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'*Diam*-BINAP'; a highly efficient monomer for the synthesis of heterogeneous enantioselective catalysts

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Abstract

The synthesis of a monomeric analogue of BINAP, *diam*-BINAP, is described. The polyaddition of this monomer with 2,6-diisocyanato toluene gave the corresponding oligomer, *poly*-NAP, with a polymerization degree of 8. The ruthenium complex of this polymer proved to be a very efficient heterogeneous catalyst for the hydrogenation of β -ketoesters (99% ee, 0.1 mol% of catalyst). Furthermore the catalyst could be easily reused four times by simple filtration without loss of activity or enantioselectivity. © 2000 Elsevier Science Ltd. All rights reserved.

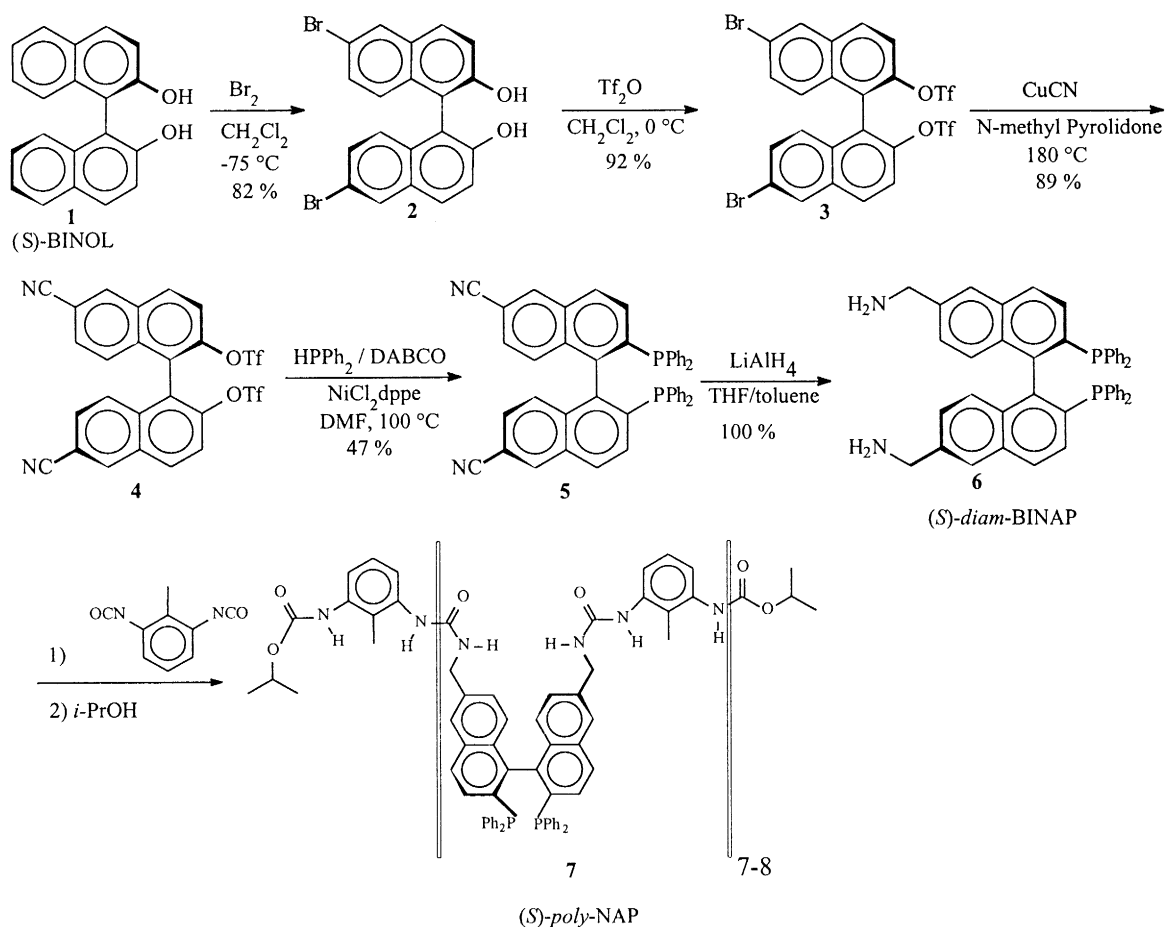
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Although asymmetric catalysis is without doubt one of the most promising methods for the synthesis of chiral compounds,¹ industrial applications are surprisingly still underdeveloped. The main reasons for this are not the qualitative aspects of the transformations where high ees and conversions are routinely obtained for a wide variety of reactions but the rather high costs of the ligand and/or metal.

These drawbacks could be avoided if the catalyst is separated and reused after reaction. An evident way of achieving this is the use of heterogeneous catalysis, allowing easy work-up procedures and possible recycling. Among many different strategies, supporting an already existing homogeneous catalyst seems the most straightforward and with this approach, it can be hoped that the advantages of homogeneous and heterogeneous catalysis can be combined.

We decided to attempt the heterogenization of probably one of the most successful known ligands, BINAP.² In contrast to a recently published method,³ we choose not to attach the ligand to an already existing polymer, but to polymerize the ligand to form a macromolecule with backbone chirality that can maintain the required C_2 symmetric character of BINAP in order to achieve high ees. Since we have obtained good results in heterogenization of chiral ligands by polycondensation of diamines with diisocyanates,⁴ we decided to synthesize a BINAP symmetrically functionalized with two amine moieties (*diam*-BINAP) which allows easy polymerization (see Scheme 1).

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Scheme 1. Synthesis of (*S*)-diam-BINAP and polymerization to (*S*)-poly-NAP

Enantiopure (*S*)-BINOL **1**⁵ was brominated at position 6,6' by the procedure described by Cram et al.⁶ Triflation of compound **2** according to Hayashi,⁷ gave **3** in 92% yield. This molecule could be directly converted by action of CuCN in *N*-methyl pyrrolidone at 180 °C into its dicyano-derivative **4**.^{8,9} The key step was the introduction of the two diphenylphosphino moieties to give diphosphine **5** without modifying the two cyano groups at the other side of the molecule. This transformation was performed in 47% yield by the recently developed procedure of Cai et al.¹⁰

The two dicyano groups were subsequently reduced with LiAlH₄ to give the (*S*)-diam-BINAP **6** in quantitative yield ($[\alpha]_{\text{D}} = -101.3$ ($c=0.3$, DMF)). No oxidation of the phosphines was observed during the last two steps.

Finally we polymerized this monomer with 2,6-tolylene diisocyanate. This reaction in CH₂Cl₂ yielded a white precipitate in 95% yield whose structure was confirmed to be polymer **7** ((*S*)-poly-NAP) with a degree of polymerization of 8 as was determined by end-group analysis by ¹H NMR and elemental analysis.

Poly-NAP is insoluble in organic solvents such as dichloromethane, toluene and methanol, but soluble in polar non-protic solvents like dimethylformamide and dimethylsulfoxide. The fact that it has the polyurea functionality in the backbone is important for obtaining the right solubility/swellability properties in methanol, which is used as solvent for the hydrogenations.

In order to evaluate the optical purity of (*S*)-diam-BINAP and the scope and limitation of the

catalytic properties of *poly*-NAP, the corresponding ruthenium complexes were prepared by reaction of $[\text{RuCl}_2(\text{benzene})]_2$ or $[(\text{COD})\text{Ru}(\text{bis-methallyl})_2]$ according to the general procedures described by Noyori et al.^{11,12} and Genêt et al.¹³ The complexes were tested for the catalytic hydrogenation of various β -keto esters (Table 1).

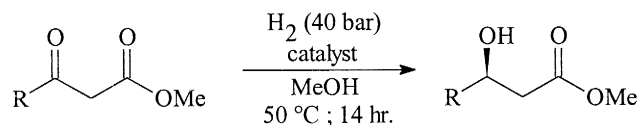


Table 1
Ruthenium catalyzed reduction of different β -keto-esters with BINAP, *diam*-BINAP and *poly*-NAP as ligands

entry	Ligand	R	pression (atm.)	substr./ cat.	conversion ^a (%)	e.e. ^a (%)
1	BINAP	Me	40	1000	100	99 ^b
2	<i>poly</i> -NAP	Me	40	1000	100	99 ^b
3	<i>diam</i> -BINAP	Me	40	2000	100	98 ^c
4	BINAP	Et	40	1000	100	99 ^d
5	<i>poly</i> -NAP	Et	40	1000	100	98 ^d
6	BINAP	3-pentene	4	500	100	99 ¹³
7	<i>poly</i> -NAP	3-pentene	40	1000	100	90 ^b

^a Conversion and enantioselectivity were determined on a Lipodex A (25 m x 0.25 mm) column, ^b Catalyst prepared according to [12], ^c Catalyst prepared according to [11], ^d Catalyst prepared according to [13].

Through heterogenization of BINAP by polymerization a negligible loss of enantioselectivity was observed (entries 1 and 2). The almost perfect enantioselection observed for *diam*-BINAP (entry 3) proves that no racemization has occurred during the synthesis. With ethylacetoacetate as substrate the same promising results were obtained (entries 4 and 5). At last with methyl 3-oxo-6-octenoate as substrate (entries 6 and 7) the selectivity lowered, but this can be explained by the higher pressure we used in our catalytic test compared to literature conditions.¹³

The most important advantage of heterogeneous catalysis over its homogeneous counterpart is the possibility of reusing the catalyst after reaction by simple filtration (Table 2).

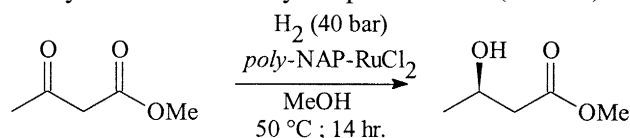


Table 2
Reuse of the *poly*-NAP–Ru catalyst

entry	utilization	subst./ cat.	Conversion (%) ^a	e.e. (%) ^a
1	1	1000	100	99
2	2	1000	100	98
3	3	1000	100	99
4	4	1000	100	99
5	5	1000	18	99

^a Conversion and enantioselectivity were determined on a Lipodex A (25 m x 0.25 mm) column

The catalyst could be reused four times without loss of neither selectivity nor activity (entries 1–4) with catalyst loading as low as 0.1 mol%.

We have thus polymerized BINAP functionalized with methylamine groups (*diam*-BINAP) to give a polymer with backbone chirality in which the complexing moieties are in a C_2 symmetric environment. This polymer is capable of hydrogenating heterogeneously different β -keto esters with high enantioselectivities and activity. It was also shown that this catalyst can be reused at least four times without loss of activity or enantioselectivity. The success of our catalyst can be explained by the balance between the heterogeneous and homogeneous character. The fact that the polymer has a polymerization degree of 8 leads to a solubility/swellability which allows the high selectivity and activity of the catalyst.

Other substrates have to be tested in order to screen the scope and limitations of this new catalytic system. The choice of the diisocyanate and the polymerization conditions can have large effects on the selectivity and activity of this type of catalysts and are currently being examined.

Experimental: All experiments were performed under an argon atmosphere and all solvents were degassed by argon bubbling followed by three freeze/thaw cycles in vacuo, under argon.

Catalysts: Catalysts have been prepared according to literature procedures,^{11–13} by doubling the reaction times.

Hydrogenation: To the above obtained catalyst was added 2 mL of MeOH and the calculated amount of β -keto-ester. This suspension was put in a stainless steel hydrogenation vessel. After purging three times with argon and three times with hydrogen, the pressure was raised to 40 bar and the reaction mixture was stirred at 50°C overnight. The liquid part of the reaction mixture was analysed by GC (lipodex A column) after centrifugation of the suspension to determine both conversion and ee.

Reuse: To the solid which was obtained after centrifugation was added the same amounts of MeOH and methylacetoacetate and the hydrogenation was performed as previously described.

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