Highly Diastereofacial *Anti*-Aldol Reaction: Practical Synthesis of Optically Active *anti*-2-Alkyl-3-Hydroxycarboxylic Acid Ester Units†

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A variety of esters derived from commercially available norephedrine were used in diastereoselective *anti*-aldol reactions. The aldol reaction of designed 2-(*N*-2-methylbenzyl-*N*-2,4,6-trimethylbenzyl)-amino-1-phenylpropanol esters **4a**−**d** with aldehydes furnished *anti*-2-alkyl-3-hydroxycarboxylic acid esters in excellent diastereomeric ratios (>98:2) when LDA−Cp_2ZrCl_2 (0.3 equiv) was used for enolization, followed by transmetalation into the zirconium enolate for aldolization. The novel auxiliary **3** for the *anti*-aldol reaction does not exhibit the ordinary basicity of *tertiary* amines; **3** can be extracted from acidic media with organic solvents. Its use is, therefore, very advantageous not only for extraction of the aldol products from the acidic water solutions, but also for recovering the chiral auxiliary **3** after the reductive cleavage. Treatment of aldol or 3-protected aldol products with DIBAL-H or $LiAlH_4$ affords the versatile synthons, 2-alkyl-propane-1,3-diols or those 3-protected diols in >98% ee's together with **3** in nearly quantitative recovery.

Introduction

Optically active 2-alkyl-3-hydroxycarbonyl units which exist as four possible stereoisomers play a very significant role in syntheses of most natural products of polyketide origin. The aldol reaction provides a rapid means for setting up several stereogenic centers in a single step.[1] The efficient construction of *syn*-aldol units[2] can be achieved by stereocontrolled aldol condensations in outstanding diastereomeric and enantiomeric purity,[3] and some of these methods have been applied in relatively large-scale synthesis.[4] However, *anti* selective aldol reactions that are able to create a variety of 2-alkyl-3-hydroxycarbonyl units are one of the remaining challenges. Efforts in this area have been made for over the past decade.[5] In many instances known technologies provide *anti*-aldols with good to excellent enantio- or diastereoselectivities but appear to be impractical, because (1) most of the reagents are not commercially available, (2) separation of diastereomers after the reaction is difficult, and (3) complete recovery of chiral catalysts including intact ligands or auxiliaries after hydrolysis or reduction is desirable. We have centered our attention on developing efficient methods for C−C bond formation by employing readily available substrates from commercial sources. We now wish to report a practical synthesis[6] of optically active *anti*-2-alkyl-3-hydroxycarboxylic acid esters using the (−)-*N*,*N*-dibenzylnorephedrine derivatives **3** (Scheme 1) and conventional reagents such as LDA−Cp_2ZrCl_2 in greater than 98% enatiomeric excess and high chemical yields.

† Dedicated to Professors Isao Kitagawa and Martin A. Schwartz on the occasion of their 70th and 60th birthdays, respectively.

(1) For selected examples of aldol reactions in natural product synthesis, see (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 47. (b) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528. (c) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (d) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.

(2) In the present paper, the main chain is drawn in zigzag fashion, and two substituents on the same side are designated syn, and those which are not are anti, see ref 3a

(3) (a) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem Soc.* **1981**, *103*, 217. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (d) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (e) Heathcock, C. H. In *Asymmetric Synthesis*; Morison, J. D, Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 2, pp 111−212. (f) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *47*, 5807. (g) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39. (h) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77. (i) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722. (j) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129. (k) Kobayashi, S.; Fujita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455. (l) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (m) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M, Ed.; Pergamon Press: Oxford, 1993; Vol. 2, Chapter 1.6, pp 181−238. (n) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. (o) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (p) Uotsu, K.; Sasai, H.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 71. (q) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1995**, *46*, 1. (r) Evans. D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (s) Evans, D. A.; Burgey, C. S.; Kozlwski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (t) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528.

(4) For example, the oxazolidinone auxiliaries of Evans have defined the standard in the synthesis of optically active *syn*-2-methyl-3-hydroxy carbonyl units.

(5) (a) Gennari, C.; Bernardi, A.; Colombo, L.; Carlo. S. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (b) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (c) Braun, M.; Sacha, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1318. (d) Sacha, H.; Waldmüller, D.; Braun, M. *Chem. Ber.* **1994**, *127*, 1959. (e) Abiko, A.; Liu, J. F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590. (f) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527. (g) Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (h) Corey, E. J.; Li, W.; Reichard, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 2330. (i) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403. For *anti*-aldol reactions with ketone enolates, see (j) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (k) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock. C. H. *J. Org. Chem.* **1991**, *56*, 2499. (l) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (m) Denmark, S. E.; Stavenger, R. A.; Ken-Tsung, W.; Xiping, S. *J. Am. Chem. Soc.* **1999**, 121, 4982.

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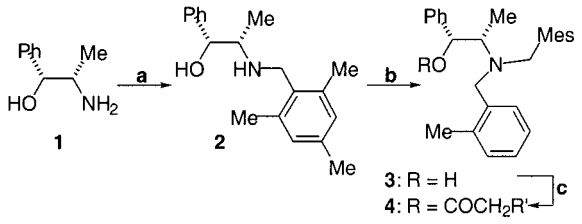
Scheme 1[a]



[a] Reagents and yields: (a) (i) mesitaldehyde $MgSO_4$, toluene, 80 °C; (ii) $NaCNBH_3$, AcOH, MeOH, rt (65%); (b) 2-methylbenzyl bromide, Cs_2CO_3, toluene, 90 °C (95%); (c) propionyl chloride, DMAP, CH_2Cl_2 (98%) or carboxylic acid, EDCI·HCl, DMAP, CH_2Cl_2 (95%).

Results and Discussion

Two general approaches to the preparation of optically active *anti*-2-methyl-3-hydroxycarbonyl units, asymmetric aldol processes and asymmetric crotylation,[7] have been utilized in natural product synthesis.[8] It is worth noting that the asymmetric aldol process possesses a strategic advantage over crotylation because of its flexibility for synthesizing a variety of 2-alkyl-substituted 3-hydroxy derivatives. The stereochemical outcome for *anti*-aldol reactions through metallo enolates is governed by two critical issues: (1) selective generation of *E*(*O*,*R*)-enolate,[9] and (2) creation of a relatively tight six-membered chelated chairlike transition state.[10] The stereochemistry of the aldol reaction with ester derivatives is limited in many cases by the difficulty of forming *E* and *Z* enolates selectively. Deprotonation of simple esters with lithium amides at low temperature generally affords the *E*-enolate in major amount.[11] However, we have observed that in the enolization of chiral propionates the *E*/*Z* selectivity is strictly controlled by the structure of the chiral moieties and that it is difficult to design chiral esters that produce *E*-lithium enolates exclusively.[12] *N*-Methylephedrine or *N*,*N*-disubstituted norephedrine esters have been introduced as a stereochemical template to direct aldol reactions, the conditions involving either a $TiCl_4$-mediated Mukaiyama reaction[13] or diastereoselective dicyclohexylboron enolate formation.[14] Their reactions possess several disadvantages because they require the preparation of commercially unavailable reagents and because they involve difficult separations of diastereomers from the reaction mixture. We envisioned using norephedrine,[15] which is readily available in bulk and is inexpensive, for diastereoselective and diastereofacial selective *anti*-aldol reactions via a conventional metalloenolate.

In preliminary studies, the transmetalations of lithium enolates derived from *N*,*N*-dibenzylnorephedrine propionates into Cp_2TiCl, $(^iPrO)_2TiCl$, and Cp_2ZrCl enolates[16] enhanced the diastereofacial selectivity in the aldol reaction. Interestingly, the Cp_2TiCl or $(^iPrO)_2TiCl$ enolates furnished *anti*-aldol products whose stereochemistries possess opposite absolute configurations to those induced by the Cp_2ZrCl enolates. Since aldolization of Cp_2ZrCl enolate with aldehydes furnished superior diasterofacial selectivity and Cp_2ZrCl_2 is more accessible in bulk, we selected Cp_2ZrCl_2 as the metal salt for transmetalation of enolate.

We then looked for suitable substituents on the nitrogen of (−)-norephedrine to induce exclusive diastereofacial selectivity for *anti*-aldols and initially selected benzylic groups to decrease the polarity of norephedrine. Of the various substituents screened, 2-(*N*-2-methybenzyl-*N*-2,4,6-trimethylbenzyl)amino-1-phenylpropyl propionate (**4a**) proved to be the most effective (entry 7 in Table 1).

Both enantiomers of esters **4** were synthesized from (+)- or (−)-norephedrine by the following sequence: (1) oxazolidine formation with mesitaldehyde in the presence of $MgSO_4$, followed by selective cleavage of the C−O bond via $NaCNBH_3$ in the presence of AcOH, (2) selective *N*-benzylation with 2-methylbenzyl bromide and Cs_2CO_3 as a base, and (3) esterification with acyl chlorides in the presence of (dimethylamino)pyridine (DMAP) or with the corresponding acids via 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) and DMAP. Through NOESY experiments[17] and molecular modeling[18] (Figure 1), we can attribute the origin of the

(6) Many of the articles on reagent-controlled asymmetric aldol reactions, most of which are enantioselective Mukaiyama aldol reactions, described that the chiral enolate technologies were not ideal from a practical point of view because they required stoichiometric amount of covalently bound auxiliaries. However, a number of total syntheses of natural products have relied on the chiral auxiliary methodologies or stoichiometric amounts of readily available chiral reagents in order to synthesize starting materials. Low catalyst loading (<2 mol %) and elimination of preconversion of ketones or esters to silyl enol ethers should be required in a practical catalytic enantioselectve aldol reaction. An outstanding development of catalytic asymmetric synthesis of *β*-hydroxy ketones was reported; see Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.

(7) Many other crotylation methods to generate *anti* adducts exist. Brown's method is the most widely used and general method. (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (b) Brown, H. C.; Ramdad, R. S.; Bhat, K. S. *J. Org. Chem.* **1989**, *54*, 1570. For selected application of Brown's crotylboration protocol, see: (c) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Steves, K. L.; Guo, J.; Kishi, Y. *Angew Chem., Int. Ed.* **1998**, *37*, 187. (b) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177.

(8) Other nonaldol processes to synthesize *anti*-2-methyl-3-alkoxy carbonyls, see (a) Kishi, Y.; Nagaoka, H. *Tetrahedron* **1981**, *37*, 3873. (b) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307.

(9) For attempts to generate *anti*-aldols from *Z*-*O*-silylketene acetal, see (a) Heathcock, C. H.; Walker, M. A. *J. Org. Chem.* **1991**, *56*, 5747. (b) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61. *Anti* selective aldolizations observed with *O*-silylenolates in the presence of Lewis acid have been ascribed to open transition states. Recently, Denmark and co-workers reported a chiral phosphoramide-catalyzed *anti*-aldol reaction with *Z*-trichlorosilyl enol ether; see ref 5m.

(10) No rationale has been made thus far for Lewis acid promoted *anti*-aldol reactions of enolsilanes with aldehydes. For an article regarding this issue, see (a) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, *42*, 4029. (b) Heathcock, C. H.; Hug, K. T.; Flippin, L. A. *Tetrahedron Lett.* **1984**, *25*, 5973. Catalytic enantioselective *anti*-aldol reactions of enolsilanes with glyoxylate and pyruvate esters via chiral Lewis acids was recorded, see Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.

(11) (a) Ireland, R. E.; Muller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Oare, A. D.; Heachcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(12) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.

(13) (a) Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754. (b) Review: Mahrward, R. *Chem. Rev.* **1999**, *99*, 1095 and references therein.

(14) Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

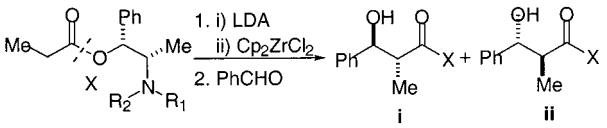
(15) Chiral *N*,*N*-dialkylnorephedrines as catalysts of enantionselective addition of dialkyllzincs to aldehydes have been reported, see: Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.

(16) (a) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876. (b) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *47*, 5807.

(17) Because none of esters prepared were crystalline, nuclear Overhauser enhancement spectroscopy (NOESY) studies proved indispensable in determining the conformation of **4a**.

(18) A SPARTAN conformational search by semiempirical calculation using the AM1 basis set indicated that lowest energy conformation of **4a** was well in agreement with the data obtained from NOESY.

Table 1. Effects of the *N,N*-Dibenzyl Group on Diastereofacial Selectivity in the Aldol Reaction[a]



entry	R^1	R^2	**i/ii**[b]
1	benzyl	benzyl	50/50
2	benzyl	SO_2Tol	55/45
3	benzyl	SO_2Mes	60/40
4[c]	benzyl	2,6-diisopropylbenzyl	75/25
5	3,5-dimethylbenzyl	2,4,6-trimethylbenzyl	75/25
6	2-bromobenzyl	2,4,6-trimethylbenzyl	82/25
7	2-methylbenzyl	2,4,6-trimethylbenzyl	>98/2

[a] All reaction were carried out in a 0.1 mmol scale at −78 °C. [b]Diastereofacial selectivity of the products was established by ^{1}H NMR. [c]Masamune ester.

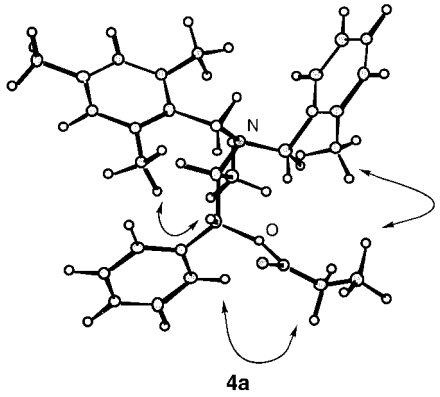


Figure 1. The lowest energy conformation of **4a** with selected NOESY correlations.

excellent diastereofacial selectivity to the following factors. The bulky mesityl group on nitrogen is on the sterically less demanding site (opposite to the ester moiety). Because of a significant steric interaction between the mesityl group and methyl of *o*-methylbenzyl group the methyl group of *o*-methylbenzyl locates toward the propionyl ester moiety. Zirconium enolate formation from the corresponding lithium enolate is known,[19] and Cp ligands of zirconium metal enhance the steric congestion of *re*-face of enolate. Therefore, the aldolizations with zirconium enolate of **4a** furnish (2*S*,3*R*)-2-methyl-3-hydroxy esters. The reactions occur on the *si*-face presumably via a chairlike transition state. Thus, enolization of **4a** with LDA (2 equiv) in THF,[20] followed by transmetalation into the zirconium enolate at −78 °C with Cp_2ZrCl_2 (2.5 equiv), and aldolization with benzaldehyde (1.1 equiv) furnishes *anti*-aldol product in greater than 98% de and in excellent yield. However, the *anti*/*syn* diastereoselectivity was disappointingly low (3.5:1).

Having accomplished a diastereofacialselective *anti*-aldol reaction, we next surveyed additives in order to increase the *anti*/*syn* ratio. Lithium salts are known to be effective in enhancing *E*/*Z* selectivity in ketone enolization.[21] Although the mechanism is not clear, their use is the most effective method to date for preparing ketone enolates with *E* geometry. We surmised that selective ester enolate formation might also be facilitated by

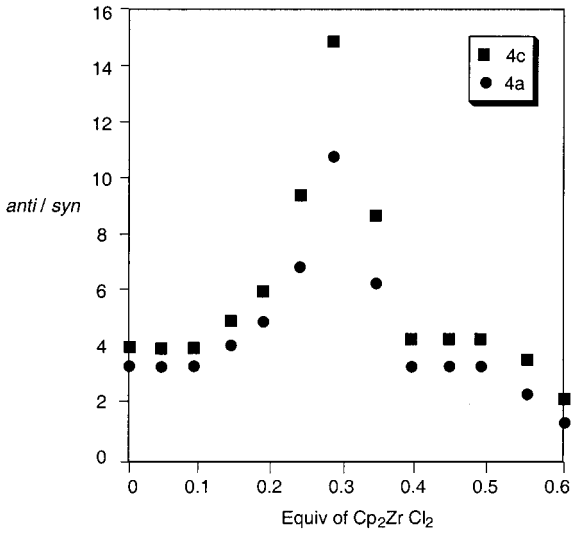


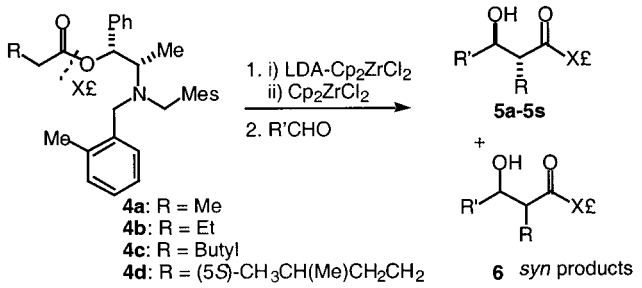
Figure 2. Anti/syn selectivity for aldol reaction of **4a** and **4c** with benzaldehyde. The reations were carried out at 0.1 M concentration with varying amount of Cp_2ZrCl_2.

addition of inorganic salts. Addition of varying amounts of LiCl or LiOTf to LDA[22] did not change the *E*/*Z* selectivity in the formation of **4a** enolate but hampered the transmetalation from lithium to zirconium enolate. However, a substantial increase in *anti*/*syn* selectivity (up to 15:1 for **4c**) was observed when Cp_2ZrCl_2 was added to LDA with maximum *anti*/*syn* selectivity being attained by addition of 0.3 equiv of Cp_2ZrCl_2.[23] Higher concentrations of Cp_2ZrCl_2 reduced the selectivities; 1 equiv of Cp_2ZrCl_2 completely quenched the reaction and ester **4a** was recovered after the reaction (Figure 2).[24] We also explored temperature and concentration variation to optimize selectivity. Enolization did not proceed at lower than −78 °C, and the generated enolate was not stable at higher than −50 °C under the LDA−Cp_2ZrCl_2 (0.3 equiv) conditions. Maximum selectivity was not decreased by varying the reaction concentration; over the range of concentrations that we have investigated (0.05−0.3 M) both diastereo- and diastereofacial selectivity remain unchanged. To the best of our knowledge this is the first example of amplification of *E*-enolization of chiral esters by addition of Cp_2ZrCl_2 to LDA.[25]

As shown in Table 2, a variety of optically active *anti*-2-alkyl-3-hydroxy ester derivatives could be synthesized

(19) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876.
(20) Except for THF, Cp_2ZrCl_2 is difficult to solubilize in commonly employed organic solvents for aldol reactions.
(21) (a) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Chem. Lett.* **1986**, 1755. (b) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571. (c) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575. (d) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Muckhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.
(22) For studies on the structure of LDA and mechanistic studies on enolization with LDA, see: (a) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452. (b) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459 and references therein.
(23) Similar to the trend observed for ketone enolization with LDA/LiCl (0.3−0.4 equiv), a maximum selectivity was given when LDA/Cp_2ZrCl_2 (0.3 equiv) was used.
(24) The origins of enhancement of *E*-enolate ratio are far from clear and a subject of current study. For a discussion of the influence of lithium halides upon the structure and reactivity of lithium enolates, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.
(25) The change of amide from LDA to lithium isopropylcyclohexylamide (LICA), and lithium 2,2,6,6-tetramethylpiperidide (LTMP) did not alter the diastereoselectivity. Lithium di-*tert*-butylamide did not deprotonate to form lithium enolate at −78 °C. Lithium diethylamide reacted with Cp_2ZrCl_2 to form a dark-red colored THF solution at −78 °C, putatively represented as "$Cp_2Zr(Cl)NEt_2$", which was an inert species for enolization of **4a**.

Table 2. Diastereoselective Aldol Reactions



ester	R′ (aldehyde)	product	yield (%)	anti/ syn[b]	ds for anti[c]
4a	Ph	**5a**	98	90:10	>90:2
4a	$Ph(CH_2)_2$	**5b**	94[a]	90:10	>98:2
4a	Et	**5c**	90[a]	90:10	>98:2
4a	$CH_3(CH_2)_4$	**5d**	90[a]	90:10	>98:2
4a	$BnOCH_2$	**5e**	92[a]	90:10	>98:2
4a	*i*-Pr	**5f**	95[a]	93:7	>98:2
4a	c-Hex	**5b**	95[a]	90:10	>98:2
4a	(*E*)-MeCH═CH	**5h**	95	90:10	>98:2
4a	(*E*)-MeCH═CH(Me)	**5i**	92[a]	90:10	>98:2
4a	PhCH═CH	**5j**	96	90:10	>98:2
4a	TMSC≡C	**5k**	90[a]	59:41	-
4a	$CH_3(CH_2)_4C≡C$	**5l**	95	56:44	-
4b	Ph	**5m**	95	94:6	>98:2
4b	*i*-Pr	**5n**	93[a]	93:7	>98:2
4c	Ph	**5o**	93[a]	94:6	>98:2
4c	*i*-Pr	**5p**	95[a]	94:6	>98:2
4d	Ph	**5q**	96	90:10	>98:2
4d	Et	**5r**	95[a]	89:11	>98:2

[a] The reaction was not completed. [b]Anti/syn ratio was determined by isolated product yield and ^{3}H NMR. [c]Diastereomeric ratio was established by ^{1}H NMR.

in good *anti*/*syn* selectivities of 90−95:10−5 and in excellent diastereomeric ratios of >98:2 for *anti* by a combination of diastereoselective *E*-enolization using LDA-Cp_2ZrCl_2 and diastereofacial selective aldolization induced by the Cp_2ZrCl enolate.[26] Importantly, the mixture of *anti*/*syn* diastereomers could be separated by silica gel chromatography. The isolated *anti*-aldol products were converted to 2-alkyl-3-silyloxypropane-1,3-diols, advanced intermediates for natural products syntheses, in two steps: (1) silylation with TESCl and imidazole in CH_2Cl_2 at 0 °C or TBSOTf and 2,6-lutidine in CH_2Cl_2 at 0 °C, 2) DIBAL-H reduction in CH_2Cl_2 at −78 °C.[27] The direct reduction of the *anti*-aldol products with DIBAL-H afforded 2-alkyl-propane-1,3-diols with greater than 98% ee's,[28] the auxiliary **3** being recovered in nearly quantitative yield. The (2*S*,3*R*) absolute chemistries for representative 2-methylpropane-1,3-diols, derived from **5a**, **5b**, **5c**, **5f**, **5g**, **5j**, were confirmed by comparison of optical rotations.[29] The multigram scale synthesis of (2*S*,3*R*)-2-alkyl-3-hydroxy esters could be achieved by this method. It should be noted, however, that a limitation exists in the use of aldehyde; the syntheses of propargyl alcohols from alkynals by this method afforded a 1:1 mixture of *anti*/*syn* diastereomers with low diastereofacial selectivity.

Conclusions

We disclose a practical synthesis of optically active 2-alkyl-3-hydroxycarboxylic acid esters using a readily synthesized norephedrine derivative **4a** as a stereocontroller and LDA−Cp_2ZrCl_2 as a selective *E*-enolization method. The *anti*-aldol reaction described herein has several advantages: (1) the high degree of diastereofacial selectivity, (2) the use of easily handled chemicals which are commercially available, (3) wide scope for both aldehydes and the length of carbon chain of ester moieties, and (4) easy purification of aldol products and quantitative recovery of auxiliary. The present method should provide a valuable asset to the synthesis of natural products.

Experimental Section

All reactions were conducted under an argon or nitrogen atmosphere. Reaction vessels were flame-dried or oven-dried and allowed to cool under an inert atmosphere. Reagents and solvents are commercial grade and were used as with the following exceptions. THF was distilled from potassium benzophenone ketyl. Dichloromethane was purified through Al_2O_3 column (MBRAUN System), and diisopropylamine was distilled from CaH_2. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz and 500 MHz spectrometer in $CDCl_3$. Electrospray mass spectra (ESI) were obtained with lithium trifluoromethanesulfonate using CH_3CN as a solvent. Poly(ethylene glycol) was added as an internal reference.

***N*-(2,4,6-Trimethylbenzyl)norephedrine 2.** To a stirred solution of (1*R*,2*S*)-(−)-norephedrine (**1**) (20 g, 0.132 mol) in toluene (100 mL) were added mesitaldehyde (21.6 g, 0.145 mol, 1.1 equiv) and $MgSO_4$ (25 g). The reaction mixture was heated at 80 °C; after 6 h the reaction was cooled to room temperature and filtered, and the solvent was concentrated in vacuo. The crude material was dissolved in MeOH (150 mL), and AcOH (30 mL) was added. At 0 °C, to the reaction mixture was added $NaCNBH_3$ (17.0 g, 0.257, 1.9 equiv), and it was stirred at room temperature for 3 h, after which it was quenched with 0.1 N NaOH. The reaction mixture was extracted with AcOEt (three times). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2 to 1:1, hexanes:EtOAc) to afford **2** (24.3 g, 0.0859 mol, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.23−7.15 ppm (5H, m), 6.79 (2H, s), 4.75 (1H, d, J = 4.2 Hz), 3.76 (2H, s), 2.97 (1H, s), 2.28 (6H, s), 2.18 (3H, s), 0.78 (3H, d, J = 7.2 Hz). ^{13}C NMR: 141.2, 136.9, 136.4, 133.2, 129.2, 128.1, 127.1, 126.1, 72.9, 59.2, 45.2, 20.8, 19.3, 14.6. IR (neat) 3557.0 cm^{-1}, 3434.9, 2964.5, 2856.0, 1668.9, 1613.2, 1580.6, 1377.2, 763.3, 743.2. HRMS (ESI): $C_{19}H_{25}NO$ ($M + H^+$) calcd. 284.200891, found 284.20126. $[\alpha]_D$ +49.2° (*c* 0.2, $CHCl_3$, at 25 °C).

***N*-(2-Methylbenzyl)-*N*-(2,4,6-trimethylbenzyl)norephedrine 3.** To a stirred solution of **2** (20.0 g, 70.7 mmol) in toluene (100 mL)−CH_3CN (30 mL) was added 2-methylbenzyl bromide (1.49 g, 77.8 mmol, 1.1 equiv). The reaction mixture was heated at 90 °C. After 1 h, the reaction was cooled to room temperature and filtered, and the combined solvent was concentrated in vacuo. The residue was purified by silica gel chromatography (8:1, hexanes:EtOAc) to afford **3** (28.8 g, 73.9 mmol, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.01−7.22 ppm (9H, m), 6.78 (2H, s), 4.83 (1H, m), 3.69 (3H, t, J = 6.9 Hz), 3.52

(26) Diastereoselectivity of *syn* products was ca. 1.5: 1. This poor selectivity for syn diastereomers would be attributed to a boatlike transition structure that can accommodate two possible orientations of aldehydes.

(27) A general transformation of (2*S*,3*R*)-2-alkyl-3-hydroxylcarboxylic acid esters into the advanced intermediates for the synthesis of propionate origin natural products is described in Supporting Information. For a general strategy for propionate-derived natural products, see: Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921.

(28) The ee values were determined by esterification of the diols with Mosher's reagent and subsequent ^{1}H NMR and ^{19}F NMR spectroscopies.

(29) (a) Suzuki, K.; Katayma, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 2479. (b) Mori. K.; Sano, S.; Yokoyama, Y.; Bando, M.; Kido, M. *J. Org. Chem.* **1941**, *6*, 1135. (c) Domon, L.; Vogeleisen, F.; Uguen, D. *Tetrahedron Lett.* **1996**, *37*, 2773. (d) Meyer, H. H. *Liebigs. Ann. Chem.* **1984**, 791.

(1H, d, J = 12.9 Hz), 3.08 (1H, q, J = 6.9 Hz), 2.75 (3H, m), 2.17 (9H, s), 2.12 (1H, m), 1.23 (3H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 143.6, 138.4, 137.6, 137.3, 136.2, 132.1, 130.6, 130.2, 129.1, 128.1, 127.1, 126.8, 126.5, 125.4, 75.9, 58.2, 51.4, 48.1, 20.7, 20.0, 19.1, 8.1. IR (neat) 2920.4 cm^{-1}, 1737.9, 1177.2, 761.9, 744.1, 698.8. HRMS (ESI): $C_{27}H_{33}NO$ (M + H$^+$) calcd. 387.25621, found 387.25652. $[\alpha]_D$ +28.9° (*c* 0.2, $CHCl_3$ at 25 °C).

2-(*N*-2-Methylbenzyl-*N*-2,4,6-trimethylbenzyl)amino-1-phenylpropylpropionate (4a). To a stirred solution of **3** (1.00 g, 2.57 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added DMAP (628 mg, 5.14 mmol, 2 equiv) and propionyl chloride (219 μL, 5.14 mmol, 2 equiv). The reaction mixture was warmed to room temperature; after 5 h, the reaction was quenched with $NaHCO_3$. The mixture was extracted with AcOEt (three times). The combined extracts were washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (15:1, hexanes:EtOAc) to afford **4a** (1.06 g, 2.39 mmol, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.04−7.22 ppm (7H, m), 6.91 (2H, dd, J = 7.5, 2.1 Hz), 6.76 (2H, s), 6.06 (1H, d, J = 6 Hz), 3.72 (2H, d, J = 12.6 Hz), 3.56 (2H, dd, J = 12.9, 7.2 Hz), 3.19 (1H, q, J = 6.6 Hz), 2.34 (2H, q, J = 8.1 Hz), 2.25 (3H, s), 2.09−2.10 (9H, s), 1.23 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 173.4, 139.8, 138.4, 137.3, 137.0, 136.2, 131.0, 130.6, 130.1, 128.9, 127.9, 127.3 126.9, 126.8, 125.3, 56.5, 51.2, 47.4, 31.5, 28.0, 22.6, 20.8, 20.1, 19.2, 14.1, 9.1. IR (neat) 2920.4 cm^{-1}, 1737.9, 1177.2, 761.9, 744.1, 698.8. HRMS (ESI): $C_{30}H_{37}NO_2$ (M + H$^+$) calcd. 443.28243, found 443.28195. $[\alpha]_D$ −13.6° (*c* 0.2, $CHCl_3$ at 25 °C).

General Procedure for the Aldol Reaction. To a stirred solution of diisopropylamine (190 μL, 2 equiv) in THF (3.5 mL) at 0 °C was added *n*-BuLi (1.5 M, 903 μL, 2 equiv). The LDA solution was cooled to −78 °C, and a THF solution of Cp_2ZrCl_2 (59.3 mg, 0.203 mmol, 0.3 equiv) was added. After 15 min, **4a** (300 mg, 0.677 mmol) in THF (1 mL) was added. The reaction mixture was stirred for 90 min, and Cp_2ZrCl_2 (495 mg, 1.69 mmol, 2.5 equiv) was added. After an additional 10 min at −78 °C, to the reaction was added PhCHO (79.1 mg, 0.745 mmol, 1.1 equiv) in THF (1.5 mL). The reaction mixture was stirred at −78 °C for 30 min and quenched with 1 N HCl. The mixture was extracted with ether (three times). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (12:1:1, hexanes:EtOAc:CH_2Cl_2, 10:1, hexanes:EtOAc) to afford **5a** (330 mg, 0.603 mmol, 89%), together with a mixture of syn products (36.4 mg, 0.0663 mmol, 9.8%): ^{1}H NMR (300 MHz, $CDCl_3$): 7.02−7.28 ppm (12H, m), 6.92 (2H, d, J = 6.9 Hz), 6.76 (2H, s), 6.05 (1H, d, J = 6.6 Hz), 4.74 (1H, dd, J = 8.7, 4.8 Hz), 3.70 (2H, dd, J = 13.5, 3.9 Hz), 3.55 (2H, dd, J = 12.0, 3.9 Hz), 3.22 (1H, q, J = 6.6 Hz), 3.00 (1H, d, J = 4.2 Hz), 2.82 (1H, q, J = 7.5 Hz), 2.25 (3H, m), 2.09−2.10 (9H, s), 1.23 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 174.5, 139.9, 138.5, 138.4, 137.3, 137.1, 136.3, 135.1, 131.6, 131.3, 130.7, 130.2, 129.8, 129.4, 129.0, 128.3, 128.1, 127.3, 127.0, 126.9, 126.8, 126.6, 125.3, 74.5, 55.6, 51.0, 47.2, 32.1, 28.2, 22.6, 20.8, 19.2, 15.5, 9.6, 9.4. IR (neat) 3500.1 cm^{-1}, 3031.1, 2971.4, 2854.9, 1731.5, 1613.5, 1585.2, 1378.3, 764.8, 742.7, 700.1. HRMS (ESI): $C_{37}H_{43}NO_3$ (M + H$^+$) calcd. 550.33157, found 550.32909. $[\alpha]_D$ −12.6° (*c* 0.1, $CHCl_3$ at 25 °C).

Experimental Procedures for the Large-Scale Aldol Reaction. To a stirred solution of diisopropylamine (2.80 mL, 2 equiv) in THF (50 mL) at 0 °C was added *n*-BuLi (1.5 M, 13.3 mL, 2 equiv). The LDA solution was cooled to −78 °C and a THF solution of Cp_2ZrCl_2 (879 mg, 3.00 mmol, 0.3 equiv) was added. After 15 min, **4d** (5.00 g, 10.0 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 90 min, and Cp_2ZrCl_2 (7.30 g, 25.0 mmol, 2.5 equiv) in THF (9 mL) was added. After additional 10 min at −78 °C, to the reaction was added propionaldehyde (794 mg, 11.0 mmol, 1.1 equiv) in THF (5 mL). The reaction mixture was stirred at −78 °C for 30 min and quenched with 1 N HCl. The mixture was extracted with ether (three times). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (12:1:1, hexanes:EtOAc:CH_2Cl_2, 10:1, hexanes:EtOAc) to afford **5r** (4.79 g, 8.60 mmol, 86%) and unreacted **4d** (250 mg, 0.05 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) 7.01−7.22 ppm (7H, m), 6.88 (2H, d, J = 6.6 Hz), 6.71 (2H, s), 5.98 (1H, d, J = 9.6 Hz), 3.67 (2H, dd, J = 13.5, 9.3 Hz), 3.47 (2H, dd, J = 13.8, 4.2 Hz), 3.34 (1H, q, J = 6.9 Hz), 2.49 (1H, m), 2.23 (3H, s), 2.04 (3H, s), 1.98 (6H, s), 1.68 (2H, td, J = 17.0, 4.0 Hz), 1.40 (3H, m), 1.32 (3H, d, J = 6.9 Hz) 1.05−1.23 (2H, m), 0.91 (3H, t, J = 9.6 Hz), 0.81 (2H, m), 0.62−0.65 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) 175.1, 139.1, 138.5, 137.3, 136.6, 136.1, 131.3, 130.9, 130.0, 128.8, 127.9, 127.7, 127.6, 126.8, 125.2, 74.4, 55.1, 50.8, 48.5, 47.3, 37.1, 32.0, 30.0, 28.5, 20.3, 20.0, 19.2, 18.3, 14.1, 11.0, 10.7, 10.0, 9.8. IR (neat) 3514.0 cm^{-1}, 2926.1, 1727.3, 1613.4, 1581.0, 1378.4, 763.2, 743.1, 699.3. HRMS (ESI): $C_{37}H_{51}NO_3$ (M + H$^+$) calcd 558.394171, found 558.39451. $[\alpha]_D$ −8.7° (*c* 0.1, $CHCl_3$ at 25 °C).

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Supporting Information Available: Experimental details including characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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