Heterogeneous asymmetric catalysis*

Marc Lemaire

Laboratoire de Catalyse et Synthese Organique UCBLCNRS, UMR 5622, CPE, 43 boul. 11 Novembre, 69622 Villeurbanne Cédex, France

Abstract: Examples of enantioselective catalysts, including homogeneous supported catalysts and biphasic liquid/liquid, are described and compared. In the case of asymmetric hydride transfer, polythiourea was proven to be more efficient for ruthenium-catalyzed reduction of aryl ketones, although the iridium complexes gave rise to higher ee when using amino sulfonamide bound to a polystyrene matrix. In the case of asymmetric reduction, the modification of the binap allows the formation of a polymer that could be used as a catalyst precursor and exhibits enantioselectivities as high as observed in solution, but easier to separate and recycle. Bisoxazoline bound to silica particules could also be used in copper-catalyzed asymmetric Diels–Alder reaction and cyclopropanation with selectivities similar to that obtained in solution.

INTRODUCTION

Research in asymmetric catalysis achieved prominence in both academic and industrial laboratories toward the end of the 1960s with the discovery of the use of chiral phosphine by Knowles [1] and Kagan [2]. Although tremendous financial and intellectual efforts have been invested in this particular field during the last 30 years, the industrial achievements appear to be rather modest. We believe that the beauty of the original results using soluble chiral phosphine are responsible for continuing interest in their applications in asymmetric catalysis, but their dominant role seems to have somewhat limited the development of other types of ligands and catalysis [3]. On one hand, the high cost of both the phosphine ligand and the precious metal require the separation and the recycling of the catalyst; on the other hand, low stability of the phosphines makes their recycling difficult, if not impossible. Already, the heterogeneous catalysis has been very successful in terms of industrial applications, and, therefore, the asymmetric version was considered as a real need for the practical development of chiral technology. Indeed, the application of heterogeneous asymmetric catalysis was tested (and observed) even before the work of Knowles and Kagan, as stated above. In 1932, Schwab showed that kinetic resolution could be observed using metal deposited onto chiral quartz [4], and in 1956, Izumi reported the use of metal deposited onto silk as a heterogeneous asymmetric catalyst [5]. Considering the complex structure of silk fiber, it is not surprising that these researchers had some difficulties in repeating their own results, which discouraged research in this field. But the interest in homogeneous asymmetric supported catalysis revived very soon after the discovery of modern asymmetric catalysis with the report of an efficient supported DIOP as early as 1973 [6]. Although the homogeneous catalysis has reached a high level of selectivity and efficiency during the intervening period, interest in further improvements continued to grow [7]. Several technologies have been proposed in order to achieve easier separation of the catalyst from the bulk of the reaction, including:

- Solid/liquid catalysis, including the use of modifier onto metal particles and homogeneous support on both organic and inorganic materials.
- Biphasic liquid/liquid catalysis, including water, fluorinated solvent, ionic liquid, and supported aqueous phase.

We have developed several of these technologies during the last few years in order to obtain asymmetric catalysts as efficient as the homogeneous counterparts, but with easy separation and recycling of the catalyst. On one hand, we have created new ligands (amine, amide, urea, thiourea) that are easy to transform into insoluble polymers, and on the other hand, we have modified some of the well-known, selective, and efficient catalysts (i.e., binap, bisoxazoline, etc.) in order to obtain easily recyclable materials.

NEW LIGANDS, NEW POLYMERS FOR HOMOGENEOUS SUPPORTED CATALYSIS

Our first approach began in 1993 [8] when we found that *N,N*-dimethyl diphenyl ethylenediamine could be used as ligand for asymmetric hydride transfer catalyzed by rhodium. Very high ee and conversion were obtained for the reduction of methyl phenyl glyoxylate, but this result suffered from several drawbacks (Fig. 1). Firstly, the catalyst is only selective with this particular substrate, and acetophenone, for example, gave rise to only 67 % ee under the same conditions. Moreover, 5 % catalyst was required and even with the more reactive substrate (methyl phenyl glyoxalate), lower concentration of the catalyst led to competitive transesterification, producing the unsoluble isopropyl ester of phenylglyoxalic acid and causing the reaction to stop.
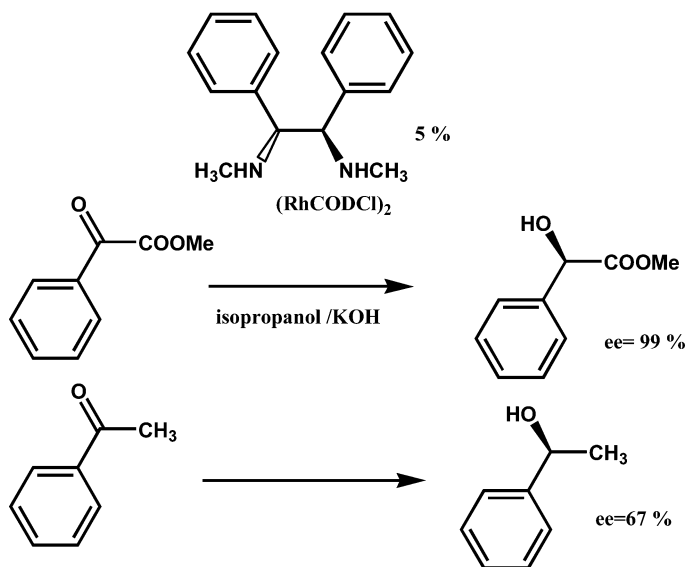

Fig. 1 Reduction of aryl ketone by catalytic hydride transfer.

The diamines are easily accessible in both enantiomeric forms [9], and they could be transformed into polyamide or polyurea by using diacid chloride or diisocyanate, respectively (Fig. 2) [10].
The first of these polymers could be used as a ligand and support for asymmetric allylic substitution with high selectivity with the very classical substrate 1,3-diphenylallyl acetate.
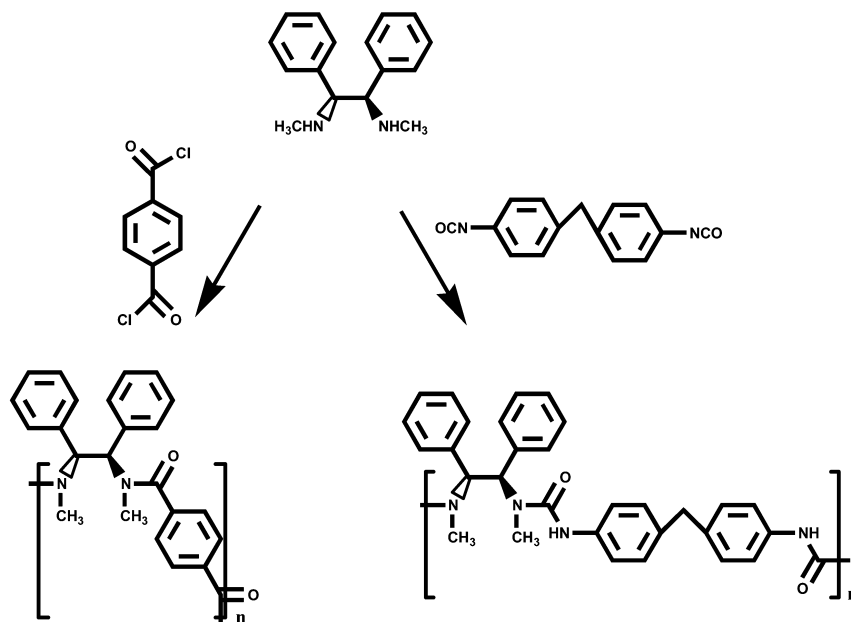
Fig. 2 Synthesis of chiral polymers for asymmetric hydride transfer.

Nevertheless, the observed ee was significantly lower than that obtained in solution with the corresponding diamine (Fig. 3). However, the separation of the catalyst from the bulk of the reaction was easy, and the recycling was possible under careful manipulation of the used material (low temperature, storage in absence of air, and a short time lapse before reuse). Unfortunately, polyamide proved to be useless in the case of asymmetric hydride transfer, but in contrast, the polyurea could be used successfully for this reaction in the presence of rhodium precursor (Fig. 4).

Although the reactions need to be performed at a higher temperature (60 °C instead of room temperature), the observed ee's are similar to those obtained in solution with diamine as ligand. Moreover, several recyclings of the catalyst could be realized by filtration and reuse without precaution or treatment. In this particular case, a small level of cross-linking of the polymer is used [11]. The enantio-selectivity of the catalyst was improved by the application of molecular imprinting (MIP) technology. In the first type of material, the metal precursor is deposited onto the polymer chain. Conversely, in the case of MIP technology, the metal-complexed diamine is first formed in solution, and, subsequently, the chloride anion of the metal precursor is exchanged by the product of the reaction with the configuration
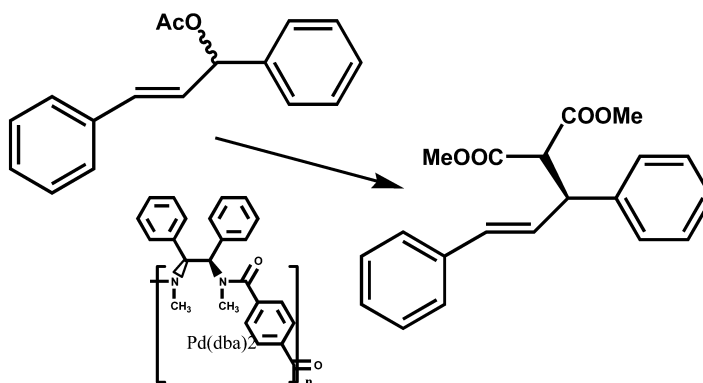
Fig. 3 Heterogeneous asymmetric Tsuji–Trost reaction ee = 80 %.
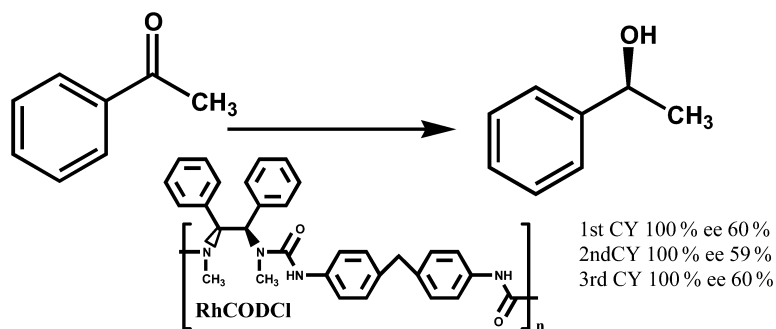
Fig. 4 Hetereogeneous asymmetric hydride transfer (60 °C, isopropanol/KOH).

of the major product followed by the polymerization and the cross-linking. After elimination of the imprinted molecule, the material should possess the catalytic sites with size and polarity adapted to the formation of one particular enantiomer. Indeed, with careful optimization of the cross-linking and other synthesis parameters, 70 % ee could be obtained [12].

Although limited in terms of ee, this result is an example of the interest of MIP technology and also of inherent limitation because the imprinted created material could be used only for the specific substrate. For example, methyl phenyl glyoxalate and isopropyl phenylketone are not reduced by the catalyst prepared in the presence of chiral phenyl ethanol.

When we became interested in using thiourea as ligand, almost no information concerning the potential of such a functional group was available, and very few reports existed concerning the coordination chemistry of thioureas. We were very pleased to be the first group who demonstrated the potential of this new ligand for asymmetric hydride-transfer catalysis. Nevertheless, upon using rhodium metal precursor, only a low ee could be observed. However, when a ratio of metal/ligand of 3 was employed, the ee could be increased to 63 %, but at the cost of slowing down the reaction rate [13]. The use of ruthenium precursor was more successful because using 2 % catalyst and an equimolar ration metal/ligand, the asymmetric reduction of acetophenone could be achieved with 91 % ee with complete conversion (Fig. 5). Polythiourea could be synthesized easily by condensing diamine and dithioisocyanate [14].
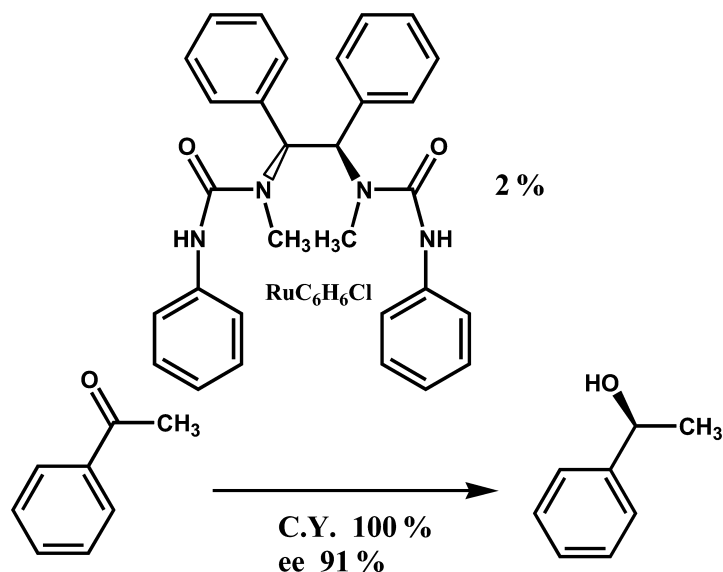

Fig. 5 Reduction of acetophenone with thiourea as ligand (isopropanol/^{t}BuOK, 60 °C).

Using polythiourea as ligand and support associated with ruthenium precursor, 77 % ee was obtained for the reduction of acetophenone by hydride transfer. The catalyst could be recycled five times with almost no loss of both reactivity and selectivity (Fig. 6).
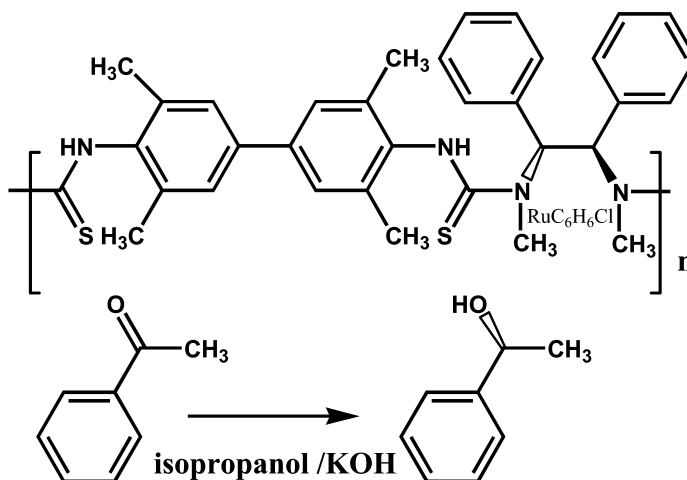

Fig. 6 Polythiourea as catalyst for asymmetric hydride transfer; 1st run ee = 77 % , 5th run ee = 69 %.

MODIFICATION OF ALREADY KNOWN AND EFFICIENT CATALYST IN ORDER TO OBTAIN EASY-TO-RECYCLE MATERIALS

Another way to obtain heterogeneous asymmetric catalyst is to modify already known ligands. During the past few years, Noyori's group has been probably one of the most successful in creating new asymmetric catalysts. For example, sulfonamide derived from Corey's diamine is one of the more efficient ligands for asymmetric hydride-transfer reaction [15]. We have prepared monomers having such amino sulfonamide group by using styrene sulfonyl chloride and the Corey diamine followed by copolymerization with styrene and divinyl-benzene under carefully controlled conditions to achieve a desired level of the site concentration and cross-linking. Noyori's best results were obtained with ruthenium precursor, but when we used our heterogeneous catalyst prepared with the same metal precursor, the results were rather disappointing. Either we used non-cross-linked material and we got good conversion but low ee or we used cross-linked material and we obtained good ee, but low conversion. We were more successful when we used iridium/cod chloride dimer as precursor. In this case, 92 % ee was obtained for the reduction of acetophenone by hydride-transfer reaction with non-cross-linked material, and even higher ee was obtained upon using the material prepared with 5 % divinyl benzene (Fig. 7) [16].

The second type of catalyst developed by the Noyori's group is the association of the binap with chiral diamines, which allows the reduction of aryl ketone with very high ee and turnover number.
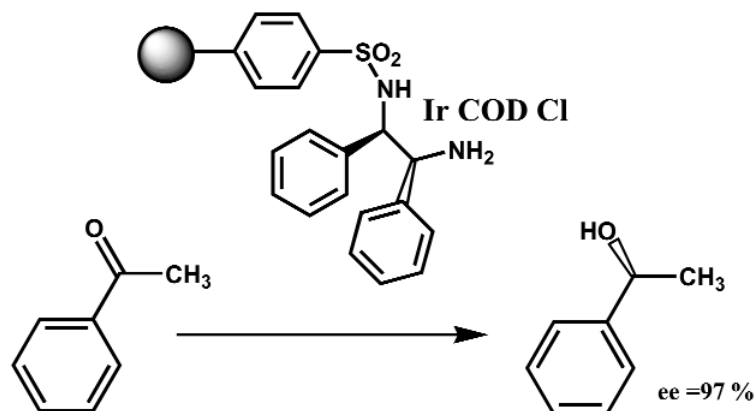
Fig. 7 Heterogeneous asymmetric hydride transfer using sulfonamide bound to polystyrene matrix.

Derivatives of binap could be synthesized starting from the chiral binol using protection of the phenol by triflate, then bromination at 6 position is performed at low temperature, followed by nucleophilic substitution using copper cyanide and the introduction of the phosphine and finally the reduction of the nitrile by aluminium hydride (Fig. 8) [17].
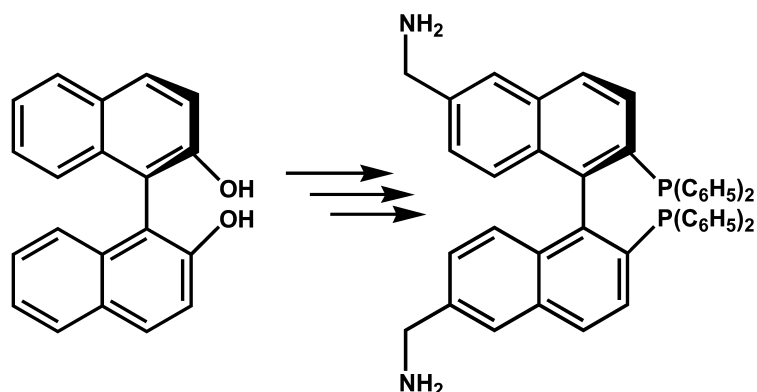

Fig. 8 Synthesis of diam binap.

The 6,6′ diam binap could be used as monomer and transformed into material such as polyamide or polyurea with various spacers between the binap moieties. When using ruthenium dibromide complexes as catalyst, the ee is largely dependent on the spacer structure. Polyamides generally give rise to poor results, and the use of polyurea with flexible chain produces nearly the same outcome. The result appears to be much better when using rigid spacers such as diphenyl methane or tolyl, which have given the best results so far [18]. Reduction of the acetyl methylacetonate is almost stereospecific (ee >98 %), and conversion is complete in one night with a substrate/catalyst ratio of 1:1000. Moreover, the catalyst could be filtrated and reused five times without any decrease of both the ee and the conversion (Fig. 9). This catalytic system also works quite well for the CC double bond reduction [19], and more interestingly, the synergetic effect between polymer bearing binap moities and diamine could also be noticed. Indeed, the enantioselective reduction of aryl ketone is achieved with ee similar to that observed in solution, and the catalyst could be recycled without adding either amine or the metal precursor [20].
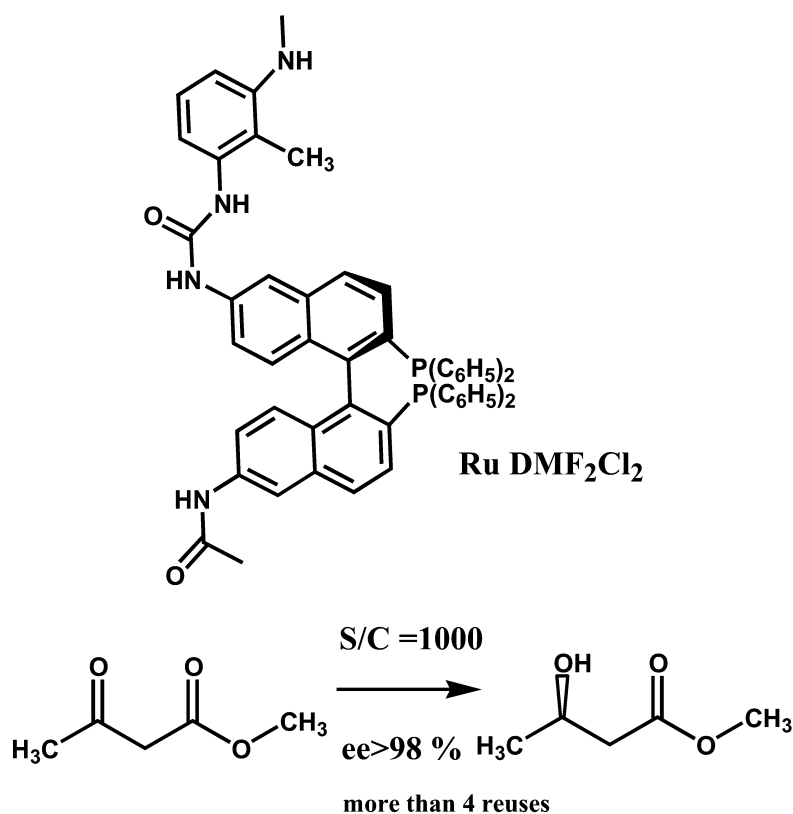
Fig. 9 Reduction by molecular hydrogen onto polynap catalyst.

Another easy way to obtain efficient separation of the catalyst from the product of the reaction, is to use water-soluble catalyst [21] and a biphasic water/organic solvent. "Diam binap" could be easily transformed into water-soluble catalyst. Firstly, the hydrobromide salt is prepared by reacting with HBr, and then the ruthenium DMF complex is formed in a manner similar to the formation of the metal complexes with binap [22] (Fig. 10). Hydrogenation of β ketoester in water gave rise to almost the same ee as observed in organic solvent. The product of the reaction was separated by extraction with heptane and the water-soluble catalyst could be reused five times without any drop either in the enantioselectivtity or the conversion.
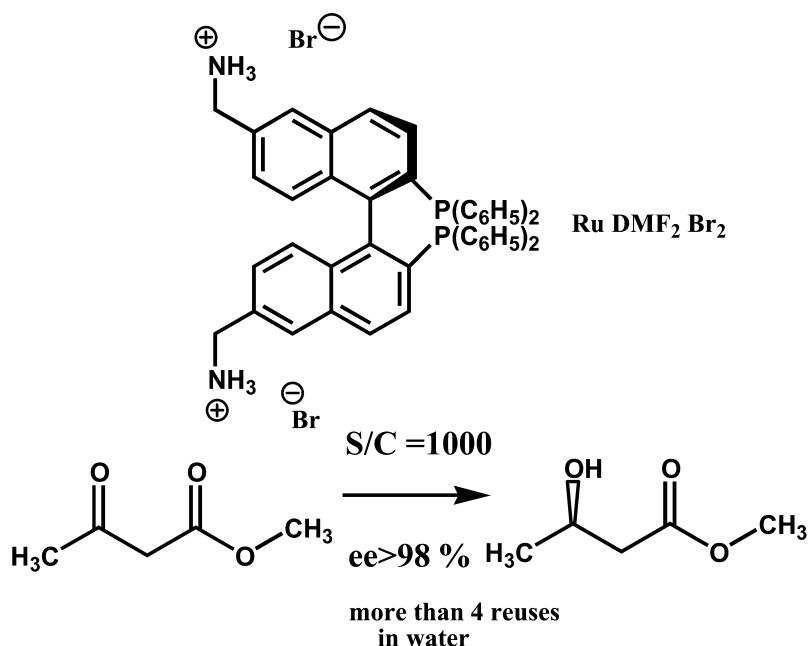
Fig. 10 Reduction of ketoester in water.

Bisoxazoline is also among the more widely used ligands allowing the formation of many kind of metal complexes which have been applied to a variety of reactions, i.e., allylic substitution, aziridination, cyclopropanation, allylic oxidation, Mukaiyama aldol reaction, hydrocynation, Diels–Alder reaction, and so on [23]. Among the bisoxazolines, the indabox is one of the more selective, but in most of the cases, 5 to 10 % of the catalyst has to be used. The recycling of the catalysts is required if practical applications are to be viable and economic. The "indabox" ligand could be transformed into diol using formaldehyde in the presence of triethylamine using a complex mixture of solvent [24]. This diol could be used as monomer for the formation of polyurethane with indabox in the backbone or transformed into ethoxysilane and used for functionalization of silica particles (Fig. 11). Polyurethane was transformed into the catalyst by addition of copper triflate. This catalyst unfortunately produced ee in the benchmark Diels–Alder reaction not exceeding 55 %, which is considerably lower than that obtained in solution [25]. In addition, the material possessed poor mechanical properties and appears to be difficult to separate and recycle. In contrast, the silica-coated catalyst could be used and recycled without difficulties. When using copper triflate as the metal precursor, ee of 70 % could be obtained, but both the conversion and the selectivity sharply declined after the third recycling. Copper perchlorate as metal precursor is less sensitive to water, and ee of 80 % could be reached. Moreover, the catalyst could be recycled without decreasing the ee and the conversion. The silica surface contains silanol group, which could act as Brønsted acid or as ligand for the copper salt and catalyze the formation of the Diels–Alder adduct without enantioselectivity. Indeed, when using soluble indabox complex as catalyst, addition of silica induced a significant decrease in the ee. We have used trimethylsilylimidazole in order to transform the silanol group into trimethyl silyl ether (Fig. 11).

The new material exhibited higher selectivity (92 % at –78 °C), which is as good as that obtained in solution under similar conditions. This material could be recycled several times without observing any decrease either in efficiency or selectivity.
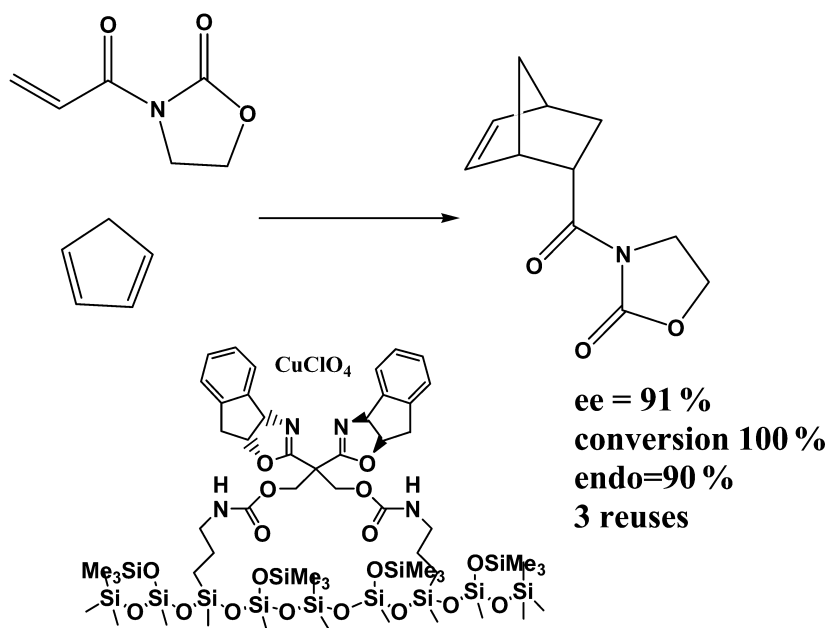
Fig. 11 Asymmetric heterogeneous Diels–Alder reaction.

CONCLUSION

We have described several examples of heterogeneous asymmetric catalysts as selective and efficient compared to their homogeneous counterparts. This is part of a large effort in both academic and industrial laboratories devoted to the recycling of asymmetric catalysts. Development of heterogeneous catalysis has played an important role in the industrial chemistry of the 20th century. The recent successes in heterogeneous asymmetric catalysis could very well allow the increasing use of catalysis in chirotechnologies.

REFERENCES

1. W. S. Knowles and M. J. Sabacky. *Chem. Commun.* 1445 (1968).
2. H. B. Kagan and T. P. Dang. *J. Am. Chem. Soc.* **94**, 6429 (1972).
3. F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire. *Chem. Rev.* **100**, 2159 (2000).
4. G. M. Schwab and L. Rudolph. *Die Natur Wissenchaft* 363 (1932).
5. S. Akabori, S. Sakurai, Y. Izumi, Y. Fuji. *Nature* **323**, 927 (1956).
6. N. Takaishi, H. Imai, C. A. Bertelo, J. K. Stille. *J. Am. Chem. Soc.* **100**, 264 (1978).
7. "Recoverable catalysts and reagents", J. A. Gladysz (Ed.), *Chem. Rev.* 102 (2002).
8. P. Gamez, F. Fache, P. Mangeney, M. Lemaire. *Tetrahedron Lett.* **34**, 6897 (1993).
9. P. Mangeney, T. Tejero, A. Alexakis, F. Grosjean, J. F. Normant. *Synthesis* 255 (1988).
10. B. Dunjic, P. Gamez, F. Fache, M. Lemaire. *J. Appl. Polym. Sci.* **59**, 1255 (1996).
11. P. Gamez, B. Dunjic, F. Fache, M. Lemaire. *J. Chem. Soc., Chem. Commun.* 1417 (1994).
12. P. Gamez, B. Dunjic, C. Pinel, M. Lemaire. *Tetrahedron Lett.* **36**, 8779 (1995); F. Locatelli, P. Gamez, M. Lemaire. *J. Mol. Catal.* **135**, 89 (1998).
13. F. Touchard, F. Fache, M. Lemaire. *Tetrahedron: Asymmetry* **8**, 3319 (1997).
14. F. Touchard, P. Gamez, F. Fache, M. Lemaire. *Tetrahedron Lett.* **38**, 2275 (1997).
15. S. Hashiguchi, A. Fujii, J. Takehara, R. Noyori. *J. Am. Chem. Soc.* **117**, 7562 (1995).
16. R. Ter Halle, E. Schulz, M. Lemaire. *Synlett* 1257 (1997).

17. T. Ohkomuna, M. Koizuma, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokoyama, T. Ikariya, R. Noyori. *J. Am. Chem. Soc*. **120**, 13529 (1998).
18. R. Ter Halle, B. Colasson, E. Schulz, M. Spagnol, M. Lemaire. *Tetrahedron Lett*. **41**, 643 (2000).
19. R. Ter Halle, E. Schulz, M. Spagnol, M. Lemaire. *Tetrahedron Lett*. **41**, 3233 (2000).
20. R. Ter Halle, E. Schulz, M. Spagnol, M. Lemaire. *Synlett* 680 (2000).
21. B. Cornils and W. A. Herrmann. *Aqueous Phase Organometallic Catalysis*, Wiley-VCH Weinheim (1998).
22. T. Lamouille, C. Salluzo, R. Ter Halle, F. Le Guyader, M. Lemaire. *Tetrahedron Lett*. **42**, 663 (2001).
23. A. K. Ghosh, P. Mathivanan, J. Cappielo. *Tetrahedron: Asymmetry* **9**, 1 (1998).
24. D. Rechavi and M. Lemaire. *J. Mol. Cat. A* **182**, 249 (2002).
25. A. K. Ghosh, H. Cho, J. Cappielo. *Tetrahedron: Asymmetry* **9**, 3687 (1998).
26. D. Rechavi and M. Lemaire. *Org. Lett*. **3**, 2493 (2001); D. Rechavi and M. Lemaire. *Chem. Rev*. **102**, 3467 (2002).