHCHO$	A′	**5e**	>95 : 5	56
10	CH_3CH=$CHCHO$	B′	**5e**	>95 : 5	66
11	PhCH=CHCHO	A′	**3f**	>95 : 5	41[d]
12	PhCH=CHCHO	B′	**3f**	>95 : 5	49[e]

[a] Method A′: Successive addition of 1.2 equiv. $TiCl_4$, 1.4 equiv. aldehyde and 1.4 equiv. *i*-Pr_2NEt. Method B′: 2.5 equiv. *n*-Bu_2BOTf instead of $TiCl_4$ and 2.6 equiv. *i*-Pr_2NEt, otherwise the same as for Method A′. For details, see the supplementary information. [b] Ratios were determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield of the major diastereoisomer **3** or **5** after column chromatography. Yields in parentheses refer to the reaction by Method B′ using 1.1 and 1.5 equiv. *n*-Bu_2BOTf, respectively. [d] 48% of starting **1** was recovered. [e] 37% of starting **1** was recovered.

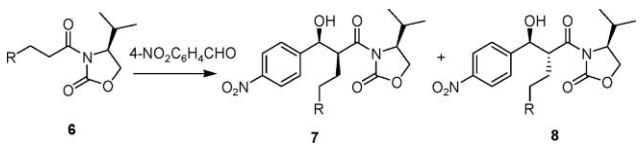
when 1.5 equiv. and 2.5 equiv. of Bu_2BOTf were used, respectively (Table 2, entry 2).

To generalize the above findings, the aldol reaction of **1** was further studied with different aldehydes (Table 1 and Table 2). Under conventional conditions (Methods A and B), *trans*-butyrolactones **4** were obtained with different aldehydes, such as 4-nitrobenzaldehyde, 2-nitrobenzaldehyde and hexanal, with high diastereoselectivity and in good yields (Table 1, entries 3 to 8). Under the inverse addition sequence (Methods A′ and B′), similar to veratraldehyde, 4-nitrobenzaldehyde, 2-nitrobenzaldehyde and cinnamaldehyde gave only the *anti*-aldol products **3** (Table 2, entries 3–6, 11 and 12). However, the aldol reaction of **1** with crotonaldehyde using Methods A′ and B′ afforded directly the lactone **5e** in good yields (Table 2, entries 9 and 10), and saturated aldehydes, such as hexanal, gave a mixture of products (Table 2, entries 7 and 8).

In order to determine the effect of the structure of the substrates, the aldol reactions were further studied with different acyl substrates **6** (Table 3). Unfunctionalized substrates such as *N*-propionyl-2-oxazolidinone (**6a**) always yielded the Evans *syn*-aldol product **7a**, irrespective of the Lewis acid and the addition sequence of base and aldehyde (Table 3, entries 1 and 2). Similar to **1**, substrates **6b** and **6c**, containing γ-methoxy and δ-carbomethoxy, respectively, showed the same trend of product profile upon inverting the addition sequence of base and aldehyde (Table 3, entries 3–6). Substrate **6d** also produced *anti*-aldol product **8d** in high diastereoselectivity by Method A′. It could now be concluded that the presence of an additional oxygen functionality in *N*-acyl-oxazolidinone substrates is responsible for the reversal of selectivity.

The formation of *syn*-aldol products **2** *via* the conventional methods could easily be explained on the basis of the well-accepted mechanism involving the Zimmerman–Traxler model.[6,8,21] On the other hand, the formation of *anti*-aldol products **3**, obtained by the inverse Method A′, could be explained by invoking a boat-like transition state (Fig. 2).[13] The pendent ester group is likely to coordinate with the Ti metal centre, forcing the transition state to adopt a boat-like conformation. Consequently, the products

Table 3 Aldol reactions of **6** under normal and inverse methods



Entry	R	Substrate	Method	dr[a] (**7** : **8**)	Yield[b] (%)
1	H	**6a**	A/B	>95 : 5	66 (52)
2	H	**6a**	A′/B′	>95 : 5	71 (58)
3	CH_2OMe	**6b**	A/B	ND	<5[c] (74)
4	CH_2OMe	**6b**	A′/B′	<5 : 95	70 (64)
5	CH_2CO_2Me	**6c**	A/B	ND	<5[c] (40)[d]
6	CH_2CO_2Me	**6c**	A′/B′	13 : 87	36[d,e] (<5)[c]
7	OMe	**6d**	A/B	—	NR
8	OMe	**6d**	A′/B′	<5 : 95	40[d] (<5)[c]

[a] Ratios were determined from the ^1H NMR spectrum of the crude reaction mixture. ND: Not determined. [b] Isolated yield of the major diastereoisomer after column chromatography. Yields in parentheses refer to the reaction under Method B or B′. NR: No reaction. [c] >90% of starting **6** was recovered. [d] 50–55% of starting **6** was recovered. [e] Combined isolated yield of **7c** and **8c** after chromatography.

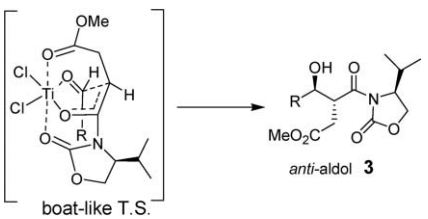


Fig. 2 Proposed mechanism for the *anti*-aldol reaction **1** by inverse methods.

arising from this transition state are *anti*-aldol products. The proposed mechanism is, in part, supported by the results with excess (−)-sparteine (Table 4, entries 1–6). Under such conditions, the excess (−)-sparteine might replace the weak chelating ester functionality and thus lead to the formation of an Evans *syn*-aldol product (Table 4, entry 6).

The effect of (−)-sparteine on the boron-mediated aldol reaction of **1** is very similar to that of Ti-mediated reactions (Table 4,

Table 4 Aldol reaction of **1** with veratraldehyde using (-)-sparteine as a base

Entry	Method	(−)-Sparteine (equiv.)	dr[a] (**2a** : **3a**)	Yield[b] (%)
1	A	1.0	>95 : 5	51
2	A′	1.0	<5 : 95	46
3	A	1.5	>95 : 5	40
4	A′	1.5	38 : 62	38[c]
5	A	2.5	>95 : 5	39
6	A′	2.5	>95 : 5	41
7	B	1.1	>95 : 5	50
8	B′	1.1	<5: 95	32
9	B	1.5	>95 : 5	37
10	B′	1.5	40 : 60	23[c]
11	B	2.5	>95 : 5	36
12	B′	2.5	Mixture of products	

[a] Determined from the ^1H NMR spectrum of the crude reaction mixture. [b] Isolated yield of the major isomer after chromatography. 42–70% of starting **1** was recovered. [c] Combined isolated yield of **2a** and **3a** after chromatography.

entries 7–12). Therefore, it is expected that the transition state in each case is similar (Fig. 2). However, further investigations are warranted to support this proposal.

In conclusion, we have developed an efficient strategy for the highly diastereoselective synthesis of both *syn*-and *anti*-aldol products from the same set of reactants by simply inverting the addition sequence of base and aldehyde. This method also provides a flexible and direct route for the synthesis of *trans*- and *cis*-4,5-disubstituted butyrolactones. Further studies on the mechanistic details, and applications to the synthesis of natural products are under way.

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Notes and references

1 S. Masamune, W. Choy, F. A. Kerdesky and B. Imperiali, *J. Am. Chem. Soc.*, 1981, **103**, 1566–1568.
2 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127–2129; D. A. Evans, D. L. Rieger, M. T. Bilodeau and F. Urpi, *J. Am. Chem. Soc.*, 1991, **113**, 1047–1049.
3 S. Yamada, T. Kumagai, M. Ochiai and E. Fujita, *J. Chem. Soc., Chem. Commun.*, 1985, 1418–1419; Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto and E. Fujita, *J. Org. Chem.*, 1986, **51**, 2391–2393.
4 H.-C. Hsiao, L. Liu and M. J. Miller, *J. Org. Chem.*, 1987, **62**, 2201–2206.
5 W. Oppolzer, J. Blagg, I. Rodriguez and E. Walther, *J. Am. Chem. Soc.*, 1990, **112**, 2767–2772.
6 M. Nerz-Stormes and E. R. Thornton, *J. Org. Chem.*, 1991, **56**, 2489–2498; M. P. Bonner and E. R. Thornton, *J. Am. Chem. Soc.*, 1991, **113**, 1299–1308.
7 T.-H. Yan, C.-W. Tan, H.-C. Lee, H.-C. Lo and T.-Y. Huang, *J. Am. Chem. Soc.*, 1993, **115**, 2613–2621; T.-H. Yan, A.-W. Hung, H.-C. Lee, C.-S. Chang and W.-H Liu, *J. Org. Chem.*, 1995, **60**, 3301–3306.
8 (*a*) M. T. Crimmins, B. W. King and E. A. Tabet, *J. Am. Chem. Soc.*, 1997, **119**, 7883–7884; (*b*) M. T. Crimmins, B. W. King, E. A. Tabet and K. Chaudhary, *J. Org. Chem.*, 2001, **66**, 894–902.
9 Z. Li, R. Wu, R. Michalczyk, R. B. Dunlap, J. D. Odom and L. A. P. Silks, III, *J. Am. Chem. Soc.*, 2000, **122**, 386–387.
10 H. Danda, M. M. Hanse and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 173–181; M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, 1991, **56**, 5747–5750.
11 A. K. Ghosh and M. Onishi, *J. Am. Chem. Soc.*, 1996, **118**, 2527–2528.
12 A. Abiko, J.-F. Liu and S. Masamune, *J. Am. Chem. Soc.*, 1997, **119**, 2586–2587.
13 D. A. Evans, J. S. Tedrow, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2002, **124**, 392–393; D. A. Evans, C. W. Downey, J. T. Shaw and J. S. Tedrow, *Org. Lett.*, 2002, **4**, 1127–1130.
14 M. Whittaker, C. D. Floyd, P. Brown and A. J. H. Geraing, *Chem. Rev.*, 1999, **99**, 2735–2776 and references therein.
15 M. P. Sibi, P. Liu, J. Ji, S. Hajra and J. Chen, *J. Org. Chem.*, 2002, **67**, 1738–1745; M. P. Sibi, P. K. Deshpande and A. J. La Loggia, *Synlett*, 1996, 343–345.
16 M. A. Ogliaruso and J. F. Wolfe, *Synthesis of Lactones and Lactums*, John Wiley & Sons, New York, 1993; R. Bandichhor, B. Nosse and O. Reiser, *Top. Curr. Chem.*, 2005, **243**, 43–72.
17 The Bu_2BOTf-mediated *syn*-aldol reaction of *N*-succinyl-2-oxazolidinone with benzaldehyde was first reported by Evans *et al.* (ref. 2). Later, Sibi *et al.* explored this chemistry for the asymmetric synthesis of paraconic acids (ref. 15).
18 The structure of the compound **4a** was confirmed by comparing it with the authentic compounds prepared by the Bu_2BOTf-mediated aldol reaction of **1** (Method B, ref. 2).
19 Aldol **3a** did not transform into a lactone when the reaction was continued at −15 °C or even at higher temperatures (0 to 5 °C).
20 *Crystal data* for **3a**: $C_{20}H_{27}NO_8$, M = 409.43, 298(2) K, monoclinic, $P2_1$, Z = 2, a = 8.632(2), b = 10.071(3), c = 12.195(2) Å, β = 95.043(10)°, V = 1056.2(4) Å^3, D_c = 1.287 Mg m^{-3}, $2\theta_{max}$ = 49.92°, λ(Mo-Kα) = 0.71073 Å, ω-scan, 2102 measured, 1967 unique (R_{int} = 0.02). $R1$ = 0.0496, $wR2$ = 0.1100 for 1397 reflections with $I > 2\sigma(I)$ and $R1$ = 0.0931, $wR2$ = 0.1271 for all data, Flack (x) parameter = 2(2), CCDC 602986. The details of crystal data collection and refinement of **3a** are listed in ESI.† For crystallographic data in CIF or other electronic format see DOI: 10.1039/b618699h.
21 B. M. Kim, S. F. Williams and S. Masamune, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. **2**, pp. 239–275.

