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A NEW AND EFFECTIVE ASYMMETRIC SYNTHESIS OF 3-PHENYLALKANALS

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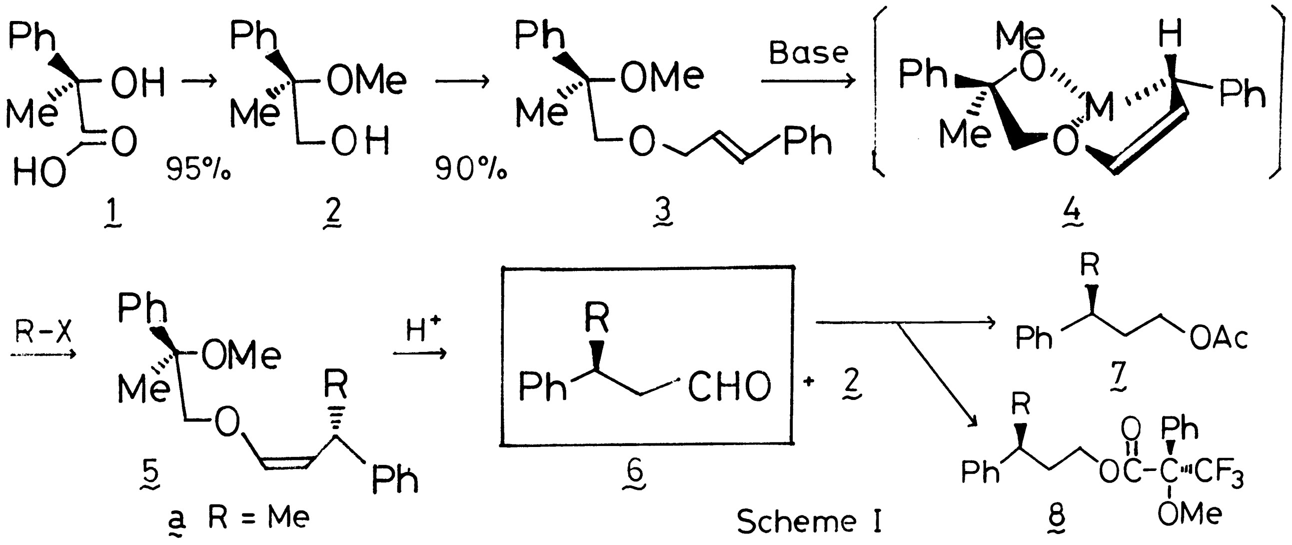
Highly optically active 3-phenylalkanals were obtained by the reaction of alkyl halides and a chiral homoenolate equivalent derived from the cinnamyl ether 3 and potassium diisopropylamide, followed by acidic hydrolysis.

Chiral β-substituted carbonyl compounds are important synthetic intermediates, and many attempts to prepare these carbonyl compounds via asymmetric synthesis have been reported. Some Michael-type addition reactions of alkyl metals to chiral α,β-unsaturated carbonyl compounds gave β-substituted carbonyl compounds in high optical yields.1) On the other hand, only one method is known for the preparation of this class of compounds by the reaction of a chiral homoenolate equivalent with alkyl halides.2) Therefore, a new reaction giving highly optically pure β-substituted carbonyl compounds based on this type of approach is strongly desired.

Now, we wish to report a new and effective asymmetric synthesis of 3-phenylalkanals by the reaction of a chiral homoenolate equivalent with alkyl halides. During our continuous investigations of asymmetric synthesis, atrolactic acid (1) derivatives have proved to be effective chiral sources.3) Thus, as a starting material for a chiral homoenolate equivalent, cinnamyl ether 3 prepared from cinnamyl bromide and a chiral alcohol 2 derived from atrolactic acid was chosen.4) It is postulated that the allyl anion derived from the cinnamyl ether 3 may, by



Scheme I

coordination of the two ether oxygen atoms to a metal cation, attain the five and five cis-fused bicyclic rigid structure which would have the conformation depicted in 4 as the most stable one. Therefore, it is expected that electrophiles such as alkyl halides should approach from below, less hindered side of the allyl anion complex 4.5)

As shown in Scheme I, the cinnamyl ether 3 was successively treated with strong base and alkyl halide to form a vinyl ether 5. Then the vinyl ether 5 was hydrolyzed with acid to give optically active 3-phenylalkanals 6.

In the first place, employing methyl iodide as an alkylating reagent, the effects of base, solvent and reaction temperature on the optical purity of 3-phenylbutanal (6a) and the chemical yield of the vinyl ether 5a6) were examined.

The optical purity of the aldehyde 6a and the chemical yield of the vinyl ether 5a varied dramatically with the kind of base and solvent used. Of the bases screened, potassium diisopropylamide (KDA) was found to be most suitable. And it is also noted that when the reaction was carried out in ether at -100°C, the best results were obtained.

Table I. The reaction of the cinnamyl ether 3 and methyl iodide.

Base	Solvent	Reaction temperature(°C)	Yield of 5a (%)	Optical purity a) of 6a (%)
LDA	THF	- 78	0 b)	–
s-BuLi	THF	-100	56	5
n-BuLi-  OCs c)	THF	-100	50	46
n-BuLi- tBuOK d)	THF	-100	32	58
KDA e)	THF	-100	44	70
KDA	Et_2O	- 78	68	78
KDA	Et_2O	-100	75	85

a) The absolute configuration of the aldehyde 6a was S when the cinnamyl ether (R)-3 was employed. The optical purity was determined by the specific rotation of the acetate 7a.10)

b) When lithium diisopropylamide was employed as base, a dark-red color of the allyl anion 4 was not observed at -78°C.

c) The Weiss' base.8)

d) The Lochmann-Schlosser's base.9)

e) The Seebach's base.

Of the methylating reagents, methyl iodide gave the best result as shown in Table II.

Table II. The effect of methylating reagents. (conditions: KDA, ether, -100°C)

Methylating reagent	Yield of 5a (%)	Optical purity of 6a (%)
MeI	75	85
$MeOSO_2CF_3$	70	54
Me_2SO_4	78	42
MeOTs	60	35

A typical procedure for the preparation of (S)-3-phenylbutanal (6a) is as follows: To an ethereal solution (7 ml) of KDA (1.5 mmol), prepared from ^{t}BuOK, diisopropylamine and butyllithium, was added dropwise (R)-(-)-cinnamyl 2-methoxy-2-phenylpropyl ether (3) (293 mg, 1 mmol) in ether (2 ml) at -100 °C (liquid N_2-methanol) under an argon atmosphere. After stirring for 5 hr at that temperature, to the resulting dark-red suspension was added methyl iodide (284 mg, 2 mmol) in ether (1 ml). The reaction mixture was stirred at -100 °C until red color disappeared (about 2 hr), then the bath was removed and the phosphate buffer (pH 7, 5 ml) was added to the reaction mixture. The organic materials were extracted with ethyl acetate for several times and the combined extracts were washed with brine, and dried over $MgSO_4$. After the solvents were removed, (2R)-2-methoxy-2-phenylpropyl (Z)-3-phenyl-1-butenyl ether (5a) (232 mg, 75% yield) was isolated by thin layer chromatography on silica gel. Then the vinyl ether 5a was hydrolyzed by aqueous 40% $HClO_4$-ether to give 3-phenylbutanal (6a). In order to determine the chemical yield and the optical purity of unstable 3-phenylbutanal (6a), the aldehyde 6a was converted to 3-phenylbutyl acetate (7a) (112 mg, 0.58 mmol, 74% yield from 5a, $[\alpha]_D^{20}$ + 43.2° (c 1.79, benzene), 85% ee).[2]

In a similar manner, other highly optically pure 3-phenylalkanals were obtained as shown in Table III. The aldehydes 6 have the configurations expected from the hypothesis mentioned above (p. 2).

Table III. The reaction of the cinnamyl ether (R)-3 and alkyl halides.[a]

RX	yield of 5 (%)	Yield of 7 based on 5(%)	$[\alpha]_D^{20}$ of 7 (c, benzene)	Optical purity of 6 (%)[b]	Absolute configuration of 6
MeI	75	74	+ 43.2°(1.79)	85	S
EtI	69	66	+ 33.9°(2.15)	84	S
n-BuI	65	66	+ 24.8°(4.63)	75	S
i-PrI	67	65	+ 31.4°(3.88)	87	R
	58	52	+ 17.2°(3.44)	55	S

a) All new compounds gave satisfactory spectral data and elemental analyses.
b) Optical purity was determined by the specific rotation of the acetate 7 and ^{1}H-or ^{19}F-NMR spectroscopy of the MTPA ester 8[11] with tris [1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctadionato-(4,6)]-europium ($Eu(fod)_3$)

It should be noted that, 3-phenylalkanals are obtained in high optical purities from easily available cinnamyl ether (R)-3 and alkyl halides. According to the present method, the other enantiomers of 3-phenylalkanals can also be obtained by a similar procedure from the cinnamyl ether (S)-3.[4] It is also noted that the chiral source, the alcohol 2, is recovered without any racemization after hydrolysis of the vinyl ether 5.

A further synthetic investigation for other useful chiral compounds based on this reaction is now in progress.

References

1) S. Hashimoto, S. Yamada, and K. Koga, J. Am. Chem. Soc., 98, 7450 (1976). A. I. Meyers, R. K. Smith, and G. C. Whitten, J. Org. Chem., 44, 2250 (1979). T. Mukaiyama, T. Takeda, and K. Fujimoto, Bull. Chem. Soc. Jpn., 51, 3368 (1978). T. Mukaiyama and N. Iwasawa, Chem. Lett., 1981, 913.

2) H. Ahlbrecht, G. Bonnet, D. Enders, and G. Zimmerman, Tetrahedron Lett., 1980, 3175.

3) T. Nakatsuka, T. Miwa, and T. Mukaiyama, Chem. Lett., 1981, 279.

4) The preparation of cinnamyl ether 3 is as follows: Optically pure atrolactic acid (1) (L. Smith, J. Prakt. Chem., [2], 84, 738 (1911).) was treated successively with CH_2N_2, MeI/NaH in DMF, and $LiAlH_4$ in THF to give the chiral alcohol 2 in 95% yield. Treatment of the chiral alcohol 2 with cinnamyl bromide and NaH in DMF afforded cinnamyl ether 3 in 90% yield. Physical data: (R)-2: mp 59-61 °C; bp 114 °C/7 mmHg; ^{1}H-NMR($CDCl_3$), δ=1.63 (3H, s), 2.20 (1H, s), 3.12 (3H, s), 3.56 (2H, s), 7.3-7.5 (5H, m); IR (KBr) 3300, 1640, 1600, 1490, 1445 cm^{-1}; $[\alpha]^{20}_{D}$ -49.9° (c 1.16, $CHCl_3$); Found: C, 72.17; H, 8.45%. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%. (R)-3: bp 180 °C/0.2 mmHg (bath temp.); ^{1}H-NMR (CCl_4), δ=1.55 (3H, s), 3.03 (3H, s), 3.41 (2H, s), 4.00 (2H, d, J=4Hz), 6.0-6.3 (2H, m), 7.1-7.3 (10H, m); IR (neat) 1595, 1490, 1445 cm^{-1}; $[\alpha]^{20}_{D}$ -2.1° (c 1.02, $CHCl_3$); Found: C, 80.52; H, 7.74%. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85%.

5) This structure provides an effective environment for the asymmetric induction; T. Mukaiyama, Y. Sakito, and M. Asami, Chem. Lett., 1978, 1253. T.Mukaiyama, A. Ikegawa, and K. Suzuki, Chem. Lett., 1981, 165.

6) The vinyl ether 5a having Z-configuration was isolated as a single product. It is noted that a trace amount of E-isomer or α-adduct was detected under some conditions.

7) B. Renger, H. Hugel, W. Wykypiel, and D. Seebach, Chem. Ber., 111, 2630 (1978).

8) L. Lochmann, J. Pospisil, and D. Lim, Tetrahedron Lett., 1966, 257. M. Schlosser, J. Organometal Chem., 8, 9 (1967).

9) E. Weiss and H. Köster, Chem. Ber., 110, 717 (1977).

10) The optical purity of 6a was also determined by the diastereomer excess of 5a which was determined by ^{1}H-NMR spectroscopy with $Eu(fod)_3$.

11) S. Yamaguchi and H. S. Mosher, J. Org. Chem., 38, 1870 (1973).

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