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ASYMMETRIC CONJUGATE ADDITION OF COPPER AZAENOLATES AS SYNTHETIC EQUIVALENT OF ENOLATES TO CYCLIC ENONES

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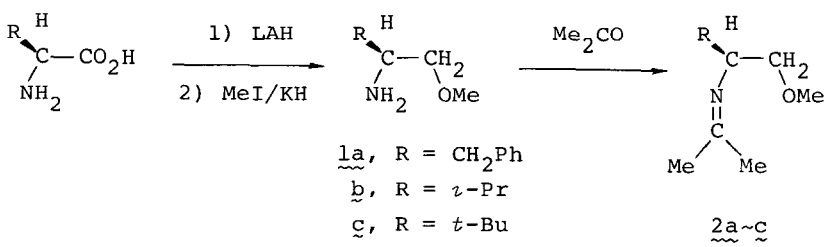
Summary: Asymmetric conjugate addition to prochiral cyclic enones was devised by using copper azaenolates derived from an acetone imine of optically active amino ethers which were prepared from α-amino acids, the optical yields of the resulting 3-acetonylcycloalkanones being found to attain as high as 75% e. e.

Organocuprates have assumed a prominent place in the carbon nucleophiles which undergo definite conjugate addition to α,β-unsaturated carbonyls.[1] Significant efforts have been made toward the asymmetric conjugate addition of these reagents which usually contain a chiral auxiliary as ligands. Most of the studies have involved unfunctionalized hydrocarbon groups to be transferred under the influence of the chiral ligands on the copper atom, resulting in rather ineffective asymmetric induction (~15% e. e.).[2] To our best knowledge only a single example of a successful enantioface-differentiating addition of a methylcuprate to chalcone with the aid of *N*-methylprolinol as ligands has recently been reported.[3]

In view of a wide variety of cuprate reactions in organic synthesis another line of research should be undertaken on asymmetric reactions of functionalized organocuprates. Among several examples of functionalized systems of cuprate reagents so far reported,[4] we were interested in the synthetic equivalent of ketone enolates. Since direct formation of reactive diorganocuprate of this type of ligands does not appear feasible, we decided to utilize a lithium azaenolate of an optically active imine for the preparation of chiral cuprate reagents.[5]

The requisite acetone imines (2a~c) were readily prepared by treating optically active amino ethers (1a~c), which were obtained from the corresponding α-amino acids by a reported procedure[6] with significant modification,[7] with excess acetone in the presence of molecular sieves.

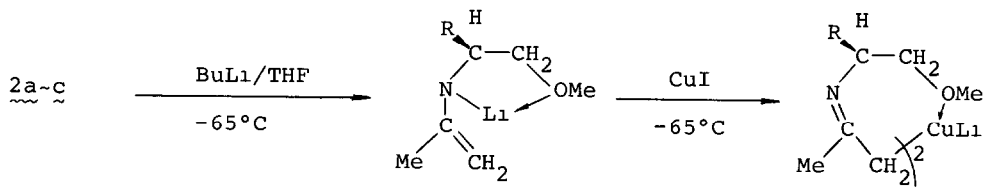


1a, R = CH_2Ph
b, R = i-Pr
c, R = t-Bu

2a~c

Since the optically active tert-leucine is an artificial α-amino acid and both enantiomers are readily obtained by resolution of racemates of its *N*-formyl derivative,[8] (*R*)-2c (optical purity 96%) was also conveniently prepared for the present reaction.

Metalation of the chiral methoxyketoimines (2a~c) (5 mmol) in tetrahydrofuran (THF) (1~0.3 mmol/mL) with one equivalent of butyllithium (or *t*-butyllithium), followed by treatment with copper(I) iodide (2.5 mmol) in the presence or absence of dimethylsulfide in THF (0~1:10 v/v, 6 mL) at -65°C gave a clear yellow solution of homocuprates (3a~c) whose chelate structures were likely assumed (*vide infra*).



3a~c

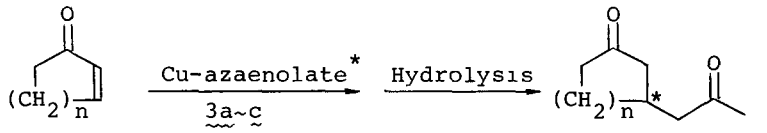
Conjugate addition of the copper azaenolate (3a~c) to an equimolar amount of 2-cyclohexenone and to 2-cyclopentenone gave, after facile hydrolysis (ammonium chloride-ammonia), partially active 3-acetonylcyclohexanone (4) and 3-acetonylcyclopentanone (5), respectively, in enantiomeric excess renging from 17 to 75%. Amino ethers (1a~c) used as a chiral auxiliary were recovered in 50-80% yield. Results thus obtained are summarized in Table 1. Although the chemical yields of purified products rather fluctuated, the optical yields were found to be reproducible within an experimental error (entries 1 and 2).

As can be seen from Table 1, (*S*)-valinol derivative 3b exhibits crucial enantioface differentiation between 2-cyclohexenone for (*R*) and 2-cyclopentenone for (*S*) Although no evidence for the distinct chelate structures of 3a~c is available, taking the steric demand of the present chiral cuprate reagents in the order of R = *t*-Bu > *i*-Pr > CH_2Ph into account, one can argue that the "face matching" of such a cyclic chiral cuprate (*S*)-3b with one enantioface of rather folded structure of 2-cyclohexenone leading to (*R*)-4 could be inverted with another face of flat 2-cyclopentenone to give (*S*)-5 predominantly. On the other hand, (*R*)-tert-leucinol derivative 3c differentiates equally one enantioface of both cyclohexenone and cyclopentenone leading to (*R*)-products with much higher enantiomeric excess than (*S*)-phenylalaninol derivative 3a.

A mixed homocuprate, prepared from lithiated 2a (5 mmol) with copper(I) acetylide of 3-methoxy-3-methyl-1-butyne[13] (5 mmol) in THF (10 mL), was found to react equally with 2-cyclohexenone (5 mmol) under gradual temperature raising from -70°C to -20°C. After usual work up there obtained diketone 4 in 16% isolated yield, $[\alpha]_D^{25}$ -3.89° (*c* 1 96, benzene), the optical yield being 26.6% ee (*R*).

The fact that a comparable optical yield was attained in the conjugate addition (cf. Table 1, entries 1 and 2) by using a chiral mixed cuprate is encouraging

Table 1. Asymmetric Conjugate Addition of Chiral Copper(I) Azaenolates (3a~c) to 2-Cyclohexenone and to 2-Cyclopentenone



4, n = 2
5, n = 1

Entry	n	Copper(I) Reagent	Yield[a] (%)	$[\alpha]_D$(Benzene) of 4[b] and 5[c]	Optical Yield (%) (Configuration)
1	2	(*S*)-3a	41	-4.02	27.5 (*R*)
2		(*S*)-3a	21	-4.17	28.6 (*R*)
3		(*S*)-3b	46	-3.28	22.5 (*R*)
4		(*S*)-3c[d]	30	+6.46	44.2 (*S*)
5		(*R*)-3c[e]	31	-6.37	43.6 (*R*)
6	1	(*S*)-3a	54	-12.7	16.5 (*R*)
7		(*S*)-3b	75	+20.7	26.9 (*S*)
8		(*R*)-3c[e]	89	-57.9	75.4 (*R*)

[a] Purified by column chromatography.
[b] (*S*)-4, $[\alpha]^{25}_{D\,max}$ +14.6° (benzene), see footnote.[9]
[c] (*S*)-5, $[\alpha]^{25}_{D\,max}$ +76.7° (benzene) estimated maximum value, see footnote.[11]
[d] (*S*)-1c with 80% optical purity was used.
[e] (*R*)-1c with 96% optical purity was used.

for synthetic purposes, as the group which is transferred becomes more complex and precious. Investigations on this line are now in progress.

In conclusion chirally functionalized systems of organocuprate reagents such as 3a~c are successfully used for the asymmetric conjugate addition to 2-cycloalkenones of a relatively plain prochiral nature.

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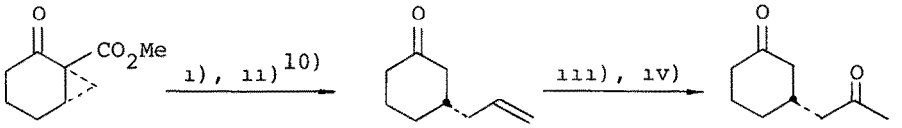
References and Notes

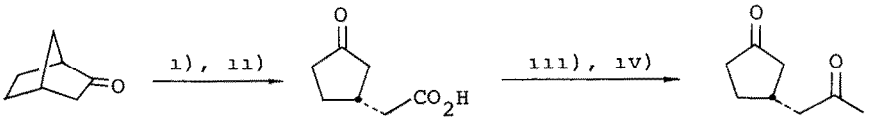
1) G. H. Posner, Org Reactions, 19, 1, (1972); J F. Normant, Synthesis, 63 (1972).
2) R. A. Kretchmer, J. Org. Chem., 37, 2744 (1972); J. S. Zweig, J. L. Luche, E. Barreiro, and P. Crabbé, Tetrahedron Lett., 2355 (1975), Idem, Bull. Chim. Soc Belg., 87, 369 (1978); W. Langer and D. Seebach, Angew. Chem. Int. Ed., 14, 634 (1975), Idem, Helv. Chim. Acta, 62, 1710 (1979); A. Hansson, M. T. Rahman, and C. Ullenius, Acta Chem. Scand., Ser. B, 32, 483 (1978); B. Gustafsson, Tetrahedron, 34, 3023 (1978).
3) T. Imamoto and T. Mukaiyama, Chem. Lett., 45 (1980), cf. M. Huché, J. Berlan, G. Pourcelot, and P. Cresson, Tetrahedron Lett., 22, 1329 (1981).
4) R. K. Beockmann, Jr. and K. J. Bruza, J. Org. Chem., 44, 4871 (1979), and references cited therin.
5) The procedure for a copper(I) azaenolate of acetone *N*,*N*-dimethylhydrazone without elements of asymmetric induction is known; E. J. Corey and D. Enders, Tetrahedron Lett., 11 (1976).
6) A. I. Meyers, G. S. Poindexter, and Z. Brich, J. Org. Chem., 43, 892 (1978).
7) The chiral methoxyamines (1a~c) were only obtained purely by a rapid methylation of amino alcohols with potassium hydride-methyl iodide mixture.
8) S. Yamada and S. Hashimoto, Chem. Lett., 921 (1976). We are indebted to Prof. K. Koga of Tokyo University for a resolution procedure.
9) The authentic (*S*)-4 was prepared independently as shown below:



(*S*)-4

i) $(CH_2=CH)_2CuLi$/THF, -35°C; ii) NaCl/DMSO, 160°C; iii) $Hg(OAc)_2$/aq. THF; iv) Na_2PdCl_4/MeOH

10) D. F. Taber, S. A. Saleh, and R. W. Koresmeyer, J. Org. Chem., 45, 4699 (1980).
11) The authentic (*S*)-5 was prepared as follows:



(+)-acid,[12] (56.7% opt. purity)

(*S*)-5, $[\alpha]_D^{25}$+43.5° (benzene)

i) mCPBA/CH_2Cl_2; ii) RuO_4-$NaIO_4$/aq. NaOH; iii) $(COCl)_2$/PhH; iv) Me_2CuLi/Et_2O

12) H. Kuritani, Y. Takaoka, and K. Shingu, J. Org. Chem., 44, 452 (1979).
13) E. J. Corey, D. Floyd, and B. H Lipshutz, J. Org. Chem., 43, 3418 (1978).
14) Presented in part at the 44th Meeting of the Chemical Society of Japan, October, 1981 (Okayama). Abstr. 1B03.

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