CHEMISTRY LETTERS, pp. 1799-1802, 1983.

EFFICIENT ASYMMETRIC INDUCTION *VIA* COORDINATION OF CHIRAL DIAMINE TO TIN(II) ENOLATE: A HIGHLY ENANTIOSELECTIVE SYNTHESIS OF 2-SUBSTITUTED MALATES

Rodney W. STEVENS* and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

In the presence of chiral diamine, (2S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine, the tin(II) enolate of 3-acetyl-thiazolidine-2-thione reacts with various α-ketoesters to afford the corresponding aldol-type products, generally, in greater than 95% enantiomeric excess.

Several 2-alkylmalic acids have been isolated from a variety of natural sources or are known to be produced by microorganisms. Of more interest, however, is their common incorporation as carboxylic acid component in a majority of pyrrolizidine alkaloids that exhibit biological activity. Recently intense efforts have been spent in the synthesis of the pyrrolizidine base moiety of these alkaloids.[1] Bearing in mind the fundamental importance of the carboxylic acid residue of such alkaloids, we undertook an investigation of an efficient asymmetric synthesis of such moieties, 2-substituted malates.

Although dramatic progress has been made in the area of asymmetric aldol reactions, *only* those reactions of achiral enolates with chiral aldehyde or of achiral aldehyde (or ketone) with chiral enolates have met with success.[2] Studies directed toward the effect on aldol stereochemistry of *chiral auxiliaries* that are *not covalently bonded to one of the reactants*[3] have led to modest asymmetric induction, in general. On the other hand, recent efforts within our laboratory on such chiral auxiliary-induced asymmetric aldol reactions[4] have led to potentially promising results. Namely, in the presence of chiral diamine, tin(II) enolates when treated with aldehyde afford aldols with high asymmetric induction. Based on these findings we undertook a study of such a chiral auxiliary-induced aldol reaction as a convenient method for the preparation of optically active 2-substituted malates.

Concerning aldol-type asymmetric syntheses of 2-substituted malates, only poor asymmetric induction has been realized.[5] For example, Solladie et al.[5a] have reported that chiral α-sulfinyl ester enolates condense with ethyl pyruvate to afford optically active aldol in albeit 8.5% enantiomeric excess. Brandänge and coworkers[5b] have demonstrated that a combination of chiral ester and optically active amine base gives desired aldol in up to 45% enantiomeric excess at best.

We thus examined the tin(II) enolate chiral auxiliary-induced asymmetric

aldol-type reaction of 3-acetylthiazolidine-2-thione with various α-ketomethyl esters as a simple and efficient route to optically active 2-substituted malate equivalents. In the first place, the tin(II) enolate of 3-acetylthiazolidine-2-thione was treated with methyl pyruvate in the presence of the chiral diamine, (2S)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine, at -78 °C. Work-up of the reaction mixture afforded the aldol-type adduct (1) with poor enantioselection (entry 1). Subsequent examination of a variety of chiral diamines revealed that incorporation of aromatic moiety into chiral auxiliary led to enhanced enantioselection. And, as can be seen from the results summarized in Table 1, when the chiral diamine (2S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine[6] (entry 6) was employed the desired citramalate precursor (1) was obtained in 85% enantiomeric excess. Although not clear at this stage, efficient coordination of bidentate chiral auxiliary (diamine) to the tin(II) metal center (possessing vacant d orbitals) is thought to be crucial for enhanced enantioselection in this reaction.

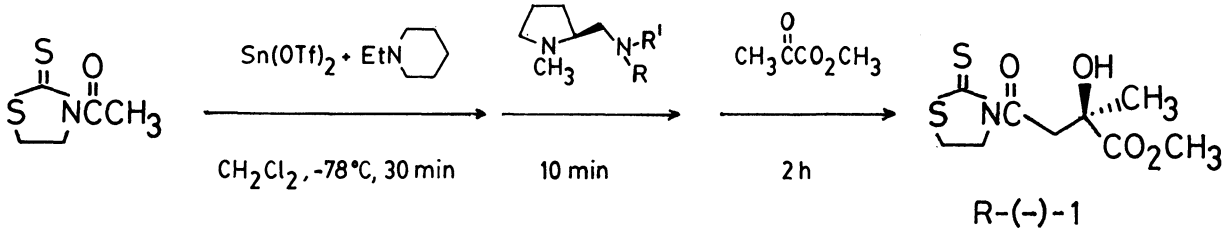

Table 1. Effect of Chiral Diamine

Entry	Chiral Diamine R	R'	Yield/%	Optical purity, %e.e.[a]
1	-$(CH_2)_5$-		53	18
2	H	cyclohexyl	44	≃2
3	H	phenyl	61	54
4	H	2,6-xylyl	75	33
5	H	β-naphthyl	66	61
6	H	α-naphthyl	74	85

a) Determined by ^{1}H NMR measurement of the corresponding dimethyl ester using chiral shift reagent, Eu(hfc)$_3$. The absolute configuration was also determined to be R.

Next, examination of this chiral auxiliary-induced asymmetric aldol-type reaction with a variety of α-ketomethyl esters revealed that, in general, greater than 95% enantiomeric excess is achievable. Results are summarized in Table 2.

A typical reaction procedure is as follows; to a suspension of stannous trifluoromethanesulfonate (331 mg, 0.79 mmol) and N-ethylpiperidine (100 mg, 0.88 mmol) in 1 ml of dichloromethane cooled to -78 °C was added dropwise 3-acetylthiazolidine-2-thione (105 mg, 0.65 mmol) in 1 ml of dichloromethane under an argon atmosphere. After the reaction mixture had been stirred for 30 min, (2S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine (193 mg, 0.80 mmol) in 1 ml of dichloro-

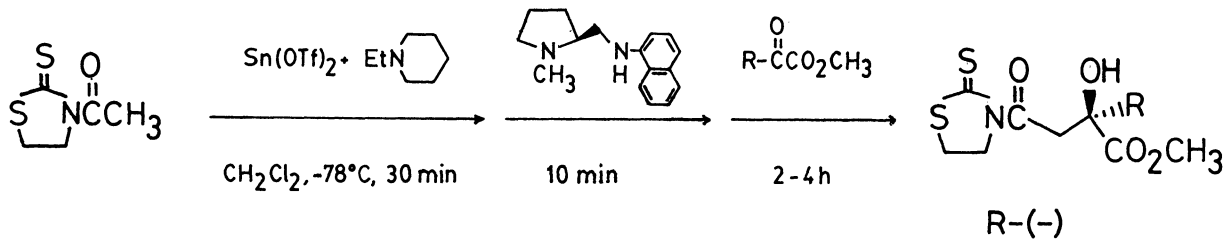

Table 2. Enantioselective Aldol-type Reaction with Various α-Ketoesters

R	Yield/%	Optical purity, %e.e.[a]
CH_3	74	85
C_6H_5-	78	> 95[b]
$(CH_3)_2CH$-	75	> 95[b]
$(CH_3)_2CHCH_2$-	65	> 95[b]
$CH_3O_2C(CH_2)_2$-	80	> 95[b]

a) Determined by ^1H NMR measurement of the corresponding dimethyl ester using chiral shift reagent, Eu(hfc)$_3$. The methoxy peak of methyl ester adjacent to tertiary carbon center cleanly separated in all cases for *racemic* forms.

b) No separation of methoxy peak could be detected at all by ^1H NMR analysis. Absolute configuration was assigned R based on determined sign of optical rotation and correlation with literature findings.[9] The stereochemical course of this reaction is thought to be the same in all examples.

methane was added dropwise, the mixture stirred for 10 min, and then methyl pyruvate (97 mg, 0.95 mmol) in 0.5 ml of dichloromethane added dropwise at this temperature. The reaction mixture was stirred for 2 h and then worked-up in the usual manner. The crude reaction product was purified by silica gel column chromatography to afford corresponding aldol product in 74% yield. Subsequent methanolysis (1.2 equiv. K_2CO_3, MeOH, 0 °C) and distillation of crude reaction mixture gave R-(-)-dimethyl citramalate[7] (60% yield) in 85% enantiomeric excess as determined by chiral shift reagent, Eu(hfc)$_3$.[8]

Thus, in the presence of chiral diamine, which is considered to coordinate efficiently to the tin(II) metal center of stannous enolate, a convenient and highly enantioselective synthesis of 2-substituted malates was realized.

References

1) For leading references see: K. Tatsuta, H. Takahashi, Y. Amemiya, and M. Kinoshita, J. Am. Chem. Soc., 105, 4096 (1983); A. Richard Chamberlin and J. Y. L. Chung, *ibid.*, 105, 3653 (1983) and references cited therein.

2) C. H. Heathcock, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., N. Y. (1983), Vol. 2, Chap. 2.

3) M. Guetté, J. Capillon, and J. -P. Guetté, Tetrahedron, 29, 3659 (1973); D. Seebach, H. O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. Dupreez, V. Ehrig, W. Langer, C. Nüssler, H. -A. Oei, and M. Schmidt, Helv. Chim. Acta, 60, 301 (1977); D. Seebach and W. Langer, *ibid.*, 62, 1701 (1979); D. Seebach, G. Crass, E. -M. Wilka, D. Hilvert, and E. Brunner, *ibid.*, 62, 2695 (1979); M. Schmidt, R. Amstutz, G. Crass, and D. Seebach, Chem. Ber., 113, 1691 (1980); C. H. Heathcock, C. T. White, J. J. Morrison, and D. VanDerveer, J. Org. Chem., 46, 1296 (1981).

4) N. Iwasawa and T. Mukaiyama, Chem. Lett., 1982, 1441; N. Iwasawa and T. Mukaiyama, *ibid.*, 1983, 297.

5) a) C. Mioskowski and G. Solladie, Tetrahedron, 36, 227 (1980); b) S. Brandänge, S. Josephson, L. Mörch, and S. Vallén, Acta Chem. Scand., B35, 273 (1981); c) S. Brandänge, S. Josephson, and S. Vallén, *ibid.*, 27, 1084 (1973); d) S. Brandänge, S. Josephson, and S. Vallén, *ibid.*, 27, 3668 (1973); also see Ref. 9; e) I. Ojima, K. Yoshida, and S. Inaba, Chem. Lett., 1977, 429.

6) Bp 190 °C/3 mmHg; $[\alpha]_D^{23}$ -2.93° (c 1.5, $CHCl_3$); Found: C, 79.95; H, 8.39; N, 11.66%. Calcd for $C_{16}H_{20}N_2$: C, 79.80; H, 8.16; N, 11.62%. NMR ($CDCl_3$): δ = 1.4-2.45 (6H, m), 2.35 (3H, s), 2.85-3.3 (3H, m), 4.4 (1H, br. s), 6.5-7.7 (7H, m); IR (neat): 3500, 1630, 1600, 830, 810 cm^{-1}.

7) Bp 90 - 110 °C/3 mmHg; $[\alpha]_D^{24}$ -25.87° (c 2.4, $CHCl_3$); gave identical spectral data with that reported in the literature for (S)-(+)-dimethyl citramalate, H. K. Spencer and R. K. Hill, J. Org. Chem., 40, 217 (1975), $[\alpha]_D^{21}$ +26.4° (c 4.22, $CHCl_3$), see also Ref. 9, $[\alpha]_D^{24}$ +27.23° (c 2.11, $CHCl_3$).

8) Tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato], europium(III).

9) S. Brandänge, S. Josephson, and S. Vallén, Acta Chem. Scand., B28, 153 (1974) and references cited therein.

(Received September 14, 1983)