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Synthesis and studies of 6,6′-BINAP derivatives for the heterogeneous asymmetric hydrogenation of methyl acetoacetate

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Abstract—New BINAP derivatives (polyamide, polyureas or ureas) were synthesized and employed in the ruthenium-catalyzed asymmetric heterogeneous hydrogenation of methyl acetoacetate. Enantiomeric excesses in the range 48–100% were observed. Furthermore, the most efficient have been recovered and the recycled catalysts were shown to maintain their efficiency in subsequent reactions.

1. Introduction

Pharmaceuticals, agrochemicals, flavors and fragrances are the principal areas that require the synthesis of enantiomerically pure chiral compounds. Most of these compounds are still synthesized starting from the chiral pool or else they are prepared in racemic form and the desired enantiomer is subsequently obtained by resolution. However, they can be obtained from prochiral substrates by enantioselective catalysis, mainly through asymmetric catalytic hydrogenation. Chiral diphosphines have been known to be catalytic ligands for this reaction for more than 30 years.[1,2] Many of them, having C_2-symmetry, lead to high activity and selectivity. Among them, BINAP, developed by Noyori et al[3] is a very active and selective ligand for which the chirality is induced by binaphthyl skeleton atropoisomerism. The BINAP, rhodium or ruthenium complexes are able to reduce a wide range of substrates such as α-ketoesters,[4] β-ketoesters,[4] alkenes[5] and ketones[5] giving from 70 to 99% e.e. It is noteworthy that the best activity has been observed in the case of the hydrogenation of acetophenone in the presence of 1,2-diphenylethylene diamine (DPEN) with a substrate/catalyst ratio (S/C) as high as 2,400,000;[6] nevertheless, in most of the practical cases, such high turnover numbers could not be reached. However, industrial applications of BINAP[7] and other chiral phosphines still remain rare, which is probably a result of problems with separation and recovery of the expensive chiral catalyst.

To overcome these drawbacks, heterogeneous catalysts can be employed, as can support homogeneous catalysts, a methodology that has been widely studied over the last few years. This latter approach consists of the 'heterogenization' of an efficient homogeneous catalyst by anchoring it to a solid support, i.e. an inorganic material[8] or an organic polymer[9] in order to perform the separation of the catalyst from the reaction mixture by filtration. Another possibility is to use soluble polymer-supported catalysts, which combine the advantages of homogeneous (mobility and accessibility of the active sites) and heterogeneous catalysis (easy separation and recovery). After the reaction the catalyst is recovered by simple precipitation upon addition of an appropriate solvent, followed by filtration. In the case of BINAP, the first concept was developed in 1998 by Bayston et al.,[10] who described their heterogeneous version by grafting a monofunctionalized BINAP derivative onto a polystyrene resin via an amide bond. This polymer-supported catalyst afforded high selectivity (from 70 to 100% e.e.) and activity (from 70 to 100% yield) with relatively low substrate/catalyst ratio ($\sim$200) in the Ru-catalyzed hydrogen reduction of β-ketoesters and functionalized olefins. Nevertheless, attempts to re-use the catalyst led to lower selectivity and activity. Noyori et al[11] have shown that this ruthenium (*R*)-polymer supported catalyst in the presence of

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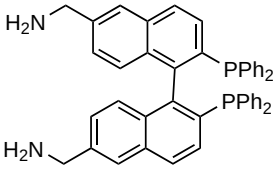
(*R*,*R*)-1,2-diphenylethylene diamine was able to reduce some ketones and particularly acetonaphthone under H_2 (8 atm) at 25°C in a mixture of *i*-PrOH/DMF (1/1) with a substrate/catalyst ratio of 2470 with 99% e.e. and 98% of conversion. The product e.e. remained consistently high (97–98%), even after the 14th experiment, but the catalytic activity gradually decreased after the 10th experiment (total TON: 33000).

On the other hand, Pu et al. have prepared a poly(BINAP),[12] an optically active copolymer formed by polymerization of BINAP derivative with 1,4-dibromo-2,5-dialkylbenzene. They used a rhodium precursor and obtained >99% conversion with enantiomeric excesses from 40 to 75% in the asymmetric hydrogenation of dehydroamino acid derivatives (substrate/catalyst ratio: 50). However, the reduction of methylarylketones performed by means of poly(BINAP) catalyst in the presence of (*R*,*R*)-1,2-diphenylethylene diamine under H_2 (200 psi) exhibited good enantioselectivities from about 90% and conversions up to 99%. The authors also obtained an optically active poly(BINOL-BINAP)[13] copolymer Ru-catalyst which was involved in the asymmetric hydrogenation of acetophenone with a conversion up to 99 and 84% e.e. with BINAP unit to substrate ratio of 1/4900.

The second concept was improved by Chan et al. who synthesized soluble chiral polyester[14] and dendritic[15] BINAP derivatives as Ru-ligands in order to study the hydrogenation of acrylic acid derivatives. Conversions from 65 to 100% with a substrate/catalyst ratio of 200 and enantiomeric excess values from 88 to 95% were obtained in the case of Ru-polyester supported catalyst. For the Ru-dendrimer catalyst, with a substrate/catalyst ratio of 125, total conversion and similar enantiomeric excesses were observed.

In 1999, we heterogenized BINAP by copolymerization of *diam*-BINAP (6,6′-diaminomethyl-BINAP) **1**[16,17] (Scheme 1), (accessible starting from BINOL unit using a five step synthesis) with diisocyanatotoluene.[18] This approach incorporated the chiral BINAP structure in the polymer backbone as a result of the careful step by step design of the material.



diam-BINAP (**1**)

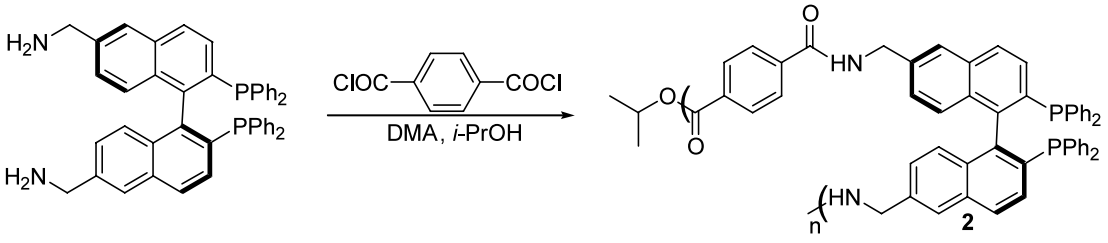
Scheme 1.

In order to obtain an insoluble, easily separable and recyclable catalyst, we have studied several structural parameters. The use of crosslinked polymer was shown to give rise to an inefficient and non-selective catalytic system. Therefore, the concept we have developed is the use of polymer chain of molecular weight sufficiently high to avoid solubilization but without crosslinking to allow swelling and chain mobility. Low accessibility of the catalytic site is obviously the main limitation of heterogeneous supported catalysis, therefore we chose to use low molecular weight non-crosslinked material. Limitation of the molecular weight was obtained by using non-polar poorly solubilizing solvent during the polymerization. On the other hand and contrary to the approach of Bayston,[10] we have focused our efforts on heterogeneization of BINAP with the conservation of a pseudo-C_2- or C_2-symmetry. Urea and amide functional groups are known as potential ligands for transition metals and could interfere with the formation of the active species.[19] So the two types of linker were tested. Various types (flexible or rigid) of spacer were also evaluated. In addition well-defined BINAP derivatives with high molecular weight and low solubility in methanol were also synthesized. Their subsequent use as Ru-ligands in the asymmetric heterogeneous catalytic hydrogenation of methyl acetoacetate was evaluated.

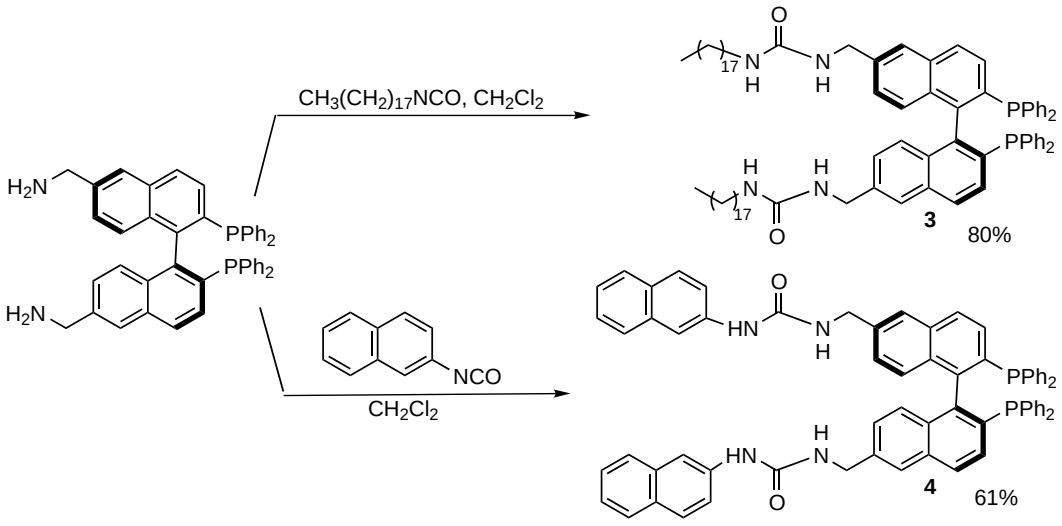
2. Results and discussion

The polyamide **2** (Scheme 2) was obtained with 60% yield by polycondensation of (*S*)-*diam*-BINAP **1** with terephthaloyl chloride in dimethylacetamide (DMA).[20] The polymer (*S*)-**2** is soluble in aprotic solvents such as DMF, DMSO, DMA, but insoluble in dichloromethane, methanol and toluene. ^{1}H NMR spectroscopy provides a means of evaluating the average degree of polymerization (DP), which is about 20 in comparison with the integrals of the signals at 4.39 ppm (CH_2) and 1.22 ppm (CH_3).

Ureas and polyureas were prepared by addition of *diam*-BINAP with mono or diisocyanate in dichloromethane. Diureas **3** and **4** were obtained in 80 and 61% yields, respectively, by addition of 2 equiv. of octadecylisocyanate or 2-naphthylisocyanate (Scheme 3).



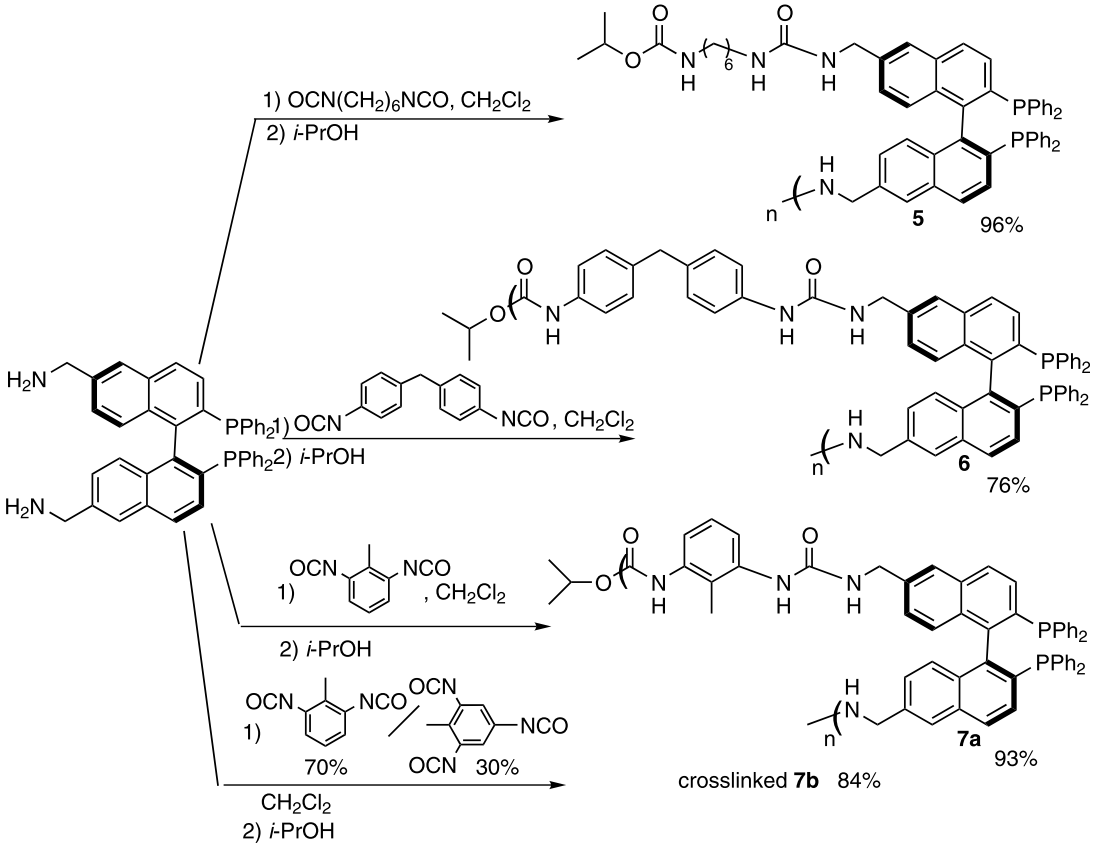
Scheme 2.



Scheme 3.

For polyurea, the addition of diisocyanatohexane led to expected polyurea **5** in 96% yield. Other less flexible diisocyanates such as di(4-isocyanatophenyl)methane and 2,6-diisocyanatotoluene were involved. They afforded polymers **6** and **7a** in 76 and 93% yield, respectively (Scheme 4). The crosslinked polymer **7b** was prepared by addition of a 7:3 w/w mixture of di- and tri-isocyanatotoluene in 84% yield.

A DP of about 15 for polymer **6** and of about 13–14 for polymer **7** was determined in the same way as for polymer **2**. Attempts to use MALDI-TOF[21] analysis have failed, probably due to the poor solubility of such polymers in the α-cyano hydroxycinnamic acid matrix. In order to validate the NMR results, we performed gel permeation chromatography analysis (GPC) for polymer **7**. An average molecular weight of 8400 g/mol and



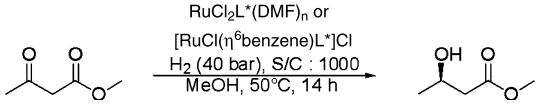
Scheme 4.

a degree of polymerization of 10 were found although the index of polydispersity was rather large (7.5). Nevertheless, we can consider that the degree of polymerization is quite similar to that obtained by NMR spectroscopy.

Unlike diurea **3**, which is soluble in all organic solvents, diurea **4** and polymers **5**, **6** and **7** are insoluble in dichloromethane, toluene and methanol, but soluble in dipolar non-protic solvents such as dimethylformamide or dimethylsulfoxide.

The neutral ruthenium complexes of polyamide **2** and ureas **3**, **5**, **6** and **7** and the cationic ruthenium complexes of compounds **2**, **3**, **4**, **5**, **6** and **7** were synthesized from the $[Ru_2(benzene)]_2$ precursor according to the procedures presented by Noyori et al.[22,23] The catalytic activities of these ruthenium complexes in the hydrogenation of ethyl acetoacetate were tested in methanol with a substrate/catalyst ratio of 1000 (Scheme 5). The results are summarized in Tables 1–3. Ruthenium complexes of **2**, **4**, **5**, **6** and **7**, insoluble in methanol, have been used for heterogeneous reduction. In contrast, the Ru-**3** complex is soluble in methanol and was used as a homogeneous catalyst.

Our first attempts were realized with ruthenium polyamide **2** neutral complex (Table 1), which led to interesting results 100% conversion and 78% e.e. (run 1). Unfortunately, after removing the catalyst from the reaction mixture and recycling it, the conversion fell down sharply, probably due to leaching (run 2). We then concentrated our efforts on diureas and polyureas as ligands (Tables 2–4) using both neutral and cationic complexes.



Scheme 5.

Table 1. Ruthenium neutral complexes with polyamide backbone ($RuCl_2$-**2** $DMF)_n$)-catalyzed asymmetric hydrogenation of methyl acetoacetate

Run	Ligand	Use	Conversion (%)[a]	E.e. (%)[a]
1	**2**	1st	100	78
2	**2**	2nd	4	99

[a] Conversion and e.e. were determined by chiral GC analysis on a Lipodex A column.

Table 2. Ruthenium neutral complexes ($RuCl_2L^*(DMF)_n$)-catalyzed asymmetric hydrogenation of methyl acetoacetate

Run	Ligand	Use	Conversion (%)[a]	E.e. (%)[a]
1	**3**[b]		36	48
2	**5**		46	88
3	**6**	1st	100	97
4		2nd	17	7
5	**7a**		100	99
6	BINAP[b]		100	99

[a] Conversion and e.e. were determined by chiral GC analysis on a Lipodex A column.
[b] Homogeneous catalysis.

Table 3. Diurea ruthenium cationic complexes ([RuCl(η^6-benzene)L*]Cl)-catalyzed asymmetric hydrogenation of methyl acetoacetate

Run	Ligand	Use	Conversion (%)[a]	E.e. (%)[a]
1	BINAP[b]		100	>99
2	*diam*-BINAP[b,c]		100	>99
3	**3**[b]		100	100
4	**4**	1st	100	100
5		2nd	99	97
6		3rd	54	33

[a] Conversion and e.e. were determined by chiral GC analysis on a Lipodex A column.
[b] Homogeneous catalysis.
[c] S/C = 2000.

For neutral ruthenium complexes (Table 2), the rigid polymeric systems **6** and **7** are more efficient; leading to 100% conversion with 97 and 99% e.e., respectively (runs 3 and 5) than diurea **3** or polymer **5** with a flexible spacer chain showing conversions of less than 50, 48 and 88% e.e. (runs 1 and 2). For the best ligand (**6**), we investigated its re-use and observed poor conversion with low e.e. (run 4).

It is noteworthy that in their first use ligands **6** and **7** gave similar results to BINAP (run 6).

Of the diurea ruthenium cationic complexes, (Table 3) Ru-**4** is the most active in heterogeneous conditions leading to complete conversion and product with 100% e.e. It has been shown to be as efficient as BINAP, *diam*-BINAP or diurea **3** (runs 1, 2 and 3), in homogeneous conditions. Attempts to re-use catalyst Ru-**4** were performed after centrifugation and filtration in order to remove the catalyst from the reaction mixture. During the second use, the product e.e. remains high and the catalyst

Table 4. Polyurea ruthenium cationic complexes ([RuCl(η^6-benzene)L*]Cl)-catalyzed asymmetric hydrogenation of methyl acetoacetate

Run	Ligand	Use	Conversion (%)[a]	E.e. (%)[a]
1	**5**	1st	52	88
2		2nd	3	30
3	**6**	1st	97	99
4		2nd	53	99
5	**7a**	1st	100	99
6		2nd	100	99
7		3rd	100	99
8	**7b**		25	9

[a] Conversion and e.e. were determined by chiral GC analysis on a Lipodex A column.

shows excellent activity, but for the third recycle, both the activity and enantioselectivity decrease. These last results are probably due to partial solubilization of the ruthenium complex in methanol.

Of the polymeric ligands (Table 4) the most effective are those formed with polymers **6** and **7a**, which present from 97% (run 3) to total conversion (run 5). Nevertheless, polymer **5** having a flexible spacer (run 1) is less selective (88% e.e.) than ligands **6** and **7** (99% e.e., runs 3 and 5). It is worth noting that for polyureas **5**, **6** and **7a**, the more rigid the polymer, the better the conversion and e.e. are (runs 1, 3 and 5).

The re-use of the catalysts was performed with the same method as for the Ru-**4** catalyst; for ligand **5**, marked decreases in conversion from 52 to 3% and also in enantioselectivity from 88 to 30% (runs 1 and 2) were observed during the second use. Concerning the re-use of polymer **6** and **7a**, no change in selectivity (runs 4, 6 and 7, respectively) was observed, but a drop in conversion from 97 to 53% was noticed for **6** (runs 3 and 4). There was no change in conversion observed for **7a**. Subsequent re-use of polymer **7a** showed no drop in either selectivity or activity after three runs. It is noteworthy that diurea **4** (Table 3, runs 4 and 5) is almost as efficient as polyurea **7a** (Table 4, runs 6 and 7). In contrast to polymer **7a**, the crosslinked ligand **7b** led to poor results both in conversion and activity (run 8).

Compared to neutral complexes, the corresponding cationic complexes have been shown to give higher conversion and e.e. For ligand **3**, an important increase of conversion from 36 to 100% and e.e. from 48 to up to 99% has been observed (Tables 1 and 2, runs 3). For ligand **6**, the difference appeared only during the re-use. With the neutral complex, a significant decrease in conversion is observed (from 100 to 17%, Table 1, runs 5 and 6) and for the cationic complex a smaller decrease in conversion with no change in enantioselectivity was observed (from 97 to 53% conversion, Table 3, runs 3 and 4).

This paper demonstrates that chiral chain, non-crosslinked polymers such as polyurea **7a** presenting pseudo C_2-symmetry or diurea **4** with C_2-symmetry are suitable as catalytic ligands for the asymmetric heterogeneous catalytic hydrogenation of ethyl acetoacetate. We have found that ruthenium cationic complexes are generally more efficient than the corresponding neutral complexes. As previously described in the literature,[12,13] we have shown that the rigidity of the spacer is one of the most influential factors upon the reaction. The less flexible the ligand, the better the conversion and enantioselectivity are. From a synthetic point of view, the use of such a heterogeneous cationic ruthenium catalyst in the reduction of C=O bonds is interesting because of high conversions and enantioselectivities. Moreover, they offer ready separation of the catalyst from the reaction products by filtration and their re-use is also effective, without loss either in conversion or enantioselectivity.

3. Experimental

3.1. General

All dried solvents used were of p.a. quality and are commercially available from Acros. Acid chloride and isocyanates were used without purification. *Diam*-BINAP was prepared according to the literature procedure.[16]

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Brüker AM 200 spectrometer (^{1}H: 200 MHz, ^{13}C: 50 MHz, ^{31}P: 81 MHz) unless otherwise stated. Chemical shifts (δ) are reported in parts per million. Coupling constants are reported in Hz, using TMS as external standard. Uncorrected melting points were determined on a Kofler apparatus. Polarimetric measurements were performed on a Perkin–Elmer 241 instrument at room temperature at 589 nm (concentration in g/100 mL solution). Conversion and e.e. were determined by chiral GC analysis on a Macherey–Nagel lipodex A column (25 m×0.25 mm), using a Shimadzu GC-14A apparatus equipped with a flame ionization detector connected to a Shimadzu C-R6A integrator. MALDI-TOF spectra have been performed on a Perkin–Elmer –Voyager-DE STR apparatus, 20 kV, N_2 laser: 2350 nm with an extraction delay of 250 ns. Matrix: α-cyano-4-hydroxycinnamic acid. GPC was carried out at the RHODIA research center. Elemental analyses were carried out by the CNRS (Service Central d'Analyse-Département Analyse Elémentaire), Solaize, France.

3.2. General procedures

3.2.1. Synthesis of polyamide 2. Under argon, a solution of (*S*)-6,6′-diamino-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (100 mg, 0.147 mmol) in dimethylacetamide (4 mL) was treated with terephthaloyl chloride (29.8 mg, 0.147 mmol). The mixture was stirred overnight at room temperature and then isopropanol (1 mL) was added dropwise. After 1 h of stirring, the solvent was removed leading to oligomer **2** (70 mg, 60%). $[\alpha]_D$= +66.1 (*c* 1, DMF); ^{1}H NMR (DMSO) (δ): 1.22 (m, CH_3), 4.39 (m, CH_2), 6.7–8.1 (m, CH). ^{31}P {^{1}H} NMR (DMSO) (δ): −15.82 (s); mp >260°C.

3.2.2. Synthesis of (*S*)-*diam*-BINAP dioctadecylurea 3. Under argon, to a solution of 100 mg (0.147 mmol) of (*S*)-*diam*-BINAP (**1**) in dichloromethane (4 mL) was added dropwise 0.087 mg (0.294 mmol) of octadecylisocyanate. The solution was stirred overnight and the resulting solid was filtered under argon and dried. 0.187 mg (0.145 mmol) of diurea **3** was obtained. Yield: 100%; $[\alpha]_D$=+62.0 (*c* 1, DMF).

^{1}H NMR ($CDCl_3$) (δ): 0.88 (t, $^3J_{HH}$=6 Hz, 3H, CH_3); 1.1–1.6 (m, 32H, CH_2); 1.6–1.7 (m, 2H, CH_2); 3.1–3.2 (m, 2H, CH_2); 6.7–6.9 (m, 1H, CH); 7.0–7.3 (m, 11H, CH); 7.40 (d, $^3J_{HH}$=9 Hz, 1H, CH); 7.63 (s, 1H, CH); 7.78 (d, $^3J_{HH}$=9 Hz, 1H, CH); ^{31}P {^{1}H} NMR($CDCl_3$) (δ): −15.07 (s); mp 69°C; elemental analysis: calcd: C, 79.33; H, 8.88; N, 4.41; O, 2.52; P, 4.87. Found: C, 79.47; H, 8.95; N, 4.52; P, 4.61%.

3.2.3. Synthesis of (*S*)-*diam*-BINAP-dinaphthylurea 4. $[\alpha]_D = +59.0$ (*c* 1, DMF); ^{1}H NMR ($CDCl_3$) (δ): 3.32 (s, 2H); 4.3–4.5 (bs, NH); 6.9–7.8 (m, 14H); 7.8–8.2 (m, 5H); 8.10 (d, $^3J_{HH} = 4$ Hz, 2H); 9.21 (s, 1H); ^{31}P {^{1}H} NMR($CDCl_3$) (δ): −15.71 (s); elemental analysis: calcd: C: 80.14, H: 5.14, N: 5.50, O: 3.14, P: 6.08. Found: C: 80.31, H: 5.23, N: 5.70, P: 5.75%.

3.3. General procedure for the formation of polyureas 5, 6 and 7

Under argon, to a solution of (*S*)-*diam*-BINAP **1** (200 mg, 0.29 mmol) in anhydrous dichloromethane (4 mL), diisocyanate (0.29 mmol, 1 equiv.) (or a mixture of 1 equiv. di- and tri-isocyanate for crosslinked **7b**) was added. The suspension was then stirred overnight and isopropanol (1 mL) was added. After stirring the mixture for 1 h, the solid was filtered under argon and washed twice with isopropanol (2 mL) and twice with dichloromethane (2 mL). The polyurea was dried under vacuum.

Polyurea 5: $[\alpha]_D = -87.0$ (*c* 0.041, DMF); ^{1}H NMR (DMSO-d_6) (δ): 1.0–1.3 (m, CH_3); 3.2–3.7 (m, CH_2); 4.2–4.3 (m, CH, NH); 6.5–8.0 (m, CH); ^{31}P {^{1}H} NMR (DMSO-d_6) (δ): −15.75 (s); mp >260°C.

Polyurea 6: $[\alpha]_D = -91.0$ (*c* 0.086, DMF); ^{1}H NMR (DMSO-d_6) (δ): 1.05(d, CH_3); (s, CH_2); 4.2–4.3 (m, CH_2, NH); 6.4–8.0 (m, CH); 8.51 (s, CH); ^{31}P {^{1}H} NMR (DMSO-d_6) (δ): −15.71 (s); mp >260°C.

Polyurea 7a: $[\alpha]_D = -96.0$ (*c* 0.345, DMF); ^{1}H NMR (DMSO-d_6), 1.21 (d, CH_3); 2.04 (s, CH_3); 4.3–4.4 (m, CH_2, NH); 6.66 (d, $^3J_{HH} = 6.2$, CH); 7–7.6 (m, CH); 7.7–8.0 (m, CH). ^{31}P {^{1}H} NMR (DMSO-d_6), −15.75 (s); mp >260°C.

Polyurea 7b: ^{1}H NMR (DMSO-d_6), 0.9–1.1 (CH_3); 2.04 (s, CH_3); 4.3 (bs, NH); 4.6–4.7 (m, CH_2); 6.5–8.1 (m, CH); ^{31}P {^{1}H} NMR (DMSO-d_6), −15.02 (s); mp >260°C.

3.4. Typical procedure for the preparation of the Ru neutral catalyst[18] and Ru-cationic catalyst[19]

The polymer (0.006 mmol) and $[RuCl_2(benzene)]_2$ (1.3 mg, 0.003 mmol) were stirred at room temperature for 3 h in DMF (1 mL)[18] or in ethanol/benzene (8/1).[19] The solvent was removed under reduced pressure to yield a brown solid.

3.5. Typical procedure for the reduction of methyl acetoacetate

To a suspension of the catalyst in methanol (1.5 mL), the substrate (5.8 mmol) was added and hydrogen introduced into the autoclave to a pressure of 40 atm (S/C: 1000). The mixture was rigorously stirred at 50°C for 18 h. After carefully venting the hydrogen, the sample was centrifuged and the liquid phase was removed by syringe to determine the activity and selectivity by GC.

In order to recycle the catalyst, the product solution was separated from the catalyst by centrifugation then transferred via cannula or by filtration under argon. After washing the catalyst with methanol, the reduction was performed according the above procedure.

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