Tetrahedron Letters No. 33, pp 2907 - 2908, 1977. Pergamon Press. Printed in Great Britain.

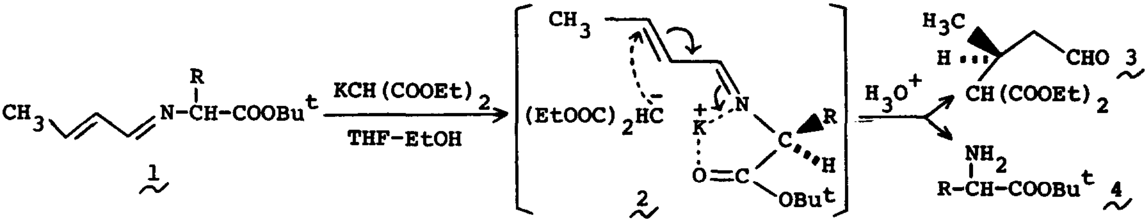
ASYMMETRIC MICHAEL REACTION VIA CHIRAL α,β-UNSATURATED ALDIMINES

Shun-ichi Hashimoto, Nobuyasu Komeshima, Shun-ichi Yamada, and Kenji Koga*
Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan

(Received in Japan 18 May 1977; received in UK for publication 27 June 1977)

Effective asymmetric C-C bond formation has only recently been developed in spite of the fact that C-C bond forming reactions play the central role in synthetic organic chemistry. We have reported that 1,4-addition of Grignard reagents to chiral α,β-unsaturated aldimines leads to optically active β-substituted aldehydes in 91-98% enantiomeric excess.[1)] As an extension of this method to the synthesis of a variety of chiral and functionalized organic compounds, we report here the asymmetric Michael addition[2)] of diethyl malonate to the chiral α,β-unsaturated aldimines **1**.

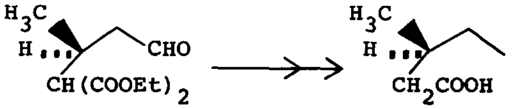
It is well known that the Michael addition of malonate system possessing two α-hydrogen atoms to α,β-unsaturated aldehydes proceeds to give the corresponding adducts in relatively low yields due to the preferential formation of the Knoevenagel condensation products.[3)] After several unsuccessful attempts, however, it has now been found that the Michael adducts of diethyl malonate with α,β-unsaturated aldimines **1** are obtained preferentially by the use of potassium tert-butoxide as a base in THF-EtOH (4.5:1).



R : a) iso-Pr, b) iso-Bu, c) tert-Bu

In a standard experiment (condition B), a solution of **1** (4.0 mmole) in THF-EtOH (4.5:1)(15 ml) was added to a thick suspension of diethyl potassiomalonate, prepared by adding potassium tert-butoxide (6.0 mmole) to a solution of diethyl malonate (12 mmole) in the same solvent (40 ml), and the whole was stirred at room temperature under N_2 for 45 hr. A usual workup under acidic condition gave the crude product, which was purified by column chromatography on silica gel and the vacuum distillation to pure aldehyde **3**. The amino acid ester **4** used as a chiral source was recovered in good yield from the acidic aqueous phase. The results thus obtained are summarized in Table I.

The optical purity and absolute configuration of 3 were determined by chemical correlation of it with the known 3-methylpentanoic acid 5. Since optically pure (S)-(+)-5 is reported to have $[\alpha]_D^{25}$+8.83° (neat),[4] it was determined that optically pure (S)-(+)-3 should have $[\alpha]_D^{20}$+16.8° (benzene).



3, $[\alpha]_D^{20}$+11.6° (benzene)

5, $[\alpha]_D^{25}$+6.11° (neat)

Table I Asymmetric Michael addition of diethyl malonate to α,β-unsaturated aldimines 1

run	α,β-unsaturated aldimine	reaction condition[a)]	3		
			Chem. Y.[b)] (%)	Opt. Y.[c)] (%)	Confign.[c)]
1[d)]	1a	A	43	50	S
2	1a	B	54	69	S
3[d)]	1b	B	49	36	S
4	1c	A	26	83[e)]	S
5	1c	B	48	86[e)]	S

a) A : KO-tert-Bu(1.2 eq)-$CH_2(COOEt)_2$(1.5 eq), B : KO-tert-Bu(1.5 eq)-$CH_2(COOEt)_2$(3.0 eq). b) Isolated yield. c) Based on $[\alpha]_D^{20}$+16.8° (benzene) for optically pure (S)-3. d) Partial racemization of the recovered amino acid ester was observed. e) Corrected for 93.5% optical purity[1)] of L-4c used.

In all cases examined, the optically active aldehyde 3 obtained by the present method using L-4 as a chiral reagent has the S configuration. This means that the stereochemical course of the present Michael reaction can be predicted by the attack of malonate anion from the less-hindered side of the S-trans conformer of the cyclic complex as shown in 2. It should be mentioned that in cases where tert-leucine tert-butyl ester 4c was used as a chiral reagent, the optical yields of 3 were found to be reasonably high (runs 4 and 5), and 4c was recovered without any loss of optical purity for reuse.

Studies on detailed mechanism of this reaction and its applications are in progress.

References

1) S. Hashimoto, S. Yamada, and K. Koga, J. Am. Chem. Soc., 98, 7450 (1976).

2) For some examples of asymmetric Michael reaction, see a) G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, Tetrahedron Letters, 323 (1973); b) H. Wynberg and R. Helder, Ibid., 4057 (1975).

3) E. D. Bergmann, D. Ginsberg, and R. Pappo, "Organic Reactions", Volume 10, J. Wiley & Sons, New York, 1959, p. 179-555.

4) K. B. Wiberg and T. W. Hutton, J. Am. Chem. Soc., 78, 1640 (1956).