STERICALLY CONGESTED CHIRAL *N*-ACETYL 2-OXAZOLIDINONE AS ACETYL ENOLATE EQUIVALENTS IN STEREOSELECTIVE ALDOL REACTIONS

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Sterically constrained and highly congested *N*-acetyl-DMAOx (**1a**) serves well as a useful chiral acetyl enolate equivalent which permits a diastereoselective and direct approach to 'acetate' aldols (**2**) including statine derivative.

KEYWORDS chiral 2-oxazolidinone auxiliary; acetyl enolate equivalent; aldol reaction; statine

High levels of enantiocontrol can be achieved in a wide variety of aldol-type reactions of synthetic importance through the stoichiometric methodology using chiral auxiliaries[1-6] as well as a catalytic process.[7] Several chiral enolate synthon systems derived from five- and six-membered heterocycle auxiliaries such as 2-oxazolidinones,[1] 2-imidazolidinones,[2] sultams,[3] 2-oxazinones,[4] 2-oxazolidinethiones,[5] and 2-thiazolidinethiones[5] have been reported over the past decade to effect aldol condensations with excellent diastereoselectivity. Despite such considerable progress, highly enantioselective synthesis of α-unsubstituted β-hydroxycarbonyl compounds (*'acetate'* aldols)[3d] by the aldol reaction using *N*-acetyl heterocycles as chiral acetyl enolate equivalents remains a challenge.[6a, 6b, 8] The optically active *N*-acetyl-2-oxazolidinones have proved of little utility as chiral acetyl enolate synthons for diastereoselective aldol reactions, as previously pointed out,[1a] and a conventional solution to this objective is accomplished by a detour *via* the *N*-methylthioacetyl derivatives followed by desulfurization.[1a]

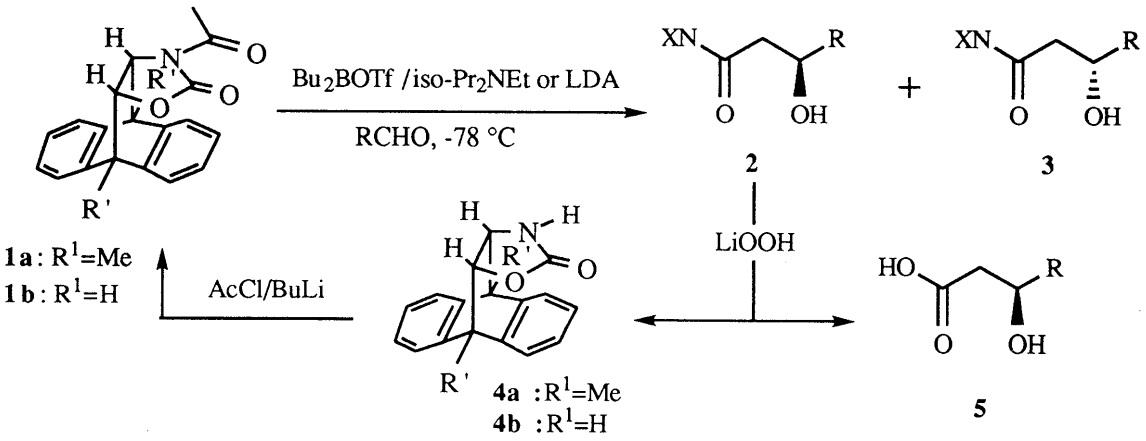

Chart 1

This paper describes the promising direct use of *N*-acetyl-2-oxazolidinone (**1a**)[9] derived from the sterically constrained auxiliary, (+)-DMAOx (**4a**),[10] which contains bulky *cis*-4,5-disubstituent groups favorably arranged for effective asymmetric induction, for the diastereoselective *'acetate'* aldol formation. The condensation between the *N*-acetyl oxazolidinone-derived boron- or lithium-enolates and the aldehydes including *N*-Boc-L-leucinal proceeded with high diastereoselectivity to give the readily separable *'acetate'* aldols (**2**).

Table I. Diastereoselective Aldol Reactions of *N*-Acetyl-2-oxazolidinone 1a with RCHO[a)]

Entry	Reagent, [Solvent]	R	Yield(%)	2 : 3[b)]
1	Bu_2BOTf, iso-Pr_2NEt, [CH_2Cl_2]	Ph	93	86 : 14
2	Bu_2BOTf, iso-Pr_2NEt, [CH_2Cl_2]	iso-Pr	93	90 : 10
3	LDA, [THF]	Ph	57	95 : 5
4	LDA, [THF]	iso-Pr	59	54 : 46
5	Bu_2BOTf, iso-Pr_2NEt, $TiCl_4$, [CH_2Cl_2]	Ph	69	23 : 77
6	Bu_2BOTf, iso-Pr_2NEt, $TiCl_4$, [CH_2Cl_2]	iso-Pr	56	93 : 7

a) Performed at -78 °C for 0.5 h. b) Determined by HPLC analysis (YMC-Pack SIL A-014).

As shown in Table I, the *N*-acetyl-DMAOx (**1a**), readily available by acylation with AcCl/BuLi, reacted with the representative aldehydes in the presence of Bu2BOTf and iso-Pr2NEt[11)] to result in a preferential formation of aldol isomers (**2**)[12)] with unexpectedly high diastereoselectivity, compared with those (less than 32% *d.e.*) obtained when the conventional auxiliaries such as DHAOx (**4b**)[13)] and the Evans' oxazolidinones were employed.[14)] Thus, the DMAOx auxiliary appears to be a favorable choice for present condensation.

When the enolizing reagents, lithium diisopropylamide (LDA)[1c)] or Bu2BOTf/TiCl4,[1d)] were used, the reaction proceeded with stereodifferentiation considerably dependent on the structural features of aromatic and aliphatic aldehydes. Thus benzaldehyde and isobutylaldehyde gave the corresponding '*acetate*' aldols (**2**) with 90% *d.e.* and 86% *d.e.*, respectively, depending on the conditions; this was, to our knowledge, the highest selectivity so far attained by 2-oxazolidinone type auxiliary.

Selective formation of the aldols might be rationalized by the non-chelated or chelated transition forms of the enolates generated *in situ*, as proposed for the *N*-propionyl derivatives.[1b, 1c)]

Removal of the auxiliary from aldols **2** was smoothly performed with LiOOH to give (*S*)-3-hydroxycarboxylic acids (**5**) of known absolute configuration with quantitative recovery of (+)-DMAOx (**4a**) without any loss of optical activity.

The method has now been successfully applied for highly diastereoselective synthesis of (*3S, 4S*)-statine derivative.[15)] The boron-mediated aldol condensation between *N*-Boc-L-leucinal (**6**)[16)] and the *N*-acethyl-DMAOx (**1a**) gave the '*acetate*' aldol (**7**)[17)] with 91% *d.e.*[18)] in 96 % yield, while the aldol reaction with (*S*)-3-acetyl-4-isopropyl-2-oxazolidinone resulted in much lower selectivity of 55% *d.e.* (98 % yield) under the identical conditions. Hydrolysis of the purified **7** with LiOOH/THF followed by esterification gave enantiomerically pure (*3S, 4S*)-*N*-Boc-statine methyl ester (**8**)[15e)] in 87 % yield.

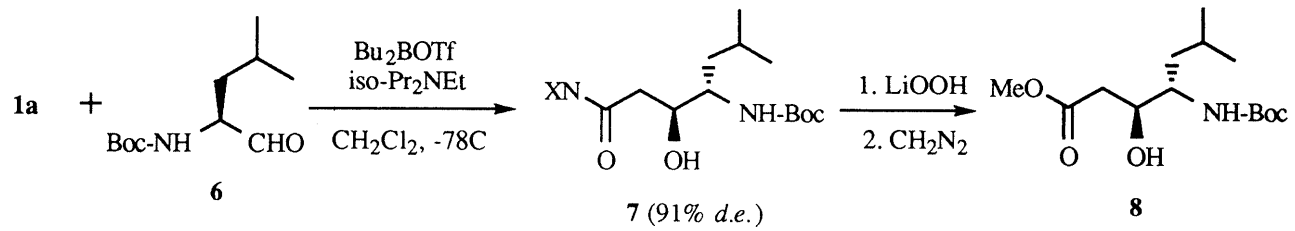

Chart 2

In conclusion, the 2-oxazolidinone type chiral auxiliary, (+) or (-)-DMAOx, with steric congestion and conformational rigidity seems well suited for highly diastereoselective and direct approach to '*acetate*' aldols as well as for efficient control of "*syn*"- and "*anti*"-aldolization.[19)]

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REFERENCES AND NOTES

1) a) D. A. Evans, J. Bartoli, T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981); b) H. Danda, M. M. Hausen, C. H. Heathcock, *J. Org. Chem.*, **55**, 173 (1990); c) M.Nerz-Stormes, E. R. Thronton, *J. Org. Chem.*, **56**, 2489 (1990); d) M. A. Walker, C. H. Heathcock, *J. Org. Chem.*, **56**, 5747 (1991); e) M. R. Borner, E. R. Thronton, *J. Am. Chem. Soc.*, **113**, 1299 (1991); f) F. B. Gonzalez, J. P. B. Fabio, F. M. Reai, *Bull. Chem. Soc. Jpn.*, **64**, 74 (1991); g) A. K. Ghosh, T. T. Dyong, S. P. McWee, *J. Chem. Soc.,Chem. Commun.*, **1992**, 1673; h) T. Yan, C. Tan, H. Lee, H. Lo, T. Haung, *J. Am. Chem. Soc.*, **115**, 2613 (1993).
2) a) W. Sankhavei, M. Yamamoto, S. Kohmoto, K. Yamada, *Bull. Chem. Soc. Jpn.*, **64**, 674 (1991); b) S. E. Drewes, D. G. S. Malissar, G. H. P. Roos, *Tetrahedron: Assymmetry*, **3**, 5515 (1992).
3) a) W. Oppolzer, I. Rodriguez,C. Starkemann, E. Walther, *Tetrahedron Lett.*, **31**, 5019 (1990); b) W. Oppolzer, J. Bragg, E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990); c) W. Oppolzer, C. Starkemann, I. Rodriguez, G. Bernardinelli, *Tetrahedron Lett.*, **32**, 61 (1991); d) W. Oppolzer, C. Starkemann, *Tetrahedron Lett.*, **33**, 2439 (1992).
4) K. H. Ahn, S. Lee, A. Lim, *J. Org. Chem.*, **57**, 5065 (1992).
5) C. Hsiao, L. Liu, M. J. Miller, *J. Org. Chem.*, **52**, 2201 (1987).
6) a) G. Helmchen, U. Leikauf, I. Taufer-Knopfel, *Angew. Chem. Int. Ed. Engl.*, **24**, 874 (1985); b) W. Oppolzer , J. Marco-Cpntelles, *Helv. Chim. Acta*, **69**, 1699 (1986); c) K. Kishikawa, M. Yamamoto, S. Kohmoto, K. Yamada, *Chem. Lett.*, **1989**, 787; d) Y. Xiang, E. Olivier, N. Ouimet, *Tetrahedron Lett.*, **33**, 457 (1992).
7) a) E. J. Corey, R. Imwinkelried, S. Pikul, Y. B. Xiang, *J. Am. Chem. Soc.*, **111**, 5493 (1989); b) T. Mukaiyama, T. Takashima, H. Kusaka, T. Shimpuku, *Chem. Lett.*, **1990**, 1777; c) A. Ando, T. Miura, T. Tatematsu, T.Shioiri, *Tetrahedron Lett.*, **34**, 1507 (1993).
8) a) S. G. Davies, I. M. Pordor, P. Warner, *J. Chem. Soc., Chem. Commun.*, **1984**, 956; b) M. Braun, R. Devant, *Tetrahedron Lett.*, **25**, 5031 (1984); c) Y. Nagao, S. Yamada, T. Kumagai, M. Ochiai, E. Fujita, *J. Chem. Soc., Chem., Commun.*, **1985**, 1418; d) R. O. Duthaler, P. Herold, W. Lottenbach, K. Oerte, M. Riediker, *Angew. Chem. Int. Ed. Engl.*, **28**, 495 (1989); e) K. Oerte, H. Beyeler, R. O. Duthaler, W. Lottenbach, M. Riediker, E. Steinen, *Helv. Chim. Acta*, **73**, 353 (1990); f) B. R. Lagu, H. M. Crane, D. C. Liotta, *J. Org. Chem.*, **58**, 4191 (1993).
9) mp 213 °C, $[\alpha]_D^{27}$ +204.8° (*c* 1.00, $CHCl_3$).
10) K. Kimura, K. Murata, K. Otsuka, T. Ishizuka, T. Kunieda, *Tetrahedron Lett.*, **33**, 4461 (1992).
11) K. Hayashi, Y. Hamada, T. Shioiri, *Tetrahedron Lett.*, **32**, 7287 (1991).
12) **2**; R=Ph: amorphous solid, $[\alpha]_D^{30}$ +128.4 ° (*c* 0.50, $CHCl_3$). R=iso-Pr: mp 178 °C, $[\alpha]_D^{30}$ +138.0 ° (*c* 0.50, $CHCl_3$). **3**; R=Ph: amorphous solid, $[\alpha]_D^{28}$ +170.9 ° (*c* 0.58, $CHCl_3$). R=iso-Pr: mp 146 °C, $[\alpha]_D^{30}$ +196.3 ° (*c* 0.50, $CHCl_3$).
13) H. Matsunaga, K. Kimura, T. Ishizuka, T. Kunieda, *Tetrahedron Lett.*, **32**, 7715 (1991).
14) Chiral *N*-acetyl-DHAOx (**1b**) and (4*S*)-3-acetyl-4-isopropyl-2-oxazolidinone gave **2** with poor diastereoselectivity of 22-24% *d.e.* and 14-32% *d.e.*, respectively, depending on the aldehydes.
15) a) R. M. Devant, H. -E. Raduntz, *Tetrahedron Lett.*, **29**, 2307 (1988); b) P. C. M. Wuts, S. R. Putt, *Synthesis*, **1989**, 951; c) R. M. McConnell, D. Frizzell, A. C. A. Evans, W. Jones, C. Cagle, *J. Med. Chem.*, **34**, 2298 (1991); d) B. H. Kim, Y. J. Chung, E. J. Ryu, *Tetrahedron Lett.*, **34**, 8465 (1993); e) T. Ishizuka, S. Ishibuchi, T. Kunieda, *Tetrahedron*, **49**, 1841 (1993).
16) Y. Hamada, M. Shibata, T. Sugiura, S. Kato, T. Shioiri, *J. Org. Chem.*, **52**, 1252 (1987).
17) **7**: $[\alpha]_D^{23}$ +88.6° (*c* 1.00, $CHCl_3$).
18) The stereodifferentiation might be considerably enhanced by a well-*matched* combination of *N*-Boc-L-leucinal and (+)-DMAOx (**4a**) to give higher diastereoselectivity than those for achiral aldehydes, while a combination of *N*-Boc-D-leucinal and **4a** resulted in poor selectivity (*erythro*-selective ; 38% *d.e.*).
19) The "Evans" *syn*- and "non-Evans" *syn*-aldolizations were nearly exclusively performed in the boron-mediated reaction of *N*-propionyl-DMAOx and benzaldehyde, while the *anti*-aldolization *via* the lithium enolates proceeded with good diastereoselectivity. The result will be reported separately.

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