Pergamon

Eur. Polym. J. Vol. 30, No. 3, pp. 395–398, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0014-3057/94 \$6.00 + 0.00

ASYMMETRIC REDUCTION OF ACETOPHENONE WITH CHIRAL POLYMERIC REAGENTS: SUPPORTED SODIUM BOROHYDRIDE ON CHIRAL QUATERNARY AMMONIUM BINDED TO A POLYMER

K. ADJIDJONOU and C. CAZE*
Laboratoire de Chimie Macromoléculaire URA CNRS 351, Université des Sciences
et Technologies de Lille, 59655 Villeneuve d'Ascq Cedex, France

(Received 22 February 1993; accepted 18 May 1993)

Abstract—We have shown the possibility of enantiomeric induction in the reduction of prochiral ketones by $NaBH_4$ supported on a chiral support. The supports involve polymers (porous or gel type) containing chiral quaternary ammonium groups in the side chain. Two chemical ways were tested to obtain these types of support, chemical modification of styrene divinylbenzene copolymers [polymers supported chiral alcohol quaternary ammonium salts (type 1)] or 4-vinylpyridine divinylbenzene copolymers [polymers supported 1,2,3,4-tetrahydro-*N*,*N*-dialkyl pyridinium salts (type 2)]. The reduction with type 1 copolymers gives good yield and enantiomeric excess (ee) (50%), the kinetic of the reduction is governed by the accessibility of the reactant then by the texture of the support and the presence of a spacer arm. The reduction with type 2 copolymers gives also good results (yield 70%, ee 56% in the best case). The kinetic is also governed by site accessibility, on the contrary ee is function only of the chemical aspect of the chiral centre.

INTRODUCTION

Resin supported quaternary ammonium groups can be used as borohydride exchange resins and such polymeric reagent have been developed since 1977 [1]. They can be used for solvent purification, generation of volatile metal hydrides and in the reduction of metal ion and some aldehydes [2]. Supported borohydride also exhibits high chemioselectivity in the reduction of ketones [3] and α–β unsaturated carbonyl compounds to the corresponding unsaturated alcohols [3, 4]. The influence on the reaction of the texture of the support and the introduction of a spacer arm have been also tested [5, 7]. Chiral quaternary ammoniums binded on a polymeric support have been used as phase transfer catalysts in the reduction of prochiral ketone by $NaBH_4$ [8, 9]. Only little asymmetric synthesis was induced. The aim of this paper is to examine the possibility to induce asymmetric reduction of prochiral aromatic ketones by $NaBH_4$ supported on gel type or porous polymers containing chiral quaternary ammonium groups in the side chain.

EXPERIMENTAL PROCEDURES

Polymeric materials

Synthesis of polymers supported chiral 1,2,3,4-tetrahydro-N,N-dialkyl pyridinium salts. The preparation of the polymeric reagent involved a three step polymer reaction starting from 4-vinylpyridine–styrene–divinylbenzene crosslinked polymer which is depicted in the Scheme 1.

The initial 4-vinylpyridine–styrene–divinylbenzene porous polymers were synthesized by suspension radical polymerization in presence of heptane as porogenic agent [10]. The first step leads to the quaternized polymer [11]: the reaction was performed in tetramethylene sulphone (1 g of polymer was swollen in 100 cm^3 of tetramethylene sulphone for 3 hr, then the methylene iodide was added with a molar ratio methylene iodide/pyridine groups = 2) at 60° during 72 hr. The polymer beads were then filtered off and thoroughly washed with methanol and extracted for 24 hr with methanol in a Soxhlet. The i.r. spectra show the appearance of the characteristic band of $=N=^+$ at 1640 cm^{-1}.

The 1,2,3,4-tetrahydro-*N*-methyl pyridine polymers were prepared as followed [12]: the polymer beads were stirred with ethanol for 1 hr at room temperature, then an excess (20%) of an ethanolic solution of sodium borohydride was added. The reaction was performed for 24 hr then the polymer beads were filtered off and thoroughly washed successively with water and acetone then extracted for 24 hr with methanol in a Soxhlet. The i.r. spectra show the disappearance of the band at 1640 cm^{-1}.

The last step corresponding to the quaternization of the 1,2,3,4-tetrahydro-*N*-methyl pyridine polymers with (*S*)-(+)-1-bromo-2-methyl butane or (*S*)-(−)-3-chloro-1-phenyl-1-propanol (Aldrich products) was performed as for quaternization by methylene iodide.

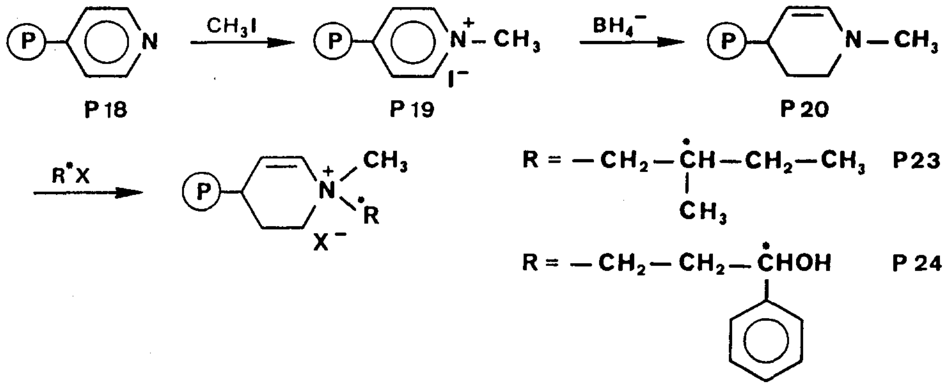
Synthesis of chiral alcohol quaternary ammonium supported polymers. The preparation of the polymeric reagent involved a three step polymer reaction starting from styrene–divinylbenzene crosslinked polymer which is depicted in the Scheme 2.

The initial styrene–divinylbenzene porous polymers were synthesized by suspension radical polymerization in presence of heptane as porogenic agent [13].

The first step corresponding to a Friedel–Crafts acylation leads to the chloroacetylated polymer, the reaction was performed as described previously [14]. The polymers were characterized by i.r. spectroscopy (they show the characteristic band of C=O at 1680 cm^{-1}) and by elementary analysis (Cl content were report in Table 3).

---

*To whom all correspondence should be addressed.



Scheme 1

Enantioselective reduction of the keto group of α-chloroacetophenone by β-chloro-diisopinocamphenyl-borane (Ipc2 BCl) [15, 16] gives good results, extension of this reaction to polymer supported chloroacetyl groups have been made [17] and the enantiomeric excess observed is at least 90%. The reduction reaction was performed according to the literature [18].

For the last step, to 5 g of supported chloro-alcohol in dimethoxymethane (50 cm^3), at 40°, was added 12 ml of an aqueous solution of trimethylamine (250 g/l) (time reaction: 5 hr). The polymer beads were then filtered off and thoroughly washed with water and HCl in solution and then extracted for 24 hr with dimethoxymethane in a Soxhlet.

Texture characterization

The pore volumes and surface areas of the dry beads were respectively measured using a Carlo Erba 800 mercury porosimeter and by nitrogen adsorption following the BET method [19]. The data for the porous polymers is summarized in Table 1, the pore volume integral distribution curves are shown in Fig. 1 (4-vinylpyridine based support) and Fig. 2 (styrene based support).

Chemical analyses

Chlorine, oxygen, nitrogen and water contents were determined by elementary analysis (CNRS microanalysis service of Vernaison). Borohydride content was calculated from the hydrogen released by reaction with an excess of chlorhydric acid in a suitable and hermetic apparatus. Infrared spectra of KBr pellets of the carefully ground polymer beads were recorded on a FT-IR Nicolet spectrophotometer.

General reducing procedure

(i) Cl^-/BH_4^- exchange. At 1 g of polymer beads was added 30 cm^3 of a solution of sodium borohydride in water (1/1.2 ratio), then the suspension was stirred for 2 hr at room temperature. The polymer beads were filtered off, washed with water to eliminate the sodium borohydride in excess and then dried in vacuum at 60° for 2 hr [20]. The amount of BH_4^- fixed was determined by measuring the volume of hydrogen obtained by acidic treatment of the resin.

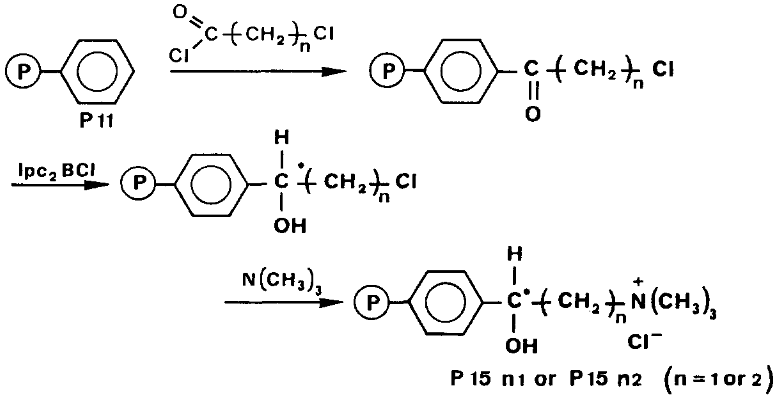
(ii) Reduction reaction. Supported borohydride (1 mmol) was stirred with 20 cm^3 of ethanol for 15 min at 20°, then acetophenone (dissolved in THF) in a 1/1 ratio was added and the reaction was performed for 20 hr.

(iii) Determination of yield and enantiomeric excess. The extent of the reaction was obtained by ^1H NMR and the enantiomeric excess was determined from optical rotation [α]D,23 = −52.5° [21] [Polartronic I (Haensch-Schmidt)] and confirmed by gas chromatography performed on a Chrompack CP 9000 instrument (temperature: injection port 250°, FID detector 260°, column 115°), with a WCOT CP-Cyclodextrin-β-2,3,6-M-19 column.

RESULTS AND DISCUSSION

(i) Polymer modification

(a) 4-Vinylpyridine copolymers. The low yields observed for the quaternization by methyl iodide of the initial 4 VP–DVB and for both porous and gel type polymers (Table 2) are due to a neighbouring



Scheme 2

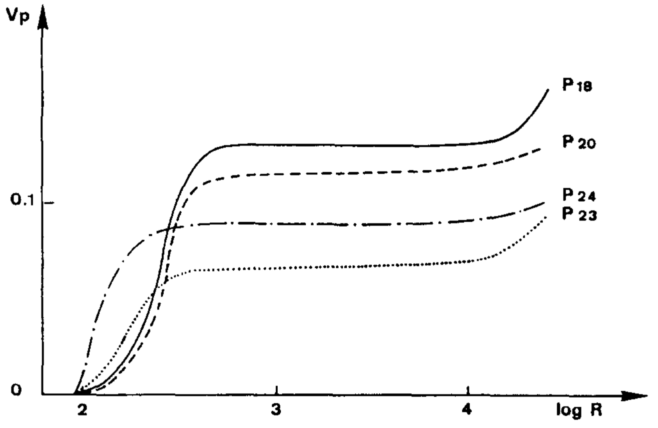


Fig. 1. Pore volume integral distribution curves for 4-vinylpyridine based support (characteristics are summarized in Table 1).

effect [22] of course less sensible for the porous system where we have only 30% (in weight) of 4 VP. The reduction of the quaternary pyridinium salt in the 1,2,3,4-tetrahydro-*N*-methyl pyridine form occurs with both porous and gel type polymers with a good yield (Table 2). The yield of the last step, quaternization of the 1,2,3,4-tetrahydro-*N*-methyl pyridine groups, depends on the alkyl halide used. The low yield observed for (*S*)-(−)-3-chloro-1-phenyl-1-propanol in comparison with (*S*)-(+)-1-bromo-2-methyl butane can be due to (i) the steric hindrance (ii) the greater reactivity, for this type of reaction, of bromide halide than chloride halide [23]. For porous polymers these chemical modifications do not affect the general morphology of the support, we only see a decrease of the porous volume (Table 1 and Fig. 1).

(b) Styrene copolymers. As we can see in Table 1 and Fig. 2 the starting polymer P1(m) has a texture different from polymer P3(m). We have a high porous volume and a small specific area therefore the average pore radii for P1(m) is greater than for P3(m). The chemical modification induces a small decrease in the pore value but does not affect the porous texture of the beads (Table 1 and Fig. 2). We have tried to determine the ee obtained for the chiral reduction of the chloro acetyl group of the support, by solid ^{13}C NMR [17], without success. For the same reaction the literature [17] give 91% for ee. The yield of quaternization of the chloro methyl group by methylene iodide is not high (Table 3).

(ii) Asymmetric reductions of acetophenone

(a) 4-Vinyl pyridine based supports: For porous support, the yield of reduction seems to be independent of the texture and of the chemical nature of the alkyl group (Table 4). Gel type polymers [P6(g) and P7(g)] give a better yield than macroporous polymers [P6(m) and P7(m)] probably because the kinetics is governed by site accessibility (generally macroporous texture present a lower site accessibility [24]). At the opposite, the enantiomeric excess is not a function of the texture of the support but essentially a function

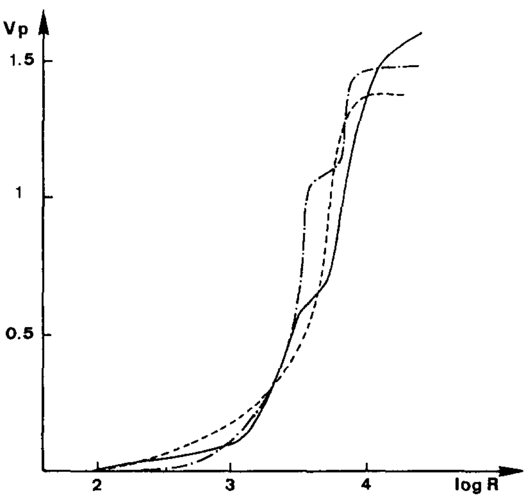


Fig. 2. Pore volume integral distribution curves for styrene based support (characteristics are summarized in Table 1).

Table 1. Textural characteristics of macroporous polymers [(m) refers to macroporous polymers]

Polymer designation*	Wt% DVB†	Wt% porogen‡	Surface area of beads (m^2/g)§	Pore volume of beads (cm^3/g)¶
	Styrene based copolymers			
P1(m)	20	60	15	1.60
P2n1(m)	20	60	13	1.48
P2n2(m)	20	60	14	1.37
	4-Vinylpyridine based copolymers			
P3(m)	35	25	145	0.13
P5(m)	35	25	139	0.12
P6(m)	35	25	137	0.07
P7(m)	35	25	125	0.09

*P1(m), initial ST–DVB copolymers; P3(m), initial DVB–4VP copolymers (30% of 4 VP); P5(m), intermediate 1,2,3,4-tetrahydro-*N*-methyl pyridine polymers; P6(m), 1,2,3,4-tetrahydro-*N*-methyl-*N*-(S)-(+)-2-methyl-butyl pyridinium bromide supported polymer; P7(m), 1,2,3,4-tetrahydro-*N*-methyl-*N*-(S)-(−)-3-phenyl-1-propanol pyridinium chloride supported polymer.

†DVB = divinylbenzene. A commercial product was used consisting of 15% *p*-DVB, 35% *m*-DVB, 15% *p*-ethylstyrene and 35% *m*-ethylstyrene. The % of DVB given is exprimed in pure DVB.

‡Heptane.

§Measured by nitrogen adsorption following the BET method.

¶Obtained by mercury penetration.

Table 2. Chemical characteristics of chiral pyridinium polymers obtained by chemical modification of 4VP–DVB copolymers

Polymer designation*	Amount of various elements in polymeric products (mmol · g^{-1}) I	Br	Cl	Reaction yield (%)
P4(m)‡	1.26			43
P5(m)	0.12			90
P6(m)		0.85		75
P7(m)			0.38	33
P4(g)†	2.57			32
P5(g)	0.13			95
P6(g)		2.06		84
P7(g)			0.60	25

*For textural characteristics of porous polymers, see Table 1; N content of polymer precurser, P3(m): 2.9 mmol · g^{-1}, P3(g): 8.0 mmol · g^{-1}.

†(g) refers to gel type polymers (2% DVB).

‡P4 refers to initial DVB–4VP copolymer P3 quaternized with methyl iodide.

Table 3. Chemical characteristics of chiral pyridinium polymers obtained by chemical modification of ST–DVB copolymers

Polymer designation	Cl (mmol · g^{-1})	N (mmol · g^{-1})	Yield of quaternization
P2n1(m)	1.71	0.80	48
P2n2(m)	1.29	0.40	32
P2n1(g)	1.08	0.42	40
P2n2(g)	0.91	0.31	35

Table 4. Reduction of acetophenone by supported $NaBH_4$

Polymer designation	Yield of reduction* (%)	ee (%)
4-Vinylpyridine based copolymers		
P6(m)	58	21
P7(m)	52	49
P6(g)	72	28
P7(g)	71	56
Styrene based copolymers		
P2n1(m)	85	23
P2n2(m)	95	21
P2n1(g)	80	48
P2n2(g)	63	52

*After 20 hr of reduction, ratio $NaBH_4/CO = 1/1$, solvent: ethanol, $T = 20°$.

of the chemical nature of the alkyl chain (Table 4). For polymer P7 the hydroxy group can interact with the ketone therefore reduces the mobility of the transition state of the reduction and then increases the ee value. The ee values are interesting and the best value obtained with polymer P7(g) is 56%.

(b) Reduction by styrene based support: The enantiomeric reduction of the ketone by supported $NaBH_4$ on this type of support occurs with a good yield (Table 4), better for the porous than for the gel type polymers. This is due to the particular texture of the porous system [7]. The introduction of a spacer (a methylene group between the chiral centre and the quaternary ammonium group) increases or decreases the accessibility of the reactant respectively for gel or porous support as described previously [7]. Ee (Table 4) obtained are lower than these observed for 4-vinylpyridine support but for the best case >50%. They depend on the texture of the support (gel type support are better) but not on the presence of the spacer arm.

CONCLUSIONS

We have shown the possibility of enantiomeric induction for the reduction of prochiral ketones by $NaBH_4$ supported on a chiral support. The reduction with chiral alcohol quaternary ammonium supported polymers gives good yield (95%) and ee (50%). The yield, so in our experimental conditions the kinetic of the reduction, is governed by the accessibility of the reactant then by the texture of the support and the presence of a spacer arm. Ee depends only on the texture of the support, gel type polymers give the best results, and it is not affected by the introduction of a spacer arm. The reduction with polymers supported chiral 1,2,3,4-tetrahydro-*N*,*N*-dialkyl pyridinium salts gives also good results (yield 70%, ee 56% in the best case). The kinetic is also governed by site accessibility, on the contrary ee is only function of the chemical aspect of the chiral centre. We tried: (i) to improve these systems, (ii) to obtain these type of supports by best chemical ways.

REFERENCES

1. H. W. Gibson and F. C. Baily. *J. Chem. Soc. Chem. Commun.* 815 (1977).
2. R. S. Hedge. *U.S. Patent*, 41,07,099 (1978).
3. M. Y. Nung, B. P. Kyoung and S. G. Young. *Tetrahedron Lett.* **24**, 5367 (1983).
4. A. R. Sande, M. H. Jagadale, R. B. Mane and M. M. Salunkhe. *Tetrahedron Lett.* **25**, 3501 (1984).
5. M. Salunkhe. Private communication.
6. M. Bacquet, M. Salunkhe and C. Caze. *React. Polym.* **18**, 185 (1992).
7. S. Wali Alami and C. Caze. *Eur. Polym. J.* **23**, 883 (1987).
8. B. Boyer, G. Lamaty, J. P. Roque and J. Sofolo. *Nouv. J. Chim.* **10**, 553 (1986).
9. S. D'Antone, M. Penco and R. Solaro. *React. Polym.* **3**, 107 (1985).
10. M. C. Maillard-Terrier and C. Caze. *Eur. Polym. J.* **20**, 113 (1984).
11. R. M. Fuoss, M. Watanabe and B. D. Coleman. *J. Polym. Sci.* **48**, 5 (1960).
12. M. F. Semmelhack, R. D. Stauffer and A. Yamashita. *J. Org. Chem.* **42**, 3180 (1977).
13. H. Jacobelli, M. Bartholin and A. Guyot. *J. appl. Polym. Sci.* **23**, 927 (1979).
14. C. Caze and P. Hodge. *Makromolek. Chem.* **191**, 1633 (1990).
15. J. Chandrasekharan, P. V. Ramachandran and H. C. Brown. *J. Org. Chem.* **52**, 5406 (1987).
16. H. C. Brown, J. Chandrasekharan and P. V. Ramachandran. *J. Am. chem. Soc.* **110**, 1539 (1988).
17. C. Moberg and L. Rakos. *React. Polym.* **15**, 25 (1991).
18. T. Antonsson, U. Jacobsson, C. Moberg and L. Rakos. *J. Org. Chem.* **54**, 1191 (1989).
19. S. Brunauer, P. Emmet and E. Teller. *J. Am. Chem. Soc.* **60**, 309 (1938).
20. N. Umino, T. Iwakuma and N. Itoh. *Chem. Pharm. Bull.* **27**, 1497 (1980).
21. U. Nagai, T. Shisdo, R. Chiba and H. Mitsuhashi. *Tetrahedron* **21**, 1701 (1965).
22. R. M. Fuoss, M. Watanabe and B. D. Coleman. *J. Polym. Sci.* **38**, 5 (1960).
23. R. M. Fuoss and B. D. Coleman. *J. Am. chem. Soc.* **77**, 5472 (1955).
24. S. Wali Alami and C. Caze. *Eur. Polym. J.* **11**, 883 (1987).