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Immobilized Oxazoline-Containing Ligands in Asymmetric Catalysis—A Review

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Abstract—Metal complexes of chiral oxazoline derivatives immobilized on soluble as well as insoluble supports serve as versatile asymmetric catalysts in a variety of applications. In a few cases recovery and reuse of the chiral ligands have been achieved.

Several types of oxazoline-containing ligands have proven to serve as highly versatile ligands in asymmetric metal catalysis.[1] Examples of widely used ligands of this type are pyridinooxazoline[2] (**1**, Fig. 1), bisoxazoline[3] (box, **2**), and bisoxazolinopyridine[3] (pybox, **3**) derivatives. The oxazoline-containing ligands are characterized by their ability to coordinate to a large number of metal ions in different oxidation states, yielding rigid metal complexes with well-defined conformational spaces. The complexes have been applied in a wide variety of catalytic applications, including hydrosilylations,[4] Diels–Alder,[5] and 1,3-dipolar cycloadditions,[6] Michael additions,[7] aldol condensations,[8] aziridinations,[9] cyclopropanations,[10] allylic substitutions,[11–13] allylation of aldehydes,[14] and ring-opening of meso-epoxides.[15]

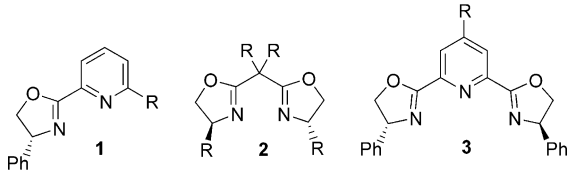

Figure 1. Pyridinooxazoline (**1**), bisoxazoline (box, **2**), and bisoxazolinopyridine (pybox, **3**).

In order to solve problems associated with the separation of the catalyst from the reaction products and to allow recovery and reuse of the often expensive ligands or metal complexes, a wide range of methods to anchor the homogeneous metal complexes to various supports have been explored.[16] At the same time such methods facilitate more efficient reaction design, including use of combinatorial methods and high-throughput screening. There are two basically different strategies for making a catalyst easy to recycle (Fig. 2). The first approach is to bind the catalyst to a polymer that is soluble under the reaction conditions but that can be recovered by for

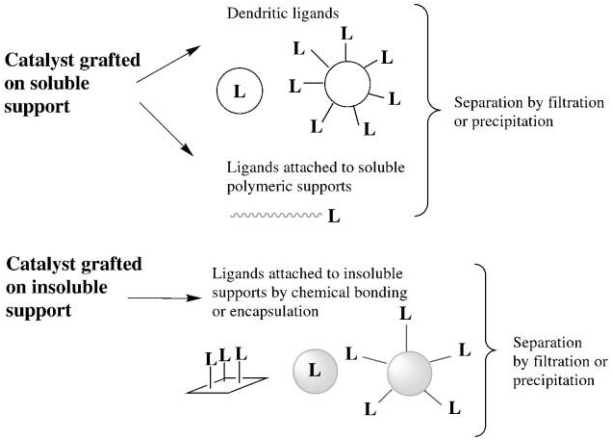

Figure 2. Illustration of the different methodologies used for the separation and recycling of the ligand (L) attached to both soluble and insoluble supports.

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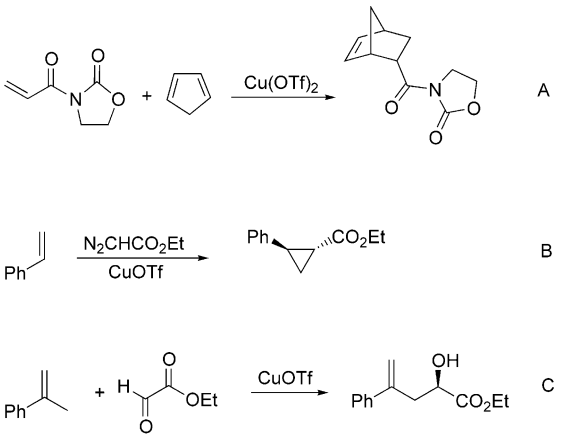


Scheme 1.

example precipitation or ultrafiltration. Examples range from soluble linear polymers to dendritic structures. The second is the immobilization of chiral catalysts on solid supports. The solid supports employed can be of different kinds and consist of inorganic matrices or cross-linked polymers in the form of beads or surfaces.

The advantage with the first methodology is that since the catalysis can be performed under homogeneous conditions, higher selectivity and activity can usually be achieved, whereas isolation of the catalyst is simpler in the second case, as simple filtration is sufficient. Common to both methodologies is that the catalytic activity and the stereoselectivity found for the solution-phase catalyst do not always correlate to those found when the catalyst is bound to a support.

This review covers oxazoline-containing catalysts immobilized on soluble and insoluble supports. The last part of this review will highlight the design of devices allowing rapid screening of the performance of catalysts.

Soluble Polymer-Supported Oxazoline-Containing Ligands

Bisoxazolines have been immobilized onto the soluble polymer MeOPEG [a monomethyl ether of poly(ethylene glycol)] and employed as ligands in the Cu-catalyzed Diels–Alder cycloaddition between *N*-acryloyl-oxazolidinone and cyclopentadiene (Scheme 1, A).[17] Only moderate enantioselectivities were observed (up to 45% ee). These ligands were also employed as catalysts in the cyclopropanation of styrenes (Scheme 1, B) and in the ene-reaction between ethylglyoxalate and α-methylstyrene (Scheme 1, C) or methylene-cyclohexane, with up to 93 and 95% ee, respectively. Reuse of the ligand was possible in the ene-reaction after precipitation and filtration, followed by removal of Cu(II) ions with an aqueous solution of KCN. The enantioselectivity decreased for each cycle (from 95% ee to 88% ee in the third run.[17]

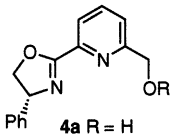
A related ligand, an aza-bisoxazoline, was also grafted onto MeOPEG and this polymer-supported ligand was assessed in Cu-catalyzed cyclopropanations.[18] The ligand was recycled 10 times and the yield varied between 80 and 39% and the enantioselectivities were 87–90% ee for the *trans* product and 81–85% ee for the *cis* product. This polymer-bound ligand was also designed for the Pd-catalyzed allylic alkylation but catalytic results were not reported. However, monomeric analogues were not very active catalysts; only moderate yields (38–66%) were obtained after 165 h reaction time.

Oxazoline derivatives attached to dendritic structures have also proven to be efficient as asymmetric catalysts. Dendrimers are highly branched, fractal-like macromolecules with well-defined, three-dimensional structures.[19] Dendrimers can be regarded as spheres, which are built up by cone-shaped dendrons. Since the first application of dendritic structures in asymmetric metal catalysis, in 1994, dendrimers and dendrons carrying catalytic functions either on their surfaces or at the focal point have been prepared and assessed in catalytic applications.[20] There are several methods for using dendrimers in catalysis. Dendritic catalysts are soluble in a wide range of solvents and thus react under homogeneous conditions, leading to properties similar to those of the parent catalytic species. Separation can often be conveniently achieved using precipitation or nanofiltration. Dendritic catalysts have been employed in flow-through reactors where they are retained by a membrane.[21]

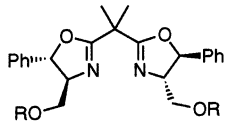
Chiral ligands with chiral dendritic wedges, named dendrizymes, were early prepared by Brunner et al.[22] The idea was to mimic enzymes. However, low selectivity was commonly observed using this type of structures, but several examples of high selectivity have been reported employing chiral ligands with achiral or chiral dendritic substituents.

A dendritic bisoxazoline-containing ligand was synthesized by Chow et al. and used as a catalyst in the Cu-catalyzed Diels–Alder reaction between crotonyl imide and cyclopentadiene.[23] The catalyst gave racemic product and this was claimed to be due to the long distance between the chiral surface of the dendrimer and the catalytic center.

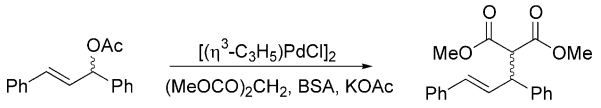
We recently undertook a study of the effect of dendritic substituents on the catalytic performance of oxazoline-containing ligands. Two different hydroxy-containing ligands, **4a**[13] and **5a**,[24] were choosen as basic structures since they could be functionalized with dendrons with carboxylic acids in the focal point by esterification procedures to give ligands **4c**–**4e**, **5c** and **5d**.[25] The dendrons used for couplings to these ligands were acetonide-protected monodendrons based on bis-MPA as the repeating unit.[26]



4a R = H
4b R = COPh
4c R = COG#1
4d R = COG#2
4e R = COG#4



5a R = H
5b R = COPh
5c R = COG#1
5d R = COG#4



Scheme 2.

The ligands were assessed in the palladium-catalyzed allylic alkylation of *rac*-1,3-(*E*)-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 2).[25] The results obtained from reactions with the dendritic oxazoline-containing ligands were compared to those from the phenyl ester derivatives **4b**[2] and **5b**. Substitution of pyridinooxazoline **4** with dendrons did not affect the selectivity or activity to any significant extent. The reason is probably that the catalytic center is situated remote from the sterically demanding substituent. Substitution of bisoxazoline **5** in the 4-position of the oxazoline rings had a more significant effect, leading to increased enantioselectivity, but at the same time decreased activity.

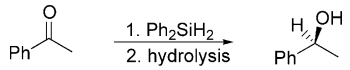
Inherently chiral fullerene dendrimers containing chiral bisoxazoline substituents were recently prepared. Preliminary studies revealed that Cu(I) complexes of the macromolecules catalyze the cyclopropanation of styrene with ethyl diazoacetate, albeit with low stereoselectivity.[27]

Insoluble Polymer-Supported Oxazoline-Containing Ligands

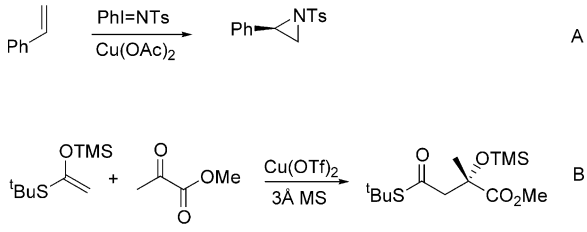
Polymer-supported pyridinooxazolines have been employed in the rhodium-catalyzed hydrosilylation of acetophenone with diphenylsilane (Scheme 3).[28] The catalyst was reused in several cycles but the activity of the catalyst was decreasing. On the other hand, the selectivity was increasing.

Use of 2-(1-alkoxy)alkylpyridinooxazolines and 2-(1-hydroxy)alkylpyridinooxazolines as ligands in the palladium-catalyzed substitution of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate with malonate has been shown to yield the product with high enantioselectivity.[12] It was therefore considered of interest to attach these types of ligands to polymers. The hydroxy function made these ligands suitable for coupling via esterifications. The ligands were attached to polymers using different methodologies.[2] One strategy was to couple the ligands to a TentaGel-HL-COOH polymer. Since this polymer was functionalized with an easily available carboxylic acid, no spacer was needed. Another strategy was to use phenol-containing spacers, which have been shown to be easy to attach to chloromethylated polymers.[29] The ligands were employed in the palladium-catalyzed substitution reaction of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate, affording products with up to 80% ee.[2] Comparison with a monomeric analogue showed similar enantioselectivities and reactivities for the two types of ligands.

Bisoxazolines have been attached to different kinds of solid supports. Clay-supported bisoxazolines have been



Scheme 3.



Scheme 4.

assessed, and in some cases recycled in the cyclopropanation of styrene; the interaction with the support resulted in modified selectivities.[30] Non-covalent attachment to zeolites has been performed with different bisoxazolines and also with a pybox ligand. Metal complexes of these ligands were used as catalysts in the aziridination of alkenes with enantioselectivities up to 61% ee (Scheme 4, A).[31] This kind of clay-supported bisoxazolines has also been utilized as ligands in the Diels–Alder reaction of (*E*)-3-butenoyl-1,3-oxazolidin-2-one with cyclopentadiene; the selectivity observed for this reaction employing supported catalysts was considerably lower than those of the monomers, and in some cases even racemic products were obtained.[32] Covalent attachment of bisoxazolines has been performed to different kinds of supports such as silica[33] and polystyrene.[34] The materials obtained have been assessed as catalysts in different kinds of reactions, such as Diels–Alder reactions,[33] cyclopropanations,[34a] and Mukaiyama aldol additions (Scheme 4, B).[34b]

A chiral bisoxazoline was attached onto ArgoGel and the ligand was assessed in palladium-catalyzed allylations (Scheme 2).[35] The enantioselectivity obtained using this ligand was 94–95% ee. After removal of precipitated palladium(0) with saturated KCN in DMSO the polymer-bound ligand could be reused without any loss in selectivity or activity.

Oxazoline–Containing Ligands on Silicon Chips

High-throughput screening (HTS) is nowadays widely used for the optimization of reaction conditions and product properties. It can be used for the optimization of catalysts in terms of reactivity and selectivity (e.g., in connection with drug discovery).[36] To allow HTS different methods have been developed.[37] Miniaturized devices offer many advantages such as the ability of the catalysts to be recycled, as well as reduced catalyst and reagent consumption. The use of a flow-through system with the catalyst attached to the surface allows product recovery without any separation step. A device consisting of parallel channels/reaction chambers functionalized with different ligands would therefore serve as an excellent tool within the HTS-area (Fig. 3).

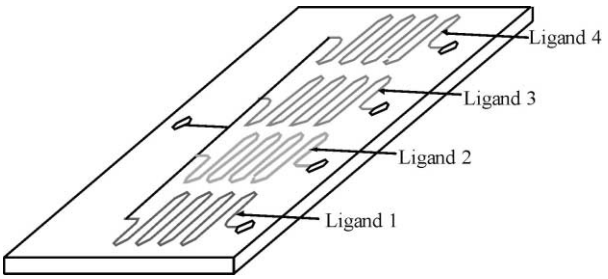
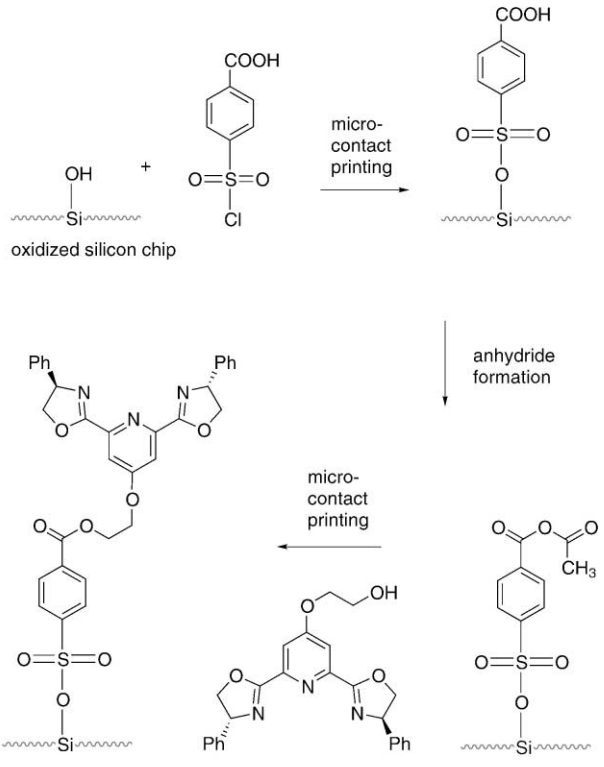


Figure 3. A conceptual drawing of an array of flow-through serpentine channels for combinatorial assays.



Scheme 5.

Several methods have been employed for the attachment of ligands to solid surfaces. Among these, microcontact printing (μCP) (soft lithography) is an attractive method as it is simple to perform and requires very small amounts of the reagents.[38] μCP is performed by inking an elastomeric poly(dimethylsiloxane) (PDMS) stamp with the reagent of choice. When applying the stamp on the substrate (e.g., glass, silicon, gold, or plastic materials) the chemicals are transferred through the stamp to the surface. This allows for modification of the surface by noncovalent interaction[39] as well as by covalent binding[40] of molecules depending on the nature of the reagent and the support.

Chemical modification of the surface prior to functionalization with the ligand is often required.[41] To allow this we have developed consecutive microcontact printing, a method based on two microcontact printing steps (Scheme 5) generating the modified surface in the first step followed by the functionalization with the ligand in the next step.[42] In the first step 4-(chlorosulfonyl)benzoic acid was covalently attached to the oxidized silicon surface. Before the next printing step activation of the acid was performed by anhydride formation using conventional solution chemistry. The second printing step was performed on top of the modified chip area, covalently attaching a pybox derivative.

Consecutive microcontact printing was successfully performed on unstructured oxidized silicon surfaces, as evidenced by for example contact angle measurements and ESCA analysis. In addition, the same method was employed for the attachment of ligands to the internal surfaces of 50 μm deep and 50–100 μm wide channels, the ligands being attached to the bottom as well as the sidewalls of the channels.[42] A method has also been developed to attach beads in a monolayer both on structured and unstructured surfaces.[43] The beads can then be functionalized with the ligand resulting in a larger amount of catalyst than obtained by direct attachment onto the silicon surface.

Conclusions

Oxazoline derivates attached to insoluble and soluble polymers serve as versatile ligands in asymmetric metal catalysis. For several types of reactions, it has been shown that the ligands can be recovered and reused without loss in activity and selectivity. The performance of catalysts attached to dendrons is more sensitive to the steric environment, which may result in increased enantioselectivity at the expense of activity. The properties of chiral catalysts attached to silicon chips remain to be explored.

Acknowledgements

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