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Enantiopure beads: a tool for asymmetric heterogeneous catalysis

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Abstract

A copolymer containing enantiopure epoxy groups was prepared in excellent yield by radical suspension copolymerization of (*S*)-glycidyl methacrylate with ethylene glycol dimethacrylate. In order to control the physical and surfaces properties of the copolymer, we studied the influence of the stirring rate reaction and the concentration of the cross-linking agent on the copolymerization reaction. This allowed the evaluation of the influence of the specific surface area, the particle size and the level of functionalization on catalytic efficiency of their copolymer derivatives. These enantiopure poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate) beads were then transformed into optically active polyamino alcohols through epoxide ring opening with different achiral or homochiral amines. In order to show the efficiency of these new copolymers, they were used as ligands of ruthenium in asymmetric hydrogen transfer reduction of acetophenone.

Keywords: Enantiopure epoxy polymers; Ruthenium; Asymmetric catalysis; Hydrogenation; Heterogeneous catalysis

1. Introduction

The preparation of the cross-linked poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate), a polymer containing epoxy group, was reported by Svec et al. [1] in 1975. Its modification by epoxide ring opening provided polymeric derivatives which were used in various applications in ion exchange chromatography [2–4], as ion exchange resin [5–7], as gas chromatography stationary phase [8], as gas sorbents [9,10], protecting groups [11] and enzyme immobilization agents [12].

We report, in the present paper, the formation of optically active glycidyl methacrylate monomer by hydrolytic kinetic resolution involving salen cobalt(III) complexes, followed by its copolymerization with ethylene glycol dimethacrylate leading to enantiopure beads. In order to evaluate the physical properties and their importance upon catalysis, the stirring rate and the cross-linking agent concentration were studied. During the copolymerization, the stirring rate was changed in order to adjust the particle size; and the concentration of the cross-linking agent was modified to obtain copolymers with various levels of functionalization.

The syntheses of optically active polyamino alcohols by epoxy ring cleavage of poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate) and their subsequent utilization as ligands of ruthenium in

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asymmetric heterogeneous catalytic hydrogen transfer reduction of acetophenone are described.

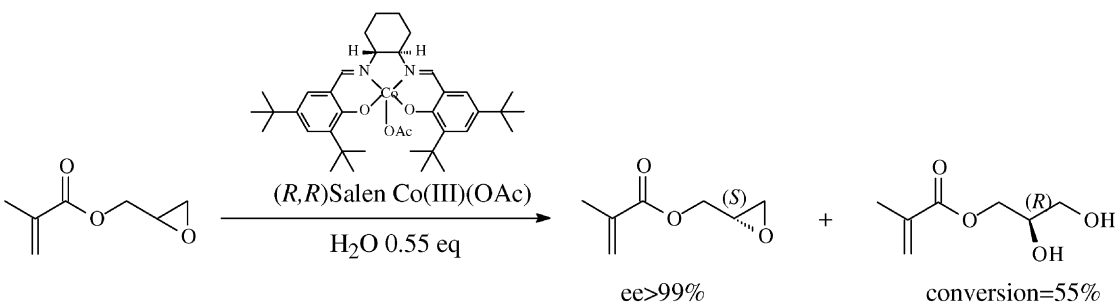
2. Results and discussion

2.1. Hydrolytic kinetic resolution

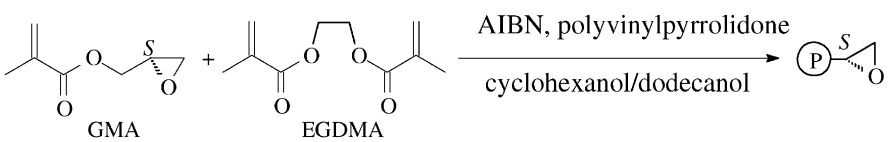
As an alternative to the Sharpless method [13], which permits enantioselective epoxidation of allylic alcohols, we chose hydrolytic kinetic resolution for the synthesis of enantiopure glycidyl methacrylate, using chiral cobalt-based salen complexes developed by Jacobsen and co-workers [14] for the asymmetric hydrolysis of saturated terminal epoxides. Thus, the hydrolysis of racemic glycidyl methacrylate in the presence of 0.5 mol% of [Co^{III}{(*R*,*R*)-salen}(OAc)] complex, led to the (*S*)-enantiomer with an excellent enantiomeric excess and to evaluate their influence on the catalytic system (Scheme 1). Svec et al. [1] previously found that the particle size depends mainly on the stirring rate during the polymerization, whereas specific surface [15] and porosity [16] were predominantly affected by the concentration of the cross-linking agent. We carried out the copolymerization in a 500 ml glass reactor equipped with a stirring anchor using the conditions of Svec et al. [1] and Jovanovic et al. [17]: cyclohexanol and dodecanol (91/9 w/w) as inert phase, AIBN as initiator and polyvinylpyrrolidone as stabilizer (Scheme 2).

In order to study the influence of the stirring rate upon the particle size, the copolymerization of (*S*)-GMA-co-EGDMA (30/70 w/w) was performed at 200, 400 and 600 rpm (Fig. 1). The results show that the faster the stirring rate, the smaller the particle size. At 200 rpm, 87% of the beads presented a diameter larger than 300 μm, whereas at 600 rpm only 10% of the beads were above 300 μm. Moreover, the measurements of specific surface area by BET analysis [18] were carried out for copolymer with different contents in cross-linking agent and for two particle sizes. Polymer **1** ($\phi > 300$ μm) and polymer **2** ($106 < \phi < 300$ μm) (runs 1 and 2, Table 1), both formed using 70% of cross-linking agent (2.11 mmol/g of epoxy group) gave, respectively, a specific surface area of 100 and 80 m^2/g. As for polymer **3** ($106 < \phi < 300$ μm) (run 3) synthesized with 30% of EGDMA (4.90 mmol/g of epoxy group) and having particle size from 106 to 300 μm a specific surface area of 50 m^2/g was found.

As expected specific area decreased when particle size increased (runs 1 and 2) and when concentration of cross-linking agent decreased (runs 2 and 3).



Scheme 1.



Scheme 2.

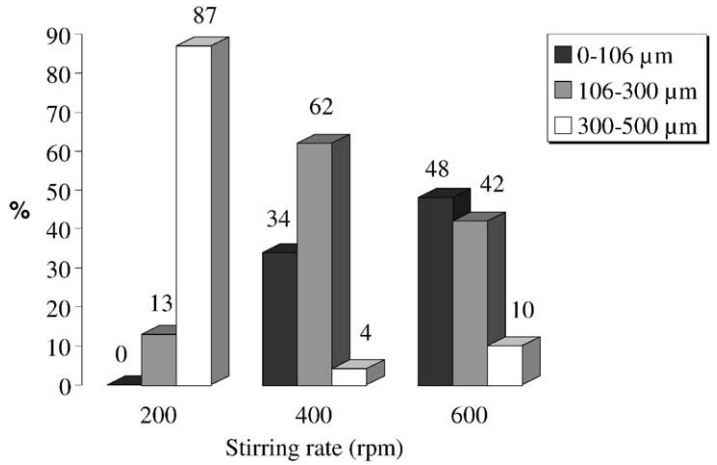


Fig. 1. Size distribution of GMA-co-EGDMA beads.

2.2. Functionalization of poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate)

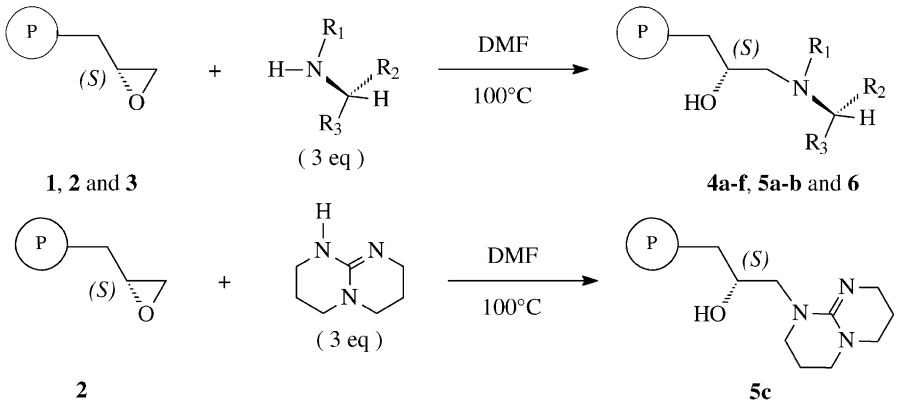
The epoxy functions of polymer **1** were submitted to ring opening with benzylamine, *N*-benzylmethylamine, (*R*)-α-methylbenzylamine, (*R*)-*N*,α-dimethylbenzylamine, (*S*)-*N*,α-dimethylbenzylamine, methylamine, those of polymer **2** with benzylamine, methylamine and 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-a]pyrimidine and those of polymer **3** with benzylamine, to afford, respectively, the polyamino alcohols **4a**–**f**, **5a**–**c** and **6** according to the procedure of Lindsay and Sherrington [6]. These conditions favored the regioselective attack at the less hindered position of the epoxide ring (Scheme 3). Elemental analysis of nitrogen was carried on to determine the grafting proportion of final polymers **4**–**6**. The results indicated that the level of functionalization of the initial epoxide group was, respectively, about 70% for **4a**–**c** and **6**, 60% for **4d**–**e** and **5a**, 55% for **5c** and 36% for **4f** and **5b** (Table 2).

It is noteworthy that polymers **1** and **2** which differ only by their particle size ($\phi > 300\,\mu m$ and $106 < \phi < 300\,\mu m$, respectively) show similar levels of functionalization when either benzylamine (runs 1 and 7) or methylamine (runs 6 and 8) are used.

Moreover, whatever the level of functionalization of the ungrafted polymers (2.11 mmol/g for polymer **1** or 4.90 mmol/g for polymer **3**), the functionalization ratio with benzylamine is almost identical (runs 1 and 10, Table 2). This allows, as expected for polymer **3**, high content of amino alcohol units.

Table 1
Copolymerization of glycidyl methacrylate and ethylene glycol dimethacrylate

Run	Polymer	GMA/EGDMA (w/w), ϕ (μm)	Elemental analysis	C (%)	H (%)	O (%)	Functional (mmol/g)	Specific surface area (m^2/g)
1	**1**	30/70, >300	Calcd.	60.17	7.06	32.77	2.11	100
			Found	59.75	7.40	32.85		
2	**2**	30/70, 106–300	Calcd.	60.17	7.06	32.77	2.11	80
			Found	59.75	7.40	32.85		
3	**3**	70/30, 106–300	Calcd.	59.50	7.19	33.25	4.90	50
			Found	59.86	7.28	32.85		



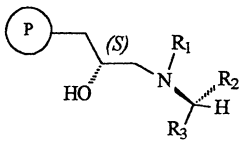
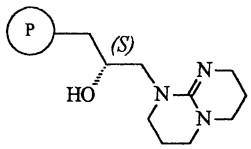
Scheme 3.

2.3. Asymmetric heterogeneous hydrogen transfer reduction of acetophenone

Chiral amino alcohols bound to transition metals are known to induce chirality in asymmetric catalysis for C–C, C–O and C–H bond formations [19]. This prompted us to use polymers **4**–**6** in heterogeneous asymmetric hydrogen transfer reduction. Table 3 summarizes the results of the hydrogen transfer reduction of acetophenone (Scheme 4), using ruthenium complexes of polyamino alcohols **4**–**6** synthesized from $[RuCl_2(p\text{-cymene})]_2$ precursor, isopropanol as hydrogen donor. The reaction was carried out under argon with a ratio acetophenone/Ru/ligand/*t*-BuOK of 20/1/4/5.

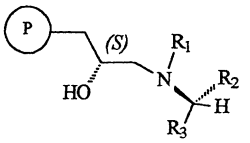
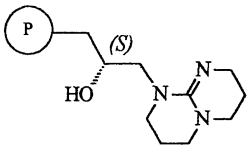
As shown in Table 3, polyamino alcohol ligands derived from primary amines (runs 1, 3, 6–8 and 10) give the best conversions and the best enantiomeric

Table 2
Functionalization ratio of the epoxy polymers **1**–**3**

Run	Epoxy polymer	Polyamino alcohol				Amine configuration	Functionalization ratio	
			R1	R2	R3		%	mmol/g
1	1	**4a**	H	H	Ph		69	1.20
2	1	**4b**	Me	H	Ph		71	1.22
3	1	**4c**	H	Me	Ph	*R*	70	1.21
4	1	**4d**	Me	Me	Ph	*R*	59	0.94
5	1	**4e**	Me	Ph	Me	*S*	60	0.95
6[a]	1	**4f**	H	H	Me		36	0.76
7	2	**5a**	H	H	Ph		62	1.14
8[a]	2	**5b**	H	H	Me		36	0.74
9	2	**5c**					53	0.96
10	3	**6**	H	H	Ph		67	2.16

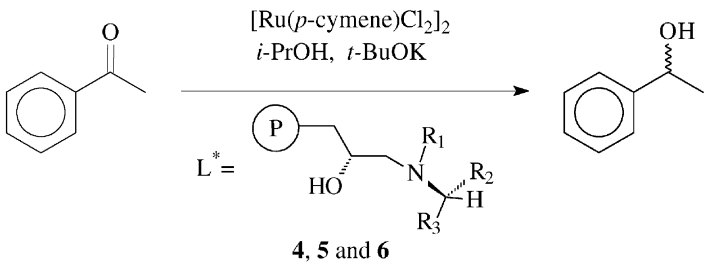
[a] Reaction at 80 °C with a solution of 30% of methylamine in water.

Table 3
Ruthenium catalyzed hydrogen transfer of acetophenone

Run	Epoxy polymer	Polyamino alcohol				Time (h)	Percentage of conversion	Percentage of ee (*R*)
			R1	R2	R3			
1	1	**4a**	H	H	Ph	3	94	70
2	1	**4b**	Me	H	Ph	22	7	29
3	1	**4c**	H	Me	Ph	22	94	45
4	1	**4d**	Me	Me	Ph	22	11	34
5	1	**4e**	Me	Ph	Me	22	7	23
6	1	**4f**	H	H	Me	1	95	65
7	2	**5a**	H	H	Ph	22	64	71
8	2	**5b**	H	H	Me	22	84	63
9	2	**5c**				8 days	5	0
10	3	**6**	H	H	Ph	22	38	56

excesses. However, polyamino alcohols **4c** from an α-substituted primary amine (run 3) lead to a lower enantiomeric excess (45%) compared to unsubstituted ones **4a** and **4f** (runs 1 and 6), which give 1-phenylethanol with 70 and 65% ee, respectively. In contrast, polyamino alcohol ligands from secondary amines **4b** and **4d** (runs 2 and 4) lead to the lowest conversions with enantioselectivities of about 30%. The chirality of the amino α-substitution shows almost no influence on the enantioselectivity values. In all cases, the 1-phenyl ethanol *R* stereochemistry is independent of the amine stereochemistry (runs 4 and 5). Unfortunately, the guanidine derivative ligand **5c** displays weak activity and no selectivity (run 9).

The particle size and then the specific surface area seem to affect the conversion but not the selectivity. Polyamino alcohol **4a** has bigger particle size, and specific surface area than **5a**, and thus give better conversion (94% instead of 64% for **5a**, runs 1 and 7), with enantiomeric excess of about 70%. The proportion of cross-linking agent also has an influence. It is noteworthy that the specific surface area (*S*) decreased when the concentration of cross-linking agent was lower (Table 1). Compared to polyamino alcohol



Scheme 4.

6 with 30% of EGDMA (level of functionalization: 2.16 mmol/g, $S = 80\,m^2/g$), copolymer **5a** with 70% of EGDMA (level of functionalization: 1.14 mmol/g, $S = 50\,m^2/g$) shows higher conversion and enantioselectivity (runs 7 and 10). This implies that for this catalytic reaction the more macroporous but the less functionalized the material, the higher the conversion and the enantioselectivity are.

An attempt to recycle the ruthenium complex **4a** led to a marked decrease in activity from 94 to 27% and lowered selectivity from 70 to 54%.

3. Conclusion

We have synthesized enantiopure poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate) with controlled particle size and level of functionalization, modifying, respectively, the stirring rate during the copolymerization and the concentration of the cross-linking agent. Opening the epoxide ring with various amines allows the synthesis of polyamino alcohols in order to use them as ruthenium ligands for asymmetric hydrogen transfer reduction of acetophenone. This heterogeneous molecular catalysis lead to encouraging results in terms of activity and enantioselectivity for beads diameter greater than 300 μm, benzylamine or methylamine are grafted onto the copolymer and EGDMA concentration is of 30%. These experiments demonstrate the significant potential of these ligands for heterogeneous asymmetric catalysis. Various substrates and metals will be investigated for hydrogen transfer reduction in order to screen the scope and the limitations of these new catalytic systems.

4. Experimental

4.1. General

For hydrolytic kinetic resolution of glycidyl methacrylate and hydrogen transfer reduction of acetophenone, enantiomeric excesses and conversions were determined by GC, respectively, on a Supelco β dex 225 (60 m × 0.25 mm) and on a Macherey-Nagel lipodex A (25 m) chiral column, using a Shimadzu GC-14A apparatus equipped with a flame ionization detector and connected to a Shimadzu C-R6A integrator.

^{1}H and ^{13}C NMR spectra were recorded with an AM200 (^{1}H: 200 MHz, ^{13}C: 50 MHz) using TMS as internal standard and $CDCl_3$ as solvent.

Polarimetric measurements were performed on a Perkin-Elmer 241 instrument, at ambient temperature, at 589 nm, at a concentration in g/100 ml solution. Elemental analyses were carried out by CNRS (Service Central d'Analyse).

The BET measurements were performed on an automatic home made "Institut de Recherche sur la Catalyse" apparatus, using N_2 adsorption, at −196 °C. Before any measurement, the support was heated to 240 °C during 3 h under vacuum.

4.2. Hydrolytic kinetic resolution

Acetic acid (76 μl, 1.336 mmol) was added to a solution of [(1*R*,2*R*)-1,2-diaminocyclohexane-*N*,*N*′-bis (3,5-di-*tert*-butylsalicylidene)cobalt(II)] (0.457 g, 0.668 mmol) dissolved in toluene (12 ml). After 1 h stirring at room temperature, the solvent was removed under vacuum. Racemic glycidyl methacrylate (19 g, 133 mmol) and bidistillated water (1.2 g, 66 mmol, 0.55 equiv.) were then added, at 0 °C, to the resulting black residue. The reaction mixture was allowed to stir for 24 h at room temperature. The (*S*)-glycidyl methacrylate (6.65 g, 46.55 mmol, yield 45%) was separated from the diol by silica gel (Merck 60, 40–60 μm) column chromatography: ee = 99%, $[\alpha]^D = +29.3$ ($c = 0.564$, CH_2Cl_2).

^{1}H NMR: 1.95 (s, 3H), 2.6–2.7 (m, 1H), 2.8–2.9 (m, 1H), 3.25 (m, 1H), 4.0–4.1 (m, 1H), 4.4–4.5 (m, 1H), 5.62 (s, 1H), 6.18 ppm (s, 1H). ^{13}C NMR: 18.3, 44.6, 49.4, 65.2, 126.2, 135.9, 167.0 ppm.

4.3. Copolymerization

4.3.1. Synthesis of poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate): 30/70 w/w (polymers *1* and *2*)

A solution of AIBN (139 mg) in a mixture of (*S*)-glycidyl methacrylate (4.21 g) and ethylene glycol dimethacrylate (9.82 g) was added to a solution of cyclohexanol (16.9 g)/dodecanol (1.66 g) (91/9 w/w). This mixture was then added to a solution of polyvinylpyrrolidone (1.03 g) in water (150 ml). The

reaction mixture was stirred at 200, 400 or 600 rpm, at 70 °C during 2 h, then at 80 °C for 6 h. After 2 h at room temperature, the spherical particles formed were washed four or five times with ethanol 95%, dried by means of a vacuum oven and finally sifted with a 106 μm and a 300 μm sifter. The particle size was confirmed by optical microscopy of each fractions.

Elemental analysis: **1** and **2**: Anal. Calcd. for $C_7H_{10}O_3$ (0.375) and $C_{10}H_{14}O_4$ (0.625) (wt.%): C, 60.17; H, 7.06; O, 32.77. Found: C, 59.75%; H, 7.40%; O, 32.85%. Functional: 2.11 mmol/g.

*4.3.2. Synthesis of poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate): 70/30 w/w (polymer **3**)*

The same procedure was applied with 105 mg of AIBN, 7 g of (*S*)-glycidyl methacrylate, 3 g of ethylene glycol dimethacrylate, 12.06 g of cyclohexanol, 1.18 g of dodecanol and 0.73 g of polyvinylpyrrolidone in 150 ml of water. The stirring rate was 400 rpm.

Elemental analysis: **3**: Anal. Calcd. for $C_7H_{10}O_3$ (0.765) and $C_{10}H_{14}O_4$ (0.235) (wt.%): C, 59.50; H, 7.19; O, 33.25. Found: C, 59.86; H, 7.28; O, 32.85%. Functional: 4.90 mmol/g.

4.4. Typical polyamino alcohol synthesis

Under argon, 3 equiv. of amine were added to the chiral copolymer (1 mmol of epoxide) in suspension in anhydrous DMF (2 ml) under mechanical stirring (180 rpm). The reaction mixture was heated at 100 °C during 22 h. After the beads were washed by ethanol 95%, dried by means of a vacuum oven and finally sifted.

Elemental analysis:

- **4a**: Anal. Calcd.: C, 62.64; H, 7.24; O, 28.45; N, 1.67. Found: C, 61.05; H, 7.15; O, 30.1; N, 1.15%. Functional: 69%, 1.20 mmol/g.
- **4b**: Anal. Calcd.: C, 64.07; H, 7.48; O, 26.10; N, 2.36. Found: C, 62.39; H, 7.67; O, 28.23; N, 1.71%. Functional: 71%, 1.22 mmol/g.
- **4c**: Anal. Calcd.: C, 64.07; H, 7.48; O, 26.10; N, 2.36. Found: C, 61.70; H, 7.50; O, 29.15; N, 1.66%. Functional: 70%, 1.21 mmol/g.
- **4d**: Anal. Calcd.: C, 64.57; H, 7.63; O, 25.49; N, 2.30. Found: C, 62.40; H, 7.75; O, 28.50; N, 1.35%. Functional: 59%, 0.94 mmol/g.
- **4e**: Anal. Calcd.: C, 64.57; H, 7.63; O, 25.49; N, 2.30. Found: C, 61.75; H, 7.41; O, 29.45; N, 1.38%. Functional: 60%, 0.95 mmol/g.
- **4f**: Anal. Calcd.: C, 58.85; H, 7.62; N, 2.78. Found: C, 58.45; H, 7.25; N, 1.01%. Functional: 36%, 0.76 mmol/g.
- **5a**: Anal. Calcd.: C, 63.54; H, 7.31; N, 2.41. Found: C, 59.52; H, 7.21; N, 1.49%. Functional: 62%, 1.14 mmol/g.
- **5b**: Anal. Calcd.: C, 58.85; H, 7.62; N, 2.78. Found: C, 58.45; H, 7.25; N, 1.01%. Functional: 36%, 0.76 mmol/g.
- **5c**: Anal. Calcd.: C, 60.24; H, 7.56; N, 6.80. Found: C, 56.25; H, 7.38; N, 3.52%. Functional: 52%, 0.96 mmol/g.
- **6**: Anal. Calcd.: C, 66.28; H, 7.66; N, 4.49. Found: C, 63.25; H, 7.57; N, 3.09%. Functional: 67%, 2.16 mmol/g.

4.5. Typical reduction procedure of acetophenone

Under argon, the polyamino alcohols **4**–**6** and $[RuCl_2(p\text{-cymene})]_2$ (**4**–**6**/Ru ratio: 4/1), in suspension in isopropanol (2 ml for 3.7 mg of $[RuCl_2(p\text{-cymene})]_2$), were stirred and heated at 80 °C for 30 min. The reaction mixture and the polymer turned red. Acetophenone was then added at room temperature (acetophenone/Ru ratio: 20/1). Afterwards, a solution of potassium tertiobutylate (0.03 mol/l) was added (Ru/base ratio: 1/5). The reaction times and ee are summarized in Table 3.

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