

Polymer supported enantioselective reactions. II. α -Methylation of cyclohexanone¹

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COLIN R. MCARTHUR, PAUL M. WORSTER, JI-LONG JIANG, and CLIFFORD C. LEZNOFF. *Can. J. Chem.* **60**, 1836 (1982).

Insoluble cross-linked copolymers of styrene and 1% divinylbenzene with covalently bonded (*S*)-2-aminoalkoxy groups were used in the enantioselective α -methylation of cyclohexanone through the corresponding imines. Enantiomeric excesses of 94% of (*S*)-2-methylcyclohexanone were observed on methylation at 20°C. An analogous optically active 2-aminoalkyl benzyl ether, under otherwise identical conditions, resulted in a lower enantiomeric excess (49%) with selectivity approaching that of the polymer only at -78°C.

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On a utilisé des copolymères de styrène et divinylbenzène réticulés à 1% et portant des groupes (*S*)-amino-2 alkoxy liés par des liaisons covalentes lors pour l' α méthylation énantiosélective de la cyclohexanone par l'intermédiaire des imines correspondantes. On a observé un excès énantiomérique de 94% de (*S*)-méthyl-2 cyclohexanone lors de la méthylation à 20°C. Un éther amino-2 alkyl benzylique analogue optiquement actif conduit dans des conditions identiques, à un excès énantiomérique de seulement 49%, la sélectivité ne se rapproche de celle du polymère qu'à -78°C.

[Traduit par le journal]

Introduction

A number of advantages over the use of the solution phase have been identified in the use of solid, insoluble polymers as media for certain operations in synthesis. Considerable documentation exists on the usefulness of the property of insolubility of such media for facilitating separations and allowing for automated processes. In addition, other properties of these systems such as the decreased interaction between reactant moieties, a phenomenon which simulates high dilution, have been recognized (for reviews see ref. 1).

Speculation that a decrease in translational and conformational mobilities of moieties covalently bonded to cross-linked polymers, relative to their solution analogues, might enhance stereoselectivities of certain types of reactions led us to investigate the applicability of this type of medium to asymmetric syntheses (2). The situation might bear some general resemblance to that at the reactive sites of some enzymes. In the only research of which we are aware, prior to our work, into an example of an asymmetric synthesis on a polymer support, it was suggested that enhancement of the enantioselectivity observed relative to an analogous reaction in solution may result from conformational rigidity in the cross-linked polymer (3).

Enantioselectivities in solution may be considerably influenced by temperature (4). In particular,

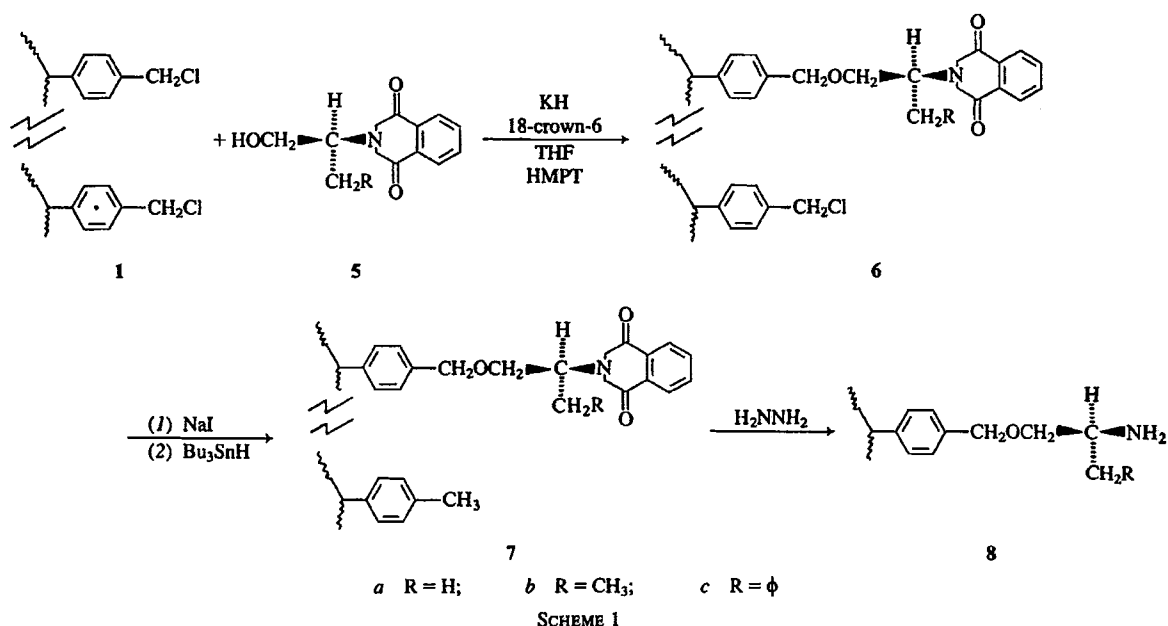
in the α -methylation of the metaloenamine formed by reaction of isopropylmagnesium bromide with the imine derived from cyclohexanone and (*R*)-1-butoxy-2-aminobutane, the enantiomeric excess of (*R*)-2-methylcyclohexanone formed after hydrolysis was 81% at -78°C, but only 20% at 65°C (5). In similar examples of the enantioselective alkylation of cyclohexanone imines, alkylation conditions routinely include temperatures of -98 and -78°C (6). Additional examples have been cited (7).

It seemed conceivable that the use of polymeric media might allow highly enantioselective reactions to occur at ambient temperatures, perhaps with concomitant increases in reaction rates relative to those observed in solution at low temperatures. Further, the separation of the optically active product after cleavage from the asymmetric induction sites on the polymer would be accomplished completely and easily by a simple filtration. At the same time, the insoluble polymer would be easily recovered and would be expected to be reusable.

In a preliminary article (2), we reported the use of a Merrifield polymer (1) bonded through ether linkages to (*S*)-2-amino-1-propyl groups. Condensation with cyclohexanone to give the corresponding polymer-bound ketimine followed by metalation, alkylation, and hydrolysis afforded optically active 2-alkylcyclohexanones in high enantiomeric excesses as well as high chemical yields and purities. In this paper we present the details of these and related studies on the enantioselective α -methylation of cyclohexanone using polymer-bound chiral amines.

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Results and discussion

Bonding (*S*)-2-aminoalkoxy groups to polystyrene
 (*S*)-2-Aminopropanol (2), (*S*)-2-aminobutanol (3), and (*S*)-2-amino-3-phenylpropanol (4) were converted, to prevent *N*-substitution by the polymer, to their corresponding *N*-phthaloyl derivatives (5a, 5b, and 5c respectively) by reaction with *N*-(ethoxycarbonyl)phthalimide (8). The corresponding potassium alkoxides reacted with 1 to give the corresponding (*S*)-2-phthalimidoalkoxy-methylated chloromethylated polystyrenes (6a, 6b, and 6c respectively) as outlined in Scheme 1. The loadings of unreacted chloromethyl groups in 6 were determined quantitatively by reaction with pyridine, followed by analysis of the solution phase for chloride (9). These chloromethyl groups would be expected to become involved in subsequent steps in the reaction sequence to cause decreases in enantioselectivities. Such expectations were borne out experimentally as will be described.

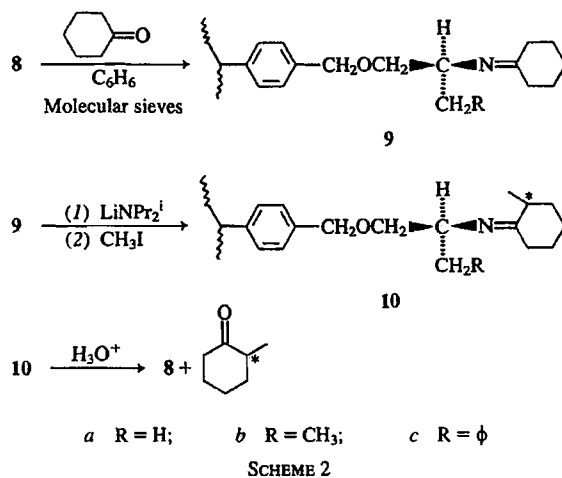
Accordingly, the chloromethyl groups of 6 were converted to unreactive methyl groups by treatment with sodium iodide and then with tributyltin hydride. The resulting polymers (7) upon hydrazinolysis afforded polystyrene derivatives functionalized only with (*S*)-2-aminoalkoxy groups (8).

Enantioselective methylation of cyclohexanone using polymers 8

Condensation of polymers 8 with cyclohexanone gave the corresponding ketimines (9) (Scheme 2).

The loadings of the ketimine functions on the polymers were in the range of 0.5 to 0.6 mmol/g as determined by hydrolysis to regenerate cyclohexanone and quantitative analysis of the solution phase by gas chromatography.³

Methylation of polymers 9 by reaction of the corresponding lithioenamines with iodomethane afforded the corresponding 2-(2-methylcyclohexyl-



³Commercially available Merrifield polymer, used in numerous other reported syntheses, affords loadings in this range. Such loadings would be expected to minimize the potential complication of site to site interactions in interpreting results, a factor which we wished to avoid at this stage of our studies.

TABLE 1. Enantioselective α -methylations of polymeric imines, **9**, of cyclohexanone at 20°C

Polymer	Loading of imine (mmol/g)	Yield of 2-methylcyclohexanones (%)	Enantiomeric excess* of (<i>S</i>)-2-methylcyclohexanone (%)
9a	0.57	32.5	92
9b	0.56	86	94
9c	0.54	87	94

*Based on optical rotation of pure (*R*)-2-methylcyclohexanone at -16.4°C (*S*).

TABLE 2. Comparison of **6c** and **7c** in subsequent enantioselectivities

Parameter	Starting polymer	
	6c	7c
ClCH ₂ loading (mmol/g)	0.4	0
Imine loading (mmol/g)	0.84	0.54
Yield of 2-methylcyclohexanones (%)	46	87
Enantiomeric excess of (<i>S</i>)-2-methylcyclohexanone (%)	32	94

idene)aminoalkoxymethylated polymers (**10**) which, on hydrolysis released (*R*)- and (*S*)-2-methylcyclohexanone to the solution phase. The predominant product under all of the variations in conditions studied (temperature, and the structure of R) was (*S*)-2-methylcyclohexanone⁴ in enantiomeric excesses of >90%.

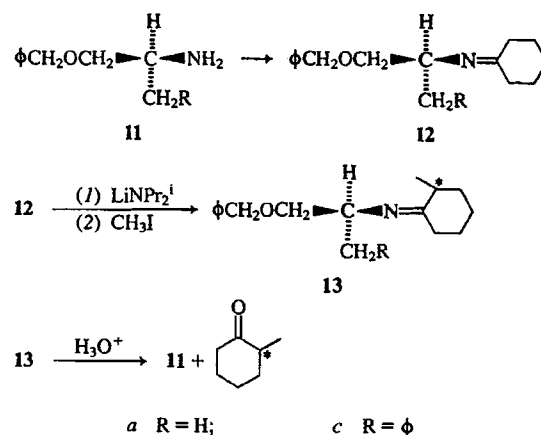
Results of methylation at ambient temperature (20°C) are shown in Table 1. In the methylation of **9a** and subsequent hydrolysis, the chemical yield was much lower than was the case with **9b** and **9c** although, in all three systems, enantioselectivities appear in the same range (>90%).

The polymeric derivative **6c** with chloro groups remaining after reaction of **1** with **5c** was treated in the same sequence as that described above for polymers **7**. The 2-methylcyclohexanones were produced with the (*S*)-enantiomer in only 32% enantiomeric excess. The results are tabulated in Table 2. It would appear that the chloromethyl groups in **6c** reacted in the hydrazinolysis step, and that the resulting hydrazyl groups formed polymer-bound cyclohexanone hydrazone functions which could methylate only non-enantioselectively.

Comparison of polymer-bound systems with analogous systems in solution

For quantitative comparison of asymmetric in-

⁴In all experiments, the identity of the 2-methylcyclohexanone produced was confirmed by comparison with an authentic sample through the use of ir, nmr, and vpc mass spectroscopy. The absence of polymethylated derivatives such as 2,6-dimethyl- and 2,2,6-trimethylcyclohexanone was confirmed by comparison of the vpc using authentic samples.



SCHEME 3

duction in the polymeric systems with analogous systems in solution, (*S*)-2-aminopropyl benzyl ether (**11a**) and (*S*)-2-amino-3-phenylpropyl benzyl ether (**11c**) were prepared. Conversion to the corresponding cyclohexanone imines (**12**) and then to their 2-methyl derivatives (**13**), followed by hydrolysis, afforded product mixtures from which the 2-methylcyclohexanones could be separated (Scheme 3). The separation, of course, was not as conveniently affected as was the case using the polymeric system.

Much lower enantioselectivities (~50%) were observed from the methylations at 20°C using the systems in solution (Scheme 3) than were observed (>90%) using the analogous polymeric systems (Scheme 2). As might be expected, the enantioselectivities in solution increased as the temperature of the methylation reaction was decreased. Thus, for example, the enantiomeric excess of (*S*)-2-methylcyclohexanone from methylation of **11c** in solution at -78°C was 85% compared with 49% at 20°C. In the polymeric systems, the enantioselectivities appeared to increase slightly (being of course already ~94% at ambient temperature) as the temperature was decreased. The chemical yields in solution at the temperatures required for enantioselectivities that approach those obtained using the polymer are much lower (compare 58%

TABLE 3. Comparison of polymeric with solution systems

Temperature (°C)	System	Yield of 2-methylcyclohexanones (%)	Enantiomeric excess of (S)-2-methylcyclohexanone (%)
20	Polymeric 9c	87	94
	Solution 11c	62	49
0	Polymeric 9a	50	94
	Polymeric 9c	97	96
-78	Polymeric 9c	72	98
	Solution 11c	58	85
	Solution 11a	43	71

TABLE 4. Enantioselectivities and yields from recycled polymer, 8c, compared with original 8c

Recycle (No.)	Imine loading of 9c (mmol/g)	Yield (%)	Enantioselectivity (%)
0	0.54	87	94
1	0.53	80	96

from 11c at -78°C with 87% from 9c at 20°C). The results are summarized in Table 3.

Recycling the regenerated polymer 8c

The facile separation of the polymer used for the optical induction reaction is an obvious technical advantage over the homogeneous system in solution. The polymer may also be recycled. Preliminary experiments using recycled 8c indicated no decrease in the enantioselectivity of the methylation reaction (Table 4). There may be some decrease in chemical yield (87% to 80%) although this variation may be within experimental error. Additional experiments are required to examine more thoroughly this practical aspect of the use of polymeric systems in asymmetric syntheses.

Conclusions

High enantioselectivities have been observed in the α -methylation, at 20°C, of cyclohexanone imines formed from cross-linked polystyrene functionalized with optically active 2-aminoalkoxy groups. Advantages over analogous systems in solution include facility in handling, separating, and recycling regenerated polymer, as well as higher enantioselectivities.

Experimental

Optical rotations were determined using a Carl Zeiss polarimeter, no. 372140. All other instrumentation and general procedures are the same as described previously in a publication from these laboratories (10).

(S)-2-Phthalimido-1-propanol (5a)

A solution of (S)-2-amino-1-propanol (2) (4.625 g, 62.5 mmol) in tetrahydrofuran (10 mL) was added to a stirred slurry of *N*-(ethoxycarbonyl)phthalimide (8) (13.94 g, 62.74 mmol) in tetrahydrofuran (50 mL) at 0°C (ice-water bath). After 5 min,

the bath was removed and the mixture stirred overnight at ambient temperature. After removal of the solvent under reduced pressure (boiling water bath), distillation (bulb-to-bulb, 0.1 Torr) gave ethyl carbamate (3.98 g, 71% yield). The residue was crystallized from a solution of toluene (25 mL) and hexane (10 mL) to give 5a (10.46 g, 74% yield); mp, 79–81°C; nmr, δ : 7.80 (d, 4H arom.), 4.30–4.66 (m, 1H), 3.80–4.10 (m, 2H), 3.10 (m, OH), and 1.40 (d, 2H) ppm. *Anal.* calcd. for C₁₁H₁₁NO₃: C 64.38, H 5.37, N 6.82; found: C 64.22, H 5.48, N 6.89.

(S)-2-Phthalimido-1-butanol (5b)

In a manner similar to that described above for 5a, (S)-2-amino-1-butanol (3) was converted to 5b (74% yield); oil; nmr, δ : 7.80 (d, 4H), 4.0–4.33 (m, 3H), 3.10 (m, OH), 1.70–2.10 (m, 2H), and 1.00 (t, 3H) ppm. *Anal.* calcd. for C₁₂H₁₃NO₃: C 65.75, H 5.94, N 6.39; found: C 65.69, H 6.31, N 6.43.

(S)-2-Phthalimido-3-phenyl-1-propanol (5c)

In a manner similar to that described for 5a, (S)-2-amino-3-phenyl-1-propanol (4) was converted to 5c (82% yield); mp 105–106°C; nmr, δ : 7.80 (d, 4H), 7.33 (s, 5H), 4.50–4.90 (m, 1H), 4.0–4.33 (m, 2H), 3.30 (d, 2H), and 2.90 (m, OH) ppm. *Anal.* calcd. for C₁₇H₁₅NO₃: C 72.59, H 5.34, N 4.98; found: C 72.64, H 5.57, N 4.94.

(S)-2-Phthalimido-1-propoxymethylated chloromethylated polystyrene (6a)

To a slurry of 1.006 g (25.02 mmol) of potassium hydride (washed with hexane) and tetrahydrofuran (100 mL) was added, with stirring, a solution of (S)-2-phthalimido-1-propanol (5a) (3.746 g, 18.27 mmol), dibenzo-18-crown-6 (200 mg, 0.56 mmol), and hexamethylphosphoric triamide (10 mL). After 1 h at ambient temperature, a slurry of chloromethylated polystyrene (1) (22.92 g, 23.30 mequiv. Cl) in tetrahydrofuran (50 mL) was added. The reaction mixture was stirred and heated under reflux for 48 h. The polymer was separated by filtration and washed successively with solutions of tetrahydrofuran and ethanol (1:1), tetrahydrofuran and methanol (1:1), and then with ether. The polymer was dried to constant weight under reduced pressure to give 6a (22.393 g); ir, ν (C=O): 1710 cm⁻¹; Cl(9), 0.5 mequiv./g.

(S)-2-Phthalimido-1-butoxymethylated chloromethylated polystyrene (6b)

In a manner similar to that described for 6a, chloromethylated polystyrene, using (S)-2-phthalimido-1-butanol (5b), was converted to 6b; ir, ν (C=O): 1710 cm⁻¹; Cl(9), 0.45 mequiv./g.

(S)-2-Phthalimido-3-phenylpropoxymethylated chloromethylated polystyrene (6c)

In a manner similar to that described for 6a, chloromethylated polystyrene, using (S)-2-phthalimido-3-phenyl-1-propanol (5c), was converted to 6c; ir, ν (C=O): 1710 cm⁻¹; Cl(9), 0.4 mequiv./g.

(S)-2-Phthalimido-1-propoxymethylated methylated polystyrene (7a)

To a solution of sodium iodide (13.182 g, 87.88 mmol) in acetone (150 mL) was added 6a prepared as described above (21.093 g, 10.55 mequiv. Cl). The mixture was stirred under reflux for 48 h and then allowed to cool to ambient temperature. The polymer was separated by filtration and washed successively with acetone, tetrahydrofuran, ethanol, methanol, aqueous methanol, methanol, and finally ether and then dried under reduced pressure to constant weight to give a polymer (22.018 g). To a stirred slurry of this polymer in tetrahydrofuran (150 mL) was added tributyltin hydride (6 mL, 22.74 mmol). The reaction mixture was heated under reflux for 48 h. The polymer was then removed by filtration and washed successively with the solvents described above and dried to constant weight to give 7a (21.903 g); ir, $\nu(\text{C}=\text{O})$: 1710 cm^{-1} ; Cl(9) not detected.

(S)-2-Phthalimido-1-butoxymethylated methylated polystyrene (7b) and (S)-2-phthalimido-3-phenyl-1-propoxymethylated methylated polystyrene (7c)

Procedures similar to that described above for 7a were used to prepare 7b and 7c from 6b and 6c, respectively.

(S)-2-Amino-1-propoxymethylated polystyrene (8a), (S)-2-amino-1-butoxymethylated polystyrene (8b), and (S)-2-amino-3-phenylpropoxymethylated polystyrene (8c)

To a slurry of either polymer 7a, 7b, or 7c prepared as described above (ca. 20 g) in a solution of tetrahydrofuran (100 mL) and ethanol (100 mL) was added, with stirring, aqueous 95% hydrazine (10 mL). The reaction mixture was stirred for 16 h at ambient temperature. The insoluble polymer was then removed by filtration and washed successively with tetrahydrofuran, acetone, ethanol, methanol, aqueous methanol, and then ether to give, after drying under reduced pressure to constant weight (ca. 20 g), polymers 8a, 8b, or 8c respectively. Each exhibited an ir spectrum with absorptions at 3300 cm^{-1} assignable to amino groups.

(S)-2-Cyclohexylideneamino-2-propoxymethylated polystyrene (9a)

A slurry of 8a prepared as described above (20 g, 10 mequiv. NH_2) in a solution of cyclohexanone (8.64 g, 88 mmol) in benzene (200 mL) was heated under reflux in a Soxhlet extractor in which the thimble contained 3 Å molecular sieves. The polymer was removed by filtration and washed successively with tetrahydrofuran, methanol, and then ether to give, after drying under reduced pressure to constant weight (20 g), 9a.

(S)-2-Cyclohexylideneamino-1-butoxymethylated polystyrene (9b) and (S)-2-cyclohexylideneamino-3-phenyl-1-propoxymethylated polystyrene (9c)

In a similar manner to that described above for the preparation of 9a, the polymers 8b and 8c were converted respectively to 9b and 9c.

Determination of loadings of 9a, 9b, and 9c

A slurry of polymer 9a (2.983 g) in a buffer solution (14 mL) prepared from acetic acid (25 mL), sodium acetate (10.8 g), and water (25 mL), and methylene chloride (15 mL) was stirred at ambient temperature for 0.5 h. The methylene chloride layer was washed with water, then saturated sodium bicarbonate solution, and dried over magnesium sulfate. Removal of methylene chloride by distillation afforded a liquid residue (0.1667 g); gc, one sharp peak (tr, 2.5) assignable to cyclohexanone (>99% purity), and representing 0.57 mmol per g of 9a.

By the same method, cyclohexanone was obtained from polymers 9b, and 9c in amounts representing loadings of 0.56 mmol and 0.54 mmol/g of 9b and 9c respectively.

2-(2-Methylcyclohexylideneamino)-1-propoxymethylated polystyrene (10a), 2-(2-methylcyclohexylideneamino)-1-butoxymethylated polystyrene (10b), and 2-(2-methylcyclohexylideneamino)-3-phenyl-1-propoxymethylated polystyrene (10c)

To a stirred slurry of either 9a, 9b, or 9c (ca. 10 g, ca. 5.4 mequiv.) in tetrahydrofuran was added, at 0°C (ice-water bath), with stirring, diisopropylamine (2.0 mL, 14 mmol) followed by a solution of butyllithium (1.55 M in hexane, 10 mL, 15.5 mmol). The reaction mixture was stirred at either ambient temperature (20°C) or 0°C (ice bath) for 20 h, or at -78°C (Dry-Ice bath) for 40 h. Then, iodomethane (2.0 mL, 40 mmol) was added, dropwise, and the reaction mixture stirred for 8 h while the same temperature was maintained. The polymer was removed by filtration and washed successively with tetrahydrofuran, methanol, and finally ether, and then dried under reduced pressure to constant weight (ca. 10 g) to give 10a, 10b, or 10c respectively.

Formation of (R)- and (S)-2-methylcyclohexanone with regeneration of polymers 8a, 8b, and 8c

A slurry of polymer 10a prepared at 20°C as described above (5.231 g 2.98 mequiv.) in a buffer solution (15 mL) prepared from acetic acid (25 mL), sodium acetate (10.8 g), and water (25 mL), and methylene chloride (15 mL) was stirred at ambient temperature for 0.5 h. The methylene chloride layer was separated and washed successively with water (15 mL), saturated sodium bicarbonate solution (15 mL), 5% aqueous sodium chloride solution, and dried over magnesium sulfate. Removal of methylene chloride by distillation afforded a liquid residue (109 mg); gc, one sharp peak (>99% assignable to (R)- and (S)-2-methylcyclohexanone (33% yield); polarimetric analysis $[\alpha]_D^{25} 15.2^\circ$ (c 0.694, MeOH) (lit. (5) $[\alpha]_D 16.4^\circ$), 92% enantiomeric excess of (S)-2-methylcyclohexanone.

In a similar manner, polymer 10a prepared at 0°C as described above gave (R)- and (S)-2-methylcyclohexanone in 50% yield and 94% enantiomeric excess of the (S)-enantiomer.

In a similar manner, the polymer 10b prepared at 20°C as described above gave a liquid product; gc, one sharp peak (tr, 2.9) assignable to (R)- and (S)-2-methylcyclohexanones (86% yield calculated from the loading of 9b); polarimetric analysis, $[\alpha]_D^{25} 15.33^\circ$ (lit. (5) $[\alpha]_D 16.4^\circ$), 93.5% enantiomeric excess of (S)-2-methylcyclohexanone.

Similarly, polymer 10c prepared at 20°C as described above gave essentially pure (R)- and (S)-2-methylcyclohexanone (87% yield calculated from loading of 9c); polarimetric analysis, $[\alpha]_D^{25} 15.40^\circ$, 93.8% enantiomeric excess of (S)-2-methylcyclohexanone.

In a similar manner, polymer 10c prepared at 0°C and -78°C as described above gave essentially pure (R)- and (S)-2-methylcyclohexanone in 97% and 72% yields respectively, and in 96 and 98% enantiomeric excesses of (S)-2-methylcyclohexanone respectively.

(S)-2-Phthalimidopropyl benzyl ether

To a slurry of potassium hydride (1.72 g, 43 mmol, washed with hexane) in tetrahydrofuran (100 mL) containing dibenzo-18-crown-6 (200 mg, 0.56 mmol) was added (S)-2-phthalimido-1-propanol (5a) prepared as described above (8.27 g, 40.33 mmol). The reaction mixture was stirred at ambient temperature for 1 h and then cooled to, and maintained at, 0°C (ice-water bath) while benzyl bromide (10.07 g, 58.9 mmol) was added. After 0.5 h, the reaction mixture was allowed to warm to ambient temperature and stirred for 48 h. After addition of methanol (10 mL), the reaction mixture was concentrated under reduced pressure. To the residue was added ether (100 mL) and water (100 mL). The ether layer was washed with water, dried over magnesium sulfate, filtered, and concentrated. The residue was fractionated by column chromatography (Kieselgel 60,

Korngrösse 0.040–0.063 mm, 230–400 mesh ASTM). An eluent of 3% methanol in ether–hexane (1:1) gave, after evaporation of solvent, crystalline 11a, (6.71 g, 56.4% yield), mp 39–41°C; $[\alpha]_D +44.6^\circ$ (c 1.0, MeOH); nmr, δ : 7.70 (d, 4H), 7.30 (s, 5H), 4.65–5.05 (m, 1H), 4.55 (s, 2H), 3.50–4.20 (m, 2H), and 1.40 (d, 3H) ppm. Anal. calcd. for $C_{18}H_{17}NO_3$: C 73.22, H 5.76, N 4.74; found: C 73.30, H 5.82, N 4.51.

(S)-2-Phthalimido-3-phenylpropyl benzyl ether

In a similar manner, *N*-2-phthaloyl-3-phenylpropanol was converted to 11c, 33% yield; mp 62–64°C; $[\alpha]_D -78.1^\circ$ (c 0.267, MeOH); nmr, δ : 7.70 (d, 4H), 7.30 (d, 10H), 4.66–5.05 (m, 1H), 4.55 (s, 2H), 3.45–4.30 (m, 2H), and 3.20–3.35 (m, 2H) ppm. Anal. calcd. for $C_{24}H_{21}NO_3$: C 77.63, H 5.66, N 3.77; found: C 77.63, H 6.18, N 3.46.

(S)-2-Aminopropyl benzyl ether (11a)

A solution of *(S)*-2-phthalimidopropyl benzyl ether prepared as described above (2.155 g, 7.30 mmol) in ethanol (15 mL) was added to an excess of 95% aqueous hydrazine solution (1.5 g). The mixture was stirred at 30°C for 2 h and then treated with an excess of dilute hydrochloric acid. The insoluble phthalhydrazide was removed by filtration. The filtrate was concentrated, cooled, and filtered to remove additional phthalhydrazide. The filtrate was treated with dilute potassium hydroxide solution (to pH 14) and the mixture extracted with ether. The ether extract was dried over magnesium sulfate and concentrated. The residue was distilled (bulb-to-bulb, 0.5 Torr, 85–90°C) to give 11a (1.110 g, 92.3% yield); oil; $[\alpha]_D +16.35^\circ$ (c 0.847, MeOH); nmr, δ : 7.50 (s, 5H), 4.65 (s, 2H); 4.50–4.90 (m, 1H), 3.10–3.45 (m, 2H), 2.10 (m, NH_2), 1.15 (d, 3H) ppm. Formation of the hydrochloride of 11a by reaction of a solution of 11a in ether with dry hydrogen chloride gave an analytical sample. Anal. calcd. for $C_{10}H_{16}ClNO$: C 59.6, H 7.94, N 6.94; found: C 60.06, H 8.16, N 6.84.

(S)-2-Amino-3-phenylpropyl benzyl ether (11c)

In a manner similar to that described above for 11a, *(S)*-2-phthalimido-3-phenylpropyl benzyl ether was converted to 11c (96.4% yield); oil; $[\alpha]_D +5.59^\circ$ (c 0.626, MeOH); nmr, δ : 7.30 (d, 10H), 4.55 (s, 2H), 3.00–3.55 (m, 3H), 2.55–2.80 (m, 2H), and 1.60 (m, NH_2) ppm. Anal. of the hydrochloride, calcd. for $C_{16}H_{20}ClNO$: C 69.18, H 7.21, N 5.04; found: C 69.11, H 7.36, N 4.93.

(S)-2-Cyclohexylideneaminopropyl benzyl ether (12a)

A solution of 11a (1.044 g, 6.33 mmol), and cyclohexanone (806.8 mg, 8.23 mmol) in benzene (100 mL) was heated under reflux for 8 h using a Dean–Stark trap for collection of water. Benzene was removed under reduced pressure and the residue distilled (bulb-to-bulb, 0.5 Torr, 165–170°C) to give crude 12a (1.488 g, 95% yield) which was redistilled to give a clear viscous oil; $[\alpha]_D +7.29^\circ$ (c 1.007, MeOH); nmr, δ : 7.50 (s, 5H aromatic), 4.55 (s, 2H), 3.00–3.80 (m, 3H), 1.65–2.25 (m, 10H), and 1.20 (d, 3H) ppm.

(S)-2-Cyclohexylideneamino-3-phenylpropyl benzyl ether (12c)

In a manner similar to that described for 12a, 11c was converted to 12c (91% yield; bulb-to-bulb, 0.5 Torr, 190–195°C); $[\alpha]_D -15.9^\circ$ (c 0.464, MeOH); nmr, δ : 7.20–7.50 (m, 10H aromatic), 4.55 (s, 2H), 3.80–4.20 (m, 1H), 3.30–3.60 (m, 2H), 2.65–3.00 (m, 2H), and 1.40–2.30 (m, 10H) ppm.

(R)- and *(S)*-2-Methylcyclohexanones from 12a at $-78^\circ C$

To a solution of diisopropylamine (0.8 mL, 5.71 mmol) in tetrahydrofuran (15 mL) was added, with stirring at 0°C, a solution of butyllithium in hexane (1.6 M, 3.60 mL, 5.76 mmol). After 15 min, the reaction mixture was cooled to $-30^\circ C$ (Dry-Ice in acetone bath) and 12a (1.225 g, 5.0 mmol) was added. After

1.5 h, the solution was cooled to $-78^\circ C$ and a solution of iodomethane (0.4 mL, 6.42 mmol) in tetrahydrofuran (5 mL) was added dropwise over 0.5 h. The reaction mixture was stirred at $-78^\circ C$ for 2 h, and then poured into a saturated solution of sodium chloride (50 mL) and extracted with ether. The extract was washed with aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated.

A solution of the residue in pentane (25 mL) was shaken for 0.5 h with a solution of sodium acetate (1.65 g) and acetic acid (3.75 mL) in water (17.5 mL). The aqueous layer was separated and washed with pentane. The combined pentane solutions were washed successively with hydrochloric acid (1 N), water, 5% aqueous sodium bicarbonate solution, water, and aqueous sodium chloride solution. Concentration of the pentane solution and distillation of the residue (bulb-to-bulb) gave a liquid product (241 mg); gc, one sharp peak assignable to *(R)*- and *(S)*-2-methylcyclohexanones (43% yield); polarimetric analysis, $[\alpha]_D 11.70^\circ$ (c 0.573, MeOH) indicating an enantiomeric excess of *(S)*-2-methylcyclohexanone of 71.3%.

(R)- and *(S)*-2-Methylcyclohexanones from 12c at $-78^\circ C$

In a manner similar to that described above for 12a, 12c produced *(R)*- and *(S)*-2-methylcyclohexanone in 58% yield and 85.3% enantiomeric excess of *(S)*-2-methylcyclohexanone.

(R)- and *(S)*-2-Methylcyclohexanones from 12c at $20^\circ C$

In a manner similar to that described above for 12c at $-78^\circ C$, 12c was treated with lithium diisopropylamide at 20°C and iodomethane at 20°C to give 2-methylcyclohexanones in 62% yield, and 49% enantiomeric excess of *(S)*-2-methylcyclohexanone.

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