Carba-Methylephedrine and Carba-*pseudo*-Methylephedrine as Tools for Probing the Role of the Nitrogen Atom of Chiral Amino Alcohols in Asymmetric Synthesis

Dominique Cahard, Laurent Ferron, Jean-Christophe Plaquevent*

Université de Rouen, UPRES-A 6014 et Institut de Recherche en Chimie Organique Fine (IRCOF), 76821 Mont Saint-Aignan Cedex, France

E-mail: Jean-Christophe.Plaquevent @univ-rouen.fr

Received 25 January 1999

Abstract: As part of our on-going program on the use of chiral alkoxides as chiral bases in asymmetric synthesis, we report that carba-ephedrine analogues of N-methylephedrines, with a simple change of bridging nitrogen for CH, served to probe the role of the nitrogen atom in the discrimination of enantiotopic protons by means of the derived alkoxides. We suggest reasons why in the *pseudo* ephedrine series the asymmetric induction is retained while in the ephedrine series the enantioselectivity is strongly affected.

Key words: chiral alkoxide, ephedrine, carba-ephedrine, enantioselective dehydrohalogenation

Chiral amino alcohols are powerful chiral auxiliaries in various asymmetric reactions. For example, their use as chiral ligands to render enantioselective a nucleophilic addition onto a prochiral electrophilic unit is well documented.[1] In this particular case, both heteroatoms (N and O) are involved in the coordination of the metal ion, suggesting that the difunctional character of the auxiliary is probably the main reason for the success in asymmetric synthesis. Another application of chiral amino alcohols has been recently examined by our group, *i.e.* the enantioselective dehydrohalogenation by means of potassium *N*-methylephedrinate.[2] During these studies, we wondered if the dimethylamino moiety of the chiral base was involved in coordination or played only a steric role. This prompted us to explore the induction ability of carba-derivatives in which the nitrogen atom is replaced by a CH group.

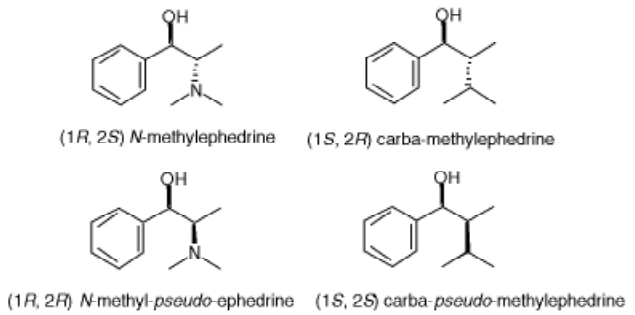
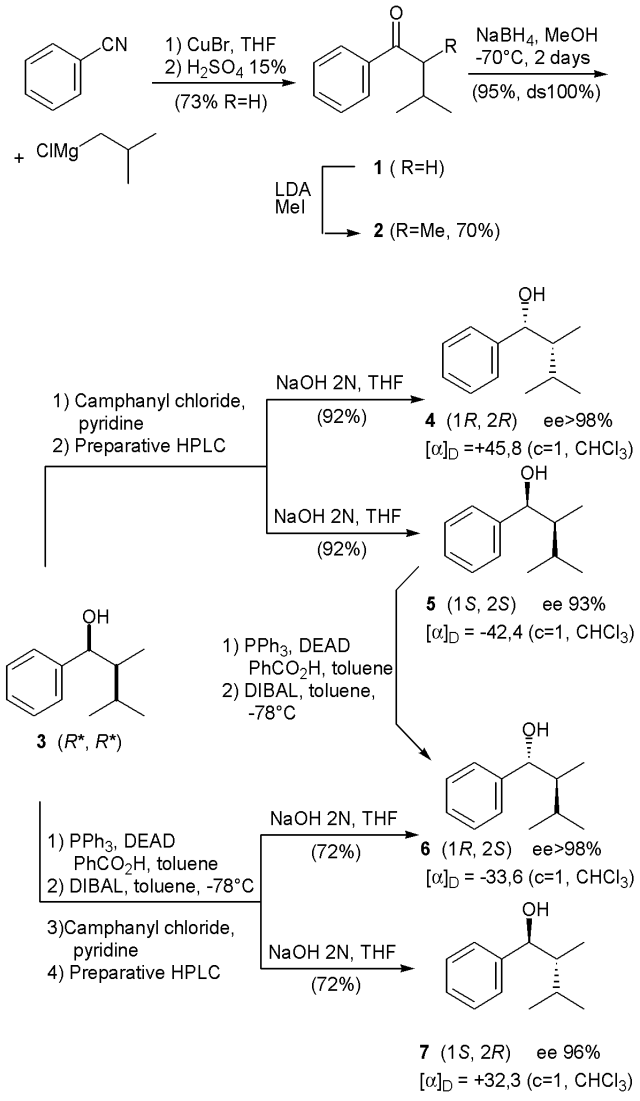


Figure 1

The carbon skeleton of carba-ephedrine[3] was built by addition of 2-methylpropylmagnesium chloride to benzonitrile and subsequent hydrolysis with sulfuric acid followed by methylation of the enolate of ketone **1** by methyl iodide. Reduction of the resulting ketone **2** was first realized at room temperature with sodium borohydride in methanol to afford the alcohol **3** in excellent yield as a diastereomeric mixture (88:12). Lowering the reaction temperature to -70°C allowed the isolation of a single diastereomer. The Felkin-Anh formulation of Cram's rule predicts the (*R**, *R**) configuration for the major stereoi-

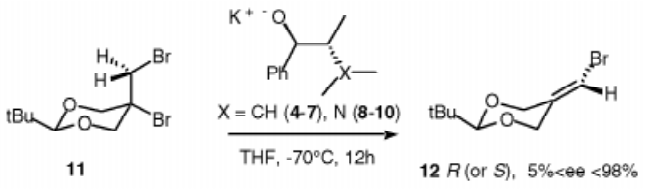


Scheme 1

somer. The racemic mixture was derivatized as its (1*S*)-(-)-camphanic ester and separated by preparative HPLC. Then the diastereoisomeric esters were saponified in aqueous sodium hydroxide to generate the pure enantiomers (1*R*, 2*R*) and (1*S*, 2*S*) carba-*pseudo*-methylephedrine **4** and **5**. The absolute configuration of each enantiomer was unambiguously established by single crystal X-ray analysis of the camphanic esters.[4]

In order to obtain the two enantiomers **6** and **7** of the carba-methylephedrine one needs the inversion of one of the stereogenic centers of the *pseudo*-derivative. Racemic carba-*pseudo*-methylephedrine **3** was subjected to Mitsunobu conditions to afford esters in which the original configuration at C-1 was inverted.[5] Reduction (DIBAL) and separation of the enantiomers by derivatization and preparative HPLC as previously described gave pure (1*R*, 2*S*) and (1*S*, 2*R*) enantiomers of carba-methylephedrine **6** and **7**. As in the carba-*pseudo*-methylephedrine series, X-ray analysis of a single crystal of camphanic ester gave access to the absolute configuration of the compounds.[4] In order to confirm X-ray analysis, enantiomerically pure (1*S*, 2*S*) carba-*pseudo*-methylephedrine **5** was subjected to the Mitsunobu inversion and saponification to give pure (1*R*, 2*S*) carba-methylephedrine **6** with specific rotation data allowing the assignment of the absolute configuration of each enantiomer.

In order to probe the role of the nitrogen atom of potassium ephedrinates, we have carried out enantioselective dehydrohalogenation of prochiral dibrominated dioxanes **11** using alkoxides obtained either from the amino alcohol or the carba derivatives. Table 1 shows the asymmetric induction obtained in both cases.



Scheme 2

The major and striking feature of these data is the opposite behaviour in the ephedrine and *pseudo*-ephedrine series. While in the latter case, the replacement of the nitrogen atom by a CH moiety does not change significantly the asymmetric induction (and even enhances it to a small extent. Table 1, entries 1, 2, 5, 6), one can observe that a dramatic decrease of enantiomeric excess is obtained in the former case (Table 1, entries 3, 4, 7). Thus a clear conclusion is that carbon cannot replace nitrogen without a loss of enantioselectivity in the ephedrine series.

As usually assumed, one can expect that the more rigid the chiral auxiliary is, the more efficient the asymmetric induction. Thus, one possible explanation for the differences discussed above could be the ability of the alkoxide to

Table 1 : Enantioselective Dehydrohalogenation of Prochiral Dioxane *trans* **11** with Potassium Alkoxides (2.5 equiv, 12 h, -70°C).

entry	chiral alcohol	ee%	conf	conv%	yield%
1	(1*R*, 2*R*) carba-*pseudo*-methylephedrine **4**	45	*R*	98	82
2	(1*S*, 2*S*) carba-*pseudo*-methylephedrine **5**	38	*S*	95	81
3	(1*R*, 2*S*) carba-methylephedrine **6**	5	*S*	94	79
4	(1*S*, 2*R*) carba-methylephedrine **7**	7	*R*	95	81
	chiral amino alcohol	ee%	conf	conv%	yield%
5	(1*R*, 2*R*) *N*-methyl-*pseudo*-ephedrine **8**	30	*S*	80	71
6	(1*S*, 2*S*) *N*-methyl-*pseudo*-ephedrine **9**	32	*R*	85	74
7	(1*R*, 2*S*) *N*-methylephedrine **10**	90	*R*	93	68

coordinate the potassium ion. One can propose that this coordination leads the alkoxide to adopt an eclipsed conformation due to the ionic radius of the metallic ion. This eclipsed conformation is sterically disfavored in the *pseudo*-ephedrine series, with respect to the ephedrine series. The chelated alkoxide would be responsible of asymmetric induction, which consequently would be inferior in the case of the *pseudo*-ephedrine series.

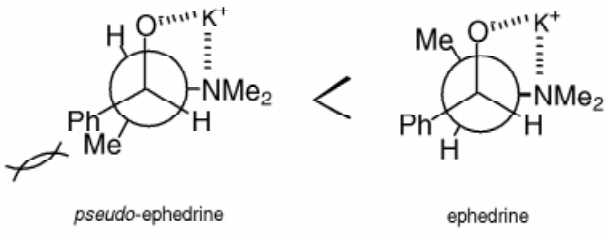


Figure 2

Replacement of the nitrogen by a CH moiety would not change the conformation in the *pseudo*-ephedrine series, thus giving similar ee's. On the other hand, the same modification would not allow coordination in the ephedrine series; this would be the reason for the dramatic decrease in enantioselection.

In conclusion, the present study describes the synthesis and the determination of the absolute configuration of the four stereoisomers of carba-methylephedrine. Their use in asymmetric synthesis makes it possible to readily probe the role of the nitrogen atom.[6]

Acknowledgement

The authors thank Dr L. Toupet (University of Rennes, France) for the determination of crystal structures.

References and Notes

(1) See for examples : Gawley, R.E.; Aube, J. *Principles of Asymmetric Synthesis*, Pergamon, Oxford **1996**.
(2) Vadecard, J.; Plaquevent, J-C.; Duhamel, L.; Duhamel, P. *J. Chem. Soc., Chem. Commun*., **1993**, 116. Vadecard, J.; Plaquevent, J-C.; Duhamel, L.; Duhamel, P.; Toupet, L. *J. Org. Chem.* **1994**, *59*, 2285. Amadji, M.; Vadecard, J.; Plaquevent, J-C.; Duhamel, L.; Duhamel, P. *J. Am. Chem. Soc*., **1996**, *118*, 12483. Amadji, M.; Vadecard, J.; Cahard, D.; Duhamel, L.; Duhamel, P.; Plaquevent, J-C. *J. Org. Chem*., **1998**, *63*, 5541.
(3) This trivial nomenclature is preferred to the systematic one to readily allow a direct comparison with the amino alcohol series.
(4) The full details of the X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC 113910).
(5) Mitsunobu, O. *Synthesis* **1981**, 1.
(6) For related studies using chiral alkoxides as Brønsted bases, see: Jones, C.D.; Simpkins, N.S.; Giblin, G.M.P. *Tetrahedron Lett.* **1998**, *39*, 1023. Hodgson, D.M.; Gibbs, A.R. *Tetrahedron Asymmetry*, **1996**, *7*, 407. Kumamoto, T.; Aoki, S.; Nakajima, M.; Koga, K. *Tetrahedron Asymmetry*, **1994**, *5*, 1431. Milne, D.; Murphy, P.J. *J. Chem. Soc., Chem. Commun*., **1993**, 884. Willems, J.G.H.; De Vries, J.G.; Nolte, R.J.M.; Zwanenburg, B. *Tetrahedron Lett*., **1995**, *36*, 3917.

Article Identifier:
1437-2096,E;1999,0,S1,0960,0962,ftx,en;W03299ST.pdf