CHEMISTRY LETTERS, pp. 429-432, 1977. Published by the Chemical Society of Japan

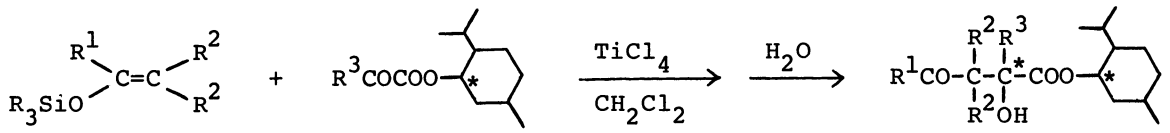
ASYMMETRIC CROSS ALDOL SYNTHESIS. ASYMMETRIC ADDITION OF SILYL ENOL ETHER AND KETENE SILYL ACETAL TO α-KETO ESTERS

Iwao OJIMA,* Katsuhiko YOSHIDA, and Shin-ichi INABA

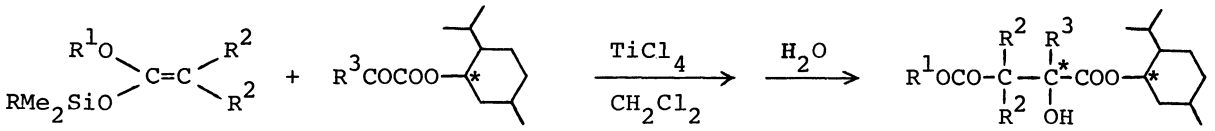
Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229

Asymmetric cross aldol synthesis was carried out by the reaction of several silyl enol ethers and ketene silyl acetals with (-)-menthyl pyruvate and phenylglyoxylate. The extent of asymmetric induction realized in the reaction was determined to be in the range 18-68% by nmr using a shift reagent, $Eu(fod)_3$, and was considerably larger than that observed in the reaction of the chiral α-keto esters with Grignard reagents.

Asymmetric Grignard addition to chiral α-keto esters has gathered much interest for a long time.[1] On the other hand, recently, aldol type reactions of silyl enol ethers and ketene silyl acetals promoted by titanium tetrachloride have been extensively studied.[2] However, any asymmetric reactions have not been reported using the reaction of this type. Banno and Mukaiyama reported that silyl enol ethers reacted with a pyruvate in the presence of titanium tetrachloride to give adducts in good yields.[3] We found that the additions of ketene silyl acetals to α-keto esters were also promoted by titanium tetrachloride, which afforded substituted 2-hydroxysuccinates in good yields. We will describe here asymmetric additions of silyl enol ethers and ketene silyl acetals to (-)-menthyl pyruvate and phenylglyoxylate. The reaction of silyl enol ethers gives 2-hydroxy-4-oxobutyrates (3), while that of ketene silyl acetals affords malates (5).



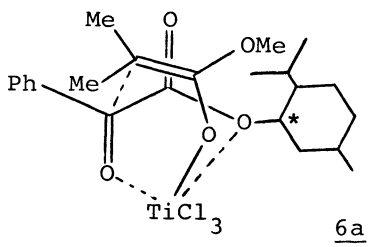
1 + 2 → 3 (eqn. 1)



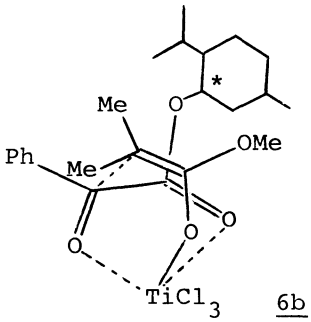
4 2 5 (eqn. 2)

A typical procedure is described for the reaction of dimethylketene methyl trimethylsilyl acetal with (-)-menthyl phenylglyoxylate: To a solution of (-)-menthyl phenylglyoxylate (20 mmol) in dichloromethane (20 ml) was added 1M solution of titanium tetrachloride in dichloromethane (20 ml) at -18°C. Then, the ketene silyl acetal (22 mmol) in dichloromethane (20 ml) was slowly added to the solution, and the reaction mixture was stirred for 2 hr at -18°C. The reaction mixture was poured into ice-water for hydrolysis and was extracted with dichloromethane. The extract was dried over anhydrous potassium sulfate, the solvent was evaporated, and the residue was concentrated in vacuo to give crude (-)-menthyl methyl 3,3-dimethyl-2-methylmalate (5b). The nmr spectrum of the ester 5b, thus obtained, using $Eu(fod)_3$ as shift reagent[4] revealed that the extent of asymmetric induction was 68%. The ester 5b was isolated in 85% yield after purification by column chromatography on silica gel: $[\alpha]_D^{20}$ -4.88° (c 2.13, benzene).

Results of asymmetric cross aldol synthesis are listed in Tables 1 and 2. As the Tables show, the extent of asymmetric induction observed in the present reaction is considerably larger than that observed in the corresponding Grignard reactions which realized 0-18% e.e. for (-)-menthyl pyruvate and 7-30% e.e. for (-)-menthyl phenylglyoxylate.[5] Especially, the asymmetric induction observed in the reaction of dimethylketene methyl trimethylsilyl acetal with (-)-menthyl phenylglyoxylate (68% e.e.) is unexpectedly large considering the simplicity in the design of steric repulsion model.[1] The fact may imply that the transition state of the reaction is relatively rigid. Thus, we postulate at this stage a cyclic transition state depicted as 6a or 6b. A further investigation of the mechanism of asymmetric induction is now in progress.



6a



6b

Table 1. Asymmetric cross aldol reaction of silyl enol ether with α-keto ester

	R	R^1	R^2	R^3	Conditions	Yield of 3 (%)	Asymmetric Induction (%)[a]
a	CH_3	C_6H_5	H	CH_3	-18°, 4 hr	75	50
b	CH_3	t-C_4H_9	H	CH_3	-18°, 4 hr	77	44
c	C_2H_5	CH_3	CH_3	CH_3	-18°, 4 hr	100	---[b]
d	CH_3	C_6H_5	H	C_6H_5	-18°, 4 hr	85	18
e	CH_3	t-C_4H_9	H	C_6H_5	-18°, 4 hr	84	34
f	C_2H_5	CH_3	CH_3	C_6H_5	-18°, 4 hr	95	60

a Estimated by nmr using $Eu(fod)_3$ as shift reagent. b Unfortunately, the extent of asymmetric induction could not be determined by nmr measurement: $[\alpha]_D^{20}$ -61.13° (c 2.20, benzene).

Table 2. Asymmetric cross aldol reaction of ketene silyl acetal with α-keto ester

	R	R^1	R^2	R^3	Conditions	Yield of 5 (%)	Asymmetric Induction (%)[a]
a	CH_3	CH_3	CH_3	CH_3	-18°, 2 hr	83	---[b]
b	CH_3	CH_3	CH_3	C_6H_5	-18°, 2 hr	85	68
c	t-C_4H_9	C_2H_5	H	CH_3	-18°, 2 hr	87	35
d	t-C_4H_9	C_2H_5	H	C_6H_5	-18°, 2 hr	88	25

a Estimated by nmr using $Eu(fod)_3$ as shift reagent. b Unfortunately, the extent of asymmetric induction could not be determined by nmr measurement: $[\alpha]_D^{20}$ -48.80° (c 2.10, benzene).

REFERENCES AND NOTES

1. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall Inc., Englewood Cliffs, New Jersey 1971, Section 2 and references therein.

2. For example, T. Mukaiyama, K. Banno, and K. Narasaka, J. Am. Chem. Soc., 96, 7503 (1974); K. Saigo, M. Osaki, and T. Mukaiyama, Chem. Lett., 989 (1975).

3. K. Banno and T. Mukaiyama, Chem. Lett., 741 (1975).

4. $Eu(fod)_3$ stands for tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionato]europium(III). The nmr spectra were measured with a Varian HA-100 spectrometer.

5. A. McKenzie and E. W. Christie, Biochem. Z., 277, 426 (1935); A. McKenzie and P. D. Ritchie, ibid., 250, 376 (1932); A. McKenzie, J. Chem. Soc., 89, 365 (1906); J. A. Reid and E. E. Turner, J. Chem. Soc., 3219 (1951).

(Received February 18, 1977)