Available online at www.sciencedirect.com
ScienceDirect
Coordination Chemistry Reviews 252 (2008) 624–646
COORDINATION CHEMISTRY REVIEWS
www.elsevier.com/locate/ccr

Review

Recent advances in the immobilization of chiral catalysts containing bis(oxazolines) and related ligands

José M. Fraile, José I. García, José A. Mayoral *

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón and Instituto Universitario de Catálisis Homogénea, Universidad de Zaragoza – C.S.I.C., E-50009 Zaragoza, Spain

Received 26 June 2007; accepted 13 October 2007
Available online 22 October 2007

Dedicated to the memory of Dr. Tibor Tarnai (1966–2007).

Contents

1. Introduction 624
2. Carbene reactions: cyclopropanation and C–H insertion 625
3. Aziridination 634
4. Lewis acid promoted reactions 635
   4.1. Diels–Alder reactions 635
   4.2. Ene reactions 639
   4.3. Mukaiyama aldol reactions 640
   4.4. Other Lewis acid catalyzed reactions 641
5. Allylic substitution 643
6. Oxidations and reductions 644
7. Conclusions 644
   Acknowledgement 645
   References 645

Abstract

Bis(oxazoline) ligands have been used to prepare chiral catalysts for a large variety of enantioselective reactions. This versatility has attracted interest towards its immobilization, to profit from the advantages of using heterogeneous catalysis with respect to catalyst separation, possible recycling or even use as a multipurpose catalyst. In this review recent results dealing with the immobilization of bis(oxazoline) and related ligands are presented, to show the scope and limitations of the different immobilization strategies. As the behavior of grafted catalysts is related to the reaction in which is used, the review is ordered by type of reaction. The influence of the immobilization on the results and the problems related to catalyst recovery and reuse are discussed in each case. Although most of the examples are referred to solid/liquid systems, immobilization is considered from a broader point of view and some liquid/liquid approaches are also presented.

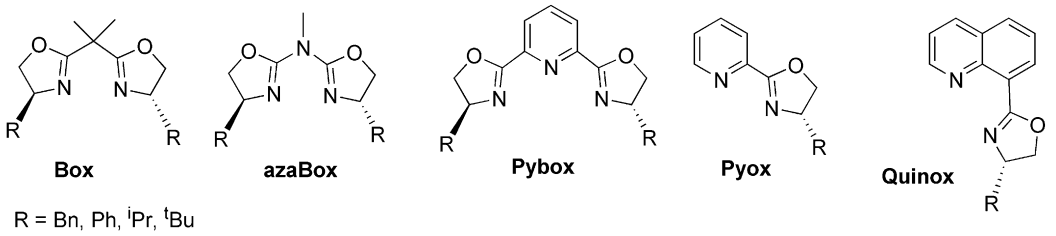
Keywords: Asymmetric catalysis; Supported catalysis; Bis(oxazoline); Azabis(oxazoline); Biphasic catalysis; Pybox

1. Introduction

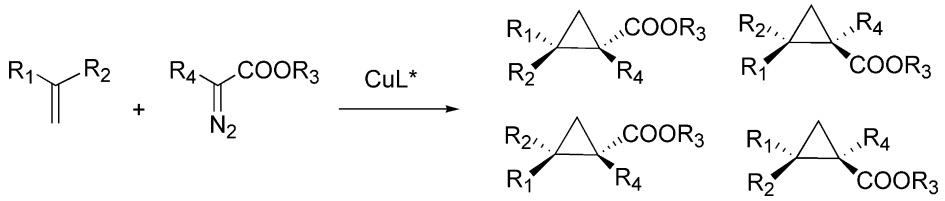
Chiral oxazoline-based ligands (Scheme 1) are among the most popular of ligands used in asymmetric catalysis because of two factors. On the one hand they are easily obtained from inexpensive amino alcohols forming a large variety of structures, on the other, they are very efficient in the promotion of an important variety of enantioselective organic reaction. The preparation and use of bis(oxazolines) have been recently reviewed [1–3]. Due to the inherent advantages, in separation and handling, of heterogeneous over homogeneous catalysts, the heterogenization of this versatile family of chiral ligands has attracted a great deal of

* Corresponding author. Fax: +34 976762077.
E-mail address: mayoral@unizar.es (J.A. Mayoral).

0010-8545/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ccr.2007.10.011



Scheme 1. General structure of the chiral ligands studied.



Scheme 2. Cyclopropanation reactions studied.

attention and the way in which this heterogenization influences the enantioselectivity of the asymmetric reactions was reviewed some time ago [4].

This new review shows the advances in the different strategies for the immobilization of chiral ligands containing oxazoline groups. Although in most cases C_2-symmetric ligands have been employed, in some others, new ligands lacking this symmetry (Scheme 1) have been used to favor the reaction itself, the immobilization strategy or the recovery of the catalyst. The word immobilization is considered in this review from a broad point of view. Solid (insoluble) catalysts are classified by the type of interaction between the solid support and the catalytic complex: covalent or non-covalent bonds. Examples dealing with soluble polymers or liquid–liquid systems, such as the use of fluorinated solvents or ionic liquids, are also presented and are considered as a different category, given that in most cases they are examples of homogeneous catalysis with biphasic separation methodology.

It is well known that the success of a chiral ligand depends on the reaction in which it is used. The same happens when immobilized systems are considered, so the best immobilization strategy for one reaction may not be the best for another one. For this reason the review is ordered by types of reaction so that different ligands, immobilization strategies and supports are compared in the same process, showing the drawbacks and advantages of all of them.

2. Carbene reactions: cyclopropanation and C–H insertion

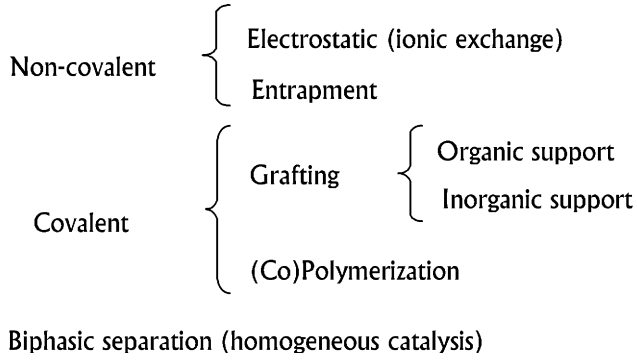
Oxazoline-derived ligands have been extensively used in enantioselective catalytic cyclopropanation reactions [1–3]. Immobilized copper and ruthenium complexes, able to form metal carbene intermediates [5,6], have been tested as catalysts for these reactions.

We can distinguish three different families of oxazoline-derived chiral ligands, used in immobilized catalytic cyclopropanation reactions, namely bis(oxazolines) themselves (Box), aza-bis(oxazolines) (azaBox), and pyridine-bis(oxazolines) (Pybox). Some other oxazoline-derived chiral ligands, lacking C_2 symmetry, have also been used, but only in very particular instances. The structures are shown in Scheme 1.

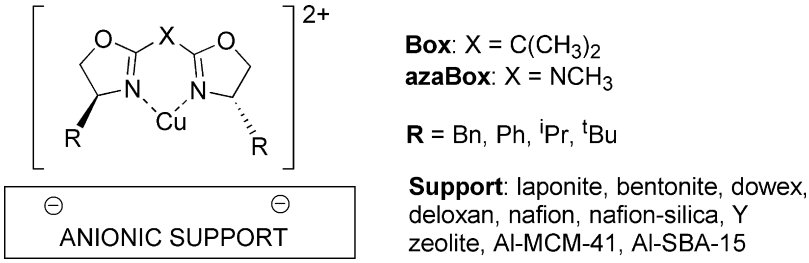
Scheme 2 shows the cyclopropanation reactions studied with these catalytic systems.

In the vast majority of cases, the reagents used are styrene (R_1 = Ph, R_2 = H) and ethyl diazoacetate (R_3 = Et, R_4 = H) (benchmark cyclopropanation reaction). However, in some cases, the reactions of other alkenes, such as 1,1-diphenylethylene ($R_1 = R_2$ = Ph), 2-methylpropene ($R_1 = R_2$ = Me), 1-methylstyrene (R_1 = Ph, R_2 = Me), 1-hexene (R_1 = *n*-Bu, R_2 = H), and other diazocompounds, such as *tert*-butyl diazoacetate (R_3 = *t*-Bu, R_4 = H), menthyl diazoacetate (R_3 = (1*R*,2*S*,5*R*)-menthyl, R_4 = H), and ethyl 2-phenyldiazoacetate (R_3 = Et, R_4 = Ph), have also been investigated.

All the main catalyst immobilization strategies have been tested in the cyclopropanation reactions. We can classify these strategies, following the chart shown in Scheme 3, in two main groups, namely non-covalent and covalent immobilization. Different kinds of supports have been used, including inorganic (silicas, clays, zeolites) and organic (synthetic and natural polymers, graphite) materials. In some cases, biphasic separation systems have also been used.



Scheme 3. Main immobilization strategies used in the enantioselective cyclopropanation reactions.



Scheme 4. Immobilization of Box-Cu and azaBox-Cu complexes by cationic exchange.

Historically, the non-covalent immobilization of Box-copper complexes through ionic exchange on anionic supports was the first strategy described, and has been thoroughly explored by Mayoral and co-workers since 1997.

The immobilization of PhBox-$CuCl_2$ and BnBox-$CuCl_2$ complexes by cation exchange onto clays (laponite and bentonite, Scheme 4), and their use in the benchmark reaction was the first case described for these systems [7], and the integrity of the supported complex was studied by different spectroscopic techniques [8]. Some interesting support effects were described, in particular the change of *trans*/*cis* selectivity towards the *cis* isomers (even with a slight *cis* preference (47:53) in some cases). In general, the results obtained with the supported catalysts were superior to those obtained in the homogeneous phase with the same complexes. In subsequent studies [9–11], ^{t}BuBox and $Cu(OTf)_2$ were also used for catalyst immobilization. In general, lower enantioselectivities with regard to the homogeneous catalytic systems were observed, as well as lower *trans*/*cis* ratios. Interestingly, some of the systems were recoverable and reusable with similar results, constituting the first example of a recoverable enantioselective catalyst for this reaction.

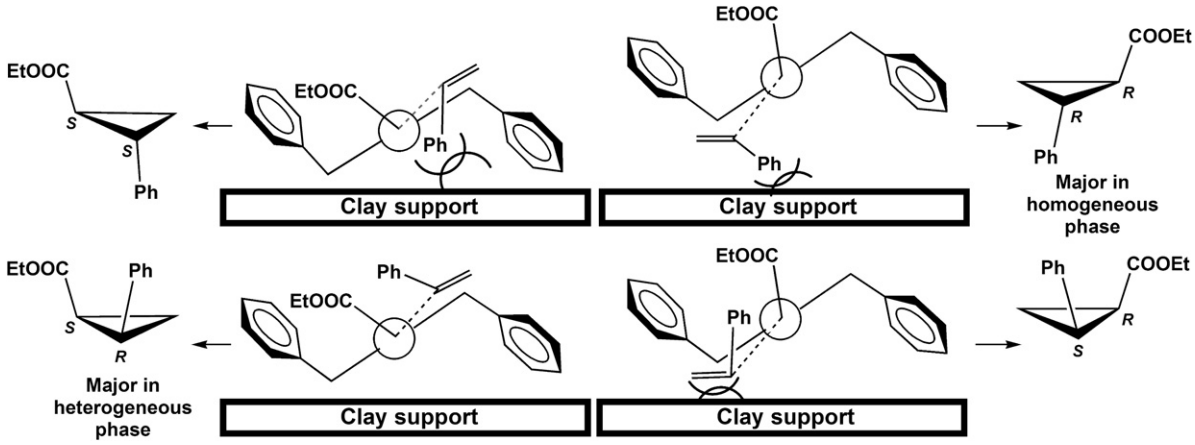
Given the importance of the counterion effect on the enantioselectivity [12], other anionic supports have also been tested, trying to approach the low coordinating ability of the trifluoromethanesulfonate (triflate) anion, used in homogeneous phase. Thus, some anionic resins, such as Dowex, Deloxan, Nafion, and Nafion-silica composites, have been tested as supports for Box-copper complexes [10,11]. The best results were obtained with the Nafion-based supports. Using the PhBox ligand, results virtually identical to those obtained in homogeneous phase have been described (ca. 60% ee in *trans*-cyclopropanes). Furthermore, the catalyst is easily recoverable and reusable with the same results. Nafion itself has a very low specific surface (<0.02 $m^2\ g^{-1}$), but the Nafion-silica nanocomposites have much better values (>80 $m^2\ g^{-1}$), allowing higher catalyst loadings and better catalytic performance. Unfortunately, the best ligand in homogeneous phase, ^{t}BuBox, did not exhibit similar performance when their copper complexes were immobilized onto the same supports, and only modest enantioselectivities were obtained, probably due to the leaching of ligand and the concurrence of non-enantioselective reaction. The same effect was subsequently reported with other Nafion-silica supports [13].

None of the anionic supports tested, apart from clays, displayed the "pro-*cis*" behavior observed with these lamellar solids, the *trans*/*cis* selectivity being in the same 66:34 range obtained in homogeneous phase. This particular effect has been ascribed to the two-dimensional nature of the clay surface, and can be magnified if a solvent with a dielectric constant lower than dichloromethane is used. Under these conditions, the cationic complex forms a tighter ion pair with the anionic surface, and the steric effect of the latter increases. Thus, when the cyclopropanation reactions were catalyzed by the laponite-exchanged PhBox-Cu complex, in hexane or styrene, a complete reversal of the *trans*/*cis* diastereoselectivity (31:69) was observed [13,14]. Even more interestingly, the major *cis*-cyclopropane obtained has the opposite absolute configuration, with regard to homogeneous phase results. When 2-(oxazolin-2-yl)pyridines (Pyox, Scheme 1) are used as ligands in the same systems, the same *cis* preference was obtained, but no reversal in the configuration of the major *cis*-cyclopropane was observed [15]. Knowledge of the mechanism of this reaction [5], including the stereoselection [16], allowed the proposition of a model to explain the behavior observed, based on the steric effect of the support surface on the incoming alkene (Scheme 5). The transition state lacking this steric interaction turns out to be the most stable in the heterogeneously catalyzed reactions, leading to the major product observed.

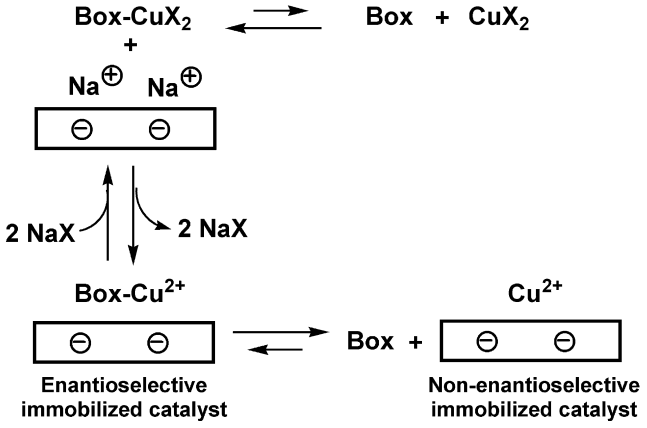
As already mentioned, a key point for the recoverability of these catalysts is the stability of the Box-copper complex, and this issue has also been thoroughly investigated [13,17]. Thus, when the ^{t}BuBox-$Cu(OTf)_2$ complex is immobilized by cationic exchange on a Nafion-silica nanocomposite (SAC-13), only about 20% ee for *trans*- and *cis*-cyclopropanes is obtained (compared with over 90% ee in homogeneous phase) in the reaction of styrene with ethyl diazoacetate, which indicates the probable leaching of the ligand from the immobilized catalysts, because of steric interactions with the support. This hypothesis was validated by adding free ^{t}BuBox ligand to the heterogeneously catalyzed reaction. In these conditions, 91% ee in *trans*-cyclopropanes and 88% ee in *cis*-cyclopropanes were obtained [13], showing the role of complexation equilibria on the enantioselectivity (Scheme 6).

Azabis(oxazoline) (azaBox) ligands possess a higher coordinating ability than their analogous Box ligands, as shown by theoretical calculations and competitive catalytic experiments [18]. This property has been exploited to prepare more stable immobilized catalysts.

When aza^{t}BuBox-$Cu(OTf)_2$ complex is exchanged on Nafion-silica SAC-40, spectroscopic and analytical results indicate the integrity of the complex [13]. When this immobilized catalyst is used in the benchmark cyclopropanation reaction,



Scheme 5. Model of the steric interactions between the different transition states of the cyclopropanation reaction and the surface of the clay support, responsible for the stereochemical changes observed in the heterogeneously catalyzed reactions.



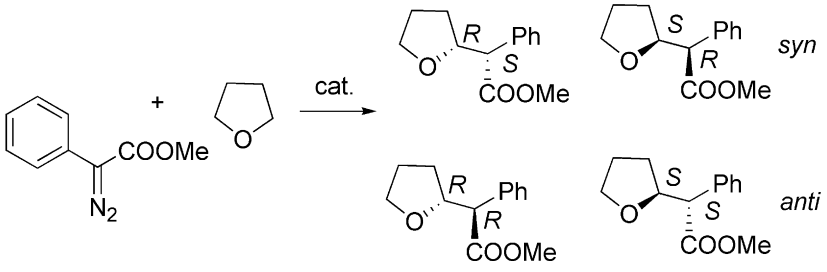
Scheme 6. Complexation equilibria affecting the preparation of immobilized enantioselective catalysts by cationic exchange.

90% ee in *trans*-cyclopropanes and 84% ee in *cis*-cyclopropanes is obtained. Furthermore, in a second run 88% ee and 80% ee is obtained in these products, indicating that most of the chiral complex remains immobilized on the support. A more extensive study, using different ligands, supports and Cu salts corroborated these conclusions [18].

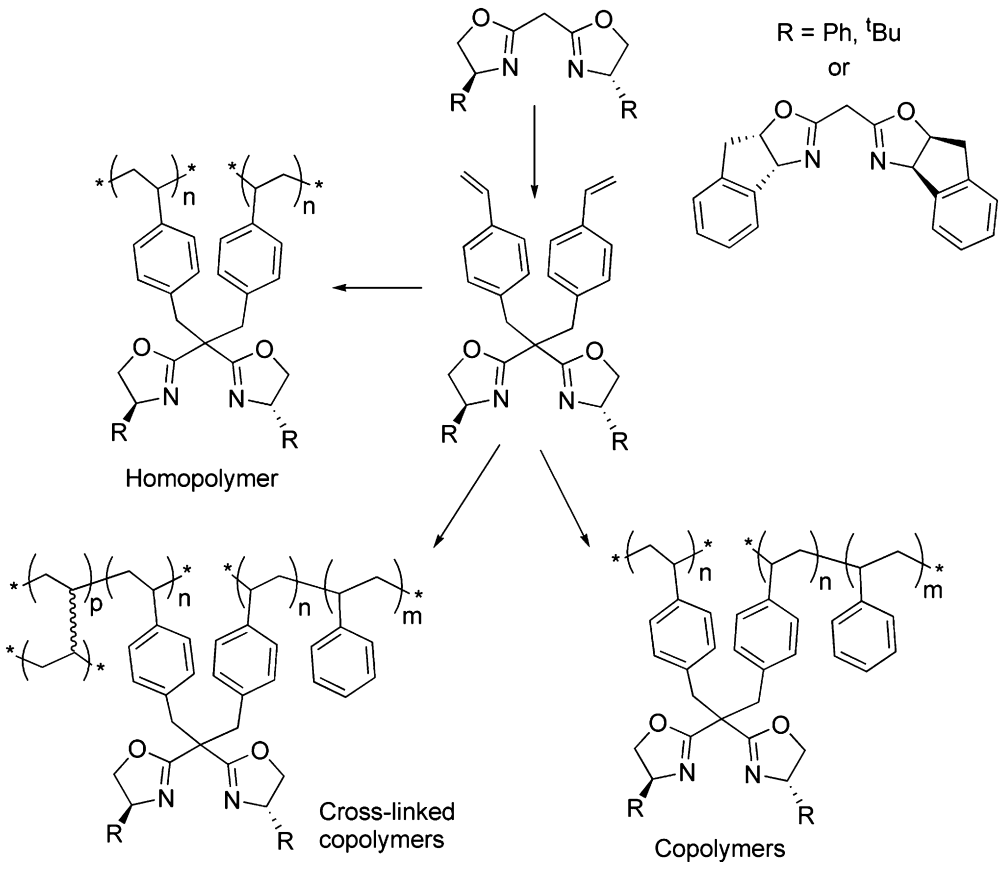
A more recent application of enantioselective catalysis using electrostatic immobilization of the catalytic complex was reported by Fraile et al. [19]. The enantioselective C–H carbene insertion of ethyl 2-phenyl-diazoacetate on THF (Scheme 7) is efficiently catalyzed for the first time with copper complexes. Only those ligands forming strong Cu(I) complexes (PhBox and AzaPhBox) lead to moderate enantioselectivities (between 40 and 60% ee). Interestingly, when the PhBox-Cu(OTf)$_2$ complex was immobilized on laponite, a more active and selective catalyst is obtained, up to 88% ee in the major *syn* product. Furthermore, the catalyst is recoverable, and can be used up to four times with the same yield and selectivity.

The other strategy for non-covalent support of oxazoline-based complexes was recently described by Cornejo et al. for the ^{i}PrPybox-RuCl$_2$ catalyst [20]. This strategy consists of the reversible microencapsulation of the catalytic complex in linear polystyrene. When the benchmark cyclopropanation reaction is carried out in CH_2Cl_2, the encapsulated catalyst is completely soluble, and the reaction takes place in homogeneous phase. However, the addition of a non-polar solvent (hexane or cyclohexane) leads to the formation of the capsules, which can be filtered-off, washed and reused. In the best conditions, up to three recycles are possible, without loss of catalytic activity and enantioselectivity.

The second main strategy for catalyst immobilization is the covalent bonding of the chiral ligand to a support, which facilitates the catalyst separation from the reaction medium and, eventually, its recycling. This strategy requires the chemical modification of the chiral ligand, which may introduce steric changes affecting the stereochemical course of the reaction. Two main classes of supports are usually employed, namely organic (polymers) and inorganic (mainly silicas). Both have general advantages and disadvantages from a practical point of view. Organic polymeric supports are more versatile and ligand polymerization strategies are more feasible, leading to a large variety



Scheme 7. Carbene insertion reaction.



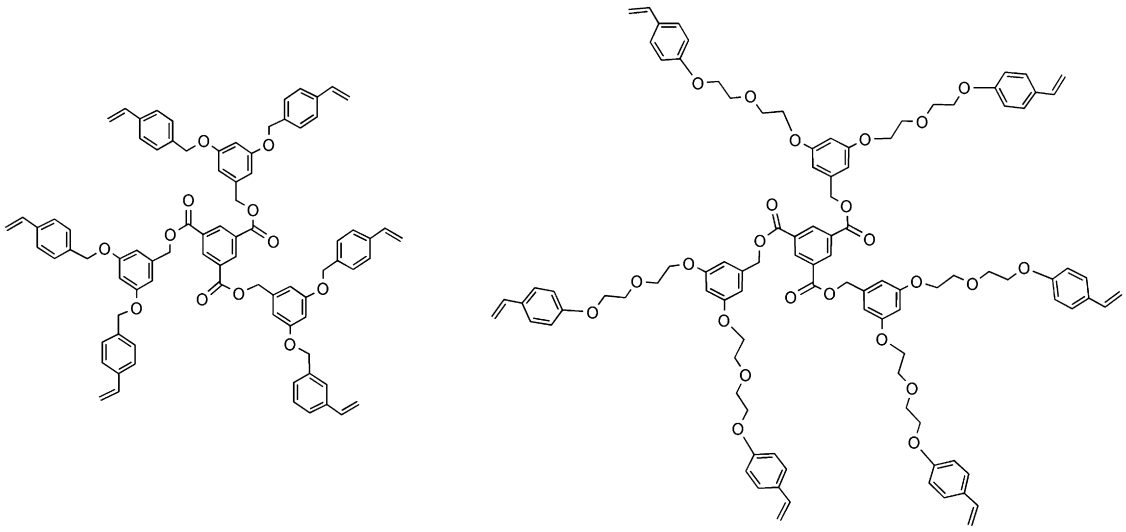
Scheme 8. Polymerization strategy for Box immobilization.

of immobilized catalysts based on the same chiral ligand motif. On the other hand, the mechanical stability of polymeric catalysts is not very good, making difficult their efficient recovery and reuse. On the other hand, silica-based catalysts possess better mechanical properties, and they are the natural choice for the eventual development of continuous-flow reactors, but the silica supports has often undesirable effects on the reactions, and they offer lower versatility with regard to organic polymers.

The first immobilization on insoluble organic polymers to be described, by Burguete et al. [21,22], used the polymerization strategy, i.e. the preparation of a Box-containing monomer that is subsequently polymerized or co-polymerized. PhBox, ^{t}BuBox and IndaBox were functionalized with vinylbenzyl groups in the Box methylene bridge, and then homo-polymerized or co-polymerized with styrene and divinylbenzene to yield macroreticular rigid polymers (Scheme 8). The best results, with moderate to good enantioselectivities in the benchmark reaction, were reported for the homopolymer. However, with the ^{t}BuBox ligand, only ca. 70% ee could be obtained, which is due to the substitution pattern of the ligand. Thus, the dibenzylated ^{t}BuBox led, in homogeneous phase, to the same enantioselectivity results. The homopolymer of the ^{t}BuBox monomer could be reused up to five times without loss of enantioselectivity [22].

One of the drawbacks of these Box-containing polymers, even with copolymers, is that most of the chiral ligand remains in the non-accessible core of the polymer, and does not participate in the catalysis. Mayoral and co-workers introduced the concept of "ligand economy" as an analogue of the Turnover Number (TON), defining it as the number of molecules of chiral product produced by molecules of chiral ligand used [23,24]. Thus, the catalytic activity of homopolymers and co-polymers using different crosslinkers, and different proportion of the different monomers was investigated in the benchmark reaction using PhBox-derived monomers [23]. Enantioselectivities similar to those found in homogeneous phase were described for most of polymers prepared, but more interestingly, the ligand economy was much higher in the case of using a dendrimeric cross-linker (Scheme 9). Thus, with the homopolymer, a cyclopropane/Box ratio of 17.0 was obtained, whereas this value increased to 70.8 when the dendrimeric polymer was used. Furthermore, this polymer was recovered, with a ratio of 50.4 in the second run, and similar stereoselectivity results. These values were later improved [24] up to 141 and 132, using PhBox and ^{t}BuBox-derived monomers, respectively, together with styrene and a dendrimeric cross-linker, showing the important influence of polymer morphology on reaction results.

As already mentioned, one of the drawbacks of the polymerization strategy is that the best ligand for enantioselective cyclopropanation reactions, i.e. the ^{t}BuBox, leads to significantly lower selectivities when it is dibenzylated in the methylene bridge [21]. Another possible problem is that difunctionalized Box monomers act as cross-linkers in the polymer, and this may affect the conformational preferences and hence the stereodirecting ability. A possible solution to these draw-

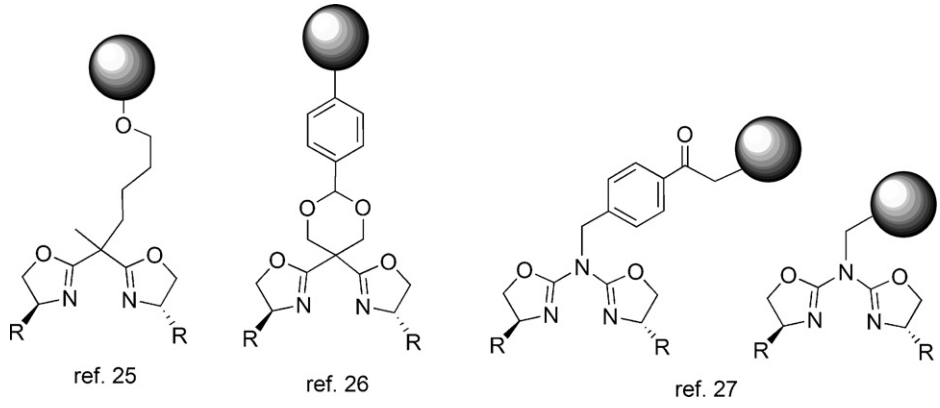


Scheme 9. Dendrimers used as cross-linking agents.

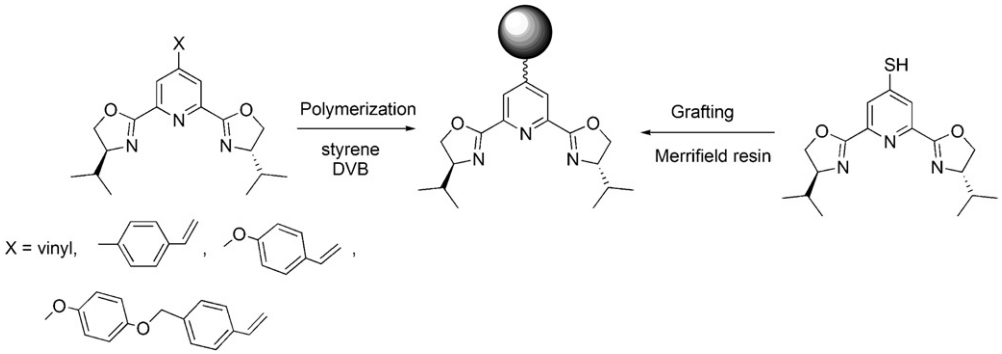
backs would be the monofunctionalization of the Box monomer by linkers different from the benzyl group. This approach was first described by Salvadori and co-workers [25], who designed a Box monomer with a minimal increase in the steric hindrance at the methylene carbon, compared with the parent ^{t}BuBox used in homogeneous phase catalysis (Scheme 10). With a highly cross-linked material (using styrene and divinylbenzene as co-monomers) excellent results were obtained in cyclopropanation reactions of several alkenes (styrene, 2-methylpropene and 1,1-diphenylethylene) with ethyl diazoacetate, with enantioselectivities over 90% ee, identical to those found in homogeneous phase. Furthermore, the catalyst is recoverable up to four times without loss of selectivity.

Concerning grafting strategies, a Box modification in the methylene bridge allowing polymer grafting through a single linker has been described, based on the synthesis of bisoxazolin-2-yl[1,3]dioxanes (Scheme 10) [26]. These modified ligands were grafted to a bromo-Wang resin, and the corresponding immobilized catalysts tested in the benchmark reaction. With the ^{t}BuBox-derived ligand, only modest enantioselectivities (ca. 60% ee) were reported, very inferior to those obtained in homogeneous phase, even with a structurally related ligand.

AzaBox ligands present some attractive advantages over Box to their immobilization through grafting. First, they have only one link point in the bridge, and second, their copper complexes are more stable, which is desirable for a better recoverability. Thus, Mayoral, Reiser and co-workers have recently described [27] the preparation of azaBox ligands grafted to Tentagel^{TM} and polystyrene, through different functionalization strategies (Scheme 10). These immobilized catalysts were used in the benchmark cyclopropanation reaction, as well as in the cyclopropanation of 1,1-diphenylethylene with ethyl diazoacetate. Polystyrene led to better results than Tentagel^{TM} as the support. After optimizing the catalyst preparation, increasing the degree of functionalization of the resin, an excellent catalyst was obtained, able to reach high chemoselectivities (up to 94%) without excess of alkene, and excellent enantioselectivities (up to 99% ee with styrene). Furthermore, the catalyst was recovered and reused with different alkenes in each run (styrene, 1,1-diphenylethylene, α-methylstyrene and 1-hexene), keeping good chemoselectivities and enantioselectivities up to the fourth run. The aza^{t}BuBox ligand immobilized in polystyrene is the first example of a multitask immobilized catalyst, since it has been tested in the Mukaiyama-aldol reaction (see Section 4.3),



Scheme 10. Different strategies for the grafting through a single linker of Box-derived ligands to a polymeric matrix.



Scheme 11. Different strategies for the immobilization of Pybox ligands to a polymeric matrix.

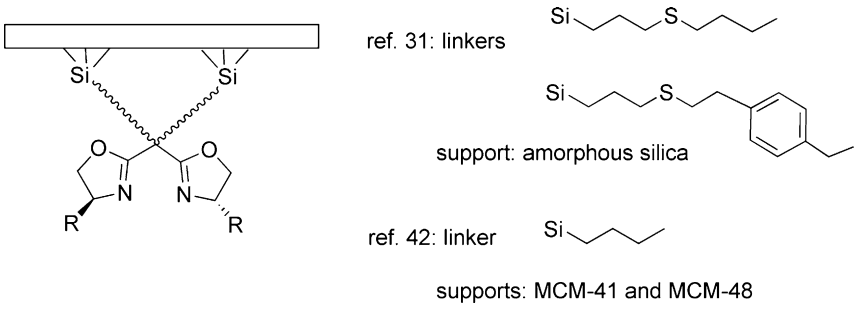
reused in the same reaction, and then reused in the benchmark cyclopropanation reaction. Under these conditions, 99% chemoselectivity (without excess of alkene), 97% ee in *trans*-cyclopropanes and 92% ee in *cis*-cyclopropanes was obtained [28]. These results are better than those obtained with any copper catalyst for this reaction in homogeneous phase, with the advantage of recoverability and reuse.

Pybox ligands have also been immobilized by grafting to organic polymers or co-polymerization. All the examples have been described by Martínez-Merino and co-workers. The first instance consisted in the co-polymerization of a 4-vinylpybox with styrene and divinylbenzene [29] in different conditions and with different degree of cross-linking (Scheme 11). With some of these polymeric catalysts, enantioselectivities in major *trans*-cyclopropanes similar to those found in homogeneous phase were obtained, although the enantioselectivity in *cis*-cyclopropanes was clearly worse. These catalysts were recoverable once, but showed deactivation in the second recovery. Co-polymerization and grafting onto Merrifield resin of Pybox ligands was compared in a subsequent study [30]. Furthermore, the experimental conditions to prepare and recover the catalysts were optimized, and with some of them, good enantioselectivities in *trans*- and *cis*-cyclopropanes, similar to those found in homogeneous phase, were obtained, and the catalysts could be reused up to five times. Co-polymerized catalysts showed better recoverability than grafted catalysts. One of the key factors to the recoverability of the catalyst was identified as the absence of oxygen in the medium (efficient degassing of the solvent, filtration under inert atmosphere). The nature of the linker to the polymer matrix is also important.

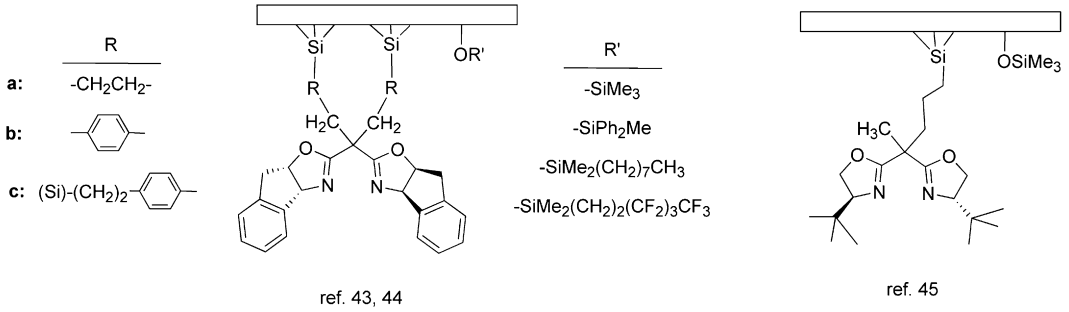
The preparation of recoverable polymeric catalysts opens the door to the design of continuous flow reactors, and this has very recently been reported in the case of immobilized Pybox-$RuCl_2$ catalysts [31]. Thus, Pybox monolithic flow minireactors have been prepared and operated under conventional and supercritical conditions. In general the continuous reactions led to chemoselectivities higher than those obtained in homogeneous phase, and to similar enantioselectivities. In the case of using supercritical CO_2 ($scCO_2$) as solvent, the enantioselectivities were even slightly higher (up to 89% ee in *trans*-cyclopropanes with 85:15 *trans*/*cis* ratio). The solventless process (only the reagents are fed into the reactor) showed a 5.8-fold productivity increase with regard to the CH_2Cl_2 process in a operation time of 8 h. Even better productivity (an increase of 7.7-fold) was obtained in the $scCO_2$ process. These results are encouraging to the development of more efficient synthetic methodologies for the asymmetric cyclopropanation reaction.

Finally, one example has also been reported for the grafting of a Pybox ligand on modified starch, a natural polymer [32]. Although the immobilized catalyst was recoverable and reusable up to three times, the chemoselectivity and enantioselectivities obtained were clearly inferior to those obtained in homogeneous phase.

The first immobilization of Box ligands on silica supports was described by Mayoral [22] and Shannon [33] (Scheme 12). In the first study, four different allyl and vinylbenzyl-functionalized Box ligands were grafted on mercaptopropylsilica to give the immobilized catalyst precursors. Some good results were obtained in the benchmark cyclopropanation reaction (up to 86% ee with the IndaBox-derived catalyst). In general, the catalyst



Scheme 12. Grafting of Box ligands on silica supports.



Scheme 13. Grafting of IndaBox ligand on mesocellular foam (MCF) silica support.

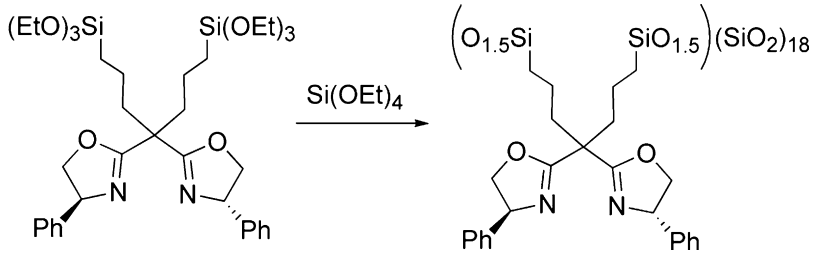
loading and the results obtained were better than those obtained with polymer-supported ligands; however, no recovery experiments were described. In the second study, a similar strategy was used to immobilize a bis(trimethoxysilylpropyl)-modified PhBox on two different mesoporous materials, namely MCM-41 and MCM-48, and then to prepare the corresponding catalysts by addition of $CuCl_2$ and $Cu(OTf)_2$. The catalytic results in the benchmark cyclopropanation reaction were similar to those obtained in homogeneous phase with the PhBox-$Cu(OTf)_2$ catalysts (even in the case of using $CuCl_2$ as catalytic precursor), and all the immobilized catalysts could be reused once, $CuCl_2$-based catalysts showing a faster deactivation.

More recently, the group of Ying and co-workers has reported the use of mesocellular foam (MCF), a silica support with a high surface area (>800 $m^2\ g^{-1}$) and open, ultra-large pores (25 nm). Thus, IndaBox differently modified in the methylene bridge were linked to the MCF (Scheme 13) [34], then the free silanol groups were silanized as trimethylsilyl derivatives, and the corresponding Cu(OTf) and $Cu(OTf)_2$ complexes were tested in the benchmark cyclopropanation reaction. The resulting catalysts showed good activity and enantioselectivities only slightly lower than the homogenous phase catalyst. Furthermore, the solids could be recovered and reused two more times with the same results. In a subsequent, more extensive study [35], different silica supports (MCM-48, SBA-15 and amorphous silica) were compared with the MCF. The effect of the silanization of the support and that of the linker structure was also studied. Thus, functionalized ^{t}BuBox were grafted to the different supports and tested in the benchmark cyclopropanation reaction, as well as in the reaction of 1,1-diphenylethylene with ethyl diazoacetate. Silanization of the free silanol groups of the supports was shown to be important for the catalytic activity and selectivity of the reactions. In general, good enantioselectivities (over 80% ee) were obtained with all the immobilized and silanized catalysts, although better yields were obtained in general with the MCF, due to the better chemoselectivity towards the cyclopropanation reaction. The nature of the linker was also important to obtain good enantioselectivities, the propyl spacer being the best among those tested. Up to eight runs with similar reaction results could be carried out with the best catalyst, showing the good recoverability of these immobilized catalysts.

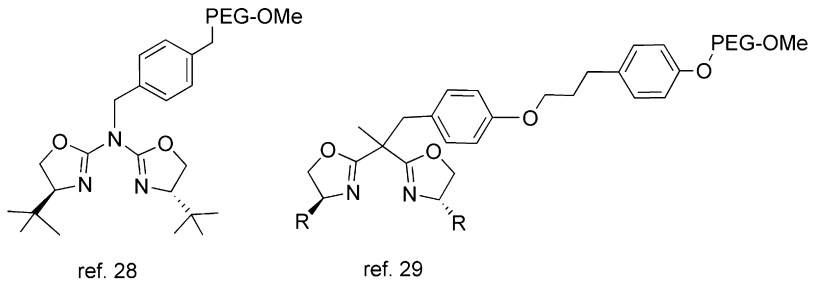
More recently, a modification of this immobilization strategy, basically consisting in grafting the Box ligand by only one linker (Scheme 13), has been described [36], and this significantly improves the enantioselectivity and recoverability of the catalytic system. Thus, in the benchmark cyclopropanation reaction, up to 95% ee (essentially the same enantioselectivity obtained in homogeneous phase with the ^{t}BuBox ligand) is obtained, with high chemoselectivities (between 70 and 80% yield in cyclopropanes). Excellent results are also obtained with 1,1-diphenylethylene and 2-methylpropene. Concerning the recoverability, up to eleven recoveries are described, keeping both the chemo-, diastereo- (*trans*/*cis*) and enantioselectivities, which constitutes one of the best recoverable catalytic systems for this reaction.

Only one example has been described to date for the synthesis of hybrid organic-inorganic materials containing chiral Box ligands (Scheme 14) [37]. This procedure consists of carrying out a sol–gel synthesis, in which the silanized ligand is included in the silica structure during its synthesis. Using derivatized PhBox and IndaBox ligands, two hybrid materials with 240 and 40 $m^2\ g^{-1}$, respectively, and a mean pore diameter of 22 Å, were prepared. In the case of PhBox, the catalytic tests in the benchmark cyclopropanation reaction led to selectivities almost identical to those found in homogeneous conditions, and the catalyst was recovered without loss of activity or selectivity.

Pybox ligands have also been immobilized by grafting onto silica by modification in the 4-position of the pyridine



Scheme 14. Immobilization of Box ligands by sol–gel synthesis.



Scheme 15. PEG-supported Box and azaBox ligands.

ring [38,39]. Enantioselectivities in the ruthenium-catalyzed benchmark cyclopropanation are in general inferior to those obtained when the Pybox ligands are immobilized on organic polymers.

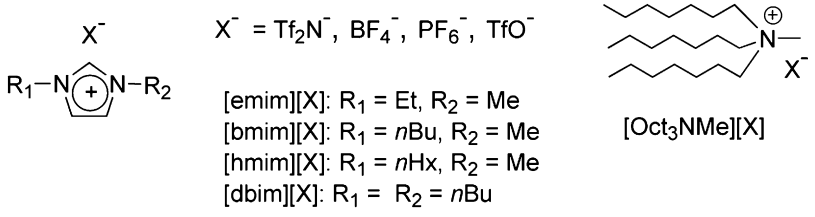
Several methods have been developed to allow separation of homogeneous chiral oxazoline-derived catalysts. The reaction takes place in a phase where the catalyst is soluble, and after the reaction the catalyst is recovered using one of these two strategies: extraction or precipitation. In the first one, the excess of reagents and products are extracted with a solvent where the catalyst is insoluble, which allows its easy recovery. In the second one a solvent is added to precipitate the catalyst, which is separated by filtration. Depending on the chosen strategy the chiral ligand may require some modifications.

The first modification described to facilitate catalyst separation in connection with cyclopropanation reactions was the grafting of poly(ethylene glycol) (PEG) chains to Box and azaBox ligands (Scheme 15). Glos and Reiser described [40] the synthesis of a chiral azabis(oxazoline) (aza^{t}BuBox) ligand, its attachment to PEG, and its use in the cyclopropanation reactions of styrene and 1,1-diphenylethylene with ethyl diazoacetate. Good yields and enantioselectivities (ca. 90% ee) were obtained with this catalyst, which could be recovered by precipitation with diethyl ether, and reused up to thirteen times without loss of enantioselectivity. Cozzi and co-workers described PEG-supported Box ligands, by grafting through a single linker in the methylene bridge of the Box [41]. Good enantioselectivities were obtained for the same cyclopropanation reactions using the ^{t}BuBox-derived catalyst. However, no recycling experiments were described.

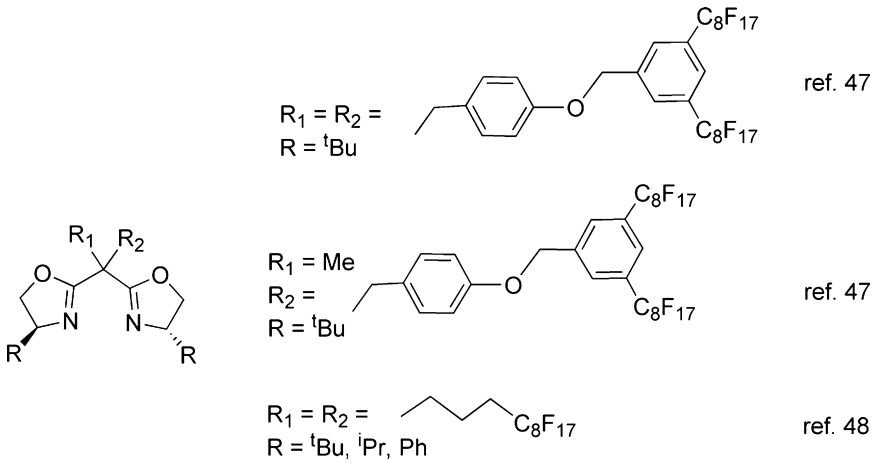
The first cyclopropanation reaction catalyzed by Box-copper complexes immobilized in ionic liquids (IL) was reported by the Mayoral group in 2001 [42]. Both PhBox and ^{t}BuBox were used in the benchmark cyclopropanation reaction. Imidazolium and tetraalkylammonium-based ionic liquids (Scheme 16) were used as catalyst phase. After reaction the IL phase was extracted with *n*-hexane, and then reused in subsequent reactions. Copper chloride salts can be used with IL without observing the negative counterion effect, usual in organic solvents, due to the total anion exchange in the bulk of the IL solvent, which prevents its coordination to the Cu centers. Catalyst recovery depends on both the nature of the ligand and the purity and dryness of the ionic liquid [43]. PhBox-$CuCl_2$ complexes are easily recovered but, with ^{t}BuBox-$CuCl_2$, enantioselectivities drop after the second recovery, even under optimal conditions.

If the halide ions are present as impurities of the IL in high amounts, the negative halide effect reappears, as shown by Davies et al. in a study of the IL anion and impurities effects on the benchmark cyclopropanation reaction, catalyzed by ^{t}BuBox-Cu(OTf) catalyst [44]. Thus, when the halide-free IL [bmim][X] was mixed with 5% [bmim][Cl/Br], a total loss of catalytic activity was obtained. The recoverability of the catalytic IL phase was studied under the optimal reaction conditions. Until the fourth run (third recovery of the catalytic phase), high yields and enantioselectivities (comparable to those reported in CH_2Cl_2) were obtained. However, in the fifth run, both the yield and the enantioselectivities drop significantly.

The main factor controlling the recoverability of these systems was investigated in a study by Fraile et al. [45], in which the ^{t}BuBox and aza^{t}BuBox ligands were compared. First, it was shown that the loss of enantioselectivity after recovery is mainly due to the loss of chiral ligand produced in the extraction step after the reaction. When ^{t}BuBox was added to the IL phase ([emim][OTf]) after five reactions, the same enantioselectivities observed in the first run were recovered. As this seems to be again a complexation equilibrium issue, the more coordinating ligand, aza^{t}BuBox, was used under the same conditions. With this ligand, up to eight consecutive reactions were car-



Scheme 16. Ionic liquids used as catalyst phase.



Scheme 17. Structures of the fluorous Box ligands used in cyclopropanation reactions.

ried out, without appreciable loss of enantioselectivity. With this highly recoverable catalytic phase, five consecutive cyclopropanation reactions using different alkenes in each recycle were carried out with excellent enantioselectivity results, constituting the first immobilized multipurpose catalyst for cyclopropanation reactions described.

Given that IL are rather expensive solvents, a strategy to minimize the volume of IL used in the catalyst phase consists in using Supported Ionic-Liquid Films (SILF). This strategy, hybrid between immobilization and separable homogeneous catalysis, has been recently described for the cyclopropanation reactions using Box-copper catalysts [46]. In this study [bmim][PF_6] was supported on different solids (clays, graphite, Y zeolite, silica and hydrotalcite). Using decreasing amounts of IL, the thickness of the IL film was reduced, in the search of surface confinement effects similar to those described for the electrostatic exchange of the same Box-copper complexes in clays [13,14]. Only when a small amount of IL was supported in clays (laponite, bentonite, K10 montmorillonite) were the confinement effects observed, pointing to a partial cation exchange of the catalytic complex, similar to that previously reported. Other lamellar solids, such as graphite or hydrotalcite did not exhibit this effect, the catalytic results being identical to those obtained in homogeneous IL phase.

The last strategy for homogeneous separable catalysis with Box ligands is the use of perfluoroalkyl-substituted (fluorous) Box ligands (Scheme 17).

The first example of this strategy was reported by Annunziata et al. [47], which described two fluorous ^{t}BuBox ligands with 49.2 and 55.5% fluorine content. Enantioselectivities lower than those obtained with the ^{t}BoxBu ligand, and a poor recoverability were described for these systems.

A more extensive study has been recently reported by Bayardon et al. [48], dealing with different fluorous Box ligands. In this case, somewhat better results were obtained with the ^{t}BuBox derived ligand (up to 84% ee), but still far from those of the parent ligand. More interestingly, the recovery procedure is easy, and consists in the precipitation of the complex with hexane, after evaporation of the reaction solvent, decantation of the supernatant solution, and reuse of the catalyst recovered from

Table 1
Summary of the best results obtained with ^{t}BuBox and aza^{t}BuBox-derived immobilized ligands in the copper-catalyzed cyclopropanation reaction of styrene with ethyl diazoacetate[a]

Ligand	Support	Immobil. strategy	*Trans*/*cis*	%ee *trans*	%ee *cis*	Reuses	Ref.
Box	Laponite	Non-coval.	66/34	69	69	1	[17]
AzaBox	Laponite	Non-coval.	69/31	81	58	NO	[18]
AzaBox	Nafion-silica	Non-coval.	66/34	90	83	1	[18]
AzaBox	SAC-40	Non-coval.	66/34	90	84	1	[13]
Box	Copolymer.	Covalent	39/61	77	73	1	[21]
Box	Copolymer.	Covalent	67/33	93	90	5	[25]
AzaBox	Polystyrene	Covalent	74/26	99	90	3	[27]
Box	Silica	Covalent	65/35	95	92	4	[36]
Box	PEG	Sep. homog.	77/23	91	–	–	[41]
AzaBox	PEG	Sep. homog.	71/29	91	87	10	[40]
Box	Ionic liquid	Sep. homog.	75/25	97	94	3	[43]
AzaBox	Ionic liquid	Sep. homog.	73/27	91	82	8	[45]
Box	Fluorous	Sep. homog.	64/36	80	79	6	[48]

[a] The results with the same ligands in homogeneous phase are: ^{t}BuBox, *trans*/*cis* 71/29, 94% ee *trans*, 91% ee *cis* [10]; aza^{t}BuBox, *trans*/*cis* 73/27, 92% ee *trans* [27].

the precipitate. Following this procedure, up to six runs were described for the ^{t}BuBox-derived ligand, without loss of enantioselectivity and only a slight loss of activity after the fourth run.

To summarize this section, we present in Table 1 a survey of the best results obtained with the same chiral inductor, based on the ^{t}BuBox motif, using different immobilization strategies, in the benchmark cyclopropanation reaction of styrene with ethyl diazoacetate. As can be seen, it has been possible to obtain excellent enantioselectivity results (over 90% ee) and some degree of recoverability with virtually every immobilization strategy tried, showing the high degree of control that chemists have on this particular catalytic system. However, apart from these general good results, it can be concluded that azaBox presents clear advantages (above all in the field of recoverability and reuse), with regard to Box ligands, most probably due to their higher coordination ability to the copper cation. Furthermore, both the liquid–liquid biphasic system using ionic liquids, and the grafting to Merrifield resins, strategies that do not require previous ligand modification, lead to excellent results, constituting the most attractive catalytic systems described for these reactions.

3. Aziridination

Hutchings and co-workers have paid attention to the use of bis(oxazoline)-Cu(II) complexes, immobilized on zeolites by electrostatic interactions (Scheme 4), as catalysts of enantioselective aziridination reactions (Scheme 18).

Catalysts were obtained by adsorbing the ligand on a copper exchanged HY zeolite. The final Cu/ligand ratio is 0.5, showing that not all the copper was accessible to the bis(oxazoline). In fact the use of an excess of ligand reduced the final yield, probably due to pore blocking [49–51]. With respect to the alkene the best enantioselectivity was obtained with methyl *E*-cinnamate, however higher aziridine yields were obtained with styrene and *E*-β-methylstyrene. Another important factor is the solvent, and the best results were obtained in acetonitrile. The nature of the nitrene donor is crucial, the enantioselectivities were higher with [*N*-(*p*-nitrophenylsulfonyl)-imino]phenyliodinane (R_2 = Ns) than with [*N*-(*p*-tolylsulfonyl)-imino]phenyliodinane (R_2 = Ts) [52]. In most aziridination reactions an excess of alkene is used to avoid side reactions and, as a consequence, increase the yield. However the best results with the immobilized catalysts were obtained using about 1.5 equivalents of nitrene donor [52,53]. As expected the nature of the chiral ligand is very important [52], in this regard the best results, considering both yield and enantioselectivity (94% ee with 1.4 eq. of Ns-nitrene donor), were obtained using PhBox (R_3 = Me, R_4 = Ph, R_5 = H) and CuHY [54]. The influence of the ligand was not the same under homogeneous and immobilized conditions, for example with PhBox (R_3 = H) and CuHY enantioselectivities up to 79% ee were reached with both nitrene donors, whereas with the same ligand and $Cu(OTf)_2$ the best result was 28% ee. Although the conditions (excess of Cu) favored the presence of non-chiral Cu catalytic centers under homogeneous conditions, these differences led the authors to propose that the confined space of the zeolite improves the behavior of some ligands [55].

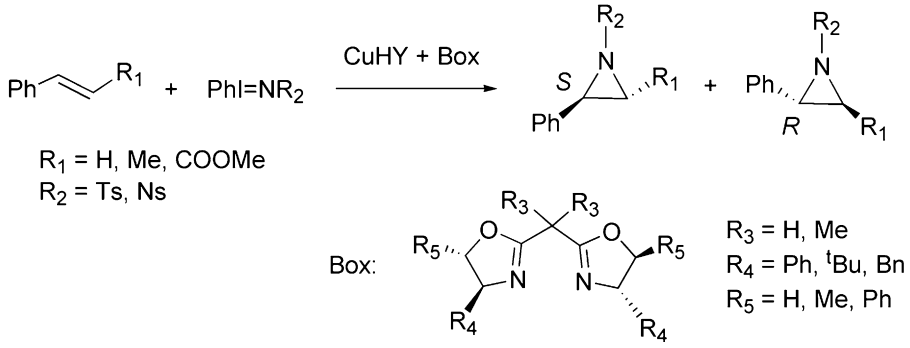
Copper leaching increased with both reaction time and nitrene donor concentration. Although filtration experiments showed that, at long times some active species were leached, they had no important influence on the reaction results [53]. A slight decrease in copper leaching, accompanied by a slight decrease in final yield, was observed when H^+, in CuHY, was substituted by group I metal cations [56].

The influence and formation of byproducts was studied too. Thus, the amount of benzaldehyde, obtained by the oxidation of styrene with the byproduct PhIO, depended on the substitution of the styrene phenyl ring, and in this regard both homogeneous and immobilized catalysts showed a similar behavior [57].

The same authors carried out some interesting mechanistic studies. EPR experiments showed the presence, in the zeolite, of square planar and square pyramidal complexes of Cu(II) with PhBox. Aziridination with PhI = NTs led to a paramagnetic intermediate that regenerated Cu(II) by reaction with styrene [58].

Another interesting observation was the increase of enantioselectivity with time. Several experiments showed that, in the presence of the catalyst, aziridine reacts with the nitrene precursor and with the sulphonamide by-product. These reactions are able to interconvert the aziridine enantiomers playing an important role in the reaction outcome [59]. These opening reactions could take place via coordination of the aziridine to Cu^{2+} behaving as a Lewis acid, as suggested by DFT calculations [60].

Using MCM-41 [51], laponite [61] or Nafion-silica nanocomposites [61] as the anionic supports, the results were not as good as with CuHY. In all cases the use of the (*S*, *S*)-ligand led to the *R*-aziridine as the major product.



Scheme 18. Aziridination reactions with immobilized Box-Cu catalysts.

4. Lewis acid promoted reactions

4.1. Diels–Alder reactions

Most of the immobilized catalysts have been tested in the reactions between cyclopentadiene and 3-acyloxazolidin-2-ones, acryloyl (R = H), *E*-but-2-enoyl (R = Me) or *E*-3-phenylpropenoyl (R = Ph) (Scheme 19).

The first example of a Diels–Alder reaction catalyzed by a covalently-supported catalyst based on bis(oxazoline) ligands was reported by Rechavi and Lemaire [62,63]. An analogous of the IndaBox ligand was functionalized in the methylene bridge (Scheme 20) with two triethoxysilyl groups via a carbamate linker. This modified ligand was grafted onto activated (acid-treated) silica, and complexes with $Cu(OTf)_2$ and $Cu(ClO_4)_2$ were formed.

These complexes were tested in the Diels–Alder reaction between cyclopentadiene and 3-acryloyloxazolidin-2-one (Scheme 19). The perchlorate complex showed better recoverability during 4 cycles at different temperatures with total conversion and enantioselectivities between 65% ee (rt) and 85% ee (−15 °C). The silanization of the silica surface with *N*-trimethylsilylimidazole was crucial in order to obtain high enantioselectivity, up to 92% ee at −78 °C. Enantioselectivities with the other dienophiles were slightly lower, 70%ee with R = Me, and 61% ee with R = Ph, in both cases at rt.

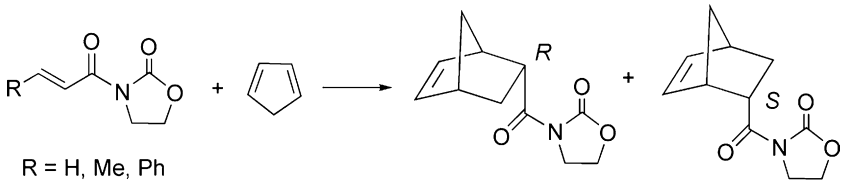
In a later study [64], the same authors report a linear relationship between enantioselectivity and silanization degree, measured both by microanalysis and ^{29}Si-CP-MAS-NMR, whereas the catalyst loading on the support has no significant effect. The possible complexation of copper with the free silanol groups is pointed out as the main reason for this behavior.

Kim and coworkers used a similar strategy [65] to immobilize IndaBox on mesocellular foam (MCF). In this case the starting IndaBox was dialkylated in the methylene central bridge with protected p-hydroxybenzyl bromide, and the deprotected phenol groups were alkylated with the grafted chloropropyl groups (Scheme 20). The high dispersion of the chloropropyl groups makes probable the grafting of the ligand through a single group, and hexamethyldisiloxane was used to silanize the remaining phenol (R = $SiMe_3$), as well as the surface silanols.

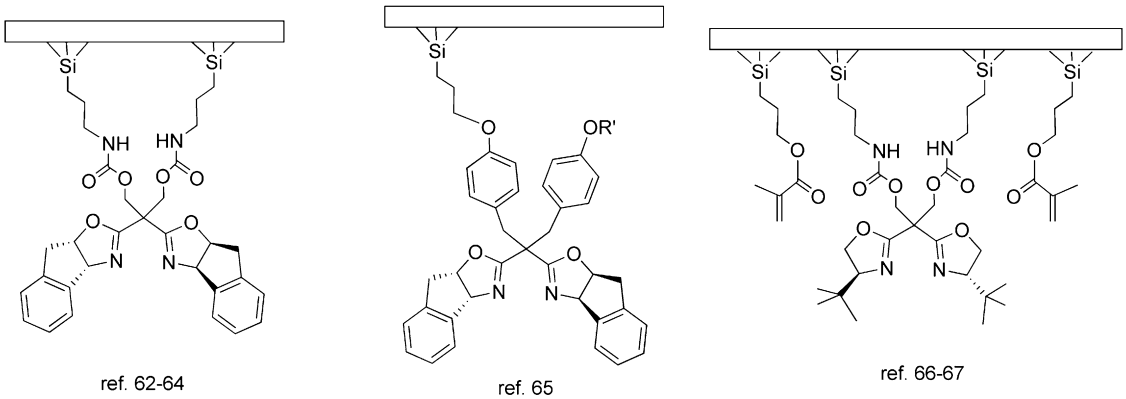
Complexes were prepared with $Cu(OTf)_2$, and were tested in the same Diels–Alder reaction (R = H, Scheme 19). The initial results were much worse than those obtained with the analogous homogeneous catalyst, but the optimization of the method to eliminate the excess of copper was critical to achieve high enantioselectivity. Up to 75% ee was obtained at −78 °C, and in this case the silanization was not positive, as the non-silanized catalyst afforded 78% ee. The decrease in enantioselectivity with regard to the homogeneous reaction was ascribed to the catalytic effect of the support, shown by the 22% yield obtained with the supported ligand, without copper salt, even at −70 °C. Other dienophiles (R = Me), and dienes, such as cyclohexadiene, led to similar or slightly worse results, between 53 and 72% ee.

The best catalyst was used up to 5 cycles with similar enantioselectivities, in the range of 70–78%ee. Even in that case, the analysis showed a considerable amount of copper leaching after each cycle, probably due to the strong complexation with cycloadducts.

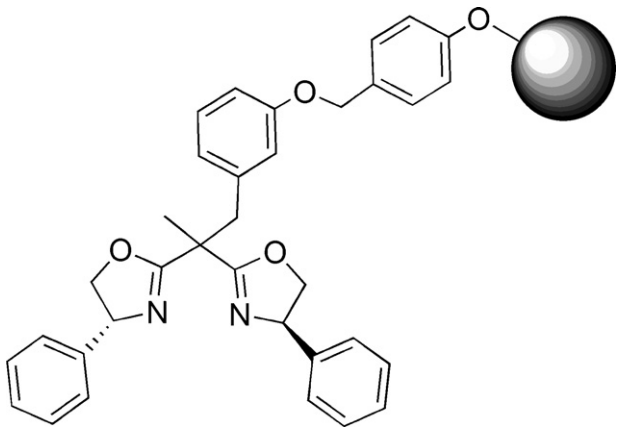
Lancaster et al. [34] have shown the effect of linker and silane groups in the performance of the same type of MCF supported catalysts. Three different linkers and four silanes (Scheme 13) were tested in the same Diels–Alder reaction (R = H, Scheme 19). In this case silanization enhanced enan-



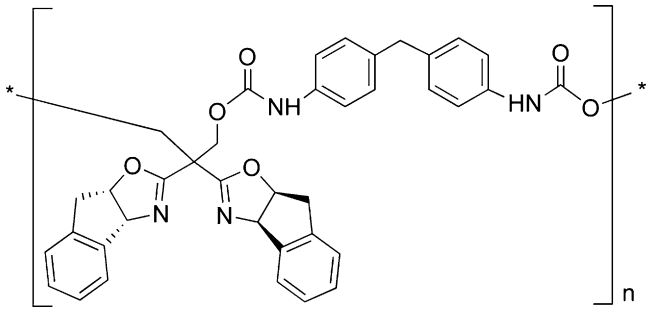
Scheme 19. Diels–Alder reactions between cyclopentadiene and 3-acyloxazolidin-2-ones.



Scheme 20. Box ligands grafted on silicas and used in Diels–Alder reactions.



Scheme 21. PhBox immobilized on ArcoGel-Wang resin.



Scheme 22. IndaBox immobilized on polyurethane.

tioselectivity, from 47% ee to 70% ee at rt, and from 77% ee to 88% ee at −78 °C. The silanized catalysts were more active than the non-silanized ones, and even than the analogous homogeneous catalyst. The nature of the linker and the silane showed a marginal effect on enantioselectivity.

A surprising effect was detected in the recycling experiments. When dichloromethane was saturated with water, the results were improved and 5 cycles were made possible.

Another surprising effect was reported by Iwasawa and coworkers [66] when immobilizing ^{t}BuBox on silica (Scheme 20). The $Cu(ClO_4)_2$ complex was much more active than the homogeneous counterpart in the reaction between 3-acryloyloxazolidin-2-one and cyclopentadiene (R = H, Scheme 19), and at the same time the enantioselectivity was increased from 5 to 15% ee at −10 °C. The silanization of the silanols with different silanes did not produce any significant positive effect, with only one exception. When silica was silanized with 3-(trimethoxysilyl)propyl methacrylate (Scheme 20), enantioselectivity was improved up to 65% ee.

In a deeper study, the same authors [67] showed that the structure of the copper complex is the same in all the catalysts, but there is no evidence for an interaction between the catalytic complex and the methacryloyl moiety. The addition of the modifier to the solution did not produce the same enhancement, although the opposite method (addition of the modified silica to the homogeneous reaction) was not tried.

PhBox functionalized with a *m*-hydroxybenzyl group in the central bridge (Scheme 21) was immobilized on ArcoGel-Wang-Cl resin and complexed with $ZnI_2 + AgSbF_6$. This catalyst showed low activity in Diels–Alder reaction (R = H, Scheme 19), leading to the racemic product [68].

In other example, IndaBox was incorporated in a linear polyurethane (Scheme 22) [63]. The results with $Cu(OTf)_2$ in Diels–Alder reactions (R = H, Scheme 19) were modest regarding enantioselectivity (51–56% ee). The catalyst was recoverable 3 times with the same activity and selectivity, but enantioselection was lost in the fourth run.

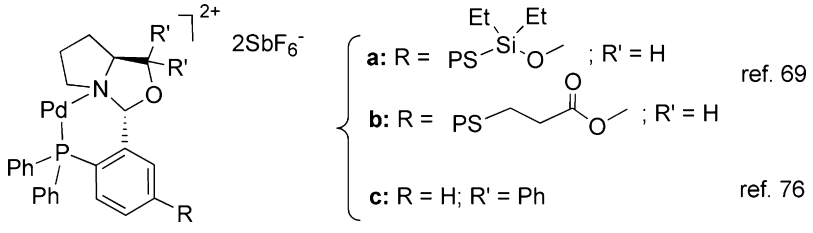
A related supported ligand is the phosphinooxazolidine showed in Scheme 23 [69]. The nature of the polymeric support and the bond between ligand and polymer showed a dramatic effect on the catalytic results of Diels–Alder reactions (R = H, Scheme 19), in both yield and enantioselectivity. Polystyrene with the silane moiety led to low yield and no enantioselectivity, whereas the same type of polymer with a carboxylate linker gave rise to 83% ee at 0 °C, improved to 92% ee when 20% catalyst was used. However, the same complex with the same linker in a TentaGel resin gave no enantioselectivity.

The catalyst was recoverable three times with loss of 30% activity and enantioselectivity. The use of other dienes, such as cyclohexadiene or 2,3-dimethylbutadiene, or dienophiles leads to very poor activity and/or reduced enantioselectivity.

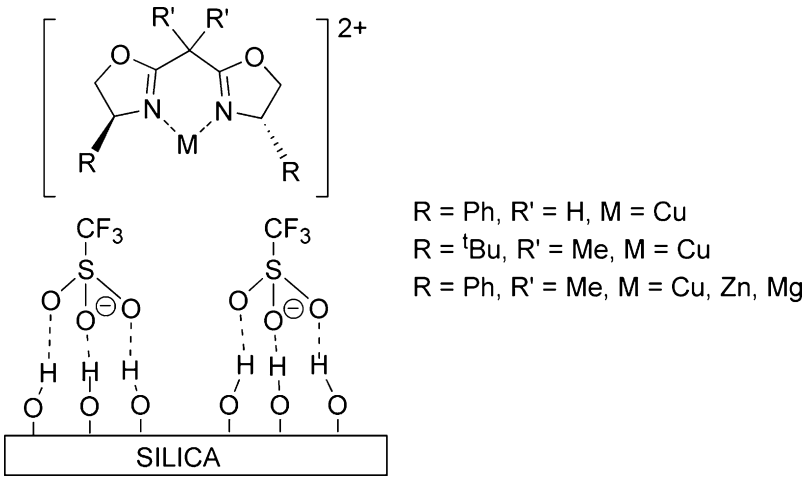
In addition to the covalent immobilization methods, several non-covalent strategies, both in solid and liquid phase, have been used to immobilize catalysts for Diels–Alder reactions.

The first attempt to use cationic exchange method in Diels–Alder reactions was described by Fraile et al. [70]. Cationic complexes of PhBox and Cu, Zn, and Mg salts were exchanged on laponite clay and Nafion-silica nanocomposite (Scheme 4). This ligand was chosen because of the higher stability of its copper complex in comparison with ^{t}BuBox [10].

In general, the results in Diels–Alder reactions (R = Me, Scheme 19) were poorer that those obtained in homogeneous



Scheme 23. Phosphinooxazolidine-Pd complexes.



Scheme 24. Immobilization of Box complexes by hydrogen bonds formation.

phase, with enantioselectivities of about 10% ee (for copper and zinc complexes). Analysis of the solids demonstrated that Zn and Mg complexes were not efficiently exchanged and most of the chiral ligand was also lost during the exchange process.

An alternative method of non-covalent immobilization is the adsorption of $Cu(OTf)_2$ complexes onto silica, where the formation of hydrogen bonds between silanols and triflate anions is proposed (Scheme 24) [71]. The immobilized complexes were tested as catalysts in the Diels–Alder reaction between 3-acryloyloxazolidin-2-one and cyclopentadiene (R = H, Scheme 19).

Catalyst ^{t}BuBox-Cu showed activity and enantioselectivity (57%ee) similar to those observed in homogeneous phase. However, a reversal of the major *endo* enantiomer obtained with catalyst PhBox-Cu (R′ = H), with regard to the homogeneous phase reaction, was noted. Whereas in solution 20% ee of *S* enantiomer was obtained, 33% ee of the *R* enantiomer was obtained with the supported catalyst at −30 °C.

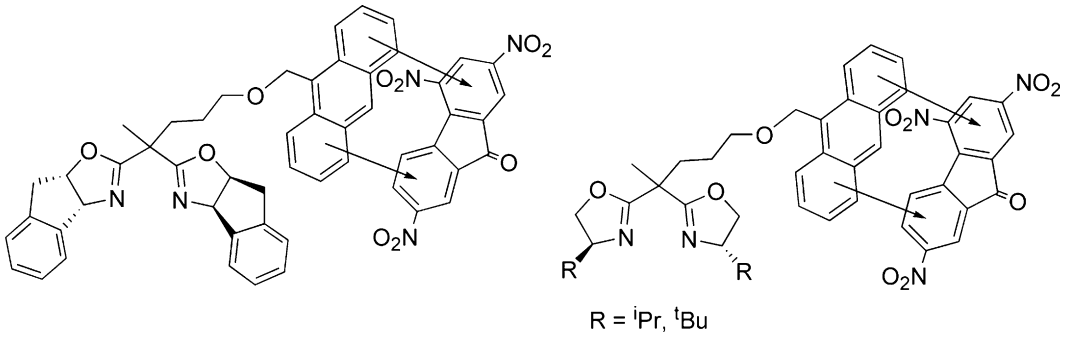
Later on, these results were revisited by Li and coworkers [72] using copper catalysts, together with analogous of Zn and Mg (Scheme 24). Results obtained with ^{t}BuBox-Cu were much better than those reported earlier, with enantioselectivities in the range of 85–93% ee at rt. Activity and recoverability were improved by using toluene as reaction solvent and 3 Å MS as water scavenger, allowing three uses with the same activity (98–92–83% conversion) and enantioselectivity (91% ee in the three runs).

The reversal in enantioselectivity with PhBox-Cu (R′ = H) was confirmed and even enhanced (up to 46% ee of the *R* enantiomer) with the analogous PhBox-Cu (R′ = Me) in toluene. The same effect was also observed with PhBox-Zn and PhBox-Mg catalysts, with a reversal in the case of the Mg catalyst from 60% ee (*S*) in solution to 30% ee (*R*) with the heterogeneous catalyst. This effect was ascribed to a change in the coordinating ability of the anion. The substitution of triflate by a less coordinating anion, SbF_6^- or ClO_4^-, produces the same reversal in solution due to a change in the geometry, from octahedral with the coordinating anion to tetrahedral with the non-coordinating one. The hydrogen bonds between silanols and triflates might be responsible for this change in coordinating character on the solid support. This explanation however cannot be applied to the copper catalyst, as the reversal is not observed in solution and the conformational preferences are completely different from the other two metals. The possibility of a surface effect of steric nature, proposed for a similar case of enantioselectivity reversal in cyclopropanation reactions [13,14], has not been invoked in this case.

As can be seen, the catalysts immobilized by non-covalent methods are less efficient for Diels–Alder reactions than the covalently immobilized analogous. However, in some cases a reversion in selectivity is observed, which can be the opening of a new route for design of chiral heterogeneous catalysts with special performance.

The first example of Diels–Alder reaction in solution with a recoverable catalyst was described by Cozzi and coworkers [41]. Complexes prepared with MeOPEG-supported ligands (Scheme 15) were used in CH_2Cl_2 and the complex was separated by precipitation with diethyl ether. The results in Diels–Alder reactions (R = H, Scheme 19) were only moderate (up to 45% ee) due, at least in part, to the contamination of the ligand with Cs or ammonium salts used in the last step of the ligand synthesis. Moreover, the catalyst was not recycled, but only the ligand after decomplexation with KCN.

Another method to improve recyclability of the homogeneous complex is the functionalization of the bis(oxazoline) ligand with an anthracene group in the central methylene bridge. This group is able to form a charge transfer complex with trinitrofluorenone (Scheme 25), which can be precipitated upon addition of pentane after reaction [73,74]. The catalyst with IndaBox was efficiently used in up to 12 consecutive runs of Diels–Alder reactions (R = H, Scheme 19) at −50 to −75 °C, with excellent conversions and *endo*/*exo* selectivity, and enantiomeric excess in the range of 84–94% ee. Even the catalyst used 6 times in this reaction was reused 5 additional times in other reactions (R = Me, Scheme 19) also with good results (77% ee at rt). The *tert*-butyl ligand was used up to 11 cycles, and the addition of 4 Å molecular sieves was highly positive for enantioselectivity, which was increased from 64–76% ee to 86–92% ee at −50 °C.



Scheme 25. Recoverable charge transfer complexes of Box ligands.

Table 2
Summary of the best results obtained with Box-derived immobilized ligands in the copper-catalyzed (10% catalyst) Diels–Alder reaction of 3-acryloyloxazolidin-2-one with cyclopentadiene

Ligand	Support	Immobil. strategy	Temperature (°C)	*Endo*/*exo*	%ee *endo*	Reuses	Ref.
Indabox	Silica-TMS	Covalent	−78	86/14	92	4	[62]
Indabox	MCF silica	Covalent	−78	95/5	78	5	[65]
Indabox	MCF-TMS	Covalent	−78 → rt	96/4	90	5	[34]
Indabox	Polyurethane	Covalent	−78 → rt	89/11	51	3	[63]
^{t}BuBox	Silica	Non-covalent	rt	90/10	91	2	[72]
IndaBox	Charge Transf.	Sep. homog.	−50	96/4	88	12	[73]
^{t}BuBox[a]	Ionic Liquid	Sep. homog.	rt	93/7[b]	92[b]	NO	[75]

[a] Zn complex.
[b] Results obtained in the reaction of *E*-3-but-2-enoyloxazolidin-2-one with cyclopentadiene.

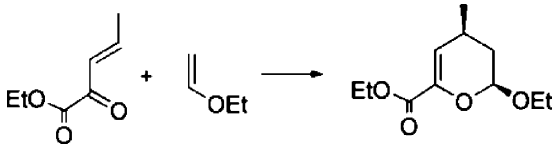
^{t}BuBox-$ZnCl_2$ in [dbim][BF_4] (Scheme 16) is the only example published of the application of ionic liquids for enantioselective catalysis of Diels–Alder reactions (R = Me, Scheme 19) with Box ligands [75]. Compared with the same process in CH_2Cl_2, the reaction was faster and both the *endo*/*exo* selectivity and the enantioselectivity in the *endo* product were excellent (92% ee). This is probably a consequence of the anion substitution around Zn. The complex of $Zn(BF_4)_2$ should be more active in Lewis acid catalyzed reactions than the analogous $ZnCl_2$ complex. However, experiments aimed at recovering the catalysts were not carried out.

Very recently, a chiral cationic Pd-phosphinooxazolidine catalyst (Scheme 23) has been also immobilized in imidazolium-based ionic liquids with different anions [76]. Results in Diels–Alder (R = H, Scheme 19) were greatly dependent on the anion of the ionic liquid, with a similar trend to the effect observed in organic solvents with complexes bearing different anions. This is an additional proof of the anion exchange in ionic liquids already observed in cyclopropanation reactions [42–45]. Enantioselectivities were slightly lower than in organic solvents, probably due to a catalytic effect of the ionic liquid itself. Reaction products were extracted with diethyl ether from the ionic liquid phase, and this solution was reused three times, with continuous loss of enantioselectivity (96–93–85–65% ee). Reaction temperature was reduced to −40 °C by mixing the ionic liquid phase with CH_2Cl_2 (1:2). After reaction, the organic solvent was evaporated and products extracted with ether. In this way, recyclability of the system was significantly improved, up to 10 consecutive runs (95–99–96–99–94–95–95–95–88–75% ee). Reactions with other dienes and dienophiles also led to excellent enantioselectivity results (85–98% ee).

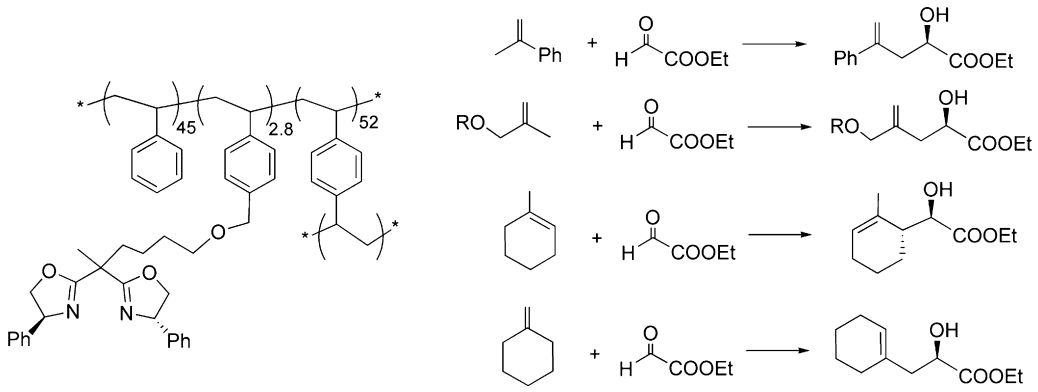
Table 2 summarizes the best results obtained in Diels–Alder reactions with immobilized and separable homogeneous catalysts. As can be seen, there are more examples of immobilization through covalent bonds to inorganic solids, which give consistently good results. However the best recycling results were obtained with the separable homogeneous charge transfer complexes.

There exist only two examples in the literature of the application of supported Box based catalysts in hetero-Diels–Alder reactions, in both cases in the reaction between ethyl(*E*)-2-oxopent-3-enoate and ethyl vinyl ether (Scheme 26).

In the first one, PhBox-Cu complex was exchanged in different zeolites and crystalline mesoporous solids (Scheme 4) [77]. The immobilized catalysts were much less active than the homogeneous counterpart. Regarding enantioselectivity, all the mesoporous catalysts gave results below the 20% ee obtained in solution. The catalyst immobilized on zeolite Y gave 41% ee with a reversal in enantioselectivity with respect to the homo-



Scheme 26. Hetero-Diels–Alder reaction.



Scheme 27. Polymerized PhBox used in carbonyl-ene reactions.

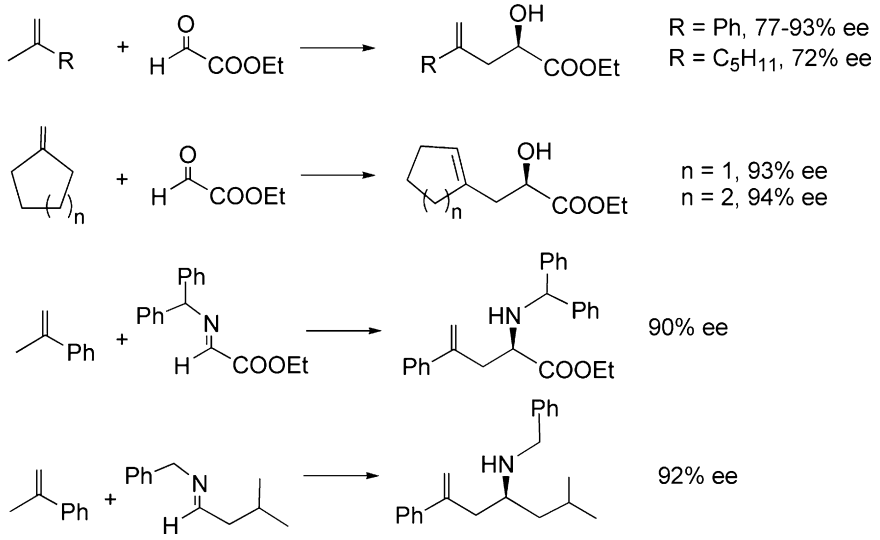
geneous reaction. This reversal, although with very low ee, was produced in all cases when conversion increased, but no explanation for it was offered.

The same reaction was tested also with catalysts immobilized by hydrogen bonding (Scheme 24) [71]. Adsorbed PhBox-Cu (R′ = H) showed a behavior, both in activity and enantioselectivity, similar to that observed in solution. A maximum of 42% ee was obtained at −60 °C, and the catalyst was reused 4 times. However adsorbed ^{t}BuBox-Cu was much less efficient than the homogeneous counterpart, 41% ee obtained at −78 °C versus 95% ee in solution. These results are in complete agreement with our own results in cyclopropanation reactions [10,17], and are probably due to a partial loss of chiral ligand, a consequence of the lower stability of the ^{t}BuBox-Cu complex.

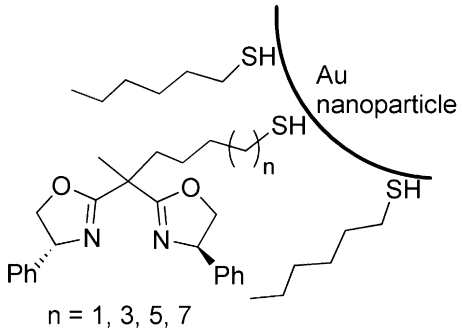
4.2. Ene reactions

Regarding the covalently immobilized ligands on solids, the only example of application to carbonyl-ene reactions was reported by Salvadori and coworkers [78]. PhBox was functionalized in the methylene bridge with one long spacer bearing a styryl group at the end. Once polymerized with styrene and divinylbenzene, the macroreticular resin (Scheme 27) was treated with $Cu(OTf)_2$ and used as catalyst in different carbonyl-ene reactions with ethyl glyoxylate (Scheme 27). The reaction is truly heterogeneous and the catalyst can be recycled 4 times with partial loss of activity, but the same enantioselectivity (90% ee). Even the catalyst was reused in different carbonyl-ene reactions with excellent results (85–95% ee), although with copper reloading. Finally the catalyst was used in a semicontinuous system, passing successive batches of reagents through a HPLC column filled with the polymer, with thorough washing between batches to prevent clogging by polymeric by-products.

Carbonyl- and imino-ene reactions (Scheme 28) were also catalyzed by the PhBox-Cu(II) exchanged on Y zeolite (Scheme 4) [79]. The enantioselectivities obtained with the supported catalysts were similar or better than those obtained in homogeneous phase with the same ligands. As relevant examples, enantioselectivity is improved with α-methylstyrene, from 66 to 80% ee, and methylenecyclopentane, from 57 to 93% ee. Less than 1% copper leaching was detected under the reaction conditions and the system is truly heterogeneous. Furthermore, the catalyst can be efficiently recovered by filtration and washing. The catalyst was reused up to three times with the reagent alternatively changed from ethyl glyoxylate to methyl piruvate without loss of activity or enantioselectivity.



Scheme 28. Carbonyl- and imino-ene reactions catalyzed by PhBox-Cu exchanged on Y zeolite.



Scheme 29. PhBox immobilized on gold nanoparticles.

Bis(oxazoline) ligands functionalized with thiol groups (Scheme 29) were immobilized onto gold nanoparticles stabilized by hexanethiol [80]. The corresponding copper complexes were tested in the reaction between α-methylstyrene and ethyl glyoxylate (Scheme 27). The dispersion degree in dichloromethane was highly dependent on the length of the spacer, which conditioned the catalyst recoverability by hexane addition and centrifugation. The best results were obtained with a tetramethylene spacer ($n = 1$), leading to five consecutive runs with the same enantioselectivity (84–86% ee) and some loss of activity.

The separable PEG-modified Box ligands (Scheme 15) were also tested in carbonyl-ene reactions between ethyl glyoxylate and two different alkenes, α-methylstyrene and methylenecyclohexane (Scheme 27) [41]. In contrast with its behavior in Diels–Alder reactions, these ligands showed high performance in the carbonyl-ene reactions, with high enantioselectivity, 95 and 87% ee, respectively. However, only the chiral modified ligand was recycled after decomplexation with KCN.

Recyclability of homogeneous bis(oxazoline) ligands was also accomplished by functionalization with fluorinated chains (Scheme 17) [47]. The higher F content reduced the solubility in conventional organic solvents, allowing the separation by extraction with perfluorooctanes. However, the presence of two bulky groups in that position significantly reduces the enantioselectivity of the carbonyl-ene reaction between ethyl glyoxylate and α-methylstyrene (Scheme 27), an effect already observed in the case of polymerized Box ligands [21].

This negative effect of the fluorous ponytails has been confirmed by the almost null enantioselectivity obtained with a bis(oxazoline) ligand containing this type of group also in the substituent of the stereogenic centres of the oxazoline rings [81].

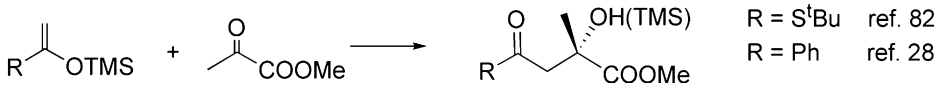
4.3. Mukaiyama aldol reactions

Catalyst shown in Scheme 27 was initially developed for use in Mukaiyama aldol reactions (Scheme 30) [82]. Its catalytic performance was excellent, with 90% yield and 90% ee in a first run. The recovered catalyst lost activity, but kept selectivity at the same level. The initial activity was regained when $Cu(OTf)_2$ was reloaded. After several cycles addition of fresh molecular sieves is also needed.

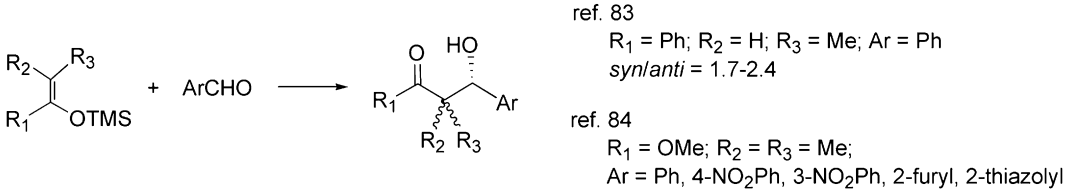
Our group tried to apply Box and azaBox-copper complexes immobilized in laponite by cationic exchange (Scheme 4) in Mukaiyama aldol reactions (Scheme 30) [28]. The supported Box complex was active both in THF and CH_2Cl_2. In the former solvent, the immobilization showed a positive effect on enantioselectivity, 86% ee versus 45% ee in solution, but this catalyst was almost completely deactivated. In CH_2Cl_2, the enantioselectivity (67% ee) was nearly the same as in solution, and the catalyst was partially recoverable. In contrast, supported azabox complexes were nearly inactive, probably due to the higher coordinating character of the ligand that leads to a reduced Lewis acidity.

The use of a non-coordinating solvent in the complexation made the polystyrene-supported azaBox (Scheme 10) suitable for this reaction. Although with moderate yields, this catalyst was active in both solvents, with high enantioselectivity (84% ee in THF). The deactivation was shown to be highly reaction dependent, as the recovered catalyst inactive for Mukaiyama aldol was used in cyclopropanation of styrene with ethyl diazoacetate, a reaction with different requirements that takes place through a completely different mechanism, with excellent results both in activity and enantioselectivity. This is one of the few examples of truly multitask catalysts in the literature.

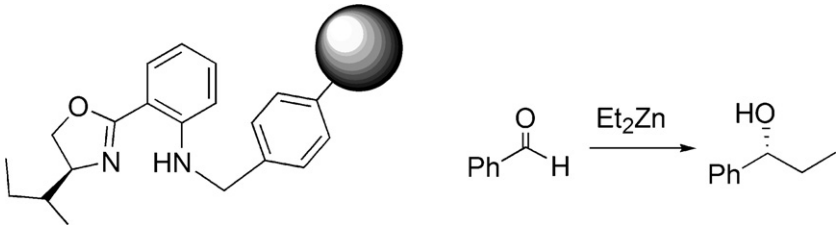
Regarding separable catalysts, dendritic box-Cu complexes were tested in a Mukaiyama aldol reaction (Scheme 31) in aqueous medium (H_2O:EtOH:THF = 2:9:9) [83]. Substitution in the methylene bridge with two bulky dendrimeric chains was not detrimental for enantioselectivity (up to 64% ee). The complex was quantitatively recovered by precipitation with cold methanol, but the recycled catalyst showed reduced activity and an important loss of enantioselectivity.



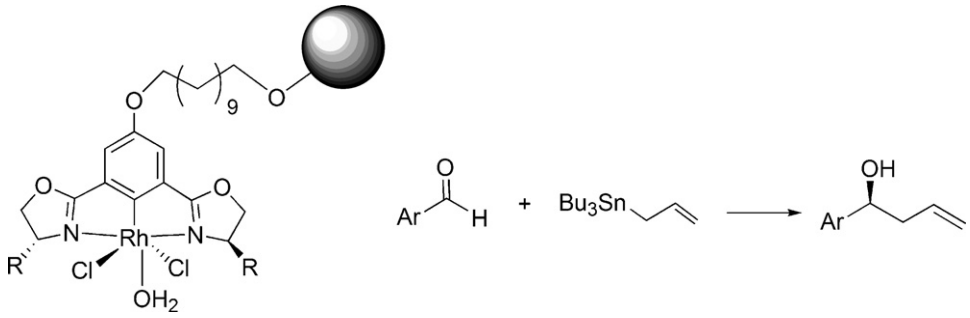
Scheme 30. Mukaiyama-aldol reactions with methyl pyruvate.



Scheme 31. Mukaiyama-aldol reactions with aromatic aldehydes.



Scheme 32. Supported aminooxazoline used in diethylzinc addition to benzaldehyde.



Scheme 33. Supported pincer-Rh complex as catalyst in allylation of benzaldehyde.

PEG-Box (Scheme 15) was also used in Mukaiyama aldol reactions (Scheme 31) in aqueous medium [84]. Results were moderate, both in activity and enantioselectivity (31–63% ee), and dependent on the substituent of the oxazoline rings and the nature of the aromatic aldehyde. Products were extracted with diethyl ether, and the ligand was recovered by decomplexation and extraction with dichloromethane. In some cases the whole complex was recovered and reused in reactions with other substrate.

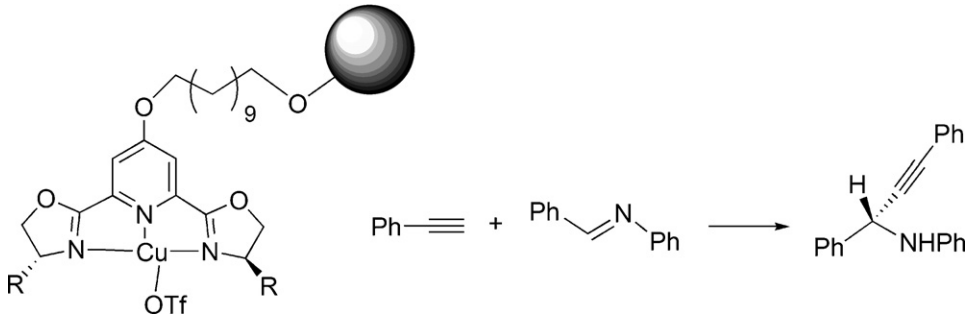
4.4. Other Lewis acid catalyzed reactions

A chiral aminooxazoline was grafted on a polymeric support, and the supported ligand was used in the enantioselective addition of diethylzinc to aromatic aldehydes (Scheme 32) [85]. Yields in the range of 70–92% and enantioselectivities between 43 and 90% ee were obtained, depending on the substitution of the aldehyde. The supported ligand can be recycled and reused with only slight lower performance.

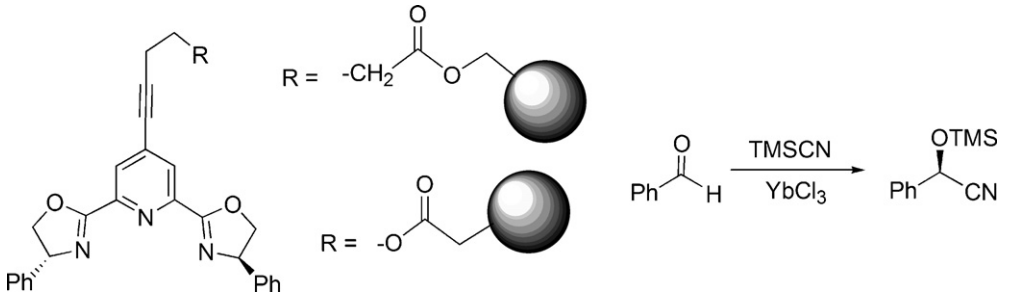
Pincer bis(oxazolinyl)phenyl ligands supported on Wang resin were prepared by solid-phase synthesis. The formation of the ligand in the last step was confirmed by gel-phase ^{13}C-NMR. The complexation with $RhCl_3$ in the presence of a base led to the metallation of the phenyl moiety, and this complex was used as catalyst for the enantioselective allylation of aromatic aldehydes with allyltributylstannane (Scheme 33) [86]. Less bulky substituents in the oxazoline rings was positive for enantioselectivity, leading to a maximum of 48% ee with the ethyl derivative. Catalysts showed a good recyclability in 2–3 cycles.

The same strategy was used later for the synthesis of a supported pyridinebis(oxazoline) ligand. The corresponding Cu(I) complex was used as catalyst in the reaction between phenylacetylene and benzylideneaniline (Scheme 34) [87]. Enantioselectivity increased with bulkiness of the oxazoline substituent, and the best result (83% ee) was obtained with the *tert*-butyl ligand in CH_2Cl_2. However this catalyst was not recoverable due to an important loss of activity, that was minimized by using THF as a reaction solvent (three runs), although with a significant reduction in the asymmetric induction (54–60% ee).

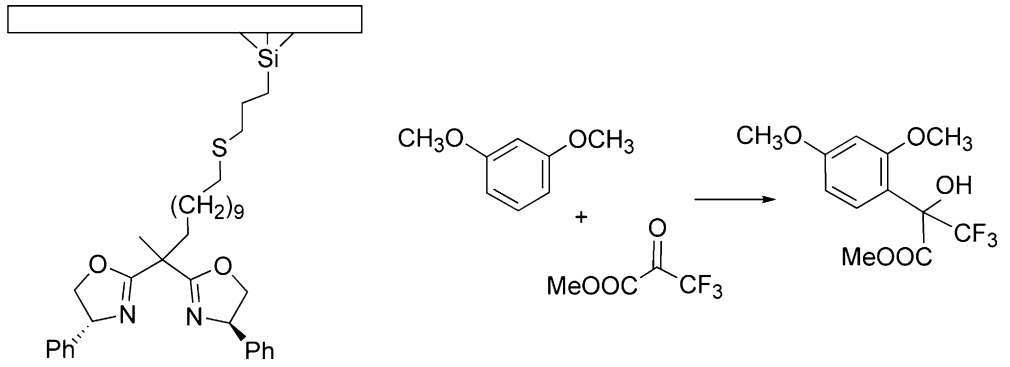
A pyridinebis(oxazoline) ligand was grafted onto TentaGel resin by functionalization through a Sonogashira coupling and an esterification reaction. This ligand was used in the $YbCl_3$ catalyzed trimethylsilylcyanation of benzaldehyde (Scheme 35) [88]. The nature of the spacer had some influence on the con-



Scheme 34. Supported Pybox-Cu as catalyst for acetylene addition to imines.



Scheme 35. Supported Pybox-Yb complex as catalyst for trimethylsilylcyanation of benzaldehyde.



Scheme 36. Friedel-Crafts reaction catalyzed by PhBox-Cu supported on silicas.

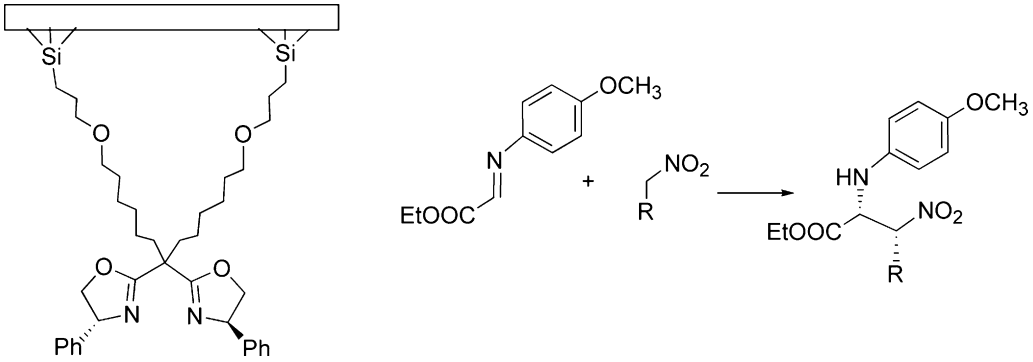
version, but enantioselectivity was always 80–81% ee during 4 runs.

PhBox was grafted on both amorphous silica and MCM-41 by monofunctionalization with undec-10-enyl chain and subsequent reaction with the mercaptopropyl support. The Cu(II) complex was used in the Friedel-Crafts alkylation of 1,3-dimethoxybenzene with methyl 3,3,3-trifluoropyruvate (Scheme 36) [89]. The reactions were truly heterogeneous, and the enantioselectivity was always higher than that obtained with the analogous ligand in solution, 92% ee with amorphous silica and 82% ee with MCM-41.

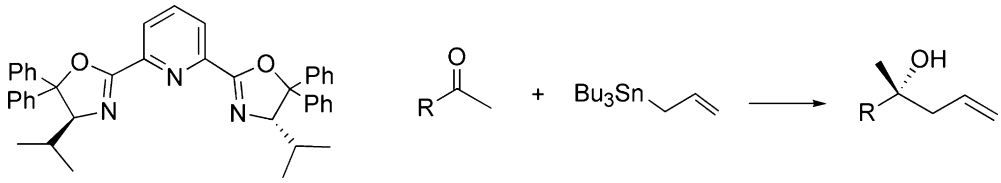
The same bis(oxazoline) was grafted onto SBA-15 by functionalization with two 6-hydroxyhexyl groups in the methylene bridge and then alkylation with chloropropyl modified support. The Cu(II) complex was used in nitro-Mannich reactions with different nitroalkanes (Scheme 37) [90]. The catalytic performance was very similar to the homogeneous complex, mainly regarding selectivities (90–94% ee with nitroethane and higher nitroalkanes), but the supported catalyst showed a significant drop in enantioselectivity upon recycling (90–50–21–22–10% ee in five consecutive runs with nitroethane).

A solution of Pybox-$InCl_3$ in [hmim][PF_6] ionic liquid (Scheme 16) was used as catalyst in the allylation of ketones (Scheme 38) [91]. Yields (58–82%) and enantioselectivities (55–91% ee) were greatly dependent on the ketone structure.

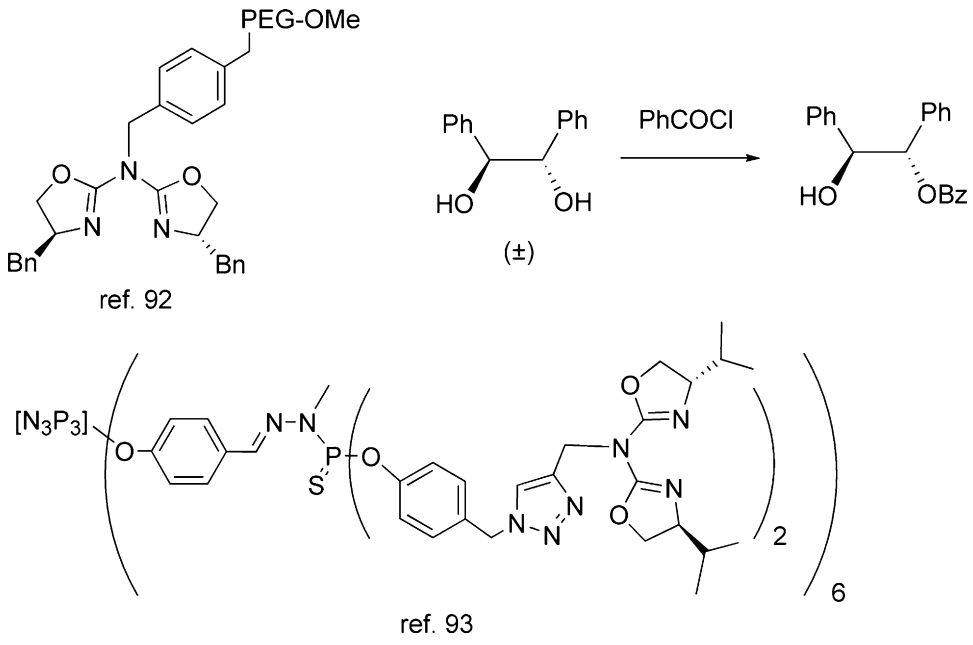
Azabox-Cu complexes are highly efficient in the asymmetric benzoylation of racemic 1,2-diols (Scheme 39). These complexes were made separable by modification with PEG_{5000} chains or dendrimers. In the first case [92] excellent enantioselectivities were obtained (91–99% ee) using only 0.7% catalyst in 5 consecutive cycles. The catalyst was recovered by precipitation with diethyl ether. P,S-Dendrimers were also efficient



Scheme 37. Nitro-Mannich reaction catalyzed by supported PhBox-Cu.



Scheme 38. Allylation of ketones catalyzed by Pybox-$InCl_3$ in ionic liquid solution.



Scheme 39. Benzoylation of 1,2-diols with separable Azabox ligands.

for this purpose [93], with an important influence of the dendrimer generation. First and second generation dendrimers led to 99% ee during 3 cycles recovered by precipitation with hexane, although 5% catalyst had to be used.

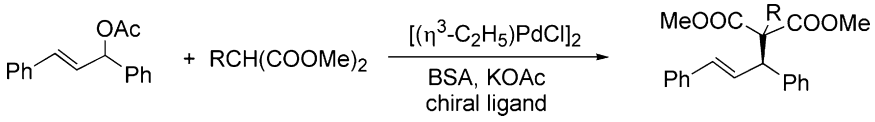
5. Allylic substitution

Several chiral ligands containing oxazoline units have been tested to obtain recoverable catalysts in the palladium-catalyzed allylic substitution of racemic (*E*)-1,3-diphenyl-prop-2-enyl acetate with dimethyl malonates (Scheme 40).

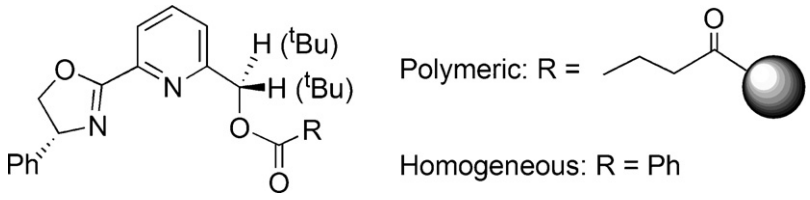
Yields obtained using PhBox ligand grafted to an Argo-Gel resin (Scheme 21) changed from one to another reaction (28–70%), as it happens in homogeneous phase (67–95%), but enantioselectivity was constant (95% ee in the *R* product). The precipitation of Pd(0) prevented recycling of the catalyst, but, after removal of palladium, the ligand was recovered and reused [68].

A Pyox ligand covalently bonded to a Tenta-Gel resin (Scheme 41) was tested in the same reaction [94]. Whereas yields were very low with the ligands containing *tert*-butyl groups, good yields (76–98% with the homogeneous and 60–100% with the polymeric) and moderate enantioselectivities (77% ee with the homogeneous and 80% ee with the polymeric) in the (*R*)-product were obtained with ligands without substitution in the α-position to pyridine, albeit after long reaction times.

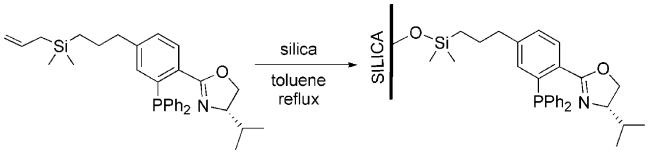
Given that an isopropyl-substituted phosphinooxazoline had been described as one of the best ligand for palladium-catalyzed allylic alkylation, it was grafted to amorphous silica by reaction of the support with an allyldimethylsilyl derivative [95] (Scheme 42). The grafted palladium catalyst showed a high activity in the reaction of allylic substitution (Scheme 40) in THF. Using NaH as a base the reaction was completed after 6 hours and the (*S*)-product was obtained with a 81% ee, significantly lower than the 98% ee obtained under homogeneous conditions. The recovered catalyst was less active than the original and 34 h were required to complete the reaction in both the second and the third runs, but the product was obtained with the same or even better % ee.



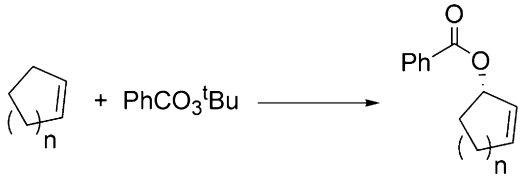
Scheme 40. Allylic substitution reaction.



Scheme 41. Tenta-Gel supported Pyox ligand.



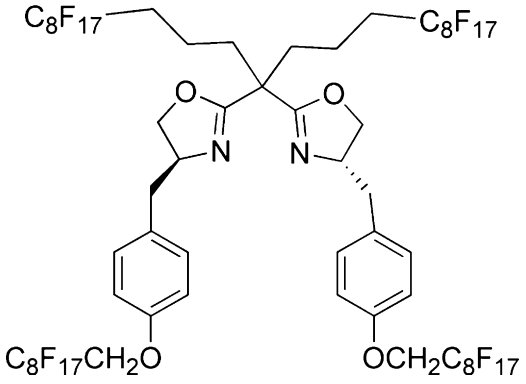
Scheme 42. Immobilization of phosphinooxazoline on silica.



Scheme 44. Allylic oxidation reaction.

Palladium complexes of a phosphinooxazolidine (Scheme 23), bonded to several polymers, were compared in the same allylic substitution reaction (Scheme 40). Using dimethyl malonate, the use of polystyrene-diethylsilyl (PS-DES)-supported ligand gave a poor chemical yield (25%) with a good 93% ee. TentaGel-supported ligand afforded a satisfactory 96% ee with a moderate 78% yield. The ligand bonded to polystyrene-ethyl (PS-Et) through an ester bond led to the best results using 5% catalyst loading [99% yield and 95% ee in the (*R*)-product], but enantioselectivity decreased to 77% ee using 2% catalyst loading. Recycled catalyst led to worse results (47% yield and 66% ee) [69].

Bayardon and Sinou have described the use of palladium complexes of several fluorous bis (oxazolines) in this reaction [96]. High yields and enantioselectivities (up to 100% conversion and 98 % ee in the *S* product) were obtained in several solvents. Whereas catalyst recovery was prevented by the formation of black palladium, ligands were reused after recovery by liquid–liquid extraction with FC72 or solid–liquid extraction using a short column of fluorous reversed phase silica gel. Ligand recovery was improved by introducing two additional ponytails in the position 4 of the oxazoline rings (Scheme 43). With this ligand 98% conversion and 92% ee were obtained in two consecutive reactions, using in the second the recovered ligand [81].



Scheme 43. Fluorous Box ligand with additional ponytails in the oxazoline rings.

6. Oxidations and reductions

Bayardon and Sinou [96] have tested the fluorous ligands mentioned above (Schemes 17 and 43) in the Cu(I)-catalyzed enantioselective oxidation of cycloalkenes with *tert*-butyl perbenzoate (Scheme 44). Moderate to good yields were obtained with all the ligands. Enantioselectivities reached 77% ee, for cyclopentene, and 73% ee, for cyclohexene, but lower values were obtained for cycloheptene (49% ee) and cyclooctene (10% ee). In all cases the (*S*)-cycloalken-2-yl benzoate is the major enantiomer. Catalyst recovery was unsuccessful, with noticeable decreases in both yield and enantioselectivity. When the ligand contained the four ponytails [81] enantioselectivity in the oxidation of cyclohexene is only 50% ee, but recovered catalyst led to an only slightly worse yield and the same enantioselectivity.

A Box-Rh complex grafted to silica gel was tested as catalyst in the hydrogenation of methyl acetoacetate [97]. The hydrogenation took place with a TON of 800 mol/mol$_{Rh}$ but leading to the racemic product. XPS binding energies accounted for the formation of Rh (0), in correlation with the absence of enantioselectivity. Similar behavior was observed with the related homogeneous catalyst.

7. Conclusions

Supported oxazoline-based complexes have been created using all the available immobilization strategies. The effect of immobilization has been extensively studied in the case of cyclopropanation reactions, where the stability of the complex is a key point for immobilizability and recyclability, and excellent results can be obtained with different approaches. In addition, surface effects have been detected, which open the door to future developments in new stereochemical features of heterogeneously catalyzed enantioselective reactions. Each reaction has its own requirements and characteristics that condition the use of one or another immobilization method. Lewis acid promoted reactions are probably among the most difficult ones, due to the concurrence of reagents and products for metal complexation, leading to severe poisoning of the catalyst. In spite of this draw-

back, the use of poisoned catalysts to promote enantioselective reactions with different mechanisms constitutes an added value for immobilized systems.

Acknowledgement

The generous financial support of the CICYT (projects CTQ2005-08016 and Consolider Ingenio 2010 CSD2006-0003) is greatly acknowledged.

References

[1] G. Desimoni, G. Faita, K.A. Jørgensen, Chem. Rev. 106 (2006) 3561.
[2] H. Lebel, J.F. Marcoux, C. Molinaro, A.B. Charette, Chem. Rev. 103 (2003) 977.
[3] G. Desimoni, G. Faita, P. Quadrelli, Chem. Rev. 103 (2003) 3119.
[4] D. Rechavi, M. Lemaire, Chem. Rev. 102 (2002) 3467.
[5] J.M. Fraile, J.I. García, V. Martínez-Merino, J.A. Mayoral, L. Salvatella, J. Am. Chem. Soc. 123 (2001) 7616.
[6] A. Cornejo, J.M. Fraile, J.I. García, M.J. Gil, V. Martínez-Merino, J.A. Mayoral, L. Salvatella, Organometallics 24 (2005) 3448.
[7] J.M. Fraile, J.I. García, J.A. Mayoral, T. Tarnai, Tetrahedron: Asymmetry 8 (1997) 2089.
[8] P.J. Alonso, J.M. Fraile, J. García, J.I. García, J.I. Martínez, J.A. Mayoral, M.C. Sánchez, Langmuir 16 (2000) 5607.
[9] J.M. Fraile, J.I. García, J.A. Mayoral, T. Tarnai, Tetrahedron: Asymmetry 9 (1998) 3997.
[10] J.M. Fraile, J.I. García, J.A. Mayoral, T. Tarnai, M.A. Harmer, J. Catal. 186 (1999) 214.
[11] M.J. Fernández, J.M. Fraile, J.I. García, J.A. Mayoral, M.I. Burguete, E. García-Verdugo, S.V. Luis, M.A. Harmer, Topics Catal. 13 (2000) 303.
[12] J.M. Fraile, J.I. García, M.J. Gil, V. Martínez-Merino, J.A. Mayoral, L. Salvatella, Chem. Eur. J. 10 (2004) 758.
[13] J.M. Fraile, J.I. García, M.A. Harmer, C.I. Herrerías, J.A. Mayoral, O. Reiser, H. Werner, J. Mater. Chem. 12 (2002) 3290.
[14] A.I. Fernández, J.M. Fraile, J.I. García, C.I. Herrerías, J.A. Mayoral, L. Salvatella, Catal. Commun. 2 (2001) 165.
[15] A. Cornejo, J.M. Fraile, J.I. García, M.J. Gil, C.I. Herrerías, G. Legarreta, V. Martínez-Merino, J.A. Mayoral, J. Mol. Catal. A 196 (2003) 101.
[16] J.I. García, G. Jiménez-Oses, V. Martínez-Merino, J.A. Mayoral, E. Pires, I. Villalba, Chem. Eur. J. 13 (2007) 4064.
[17] J.M. Fraile, J.I. García, C.I. Herrerías, J.A. Mayoral, M.A. Harmer, J. Catal. 221 (2004) 532.
[18] J.M. Fraile, J.I. García, C.I. Herrerías, J.A. Mayoral, O. Reiser, A. Socuéllamos, H. Werner, Chem. Eur. J. 10 (2004) 2997.
[19] J.M. Fraile, J.I. García, J.A. Mayoral, M. Roldán, Org. Lett. 9 (2007) 731.
[20] A. Cornejo, J.M. Fraile, J.I. García, M.J. Gil, V. Martínez-Merino, J.A. Mayoral, Tetrahedron 61 (2005) 12107.
[21] M.I. Burguete, J.M. Fraile, J.I. García, E. García-Verdugo, S.V. Luis, J.A. Mayoral, Org. Lett. 2 (2000) 3905.
[22] M.I. Burguete, J.M. Fraile, J.I. García, E. García-Verdugo, C.I. Herrerías, S.V. Luis, J.A. Mayoral, J. Org. Chem. 66 (2001) 8893.
[23] M.I. Burguete, E. Díez-Barra, J.M. Fraile, J.I. García, E. García-Verdugo, R. González, C.I. Herrerías, S.V. Luis, J.A. Mayoral, Bioorg. Med. Chem. Lett. 12 (2002) 1821.
[24] E. Díez-Barra, J.M. Fraile, J.I. García, E. García-Verdugo, C.I. Herrerías, S.V. Luis, J.A. Mayoral, P. Sánchez-Verdú, J. Tolosa, Tetrahedron: Asymmetry 14 (2003) 773.
[25] A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, Chem. Commun. (2003) 2466.
[26] J.G. Knight, P.E. Belcher, Tetrahedron: Asymmetry 16 (2005) 1415.
[27] H. Werner, C.I. Herrerías, M. Glos, A. Gissibl, J.M. Fraile, I. Pérez, J.A. Mayoral, O. Reiser, Adv. Synth. Catal. 348 (2006) 125.
[28] J.M. Fraile, I. Pérez, J.A. Mayoral, O. Reiser, Adv. Synth. Catal. 348 (2006) 1680.
[29] A. Cornejo, J.M. Fraile, J.I. García, E. García-Verdugo, M.J. Gil, G. Legarreta, S.V. Luis, V. Martínez-Merino, J.A. Mayoral, Org. Lett. 4 (2002) 3927.
[30] A. Cornejo, J.M. Fraile, J.I. García, M.J. Gil, S.V. Luis, V. Martínez-Merino, J.A. Mayoral, J. Org. Chem. 70 (2005) 5536.
[31] M.I. Burguete, A. Cornejo, E. García-Verdugo, M.J. Gil, S.V. Luis, J.A. Mayoral, V. Martínez-Merino, M. Sokolova, J. Org. Chem. 72 (2007) 4344.
[32] A. Cornejo, V. Martínez-Merino, M.J. Gil, C. Valerio, C. Pinel, Chem. Lett. 35 (2006) 44.
[33] R.J. Clarke, I.J. Shannon, Chem. Commun. (2001) 1936.
[34] T.M. Lancaster, S.S. Lee, J.Y. Ying, Chem. Commun. (2005) 3577.
[35] S.S. Lee, J.Y. Ying, J. Mol. Catal. A 256 (2006) 219.
[36] S.S. Lee, S. Hadinoto, J.Y. Ying, Adv. Synth. Catal. 348 (2006) 1248.
[37] J.M. Fraile, J.I. García, C.I. Herrerías, J.A. Mayoral, Chem. Commun. (2005) 4669.
[38] A. Cornejo, J.M. Fraile, J.I. García, M.J. Gil, V. Martínez-Merino, J.A. Mayoral, Mol. Diversity 6 (2003) 93.
[39] A. Cornejo, J.M. Fraile, J.I. García, M.J. Gil, S.V. Luis, V. Martínez-Merino, J.A. Mayoral, CR Chimie 7 (2004) 161.
[40] M. Glos, O. Reiser, Org. Lett. 2 (2000) 2045.
[41] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, J. Org. Chem. 66 (2001) 3160.
[42] J.M. Fraile, J.I. García, C.I. Herrerías, J.A. Mayoral, D. Carrié, M. Vaultier, Tetrahedron: Asymmetry 12 (2001) 1891.
[43] J.M. Fraile, J.I. García, C.I. Herrerías, J.A. Mayoral, S. Gmough, M. Vaultier, Green Chem. 6 (2004) 93.
[44] D.L. Davies, S.K. Kandola, R.K. Patel, Tetrahedron: Asymmetry 15 (2004) 77.
[45] J.M. Fraile, J.I. García, C.I. Herrerías, J.A. Mayoral, O. Reiser, M. Vaultier, Tetrahedron Lett. 45 (2004) 6765.
[46] M.R. Castillo, L. Fousse, J.M. Fraile, J.I. García, J.A. Mayoral, Chem. Eur. J. 13 (2007) 287.
[47] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Pozzi, Eur. J. Org. Chem. (2003) 1191.
[48] J. Bayardon, O. Holczknecht, G. Pozzi, D. Sinou, Tetrahedron: Asymmetry 17 (2006) 1568.
[49] C. Langham, P. Piaggio, D. Bethell, D.F. Lee, P. McMorn, P.C. Bulman-Page, D.J. Willock, C. Sly, F.E. Hancock, F. King, G.J. Hutchings, Chem. Commun. (1998) 1601.
[50] C. Langham, D. Bethell, D.F. Lee, P. McMorn, P.C. Bulman-Page, D.J. Willock, C. Sly, F.E. Hancock, F. King, G.J. Hutchings, Appl. Catal. A 182 (1999) 85.
[51] C. Langham, S. Taylor, D. Bethell, P. McMorn, P.C. Bulman Page, D.J. Willock, C. Sly, F.E. Hancock, F. King, G.J. Hutchings, J. Chem. Soc. Perkin Trans. 2 (1999) 1043.
[52] S. Taylor, J. Gullick, P. McMorn, D. Bethell, P.C. Bulman-Page, F.E. Hancock, F. King, G.J. Hutchings, J. Chem. Soc. Perkin Trans. 2 (2001) 1714.
[53] S. Taylor, J. Gullick, P. McMorn, D. Bethell, P.C. Bulman-Page, F.E. Hancock, F. King, G.J. Hutchings, J. Chem. Soc. Perkin Trans. 2 (2001) 1724.
[54] J. Gullick, S. Taylor, P. McMorn, D. Bethell, P.C. Bulman-Page, F.E. Hancock, F. King, G.J. Hutchings, J. Mol. Catal. A 182 (2002) 571.
[55] S. Taylor, J. Gullick, P. McMorn, D. Bethell, P.C. Bulman-Page, F.E. Hancock, F. King, G.J. Hutchings, Topics Catal. 24 (2003) 43.
[56] J. Gullick, D. Ryan, P. McMorn, D. Bethell, F. King, F. Hancock, G. Hutchings, New J. Chem. 28 (2004) 1470.
[57] D. Ryan, P. McMorn, D. Bethell, G. Hutchings, Org. Biomol. Chem. 2 (2004) 3566.
[58] Y. Traa, D.M. Murphy, R.D. Farley, G.J. Hutchings, Phys. Chem. Chem. Phys. 3 (2001) 1073.
[59] J. Gullick, S. Taylor, D. Ryan, P. McMorn, M. Coogan, D. Bethell, P.C. Bulman-Page, F.E. Hancock, F. King, G.J. Hutchings, Chem. Commun. (2003) 2808.
[60] S. Taylor, J. Gullick, N. Galea, P. McMorn, D. Bethell, P.C. Bulman- Page, F.E. Hancock, F. King, D.J. Willock, G.J. Hutchings, Topics Catal. 25 (2003) 81.
[61] J.M. Fraile, J.I. García, G. Lafuente, J.A. Mayoral, L. Salvatella, Arkivoc (2004) 67.
[62] D. Rechavi, M. Lemaire, Org. Lett. 3 (2001) 2493.

[63] D. Rechavi, M. Lemaire, J. Mol. Catal. A 182 (2002) 239.
[64] D. Rechavi, B. Albela, L. Bonneviot, M. Lemaire, Tetrahedron 61 (2005) 6976.
[65] J.K. Park, S.W. Kim, T. Hyeon, B.M. Kim, Tetrahedron: Asymmetry 12 (2001) 2931.
[66] M. Tada, S. Tanaka, Y. Iwasawa, Chem. Lett. 34 (2005) 1362.
[67] S. Tanaka, M. Tada, Y. Iwasawa, J. Catal. 245 (2007) 173.
[68] K. Hallman, C. Moberg, Tetrahedron: Asymmetry 12 (2001) 1475.
[69] H. Nakano, K. Takahashi, R. Fujita, Tetrahedron: Asymmetry 16 (2005) 2133.
[70] J.M. Fraile, J.I. García, M.A. Harmer, C.I. Herrerías, J.A. Mayoral, J. Mol. Catal. A 165 (2001) 211.
[71] P. O'Leary, N.P. Krosveld, K.P. De Jong, G. van Koten, R. Gebbink, Tetrahedron Lett. 45 (2004) 3177.
[72] H. Wang, X. Liu, H. Xia, P. Liu, J. Gao, P. Ying, J. Xiao, C. Li, Tetrahedron 62 (2006) 1025.
[73] G. Chollet, F. Rodriguez, E. Schulz, Org. Lett. 8 (2006) 539.
[74] G. Chollet, M.G. Guillerez, E. Schulz, Chem. Eur. J. 13 (2007) 992.
[75] I. Meracz, T. Oh, Tetrahedron Lett. 44 (2003) 6465.
[76] K. Takahashi, H. Nakano, R. Fujita, Chem. Commun. (2007) 263.
[77] Y. Wan, P. McMorn, F.E. Hancock, G.J. Hutchings, Catal. Lett. 91 (2003) 145.
[78] A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, Tetrahedron: Asymmetry 15 (2004) 3233.
[79] N.A. Caplan, F.E. Hancock, P.C.B. Page, G.J. Hutchings, Angew. Chem. Int. Ed. 43 (2004) 1685.
[80] F. Ono, S. Kanemasa, J. Tanaka, Tetrahedron Lett. 46 (2005) 7623.
[81] J. Bayardon, D. Sinou, Tetrahedron; Asymmetry 16 (2005) 2965.
[82] S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, Angew. Chem. Intern. Ed. 40 (2001) 2519.
[83] B.Y. Yang, X.M. Chen, G.J. Deng, Y.L. Zhang, Q.H. Fan, Tetrahedron Lett. 44 (2003) 3535.
[84] M. Benaglia, M. Cinquini, F. Cozzi, G. Celentano, Org. Biomol. Chem. 2 (2004) 3401.
[85] N.S. Shaikh, V.H. Deshpande, A.V. Bedekar, Tetrahedron Lett. 43 (2002) 5587.
[86] A. Weissberg, M. Portnoy, Chem. Commun. (2003) 1538.
[87] A. Weissberg, B. Halak, M. Portnoy, J. Org. Chem. 70 (2005) 4556.
[88] S. Lundgren, S. Lutsenko, C. Jonsson, C. Moberg, Org. Lett. 5 (2003) 3663.
[89] A. Corma, H. García, A. Moussaif, M.J. Sabater, R. Zniber, A. Redouane, Chem. Commun. (2002) 1058.
[90] A. Lee, W. Kim, J. Lee, T. Hyeon, B.M. Kim, Tetrahedron: Asymmetry 15 (2004) 2595.
[91] J. Lu, S.-J. Ji, Y.-C. Teo, T.-P. Loh, Tetrahedron Lett. 46 (2005) 7435.
[92] A. Gissibl, M.G. Finn, O. Reiser, Org. Lett. 7 (2005) 2325.
[93] A. Gissibl, C. Padié, M. Hager, F. Jaroschik, R. Rasappan, E. Cuevas-Yañez, C.-O. Turrin, A.-M. Caminade, J.-P. Majoral, O. Reiser, Org. Lett. 9 (2007) 2895.
[94] K. Hallman, E. Macedo, K. Nordström, C. Moberg, Tetrahedron: Asymmetry 10 (1999) 4037.
[95] K. Aoki, T. Shimada, T. Hayashi, Tetrahedron: Asymmetry 15 (2004) 1771.
[96] J. Bayardon, D. Sinou, J. Org. Chem. 69 (2004) 3121.
[97] N. Debono, L. Djakovitch, C. Pinel, J. Organomet. Chem. 691 (2006) 741.