Tetrahedron: Asymmetry Vol. 1, No. 7, pp. 437-440, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

A NEW REAGENT FOR A VERY SIMPLE AND EFFICIENT DETERMINATION OF ENANTIOMERIC PURITY OF ALCOHOLS BY ^{31}P NMR

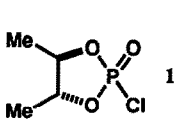
Alexandre Alexakis*, Stephane Mutti, Jean F. Normant and Pierre Mangeney

Laboratoire de Chimie des Organo-Eléments, CNRS UA 473
Université P. et M. Curie, 4, Place Jussieu , F-75252 Paris Cedex 05, France

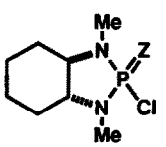
(*Received* 30 *May* 1990)

Abstract : A new reagent is described for the determination of enantiomeric excess of chiral alcohols. This derivatizing agent allows an accurate analysis by ^{31}P NMR . A large array of primary, secondary, and tertiary alcohols, functionalized or not , were successfully tested. Reagent 7 is easy to prepare and reacts alone with the chiral alcohol , at room temperature, eventually directly in the NMR tube.

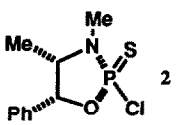
The determination of the enantiomeric purity of a chiral alcohol is routinely performed by NMR techniques through the use of a chiral derivatizing agent (CDA)[1], among which the most common is Mosher's reagent[2]. The so called MTPA derivatives can be analyzed by ^{1}H , ^{13}C and ^{19}F NMR as well as by gas or liquid chromatography. Despite these advantadges, the formation and the analysis of these derivatives are often troublesome and new CDA's were , recently, developped[1]. Noteworthy are reagents **1**[3] and **2**[4] which allow an easy ^{31}P NMR analysis . Although less efficient, reagent **1** is unique in that the phosphorous atom is not chiral , due to the C_2 symmetry of the chiral glycol. Therefore, either retention or inversion at phosphorous during derivatization of an enantiomerically pure alcohol yields a single diastereomer. Our recent work on chiral diamines having, also, a C_2 symmetry taught us that much higher stereodifferentiations are usually attained whenever they can replace a diol. We have thus prepared reagents **3**, **4**, **5** and **6**, and reacted them with 2-butanol in order to compare them with **1** and **2** .



1

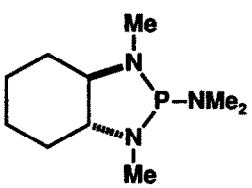


3 Z=O
4 Z=S

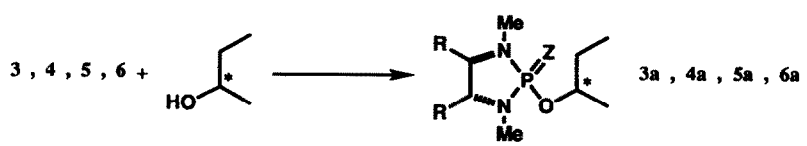


2

5 Z=O
6 Z=S



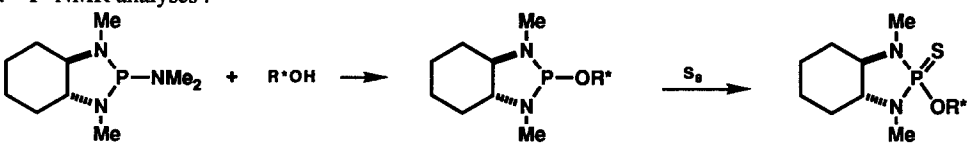
7



As expected, the diastereomeric pairs of derivatives **3a** , **4a** , **5a** and **6a**, obtained from our new reagents, exhibit shift differences twice as good : ^{31}P $\Delta\delta$(ppm) 0.0056 for **1a** , 0.200 for **2a** , 0.337 for **3a** , 0.269 for **4a** , 0.454 for **5a** and 0.336 for **6a**. Despite these interesting results, the presence of two nitrogen atoms on phosphorous decreases its reactivity to a too large extent and, relatively, harsh conditions were needed to prepare **3a**-**6a**[5]. However , turning to the lower oxidation state at phosphorus, we synthesized reagent **7**. This new reagent combines several extraordinary advantages over all previous CDAs .

7 is easily and quantitatively prepared by amine exchange on $P(NMe_2)_3$ with 1,2-N,N'-dimethylamino-cyclohexane[6] in refluxing benzene or toluene. It is conveniently stored, under nitrogen, in these solvents as a 0.2M solution[7]. All of the chiral alcohols **8a-8l**, examined thus far, reacted with **7**[8], at room temperature, within a few hours[9]. *No other co-solvent or co-reagent are needed and the reaction may, eventually, be run in the NMR tube!* Some representative examples of primary, secondary, and even tertiary alcohols are shown in the Table.

The obtained diastereomeric pairs of derivatives **7a-7l** are not stable to TLC or GC analyses, and , although a 10-15% excess of **7** is used, one might be willing to check if the reaction is completed. This is easily accomplished by *in situ* and instantaneous sulfuration of phosphorus with sulfur powder. In fact this transformation is a much simpler way to prepare derivatives of **4** . Derivatives **4a-4l** are air stable and allow not only a TLC and GC but also a ^{31}P NMR analyses .



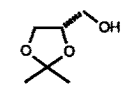
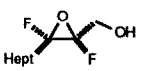
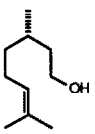
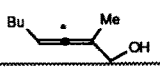
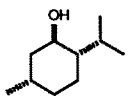
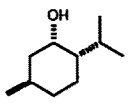
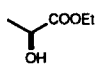
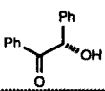
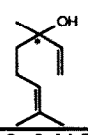
7 **8a-8l** **7a-7l** **4a-4l**

The ^{31}P NMR analysis has the great advantage that no other signals than those of CDA's are present in the spectrum. Thus, derivatives **7a-7l** or **4a-4l** appear as two singlets (P-H decoupled) corresponding to each diastereomer and which are very easy to integrate[10]. The chemical shift of diastereomeric derivatives **7a-7l** are clearly different for each pair of diastereomer. *Moreover the Δδ(ppm) are 10-60 times higher than for previous CDA's 1 or 2 !* Even derivatives **4a-4l** are very cleanly separated in the spectrum : $\Delta\delta$(ppm) are usually twice as good as those with **1** or **2**. We have checked that with chiral racemic **7** and chiral racemic alcohols R*OH **8a-8l** there is no kinetic or preferential formation of one diastereomer over the other one. In all the cases the integration of the NMR signals gave a 50:50 ratio (± 2%).

In many instances we have compared the e.e's found by our method with those obtained via other methods. An excellent agreement occured in all cases. We did not yet explore completely the structural variation allowed for the chiral alcohol R*OH , but, from the examples shown in the table, it seems really very large. Noteworthy are the primary alcohols having an α (**8b** and **8c**) or β (**8d**) stereogenic center, or even an axial chirality (**8e**), which are easily resolved.It should also be pointed out that no racemization occurs during derivatization as examplified with ethyl lactate (**8j**) and hydrobenzoin (**8k**). On the other hand, steric hindrance does not seem to be an obstacle in the derivatization process. Indeed, in contrast to most other CDA's, tertiary alcohols, such as linalool (**8l**), react readily with **7** .

TABLE

7 + 8a-8l ⟶ 7a-7l ⟶ 4a-4l

Alcohol R*OH		^{31}P NMR of 7a-7l Δδ(ppm) (C_6D_6)	^{31}P NMR of 4a-4l Δδ(ppm) (C_6D_6)	Enantiomeric excess %	
				By 7	By other means
	8b	0.337	0.004[a]	76.4	76.2[b] 75.1[c]
	8c	0.673	0.089	78.2	80[d]
	8d	0.538	0.032	36.2	35.9[c]
	8e	0.337	0.125	—	racemic
	8a	3.702	0.269	—	racemic
	8f	4.173	0.269[e]	91.4	92.4[c]
	8g	0.538	0.270	—	racemic
	8h	6.259	0.404[f]	81.2	82.0[c] 79.04[d]
	8i	6.192	0.606	100	100 (commercial product)
	8j	3.365	0.337	35.0	34.9[b] 37.6[d]
	8k	2.759	0.337	≥96.0	100 (commercial product)
	8l	0.606	0	—	racemic

a) Ref 3 : 0 .b) Determined by polarimetry. c) Artificial mixture made by weighting each enantiomer or a pure enantiomer with the racemic material. d) From MTPA derivative. e) Ref. 4: 0.347. f) Ref. 3 : 0.137

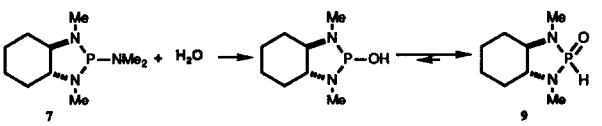
Thus, it seems that the new chiral derivatizing agent (CDA) **7** is very versatile and very efficient. It is easily prepared and it reacts readily with a wide range of alcohols. And finally it provides an accurate measure of e.e's. Preliminary results indicate that it should also be possible to perform GC and HPLC analyses. Work is in progress in this area.

Typical procedure : In a well flame dried small round bottomed flask is placed, under a slow stream of argon, a benzene solution of **7** (550 µl ; 0.2M solution ; 0.11 mmol). Then, R*OH (0.1 mmol) is added and the mixture is stirred (2-15 h) until no Me_2NH is evolved (check with pH paper). A more careful control may be done by taking a small sample and adding it to a suspension of S_8 in dry Et_2O. **4a-4l** are formed instantly and may be checked by TLC or GC. When the formation of **7a-7l** is completed, the containt of the flask is transfered in a 5 mm NMR tube along with 100 µl of C_6D_6, for locking. After this first ^{31}P NMR analysis, S_8 (10mg) is added into the NMR tube, and the spectrum of **4a-4l** is also recorded[11].

***Aknowledgments** : The authors wish to thank Dr R. Burgada for fruitful discussions. The financial help of Rhône-Poulenc company for a grant to S.M. is also greatly appreciated.*

References and notes.

1. Morrisson, J.D.: "*Asymmetric Synthesis*", Vol. 1 , Academic Press, 1983.
2. a) Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.
   b) Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
3. Anderson, R.C.; Shapiro, M.J. *J. Org. Chem.* **1984**, *49*, 1304.
4. Johnson, C.R.; Elliott, R.C.; Penning, T.D. *J. Am. Chem. Soc.* **1984**, *106*, 5019.
5. The reaction is performed with NaH (1.5 eq.) in refluxing THF ; the yield is quantitative after 1-5h.
6. 1,2-N,N'-Dimethylamino-cyclohexane is easily prepared from *trans*-1,2-diamino-cyclohexane by : 1) formation of the di-carbamate (ClCOOEt and aq. NaOH in toluene) and 2) reduction ($LiAlH_4$ in refluxing THF).For more details see: a) Hannessian, S.; Delorme, D.; Beaudouin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. b) Fiorini, M.; Giongo, G.M. *J. Molec. Catal.* **1979**, *5*, 303. *Trans*-1,2-diamino cyclohexane is commercially available in racemic and optically active form (Fluka).
7. Such solutions are stable for weeks at room temperature. During the preparation or handling of **7** it may be hydrolyzed :



7 9

This compound does not react with alcohols but its amount (usually less than 5%) should be taken into account during derivatization. (^{31}P NMR δ(ppm) for **7** and **9** : 117.8 and 19.5 respectively)
8. Burgada, R. *Bull. Soc. Chim. Fr.* **1971**, 136.
9. The only volatile by-product is Me_2NH.
10. The ^{31}P NMR were performed on a JEOL FX90Q spectrometer and the ^{1}H or ^{13}C analyses on a Bruker AC200 apparatus. The range of chemical shifts for **7a-7l** is : ^{31}P δ(ppm) 130-145 ; for **4a-4l** : 79-84 .
11. Excess of **7** is also sulfurated; ^{31}P δ(ppm) : 78.6 .