Tetrahedron Letters No. 6, pp 573 - 576, 1978. Pergamon Press. Printed in Great Britain.

ASYMMETRIC SYNTHESIS OF α-ALKYLATED CYCLIC KETONES VIA CHIRAL CHELATED LITHIOENAMINES

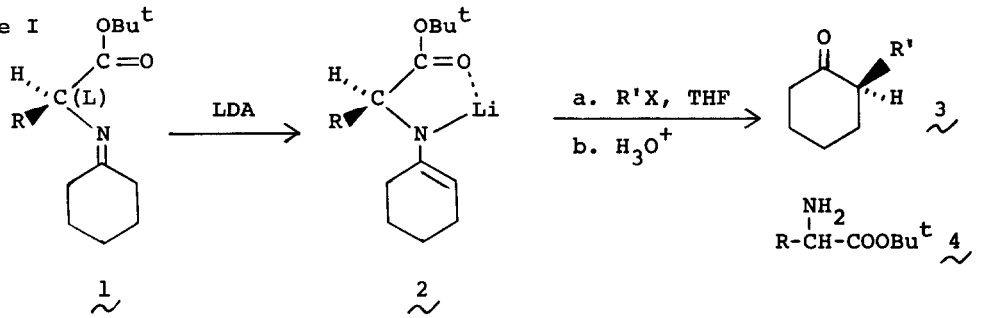
Shun-ichi Hashimoto and Kenji Koga*
Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-Ku, Tokyo 113, Japan

(Received in Japan 28 November 1977; received in UK for publication 15 December 1977)

We have recently reported highly efficient asymmetric 1,4-addition reactions of Grignard reagents and diethyl malonate to chiral α,β-unsaturated aldimines.[1,2] As an extention of our studies on asymmetric C-C bond forming reactions, we now wish to report an asymmetric synthesis of α-alkylated cyclic ketones by metalation and alkylation of chiral cyclic imines using amino acid tert-butyl ester as a chiral source. Although there have been reported many studies on this type of asymmetric synthesis,[3,4,5] the present method has advantages in providing a variety of α-alkylated cyclic ketones in quite high enantiomeric purity wherein the absolute configuration can be predicted with a great degree of confidence, and including operational simplicity.

First, the asymmetric synthesis of α-alkylated cyclohexanones 3 was undertaken as shown in Scheme I. The general procedure is as follows. To a stirred solution of LDA(1.03 eq) in THF was added dropwise a solution of the freshly distilled, chiral imine 1[6] in THF at -78° under argon. After 30 min of stirring, a solution of alkylating agent(1.05 eq) in THF was gradually added to the yellow solution of the lithioenamine 2 at -78°. After stirred for 1 hr, the whole reaction mixture was hydrolyzed with 5% aq. citric acid in an ice bath under vigorous stirring for 25 min. A usual workup, followed by short-path

Scheme I



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

Table I Asymmetric Synthesis of α-Alkylated Cyclohexanones 3

Run	R	R'X	Isolated yield,%	$[\alpha]_D^{25}$(MeOH) Obsd(calcd)[c]	Optical yield,%[c,d] (Confign.)
1	i-Pr[a]	Me_2SO_4	59	+11.7°	84(S)[e]
2	i-Pr[a]	CH_2=$CHCH_2Br$	71	+11.6°	73(R)[f]
3	t-Bu[b]	Me_2SO_4	65	+12.4°(+13.7°)	98(S)[e]
4	t-Bu[b]	MeI	57	+12.3°(+13.6°)	97(S)[e]
5	t-Bu[b]	CH_2=$CHCH_2Br$	75	+12.0°(+13.3°)	84(R)[f]
6	t-Bu[b]	n-PrI	70	+24.7°(+27.3°)	97(S)[g]

a) Optically pure L-4a was used. b) L-4b of 90.5% optical purity was used. c) Corrected for the optical purity of L-4b used. d) Based on highest rotation available in the literature. e) Based on $[\alpha]_D$14°(MeOH) reported by C. Beard, C. Djerassi, J. Sicher, F. Sipos, and M. Tichy, Tetrahedron, 19, 919(1963). f) Based on $[\alpha]_D^{25}$15.8°(MeOH) reported in ref. 5a. g) Based on $[\alpha]_D^{25}$28.2°(MeOH) reported in ref. 5a.

column chromatography on silica gel and subsequent vacuum distillation afforded pure α-alkylated cyclohexanone 3.[6] From the acidic aqueous phase, amino acid ester 4 was recovered in good yield. The results obtained with a variety of alkylating agents are summarized in Table I.

In all cases examined, the absolute configuration of the products 3 obtained by the present method using L-4 was as shown in Scheme I, and tert-leucine tert-butyl ester 4b induced a higher percent asymmetric synthesis than valine tert-butyl ester 4a. The abstraction of a proton from the asymmetric carbon atom by LDA was not observed under the present reaction condition, even when 4a was used, and the chiral sources were recovered without any loss of optical purity for reuse. Since methyl iodide has been known to be too reactive to afford reasonable stereoselectivity,[5b,7] it is of interest to note that methylation with methyl iodide proceeded with stereoselectivity comparable to that with dimethyl sulfate(runs 3 and 4).

Scheme II

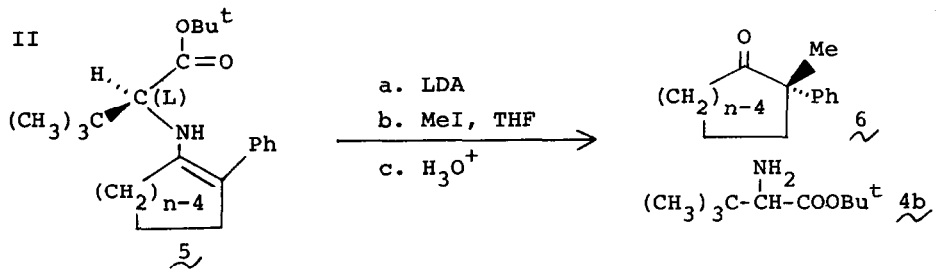


Table II Asymmetric Synthesis of α-Methyl-α-Phenyl Cyclic Ketones 6

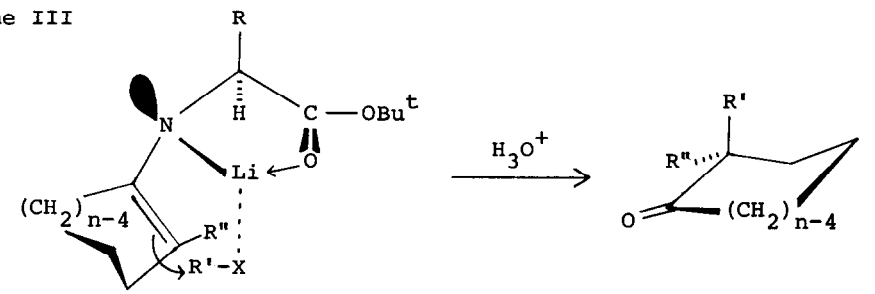
n	Isolated yield,%	$[\alpha]_D^{25}$ Obsd(calcd)[a]	Optical yield,%[a] (Confign.)
5	62	-76.3°(-89.7°)[b]	94(S)[d]
6	40	-133°(-156°)[c]	96(S)[e]

a) Corrected for 85.1% optical purity of L-4b used. b) c 2.26 in EtOH. c) c 1.92 in cyclohexane. d) Based on $[\alpha]_D^{25}$ 95.3°(EtOH) reported by T. D. Hoffman and D. J. Cram, J. Am. Chem. Soc., 91, 1000(1969). e) Determined in CCl_4 using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III). Absolute configuration was assigned by A. G. Brook, H. W. Kucera, and D. M. MacRae, Can. J. Chem., 48, 818(1970).

We next applied the present method to the creation of an asymmetric quaternary carbon atom using α-phenyl cyclic ketones as shown in Scheme II. The metalation of the chiral enamines 5[6] formed from α-phenyl cyclic ketones and L-tert-leucine tert-butyl ester 4b, followed by addition of methyl iodide afforded, after hydrolysis, chiral α-methyl-α-phenyl cyclic ketones 6[8] in high enantiomeric purity(Table II). The absolute configuration of the products 6 was found to be as shown in Scheme II, suggesting the existence of the similar chelate intermediate in the alkylation step.

All the experimental results obtained in this asymmetric synthesis can be explained by the mechanism shown in Scheme III, which is synonymous with that proposed by Meyers et al. in a quite similar system.[5a] The coordination of the unshared electron pairs on the oxygen atom and the leaving group of alkylating agent to the lithium cation play a central role in this highly orientated alkylation, while the bulkiness of R group only displaces the equilibrium between the cis and trans conformers in favor of the latter, controlling stereochemical approaches in alkylation indirectly. The approach of R' group

Scheme III



would take place preferentially from one direction in the trans conformer by virtue of these coordination and stereoelectronic control. It should be noted that inherent 1,4-asymmetric induction can be, in fact, replaced by 1,2-asymmetric induction(generation of a new chirality on the nitrogen atom).

Further exploitation of this asymmetric reaction to more complex system is now in progress.

References

1) S. Hashimoto, S. Yamada, and K. Koga, J. Am. Chem. Soc., 98, 7450(1976).
2) S. Hashimoto, N. Komeshima, S. Yamada, and K. Koga, Tetrahedron Letters, 2907(1977).
3) For enamine method, see a) S. Yamada, K. Hiroi, and K. Achiwa, Tetrahedron Letters, 4233(1969); b) K. Hiroi, K. Achiwa, and S. Yamada, Chem. Pharm. Bull., 20, 246(1972).
4) For metalloenamine method, see a) D. Mea-Jacheet and A. Horeau, Bull. Soc. Chim. Fr., 4571(1968); b) M. Kitamoto, K. Hiroi, S. Terashima, and S. Yamada, Chem. Pharm. Bull., 22, 459(1974).
5) For rigid metalloenamine method, see a) A. I. Meyers, D. R. Williams, and M. Druelinger, J. Am. Chem. Soc., 98, 3032(1976); b) D. Enders and H. Eichenauer, Angew. Chem. Int. Ed. Engl., 15, 549(1976); c) J. K. Whitesell and M. A. Whitesell, J. Org. Chem., 42, 377(1977).
6) All compounds exhibited nmr, ir, and mass spectral data in agreement with the indicated structures.
7) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, J. Am. Chem. Soc., 98 567(1976).
8) Identical in all respects with an authentic sample.