

ENANTIOSELECTIVE ADDITION OF OPTICALLY ACTIVE ORGANOTITANIUM REAGENTS TO BENZALDEHYDE*

Otakar ČERVINKA, Marcel PÁTEK and Vladimír STRUŽKA

Department of Organic Chemistry, Prague Institute of Technology, 166 28 Prague 6

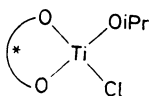
Received July 23, 1990

Accepted October 26, 1990

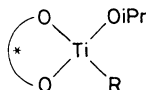
Dedicated to the memory of Professor František Šorm.

Addition of optically active alkyltitanium(IV) reagents *IIf* and *IIfc* to benzaldehyde afforded optically active 1-phenylethanol (*V*) of 37–48% optical purity and 1-phenylpentanol (*VI*) of 10–24% optical purity. Reagents *IIf* and *IIfc* were prepared with the use of (1*R*,2*S*)-(–)-1-phenyl-1,2-propanediol (*III*) and (1*R*,2*S*)-(+)-1-cyclohexyl-1,2-propanediol (*IV*) as optically active components. Relations between the enantioselectivity achieved and reaction conditions are discussed.

Organotitanium(IV) reagents have become indispensable in the modern organic synthesis, especially due to their higher chemical selectivity as well as stereoselectivity when compared to organolithium or organomagnesium reagents in a number of studied reactions^{1–3}. The character of organotitanium(IV) reagents makes it possible to bind the optically active components directly at the titanium atom and thus to strengthen its effect on stereoselectivity of a given reaction. The addition of organotitanium reagents *IIfa* modified by optically active 1,1'-binaphthyl-2,2'-diol to various aromatic aldehydes afforded optically active benzhydrols of high optical purity^{4,5}. The addition of methyltitanium reagents *IIfb* modified by 1,1'-binaphthyl-2,2'-diol, menthol, 2-butanol and threitol derivatives to benzaldehyde does not proceed however with the so high optical yield^{1,6}. The enantiomeric excess of the 1-phenylethanol obtained did not exceed 60 per cent.



I



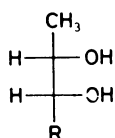
IIfa, R = aryl

IIfb, R = CH₃

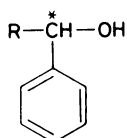
IIfc, R = C₄H₉

* Part LXVII in the series Asymmetric Reactions; Part LXVI: Collect. Czech. Chem. Commun. 55, 2685 (1990).

The synthesis of the reagent *II* involves modification of chlorotris(2-propoxy)-titanium by the optically active alcohol or diol, followed by alkylation of the intermediate *I* with appropriate organolithium or organomagnesium reagent. Within the framework of our study of the addition of reagents *I**b*** and *I**c*** to benzaldehyde, in preparing these reagents we used (1*R*, 2*S*)-(-)-1-phenyl-1,2-propanediol (*III*) and (1*R*, 2*S*)-(+)-1-cyclohexyl-1,2-propanediol⁷ *IV*) as optically active components. Alkylation of the corresponding intermediate *I* was effected with methyllithium or butyllithium.



III, R = C₆H₅
IV, R = C₆H₁₁



V, R = CH₃
VI, R = C₄H₉

Organotitanium reagents *I**b*** and *I**c*** so obtained were subjected to the reaction with benzaldehyde, the effect of reaction conditions on enantioselectivity of the reaction being examined. The enantioselectivity was determined by comparing the optical rotation of isolated 1-phenylethanol (*V*) or 1-phenylpentanol (*VI*) with reported specific rotations of the optically pure compound. Results are summarized in Table I.

RESULTS AND DISCUSSION

The conversion of benzaldehyde (0.75 mol. equivalent) in its reaction with methyltitanium reagents *I**b*** was nearly quantitative, while in the reaction with butyltitanium reagents *I**c*** it varied from 65 to 82 per cent, likely due to the greater steric demands of the butyl group. The isolated yields are lower because of product losses during its chromatographic isolation. Sometimes, the chromatography yielded also the smaller amounts of the corresponding phenones (5–10%) which are formed by oxidation of alcohols *V* and *VI* on chromatographic phase (silica gel).

At the temperature -20°C , the higher optical purity of isolated 1-phenylethanol was obtained by the reaction carried out in ether (48%) than in tetrahydrofuran (40%). On the other hand, the significant temperature dependence of enantioselectivity of the reaction has not been observed in the -120°C up to -20°C region. A simple explanation of this finding is difficult to suggest. We believe that this phenomenon is connected with the complex composition of the reaction mixture. The reagent *II* modified by diols *III* and *IV* (that are not C₂ symmetry substances) can exist in two diastereoisomeric forms which differ from each other by the absolute configura-

tion at the titanium atom. Furthermore, the presence of dimers or higher oligomers of reagent *II* cannot be excluded, too. In such compounds, diol *III* or diol *IV* molecules form bridges between different titanium atoms. The overall stereoselectivity results thus from combination of the effects depending on the proportion of single compounds in the mixture. Our attempt at determining this proportion by Ti or ^1H NMR spectroscopy has not been successful. The spectra obtained showed very broad resonance signals, which made reliable interpretation impossible.

The optical purity of the alcohol *V* obtained by the reaction of reagent *IIb* modified by diol *III* with benzaldehyde is only slightly higher than the purity of the same product obtained by the reaction of the analogous reagent derived from diol *IV*. In both cases, (*R*)-configuration is prevailing in the product. With the reagent *IIc*, the enantioselectivity of the addition is lower.

Reagent *IIc* modified by diol *III* gives the product with prevailing (*R*)-configuration, i.e. the stereoselectivity of the process is similar to that mentioned above. In contradistinction to it, the same reagent modified by diol *IV* affords the product with prevailing (*S*)-configuration, likely due to steric interactions of the cyclohexyl with butyl group.

TABLE I
Enantioselective addition of reagents *IIb* and *IIc* modified by diols *III* and *IV* to benzaldehyde

Reagent	Diol	Temperature °C	Solvent	Conversion ^a %	Optical purity ^b (absol. configuration of product)
<i>IIb</i>	<i>III</i>	-20	ether	78 (54) ^c	48 (<i>R</i>)
	<i>III</i>	-20	THF	95 (86)	40 (<i>R</i>)
	<i>III</i>	-78	ether	95 (82)	44 (<i>R</i>)
	<i>III</i>	-95	ether	95 (83)	47 (<i>R</i>)
	<i>III</i>	-120	ether	95 (80)	43 (<i>R</i>)
	<i>IV</i>	-20	ether	95 (80)	37 (<i>R</i>)
	<i>IV</i>	-78	ether	95 (72)	38 (<i>R</i>)
<i>IIc</i>	<i>III</i>	-20	ether	82 (70)	15 (<i>R</i>)
	<i>III</i>	-78	ether	65 (45)	10 (<i>R</i>)
	<i>IV</i>	-20	ether	80 (65)	21 (<i>S</i>)
	<i>IV</i>	-78	ether	75 (55)	24 (<i>S</i>)

^a Reaction carried out with 0.75 mol. equiv. of benzaldehyde, the conversion determined by gas chromatography, number in parenthesis gives isolated yield of the product; ^b determined on the basis of the following values of specific optical rotations for (*R*)-(+)-*V*, $[\alpha]_{\text{D}}^{20} = +43.1^\circ$ (*c* 7.2, cyclopentane)⁸, for (*R*)-(+)-*VI*, $[\alpha]_{\text{D}}^{20} = +37.6^\circ$ (*c* 3.0, benzene)⁹; ^c reaction with 1.0 mol. equiv. of benzaldehyde.

The results just discussed show that diols *III* and *IV* do not affect enantioselectivity of the studied addition such as does the optically active 1,1'-binaphthyl-2,2'-diol (59% enantiomeric excess). On the other hand, diols *III* and *IV* were found^{1,6} to be of the same or of the higher efficiency when compared to the optically active menthol (23% enantiomeric excess).

EXPERIMENTAL

Melting points were determined on Boetius hot block and temperature data are uncorrected. NMR spectra were measured on Tesla BS-567 and Bruker AM-400 spectrometers in deuteriochloroform, using tetramethylsilane as the internal reference. Optical rotations were measured on Zeiss Opton LEP 2 objective polarimeter, the reading error being 0.01°. Gas chromatographic analyses were made on Chrom 5 instrument provided with a flame-ionisation detector (column filled with 15% Carbowax 20 m on Chromaton N). Standards of racemic alcohols *V* (Koch-Light) and *VI* (prepared by addition of butyllithium to benzaldehyde in ether¹⁰) were distilled before use. Thin layer chromatography was carried out on Silufol UV 254 (produced by Kavalier Votice), flash chromatography¹¹ of the product was performed on Merck 9385 silica gel. Glass ware for reactions in inert atmosphere was dried by flame and allowed to cool to room temperature in a stream of argon. Ether and tetrahydrofuran were dried over sodium and by benzophenone, and these solvents were then distilled prior to using in the reaction. Cooling of the reaction mixture to -120°C was effected with a liquid nitrogen-ether mixture. Chlorotris(2-propoxy)titanium was obtained by the reaction of tetrakis(2-propoxy)titanium¹² with titanium tetrachloride, using the reported procedure⁷. The optical rotation and spectral data agreed well with those reported.

General Procedure for the Addition of Reagents *III* and *IV* to Benzaldehyde⁴

To 1.2 mmol of the optically active alcohol *III* or diol *IV* placed in a flask provided with a septum, and a distillation column topped with rectification head, 40 ml of dry benzene were added through the septum. A total of 10 ml of benzene were immediately distilled off through the distillation column (for final drying of the diols *III* and *IV*), and then 11.2 mmol of chlorotris(2-propoxy)titanium as 1.4M solution in dry pentane were added to the residual mixture. The mixture was then slowly heated to boiling point so that pentane be distilled off, followed by a benzene-isopropanol azeotropic mixture and finally by benzene. By this way, the mixture was condensed to the minimal volume, heating was stopped and the last remains of the solvents were removed in vacuo. The distillation residue was dissolved in 60 ml of dry ether or tetrahydrofuran (see Table I) which were fed into the reaction flask by argon under pressure. The solution so obtained was cooled to 0°C on ice bath and the equivalent amount of methylolithium (1.2M solution in ether) or butyllithium (1.60M solution in hexane) was added through the septum. The mixture was stirred at room temperature for 30 min and then cooled to the temperature given in Table I. Benzaldehyde was added as 0.60M solution in dry ether (see Table I), the mixture was stirred at given temperature for another 30 min and then overnight with slow increase of temperature to ambient one. After addition of 60 ml of 20% solution of potassium fluoride, the aqueous layer was extracted with 3 × 30 ml of ether. The combined organic extracts were dried over anhydrous sodium sulphate and the sample of the mixture was analysed by gas chromatography to determine the benzaldehyde conversion. The mixture was concentrated in vacuo and chromatographed by using the flash chromatography method¹¹ with a pentane-ether (2 : 1) mixture as the eluent. The product so obtained was distilled in vacuo and its purity was

checked by ^1H NMR spectrometry and by gas chromatography. Boiling points of alcohols *V* and *VI* agreed well with reported data (for alcohol *V* ref.¹³ gives b.p. $91^\circ\text{C}/2\text{ kPa}$; for alcohol *VI* ref.¹⁴ reports b.p. $84^\circ\text{C}/133\text{ Pa}$). The optical rotation was compared with reported data (see Table I).

REFERENCES

1. Seebach D., Weidmann B.: *Angew. Chem., Int. Ed.* **22**, 31 (1983).
2. Reetz M. T., Westermann J., Steinbach R., Ostarek R.: *Chem. Ber.* **118**, 1421 (1985).
3. Reetz M. T., Westermann J., Steinbach R., Peter R.: *Chem. Ber.* **118**, 1441 (1985).
4. Seebach D., Beck A. K., Roggo S., Wonnacott A.: *Chem. Ber.* **118**, 3673 (1985).
5. Wang J.-T., Fan X., Feng X., Qian Y.-M.: *Synthesis* **1989**, 291.
6. Olivero A. G., Weidmann B., Seebach D.: *Helv. Chim. Acta* **64**, 2485 (1981).
7. Červinka O., Stružka V.: *Collect. Czech. Chem. Commun.* **55**, 2685 (1990).
8. Yamaguchi S., Mosher H. S.: *J. Org. Chem.* **38**, 1870 (1973).
9. Horeau A., Guetté J. P., Weidmann R.: *Bull. Soc. Chim. Fr.* **1966**, 3513.
10. Hauser C. R., Kantor S. W.: *J. Am. Chem. Soc.* **73**, 1437 (1951).
11. Still W. C., Kahn M., Mitra A.: *J. Org. Chem.* **43**, 2923 (1978).
12. Bradley D. C., Hancock D. C., Wardlaw W.: *J. Chem. Soc.* **1952**, 2773.
13. Červinka O.: *Collect. Czech. Chem. Commun.* **30**, 1684 (1965).
14. Seebach D., Kalinowski H.-O., Bastani B., Crass G., Daum H., Dörr H., DuPreez N. P., Ehrig V., Langer W., Nüssler C., Oei H.-O., Schmidt H.: *Helv. Chim. Acta* **60**, 301 (1977).

Translated by J. Hetflejš.