UNIVERSITAT ROVIRA I VIRGILI

SUPPORTED LIGANDS FOR METAL CATALYZED REACTIONS

Rocío Marcos Escartín

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ROCÍO MARCOS ESCARTÍN

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Ph.D. Thesis

UNIVERSITAT
ROVIRA I VIRGILI

Institut
Català
d'Investigació
Química

UNIVERSITAT ROVIRA I VIRGILI

Ph.D. THESIS

SUPPORTED LIGANDS FOR METAL CATALYZED REACTIONS

ROCÍO MARCOS ESCARTÍN

TARRAGONA 2011

SUPERVISED BY

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Prof. Miquel A. Pericàs Group Leader and Director of the Institute of Chemical Research of Catalonia (ICIQ).

CERTIFIES, that the present research work entitled "Suported Ligands for Metal Catalyzed Reactions" that **Rocío Marcos Escartín** presents to obtain the PhD degree in Chemistry, has been carried out under my supervisión in the ICIQ and and fulfils all the requirements to be awarded with the "Doctor Europaeus" Mention.

Tarragona, 21 February 2010

PhD Thesis supervisor

Prof. Miquel A. Pericàs

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-Gracias por invitarme a soñar y enseñarme a no tener miedo de cumplir mis sueños-

Cuando emprendas tu viaje hacia Ítaca,
desea que el camino sea largo,
rico en experiencias, de aventuras colmado.

No has de temer a los Lestrígones ni a los Cíclopes,
ni a la cólera del airado Poseidón,
Pues nunca encuentros tales tendrás en tu camino,
si tu pensamiento se mantiene elevado, si una exquisita
emoción a tu alma y a tu cuerpo les guía.
Los Lestrígones y los Cíclopes,
y el fiero Poseidón no podrán encontrarte,
si no los llevas ya dentro, en tu alma,
si tu alma no los conjura ante de ti.

Desea que el camino sea largo.
Que numerosas sean las mañanas estivales
en que -¡y con qué alegre placer!-
entres en puertos que ves por vez primera.
Detente en los mercados fenicios,
para adquirir hermosas mercancías,
madreperlas y nácares, ébanos y ámbares,
y sensuales perfumes de todas clases,
los más abundantes y sensuales perfumes que puedas.
Y acude a muchas ciudades de Egipto,
y aprende, aprende de los sabios.

Mantén siempre a Ítaca en tu mente.
llegar ahí es tu destino.
Pero no precipites el viaje en absoluto.
Es mejor que largos años dure,
y que, ya anciano, al fin, arribes a la isla,
rico con cuanto obtuviste en el camino,
sin esperar que riquezas te dé Itaca.

Ítaca te dio el hermoso viaje.
Sin ella, no hubieras emprendido el camino.
mas no tiene otra cosa que ofrecerte.

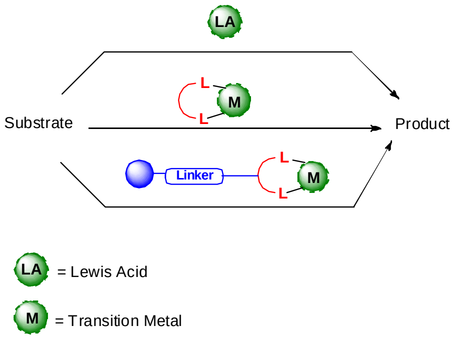
Si la encontrarás pobre, Ítaca no te engañó.
Rico en saber y en vida, como te has vuelto,
comprendes ya qué significan las Ítacas.

K. P. Kavafis (1863-1933)

A mis padres y hermanas

GRAPHICAL ABSTRACTS

Chapter 1. General Introduction (pages 1-29)

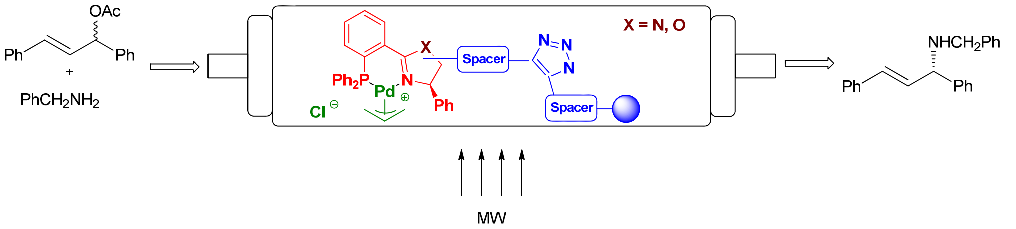


To situate the reader in the field of study of the present thesis is the aim of this chapter. General aspects about metal catalyst (Lewis acids and organometallic ones) are described. Brief summary about heterogenization of homogeneous ligands is also reported. Of these topics, supported ligands for metal catalyzed reactions will be central matters in Chapters 3 and 4. Several Lewis acids catalysts will be applied Chapter 5 for the aryl glicidyl ether rearrangement.

Chapter 2. Aims of this Thesis (pages 31-34)

Chapter 3. Papers A and B (pages 35-116)

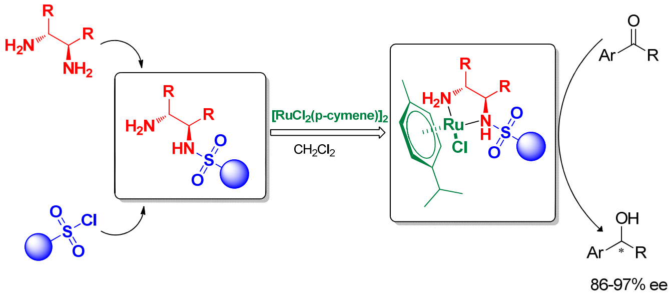
Immobilization of *P,N*-Ligands and their use in Pd-Catalyzed Asymmetric Allylic Amination Reaction



Two families of enantiopure diphenylphosphinooxazolines (PHOX) and diphenylphosphinoimidazolines (PHIM) have been optimized for the palladium-catalyzed asymmetric allylic amination. The optimal catalysts have been modified to include alkynyloxy moiety for polymer supporting *via click chemistry* and have been anchored onto cross-linked azidomethyl polystyrene. Conditions for catalyst recovery and reuse in microwave-promoted amination reactions have been established, and the supported PHOX system has been finally adapted to continuous flow operation.

Chapter 4. Paper C (pages 117-152)

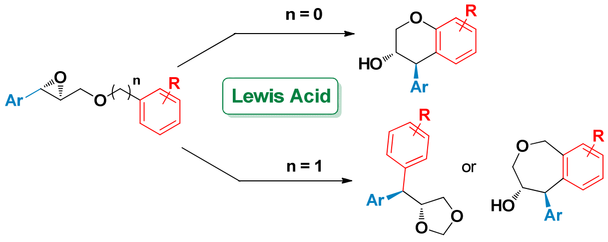
Immobilization of *N,N*-Ligands and their use in Ru-Catalyzed Asymmetric Transfer Hydrogenation Reaction



Polystyrene-supported mono-N-tosyldiamines have been prepared in a single step by directly reacting chlorosulfonylated polystyrene with the corresponding enantiopure 1,2-diamines. The stable RuCl(p-cymene) complexes formed from these functional, high loading resins have been shown to efficiently catalyze the asymmetric transfer hydrogenation (ATH) of alkyl aryl ketones under essentially solvent-free conditions. The best results for ATH have been obtained using immobilized version of TsDPEN and this resin could be recycled with virtually no limits.

Chapter 5. Paper D (pages 153-201)

Lewis Acid-mediated Stereospecific Rearrangement of Aryl Glicidyl Ethers



The behaviour of different Lewis acids to induce stereospecific cyclizations from enantiomerically pure aryl glicidyl ethers has been evaluated. Through the research work herein described, we have demonstrated, contrary to previous claim about only gold mediating this reaction, Lewis acids do in fact catalyze this rearrangement. In particular, $FeBr_3$ (alone or in combination with silver triflate) can be considered as the reagent of choice for this operation.

Chapter 6. Conclusions (pages 203-206)

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ACRONYMS AND ABBREVIATIONS

In this document the abbreviations and acronyms most commonly used in organic chemistry have been used, according to the recommendations of “*Guidelines for authors*” *J. Org. Chem*. **2007**, *72*, 23A-24A.

CHAPTER 1

GENERAL INTRODUCTION

1.1 METAL-CATALYZED REACTIONS

Homogeneous metal catalysts are composed by a metal complex modified with organic ligands. Although the first non enzymatic asymmetric catalysts known were simple organic molecules,[1] the research regarding catalysis reached full development with metal-based systems, which have been predominant for long time.

Regarding the mode of action, and consequently, to some extent, the metals used and the kind of processes involved, metal-based catalysts can be classified as Lewis acid catalysts and organometallic catalysts.

1.1.1 LEWIS-ACID CATALYSTS

Similarly to Brønsted acids, Lewis acids are applied as catalysts in various chemical processes. The wide variety of different Lewis acids available, with significantly different properties, as well as the possibility of tuning them by the use of organic ligands renders them an extremely versatile alternative to classical Brønsted acids. For their application as catalysts, Lewis acids need to fulfil two important requirements: i) The bond-formation between the Lewis acid and the reagent/reactant needs to be reversible and ii) Lewis acid-reactant binding should be stronger than Lewis acid-product binding (in order to avoid product inhibition of the reaction).[2]

The way in which Lewis acids act in the chemical processes can be summarized in three stages (Figure 1): First, the Lewis acid coordinates the substrate, resulting in a decrease of its electron density. Consequently, the activated substrate experiences the transformation with lower activation energy than it would have for a non catalyzed process, due to the polarization induced by the Lewis acid. Finally, the Lewis acid-product adduct dissociates, releasing the product and regenerating the catalyst. Therefore, the efficiency of the process depends on the rate constants of each stage (k_a, k_r, and k_d).[2,3]

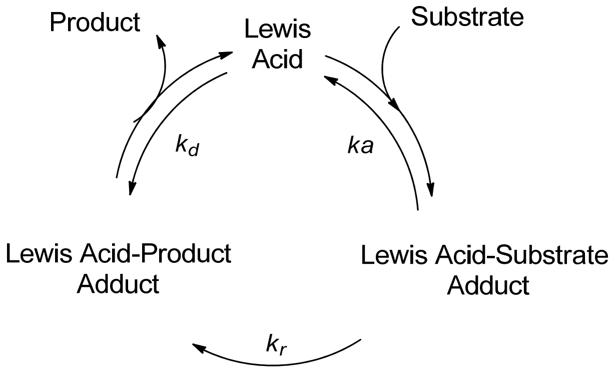


Figure 1: Schematic catalytic cycle of Lewis acid-catalyzed reactions.

Lewis acid-promoted carbon-carbon bond forming reactions are among the most important processes in modern organic chemistry.[5] Classically, the Friedel-Crafts reaction,[6] the Diels-Alder reaction[7] and reactions related to the carbonyl group, such as addition of organometallic carbon nucleophiles[8] and aldol-type reactions (Mukaiyama aldol synthesis),[9] are catalyzed by ordinary and commercially available Lewis acids such as $AlCl_3$, $TiCl_4$, BF_3 or $SnCl_4$.

As mentioned above, a Lewis acidic metal can be tuned by binding an appropriate ligand (in fact, ligand coordination can be interpreted as a Lewis acid-Lewis base equilibrium, the metal acting as the Lewis acid and the ligand as the Lewis base). (Figure 2) Importantly, the use of chiral ligands allows the performance of asymmetric catalysis,[4] something that only very recently has been achieved with Brønsted acids and only for a limited variety of processes. Thus, an uninterrupted expansion of this field has continued during the last decade.

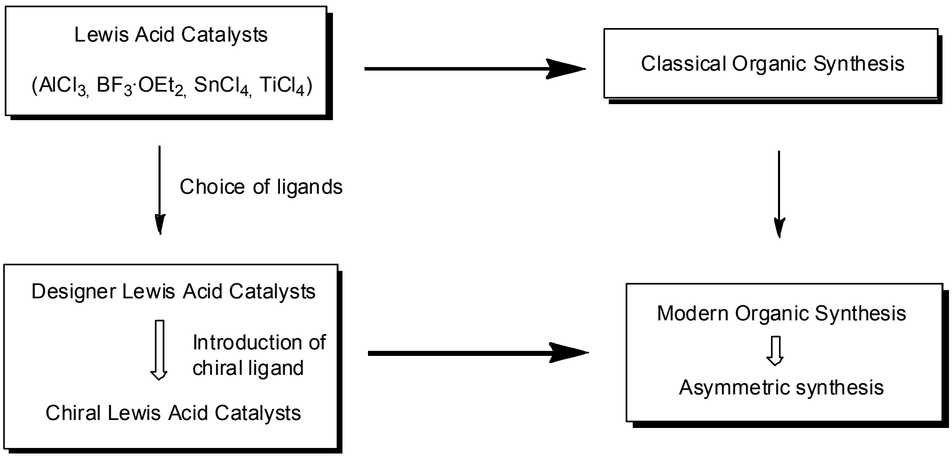


Figure 2: Tuning of Lewis-acid catalysts.

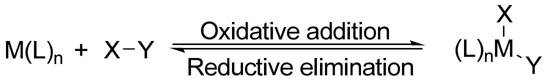
In recent years, the application of gold chemistry to catalysis has emerged as one of the most discussed topics of the catalysis research community[10] with a significant increase in scientific publications describing the use of gold species as homogeneous catalysts.[11] Generally, gold catalysts act as extremely carbophilic Lewis acids (very selective for alkynes and allenes),[12] although in some cases changes in the gold oxidation state have been claimed.[13,14] Their chemistry being (almost completely) explained by their Lewis acid character, together with their ability of forming stable C-M bonds make gold catalysts something between the classical definitions of organometallic and Lewis acid catalysts.

1.1.2 ORGANOMETALLIC CATALYSTS

Organometallic compounds are *"those having bonds between one or more metal atoms and one or more carbon atoms of an organyl group"*.[15] Although some metal-based Lewis-acid catalysts, such as those containing ferrocenyl groups,[16] are included in this definition, they are not organometallic catalysts regarding their mode of action. Rather, the term 'organometallic catalysts' refers to compounds in which the reactivity of carbon–metal bonds is relevant for the catalytic process.[17]

These systems are most frequently based on late transition metals, such as Ru, Co, Rh, Ir, Ni, Pd, Pt and Cu and they are usually applied for processes involving multiple bonds or heteroaryl groups, due to the ability of these metals to form π–complexes. These transition metal catalysts not only enhance selectivity for known reactions, but they also open up entirely novel synthetic pathways that can be applied to complex molecule synthesis. They avoid the waste formation associated with main-group reagents and thus contribute to green chemistry. In addition, an important aspect of such reactions is atom economy.

The catalytic mechanisms they follow are quite diverse, although usually based on the classical transition metal organometallic chemistry, involving the basic processes of oxidative addition, reductive elimination, insertion and β-elimination (Equations 1 and 2).



$$M(L)_n + X{-}Y \underset{\text{Reductive elimination}}{\overset{\text{Oxidative addition}}{\rightleftharpoons}} (L)_nM(X)(Y)$$

Equation 1

$$(L)_nM(X)(Y) \underset{\beta\text{-elimination}}{\overset{\text{Insertion}}{\rightleftharpoons}} (L)_nM{-}Y{-}X$$

Equation 2

As an exception, some transfer hydrogenation catalysts, which do not form any C–M bond during the catalytic process, but activate C–H bonds to form metal hydrides are also considered organometallic catalysts, although the mechanism is clearly different[18] (Figure 3, for more detailed explanation see Chapter 4).

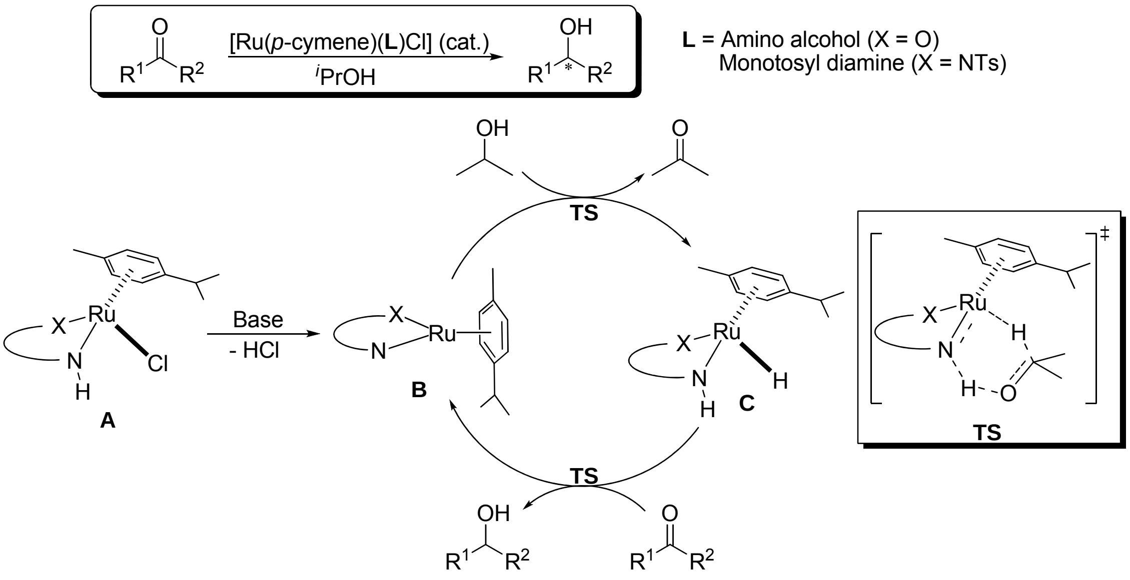


Figure 3: Ruthenium–catalyzed asymmetric transfer hydrogenation.

Originally the role of the ligands was thought to be only to impart solubility to the organometallic catalyst in organic solvents and prevent loss of the metal. However, the ligands strongly influence the electronic and steric properties of the complex thus allowing the appearance of completely new reactivity which can eventually lead to solving synthetic challenges.

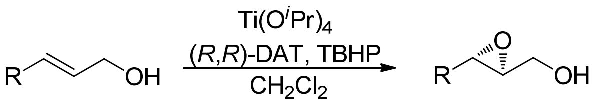
An important part of the art of organometallic chemistry is to design the appropiate ligand to elicit desired properties. In this context, controlling absolute stereochemistry certainly must be classified as one of the major challenges of contemporary organic synthesis, and doing so wherein the asymmetry inducing entity is used only catalytically is the most effective approach. The range of chiral ligands used for this aim is only limited by the imagination of the synthetic chemist.

1.1.3 EPOXIDES AS A SOURCE OF MODULAR LIGANDS

Hystorically, enantiopure chiral ligands have been taken from the shelf of nature and used either directly or after some simple manipulation. However, the use of ligands derived from enantiopure "*non-natural*" starting materials has broadened the structural diversity of available catalysts.[19] The use of enantiopure synthetic precursors has several advantages: i) It allows access to both enantiomers at similar cost, ii) It allows the development of modular syntheses of ligands modifying the steric and electronic properties of the different modular fragments (modules).[20]

The catalytic asymmetric epoxidations of alkenes opened the door to the utilization of synthetic optically active epoxides as intermediates for the construction of a wide range of modular, chiral precursors of ligands.[21]

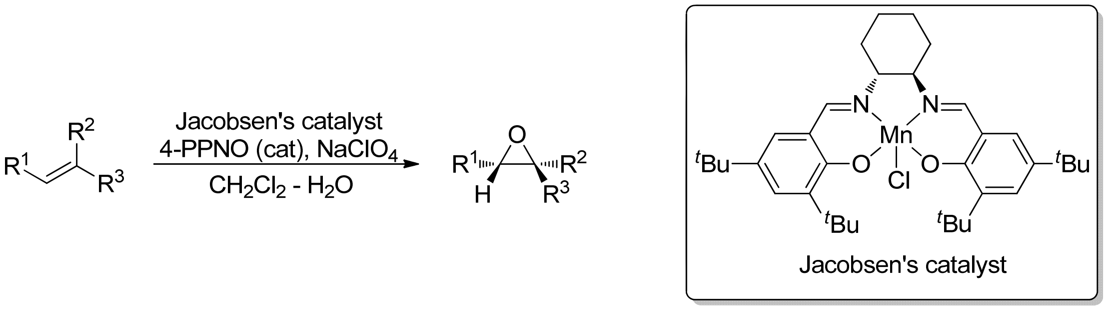
Despite the existence of some enantioselective oxidation reactions of olefins prior to 1980,[22] the development of Sharpless-Katsuki asymmetric epoxidations of allylic alcohols[23,24] in that year was an extraordinary breakthrough in enantioselective epoxidation and to date this method has been widely applied as a general asymmetric epoxidation protocol.[25] A mixture of $Ti(O^iPr)_4$ and dialkyl tartrate (DAT) is used for the *"in situ"* formation of the catalyst, and the most common oxidant is *tert*-butyl hydroperoxide (TBHP) (Scheme 1).



Scheme 1**:** Sharpless epoxidation.

A wide range of primary allylic alcohols can be used in this reaction. Particularly, excellent enantioselectivities are generally obtained with (*E*)-allylic alcohols (>90% ee) while the reaction is more substrate dependent for (*Z*)-allylic alcohols. A very significant advantage of this reaction is that many functional groups tolerate the mild reaction conditions employed.

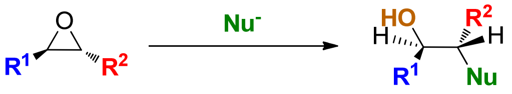
Ten years after Sharpless' discovery, Jacobsen[26] and Katsuki[27] reported, almost simultaneously, a manganese-catalyzed asymmetric epoxidation of unfunctionalized olefins. This enantioselective method is the most used for epoxidation of simple substituted olefins.[28] In this reaction, most frequently, commercial bleach is the oxidant (an aqueous solution of sodium hypochlorite), and the catalyst is a manganese(III)-salen complex (Scheme 2).



Scheme 2: Jacobsen epoxidation.

The major limitation of the Jacobsen's epoxidation, the lack of broad applicability for monosubstituted and *trans* disubstituted olefins, appears to be circumvented in most recent methodologies by the use of chiral dioxirane derivatives as catalytic oxidants.[29,30] These asymmetric epoxidation methods, in combination with others that were developed since then, cover nearly all possibilities to obtain synthetic optically active epoxides in an enantiopure form.

The idea of using enantiopure synthetic epoxides as starting materials for the preparation of modular, chiral ligands for asymmetric catalysis has been extensively developed by our research group, although notorious contributions by Nugent[31] and Kotsuki[32] have also to be mentioned. Thus, epoxides, prepared by Sharpless or Jacobsen epoxidations, have been proved to provide an excellent way of access to a wide variety of stereodefined 1,2-difunctional compounds through regioselective ring-opening reactions.



Following this strategy, different families of highly active and enantioselective modular ligands have been developed and applied in several asymmetric catalytic transformations. These ligands can be classified in two main groups according to the starting epoxide: i) ligands derived from the Sharpless epoxidation, ii) ligands emanating from Jacobsen epoxidation.

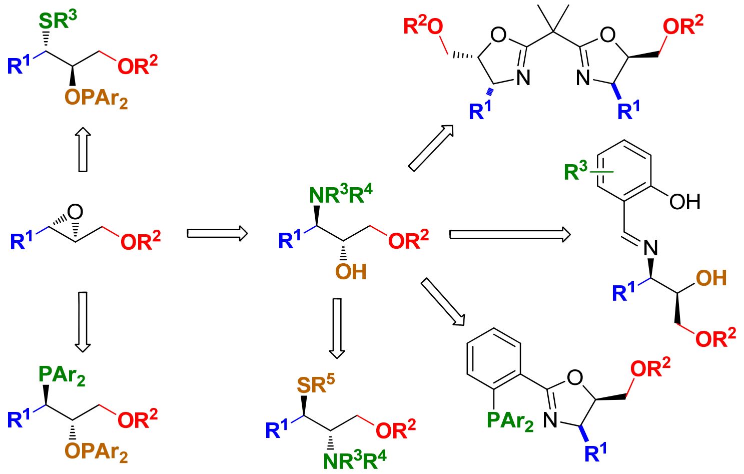


Figure 4: Wide library of highly modular ligands derived from Sharpless epoxides.

Regarding Sharpless-type epoxides, (*2S,3S*)-phenylglycidol has revealed as an extraordinarily versatile plataform. (Figure 4) Thus, ring-opening with amines as nucleophiles has allowed the straightforward preparation of synthetic, yet enantiopure amino alcohols. In this way, it was possible to vary the substituents on the amino and the terminal hydroxyl groups obtaining a wide library of ligands (see in Figure 4).[33] The different amino alcohol ligands generated were screened for the asymmetric addition of diethylzinc onto carbonyl compounds and imines and enantioselective transfer hydrogenations. When bearing a primary amine, these intermediate compounds were used for preparation of Schiff bases,[34] bisoxazolines[35] and phosphinooxazolines.[36] Also, their derived oxazaborolidines were used in the enantioselective borane reduction of prochiral ketones[33b]. Finally, via the aziridine, the amino alcohols could be converted into *S,N*-ligands, which have been applied for the addition of diethylzinc to aldehydes.[37]

In addition, opening the epoxide directly with thiolates has allowed obtaining β-hidroxysulfides that can be derivatized by phosphinylation of the alcohol.[38] These *P,S*-ligands obtained were subsequently applied in several benchmark reactions to check their performance, such as asymmetric allylic substitutions[38a] and asymmetric hydrogenation.[38b] Recently, opening of the epoxide with phosphorus-centred nucleophiles, followed by phosphinylation of the alcohol, has allowed preparation of *P,OP*-ligands, applied in asymmetric hydrogenation and asymmetric allylic substitutions.[39]

In a similar approach, ligands obtained by Jacobsen epoxidation of internal olefins have been developed[40] (Figure 5). In the same way as with those ligands derived from Sharpless epoxides, complete families of chiral amino alcohol or *P,S*-ligands were tested in the addition of organozinc compounds to aldehydes or asymmetric allylic substitutions, respectively.

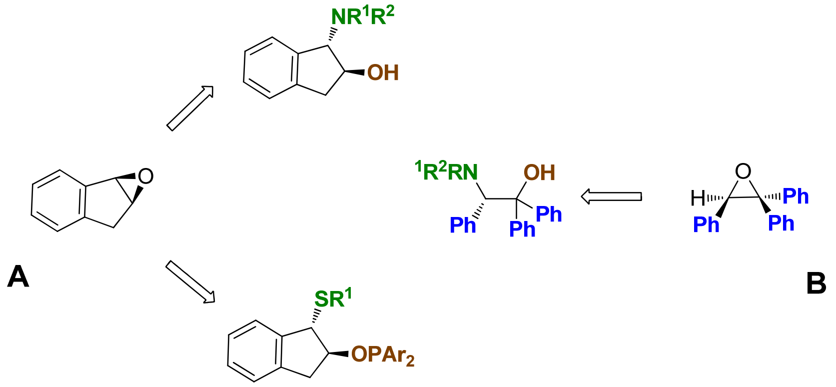


Figure 5: Ligands derived from Jacobsen epoxides. (**A**) Indene oxide family; (**B**) Triphenylethylene family.

1.2 HETEROGENIZATION OF HOMOGENEOUS LIGANDS

Synthesis of homogeneous ligands and their use in catalysis constitutes one of the most important subjects in chemistry originating thousands of published reports every year. Many of these catalysts are able to perform asymmetric reactions. From an industrial point of view, the application of such methodologies is rather limited due to the high cost of enantiomerically pure catalysts used in such transformations.

In order to combine the efficiency of homogeneous asymmetric catalysts with the easy separation, reuse and recycling of heterogeneous ones, strategies for immobilization of homogeneous catalysts onto bulk materials have been developed.[41]

The resulting heterogenized catalysts present several additional advantages inherent to the catalyst separation: i) continuous flow processes can be envisaged and in the case of metal complexes ii) supporting catalysts can avoid or minimize metal contamination in the final product. (See below in the corresponding sections)

In addition, immobilization can be a more than interesting solution in case of very sophisticated, expensive and time-consuming synthesis of catalysts. It is important, however, that the synthesis of the supported catalyst should not add further synthetic complexity, or require as starting materials very expensive reagents. Even more, wherever possible, the support should be commercially available.[42] As a result of the immobilization, a decrease in chemical activity should be expected and this is indeed what happens in most of the cases.[43] Nevertheless, the idea that the support can exert some sort of control on the relative orientation of the substrate/catalyst pair has been used in a positive sense to enhance the stereoselectivity of various catalytic reactions.[44]

Notwithstanding, the preparation and characterization of these heterogenized catalysts are frequently not trivial, requiring a specific know-how, since the techniques used are not restricted to those of standard organic synthesis.[41]

Several factors must be considered in the design of a successful immobilization; an optimal heterogenized catalyst should (i) be mechanically robust and stable under reaction conditions, (ii) have reagent-accesible sites; (iii) show acceptable loadings and (iv) no decrease in performance (catalyst activity or stereoselectivity). **Catalyst stability** appears to be of paramount importance as the ultimate goal of the immobilization of a catalyst is its recovery and reuse.[45,46] At the same time, **high catalytic efficiency** and **stereoselectivity** seem to be other prerequisite conditions for catalyst immobilization.[47]

A number of approaches for the immobilization of the catalysts have been reported. Depending on whether the modifications are made on the catalyst structure or on the reaction medium the immobilization techniques can be categorized into two general classes, namely heterogenized catalysts (inorganic supports, organic polymeric supports, dendrimeric support and organic-inorganic coordination polymers) and biphasic catalysts (the catalyst is dissolved or anchored into nonconventional media, such as perfluorinated solvents, ionic liquids, supercritical liquids).

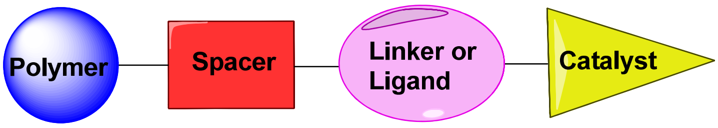
Also, the homogeneous catalysts can be covalently or non-covalently bound to solid supports. In recent times, the idea of covalently binding homogeneous catalysts onto solid supports has gained wide acceptation[41,48] because of the robustness of the catalyst and the simplicity of the work-up conditions. However, it usually requires higher synthetic effort due to the chemical modifications of the catalyst typically needed for linking it to the support. On the other hand, immobilization of catalysts through adsorption or electrostatic interactions is simple, but in general, the weak nature of these interactions makes the resulting catalysts less robust and with a narrower applicability. Entrapment of homogeneous catalysts within solids is another option.

The choice of the support and the kind of catalyst immobilization are crucial, because their properties influence every aspects of the catalyst behaviour. In this chapter, emphasis will be put on polymers since to our work has been developed using these supports to covalently immobilize our homogeneous ligands.

1.2.1 POLYMER-SUPPORTED CATALYSTS

Since the 1960s, when B. R. Merrifield[49] developed the solid-phase peptide synthesis, the use of polymeric supports in chemistry has been expanding its range of applications up to polymer supported catalysts.

These immobilized catalysts are readily available, since they can be easily prepared from commercial resins and polymers or by (co)polymerization of the monomers. Furthermore, it is in principle easier to translate the properties of a homogeneous catalyst into a grafted polymer by optimizing a few key points, such as the nature of the polymer backbone, the kind of the spacer chosen, the nature of potential linkers connecting the ligand with the polymer, and the structural modifications introduced in the ligand molecule to allow covalent supporting onto the resin (anchoring points).



Given the tremendous development in the application of polymer-supported catalysts in organic synthesis[50] the discussion below will focus on transition metal catalysts.

1.2.1.1 Polymer-Bound Metal Catalysts

Homogeneous metal complexes are widespread in catalysis because their properties can be fine-tuned by modifying the steric and electronic environment of the ligands around the metal centre. However, sometimes the final products contain high levels of metal contamination which can become a serious drawback if the metal is toxic. Thus, there are regulations in pharmaceuticals and food additives (some of the main industrial users of homogeneous catalysts) allowing only trace amounts of metal impurities. A plausible solution to avoid this problematic contamination is the use of robust and stable supporting metal catalysts.

Notwithstanding, the most common form of catalyst decomposition is metal leaching. Partial removal of the metal during the recovery of the catalyst carriers –the washing cycles– is likely to occur, causing contamination of the products. In these cases, it is necessary reconditioning of the catalyst (eliminating the plausible byproducts and/or performing another complexation step by adding new metal).

Furthermore, many catalysts contain the seeds of their own destruction (labile or unstable functional groups), and simply deactivate in the course of many turnovers. In this case, any decomposition products that can be fished out can provide valuable guidance on how to design longer-lived catalysts that give higher turnover numbers.

In the permanent effort of developing robust catalysts tightly linked to the polymeric matrix, the choice of the polymer itself has a fundamental impact.[41,51,52] The solubility and swelling properties of the different polymers are a critical issue in most cases, resulting in the need of having in mind the target reaction in which they will be applied when designing new immobilized catalysts.

The utmost advantage associated with the use of insoluble polymers[1] resides in the more ready recovery and thus easier reuse respect to soluble ones.[52-54] However, catalysts supported on soluble polymers require solvent swelling for the reagents to access to the internal reactive sites. Especially when protic solvents must be used for certain reactions and sufficient swelling could not be attained, the use of insoluble resins may encounter serious problems.[53,54] By combining these two aspects, it can be anticipated that, if an insoluble system is selected, what is sacrificed in terms of reactivity can be gained in terms of operational simplicity in recovery and reuse (and the other way around with a soluble system). A viable alternative is therefore the immobilization onto amphiphilic hybrid resins (PS-PEG), which have been recently introduced to overcome the solubility problem.[41c,48a,55]

Moreover, solubility profiles of the polymer can also be varied by changing the cross-linking degree (commonly used supports are styrene-divinylbenzene copolymers).[56] A clear example of the influence of resin swellability is shown next (Figure 6).

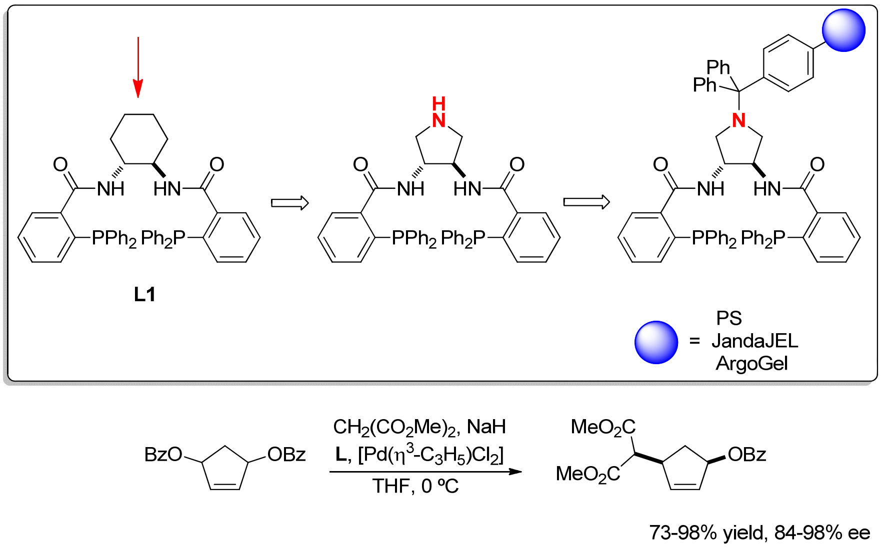


Figure 6. Modifications of Trost ligands in order to develop heterogenized analogues for allylic substitution.

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[1] Most insoluble resins used as catalyst carriers are polystyrene-based cross-linked polymers (Merrifield resins and their derivatives). On the other hand, soluble ones are frequently based in polyethylenglycol fundamentally.

The ligand **L1**, developed by Trost for the palladium-catalyzed asymmetric allylic substitutions, was modified by Song, Han and coworkers by replacing the cyclohexanediamine by a pyrrolidine moiety. Different polymers with diverse solubility properties were tested. The authors stated that the JandaJel support (containing flexible tetrahydrofuran-derived cross-linkings) swelled better than other resins and thus, gave more degrees of freedom to the bulky ligand. As a result, it acted more like a homogeneous catalyst.[57]

The degree of functionalization is also a very important factor in determining the choice of a polymer for catalyst immobilization. In principle, a high number of functional groups per gram should allow the introduction of a high number of catalytic sites. Consequently, the mass of supported catalyst employed in the reaction can be decreased. Nevertheless, a too high density of catalytic sites can in some cases be detrimental, whenever undesired interactions between them can take place.[58]

1.2.2 INFLUENCE OF THE LINKER AND THE METAL CATALYST LINKING POINT

As mentioned at the beginning of this section, the location of the catalyst connection to the support is quite relevant. A very common approach is based on the assumption that the support should exert the minimum effect on the catalyst, avoiding perturbation of the catalytic centre with the aim of mimicking the behaviour and activity of the homogeneous system. As a matter of fact, the catalyst active site and the polymeric support should be as much separated as possible.[59]

The problem of securing a suitable separation between the active site and the support to enhance catalyst accessibility can also be approached by the insertion of a linker or spacer. The insertion of a spacer can solve problems of catalyst reactivity not only related to accessibility. For instance, a linker can help to create a microenvironment around the catalyst active site more suitable to the catalytic activity than that provided by the support.[43,60]

The linker and the anchoring point of the catalyst are usually optimized against a model reaction.

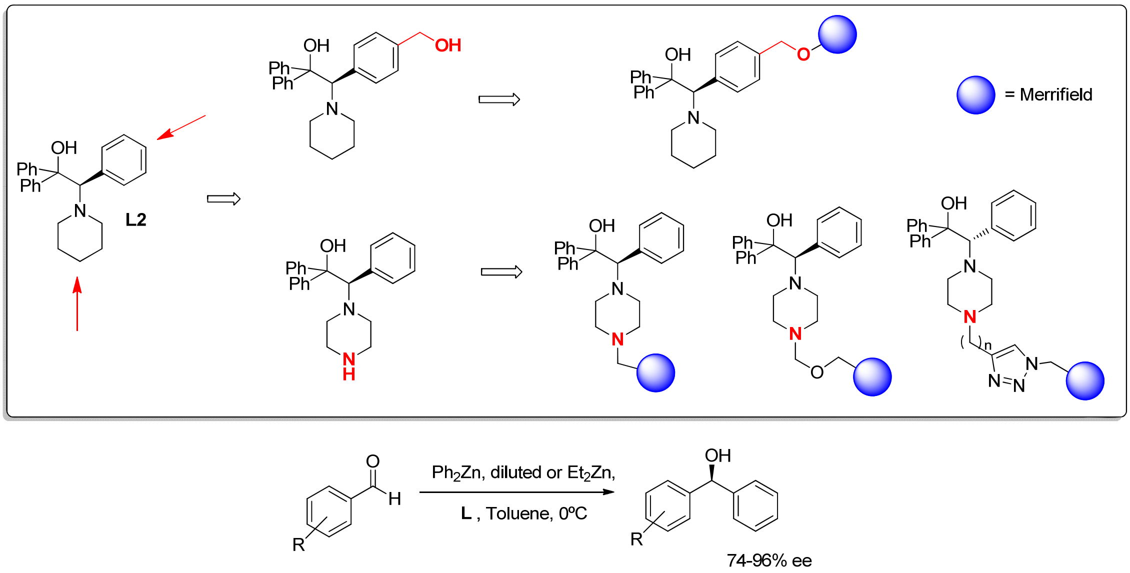

Figure 7. Modifications of β-amino alcohol ligands in order to develop heterogenized analogues for the asymmetric alkylation of aldehydes.

An example in this line is provided by the simple yet highly efficient β-amino alcohol **L2** in the asymmetric addition of alkylzincs to aldehydes.[40c,61] In order to mimic as much as possible the catalytic properties of the non-supported system, Pericàs *et al.* developed several "*tail-tied* ligands". Likewise, they tested a wide scope of linkers, spacers and anchoring points trying to maintain the catalytic site unaltered. This idea is shown in Figure 7.[62] The most efficient ligand for this reaction was the homogeneous ligand directly attached through a remote position of the piperidino group (by using piperazine). [62b,62c]

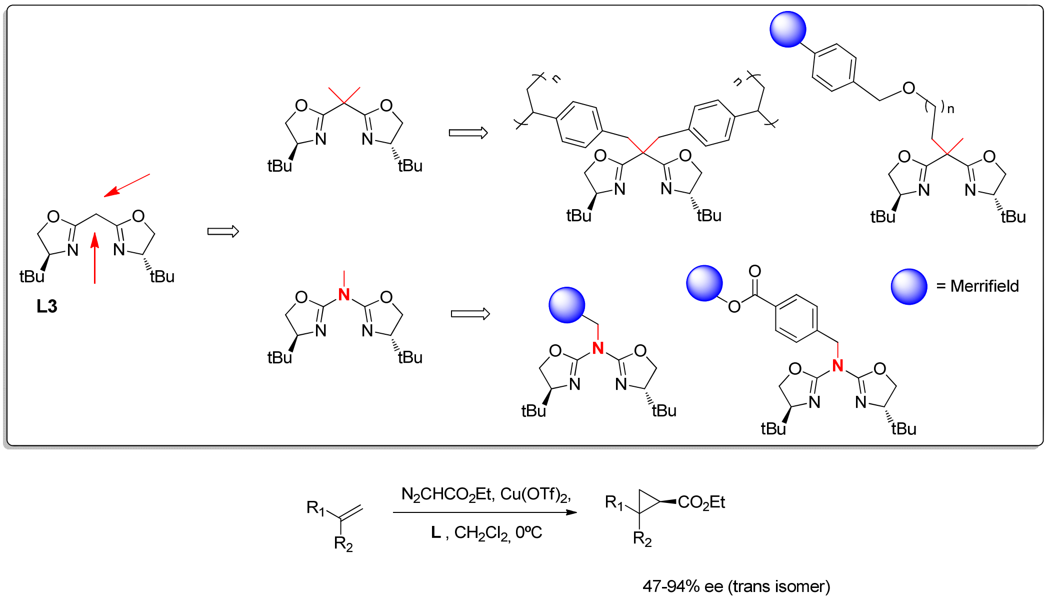

Figure 8. Modifications of bis(oxazoline) ligands in order to develop heterogenized analogues for the asymmetric cyclopropanation of olefins.

Finally, another interesting example of the effect of the anchoring point of the ligand is found in the attempts to heterogenize the bis(oxazoline) ligands **L3** used for the asymmetric cyclopropanation of olefins.[63,64] Diverse strategies of heterogenization were studied through polymerization of the monomeric compounds or simply grafting on polymeric supports (Figure 8). In the latter cases, the linker placed the ligand at a reasonable distance from the polymer backbone in order to avoid undesired steric hindrance.[64] The highly cross-linked polymer, where the bis(oxazoline) contained a fragment mimicking the key dimethylmethylene unit bridging the two oxazoline groups, was finally the most effective asymmetric catalyst amongst them for the cyclopropanation of styrene.

1.2.2.1 Use of the Triazole Unit as a Linker

Ligation reactions have had a great impact in recent years for medicinal chemistry and materials.[65] They allow the reliable connection between two functional groups irrespective of other functionalities present. This fundamental feature has also been recognized for attaching catalysts to supports. For this purpose, the copper-catalyzed Huisgen 1,3-dipolar cycloaddition (known as "click chemistry" [2]) has become popular.[66]

This reaction was first applied for the immobilization of ligands in 2005, aza(bisoxazoline) ligand[67] were grafted onto MeOPEG$_{5000}$.[68] Since then, there has been a spectacular development of many new ligands which have been attached to supports using a triazole linker, resulting in highly active, stereoselective and reusable catalysts.[50,68,69]

However, the triazole moiety is also a potential coordinating point for metal. It bears the danger of creating catalytically active metal centres in an

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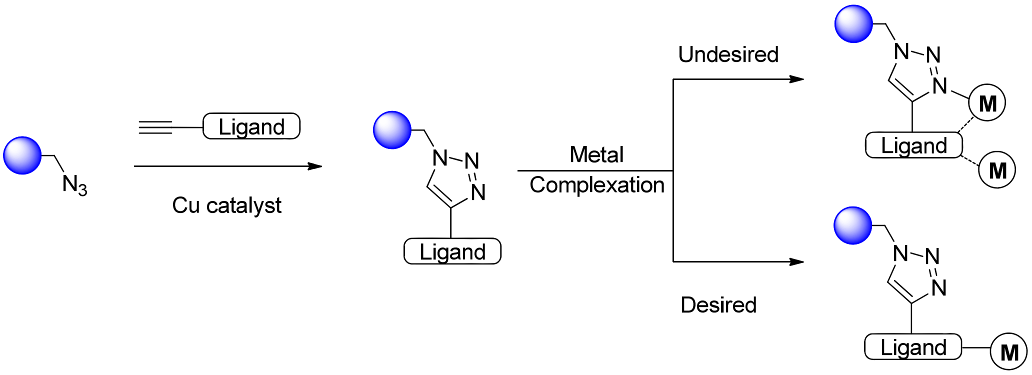
[2] Click chemistry was initially introduced in 2001 by Sharpless,[24] as a new concept for drug science, based on properties rather than structures. It is defined as *"a set of powerful, highly reliable and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom (C–X–C) links"*.[66d] However, this expression has become commonly used for naming the Cu-catalyzed 1,3-dipolar cicloaddition of azides and alkynes, which constitutes one paradigmatic example of this concept.

achiral environment, thus lowering the enantioselectivity of a given reaction (Scheme 3).[68,70]



***Scheme 3**.* Copper-catalyzed Huisgen 1,3-dipolar cycloaddition as a ligation strategy towards polymer-bound metal-catalyst.

The use of “click chemistry” to attach ligand onto polymers is also interesting since it facilitates monitoring of the immobilization reaction. The progress of the cycloaddition reaction can be easily followed by IR spectroscopy, through the disappearance of the azide band (*ca.* 2094 cm^{-1}). Elemental analysis of the final resins allows accurately determining the degree of functionalization.

1.2.3 FLOW CHEMISTRY

High performance automation and combinatorial chemistry continues to attract considerable attention in the scientific community with new and innovative applications being reported. In fact, so-called *enabling techniques* have emerged in the last decade due to the importance of improved technologies for these issues.[41b,71] This concept embraces various traditional as well as new techniques which have been developed to facilitate and accelerate synthetic transformations and fundamentally simple work-up as well as isolation of products.

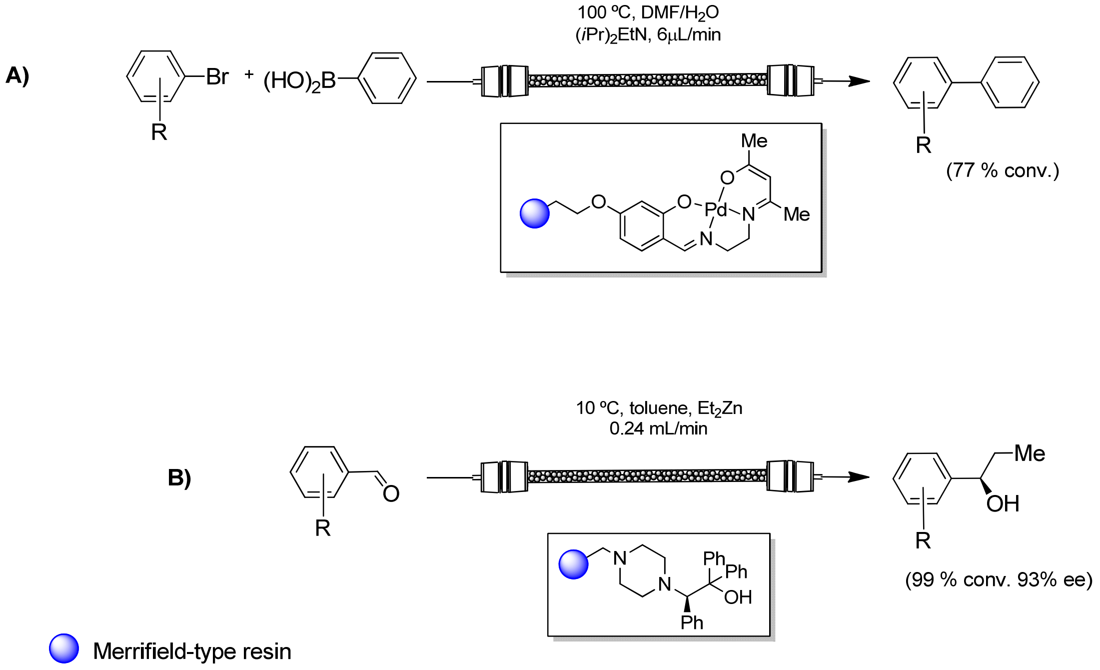
Indeed, the final aim is the minimization of the gap between bench chemistry and chemical engineering by mimicking large-scale productions in the laboratory.

Flow-through processes have been particularly useful for chemical and bio production processes, where many advantages over batch processes have been shown.[72] It is worth to mention some of them: the facile automation, reproducibility, safety and process reliability can be advantageously assured due to constant reaction parameters (such as temperature, time, amount of reagents, solvents and efficient mixing). Other benefits of the use of continuous flow reactors, is that they can be combined with the use of immobilized reagent or catalysts.

Additionally, flow devices can be used in combination with several new techniques for example, microwave assistance.[73] Likewise, microwave-accelerated synthesis under continuous-flow conditions was achieved in the synthesis of substituted pyridines.[73e] Even chemistry in flow can be coupled with purification concepts using solid phase scavengers,[74] chromatographic separation or liquid/liquid extraction. [75]

Besides the inherent advantages of immobilization of a catalyst (see a detailed explanation in pg 13), the use of a flow-through heterogenized system (flow reactors in combination with heterogenized catalysts) presents the possibility of maintaining the catalyst permanently in the reactor while unreacted materials, products, and byproducts are readily removed; it seems to be the best possible approach to catalyst recycling.[76] Indeed, the development of a heterogenized catalyst based on a monolithic support is considered to be particularly advantageous for combining high surface area with very low pressure drop (meaning the mixture can be pumped readily through the catalyst bed) and excellent catalytic activity. As an alternative approach to a particulate or monolithic catalyst bed, it is possible to simply coat the walls of the reactor with catalyst in order to contact the reaction mixture.

If we think in combining flow chemistry with polymer supported metal-catalysts, we can find different approaches depending on the packed-bed application. Examples include the use of supported borane complexes of amino acids for enantioselective Diels-Alder reactions,[77] and ruthenium-catalyzed oxidation of alcohols using incarceration techniques.[78] By incorporating catalysts supported onto Merrifield-type resins a packed-bed Omnifit glass column it have been possible to carry out different reactions; as Suzuki-Miyaura cross coupling reactions[79] and/or enantioselective addition of organozinc reagents to aldehides.[80] (Scheme 4) Polymer monoliths have also been successfully developed and used.[81]



Scheme 4. Examples of reactions catalyzed in Omnifit glass column using Merrifield-type resins supported catalysts. A: Suzuki-Miyaura cross coupling reactions under flow conditions, B: Asymmetric alkylation of benzaldehyde under flow conditions.

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CHAPTER 2

AIMS OF THIS THESIS

2.1. AIMS OF THIS THESIS

The aims of this thesis can be divided in two main parts: i) the study of supported ligands for metal catalyzed reactions (Chapters 3, 4) and ii) the evaluation of Lewis-acid behaviour in the rearrangement of aryl glycidyl ethers to 3-chromanols (Chapter 5).

In the first part, we will describe different approaches for the immobilization of the ligands onto polymers. The effect of the spacer, the linker, the different polymers, and the different points of anchoring of ligands onto support are evaluated. In addition, we will try to demonstrate the importance of triazole ligations in catalysis, by using it as a simple linker for heterogenized catalysts. Well–known reactions are used in each chapter for evaluation of metal-polymer ligands or catalysts in asymmetric processes. Moreover, the recycling studies are made with the best supported ligands. The different immobilized catalysts are evaluated from the point of view of catalytic activity, (enantio)selectivity and, with particular attention, reusability.

In the second part of the thesis, we will evaluate the behaviour of different Lewis acids to induce the formation of 3-chromanols from aryl glycidyl ethers.

More specifically, the aims for each individual chapter should be summarized as follows:

Chapter 3, is divided in two parts.

a) The first topic was developed in collaboration with Dra. Dana Popa (she was a member of the Prof. Vidal's research group, ICIQ). We describe the use of an epoxidation–ring opening-cycloaddition sequence for the preparation of phosphinooxazoline ligands. In addition, different approaches for the immobilization of these ligands onto polymers are developed. Evaluation of their performance in asymmetric allylic amination is reported. Also, the recovery and reuse of these polymer ligands in this reaction are tested. Importantly, continuous flow of this process is carried out.

b) The second topic was developed in collaboration with Veronica de la Fuente (she is a member of the Prof. Claver and Prof. Castillon's research group, Universitat Rovira i Virgili). We describe the synthesis and evaluation of phosphinoimidazoline-ligands in palladium-catalyzed allylic substitutions.

In the same way than the previous topic, a study of the immobilization of these PHIM ligands is developed. The performance of these polymer ligands in the asymmetric allylic amination is evaluated. Recycling experiments are carried out.

Chapter 4. Polystyrene-supported enantiopure 1,2-diamine ligands in one step from commercial reagents were prepared. The Ru polymer complexes were applied in the asymmetric transfer hydrogenation of alkyl aryl ketones. The recovery and reuse of these polymer catalysts is evaluated.

Chapter 5. The Lewis acid reactivity of a family of aryl glycidyl ethers is studied, most of them in enantiomerically pure form. The mechanism of this transformation is elucidated based on the previous results with different Lewis acids.

CHAPTER 3

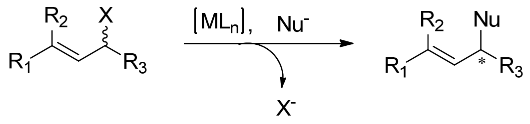
IMMOBILIZATION OF *P,N*-LIGANDS AND THEIR USE IN PD-CATALYZED ASYMMETRIC ALLYLIC AMINATION REACTION

3.1 INTRODUCTION

3.1.1. PD-CATALYZED ASYMMETRIC ALLYLIC SUBSTITUTIONS

The stereoselective formation of carbon-carbon and/or carbon-heteroatom bonds represents an important challenge in the field of asymmetric synthesis. The enantioselective allylic substitution reaction has proven to be a useful process for the synthesis of natural products and for the creation of several frameworks of diverse organic molecules.[1]

The reaction consists on the substitution of an adequate leaving group in an allylic position by a nucleophile. This transformation is catalyzed by a transition metal complex (Scheme 1).[2-4] Some important characteristics about this reaction are: i) It often proceeds under much milder conditions than ordinary S_N2 or S_N2' reactions, ii) It allows transformation of achiral or chiral racemic substrates into enantiopure products under similar conditions, iii) It owns several mechanisms for enantiodiscrimination and iv) diversity of bond types can be formed towards the asymmetric allylic reactions.[2-4]

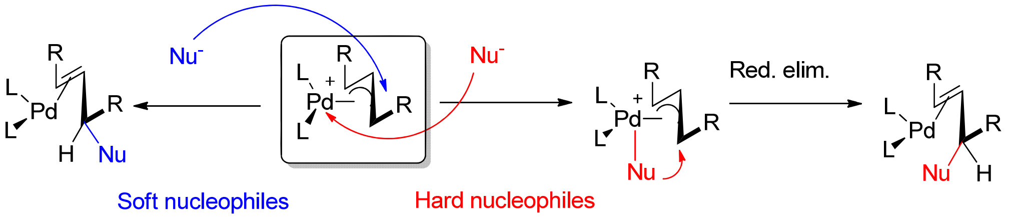


Scheme 1. Asymmetric Allylic Substitutions.

The first example of an enantioselective allylic substitution was reported in 1973 by the Trost's group using stoichiometric amounts of palladium with poor stereoselectivity (24% ee).[5,6] In 1977 the same authors developed a catalytic procedure[7] and, since then, many efforts have been devoted to the optimization of the catalytic process.

Substrates containing acetates, carbonates and phosphates as leaving groups are the most studied ones in the field of asymmetric allylic substitution due to their low reactivity towards nucleophiles in the absence of a catalyst.[8] Leaving groups with higher reactivity, such as halides or trifluoroacetates have not been considered in asymmetric allylic substitutions, because of the possibility of competition between the uncatalyzed and the catalyzed reactions.[9]

Since their original finding, a wide variety of nucleophiles have been employed in the metal-catalyzed allylic substitutions. The nucleophiles can be classified as "hard" and "soft" depending on the stereochemical outcome of the reaction (overall retention or inversion of the configuration at the allyl system).



Scheme 2. The mechanistic pathways of nucleophilic attack on palladium allyl complexes by soft and hard nucleophiles.

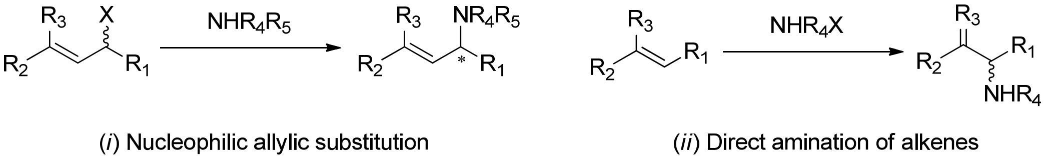
The "soft" nucleophiles are defined as those derived from conjugated acids whose pK_a is lower than 25. They lead in turn to the product with overall retention of the configuration at the allyl carbon. (Scheme 2) The attack of the nucleophile to the allyl ligand takes place outside the coordination sphere of the metal, namely from the side of the allyl unit opposite to the metal. "Soft" nucleophiles such as stabilized carbanions and amines are the most commonly used for the allylic substitutions.[10,11]

The "hard" or unstabilized nucleophiles are derived from conjugated acids with a pK_a higher than 25. There are only a few examples of enantioselective reaction with these nucleophiles, such as organozinc[12] or Grignard reagents.[4b,13] In this case, "hard" nucleophiles bind to the metal center *via* transmetallation. Subsequent attack of the bound nucleophile to the allyl unit results in the product of opposite configuration, with respect to the starting material, as the attack occurs on the same face occupied by the metal.[14]

While there are several metals[4b] (palladium,[1,8] iridium,[4e,15] nickel,[16] platinum,[17] rhenium,[18] rhodium,[19] iron,[20] copper,[13a,21] ruthenium,[22] molybdenum[23] and tungsten[24]) utilized for this transformation, the majority of examples regarding enantioselective allylic substitutions that appear in the literature have been carried out by very efficient chiral palladium complexes. As a spin off, not only the alkylation, but also the allylic amination can now be performed with a high degree of efficiency and selectivity, and the palladium-catalyzed allylic amination has become quite established in organic synthesis.[2]

3.1.2.1. Pd-Catalyzed Asymmetric Allylic Amination Reaction

Allylamines, are fundamental building blocks in organic chemistry and their preparation is an important industrial and synthetic goal.[4,25] The allylamine fragment appears in natural products, but often the allylamine is transformed to a range of products by functionalization, reduction, or oxidation of the double bond.[26] Thus allylamines have been used as starting materials for the synthesis of numerous optically active compounds such as amino acids,[27] alkaloids,[2a,28] and carbohydrate derivatives.[29] In principle the synthesis of allylamines can be achieved *via* one of the following strategies: The first type includes allylamines synthesized by nucleophilic allylic substitution and the second is the direct allylic amination of simple alkenes. (Scheme 3)



Scheme 3. Different strategies for the synthesis of allylamines

Since the first reported asymmetric allylic reaction with a nitrogen nucleophile by the Trost group,[30] primary[30,31] or secondary amines,[32] azides, amides and imines[33] have been employed as nucleophiles *via* π-allyl complex as intermediates.

A broad variety of structurally different substrates have been used for enantioselective allylic amination. Among them, allyl derivates with identical substituents are the most widely studied class of substrates because they are interesting building blocks in the synthesis of several compounds with biological and pharmaceutical activity. For studying different ligands in this transformation, the enantioselective allylic amination of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (substrate) with benzylamine (nucleophile) is most frequently used as a benchmark reaction.

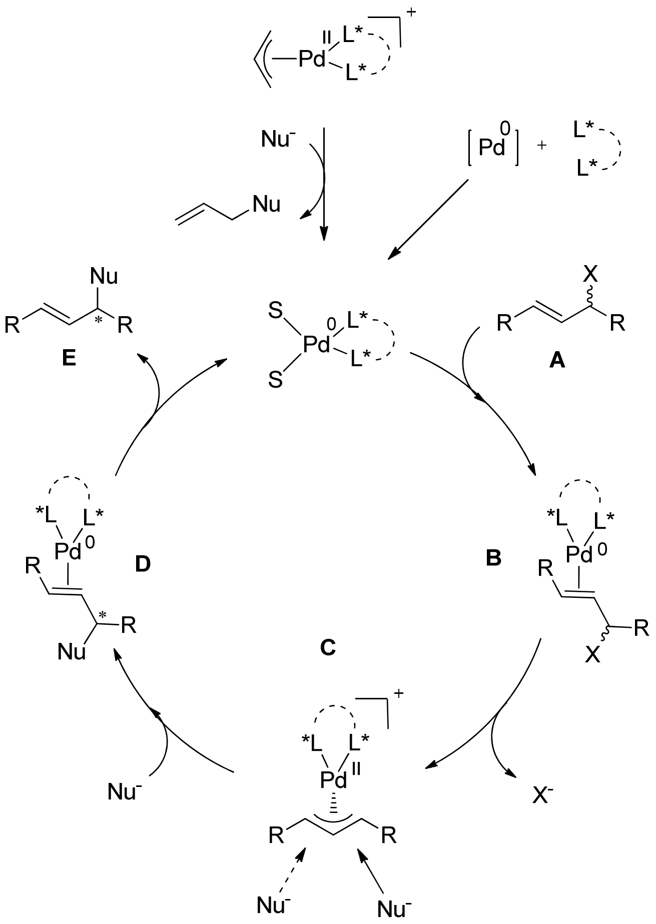
In addition, structural and mechanistic studies have considerably improved the understanding of how the palladium catalysts work in this reaction.

3.1.2.2. Mechanism

The reaction mechanism has been deeply investigated and elucidated in detail. The classical catalytic cycle for “soft” or stabilized nucleophiles is shown in Scheme 4.

The catalyst enters the catalytic cycle on the Pd(0) oxidation state. The active species can be originated *in situ* by the attack of the nucleophile to a cationic Pd(II) precatalyst,[34] or using directly Pd(0) species, such as [$Pd_2(dba)_3$], in the presence of the corresponding ligand.

The first step in the catalytic cycle is the coordination of an allylic substrate **A** to the metal center forming a π-complex **B**. Afterwards, the elimination of the leaving group **X** to generate a η^3-allyl palladium(II) complex **C** takes place**.** The product of this oxidative addition can be a cationic complex, as shown in scheme 4, or a neutral complex if the resulting anion **X**$^-$ coordinates to the palladium centre. This process happens depending on the structure of the ligand, the solvent, and the anion. With bidentate ligands the cationic complex **C** usually predominates.



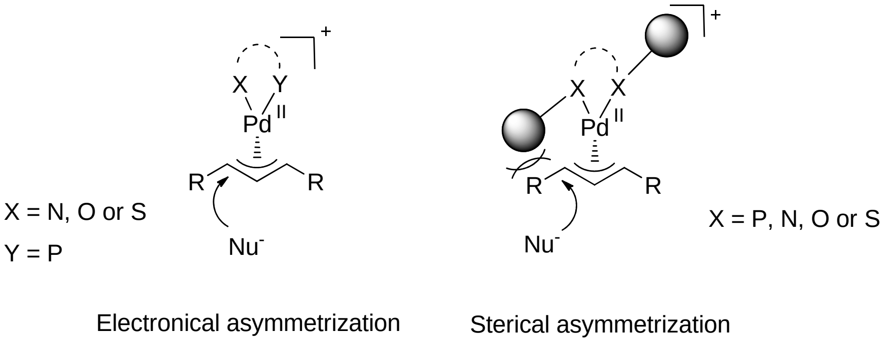
Scheme 4. Mechanism of palladium-catalyzed allylic substitutions.

The electrophilic palladium(II) center activates the allylic system for nucleophilic attack, which can occur at either terminus of the fragment. In spite of the fact that the attack at the central carbon atom is in principle possible, it is not common.[35] Various chiral ligands can control this addition through steric or electronic effects (see below).[36] After nucleophilic addition, an unstable palladium(0) olefin complex **D** is formed, which readily releases the final product **E** by decomplexation and regenerates the active catalyst that can re-enter in the cycle. Both the oxidative addition and the subsequent nucleophilic attack proceed with inversion of the configuration at the reacting allyl carbon atom, which results in an overall retention of stereochemistry.

In general the formation of allyl intermediate **C** is fast, while the nucleophilic attack to the allyl system is slower (rate-limiting step). As a consequence the cationic intermediate **C** represents the resting state of the catalyst. In the absence of a suitable nucleophile this species is stable, can be detected and even isolated.[37] This is an attractive, nearly unique feature of palladium-catalyzed allylic substitutions, because in most catalytic processes it is difficult to isolate or even detect intermediates of the catalytic processes.

Origin of the enantioselectivity for the allylic substitution of 1,3-diphenyl allyl acetate

Except for decomplexation of the olefin from palladium-ligand system, where the chirality has already been set, each step provides opportunity for enantioselection. If we refer only to 1,3-disubstituted substrates, since the chiral center in the allylic substrate is lost in the formation of the π–allyl complex, both enantiomers of the substrate lead to the same allyl complex. Thus, the enantioselectivity of the reaction is governed by the regioselective attack of the nucleophile onto one of the allylic terminus of the palladium complex. Desymmetrization of the allyl system depends on the electronic and/or steric effects of the ligands (Scheme 5).



***Scheme 5**.* Asymmetrization of the allyl system.

In the case of *P,N* -ligands, desymmetrization takes place due to the *trans* effect of the P and N donor groups.The P atom has a marked trans effect and, consequently, the Pd-C bond *trans* to the P- atom is significantly longer.[39] In this way, carbocationic character in the carbon trans to phosphorous is increased, thus favouring the attack of the nucleophile at that position.[36,40] In other type of ligands, such as C_2-symmetric chiral bisoxazolines, desymmetrisation arises from a sterical interaction between the ligand and substrate substituents.[41]

The stereoelectronic differentiation showed by bidentate *P,N*–ligands with this type of substrates, is the main reason of the choice of this kind of ligands for the work described in this chapter.

3.1.2 DONOR BIDENTATE *P,N*-LIGANDS IN THE ASYMMETRIC ALLYLIC AMINATION REACTION

In the last years, many chiral *P,N*-ligands posessing either C_2 or C_1 symmetry have been developed, which provide high enantiomeric excesses for several types of disubstituted substrates. Their efficiency in asymmetric allylic substitutions has been well established.[1-4,39,42] Ligand structural diversity has included variation of the substituents on the phosphorous atom, the nature of the spacer between the *P*- and *N*-donor groups, and the nature of the *N*-donor group. Selected examples of bidentate *P,N*-ligands successfully applied for asymmetric allylic amination with benzylamine are shown in Figure 1.

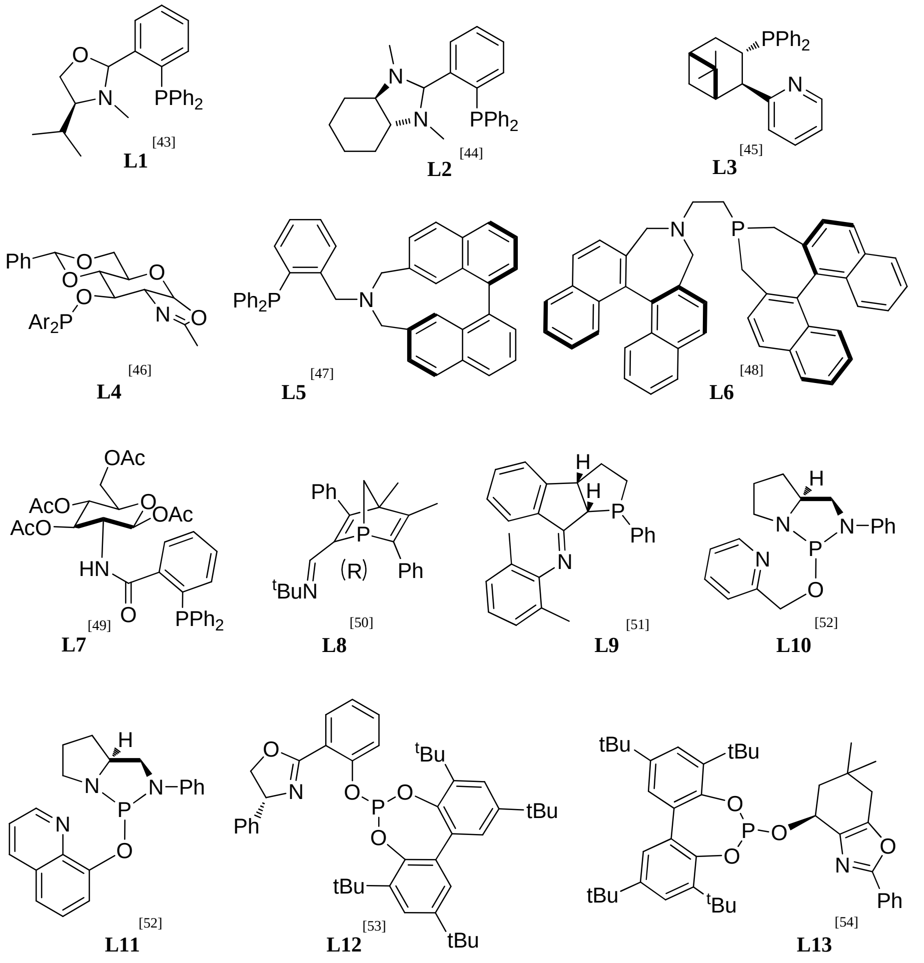
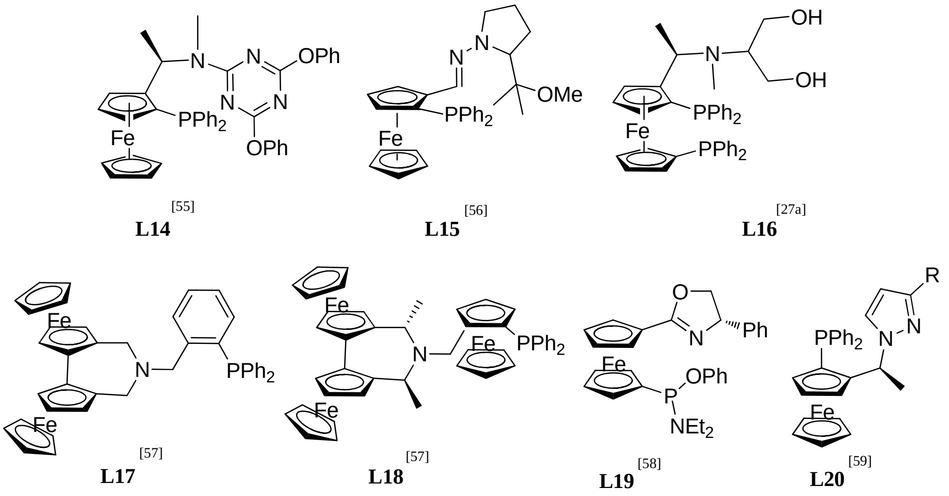


Figure 1. Donor bidentate *P,N*-ligands in the asymmetric allylic amination with benzylamine.

Regarding the nature of the nitrogen donor atom, different N-heterocycles have been used, as oxazoline (**L1**),[43] imidazoline (**L2**),[44] pyridine (**L3**,**10**),[45,52] oxazolidine (**L4**,**12**),[46,53] and quinoline (**L11**),[52] as well as binaphtyl-derived amines (**L5**,**6**),[47,48] amides (**L7**)[49] and imines (**L8**,**9**).[50,51] On the other hand, phosphorus-containing groups range from acyclic (**L1-3**,**5**,**7**),[43-45,47,49] and cyclic (**L6**,**8**,**9**)[48,50,51] phosphines, phosphinites (**L4**),[46] phosphites (**L12**,**13**) [53-54] and phosphorodiamidites (**L10,11**).[52]

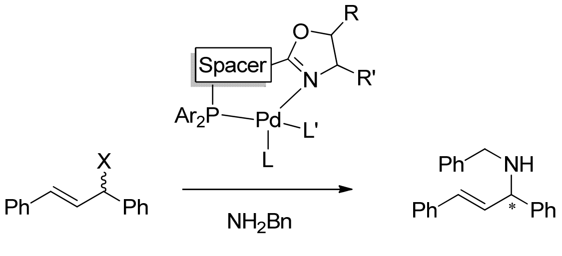


L14[55] **L15**[56] **L16**[27a]

L17[57] **L18**[57] **L19**[58] **L20**[59]

Figure 2. Donor bidentate *P,N*-ligands based on ferrocene unit used in the asymmetric allylic amination with benzylamine.

The ferrocene unit[60] has been widely introduced to build highly enantioselective chiral *P,N*-ligands (**L14-20**)[55-59,27a] (Figure 2). The best results in this transformation have been reported by Togni with ferrocenylpyrazole ligand **L20** (99% ee).[59]



Scheme 6. Allylic amination with PHOX-based ligands.

Some of the most well-studied metal complexes in the asymmetric allylic amination are the palladium phosphinooxazoline (PHOX) complexes[61] described for the first time in 1993 by Pfaltz, Helmchen and Williams,[10,62] based on oxazoline and phosphorus groups separated by a spacer. Only a year later, these PHOX ligands were successfully applied in the asymmetric allylic amination of symmetrical allylic substrates with various nitrogen nucleophiles[61] (Scheme 6). Although the most common spacer has been a 1,2-disubstituted phenyl ring, binaphthyl group, different heterocyles, cyclopentadienyl and several ferrocene backbones have also been reported. The modular construction of the phosphinooxazoline ligands also allows extensive and independent variation of the phosphine part and the oxazoline ring.

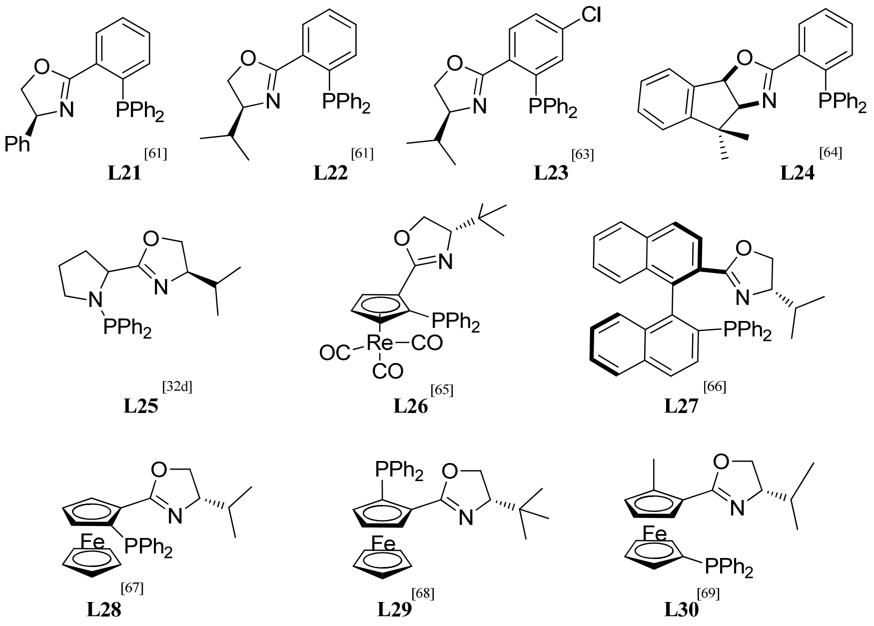
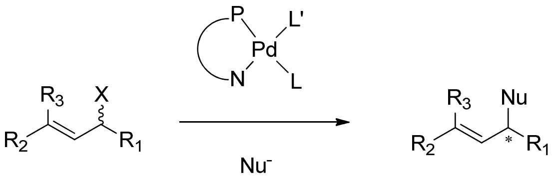


Figure 3. PHOX ligands in the asymmetric allylic amination with benzylamine.

A wide variety of PHOX ligands have been successfully applied for the asymmetric allylic amination[61] (Figure 3). Pfaltz *et al.* showed that the substituents on the oxazoline framework play an important role in the enantioselectivity of the reaction. For instance, simply changing from an *i*Pr group to a more sterically demanding substituent induced a change in the enantiomeric purity of the product obtained from 87% to 97% ee **(L21-L24)**.[61,63,64]

Ferrocenyl-containing PHOX ligands have proven to be efficient ligands for the amination of the diphenylallyl substrate. Depending on the position of the diphenylphosphino group, the product is obtained in 72% to 97% ee (**L28-L30**).[67-69]

However, substrate specificity and low reaction rates are still important limitations to overcome, commonly for unhindered disubstituted substrates and particularly in the case of monosubstituted ones, which have proved to require more active catalysts (Scheme 7). In the case of cinnamyl acetate, the regioselectivity in the allylic substitution is usually dependent on the metal present in the catalytic system. Ir complexes preferentially lead to the formation of branched products, whereas Pd complexes normally favour the formation of achiral linear ones.[40c] However, Xia's PHOX-ferrocenyl ligand, **L19,** and Hayashi's ferrocene ligand **L16,** contrary to the general observations on the regioselectivity dictated by the metal, lead to major formation of the branched product (br/li 94:6, 94%, 98% ee, br/li 97:3, 87%, 84% ee).[58]



Scheme 7. Allylic amination with different substrates.

Nitrogen nucleophiles, different than benzylamine, have also been reported in this transformation; such as phthalimide, morpholine, diallylamine, 4-methoxybenzylamine and *p*-anisidine.[70] Of the representative results presented in the amination reaction with PHOX and other *P*,*N*-ligands, Xia's phosphinooxazoline **L30**, Claver's phosphiteoxazoline **L12**, and Togni's ferrocenyl-pyrazole ligand **L20,** should be recalled as the most efficient ligands for the model amination reaction.

3.1.3. SUPPORTED *P,N*-LIGANDS IN PD-CATALYZED ASYMMETRIC ALLYLIC AMINATION REACTION

The preparation and use of solid-supported catalytic systems able to induce enantioselective transformations has gained a considerable importance over the last decade. Thus, it is an area of increasing relevance in chemistry due to the improved sustainability characteristics of this type of process. This obviously involves important advantages, as the suppression of wasteful work-up treatments for catalyst separation and the removal of metal-containing by-products from reaction mixtures, leading to cleaner alternatives for the production of metal-free, enantioenriched compounds. In the case of industrial applications of the asymmetric reactions, avoiding metal contamination of the catalysts into the final products is a real demand. As an additional advantage inherent to this approach, the recovery and reuse of the catalytic system can be readily performed.[71,72]

Although many examples of supported ligands based on P/P, N/N, O/O, P/N or P/S coordination modes can be found in the literature applied to the asymmetric allylic alkylation reaction,[71,72] to the best of our knowledge there are just a few examples of supported ligands used in the Pd(II)-catalyzed allylic amination reaction (Figure 4) and the use in catalysis of immobilized chiral phosphinooxazoline ligands remains completely unexplored.[73]

The main strategies for catalyst recycling explored in the literature consider the use of ionic liquids (IL), perfluoruous techniques, and polymer-supported ligands. Recently, other strategies for heterogenizing homogeneous ligands have been developed such as adsortion onto silica or use of dendrimer supports. In this respect it is worth mentioning that the performance of heterogenized catalysts is strongly dependent upon the choice of the support and the immobilization method (in such a way that the reaction site remains unperturbated). (See Chapter 1, General Introduction). The main problem is frequently low recyclability of the catalyst due to metal leaching.[74]

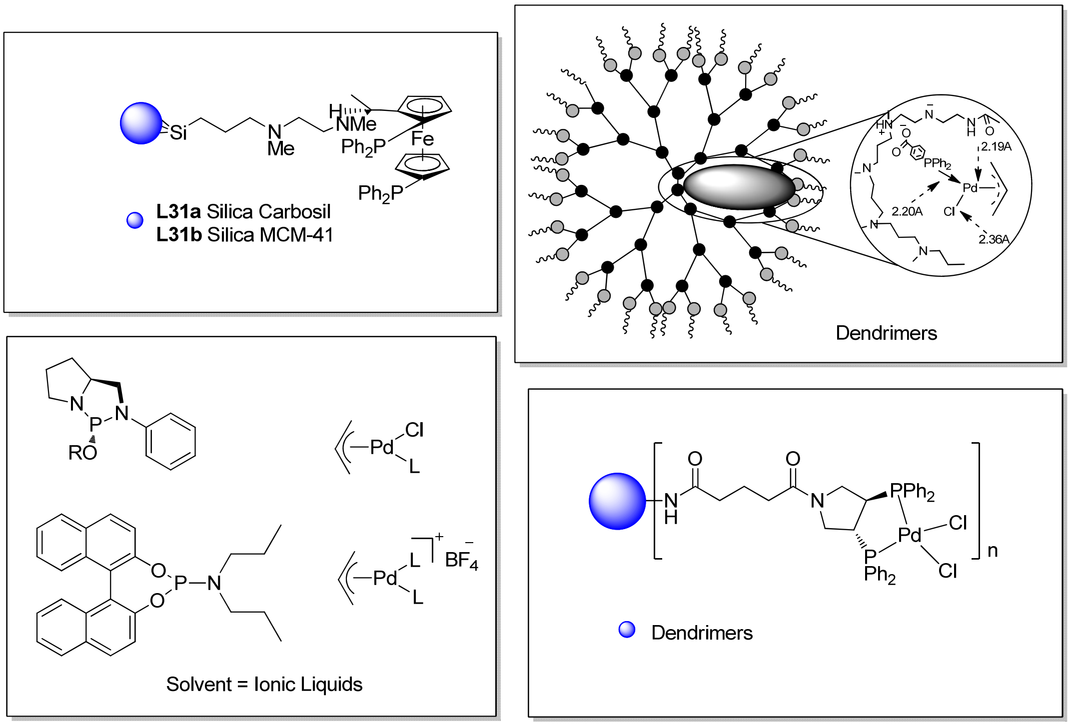


Figure 4. Selected examples of supported ligands used in the asymmetric allylic amination.

The catalyst's stereoselectivity is "a usual victim" of immobilization, because of the substrate finding in the presence of the support more difficulties in adopting the required orientation for the transformation to occur in a stereoselective fashion. However, in 1999, Thomas and coworkers reasoned that spatial confinement of transition states formed around a chiral catalyst's active site could provide a new method of boosting the enantioselectivity of a supported catalyst.[75] In a revealing experiment, they compared the behaviour of ferrocenylphosphine/Pd(II) catalyst (homogeneous), **L31a** (supported on the convex surface of the nonporous, high-surface area silica Carbosil), and **L31b** (supported on the concave surface of mesoporous silica MCM-41) in promoting the allylic amination reaction between cinnamyl acetate and benzylamine. The **L31b** catalyst showed better ability to control both regio- and stereoselectivity of the process than the other two complexes.

In spite of the existence of several examples of metalladendrimers in catalysis,[76] to date there are still only a couple of examples of applications in asymmetric allylic amination catalysis with ligands supported on dendrimers.

In 2003, Gade *et al.* reported the anchoring of the Phyrphos ligand to the endgroups of poly(propyleneimine) (PPI) and of the analogous poly(amidoamine) (PAMAM) dendrimers to employ them in Pd-catalyzed allylic amination reaction between 1,3-diphenyl-1-acetoxypropene and morpholine.[77] As a function of the dendrimer generation, an increase in catalyst selectivity was observed in comparison with the corresponding monomeric catalyst (9% ee to 69% ee). However, recycling experiments were not reported.

With the aim of enhancing the stability of the immobilized catalyst , thus avoiding deactivaction, a novel catalyst immobilized within the core of dendrimers through ionic bonds was described.[78] The specific nanoenvironment created by the dense amino groups inside the dendrimers provided high catalytic activity and stability for the Pd complexes. The employment of a thermomorphic system allowed the recycling of the dendritic Pd catalysts (four cycles were reported).

Despite the fact that the Pd-catalyzed synthesis of *rac*-((*E*)-1,3-diphenylallyl)pyrrolidine from 1,3-diphenyl-2-propenyl acetate in an IL was reported as early as 1999,[79] no asymmetric allylic amination in an IL has been described until 2006.[80] Lyubimov and coworkers described the first application of chiral phosphate ligands in various catalytic reactions, including asymmetric amination reaction, occurring in an IL. They demonstrated that it is possible to recycle the chiral catalyst in the IL at least three times with moderate enantioselectivities, although a gradual decrease of conversion was observed, probably due to partial leaching of the catalyst.

Since the appearance of the pioneering works on catalyst immobilization in the 1960's,[81] polymers have been probably the most frequently used supports in heterogeneous catalysis.[71,72] Insoluble crosslinked polystyrene (PS) resins, as well as soluble polyethylene glycol (PEG) linear polymers have been frequently used. In addition, “amphiphilic” PS-PEG hybrid resins are being introduced to solve the swelling problem of the insoluble polymers (Figure 5).

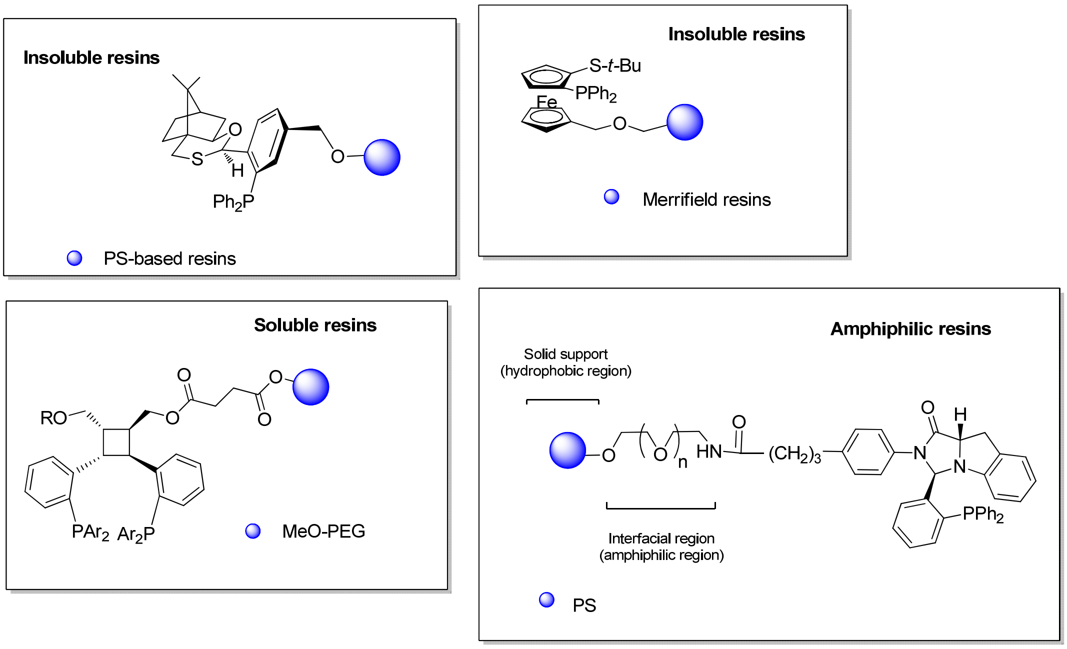


Figure 5. Selected examples of polymer supported ligands used in the asymmetric allylic amination.

Nakano *et al.*[82] grafted a chiral phosphinooxathiane ligand to several polystyrene-based resins and tested them in palladium-catalyzed allylic amination of allyl acetates. The authors found that the support had a significant influence on the reaction efficiency, (chlorodiethylsilyl)polystyrene providing the best results (90%, 99% ee). The heterogeneous Pd-ligand complex was reused twice giving 30% and 20% yield and marked erosion in enantioselectivity (99% to 79% ee). Interestingly, Carretero and co-workers later reported the synthesis of polymer supported bidentate *P,S*-type ligands (based in Fesulphos)[83] and their application in asymmetric allylic amination.[84] Although the yield was slightly lower than that obtained when using the homogeneous analogue, the enantioselectivity was similar. However, no information regarding the recovery and reuse of the supported complex was provided for this transformation.

Ding *et al.* prepared a new type of C_2-symmetric bisphosphine ligand bearing a cyclobutane backbone and tested it in the palladium-promoted allylic amination reaction.[85] Due to the good results obtained with those ligands, the same research group prepared the heterogenized analogue. Considerable efforts were made to link the ligand to soluble poly(ethylene glycol) polymers, and the resulting supported catalyst was found to be clearly more enantioselective than its homogeneous partner. The supported catalyst was recovered by filtration and reused eight times in allylic amination reaction, though with slight yield erosion (11-18%) and almost unaltered enantioselectivity (6-8% erosion).

With the aim of combining the advantages of both aqueous and heterogeneous switching, amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium complexes were developed by Uozumi and coworkers.[86] The authors achieved excellent results with this resin-supported chiral imidazoindole phosphine ligand in allylic amination reactions of cycloalkenyl esters forming optically active cyclic allylamines in water. The catalysts could be recovered and reused without any additional loading of palladium, with the same level of yields and enantioselectivity after the third use.

In spite of the fastly growing number of examples of solid-supported catalytic systems in the allylic amination reactions, this field still presents many areas to be explored and important problems to be satisfactorily solved, as the implementation of practical continuous flow processes for this type of transformations. In any case, it holds the promise of providing the chemical community with highly active, fully recoverable and reusable catalytic systems leading to similar or even better enantioselectivities than those depicted by referable homogeneous systems.

3.1.4. AIMS

The goal of this work is reporting the synthesis of different bidentate *P,N* ligands (PHOX and PHIM) and their supported version onto polymers, and their use in the palladium-catalyzed asymmetric allylic amination. We want to evaluate the recyclability and reuse of these supported ligands in this reaction. Motivated by our experience in the implementation of continuous-flow processes for polymer-supported catalysts,[87] and in view of the continuous-flow experiments which van Leeuwen *et al.* described for allylic reactions using dendrimeric ligands,[88] we decided to test the stability of our polymer-supported PHOX catalyst by applying it to a continuous flow process for asymmetric allylic amination of 1,3-diphenyl-allyl acetate and benzylamine.

3.1.5. REFERENCES

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3.2 PAPER A

TOWARDS CONTINUOUS FLOW, HIGHLY ENANTIOSELECTIVE ALLYLIC AMINATION: LIGAND DESIGN, OPTIMIZATION AND SUPPORTING

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Towards Continuous Flow, Highly Enantioselective Allylic Amination: Ligand Design, Optimization and Supporting

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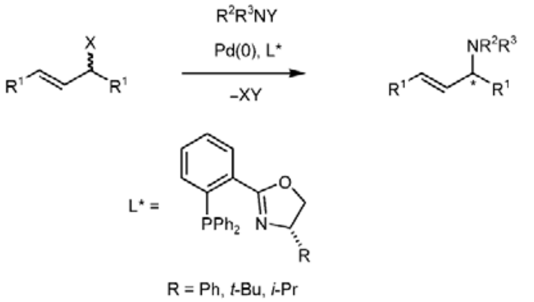
Abstract: A family of enantiopure diphenylphosphinooxazolines (PHOX) containing in their structures a sterically tunable alkoxymethyl group (-CH_2OR) has been optimized for the palladium-catalyzed asymmetric allylic amination. The optimal catalyst ($R=CH_3$), depicting very high catalytic activity and broad scope applicability, has been further modified to include an ω-alkynyloxy substituent of variable length for polymer supporting *via click chemistry*, and has been anchored onto slightly cross-linked azidomethyl poly(styrene). The length of a polymethylene chain connecting the PHOX unit with the 1,2,3-triazole linker has been optimized, and the first polymer-supported PHOX ligands for the highly enantioselective allylic amination have been prepared in this manner. Conditions for catalyst recovery and reuse in microwave-promoted amination reactions have been established, and the system has been finally adapted to continuous flow operation.

Keywords: amination; catalyst recycling; flow process; immobilization; palladium; P,N ligands

Introduction

The palladium-catalyzed asymmetric allylic substitution reaction is a versatile and widely employed methodology for the enantioselective construction of carbon-carbon and carbon-heteroatom bonds.[1] The development of new chiral ligands for asymmetric allylations, mainly phosphorus-, nitrogen- or sulfur-containing bidentate species, has attracted a considerable degree of attention over the last years.[1d] In particular, the efficiency of chiral phosphinooxazoline- and other related P,N-palladium complexes in the asymmetric allylic amination reaction has been well established.[1,2]

Phosphinooxazolines (PHOX) belong to a non-C_2 symmetrical class of bidentate ligands which present the advantage of producing electronic discrimination between the two terminal allylic carbons in the η^3-allylpalladium intermediates due to the combination of the characteristics of a "soft" phosphorus donor group with π-acceptor properties and a "hard" nitrogen σ-donor group.[2] In a pioneering study, Pfaltz and Helmchen described moderate to high enantioselection in the allylic amination of symmetrical π-allyl substrates with various nitrogen nucleophiles in the presence of 2-(diphenylphosphinophenyl)ozaxoline ligands (Scheme 1).[3] These initial results, and those obtained with analogous PHOX ligands[4] suggest that the asymmetric allylic amination is quite sensitive to modifications in the electronic characteristics of the structural aryl group or in the environment of the stereogenic center adjacent to the nitrogen in the oxazoline moiety (C-4). The modification of the spacer between the two coordinating heteroatoms in the ligand framework has provided a diversity of PHOX[5] and oxazoline-based P,N ligands[6] with useful characteristics in this palladium mediated process. However, substrate specificity and low reaction rates are still important limitations to overcome, commonly for unhindered disubstituted substrates and especially in case of the monosubstituted ones, which have proved to require more active catalysts.[1] Although several ex-



Scheme 1. Enantioselective allylic amination of 1,3-disubstituted allyl substrates in the presence of a Pfaltz–Helmchen chiral PHOX ligand.

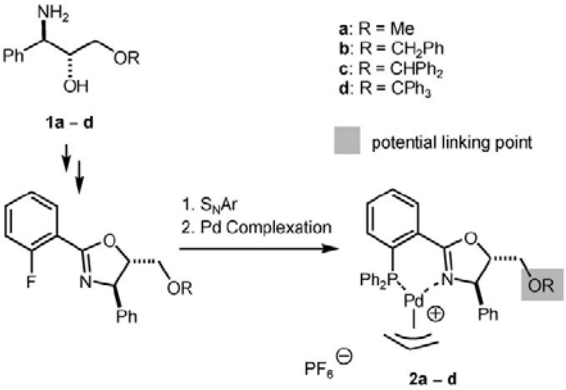


Figure 1. Polymer-supportable, modular phosphinooxazoline complexes **2a–d**.

amples of solid-supported chiral phosphine ligands, and bidentate N,N-, P,N- and P,S-palladium complexes as catalysts for asymmetric allylic substitution reactions can be found in the literature,[1d,7] the use in catalysis of immobilized chiral phosphinooxazoline ligands remains completely unexplored.[8]

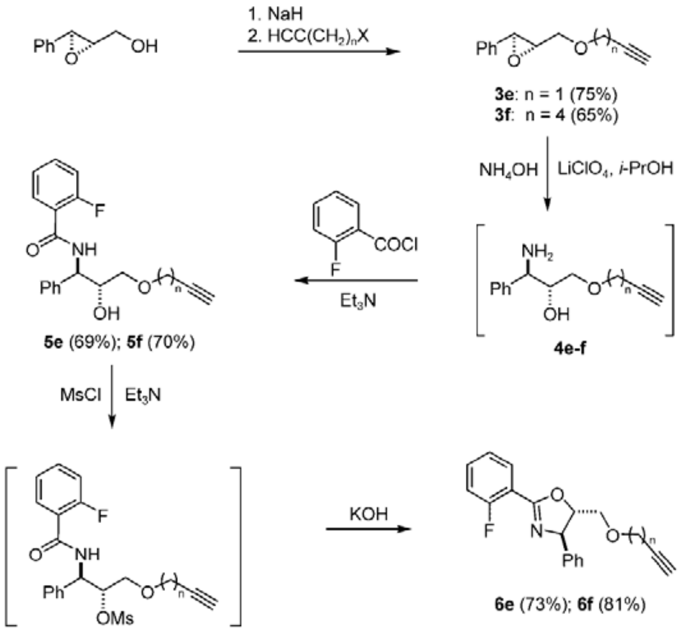
The preparation and use of solid-supported catalytic systems able to induce enantioselective transformations is an area of increasing relevance in chemistry due to the improved sustainability characteristics of this type of process. Thus, the suppression of complex work-up operations for catalyst separation and the removal of metal-containing by-products from reaction mixtures lead to cleaner alternatives for the production of metal-free, enantioenriched compounds. As an additional bonus, the recovery and reuse of the catalytic system becomes possible.[9]

The ultimate goal in this type of catalysis is performing chemical transformations in a continuous mode in a flow reactor under single-pass conditions, where reaction and catalyst separation are carried out simultaneously.[10] In spite of these potential advantages, the application of flow-through processes in catalytic enantioselective reactions has received little attention, probably due to the apparently inherent low activity associated to supported systems and to the need of *engineering* effort for the optimization of the different parameters controlling conversion and enantioselectivity in this kind of process.

In recent years, we have been involved in the design and synthesis of functional amino alcohol ligands that could be immobilized onto inorganic or polymeric supports without perturbation of the molecular regions where the catalytic activity resides.[11] As a fruit of this effort, we have recently succeeded in developing the first polymer-supported ligand for the fast, continuous-flow, highly enantioselective alkylation of aldehydes.[11g] Taking into account the limitations associated to ligand anchoring through nucleophilic substitution, we have thoroughly investigated a new strategy for supporting catalysts onto Merrifield-type resins through copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (*click chemistry*)[12–14] and have shown that the resulting resins behave as highly active, enantioselective and diastereoselective, yet reusable, catalysts.[11f,13]

On the other hand, we have recently described a new family of PHOX ligands derived from modular, enantiopure β-amino alcohols (Figure 1). The presence of an additional alkoxymethyl substituent at C-5 in the oxazoline ring of **2a–d** leads to improved catalytic characteristics with respect to analogous PHOX ligands also bearing a phenyl substituent in C-4, but lacking the alkoxymethyl substituent at C-5. Thus, palladium complexes **2a–d** have proved to be highly efficient chiral mediators for the asymmetric allylic alkylation.[15] Besides its primary effect on catalytic activity and on enantioselectivity, the alkoxymethyl susbstituents at C-5 offer the additional possibility of allowing the heterogenization of the PHOX ligands onto insoluble supports. The remarkably good performance and robustness of complexes **2a–d** make them attractive for evaluation as catalysts in the more challenging asymmetric allylic amination.[1] Moreover, the results of a benchmark-guided structure optimization suggest that their immobilization onto polymers should lead to minimal deterioration of catalytic properties, thus opening the way to continuous flow operation.

Herein we report the development of modular, polymer-supported chiral phosphinooxazoline ligands and their use in the palladium-catalyzed enantioselective amination of allyl acetates under batch and continuous flow conditions.



Scheme 2. Preparation of 2-fluorophenyloxazolines **6e–f**.

Results and Discussion

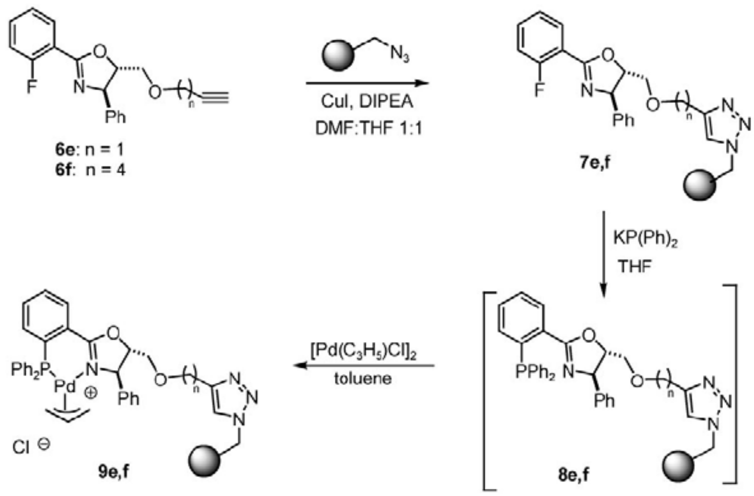
Ligand Synthesis

The starting point of this research was the modular phosphinooxazoline π-allylpalladium complexes **2a–d**, readily available from Sharpless epoxy ethers through well established synthetic transformations (Figure 1).[15] The preparation of oxazolines **6**, specifically designed for polymer-supporting, was planned through a similar, five-step sequence (Scheme 2). The presence of alkynyloxy side chains in **6** is instrumental for the supporting of PHOX ligands onto slightly cross-linked polystyrene resins through a click chemistry strategy. Within this strategy, the variable length spacers were designed to allow testing the effect of the distance between the bulky polymeric backbone and the catalytic site on the performance of the catalytic process.

The alkynyl fragments were installed on enantiopure phenylglycidol (>99% *ee*) by alkylation with the corresponding halides in the first step of the sequence.[16] The so-prepared epoxy ethers **3e–f** were next submitted to aminolysis in 25% aqueous ammonia with thermal activation.[17] The epoxide ring-opening took place stereospecifically and with complete regioselectivity leading to amino alcohols **4e,f** which were not isolated. The crude amino alcohols were directly *N*-acylated under standard conditions with 2-fluorobenzoyl chloride in the presence of triethylamine to afford hydroxybenzamides **5e,f** (69–70% overall yield from **3e,f**). Finally, the hydroxybenzamides were converted into the oxazolines **6e,f** by a two-step sequence[18] involving mesylation and base-induced cyclization (5% KOH/MeOH) through an S_N2 mechanism. Due to the limited stability of the mesylates, the cyclization was carried out within a few hours after their preparation. The activation-cyclization sequence took place in 73–81% overall yield for the two steps. The *trans* stereochemistry at C-4/C-5 in the oxazoline ring was confirmed by the values of the coupling constant (J=7.2–7.3 Hz) between C-4 ad C-5 protons, similar to those reported for analogous, *trans*-4,5-disubstituted oxazolines.[15] (See Supporting Information for NOE experiments on **6f**).

Polymer-Supported Phosphinooxazolines

Our strategy for the preparation of click-PHOX resins is outlined in Scheme 3. The complementary azido group for the dipolar cycloaddition was incorporated onto commercial Merrifield resin (1% DVB, f_0=0.81 mmol Cl g^{-1} resin) by reaction with sodium azide.[19] According to elemental analysis data,[11a] the calculated degree of functionalization of the resulting azido resin was f=0.8 mmol g^{-1}. Oxazolines **6e,f** were grafted onto that resin by a Cu-catalyzed Huisgen cycloaddition to afford 2-fluorophenyl oxazoline-functionalized resins **7e,f**. As a general rule, stirring the re-



Scheme 3. Synthesis of click-supported PHOX and of their π-allyl Pd-complexes.

action mixture (shaker) in 1:1 DMF/THF at 45 °C for 16 h led to complete conversion. The progress of the cycloaddition reaction could be easily followed by IR spectroscopy, through the disappearance of the azide band (*ca.* 2094 cm^{-1}). Elemental analysis of the final resins in conjunction with high-resolution magic angle spinning (HRMAS) ^{13}C NMR spectroscopy allowed us to establish that the oxazoline anchors to the resin in quantitative yield. Treatment of resins **7e,f** with potassium diphenylphosphide in THF at 0 °C provided the desired click-PHOX resins **8e,f**. The ^{19}F NMR spectra (gel phase) of the resulting resins provided evidence for total conversion in the nucleophilic displacement of the fluoride group. Finally, formation of the π-allyl complexes **9** was easily performed by addition of π-allylpalladium chloride dimer [Pd(η^3-C_3H_5)Cl]$_2$ to the resins previously swollen in toluene. The final resins **9e,f** had functionalization degrees f = 0.49–0.53 mmol g^{-1}, in agreement with those expected for quantitative complexation. This was also indicated by ^{31}P NMR (See Supporting Information for ^{31}P NMR spectra of **8e,f** and **9e,f**).

For comparison purposes, compounds **11e,f** (Figure 2) were prepared following a similar procedure. The Cu(I)-catalyzed reaction between **6e,f** and *in situ* generated benzyl azide (from benzyl bromide and sodium azide), took place uneventfully in 1:1 *t*-BuOH/water under microwave irradiation to afford compounds **10e,f** in 81–82% yield. The nucleophilic displacement of fluoride from **10** with potassium diphenylphosphide proceeded smoothly in THF at −20 °C, the corresponding PHOX ligands being isolated in essentially pure form in 85–90% yield after filtration through a short pad of deoxygenated SiO$_2$. The crude PHOX ligands were directly converted to the corresponding π-allylpalladium complexes **11e,f** by reaction with π-allylpalladium chloride dimer [Pd(η^3-C_3H_5)Cl]$_2$ in ethanol in the presence of NH_4PF_6.[18] Complexes **11e,f** were isolated in 80–82% yield by precipitation from the reaction mixture at 4 °C.

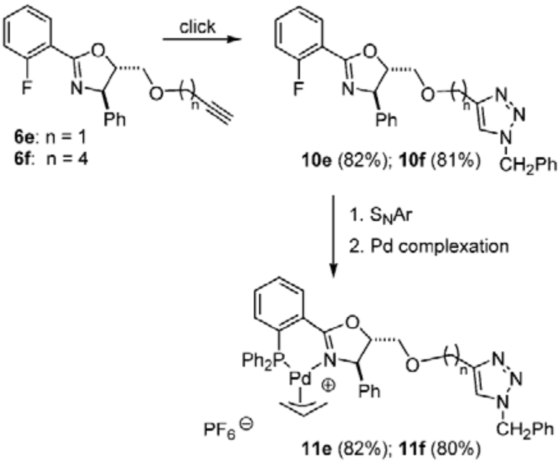
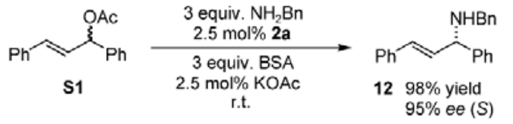


Figure 2. Preparation of reference, monomeric PHOX-Pd complexes **11e–f**.

Allylic Aminations with Pd-PHOX Complexes 2

The modular π-allylpalladium complexes **2a–d** were first evaluated in the amination reaction of *rac*-(*E*)-3-acetoxy-1,3-diphenyl-prop-1-ene (**S1**) with benzylamine (both widely used as a model substrates).[3–6]



Scheme 4. Asymmetric allylic amination of **S1** with benzylamine catalyzed by **2a**.

Since **2a** (R = Me) had proven to be the optimal catalyst for the allylic alkylation of **S1** with dimethyl malonate,[15] experiments aimed at optimizing reaction conditions were performed with this catalyst. To our delight, 98% yield and 95% *ee* were achieved in 2 h in the presence of 2.5 mol% of **2a** at room temperature under solvent-free conditions, by using an excess of benzylamine, *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate as additives (Scheme 4). It is interesting to note that this result is among the best ones reported in the literature for this particular reaction using PHOX-like ligands.[3-4] In addition, the reaction was remarkably fast and nearly total conversion was achieved after 2 h at room temperature. On the basis of previously reported data, the absolute configuration of **12** formed in the reaction was determined to be *S*.[3]

Encouraged by these results we next examined the activity of complexes **2b–d** under our optimized experimental conditions (Table 1). While complexes **2b–d** (entries 2–4) provided full conversion after 2 h, the corresponding enantioselectivities were significantly lower than those with **2a**, ranging from 83 to 88% *ee*. Thus, the presence of a non-bulky alkoxymethyl substituent at C-5 in the oxazoline ring is the key to high enantioselectivity in the asymmetric allylic amination reaction (entry 1).

To extend the scope of the asymmetric allylic amination, the reaction of **S1** was evaluated using a wide range of nitrogen nucleophilic compounds (Table 2). Excellent results were obtained in terms of yield and enantioselectivity except in the case of phthalimide potassium salt, which required higher temperatures and longer reaction times (65% yield, entry 6). In any case, this result is comparable with those observed for this nucleophile with other PHOX-based ligands.[4a] Under the optimized reaction conditions, *p*-methoxybenzylamine, propargylamine and diallylamine reacted in 2–4 h to give the expected products with excellent enantiomeric excess and in essentially quantitative yield (entries 1–3). Interestingly, neither propargylamine nor diallylamine have been previously studied as nitrogen nucleophiles in asymmetric allylic amination processes, despite the potential application of the resulting products **14** and **15** in Pauson–Khand, enyne cyclization, or metathesis-type reactions. With bulkier nucleophiles such as benzhydrylamine, benzoylhydrazine and phthalimide, longer reaction times were required for complete conversion. Although the reaction with benzoylhydrazine required a large excess of BSA, the corresponding product **17** was isolated in quantitative yield and 94% *ee* (entry 5). In any case, enantioselectivities, which range from 94 to 99% *ee*, are among the highest recorded with this type of nucleophiles.[1]

Table 1. Asymmetric allylic amination of **S1** with benzylamine catalyzed by Pd/PHOX complexes **2a–d**.[a]

Entry	Catalyst	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	**12**	98	95
2	**2b**	**12**	99	84
3	**2c**	**12**	99	83
4	**2d**	**12**	99	88

[a] All reactions were run at room temperature for 2 h with 2.5 mol% catalyst, 3 equiv. of benzylamine, 3 equiv. of BSA and 2.5 mol% KOAc.
[b] Yield of isolated product after purification by flash chromatography.
[c] Enantiomeric excesses were measured by chiral HPLC.

Table 2. Asymmetric allylic amination of **S1** with different N-nucleophiles catalyzed by Pd/PHOX complex **2a**.[a]

Entry	Nucleophile	Product	Time [h]	Yield [%][b]	*ee* [%][c]
1	*p*-Methoxybenzylamine	**13**	4	94	94
2	Propargylamine	**14**	2	99	97
3	Diallylamine	**15**	4	99	99
4	Benzhydrylamine	**16**	24	94	96
5	Benzoylhydrazine[d]	**17**	24	99	94
6	Phthalimide[e]	**18**	48	65	92

[a] All reactions were run at room temperature with 2.5 mol% catalyst, 3 equiv. of amine nucleophile, 3 equiv. of BSA and 2.5 mol% KOAc.
[b] Yield of isolated product after purification by flash chromatography.
[c] Enantiomeric excesses were measured by chiral HPLC.
[d] 6 equiv. of BSA were needed.
[e] Phthalimide potassium salt was used. The reaction was carried out at 50 °C.

The configurations of (*S*)-**17**[3] and (*S*)-**18**[4b,20] were established by comparison of the signs of their optical rotations or the elution order in HPLC with those reported in the literature. The absolute configurations of **13–16** were assigned as *S* by analogy.[1]

Allylic Aminations with Polymer-Supported Pd-PHOX Complexes 9

The results obtained with complexes **2a–d** clearly indicated that a non-bulky substituent at C-5 in the oxa-

Table 3. Asymmetric allylic amination of **S1** with different N-nucleophiles catalyzed by Pd/PHOX complexes **11e**,[a] **9e**[a] and **9f**.[b]

Entry	Catalyst	Nucleophile	Product	Time [h]	Yield [%][c]	*ee* [%][d]
1	**11e**	Benzylamine	**12**	24	95	91
2	**11e**	*p*-Methoxybenzylamine[e]	**13**	24	98	91
3	**11e**	Propargylamine	**14**	30	97	93
4	**11e**	Diallylamine	**15**	48	99	99
5	**11e**	Benzhydrylamine[e]	**16**	42	99	89
6	**9e**	Benzylamine[f]	**12**	48	99	86
7	**9e**	Benzylamine[g]	**12**	2.5	99	81
8	**9e**	*p*-Methoxybenzylamine[e]	**13**	240	85[h]	85
9	**9e**	Propargylamine[f,i]	**14**	72	91	84
10	**9e**	Diallylamine[e]	**15**	72	99	88
11	**9e**	Benzhydrylamine[e]	**16**	240	89[j]	82
12	**9f**	Benzylamine	**12**	2	99	91
13	**9f**	*p*-Methoxybenzylamine[k]	**13**	2	99	85
14	**9f**	Propargylamine	**14**	4	95	93
15	**9f**	Diallylamine	**15**	12	98	87
16	**9f**	Benzhydrylamine[k]	**16**	4	99	83

[a] Unless otherwise specified, the reactions were run at room temperature with 2.5 mol% catalyst, 3 equiv. of amine nucleophile, 3 equiv. of BSA and 2.5 mol% KOAc.
[b] All reactions were run at 40°C (setting temperature) under microwave irradiation with 7 mol% catalyst, 3 equiv. of amine nucleophile and 3 equiv. of BSA.
[c] Yield of isolated product after purification by flash chromatography.
[d] Enantiomeric excesses were measured by chiral HPLC.
[e] 9 mol% of catalyst was used.
[f] No KOAc was used
[g] Reaction was run at 40 °C (setting temperature) under microwave irradiation.
[h] 13% of **S1** was recovered with 21% *ee* determined by HPLC.
[i] 4 mol% of catalyst was used.
[j] 10% of **S1** was recovered with 27% *ee* determined by HPLC.
[k] 9 mol% of catalyst and 2.5 mol% KOAc were used.

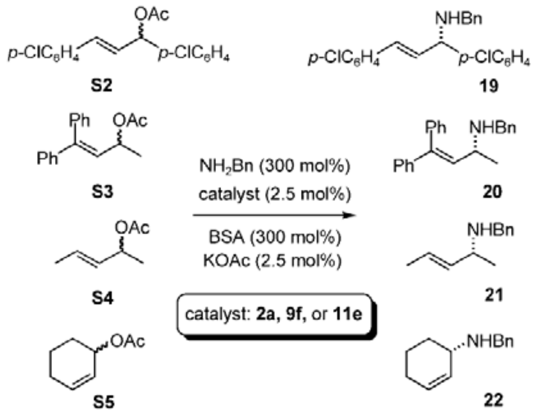
zoline ring was optimal for high enantioselectivity in the amination reaction. This observation guided the design of the clickable precursors of the **e** and **f** families, where one or four methylene groups are intercalated between the oxygen atom in the C-5 substituent and the carbon-carbon triple bond on the same moiety.

For reference purposes, we first examined the behaviour of the monomeric model for click-supported PHOX/Pd complexes **11e** (containing the short methylene spacer) in the allylic amination of **S1**. To this end, **S1** was reacted with several N-nucleophiles at room temperature in the presence of **11e**, BSA and potassium acetate. As can be seen in Table 3 (entries 1–5) the reaction was slower in all cases than with **2a**, 24–48 h being needed to achieve complete conversion. Nevertheless, the results obtained with this model catalyst are noteworthy since they are comparable with those obtained with **2a** (see Table 2). Accordingly, we anticipated that the enantioselectivity of the amination reaction would remain essentially unaffected by the immobilization of the phosphinooxazoline-palladium complexes through a 1,2,3-triazole linker as a part of the alkoxy substituent at C-5 in the oxazoline ring.

Reactions with the resin-supported Pd complex **9e** were run under the same reaction conditions as with **11e**, but with smooth stirring in an orbital shaker to avoid mechanical deterioration of the polymer beads. When the reactions were performed in this manner, the amination products could be obtained in high to excellent yields, but after long reaction times (entries 6 and 8–11 in Table 3). Except for the highly reactive benzylamine (entry 6), more than 2.5 mol% of **9e** was required in order to complete the reaction in 48 h. Taking into account that no work-up is required under these conditions, and that the catalyst can be separated by simple filtration, we decided to investigate the possibility of performing the reaction without the presence of the potassium acetate additive. This would avoid the presence of insoluble solids in the reaction media and would facilitate catalyst recovery. Interestingly, with highly reactive substrates such as benzylamine (entry 6) and propargylamine (entry 9) the reactions take place to completion in reasonable periods of time under these conditions. Microwave irradiation[15] was also studied as an alternative activation method. Thus, benzylamine reacted with **S1** at 40 °C (temperature setting) providing the amination product in quantitative yield in only 2.5 h, with only slightly lower enantioselectivity than in the reaction at room temperature (compare entries 6 and 7). In summary, **9e** showed the viability of performing asymmetric allylic aminations with a click-supported phosphinooxazoline palladium complex, but its overall catalytic activity and enantioselectivity still required further refinement.

Since the reaction environment with the polymer-supported catalyst is quite different from that of the homogeneous reaction, both the catalytic activity and the enantioselectivity could be affected by the close vicinity of the bulky polystyrene backbone. To mitigate this problem, catalyst **9f** containing a longer tetramethylene spacer between the PHOX moiety and the 1,2,3-triazole linker was synthesized. Gratifyingly enough, resin **9f** exhibited an optimal catalytic performance under microwave irradiation, with improved enantioselectivity over **9e** (entries 12–16 in Table 3). Furthermore, microwave-assisted allylic amination turned out to be more effective for all the nucleophiles tested and, in general, complete conversions were achieved at 40 °C in only 2–4 h. As an additional bonus, it was in general possible to perform the aminations catalyzed by **9f** without the presence of the potassium acetate additive; only with the less reactive amines, like *p*-methoxybenzylamine and benzhydrylamine, was the presence of this additive required to ensure complete conversion in short reaction times. This characteristic is relevant in connection with our ultimate goal of developing a flow system for continuous catalytic enantioselective amination.

In a further attempt to improve the characteristics of the supported catalysts **9e,f**, we studied the effect of the counterion on their performance. Displacement of chloride anion by the poorly coordinating hexafluorophosphate anion in resins **9e,f** was easily performed in the presence of NH_4PF_6 (See Supporting Information). In particular, these anion-exchanged complexes were tested in the amination of **S1** with benzylamine in the reaction conditions optimized for **9e,f**. Somewhat dissappointingly, while the yield remained quantitative, the enantioselectivity was rather low in comparison with that recorded with **9e,f** (69–71% *ee*, see with entries 6 and 12 in Table 3 for the results with **9e,f**). As the *exo-endo* ratio of the two isomeric allylpalladium species formed in the catalytic cycle determines the stereochemical outcome of the reaction, a fast equilibrium between the two isomers is essential for elevated enantioselectivities. The equilibrium rate is affected by the anion either by ion pairing or by coordination to palladium. Anions that stick to the Pd(II) complexes (ion pairing) modify the steric hindrance around the metal, as in the case of PF_6^- anion.[21]



Scheme 5. Asymmetric allylic amination of allyl acetates **S2–S5** with benzylamine.

In summary, high activities and good to excellent enantioselectivities (in general, higher than 85% *ee*) can be achieved in the amination of **S1** with different N-nucleophiles under microwave irradiation using polymer-supported PHOX/Pd complex **9f** as the catalyst. Notably, these results are similar to those recorded with the monomeric analogue **11e** (89–99% *ee*) and, therefore, comparable with those obtained with **2a** (94–99% *ee*).

Amination of a Family of Allylic Substrates with Benzylamine

Regarding the allylic acetate counterpart, a representative set of substrates was reacted with benzylamine in the presence of the catalysts **2a** and **9f** (Scheme 5). For comparison purposes, the model complex **11e** was also tested in the reactions. The results of this study are collected in Table 4. Products **19–22** are known compounds, and their absolute configuration was confirmed by comparison of the signs of their optical rotation with those reported in the literature.

While the remarkable catalytic activity depicted by the new family of PHOX ligands is rather independent on the nature of the allylic substrate, the enantioselectivity of the process is strongly substrate-dependent, as is generally observed in this reaction. In particular, the amination of **S2** and **S3** with **2a** (entries 1 and 4) leads to *ee* values among the highest recorded with PHOX ligands in the considered reaction.[4b] Following the same trend previously observed for **S1**, resin **9f** provided slightly lower enantiomeric excesses than **2a** (entries 2 and 5). In any case, the results are

Table 4. Asymmetric allylic amination of allyl acetates **S2**–**S5** with benzylamine catalyzed by Pd/PHOX complex **2a**,[a] **9f**[b] and **11e**.[a]

Entry	Catalyst	Substrate	Product	Time [h]	Yield [%][c]	*ee* [%][d]
1	**2a**	**S2**	**19**	1[e]	99	94
2	**9f**	**S2**	**19**	6[f]	96	82
3	**11e**	**S2**	**19**	72	98	86
4	**2a**	**S3**	**20**	15[g]	99	89
5	**9f**	**S3**	**20**	4	70[h]	82
6	**11e**	**S3**	**20**	7[i]	85	83
7	**2a**	**S4**	**21**	4	99	63
8	**9f**	**S4**	**21**	4	99	62
9	**11e**	**S4**	**21**	72	82	43
10	**2a**	**S5**	**22**	4	99	37
11	**9f**	**S5**	**22**	3	99	29
12	**11e**	**S5**	**22**	72	96	39

[a] All reactions were run at room temperature with 2.5 mol% catalyst, 3 equiv. of benzylamine, 3 equiv. of BSA and 2.5 mol% KOAc.

[b] Reactions were run at 40 °C (setting temperature) under microwave irradiation with 5 mol% catalyst, 3 equiv. of benzylamine, 3 equiv. of BSA and 2.5 mol% KOAc.

[c] Yield of isolated product after purification by flash chromatography.

[d] Enantiomeric excesses were measured by chiral HPLC.

[e] 6 equiv. of benzylamine and 6 equiv. of BSA were used

[f] KOAc was not added.

[g] Reaction was run at 50 °C. 5 Equiv, of benzylamine were required.

[h] 28% of **S3** was recovered. Kinetic resolution was not observed.

[i] Reaction was heated at 45 °C (setting temperature) in a microwave reactor. 13% of **S3** was recovered. Kinetic resolution was not observed.

comparable with those obtained in solution with the monomeric analogue **11e** as the catalyst (entries 3 and 6). The bulkiness of the *ipso* substituent on the acetate substrate has a remarkable influence on enantioselectivity. Thus, replacement of a rather bulky aryl substituent (like in **S1** or **S2**) by a less bulky methyl group at the reaction site (as in **S3** or **S4**) is accompanied by a decrease in enantioselectivity, which is notable in case of **S4** (entries 7 and 8). Nevertheless, either **2a** or **9f** afforded product **21** in higher enantiomeric excess than related PHOX ligands reported in the literature.[4b] Notably, no decrease in enantioselectivity is observed for this substrate between **2a** and **9f**, while **11e** is much less effective (entry 9). This provides a clear indication on the importance of the spacer when phosphinooxazolines are supported onto polymers *via* click chemistry. Finally, the cyclic substrate **S5** was also explored. Although enantioselectivities are only moderate in this case (entries 10–12), these are the first results on the amination of cyclic substrates reported with PHOX ligands.

Recovery and Reuse of Polymer-Supported Catalysts 9

As a further step towards our ultimate goal of developing a continuous amination process, the possibility of recycling and reusing the polymer-supported PHOX catalysts **9e,f** in the allylic amination of **S1** with benzylamine was studied. All the reactions were carried out under the conditions previously optimized for each catalyst, without the addition of potassium acetate. After each run, the reaction mixture was separated by decantation, and the resin was simply rinsed with deoxygenated dichloromethane and dried under Ar before the next use. In the case of **9e**, the reactions were performed at room temperature with orbital shaking. Although, as already discussed, reactions mediated by this catalyst take a long time for completion, it is worth mentioning that both catalytic activity and enantioselectivity remain essentially unaffected after three consecutive runs (entries 1–5 in Table 5).

On the other hand, a significant decrease in catalytic activity was observed in the recycling of **9f** under microwave irradiation with a temperature setting of 40 °C (entries 9–13). In this case, reaction times had to be increased up to four times to achieve the conversion of the preceding cycle (compare entries 9, 11, and 13). Less satisfactory results were achieved when the reactions were performed at 55 °C (entries 6–8). Under these conditions, the decrease in the activity of the catalyst was more evident after the first cycle (compare entries 7 and 10). Since the resin turned black as the recycling progressed, we interpreted that thermally-induced precipitation of Pd(0) was taking place, and that this fact was responsible for the activity decrease. In an attempt to minimize this deactivation mechanism, a new set of recycling experiments (entries 14–17) was performed at low temperature (27 °C) with the following experimental modifications. First, the resin was pre-swollen with dichloromethane in order to improve the flow of the reactants into the polymer beads. Second, to avoid temperature peaks that could be deleterious for the stability of the palladium complex, the reactions were performed in power control mode (the reaction time was fixed at 35 min and the microwave power at 1 W). Interestingly, this importantly mitigated the loss of catalytic activity, while enantioselectivity reached 87% and remained essentially constant over four cycles. Conversion and enantioselectivity were determined after each cycle.

Taken together, these results clearly show that while microwave activation is the key to high catalytic activity when the polymer-supported PHOX catalyst **9f** is used, temperature control during these experiments is of paramount importance to avoid catalyst deactivation.

Table 5. Asymmetric allylic amination of **S1** with benzylamine catalyzed by polymer-supported Pd/PHOX complexes **9e**[a] and **9f**.[b,c]

Entry	Cycle	Catalyst	Temp. [°C]	Time [h]	Yield [%][d] (Conv. [%])[e]	*ee* [%][f]
1	1	**9e**	25	48	99	86
2	2		25	48	(90)	nd
3				57	99	86
4	3		25	48	(89)	nd
5				58	99	84
6	1	**9f**[b]	55[g]	2	99	88
7	2		55[g]	2	(20)	nd
8				8	86	82
9	1	**9f**[b]	40	2	99	91
10	2		40	2	(47)	nd
11				8	97	87
12	3		40	7	(10)	nd
13				35	95	86
14	1	**9f**[c]	27[h]	0.58	(99)	87
15	2		27[h]	0.58	(91)	87
16	3		27[h]	0.58	(82)	86
17	4		27[h]	0.58	(76)	86

[a] All reactions were run with 2.5 mol% catalyst, 3 equiv. of benzylamine and 3 equiv. of BSA.

[b] Reactions were run under microwave irradiation with 7 mol% catalyst, 3 equiv. of benzylamine and 3 equiv. of BSA.

[c] Reactions were run under microwave irradiation with 10 mol% catalyst, 4 equiv. of benzylamine, 4 equiv. of BSA and 7 equiv. of CH_2Cl_2.

[d] Yield of isolated product after purification by flash chromatography.

[e] Conversion determined by ^1H NMR of an aliquot.

[f] Enantiomeric excesses were measured by chiral HPLC.

[g] 4 mol% of catalyst was used.

[h] Reactions were performed in power control mode (1 W). Temperature of the reaction mixture was measured with a teflon-coated Pt-100 probe.

Continuous Flow System for the Single-Pass Allylic Amination of S1

With the optimal conditions for recycling the polymer-supported Pd catalyst in hand, efforts were then directed towards the implementation of **9f** in a continuous flow system. Thus, with the experience gained in the design of a system for the enantioselective ethylation of aromatic aldehydes through a single-pass, continuous flow process,[11g] we planned a similar setup suited to the new purposes.

The simplicity of the system used for the study of the allylic amination of **S1** with benzylamine can be appreciated in Figure 3. The continuous flow system consists of a vertical, 1/4 inch internal diameter teflon tube containing the supported catalyst, fitted with two adapters which allows to connect it with 1/16 inch internal diameter tubes to pump in the reagents and to collect the products (Figure 4). The microwave-assisted flow experiment was performed in an open-vessel manner at 1 W irradiation power. During operation, the reagents were pumped in through the bottom end of the tube using a piston pump.

Chemical reactions in continuous, flowing systems are best described by the plug flow reactor model.[22] In this model, the tubular reactor is considered as a series of infinitely thin coherent plugs, each of them characterized by a uniform composition which varies along the axial direction of the reactor as the reaction proceeds. For this model to be applicable, the fluid traveling through the reactor must be perfectly mixed in the radial direction but not in the axial one. In the flow system under consideration, where the tubular reactor is completely filled with the swollen functional resin, isothermal piston flow operates.[23] Under these conditions, conversion achieved in a given reactor (of given geometry and containing a given amount of catalyst) is only determined by the feed composition, reaction temperature, and mean residence time of the reactants in the reactor.

In the continuous flow allylic amination experiments, the resin was first swollen by pumping anhydrous dichloromethane at a 0.12 mL min^{-1} flow rate during 30 min. Then, microwave irradiation (1 W) was started and a solution of BSA, **S1** and benzylamine in the right proportions in dichloromethane, placed in a flask under argon, was pumped through the system for 180 min at the same flow rate (0.12 mL min^{-1}). Under these conditions, temperature of the reaction mixture (measured at the inlet and outlet of the tubular reactor with a Pt-100 probe) kept constant within 1 °C (22 ± 1 °C). The system was operated in single-

Figure 3. Continuous flow system used in the allylic amination of **S1** with benzylamine.

Figure 4. Detail of the teflon tube containing the polymer-supported catalyst in the microwave cavity.

Table 6. Continuous flow asymmetric allylic amination of **S1** with benzylamine catalyzed by polymer-supported Pd/PHOX complex **9f** under single-pass conditions.[a]

Entry	Time [min]	Conv.[%][b]	*ee* [%][c]
1	15	–[d]	–
2	30	85	81
3	45	86	83
4	60	80	82
5	75	75	83
6	90	70	83
7	105	66	83
8	120	63	85
9	135	60	84
10	150	55	84
11	165	55	84
12	180	54	86

[a] Reaction was run under microwave irradiation (1 W). A loading of 240 mg of resin **9f** (12 mol%) was used. The employed dichloromethane solution of reagents was prepared by mixing **S1** (9.6 mmol) in CH_2Cl_2 (4.3 mL) with benzylamine (48.1 mmol) and BSA (38.5 mmol).

[b] Conversions were determined by ^1H NMR.

[c] Enantiomeric excesses were measured by chiral HPLC.

[d] Only CH_2Cl_2 was collected.

pass manner, so that the output flow was directly collected. Samples of the output solution were taken every 15 min for analysis purposes. At the end of the experiment, dichloromethane was pumped for a further 30 min in order to wash the resin and the mechanical parts of the reactor. The conversion and *ee* of each aliquot are plotted in Table 6 and Figure 5. As shown, while the conversion slowly decays from 85% in the first 30 min (entry 2) to 54% after 3 h (entry 12), the *ee* increases in a slight but regular manner from 81% to 86% *ee*. Gratifyingly enough, conversion remains near 55% after 3 h of continuous flow allylic amination of **S1** (entry 12) and the level of enantioselectivity achieved (86% *ee*) is comparable with those obtained in batch processes.

The flow rate used in this experiment involves a residence time of the reagents within the catalyst bed of only 8.5 min.[24] The output flow corresponding to the whole operation period (3 h) was concentrated in

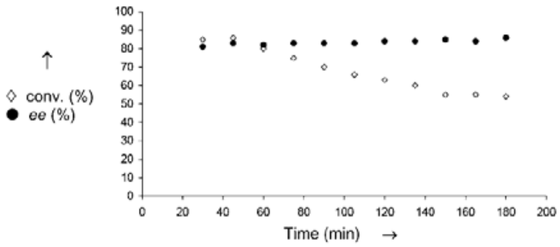


Figure 5. Results of the continuous flow allylic amination of **S1** with benzylamine.

vacuum, diluted with diethyl ether and washed with water. After evaporation, flash chromatography of the reaction crude furnished the desired product **12** in 68% yield and 83% *ee*. Using a flow rate of 0.12 mL min^{-1} the system has a production of 9.18 mmol h^{-1} per gram of resin **9f**, allowing the preparation of 1.98 g of pure (+)-(*S*,*E*)-*N*-benzyl-(1,3-diphenyl-2-propenyl)amine (**12**) with high enantioselectivity in a 3 h run.

The role exerted by microwave irradiation on the acceleration of these reactions is rather intriguing since, as discussed above, the very low microwave power used is not enough to provoke any significant increase in the macroscopic temperature of the flowing reaction mixture. This is in agreement with the low loss tangent values (tan δ) of dichloromethane and polystyrene,[25a] which should make very inefficient the conversion of electromagnetic energy into heat in the employed reaction system. Although the highly selective microwave heating of the Pd(I) complexes grafted onto the polymer chains could be the primary origin of the observed rate enhancement,[25b] the dissipation of the energy harvested by the metal complexes through the polymer chains where they are imbedded could also play a role in this behaviour. Thus, an increased mobility of the rather flexible polymer matrix would greatly facilitate the contact between the polymer-supported catalyst and the liquid phase containing the reactants by opening all the possible channels in the polymer structure. In this way, mass transfer limitations to reaction rate could be efficiently overcome.

Conclusions

In summary, we have described a family of highly modular PHOX ligands (**2**) for the Pd-catalyzed asymmetric allylic amination, and have used this result as a guide for the design of an analogue that could be supported onto polystyrene *via* click chemistry. The corresponding polymer-supported catalysts (**9e,f**), efficiently induce allylic amination, especially when the reactions are promoted by microvawes. The careful optimization of reaction conditions for catalyst recovery and recycling has ultimately served to fix the technological aspects allowing the conversion of the initial, batch amination process into the first, single-pass, continuous flow process of this class. During this optimization, an important acceleration of the heterogeneously-catalyzed reaction by microwave irradiation that does not involving macroscopic heating of the reaction mixture has been observed. Work aimed at improving the thermal stability of the polymer-supported palladium complex for an extended life of the catalytic system and at applying highly selective microwave activation to other processes where polymer-supported reactants or catalysts are involved is being actively pursued in our laboratories and will be reported in due course.

Experimental Section

General aspects of the experimental section can be found in the Supporting Information.

Typical Procedure for the *O*-Alkylation of (2*S*,3*S*)-3-Phenylglycidol; Synthesis of Alkynyloxy Epoxides 3e,f

A solution of enantiomerically pure (2*S*,3*S*)-3-phenylglycidol (10 mmol) in anhydrous DMF (10 mL) was added under argon to a suspension of sodium hydride (60% in mineral oil, 11.7 mmol) in anhydrous DMF (15 mL) previously cooled at −20 °C. The mixture was stirred for 20 min and then the corresponding propargyl halide (13 mmol) was added dropwise. The reaction mixture was stirred at −20 °C for 3 h, then allowed to reach room temperature and further stirred for 24 h. The reaction was quenched with MeOH (10 mL) and brine (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The purification of the products **3e,f** was carried by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

3e: Following the general method from (2*S*,3*S*)-3-phenylglycidol (1.4 g, 9.3 mmol), sodium hydride (0.45 g, 11.2 mmol) and propargyl bromide (80% in toluene, 1.3 mL, 12 mmol), compound **3e** was obtained as a pale yellow oil; yield: 1.32 g (75%); $[\alpha]_D^{23}$: −49.0 (*c* 1.1 in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.36$–7.25 (m, 5H), 4.29–4.20 (m, 2H), 3.90 (dd, $J = 11.5$, 3.0 Hz, 1H), 3.81 (d, $J = 2.3$ Hz, 1H), 3.68 (dd, $J = 11.5$, 5.0 Hz, 1H), 3.24–3.21 (m, 1H), 2.47–2.46 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 136.7$ (C), 128.5 (2CH), 128.3 (CH), 125.7 (2CH), 79.2 (C), 75.0 (CH), 69.4 (CH_2), 60.7 (CH_2), 58.6 (CH), 55.9 (CH); IR (film): $\nu = 3285$, 2854, 1461, 1100, 879, 699 cm^{-1}; HR-MS (ESI+): *m/z* = 211.0721, calcd. for $C_{12}H_{12}NaO_2$ $[M+Na]^+$: 211.0735.

3f: Following the general method from (2*S*,3*S*)-3-phenylglycidol (1.5 g, 10 mmol), sodium hydride (0.47 g, 11.7 mmol) and 6-chloro-1-hexyne (1.6 mL, 13 mmol), compound **3f** was obtained as a pale yellow oil; yield: 1.5 g (65%); $[\alpha]_D^{23}$: −148.6 (*c* 1.3 in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta =$ 7.35–7.25 (m, 5H), 3.81–3.76 (m, 2H), 3.59–3.50 (m, 3H), 3.2–3.17 (m, 1H), 2.22 (td, $J=7.1$, 2.7 Hz, 2H), 1.95 (t, $J=2.7$ Hz, 1H), 1.76–1.67 (m, 2H), 1.65–1.58 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=136.9$ (C), 128.5 (2CH), 128.2 (CH), 125.7 (2CH), 84.2 (C), 71.1 (CH_2), 70.6 (CH_2), 68.5 (CH), 61.2 (CH), 55.9 (CH), 28.7 (CH_2), 25.1 (CH_2), 18.2 (CH_2); IR (film): $\nu=3293$, 2921, 1459, 1259, 1112, 880, 750 cm^{-1}; HR.MS (ESI+): $m/z=253.1198$, calcd. for $C_{15}H_{18}NaO_2$ $[M+Na]^+$: 253.1204.

Preparation of Amino Alcohols 4e,f

The corresponding epoxy ether (1.0 mmol), 30% aqueous NH_3 (50 mmol), $LiClO_4$ (1 mmol) and isopropyl alcohol (5 mL), were heated in a sealed pressure tube at 100 °C for 6–7 h. The mixture was left to reach room temperature and the solvent was removed under reduced pressure. The crude reaction product was dissolved in CH_2Cl_2 (5 mL) and washed with water (3×5 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting amino alcohols **4e,f** were used in the next step without further purification.

4e: Obtained as a pale yellow oil after flash chromatography (hexanes/AcOEt from 100:0 to 50:50); yield: 99%; $[\alpha]_D^{23}$: −33.3 (*c* 0.9 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.36$–7.20 (m, 5H), 4.12–4.10 (m, 3H), 3.95 (ddd, $J=5.1$, 5.1, 5.1 Hz, 1H), 3.48–3.46 (m, 2H), 2.44 (bs, 2H), 2.41–2.40 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=141.7$ (C), 128.4 (2CH), 127.5 (CH), 127.2 (2CH), 79.4 (C), 74.8 (CH), 73.5 (CH), 71.1 (CH_2), 58.6 (CH_2), 57.8 (CH); IR (film): $\nu=3337$, 3277, 2852, 1601, 1494, 1453, 1071, 763, 701 cm^{-1}; HR-MS (ESI+): $m/z=206.1178$, calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181.

4f: Obtained as a pale yellow oil after flash chromatography (hexanes/AcOEt from 100:0 to 50:50); yield: 90%; $[\alpha]_D^{23}$: −68.8 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.36$–7.20 (m, 5H), 4.13 (d, $J=5.0$ Hz, 1H), 3.95 (ddd, $J=5.0$, 5.0, 5.0 Hz, 1H), 3.40–3.28 (m, 4H), 2.19 (td, $J=7.1$, 2.6 Hz, 2H), 1.94 (t, $J=2.7$ Hz, 1H), 1.69–1.62 (m, 2H), 1.69–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=141.0$ (C), 128.5 (CH), 127.6 (CH), 127.2 (3CH), 84.2 (C), 73.0 (CH), 71.7 (CH_2), 70.9 (CH_2), 68.6 (CH), 57.8 (CH), 28.5 (CH_2), 25.1 (CH_2), 18.2 (CH_2); IR (film): $\nu=3287$, 2865, 1668, 1454, 1114, 704, 632 cm^{-1}; HR-MS (ESI+): $m/z=248.1658$, calcd. for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651.

Preparation of Hydroxy Amides 5e,f

Et_3N (1.95 mmol) was added under argon to a solution of the corresponding amino alcohol **4e,f** (1.0 mmol) in anhydrous THF (1.5 mL) and the mixture was cooled at 0 °C. A solution of 2-fluorobenzoyl chloride (0.95 mmol) in anhydrous THF (1.3 mL) was slowly added to the previous solution. The mixture was left to reach room temperature and stirred for an additional 2 h period. The solvents were removed under reduced pressure. The crude reaction product was diluted with CH_2Cl_2 (5 mL) and washed with brine (3×5 mL). The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 60:40).

5e: Yield: 1.32 g (69%); white foam; $[\alpha]_D^{23}$: +46.1 ($c=0.8$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=8.11$ (bs, 1H), 8.06 (ddd, $J=7.8$, 1.9 Hz, 1H), 7.49–7.10 (m, 8H), 5.48–5.44 (m, 1H), 4.19–4.14 (m, 3H), 3.59 (dd, $J=9.6$, 3.6 Hz, 1H), 3.41 (dd, $J=9.8$, 5.1 Hz, 1H), 2.67 (d, $J=6.35$ Hz, 1H), 2.43–2.41 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=162.9$ (d, $J_{C,F}=3.5$ Hz, C=O), 160.9 (d, $J_{C,F}=248.0$ Hz, CF), 138.3 (C), 133.2 (d, $J_{C,F}=9.3$ Hz, CH), 132.2 (d, $J_{C,F}=2.1$ Hz, CH), 128.6 (2CH), 127.7 (CH), 127.3 (2CH), 124.7 (d, $J_{C,F}=3.2$ Hz, CH), 120.9 (d, $J_{C,F}=11.0$ Hz, CH), 115.9 (d, $J_{C,F}=24.8$ Hz, CH), 78.8 (C), 75.1 (CH), 72.0 (CH), 70.8 (CH_2), 58.6 (CH_2), 56.8 (CH); IR (film): $\nu=3316$, 3266, 3032, 2941, 1636, 1613, 1527, 1481, 1452, 1099, 752, 702 cm^{-1}; HRMS (ESI+): $m/z=350.1153$, calcd. for $C_{19}H_{18}FNNaO_3$ $[M+Na]^+$: 350.1168, found.

5f: Yield: 1.32 g (70%); white foam; $[\alpha]_D^{23}$: +32.8 (*c* 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=8.35$–8.30 (m, 1H), 7.95 (dt, $J=7.9$, 1.9 Hz, 1H), 7.39–7.02 (m, 8H), 5.49–5.48 (m, 1H), 4.09–4.03 (m, 1H), 3.38–3.22 (m, 4H) 2.17 (td, $J=7.1$, 2.7 Hz, 2H), 1.95 (t, $J=2.7$ Hz, 1H) 1.69–1.64 (m, 2H), 1.58–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=163.0$ (d, $J_{C,F}=3.0$ Hz, C=O), 160.4 (d, $J_{C,F}=248.2$ Hz, CF), 138.8 (C), 133.2 (d, $J_{C,F}=9.3$ Hz, CH), 131.8 (d, $J_{C,F}=2.0$ Hz, CH), 128.4 (2CH), 127.4 (CH), 127.2 (2CH), 124.6 (d, $J_{C,F}=3.3$ Hz, CH), 121.2 (d, $J_{C,F}=12.0$ Hz, CH), 115.9 (d, $J_{C,F}=24.3$ Hz, CH), 84.1 (C), 71.7 (CH), 71.6 (CH_2), 71.0 (CH_2), 68.7 (CH), 57.1 (CH), 28.4 (CH_2), 25 (CH_2), 18.2 (CH_2); IR (film): $\nu=3316$, 3266, 3032, 2941, 1636, 1613, 1527, 1481, 1452, 1099, 752, 702 cm^{-1}; HR-MS (ESI+): $m/z=392.1638$, calcd. for $C_{22}H_{24}FNNaO_3$ $[M+Na]^+$: 392.1650.

Preparation of (2-Fluoro)phenyloxazolines 6e,f

Methanesulfonyl chloride (1.1 mmol) was slowly added to a solution of the corresponding compound **5e,f** (1.0 mmol) and Et_3N (2.2 mmol) in CH_2Cl_2 (8.2 mL) under an argon atmosphere at 0 °C. The mixture was left to reach room temperature and stirred for an additional 2 h period. This mixture was added to a saturated aqueous solution of NH_4Cl (9 mL), the two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×6 mL). The organic phases were washed with brine (5 mL) and dried (Na_2SO_4). The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was added to a 5% solution of KOH in MeOH (9 mL, 2.0 mmol), and the mixture was stirred for 15 h at room temperature. The reaction was quenched with water (5 mL) and the mixture extracted with CH_2Cl_2 (3×5 mL). The organic phases were dried (Na_2SO_4) and solvent removed under reduced pressure. The final product was purified by flash chromatography (hexane/EtOAc from 100:0 to 90:10).

6e: Yield: 0.85 g (73%); colourless oil; $[\alpha]_D^{23}$: +52.0 (*c* 1.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.98$ (ddd, $J=7.5$, 1.8, 1.8 Hz, 1H), 7.5–7.14 (m, 8H), 5.18 (d, $J=7.3$ Hz, 1H), 4.64 (ddd, $J=7.3$, 4.7, 4.7 Hz, 1H), 4.32–4.23 (m, 2H), 3.89–3.83 (m, 2H), 2.47–2.45 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=161.1$ (d, $J_{C,F}=258.5$ Hz, CF), 160.8 (d, $J_{C,F}=5.4$ Hz, C=N), 141.7 (C), 133.0 (d, $J_{C,F}=8.4$ Hz, CH), 131.3 (d, $J_{C,F}=1.4$ Hz, CH), 128.7 (2CH), 127.6 (CH), 126.6 (2CH), 123.9 (d, $J_{C,F}=3.8$ Hz, CH), 116.6 (d, $J_{C,F}=21.0$ Hz, CH), 115.8 (d, $J_{C,F}=10.2$ Hz, C), 85.4 (CH), 79.1 (C), 75.1 (CH), 72.4 (CH), 70.3 (CH_2), 58.7 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-108.8$ (s, F); IR (film): $\nu=290$, 2857, 1648, 1495, 1457, 1053, 766, 701 cm^{-1}; HR-MS (ESI+): $m/z=332.1049$, calcd. for $C_{19}H_{16}FNNaO_2$ $[M+Na]^+$: 332.1063.

6f: Yield: 0.7 g (81%); colourless oil; $[\alpha]_D^{23}$: +47.2 (*c* 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=8.00$ (ddd, $J=7.5$, 1.8, 1.8 Hz, 1H), 7.50–7.15 (m, 8H), 5.19 (d, $J=7.2$ Hz, 1H), 4.64 (ddd, $J=7.4$, 5.0, 5.0 Hz, 1H), 3.79–3.74 (m, 2H), 3.64–3.54 (m, 2H), 2.27 (td $J=7.1$, 2.7 Hz, 2H), 1.95 (t, $J=$ 2.7 Hz, 1H), 1.78–1.71 (m, 2H), 1.68–1.59 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=161.5$ (d, $J_{C,F}=260.0$ Hz, CF), 160.9 (d, $J_{C,F}=5.4$ Hz, C=N), 141.9 (C), 133.0 (d, $J_{C,F}=8.9$ Hz, CH), 131.3 (d, $J_{C,F}=1.5$ Hz, CH), 128.7 (2CH), 127.6 (CH), 126.7 (2CH), 123.9 (d, $J_{C,F}=4.0$ Hz, CH), 116.7 (d, $J_{C,F}=$ 22.0 Hz, CH), 116.0 (d, $J_{C,F}=11$ Hz, C), 85.7 (CH), 84.2 (C), 72.5 (CH), 71.6 (CH), 71.2 (CH_2), 68.5 (CH_2), 28.6 (CH_2), 25.1 (CH_2), 18.1 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-108.9$ (s, F); IR (film): $\nu=3300$, 2863, 1648, 1613, 1495, 1457, 1111, 760 cm^{-1}; HR-MS (ESI+): $m/z=352.1720$, calcd. for $C_{22}H_{23}FNO_2$ $[M+H]^+$: 352.1713.

Preparation of the Click Resins 7e,f

The N_3-functionalized resin[19] (1.54 g, $f=0.98$ mmol g^{-1}) was reacted with the corresponding alkynyloxymethyl oxazoline **6e,f** (1.62 mmol), CuI (2 mg, 0.01 mmol) and DIPEA (0.17 mL, 0.99 mmol) in a 1:1 mixture of DMF and THF (10 mL) at 45 °C. The progression of the reaction was monitored by IR spectroscopy. After disappearance of the azide signal (40 h) the resin was collected by filtration and sequentially washed with water (250 mL), DMF (250 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL). The solid was dried under vacuum overnight at 40 °C.

Resin 7e: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=7.99$–7.91 (m, 1H), 7.45–6.27 (m, polymer), 5.40–5.10 (m, polymer), 5.12 (m, 1H), 4.73–4.66 (m, 2H), 4.65–4.60 (m, 1H), 3.85–3.81 (m, 2H), 2.12–0.85 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=161.1$ (d, $J_{C,F}=258.5$ Hz, CF), 160.0 (C=N), 146.3–144.6 (m, polymer), 141.8 (C), 135.3 (CH), 133.2 (d, $J_{C,F}=8.4$ Hz, CH), 131.4 (CH), 128.8 (CH), 128.0 (CH), 127.7 (CH), 126.7 (CH), 125.7 (CH), 124.0 (d, $J_{C,F}=3.7$ Hz, CH), 116.6 (d, $J_{C,F}=22.0$ Hz, CH), 115.8 (C), 112.3–109.5 (m, polymer), 85.7 (CH), 72.3 (CH), 71.2 (CH_2), 68.0 (CH_2), 40.7–40.1 (m, polymer), 29.7 (CH_2), 25.6 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-109.6$ (s, F); IR (ATR): $\nu=3058$, 3024, 2919, 1647, 1600, 1492, 1451, 1308, 1221, 1180, 1066, 1027, 753, 696, 556 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 3.61; found: N 3.91; $f=0.71$ mmol g^{-1}.

Resin 7f: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=7.99$–7.91 (m, 1H), 7.42–6.20 (m, polymer), 5.38–4.96 (m, polymer), 5.15 (m, 1H), 4.62–4.34 (m, 1H), 3.72–3.66 (m, 2H), 3.60–3.47 (m, 2H), 2.74–2.55 (m, 2H), 2.12–0.85 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=161.5$ (d, $J_{C,F}=263.9$ Hz, CF), 160.0 (C=N), 146.3–144.6 (m, polymer), 142.0 (C), 133.2 (CH), 131.4 (CH), 128.8 (CH), 128.0 (CH), 127.7 (CH), 126.8 (CH), 125.7 (CH), 124.0 (CH), 116.7 (d, $J_{C,F}=$ 23.0 Hz, CH), 116.1 (C), 112.3–109.5 (m, polymer), 85.9 (CH), 72.5 (CH), 71.8 (CH_2), 71.6 (CH_2), 68.0 (CH_2), 40.7–40.1 (m, polymer), 29.3 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 25.5 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-109.6$ (s, F); IR (ATR): $\nu=$ 3058, 3024, 2919, 1647, 1600, 1492, 1451, 1308, 1255, 1180, 1066, 1027, 753, 696, 556 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 3.52; found: N 3.82; $f=0.68$ mmol g^{-1}.

Preparation of the Polymer-Supported Phosphino-oxazolines 8e,f

A solution of $KPPh_2$ (1.37 mmol, 2.74 mL of 0.5 M solution in THF) was added dropwise under argon at 0 °C to an oven-dried Schlenk flask which contained the corresponding resin **7e,f** (0.98 mmol) previously swollen with anhydrous and degassed THF (10 mL). The reaction mixture was shaken at 0 °C for 2 h, then allowed to reach room temperature and further shaken for 12 h at this temperature. The solution was removed under argon *via* cannula and the resin was washed with anhydrous and degassed CH_2Cl_2 (7× 10 mL) and dried under vacuum for 10 h. Resins **8e,f** were characterized by gel-phase ^{31}P NMR and were immediately transformed into the corresponding palladium complexes **9e,f** to minimize oxidative deterioration.

Resin **8e**: ^{31}P NMR ($CDCl_3$): $\delta=-3.2$ (s, PPh_2).

Resin **8f**: ^{31}P NMR ($CDCl_3$): $\delta=-3.0$ (s, PPh_2).

Preparation of the Polymer-Supported Phosphino-oxazoline π-Allylpalladium Complexes 9e,f

A solution of $[Pd(C_3H_5)Cl]_2$ (0.018 mmol, 67 mg) in anhydrous and deoxygenated toluene (1 mL) was added to an oven-dried Schlenk flask which contained the corresponding resin **8e,f** (0.5 g) previously swollen with anhydrous and degassed toluene (5 mL). The reaction mixture was shaken for 1 h. The resin was filtered, rinsed with toluene (10 mL) and CH_2Cl_2 (200 mL) and dried in vacuo for 12 h. Spherical beads with a 0.102 mm diameter (120 mesh) were obtained in this way.

Resin 9e: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=8.32$–8.20 (m, 1H), 7.65–6.25 (m, polymer), 5.78–5.41 (m, polymer), 5.30 (m, 1H), 4.96–4.34 (m, 2H), 4.61 (m, 1H), 4.07–3.69 (m, 4H), 3.34–3.08 (m, 2H), 2.99–2.76 (m, 2H), 2.33 (d, $J=$ 16.5 Hz, 2H), 2.14 (d, $J=23.6$ Hz, 2H), 1.99–0.90 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=146.3$–144.3 (m, polymer), 139.6 (CH), 135.4–130.9 (m, CH), 130.7–124.8 (m, CH), 114.0–108.5 (m, polymer), 87.2 (CH), 75.2 (CH), 69.5 (CH_2), 64.5 (CH_2), 55.3–53.4 (m, CH_2), 47.1–41.5 (m, polymer), 41.3–38.5 (m, polymer), 29.7 (CH_2), 25.6 (CH_2); ^{31}P NMR ($CDCl_3$): $\delta=25.5$ (s, PPh_2, *exo*), 24.8 (s, PPh_2, *endo*); IR (ATR): $\nu=3057$, 3024, 2919, 1625, 1600, 1542, 1492, 1451, 1435, 1350, 1116, 1098, 728, 696, 538 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.95; found: N 2.93; $f=0.53$ mmol g^{-1}.

Resin 9f: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=8.33$–8.24 (m, 1H), 7.71–6.18 (m, polymer), 5.65–5.08 (m, polymer), 5.48 (m, 1H), 4.89–4.46 (m, 2H), 4.61 (m, 1H), 3.93–3.64 (m, 4H), 3.62–3.46 (m, 2H), 3.32–3.05 (m, 2H), 3.03–2.80 (m, 2H), 2.79–2.54 (m, 2H), 2.34 (d, $J=18.0$ Hz, 2H), 2.14 (d, $J=24.3$ Hz, 2H), 2.03–1.21 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=146.3$–144.3 (m, polymer), 139.5 (CH), 134.9–130.8 (m, CH), 129.9–124.6 (m, CH), 114.1–105.6 (m, polymer), 87.2 (CH), 75.6 (CH), 71.5 (CH_2), 70.4 (CH_2), 54.1 (CH_2), 46.4–41.8 (m, polymer), 41.6–39.4 (m, polymer), 29.6 (CH_2), 26.0 (CH_2), 25.5 (CH_2); ^{31}P NMR ($CDCl_3$): $\delta=25.5$ (s, PPh_2); IR (ATR): $\nu=3024$, 2919, 1624, 1600, 1491, 1451, 1435, 1307, 1180, 1118, 749, 695, 540 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.88; found: N 2.99; $f=0.68$ mmol g^{-1}.

Preparation of Model Fluorooxazolines 10e,f

Benzyl bromide (0.13 mL, 1.07 mmol) was added to a mixture of the corresponding alkynyloxymethyloxazoline **6e,f** (1 mmol), sodium azide (0.148 g, 2.13 mmol), $CuSO_4{\cdot}5H_2O$ (5 mg, 0.002 mmol) and sodium L-ascorbate (43 mg, 0.21 mmol) in *tert*-butyl alcohol:water 1:1 (3 mL). The mixture was submitted to microwave irradiation (150 W, 100 °C, 2 min ramp and 40 min hold time). The reaction mixture was extracted with ethyl acetate (3×25 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 80:20 to 20:80). See Supporting Information for the physical and spectroscopic data of compounds **10e,f**.

Preparation of Model Phosphinooxazoline π-Allylpalladium Complexes 11e,f

A solution of $KPPh_2$ (0.77 mmol, 1.55 mL of 0.5 M solution in THF) was added dropwise under Ar at −78 °C to an oven-dried Schlenk flask which contained the corresponding fluorooxazoline **10e,f** (0.55 mmol) in THF (2 mL). The temperature was allowed to reach −20 °C. The reaction mixture was stirred for an additional 2 h period at this temperature, then allowed to reach room temperature, further stirred for 12 h at this temperature, quenched with $Na_2SO_4{\cdot}10H_2O$ in order to hydrolyze the excess of diphosphine, and filtered through a short SiO_2 pad eluting with CH_2Cl_2. Solvents were removed under vacuum, and the residue was purified by flash chromatography over SiO_2 under argon using deoxygenated solvents. The resulting phosphinooxazolines (see Supporting Information for ^1H- and ^{31}P NMR spectra) were immediately transformed into the corresponding palladium complexes **11**.

A solution of the corresponding phosphinooxazoline (0.38 mmol) in deoxygenated EtOH (4 mL) was *via* cannula to a Schlenk flask which contained a solution of $[Pd(C_3H_5)Cl]_2$ (0.20 mmol, 0.073 g) in EtOH (5 mL). The mixture was stirred 1 h under argon at room temperature; NH_4PF_6 (0.41 mmol, 0.068 g) was then added, and the resulting solution was further stirred for 14 h. Then, the mixture was cooled to −20 °C and allowed to stand at this temperature for several hours to induce crystallization of the π-allylpalladium complex. The crystallized phosphinooxazoline π-allylpalladium complex was filtered off, washed with cold EtOH (3 mL) and dried under vacuum. See Supporting Information for the physical and spectroscopic data of compound **11f**.

Model compound 11e: Yield: 82%; orange solid; $[\alpha]_D^{27}$: −27.9 (*c* 1.1 in $CHCl_3$); ^1H NMR (CD_3CN): δ=8.28–8.22 (m, 2H), 7.83–6.97 (m, 42H), 6.85 (d, *J*=7.4 Hz, 4H), 5.56 (m, 4H), 5.30 (d, *J*=7.4 Hz, 2H), 4.74–4.61 (m, 6H), 3.95 (d, *J*=12.0 Hz, 2H), 3.78 (d, *J*=12.0 Hz, 2H); ^{13}C NMR (CD_3CN): δ=165.2 (CN), 139.5 (C), 134.7 (CH), 133.9 (CH), 133.8 (CH), 133.5 (CH), 133.3 (CH), 132.7 (CH), 132.3 (CH), 132.1 (CH), 131.9 (CH), 129.8 (CH), 129.7 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.1 (CH), 87.0 (CH), 76.3 (CH), 69.3 (CH_2), 64.1 (CH_2), 56.0 (CH_2); ^{31}P NMR ($CDCl_3$): δ=24.9 (s, PPh_2, *exo*), 24.4 (s, PPh_2, *endo*), −141.05 (h, *J*=712.5 Hz, PF_6); IR (film): ν=3060, 2920, 1622, 1480, 1456,1436, 1451, 1307, 1118, 831, 746, 694, 556, 538 cm^{-1}; HR-MS (ESI+): *m/z*=755.1763, calcd. for $C_{41}H_{38}N_4O_2PPd$ $[M-PF_6]^+$: 755.1767.

General Procedure for the Palladium-Catalyzed Allylic Amination of S1 with Different N-Nucleophiles in the Presence of 2a–d

To an oven-dried Schlenk flask containing the corresponding phosphinooxazoline palladium complex **2a–d** (0.025 mmol) under argon were successively added (*E*)-3-acetoxy-1,3-diphenyl-1-propene (**S1**) (0.25 g, 1 mmol), the N-nucleophile (3 mmol), BSA (0.74 mL, 3 mmol) and KOAc (2.5 mg, 0.025 mmol). The mixture was stirred at room temperature for 2–24 h (unless otherwise stated, see Table 1) and then diluted with diethyl ether and washed with water. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

(+)-(*S,E*)-*N*-Benzyl-(1,3-diphenyl-2-propenyl)amine (12)[3]: From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), benzylamine (0.33 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.29 g (98%); colourless oil; $[\alpha]_D^{23}$: +16.4 (*c* 0.85 in $CHCl_3$), 95% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.6 mL min^{-1} *n*-hexane/isopropyl alcohol 99:1, 254 nm): (*R*)-**12** Rt=19.5 min, (*S*)-**12** Rt=20.8 min.

(+)-(*S,E*)-*N*-(*p*-Methoxybenzyl)-(1,3-diphenyl-2-propenyl)-amine (13): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), *p*-methoxybenzylamine (0.396 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.31 g (94%) yellow oil; $[\alpha]_D^{23}$: +28.2 (*c* 0.82 in $CHCl_3$), 94% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.7 mL min^{-1} *n*-hexane/isopropyl alcohol 94:6, 254 nm): (*S*)-**13** Rt=18.0 min, (*R*)-**13** Rt=20.9 min; ^1H NMR ($CDCl_3$): δ=7.29–7.17 (m, 12H), 6.88–6.84 (m, 2H), 6.56 (d, *J*=15.8 Hz, 1H), 6.30 (dd, *J*=15.8, 7.5 Hz, 1H), 4.37 (d, *J*=7.5 Hz, 1H), 3.79 (s, 3H), 3.75–3.68 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=158.7 (C), 143.0 (C), 137.0 (C), 132.7 (CH), 132.5 (C), 130.3 (CH), 129.4 (2CH), 128.6 (2CH), 128.5 (2CH), 127.5 (CH), 127.4 (2CH), 127.3 (2CH), 126.4 (CH), 113.8 (2CH), 64.5 (CH), 55.3 (CH_3), 50.8 (CH_2); IR (film): ν=3024, 2832, 1610, 1510, 1492, 1245, 1174, 966, 914, 745 cm^{-1}; HR-MS (ESI+): *m/z*=352.1666, calcd. for $C_{23}H_{23}NONa$ $[M+Na]^+$: 352.1677.

(+)-(*S.E*)-*N*-Propargyl-(1,3-diphenyl-2-propenyl)amine (14): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), propargylamine (0.19 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.247 g (99%); yellow oil; $[\alpha]_D^{23}$: +26.6 (*c* 1.15 in $CHCl_3$), 97% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 90:10, 254 nm): (*R*)-**14** Rt=17.0 min, (*S*)-**14** Rt=18.4 min; ^1H NMR ($CDCl_3$): δ=7.43–7.12 (m, 10H), 6.63 (d, *J*=15.9 Hz, 1H), 6.26 (dd, *J*=15.9, 7.7 Hz, 1H), 4.60 (d, *J*=7.7 Hz, 1H), 3.43 (dd, *J*=17.3, 2.6 Hz, 1H), 3.34 (dd, *J*=17.3, 2.6 Hz, 1H), 2.24–2.25 (m, 1H); ^{13}C NMR ($CDCl_3$): δ=142.0 (C), 136.8 (C), 131.6 (CH), 130.8 (CH), 128.6 (2CH), 128.5 (2CH), 127.5 (2CH), 127.4 (2CH), 126.4 (2CH), 82.1 (C), 71.5 (CH), 63.6 (CH), 35.7 (CH_2); IR (film): ν=3290, 3025, 2832, 1491, 1449, 1330, 1110, 968, 913, 749 cm^{-1}; HR-MS (ESI+): *m/z*=270.1259, calcd. for $C_{18}H_{17}NNa$ $[M+Na]^+$: 270.1268.

(+)-(*S,E*)-*N,N*-Diallyl-(1,3-diphenyl-2-propenyl)amine (15): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), diallylamine (0.37 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.287 g (99%); yellow oil; $[\alpha]_D^{23}$: +27.3 (*c* 2.2 in $CHCl_3$), 99% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.4 mL min^{-1} *n*-hexane from 0 to 5 min, 0.2 mL min^{-1} *n*-hexane from 5 to 40 min, 254 nm): (*R*)-**15** Rt = 19.0 min, (*S*)-**15** Rt = 20.0 min; ^1H NMR ($CDCl_3$): δ = 7.39–7.20 (m, 10H), 6.54 (d, *J* = 15.7 Hz, 1H), 6.33 (dd, *J* = 15.7, 9.1 Hz, 1H), 5.92–5.82 (m, 2H), 5.19–5.12 (m, 4H), 4.43 (d, *J* = 9.1 Hz, 1H), 3.23–3.10 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 142.2 (C), 137.0 (C), 136.0 (CH), 132.4 (CH), 129.8 (CH), 128.6 (CH), 128.5 (2CH), 128.3 (2CH), 127.9 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 126.4 (2CH), 117.1 ($2CH_2$), 67.1 (CH), 52.6 ($2CH_2$); IR (film): ν = 3059, 3025, 2920, 2813, 1739, 1641, 1599, 1492, 1448, 1417, 1229, 1028, 968, 917, 743 cm^{-1}; HR-MS (ESI+): *m/z* = 290.1917, calcd. for $C_{21}H_{24}N$ $[M+H]^+$: 290.1909.

(+)-(*S,E*)-*N*-Benzhydryl-(1,3-diphenyl-2-propenyl)amine (16): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), benzhydrlylamine (0.53 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.287 g (94%); colourless oil; $[\alpha]_D^{23}$: +30.6 (*c* 1.2 in $CHCl_3$), 96% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.6 mL min^{-1} *n*-hexane/isopropyl alcohol 98:2, 254 nm): (*S*)-**16** Rt = 8.0, (*R*)-**16** Rt = 9.2 min; ^1H NMR ($CDCl_3$): δ = 7.75–7.05 (m, 20H), 6.49(d, *J*=15.8 Hz, 1H), 6.29 (dd, *J* = 15.8, 7.5 Hz, 1H), 4.87 (s, 1H), 4.28 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 144.0 (C), 143.9 (C), 143.0 (C), 137.0 (C), 132.4 (CH), 130.6 (CH), 128.4 (2CH), 128.6 (2CH), 128.5 (2CH), 128.3 (2CH), 127.6 (2CH), 127.4 (2CH), 127.3 (2CH), 127.0 (2CH), 126.9 (2CH), 126.4 (2CH), 63.5 (CH), 61.9 (CH); IR (film): ν = 3025, 2925, 2850, 1949, 1810, 1598, 1492, 1180, 966, 914, 745 cm^{-1}; HR-MS (ESI+): *m/z* = 376.2056, calcd. for $C_{28}H_{25}N$ $[M+H]^+$: 376.2065.

(+)-(*S,E*)-*N*-(1,3-Diphenyl-2-propenyl)-*N′*-benzoylhydrazine (17)[3]: From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), benzoylhydrazine (0.42 g, 3.0 mmol), BSA (1.48 mL, 6.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.325 g (99%); $[\alpha]_D^{28}$: +36.4 (*c* 0.73 in $CHCl_3$), 94% *ee*. The enantiomeric excess was determined by HPLC on an OJ column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 85:15, 254 nm): (*S*)-**17** Rt = 27.7 min, (*R*)-**17** Rt = 31.4 min; (AD-H column, 0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 85:15, 254 nm): (*R*)-**17** Rt = 32.1, (*S*)-**17** Rt = 36.9 min.

(+)-(*S,E*)-*N*-(1,3-Diphenyl-2-propenyl)phthalimide (18)[4b,20]: From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), potassium phthalimide (0.573 g, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.22 g (65%); $[\alpha]_D^{29}$: +21.5 (*c* 0.87 in $CHCl_3$), 92% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 98:2, 254 nm): (*S*)-**18** Rt = 25.6 min, (*R*)-1**8** Rt = 31.6 min.

General Procedure for the Palladium-Catalyzed Allylic Amination of Substrates S2–S5 in the Presence of 2a

The procedure was analogous to the one described above for **S1** but using **2a** as the catalyst, the corresponding allylic acetate **S2–S5** as starting material and benzylamine as *N*-nucleophile at room temperature (unless stated otherwise, see Table 2).

(+)-(*S,E*)-*N*-Benzyl-[1,3-bis(2-chlorophenyl)-2-propenyl]-amine (19)[4b]: $[\alpha]_D^{23}$: +3.8 (*c* 0.93 in $CHCl_3$), 94% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 99:1, 254 nm): (*R*)-**19** Rt = 13.1 min, (*S*)-**19** Rt = 15.6 min.

(+)-(*R*)-*N*-Benzyl-[1-methyl-3,3-diphenyl-2-propenyl]amine (20)[4b,26]: $[\alpha]_D^{28}$: +89.0 (*c* 1.28 in $CHCl_3$), 89% *ee*. The enantiomeric excess was determined by HPLC on an OJ-H column (0.6 mL min^{-1} *n*-hexane/isopropyl alcohol 90:10, 254 nm): (*S*)-**20** Rt = 12.0 min, (*R*)-**20** Rt = 18.2 min.

(+)-(*R,E*)-*N*-Benzyl-(1-methyl-2-butenyl)amine (21)[3,26]: $[\alpha]_D^{28}$: +16.0 (*c* 1.76 in $CHCl_3$), 63% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.5 mL min^{-1} *n*-hexane, 230 nm): (*R*)-**21** Rt = 30.7 min, (*S*)-**21** Rt = 36.4 min.

(*R*)-*N*-Benzyl-(cyclohex-2-enyl)amine (22)[27,28]: The enantiomeric excess was determined by HPLC on an OB-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 95:5, 230 nm): (*R*)-**22** Rt = 10.7 min, (*S*)-**22** Rt = 12.0 min.

General Procedure for the Palladium-Catalyzed Allylic Amination of Substrates S1–S5 in the Presence of 11e

To an oven-dried, 5-mL conical flask equipped with a septum, containing **11e** (22.5 mg, 0.025 mmol) under argon were successively added the corresponding allylic acetate **S1–S5** (1 mmol), the corresponding N-nucleophile (3 mmol), BSA (0.74 mL, 3 mmol) and KOAc (2.5 mg, 0.025 mmol). The mixture was stirred at room temperature for 24 –72 h (unless stated otherwise, see Table 3 and Table 4) and then concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

General Procedure for the Palladium-Catalyzed Allylic Amination of S1 in the Presence of 9e

S1 (0.05 g, 0.2 mmol), the corresponding N-nucleophile (0.6 mmol) and BSA (0.148 mL, 0.6 mmol) were syringed into an oven-dried, 5-mL conical flask equipped with a septum, containing **9e** (9.5 mg, 0.005 mmol) and KOAc (2.5 mg, 0.025 mmol) under argon. The reaction mixture was smoothly shaken (orbital shaker) at room temperature for the time indicated in Table 3. Then the resin was filtered off and rinsed with anhydrous CH_2Cl_2 (3×3 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

General Procedure for the Palladium-Catalyzed Allylic Amination of S1 in the Presence of 9f

Reactions were performed as described for the allylic amination of **S1** in the presence of **9e**, but in a vial for microwave reactor and without the presence of the KOAc additive, using **9f** (26 mg, 0.014 mmol) as the catalyst and heating the reaction mixture in a microwave reactor at 40°C (setting temperature) for 2–12 h (unless stated otherwise, see Table 3). Isolation of compounds **12–16** was performed as stated before (*vide supra*).

General Procedure for the Palladium-Catalyzed Allylic Amination of Substrates S2–S5 in the Presence of 9f

The procedure was analogous to the one described for allylic amination of **S1** under microwave-assisted conditions but using 5 mol% of **9f** (18.6 mg, 0.01 mmol) and KOAc (2.5 mg, 0.025 mmol) as co-additive (unless stated otherwise, see Table 4). Isolation of compounds **19**–**22** was performed as stated before (*vide supra*).

Recycling Experiments

As a representative example: **S1** (0.062 g, 0.25 mmol), benzylamine (0.107 mL, 0.98 mmol) and BSA (0.24 mL, 0.98 mmol) were added *via* syringe to an oven-dried vial for microwave reactor containing **9f** (51 mg, 0.025 mmol), previously swollen with anhydrous and degassed CH_2Cl_2 (0.11 mL, 1.72 mmol), under argon. The reaction mixture was heated in a microwave reactor in power control mode (1 W) for 35 min. The temperature of the reaction mixture, measured with an internal, teflon-coated Pt-100 probe, was 26–27 °C. Then, the solution was removed under argon *via* cannula and the resin was rinsed with CH_2Cl_2 (3×1 mL) and dried under argon for 10 min. The resin was swollen again with CH_2Cl_2 (0.11 mL, 1.72 mmol), the reactants were added and the mixture was reacted as indicated before. The same resin was used for each cycle and no further Pd source was added. Isolation of compound **12** was performed as stated before (*vide supra*).

Continuous Flow System Description and Details of the Reaction Procedure

The continuous flow system (see Figure 4) was set up around a vertically mounted 1/4 inch teflon tube, which was loaded with resin **9f** (240 mg). Teflon connectors allowed us to connect it through 1/16 inch teflon tubes to an Ismatec piston pump (reagents input) and to a collector vessel. A schematic drawing of all the pieces and connections appears in the Supporting Information. A solution of **S1** (9.63 mmol, 2.43 g), BSA (38.52 mmol, 9.56 mL), and benzylamine (48.15 mmol, 5.27 mL) in dry CH_2Cl_2 (67.42 mmol, 4.32 mL) was prepared in a flask under argon. Dry CH_2Cl_2 was kept in an independent bottle with a connector cap with valves for an easy and inert connection to the tubing. The resin was swollen by pumping CH_2Cl_2 at a 0.12 mL min^{-1} flow during 30 min. Care was taken that all the resin beads packed in the tube were inside the microwave cavity (see Figure 5). Then, the microwave apparatus was connected (1 W, open-vessel) and the solution of the reagents was pumped through the system at a 0.12 mL min^{-1} flow for 3 h. The effluent reaction mixture was collected through the upper end of the reactor, taking aliquots every 15 min to measure ^{1}H NMR spectra and to determine the *ee* of the amination product by HPLC. Temperature of the effluent (22–23 °C) was monitored with a Pt-100 probe, and turned out to be identical (±1 °C) to that of the reagents mixture. When all the reacting solution had been pumped, CH_2Cl_2 was passed for an additional 30 min period in order to wash the resin and the mechanical parts of the reactor. The collected output flow was concentrated, diluted with Et_2O (5 mL), washed with water (3×20 mL), dried ($MgSO_4$) and concentrated under vacuum. Flash chromatography of the reaction crude (hexanes/EtOAc from 100: 0 to 90:10) afforded **12** in 68% yield and 83% *ee*.

Acknowledgements

We thank MICINN (Grant Nos. CTQ2005–02193/BQU, CTQ2008–00947/BQU, CTQ2008–00950/BQU), DURSI (Grant No. 2005GR225), Consolider Ingenio 2010 (CSD2006–0003) and ICIQ and Ramón Areces Foundations for financial support. R. M. is grateful to the Spanish Ministerio de Ciencia e Innovación for a predoctoral fellowship. We also thank Dr. G. González and Dr. K. Gómez (ICIQ support unit) for their help with HRMAS ^{13}C NMR measurements and Dr. C. Rodríguez-Escrich for his assistance in the design and performance of the continuous flow system.

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[23] Visual inspection of the system when a dichloromethane solution of highly fluorescent *coumarin 6* [3-(2-benzothiazolyl)-7-(diethylamino)coumarin; CAS number 38215–36–0] is circulated through the tubular reaction in the dark under ultraviolet irradiation (λ = 365 nm) shows a flat and uniform liquid front.

[24] Residence time of the reaction mixture in the resin-filled reactor was estimated by circulating a dichloromethane solution of *coumarin 6* through the column loaded with previously swollen resin **9f** in the dark under ultraviolet irradiation ($\lambda = 365$ nm), and measuring the times when fluorescence is first observed in the section of the reactor occupied by the resin and when fluorescence first appears after this section of the reactor.

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Supporting Information

Towards Continuous Flow, Highly Enantioselective Allylic Amination: Ligand Design, Optimization and Supporting

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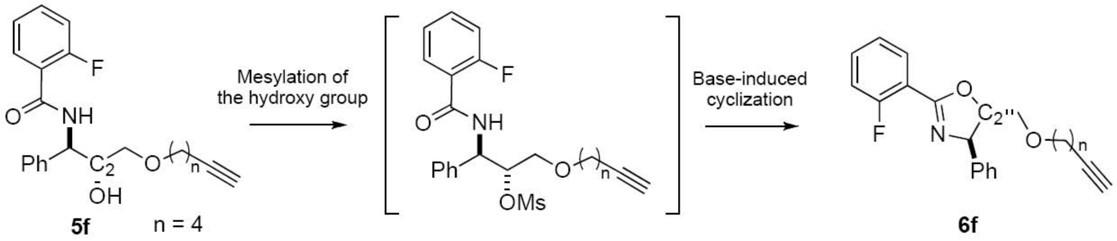
Table of Contents

1.- Relative stereochemistry of the oxazoline substituents in 6f

This formation of the oxazoline ring involves the activation of the free hydroxy group in **5f** as the mesylate (MsCl, NEt_3 as auxiliary base) followed by base-induced cyclization (5% KOH/MeOH).[1] The *trans* stereochemistry in the oxazoline ring arises from the fact that the cyclization step takes place with inversion of configuration at C-2.



Scheme i

The relative *trans* stereochemistry of the chiral centres in the oxazoline ring could be confirmed by means of a 1D-GOESY experiment on **6f**, where a NOE between the C*H*-N and the CH_2O(CH_2)$_2$CCH units could be observed (See Figure i).

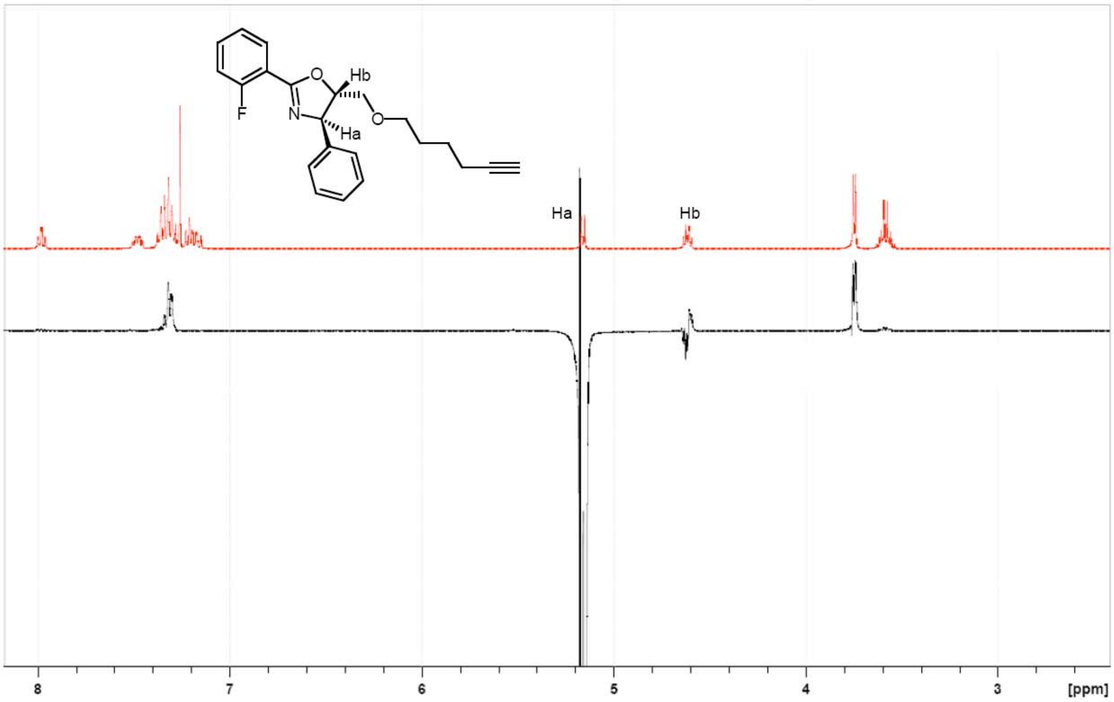


Figure i. ^{1}H NMR (red) and 1D-GOESY (black) spectra of oxazoline **6f**

2.- Experimental details.

General Remarks. All compounds were prepared under argon atmosphere using standard vacuum-line and Schlenk techniques. Tetrahydrofuran, dichloromethane, toluene, dimethylformamide and hexane were dried and deoxygenated by using a Solvent Purification System (SPS) and ethanol was deoxygenated with two freeze-thaw cycles.

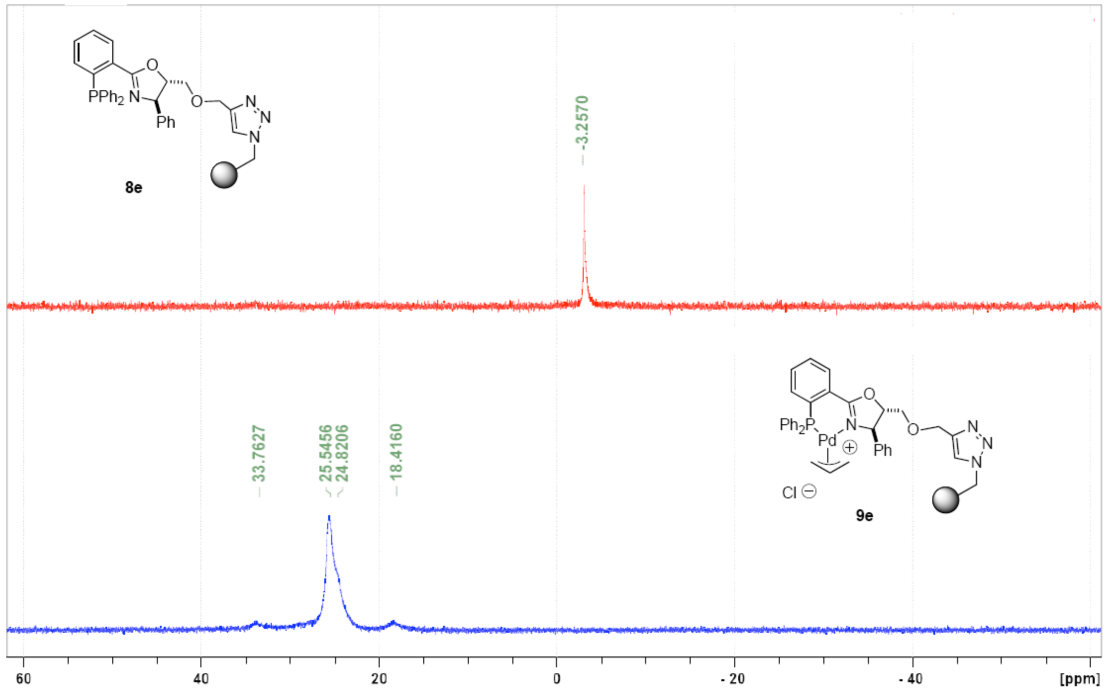
All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Phosphinooxazolines derived from **10e-f** were filtered through a short SiO_2 pad, which was previously deoxygenated with Argon, immediately before being converted into the Palladium complexes **11e-f**.

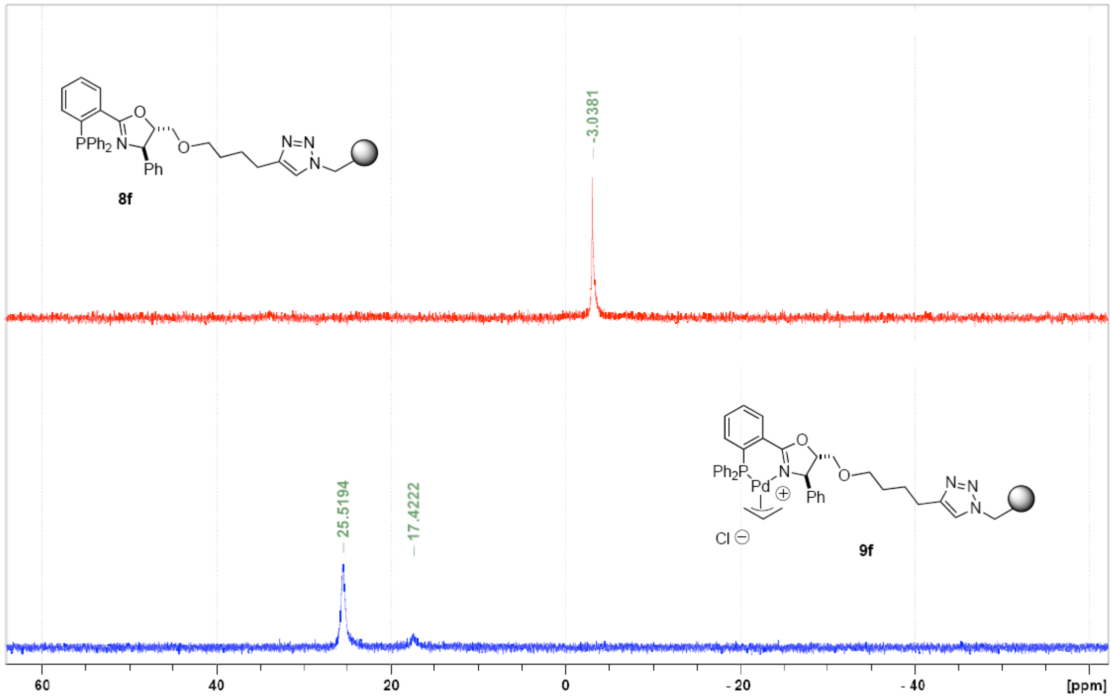
The experiments under microwave irradiation were carried out in a CEM discover microwave reactor (the temperature is automatically controlled by a non-contact infrared sensor that monitors and controls the temperature conditions of the reaction vessel).

NMR spectra were recorded on Bruker Avance 400 and 500 Ultrashield spectrometers in $CDCl_3$ at room temperature unless otherwise cited operating at 400.13 MHz (^1H), 100.63 MHz ($^{13}C\{1H\}$), 161.98 MHz ($^{31}P\{1H\}$). and 282 MHz ($^{19}F\{1H\}$). ^1H NMR chemical shifts are quoted in ppm relative to internal TMS and ^{13}C NMR spectra to $CDCl_3$ whereas ^{31}P NMR chemical shifts are quoted in ppm relative to 85% phosphoric acid in water and ^{19}F NMR relative to $CFCl_3$. ^1H and ^{13}C NMR experiments of resins **7-9e,f** were performed with a Bruker Avance spectrometer operating at a frequency of 500.13 MHz using a Bruker 4 mm $^1H/^{13}C/^2H$ gradient HR-MAS probe. IR spectra were recorded on a Bruker Tensor 27 spectrometer in Fourier transform mode. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. Enantiomeric excesses were determined by HPLC on Agilent 1100 Series chromatograph with a UV detector. Elemental analyses (C; H; N; Cl) were performed by Servei de Microanalisi, Consell Superior d'Investigacions Cientifiques, Barcelona, Spain.

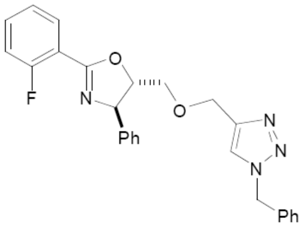
$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was purchased from Alpha Aesar and $KPPh_2$ from Aldrich and were used without any further purification. Merrifield resin (1% DVB, f = 0.81 mmol Cl g^{-1} resin) was obtained from Novabiochem. The racemic acetates **S1-S5** were prepared following known procedures.[2]

^{31}P NMR spectra of resins 8e-f and 9e-f

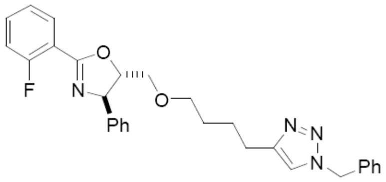




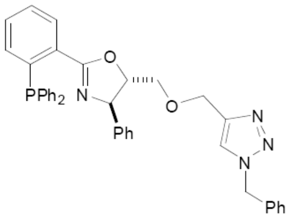
(4*R*,5*S*)-5-[(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)methyl]-2-(2-fluorophenyl)-4-phenyl-4,5-dihydrooxazole 10e. Following the general method from compound **6e** (0.25 g, 0.81 mmol), benzyl bromide (0.1 mL, 0.81 mmol), sodium azide (0.11 g, 1.73 mmol), $Cu_2SO_4{\cdot}5H_2O$ (4 mg, 0.016 mmol) and sodium L-ascorbate (34 mg, 0.0172 mmol). Yield: 80%. Pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 7.95 (ddd, J = 7.5, 2.0 Hz, 1H), 7.53-7.13 (m, 14H), 5.51 (s, 2H), 5.11 (d, J = 7.3 Hz, 1H), 4.75 (m, 2H), 4.60 (ddd, J = 7.3, 3.5 Hz, 1H), 3.85 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 161.4 (d, $J_{C,F}$ = 258.5 Hz, CF), 160.8 (d, $J_{C,F}$ = 5.4 Hz, C=N), 148.5 (C), 141.9 (C), 135.0 (CH), 133.0 (d, $J_{C,F}$ = 8.4 Hz, CH), 131.3 (C), 129.0 (CH), 128.7 (CH), 128.6 (2CH), 128.3 (CH), 127.9 (2CH), 127.6 (CH), 126.7 (2CH), 123.9 (d, $J_{C,F}$ = 3.8 Hz, CH), 120.6 (CH), 116.6 (d, $J_{C,F}$ = 21.0 Hz, CH), 115.8 (d, $J_{C,F}$ = 10.2 Hz, C), 85.4 (CH), 72.54 (CH), 71.2 (CH_2), 65.1 (CH_2), 54.2 (CH_2).



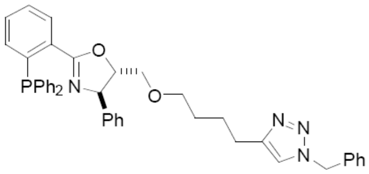
(4*R*,5*S*)-5-[(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)butoxy)methyl]-2-(2-fluorophenyl)-4-phenyl-4,5-dihydrooxazole 10f. Following the general method from compound **6f** (0.15 g, 0.42 mmol), benzyl bromide (0.06 mL, 0.51 mmol), sodium azide (66 mg, 1.04 mmol), $Cu_2SO_4{\cdot}5H_2O$ (2 mg, 0.085 mmol) and sodium L-ascorbate (17 mg, 0.089 mmol) in *tert*-butanol and water 1:1 (1 mL). Yield: 81%. Pale yellow oil. $[\alpha]_D^{23}$ = + 27.3 (c = 1.12 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.97 (ddd, J = 7.5, 1.9, 1.9 Hz, 1H), 7.49-7.12 (m, 14H), 5.47 (s, 2H), 5.16 (d, J = 7.6 Hz, 1H), 4.60 (ddd, J = 7.4, 5.0, 5.0 Hz, 1H), 3.75-3.71(m, 2H), 3.62-3.53 (m, 2H), 2. 72 (t, J = 7.7 Hz, 2H), 1.78-1.70 (m, 2H), 1.69-1.62 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ = 161.5 (d, $J_{C,F}$ = 260.0 Hz, CF), 160.9 (d, $J_{C,F}$ = 5.4 Hz, C=N), 148.5 (C), 141.9 (C), 135.0 (CH), 133.0 (d, $J_{C,F}$ = 8.9 Hz, CH), 131.3 (C), 129.0 (CH), 128.7 (CH), 128.6 (2CH), 128.3 (CH), 127.9 (2CH), 127.6 (CH), 126.7 (2CH), 123.9 (d, $J_{C,F}$ = 4.0 Hz, CH), 120.6 (CH), 116.7 (d, $J_{C,F}$ = 22.0 Hz, CH), 116.0 (d, $J_{C,F}$ = 11.0 Hz, C), 85.7 (CH), 72.4 (CH), 71.6 (CH_2), 71.5 (CH_2), 53.9 (CH_2), 29.1 (CH_2), 25.9 (CH_2), 25.4 (CH_2); IR (film): ν = 2939, 2861, 1733, 1495, 1456, 1127, 700 cm^{-1}; HRMS (ESI+): *m/z* calcd. for $C_{29}H_{30}FN_4O_2$ $[M+H]^+$: 485.2353, found: 485.2343.



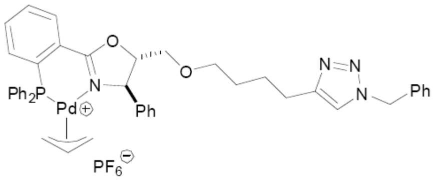
(4*R*,5*S*)-5-[(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)methyl]-2-(2-diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole. Yield: 91%. Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 8.05-7.92 (m, 1H), 7.54-7.13 (m, 22H), 6.91-6.85 (m, 2H), 5.49 (s, 2H), 4.91 (d, J = 8.1 Hz, 1H), 4.69 (dd, J = 12.5 Hz, 2H), 4.34 (ddd, J = 8.0, 5.0, 5.0 Hz, 1H), 3.62 (m, 2H); ^{31}P NMR ($CDCl_3$): δ = – 2.86 (s, PPh_2).



(4*R*,5*S*)-5-[(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)butoxy)methyl]-2-(2-diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole. Yield: 92%. Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 7.93-7.90 (m, 1H), 7.30-7.08 (m, 22H), 6.85-6.82 (m, 2H), 5.38 (s, 2H), 4.87 (d, J = 8.0 Hz, 1H), 4.26 (ddd, J = 8.0, 5.0, 5.0 Hz, 1H), 3.47-3.33 (m, 4H), 2.63 (t, J = 8.0 Hz, 2H), 1.68-1.60 (m, 2H), 1.57-1.50 (m, 2H); ^{31}P NMR ($CDCl_3$): δ = – 3.0 (s, PPh_2).

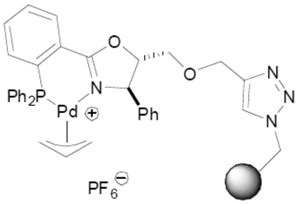


(η^3-allyl)-{(4*R*,5*S*)-5-[(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)butoxy)methyl]-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole} palladium (II) hexafluorophosphate 11f. Yield: 79%. Orange solid. $[\alpha]_D^{23}$= – 30.3 (c = 1.10 in $CHCl_3$); ^{1}H NMR (CD_3CN): δ = 8.28-8.25 (m, 2H), 7.74-7.08 (m, 42H), 6.87 (d, J = 7.5 Hz, 4H), 5.45 (s, 4H), 5.30 (d, J = 7.0 Hz, 2H), 4.68-4-71 (m, 2H), 3.82 (dd, J = 11.5, 3.5 Hz, 2H), 3.70 (dd, J = 11.5, 3.5 Hz, 2H), 3.53 (bt, 4H), 2.62 (bt, 4H), 1.67-1.60 (m, 4H), 1.57-1.50 (m, 4H); the allylic protons could not be assigned due to *endo*-*exo* isomerization.^{13}C NMR (CD_3CN): δ = 165.1 (C=N), 139.5 (C), 134.8 (CH), 133.9 (CH), 133.8 (CH), 133.5 (CH), 133.4 (CH), 132.7 (CH), 132.6 (CH), 132.2 (CH), 131.9 (CH), 129.8 (CH), 129.7 (CH), 129.5 (CH), 129.4 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.0 (CH), 87.2 (CH), 76.5 (CH), 71.0 (CH_2), 69.9 (CH_2), 54.0 (CH_2), 28.7 (CH_2), 25.7 (CH_2), 25.2 (CH_2), the allylic carbons could not be assigned due to *endo*-*exo* equilibrium isomerization; ^{31}P NMR ($CDCl_3$): δ = 24.9 (s, PPh_2, *exo*), 24.5 (s, PPh_2, *endo*), – 141.05 (h, J = 712.5 Hz, PF_6); HRMS (ESI+): m/z calcd. for $C_{44}H_{44}N_4O_2PPd$ $[M–PF_6]^+$: 797.2237, found: 797.2233.

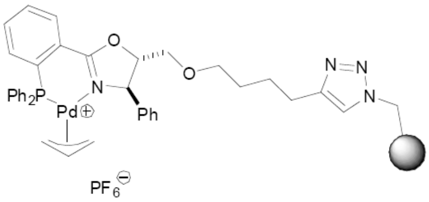


Synthesis of polymer-supported [(Pd(η^3-C_3H_5)(L)]PF_6 complexes from resins 9e-f: NH_4PF_6 (0.35 mmol) was added to a suspension of resin **9** (0.34 mmol) in deoxygenated ethanol (5 mL) placed in a schlenk flask under argon. The mixture was shaken for 14 h at room temperature. Then the resin was filtered off, washed with ethanol (10 mL) and THF (200 mL) and dried *in vacuo* for 12 h.

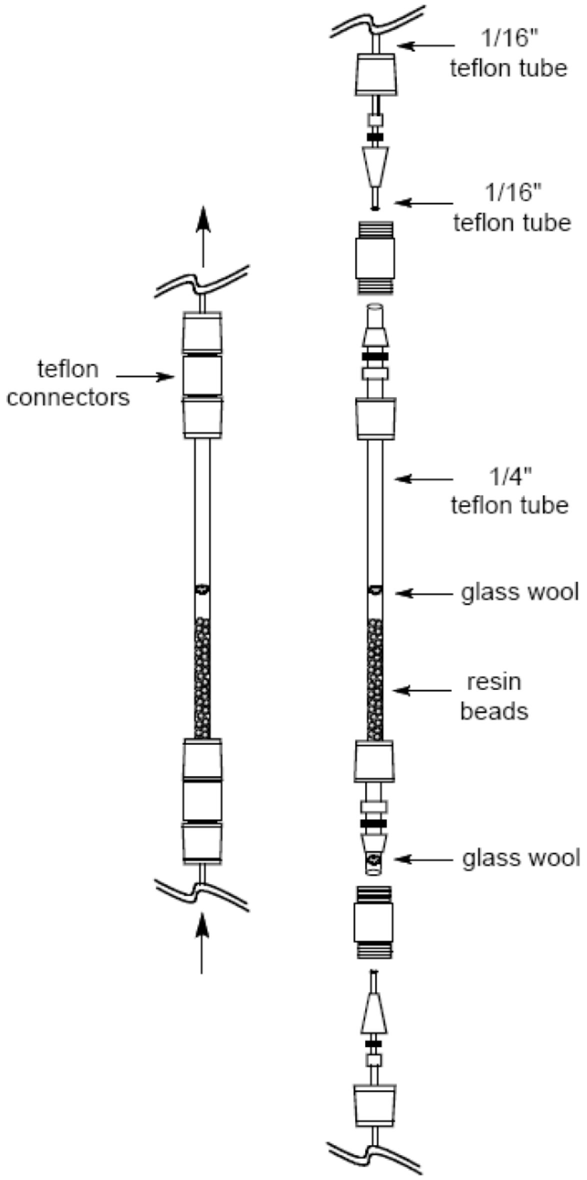
Polymer-supported (η^3-allyl)-{(4*R*,5*S*)-5-[(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)methyl]-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole} palladium (II) hexafluorophosphate. Following the general method from compound **9e** (0.5 g, 0.265 mmol) and NH_4PF_6 (43.7 mg, 0.27 mmol). Total conversion. *f* = 0.53 mmol g^{-1}. ^{31}P NMR ($CDCl_3$): δ = 24.7 (s, PPh_2), -141.01 (h, *J* = 714.7 Hz); IR (ATR): ν = 3024, 2918, 1619, 1600, 1492, 1451, 1352, 1060, 1118, 836, 749, 696 cm^{-1}.



Polymer-supported (η^3-allyl)-{(4*R*,5*S*)-5-[(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)butoxy)methyl]-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole} palladium (II) hexafluorophosphate. Following the general method from compound **9f** (0.5 g, 0.34 mmol) and NH_4PF_6 (56.6 mg, 0.35 mmol). Total conversion. *f* = 0.68 mmol g^{-1}. ^{31}P NMR ($CDCl_3$): δ = 25.5 (s, PPh_2), -141.01 (h, *J* = 714.7 Hz); IR (ATR): ν = 3024, 2919, 1620, 1600, 1491, 1451, 1307, 1060, 1118, 749, 696 cm^{-1}.



3.- Diagram of the reactor for the continuous flow system



4.- References

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[2] a) J. V. Allen, S. J. Coote, G. J. Dawson, C. G. Frost, C. J. Martins, J. M. J. Williams *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2065-2072; b) Y. D. Ward, L. A. Villanueva, G. D. Allred, S. C. Payne, M. A. Semones, L. S. Liebeskind, *Organometallics* **1995**, *14*, 4132-4156; c) G. J. Dawson, J. M. J. Williams, S. J. Coote, *Tetrahedron: Asymmetry* **1995**, *6*, 2535-2546; e) J. Singh; I. Kaur, J. Kaur, A. Bhalla, G.L. Kad, *Synth. Commun.* **2003**, *33*, 191-197; f) N. Kinoshita, T. Kawabata, K. Tsubaki, M. Bando, K. Fuji, *Tetrahedron* **2006**, *62*, 1756-1763.

3.3 PAPER B

HOMOGENEOUS AND POLYMER-SUPPORTED PHOSPHINOIMIDAZOLINE LIGANDS FOR ASYMMETRIC CATALYSIS. ALTERATION OF THE PALLADIUM COORDINATION MODE TRIGGERED BY A REMOTE TRIAZOLE SUBSTITUENT

Manuscript in preparation

The syntheses and characterization of most of the homogeneous ligands reported in this work and their application in catalysis were carried out by Veronica de la Fuente as part of her PhD in the groups of Dr. Claver and Dr. Castillón.

Homogeneous and Polymer-Supported Phosphino-imidazoline Ligands for Asymmetric Catalysis. Alteration of the Palladium Co-ordination Mode Triggered by a Remote Triazole Substituent

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KEYWORDS. Imidazolines. P,N ligands. Palladium. Amination. Catalysis. Immobilization. Recycling.

BRIEFS. Triazole-containing phosphinoimidazoline (PHIM) ligands exhibit excellent levels of catalytic activity and enantioselectivity in Palladium-catalyzed allylic substitutions.

ABSTRACT. A library of enantiopure phosphino-imidazoline (PHIM) ligands has been synthesized using C_2-symmetric diamines as the chirality source. A systematic modification of the three structural elements allowing the introduction of diversity in the ligands (i.e. the diamino moiety, the substituent of the sp^3 nitrogen of the imidazoline ring and the phosphino unit) has been carried out and the performance of the resulting ligands has been tested in the palladium-catalyzed allylic alkylation and amination. The presence of a triazolylmethyl substituent at the sp^3 nitrogen atom of the imidazoline ring leads to highly improved catalytic activity and enantioselectivity (up to 99% ee) with respect to analogous ligands with substituents lacking the triazolylmethyl unit. The performance of the triazolyl-containing PHIM ligands is preserved in its immobilized version, where the Cu-catalyzed alkyne-azide cycloaddition (CuAAC) has been used to support the ligands on azidomethylpolystyrene. NMR studies and theoretical calculations support a shift in the coordination mode of the PHIM ligand to palladium, triggered by an interaction with the triazole unit that makes unfavourable the normal P,(sp^2)N coordination.

Introduction.

The stereoselective formation of C-C and C-N bonds on allylic systems through substitution processes has attracted the interest of synthetic chemists over the last two decades. Namely, metal-mediated processes taking place through achiral π-allyl systems represent the most practical entry to enantiopure allylic derivatives, which can be subsequently submitted to a variety of stereoselective processes with important increases of molecular complexity. In this context, the palladium-catalyzed asymmetric allylic substitution reaction stands as the most reliable and versatile procedure.[1]

Different C_2- and C_1-symmetric chiral ligands have been tested in this reaction. While high enantioselectivities can be achieved with both ligand types, the higher catalytic efficiency depicted by P,N-ligands has importantly contributed to a progressive shift towards C_1-symmetric ones. In this case, the key for inducing enantioselectivity in the substitution event is the electronic discrimination between the two terminal allylic carbons in the η^3-allylpalladium intermediates containing a "soft" phosphorus donor group associated with π-acceptor properties and a "hard" nitrogen σ-donor group.[1]

In particular, phosphino-oxazolines (PHOX)[2] and phosphite-oxazolines[3] have afforded excellent results in the enantiocontrol of asymmetric allylic substitution reactions, showing that the process is sensitive to modification of: a) the electronic characteristics of the aryl groups in the diarylphosphino moiety, b) the environment of the stereogenic center adjacent to the nitrogen in the oxazoline moiety (C-4), c) the linker which separates the two coordinating heteroatoms,[4] and d) the substituents at C-5 of the oxazoline moiety[5] (Figure 1, top).

Phosphino-imidazoline (PHIM) ligands (Figure 1, bottom) could represent a convenient alternative to the well-established PHOX ones. Thus, the topology of the imidazoline ligand allows for the introduction of *local* C_2-symmetry, while the second nitrogen atom represents an additional source of molecular diversity (R^2), allowing the programmed modification of the electronic properties of the coordinating nitrogen atom. The additional nitrogen atom could also serve for the heterogenization of the phosphino-imidazoline ligand onto insoluble organic resins, a field which still remains completely unexplored. PHIM ligands have shown to be very efficient in the Ir-catalyzed enantioselective hydrogenation of prochiral olefins[6] and imines,[7] as well as in the Pd-catalyzed asymmetric Heck reaction.[8] However, and as far as we know, they have never been used in the Pd-catalyzed asymmetric allylic substitution reaction.

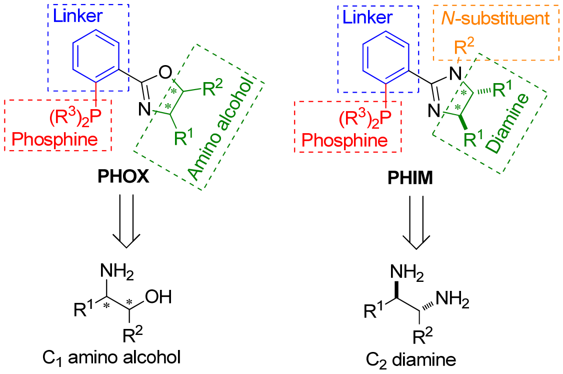


Figure 1. Phosphino-oxazoline (PHOX) and phosphino-imidazoline ligands (PHIM).

The preparation and use of solid-supported catalytic systems able to induce enantioselective transformations is an area of increasing relevance in chemistry due to the improved sustainability characteristics of this type of processes. Thus, the suppression of complex work-up operations for catalyst separation and the removal of metal-containing byproducts from reaction mixtures lead to cleaner alternatives for the production of metal-free, enantioenriched compounds. As an additional bonus, the recovery and reuse of the catalytic system becomes possible.[9]

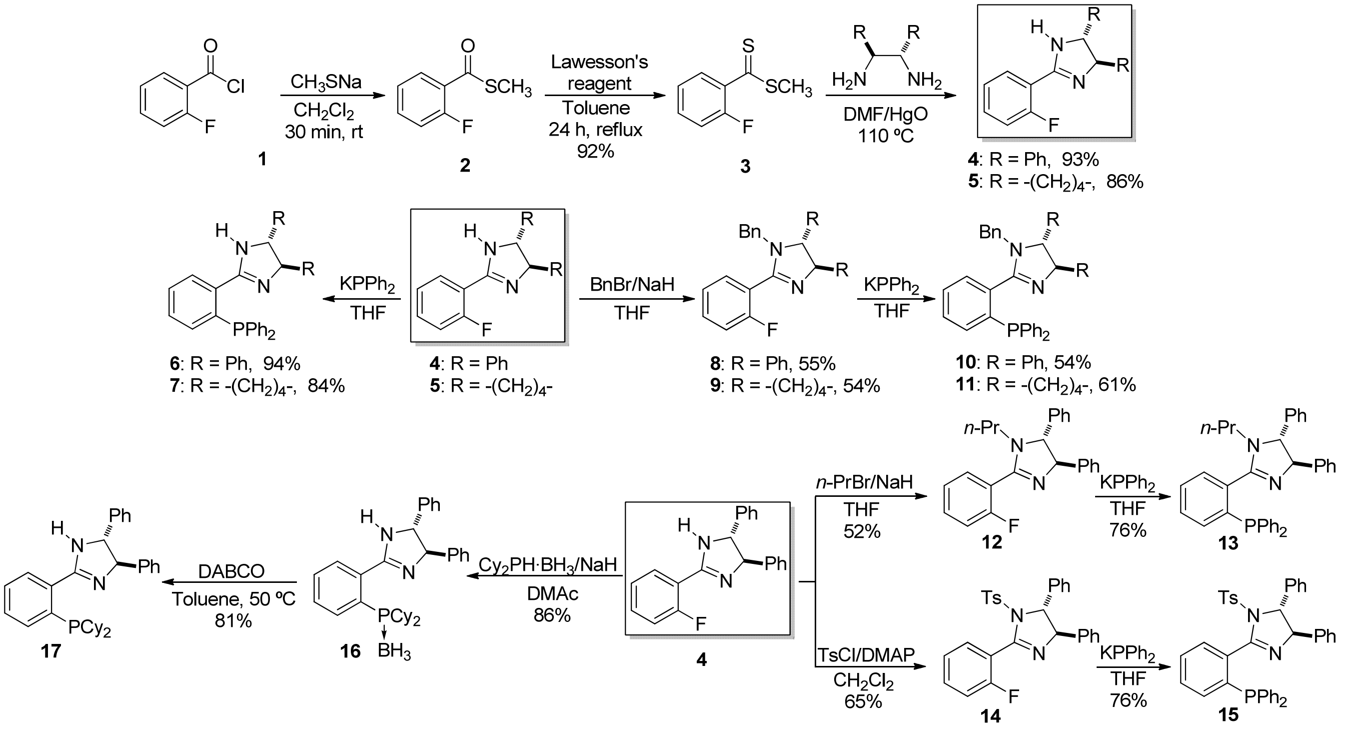
In recent years, we have been involved in the design and synthesis of ligands that could be immobilized onto inorganic or polymeric supports without perturbation of the molecular regions where the catalytic activity resides.[10] In a parallel effort, we have thoroughly investigated a new strategy for supporting catalysts onto Merrifield-type resins through the copper(I)-catalyzed alkyne-azide cycloaddition reaction (CuAAC)[11] and have shown that the resulting resins behave as highly active, enantioselective and diastereoselective, yet reusable, catalysts.[10f,12] In a recent development, this strategy has been applied with success to the immobilization of π-allylpalladium complexes of phosphinooxazolines for asymmetric allylic aminations under batch and continuous flow conditions.[13]

We wish to report in the present paper the structural optimization of modular PHIM ligands for the Pd-catalyzed asymmetric allylic substitution reaction. A first generation of PHIM ligands results from the optimization of the substituents at C-4 and C-5 on the imidazoline moiety (R^1), the substituent at the non-coordinating nitrogen atom of the imidazoline ring (R^2), and the substituents of the phosphine moiety (R^3). A second generation of PHIM ligands, resulting from the introduction of triazolylmethyl moieties as nitrogen substituents in the imidazoline ring, has led to new catalytic systems which provide highly improved enantioselectivities for a variety of substrates and nucleophiles. In a later stage, the triazolyl units have been used to support the optimized ligands onto slightly cross-linked poly(styrene) through CuAAC reactions.

Results and Discussion.

Synthesis of first generation phosphino-imidazoline ligands. Phosphinoimidazolines could be easily prepared from the known dithioester **3** in two steps[12] (Scheme 1). First, the imidazoline ring was constructed by condensation of **3** with the selected enantiopure C_2 diamine in the presence of HgO as a desulfurizing agent.[14] The thus obtained fluoroimidazolines **4** and **5** are key intermediates allowing access to structurally diverse PHIM ligands, through sequences involving *N*-alkylation and/or S_NAr introduction of R_2P- groups. In this manner **4** and **5** were reacted with Ph_2PK in THF at room temperature, under racemization-free reaction conditions,[15] to afford the phosphino-imidazoline ligands **6** and **7** in 93 and 86% yield, respectively. Different substituents could be readily introduced in the free imidazolic N-H nitrogen by treatment with the appropriate electrophile/base combination. Thus, *N*-alkylated ligands **10**, **11** and **13** were prepared by phosphinylation of the *N*-alkyl fluoroimidazolines **8**, **9** and **12**, obtained by treatment of **4** or **5** with sodium hydride and the corresponding alkyl bromide. In the same manner, treatment of **4** with tosyl chloride in the presence of a base (DMAP) afforded *N*-tosyl fluoroimidazoline **14**, which could be readily converted to *N*-tosyl PHIM ligand **15**.[16]

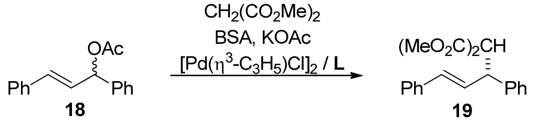
In order to explore also the possibility of modifying the phosphine substituents, ligand **17** was prepared by reaction of **4** with the combination of dicyclohexylphosphine borane complex and sodium hydride,[16] followed by subsequent deprotection with DABCO of the resulting PHIM-borane complex **16**.[17]



Scheme 1. Synthesis of first generation PHIM ligands.

Pd-Catalyzed asymmetric allylic alkylation reactions with first-generation PHIM ligands. The alkylation of (*E*)-1,3-diphenylallyl acetate (**21**) with dimethyl malonate in the presence of Pd/**9** was studied as a model reaction,[18,19] and the reaction conditions optimized. Results are collected in Table 1. The reaction was first studied in dichloromethane at room temperature in the presence of KOAc and BSA. Complete conversion was observed after 24h, although enantioselectivity was low (entry 1). Very interestingly, enantioselectivity increased up to 81% when the reaction was performed in dichloromethane under reflux (entry 2). A similar effect of temperature on enantioselectivity has been previously observed by Helmchen *et al.* in the iridium catalyzed allylic alkylation.[20] When the reaction was performed under microwave irradiation at 65 ºC (entry 3), conversion was complete in 3 h while enantioselectivity was slightly improved. The use of toluene or THF as solvents under similar conditions did not lead to any significant improvement in the reaction outcome.

Table 1. Pd-Catalyzed allylic alkylation of 18 with first generation PHIM ligands.[a]



Entry	Ligand	T	t (h)	Conv. (%)[b]	ee (%)[c]
1	**6**	rt	12	99	44
2	**6**	Reflux	24	100	81
3	**6**	65 ºC (MW)	3	100	83
4	**7**	65 ºC (MW)	3	91	53
5	**10**	65 ºC (MW)	3	71	85
6	**11**	65 ºC (MW)	3	88	87
7	**13**	65 ºC (MW)	3	99	81
8	**15**	65 ºC (MW)	3	100	73
9	**17**	65 ºC (MW)	3	74	78

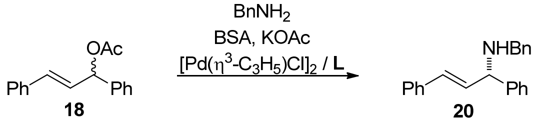
[a]Reaction conditions: 0.02 mmol $[Pd(h^3\text{-}C_3H_5)Cl]_2$; 0.044 mmol ligand; 1 mmol substrate; 3 mmol dimethyl malonate; 3 mmol BSA, 0.02 mmol KOAc in 2 ml CH_2Cl_2. 65ºC, MW irradiation. [b]Conversion determined by NMR. [c]Ee determined by HPLC on a chiral stationary phase.

Pd-Catalyzed asymmetric allylic alkylation reactions with first-generation PHIM ligands. The alkylation of (*E*)-1,3-diphenylallyl acetate (**21**) with dimethyl malonate in the presence of Pd/**9** was studied as a model reaction,[50-52] and the reaction conditions optimized. Results are collected in Table 1. The reaction was first studied in dichloromethane at room temperature in the presence of KOAc and BSA. Complete conversion was observed after 24h, although enantioselectivity was low (entry 1). Very interestingly, enantioselectivity increased up to 81% when the reaction was performed in dichloromethane under reflux (entry 2). A similar effect of temperature on enantioselectivity has been previously observed by Helmchen et al. in the iridium catalyzed allylic alkylation.[53] When the reaction was performed under microwave irradiation at 65 ºC (entry 3), conversion was complete in 3 h while enantioselectivity was slightly improved. The use of toluene or tetrahydrofuran as solvents under similar conditions did not lead to any significant improvement in the reaction outcome.

Thus, the performance of the different ligands was evaluated under the same reaction conditions of entry 3. As shown in Table 1 (entries 3-9), all the ligands tested resulted in good conversion in a reasonable reaction time. In terms of enantioselectivity, *N*-benzylated ligands **10** and **11** (entries 5 and 6), offered the best results (85 and 87% ee, respectively), with little influence of the diphenylethylene or cyclohexane diamine backbones being used. On the other hand, comparison of ligands **6** and **17** (entries 3 and 9) shows the phenyl-substituted phosphine is better than the cyclohexyl-substituted one (83 and 78% ee, respectively).

Pd-Catalyzed allylic amination reactions with first-generation PHIM ligands. Encouraged by the results obtained in allylic alkylation, we decided to further explore the behaviour of PHIM ligands in a different type of allylic substitutions, such as allylic amination. For this purpose, we studied the reaction of **18** with benzylamine as the nucleophile, in the presence of BSA and KOAc in dichloromethane under reflux.[21,22,23,24a-c,25] Table 2 summarizes the results of this evaluation. Gratifyingly enough, in all the cases the reaction proceeded to completion in 24 h, with excellent enantioselectivity in the case of ligand **6**.

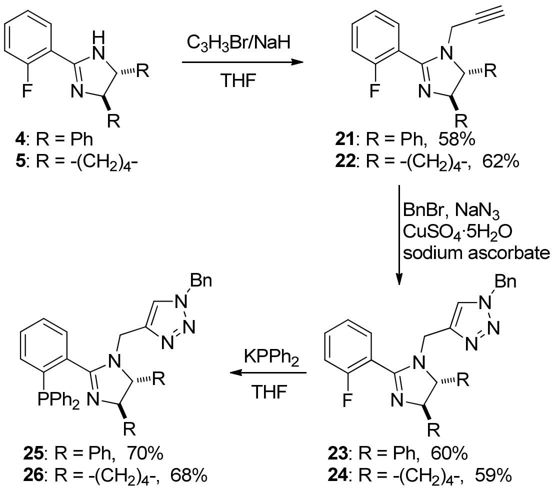
Table 2. Amination of allyl acetate 18 with benzylamine, using Pd/PHIM catalysts.[a]



Entry	Ligand	Conv. (%)[b]	ee (%)[c]
1	**6**	>99	92
2	**7**	>99	74
3	**10**	95	79
4	**11**	>99	82

[a]Reaction conditions: 0.02 mmol $[Pd(h^3\text{-}C_3H_5)Cl]_2$; 0.044 mmol ligand, 1 mmol substrate; 3 mmol benzylamine; 3 mmol BSA in 2 ml CH_2Cl_2 under reflux for 24 h. [b]Conversion determined by NMR. [c]Ee determined by HPLC on a chiral stationary phase.

Synthesis of second generation phosphino-imidazoline ligands. Having in mind the ultimate goal of supporting the PHIM ligands onto polymer supports for easy recovery and recycling, we decided to study the catalytic behavior of PHIM derivatives bearing triazolylmethyl substituents on the imidazoline moiety. They would be prepared through CuAAC reactions[26] from the corresponding *N*-propargyl derivatives and, after structural optimization, they could guide the synthesis of the polymer-supported analogues through the same constructive methodology. For comparative purposes, ligands **25** and **26** were initially prepared (Scheme 2). Since the phosphorus moiety should be preferably introduced in the last step of the sequence, the key intermediates in our strategy were the propargyl derivatives **21** and **22**. Thus, compounds **4** and **5** were treated with propargyl bromide to afford *N*-propargyl derivatives **21** and **22**, which then were reacted with benzyl bromide in the presence of sodium azide, L-ascorbic acid and catalytic amounts of $CuSO_4$ to afford triazoles **23** and **24** in good yields. Finally, the phosphine moiety was efficiently introduced by nucleophilic displacement of fluoride with $KPPh_2$ to afford the target phosphino-imidazoline ligands **25** and **26** in high yields.

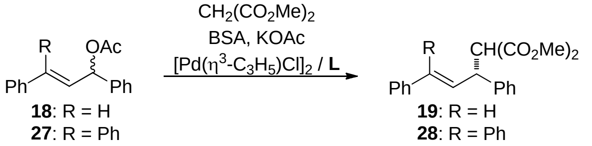


Scheme 2. Synthesis of second-generation PHIM ligands **25** and **26**.

Pd-Catalyzed allylic alkylation reactions with second generation PHIM ligands. The performance of ligands **25** and **26** was first examined in the alkylation of substrates **21** and **26** with dimethyl malonate under the previously optimized reaction conditions (see above).

The results (Table 3) showed the diphenylethylenediamine-derived ligand **25** to be clearly superior to the cyclohexanediamine-derived one **26**, both in terms of catalytic activity and enantioselectivity. In addition, and quite notably, this *N*-triazolylmethyl PHIM ligands turned out to induce higher enantioselectivity than its *N*-alkyl or unsubstituted counterparts (see above, Table 1).

Table 3. Pd-Catalyzed allylic alkylation of **18** and **27** with second generation PHIM ligands **25** and **26**.[a]



Entry	Substrate	Ligand	Conv. (%)[b]	ee (%)[c]
1	**18**	**25**	94	96
2	**18**	**26**	85	86
3	**27**	**25**	63	99
4	**27**	**26**	32	75

[a]Reaction conditions: 0.02 mmol $[Pd(h^3-C_3H_5)Cl]_2$; 0.044 mmol ligand; 1 mmol substrate; 3 mmol benzylamine; 3 mmol BSA; 0.04 mmol KOAc in 2 ml CH_2Cl_2 at 65ºC under MW irradiation. [b]Conversion determined by ^1H NMR on the crude mixture. [c]Ee determined by HPLC on a chiral stationary phase.

Pd-Catalyzed allylic amination reactions with second-generation PHIM ligands. Finally, ligands **25** and **26** were also tested in the palladium catalyzed allylic amination of **18** using different amines **29**-**34** (Figure 2 and Table 4).

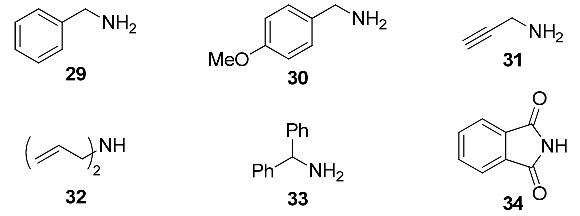
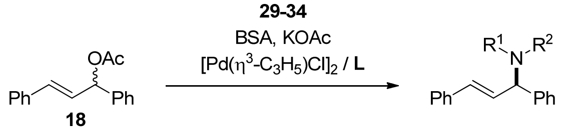


Figure 2. Nucleophiles used in the Pd-catalyzed allylic amination of substrate **18**.

Table 4. Pd-Catalyzed allylic amination of **18** using amines **29**-**34** with second-generation PHIM ligands **25** and **26**.[a]



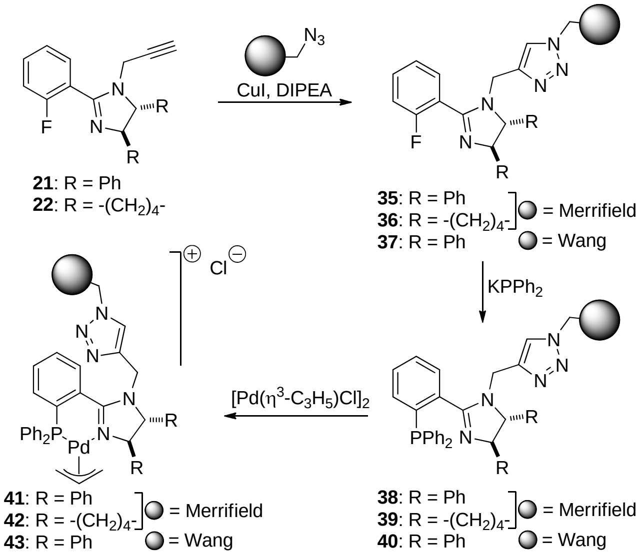
Entry	Ligand	Nucleophile	Conv. (%)[b]	ee (%)[c]
1	**25**	**29**	99	98
2	**25**	**30**	99	82
3	**25**	**31**	99	96
4	**25**	**32**	99	99
5	**25**	**33**	99	97
6	**25**	**34**[d]	47	99
7	**26**	**29**	99	84
8	**26**	**32**	49	67
9	**26**	**34**	0	-

[a]Reaction conditions: 0.02 mmol $[Pd(n^3-C_3H_5)Cl]_2$; 0.044 mmol ligand; 1 mmol substrate; 3 mmol nucleophile; 3 mmol BSA in 2 ml CH_2Cl_2 at 65 ºC under MW irradiation. [b]Conversion determined by NMR. [c]Ee determined by HPLC. [d]Reaction time: 48h.

The results confirmed that the structure of **25** incorporates the optimal chiral fragment for high enantioselectivity in the amination reaction. Very remarkably, when this ligand is used some of the synthetically equivalent amine delivering reagents (**29**, **32**, **33**) lead to complete conversion of the starting material to the corresponding allylamines with virtually complete enantioselectivity. The excellent enantiomeric excesses obtained in these reactions with ligand **25** are among the highest reported for this type of reaction.[13a,21,27]

Supporting the second generation ligands onto polystyrene-type resins. With these excellent results in hand, we envisioned to immobilize the PHIM ligands on polystyrene, by simply modifying the strategy used for the preparation of the homogeneous *N*-triazolylmethyl ligands. Thus, the complementary azido group for the dipolar cycloaddition was incorporated onto commercial Merrifield resin (1% DVB, f_0 = 0.54 mmol·g^{-1}) and onto commercial Wang resin (2% DVB, f_0 = 1.50 mmol·g^{-1}) by reaction with sodium azide[28] (Scheme 3). According to elemental analysis data,[10a] the calculated degree of functionalization of the resulting azido Merrifield resin was f = 0.53 mmol·g^{-1}, and that of the azido Wang resin was f = 1.57 mmol·g^{-1}.

Imidazolines **21** and **22** were then grafted onto these resins by Cu-catalyzed cycloadditions to afford 2-fluorophenyl imidazoline-functionalized resins **35**, **36** (Merrifield) and **37** (Wang). As a general rule, stirring the reaction mixture (shaker) in 1:1 DMF/THF at 45 ºC for 16 h led to complete conversion. The progress of the cycloaddition reaction could be easily monitored by IR spectroscopy, through the disappearance of the azide band (ca. 2094 cm^{-1}). Elemental analysis of the final resins allowed us to establish that the imidazoline anchors to the resin in quantitative yield. Treatment of resins **35** and **36** with potassium diphenylphosphide in THF at room temperature provided the target PHIM-functionalized resins **38** and **39**. With the Wang-type resin **37**, in turn, it was necessary to perform the reaction at 65ºC to achieve complete conversion into resin **40**. The progress of these reactions was readily assessed by a combination of ^{31}P and ^{19}F NMR spectroscopy in gel phase.



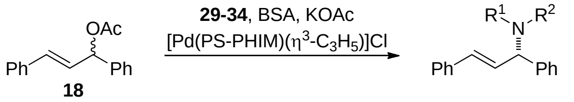
Scheme 3. Synthesis of polymer-supported PHIM and their π-allyl Pd-complexes.

Finally, formation of the π-allylpalladium complexes **41-43** was easily performed by addition of π-allylpalladium chloride dimer $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ to resins **38-40**, previously swollen in toluene. The final Merrifield resins **41** and **42** had functionalization degrees f = 0.31-0.33 $mmol\cdot g^{-1}$, while the Wang resin **43** had f = 0.69 $mmol\cdot g^{-1}$, in agreement with the values calculated for quantitative complexation. The complexation process could be easily monitored by ^{31}P NMR spectroscopy (See Supporting Information for ^{31}P NMR spectra).

With polymer-supported Pd complexes **41-43** in hand, the reaction of **18** with benzylamine catalyzed by these three species was studied (Table 5, entries 1-3). According to precedents with other polymer-supported catalysts,[12e,13a] the reactions were performed under microwave irradiation and essentially solventless conditions[29] in order to shorten reaction times. When PHIM Pd complexes supported on Merrifield resins (**41**,**42**) were employed as catalysts, significant precipitation of Pd black was observed at the selected reaction conditions (8 W, 40 ºC),[30] resulting in deterioration of catalytic activity. This difficulty could be partially circumvented, although precipitation of Pd black was not completely suppressed, by performing the reactions at lower microwave power (entries 1-2). In any case, these experiments confirmed that the use of enantiopure 1,2-diamino-1,2-diphenylethane as chiral educt for the formation of the imidazoline is clearly advantageous from the point of view of the enantioselectivity of the substitution process.

Very gratifyingly, when catalyst **43**, incorporating the optimal characteristics of the second-generation ligand **25** on a Wang-type resin, was used (entry 3), precipitation of Pd black was completely suppressed, and the substitution process took place in high yield and with high enantioselectivity after a short reaction time (3 h, *vs.* 24 h with the homogeneous ligand **25**). It is thus strongly suggested that increasing the distance between the π-allylpalladium complex and the polymer backbone (as it is the case when passing from Merrifield to Wang resins) exerts a very positive influence on the thermal stability of the catalytic species.

Table 5. Asymmetric allylic amination of **18** with different nitrogen nucleophiles catalyzed by Pd/supported PHIM complexes **41-43**.[a]



Entry	Catalyst	Nucleophile	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	**41**	**29**	2	80	91
2[e]	**42**	**29**	3	82	76
3	**43**	**29**	3	99	92
4	**43**	**30**	3	99	83
5	**43**	**31**	3	98	96
6	**43**	**32**	4	99	90
7	**43**	**33**	4	99	91

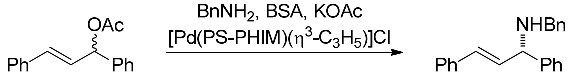
[a] All reactions were run under microwave irradiation at 8W power (40 ºC) with 12 mol% catalyst, 3 equiv. of nucleophile, 3 equiv. of BSA, and 7 equiv. of CH_2Cl_2. [b] Yield of isolated product after purification by flash chromatography. [c] Ee's were measured by HPLC on a chiral stationary phase. [d] Reaction at 3 W microwave power (31 ºC). [e] Reaction at 5 W microwave power (38 ºC).

The performance of resin **43** was then tested in the asymmetric allylic amination of **18** with a variety of nitrogen nucleophiles (Table 5, entries 4-7). The reactions were run under the conditions previously optimized for benzylamine. The tested nucleophiles completely converted **18** in 3-4 hours to give the expected products with high enantiomeric excess and in essentially quantitative yield. Except for *p*-methoxybenzylamine, the enantioselectivities obtained with supported PHIM/Pd catalysts **41-43** were consistently higher those reported with supported PHOX/Pd systems.[13a] Furthermore, when a comparison is made with the second-generation homogeneous ligands (Table 4), the microwave-assisted allylic amination catalyzed by **43** turned out to be more effective for all the tested nucleophiles, taking place with quite similar enantioselectivities in much shorter reaction times. As an additional bonus, it was possible to perform the aminations catalyzed by **43** without the presence of the potassium acetate additive.

As we have already mentioned, catalyst **43**, involving the use of a Wang resin as support, did not lead to the formation of palladium black during its operation under microwave irradiation. Accordingly, it could be recovered without apparent modification by simple filtration at the end of the reaction. This characteristic is relevant in connection with our ultimate goal of recovering and reusing the polymer-supported PHIM catalysts.

In this sense, the robustness of the polymer-supported PHIM catalyst **43** in the allylic amination of **18** with benzylamine is illustrated by the possibility of repeated recovery and reuse, as illustrated in Table 6. The reactions in the recycling study were carried out under the conditions previously optimized for catalyst **43** and without the addition of potassium acetate. After each run, the reaction mixture was separated by decantation, and the resin was rinsed with deoxygenated dichloromethane, dried under an Ar flow, and pre-swollen with dichloromethane just before the next use. To have an estimate on the level of leaching of palladium during use, no reconditioning of the resin with π-allylpalladium chloride dimer was performed between cycles.[31] It is worth mentioning that enantioselectivity remain almost intact after three consecutive runs while catalytic activity shows only marginal erosion (entries 1-3 in Table 6). A more significant decrease in catalytic activity was observed for the fourth cycle (entry 4); in this case, reaction time had to be increased to 6 h in order to achieve complete conversion. Since the colour of the resin darkened as the recycling progressed, we interpreted that thermally-induced precipitation of Pd(0) was partially taking place, and that this fact was responsible for the activity decrease. All together, these results clearly show that while microwave activation is key to high catalytic activity when the polymer-supported PHIM catalyst **43** is used, power and temperature control during these experiments are of paramount importance.

Table 6. Asymmetric allylic amination of **18** with benzylamine catalyzed by polymer-supported PHIM/Pd complex **43**.[a]



18 **20**

Cycle	Time (h)	Yield (%)[b]	ee (%)[c]
1	3	99	96
2	3	96	96
3	4	97	93
4	6	98	93

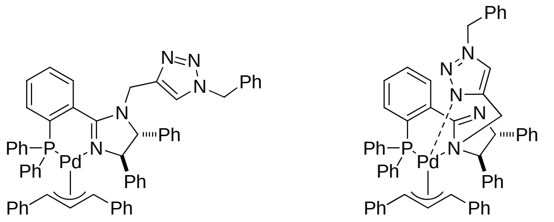
[a]Reactions were run under microwave in power control mode (8W) with 12 mol% catalyst, 3 equiv of benzylamine, 3 equiv of BSA and 7 equiv of CH_2Cl_2. [b]Yield of isolated product after purification by flash chromatography. [c]Enantiomeric excesses determined by HPLC on a chiral stationary phase.

Effect of the triazolyl substituents on the catalytic behaviour of second-generation PHIM ligands. As we have already discussed, the introduction of a triazolylmethyl substituent at the sp^3 nitrogen atom of the imidazoline ring in the second generation PHIM ligands provokes a very important increase in catalytic activity and in enantioselectivity in comparison with referable ligands where the triazole unit is absent (compare **25** with **10**, above). This behaviour is hardly understandable by an analysis of the transition states for the Pd-catalyzed substitution reactions, since the aromatic part of the substituent on the imidazoline N-1 position is both electronically isolated and spatially remote from the molecular region where the bond-making process takes place (Figure 3, structure A). This led us to speculate with the possibility of the triazolylmethyl substituent triggering a change in the coordination mode of the phosphinoimidazoline with palladium, from the usual N-3 nitrogen atom of the imidazoline to the N-1 one (Type B) or even to the triazole group (Type C).

Both these possibilities would be reasonably expected to cause an increase in the enantioselectivity of the process, in the case of the N-1 nitrogen acting as donor for a further desymmetrization of the allyl group environment, and in the case of one of the triazole group acting as donor for a resulting increase in the ligand's bite angle.

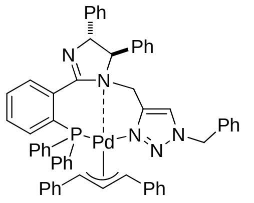
To test this hypothesis, we decided to study by theoretical means (DFT) the π-(1,3-diphenylallyl)palladium intermediates arising from the three proposed coordination modes of the PHIM ligand to palladium. For each coordination mode, *exo* and *endo* isomers of *syn-syn* type were considered. The calculations were performed with the Minnesota 06 (M06) functional,[32] as implemented in Gaussian09.[33] The triple zeta Stuttgart-Dresden (SDD) basis set and effective core potentials were used for palladium and the split-valence double-zeta 6-31G basis set with additional d polarization functions for all the other atoms.

To start with, a simplified model was studied in which all the substituents exocyclic respect to the chelate ring had been removed. After an exhaustive conformational analysis, six absolute minima for the *endo* and *exo* isomers of the three coordination modes were determined (Figure 4).



Type A
Imidazoline sp^2 N

Type B
Imidazoline sp^3 N



Type C
Triazole sp^2 N

Figure 3. Alternative coordination modes in $[Pd(PHIM)(\eta^3\text{-}C_3H_5)]^+$ cationic complexes.

Interestingly, although the most stable structures were predicted to be those with the *normal* imidazoline sp^2 coordination, the energy gap whith the triazole-coordinated structures was reasonably small (1.8 to 2.6 kcal·mol^{-1}). The sp^3 N-coordinated structures, on the other hand, laid significantly higher in energy respect to the other two types (8.5 to 9.6 kcal·mol^{-1}). This result clearly suggests the triazole to be a good ligand for palladium, this allowing it to be significantly competitive even in this situation where the imidazoline coordination leads to a very stable six-membered chelate ring.

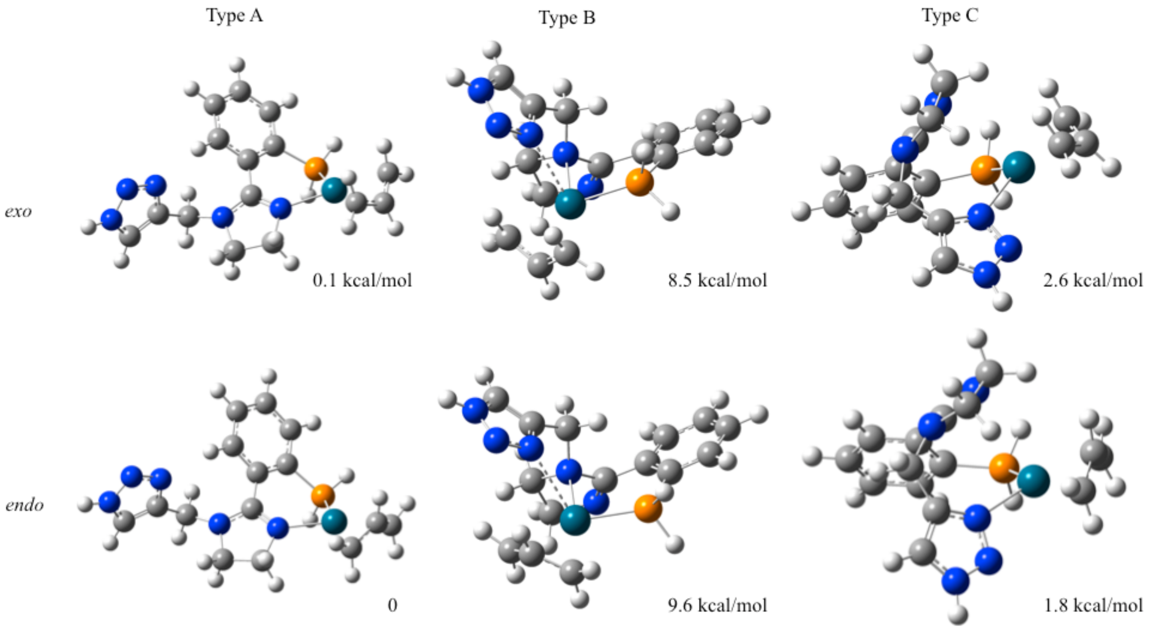


Figure 4. Optimized structures and relative Gibbs free energies for the three possible coordination modes in simplified models of [Pd(PHIM)(η^3-C_3H_5)]$^+$ cationic complex. Green: Pd; Orange: P; Blue: N; Grey: C; White: H.

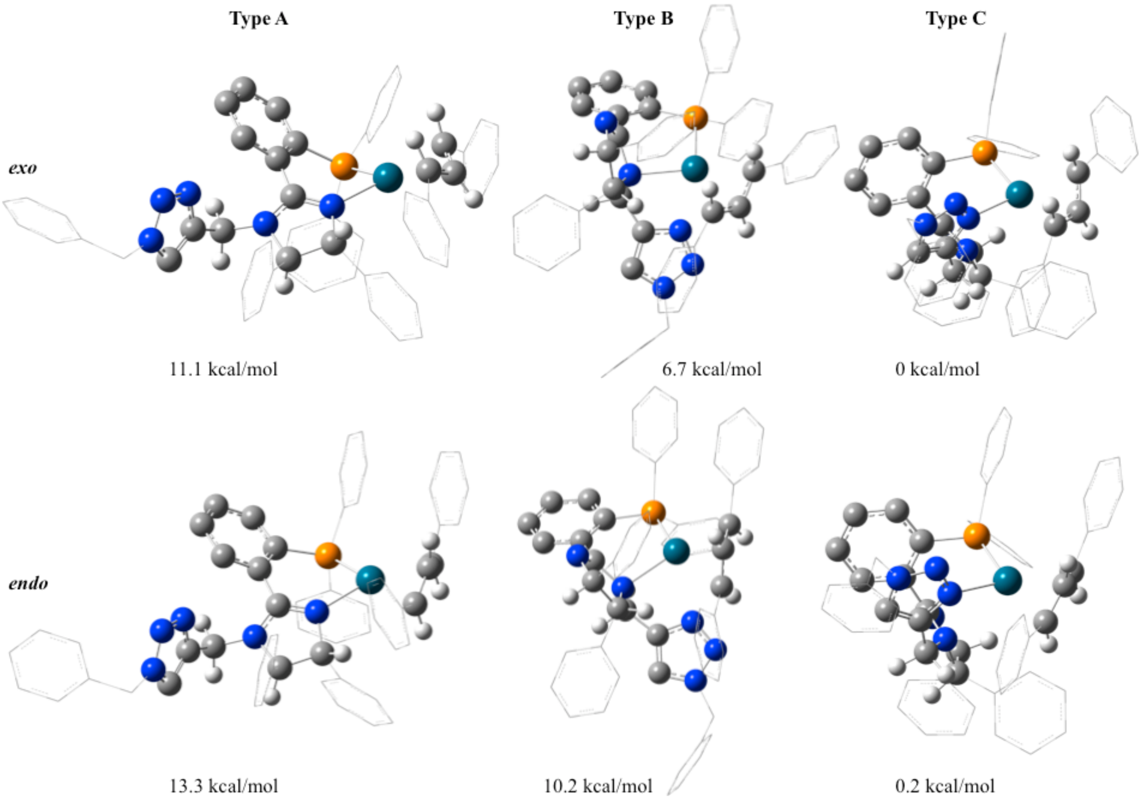


Figure 5. DFT-optimized structures and energies of the [Pd(η^3-diphenylallyl)(**25**)]$^+$ cationic complex. Non relevant hydrogen atoms have been removed for clarity. Exoskeletal substituents represented as wireframe. Green: Pd; Orange: P; Blue: N; Grey: C; White: H.

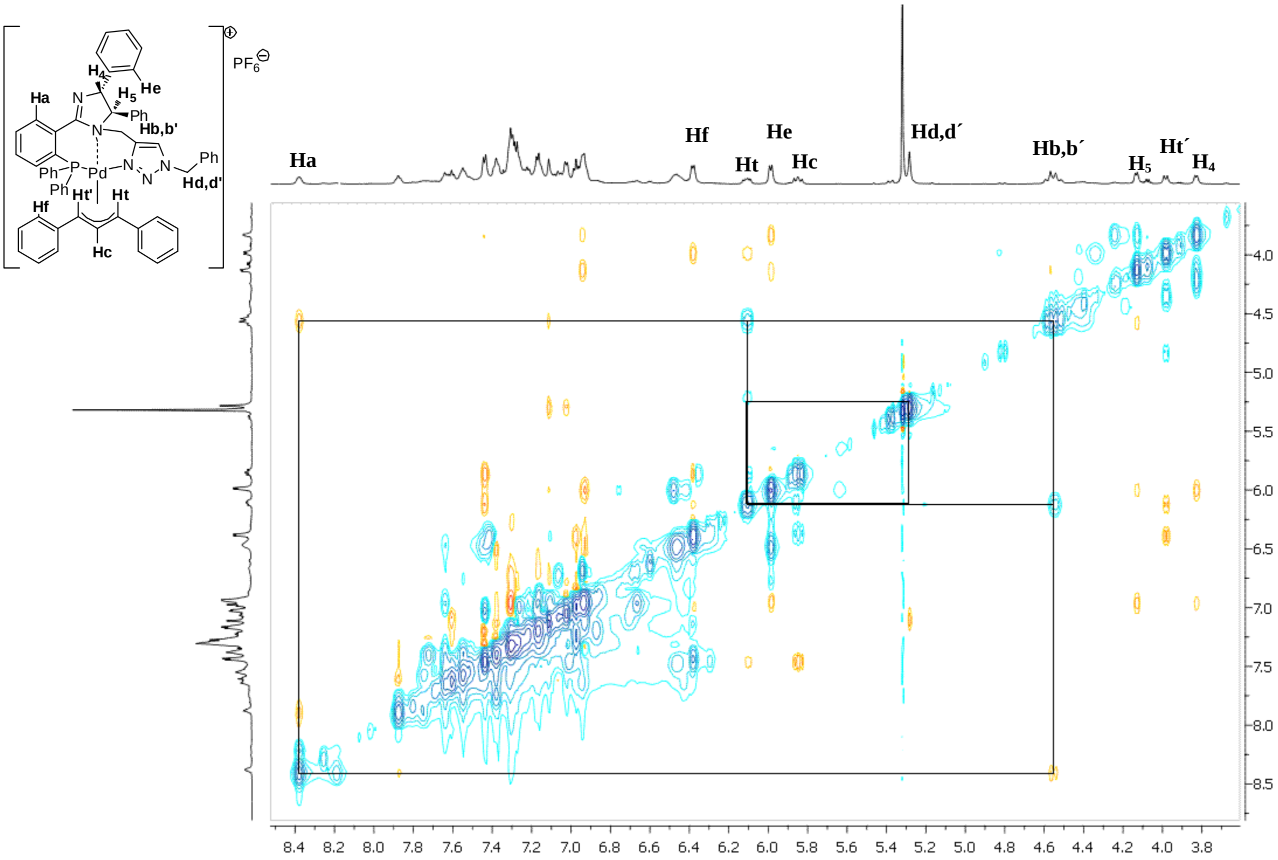


Figure 6. NOE spectrum of the [Pd(η^3-diphenylallyl)(**25**)]PF_6 complex in CD_2Cl_2.

Table 7. NOE-relevant H-H distances in the computed optimized structures of [Pd(η^3-1,3-diphenylallyl)(**25**)]$^+$ cationic complex.[a]

H	H	NOE observed?	Distance (Å)					
			A	A’	B	B’	C	C’
H_a	H_b	Yes	2.36	2.43	3.67	3.53	3.15	3.17
H_a	$H_{b'}$	Yes	3.77	3.82	4.05	3.59	4.66	4.68
$H_{b'}$	H_t	Yes	**7.23**	**7.59**	4.55	**5.59**	3.61	4.89
H_t	H_{C4}	No	**2.97**	**3.77**	6.28	**4.81**	5.03	7.21
H_t	H_{C5}	No	5.52	6.38	**3.51**	**2.88**	5.24	7.05
H_c	H_{C4}	No	**4.78**	**4.83**	5.70	6.96	7.07	5.36
H_c	H_{C5}	No	7.45	6.73	**3.79**	**4.37**	7.74	5.80

[a] Highlighted in boldface are the distances considered not to be consistent with the experimental data. For this simplification we have assumed a cut between observable or not observable NOE in 5.00 Å, which is in fact a somewhat extreme distance [REF. NOE a 5Å]. However, the computational techniques used are known to frequently overestimate to some extent the length of Pd-C and Pd-heteroatom bonds, so it is not wrong to assume the real distances can be slightly shorter.

To further explore this possibility, we performed optimizations of these basic structures with real model systems using the M06 functional and SDD/6-31G(d) basis sets as described above. In order to obtain as accurate energies as possible, single point frequencies calculations were run on the optimized structures with scrf solvent model for dichloromethane. The results, summarized in Figure 5, surprisingly revealed an extremely strong stabilization of the type C structures respect to the *normal* type A one (> 11 kcal/mol) as well as respect to the type B ones (> 6 kcal/mol).

In order to contrast this conclusion with additional experimental data, we decided to study in detail the cationic Pd(II) complex [Pd(η^3-diphenylallyl)(**25**)]PF_6, which could be easily obtained upon treatment of **25** with the dimeric precursor [Pd(η^3-diphenylallyl)Cl]$_2$ and NH_4PF_6. Although, unfortunately, no crystals suitable for X-Ray analysis could be obtained, a profound NMR study (see Supporting Information for details) revealed some important data.

Particularly remarkable are the conclusions obtained from NOE experiments (Figure 6), which showed significant differences with those of the PHIM ligands lacking the triazolylmethyl moiety. Namely, *i*) No NOE coupling between the imidazoline C-4 or C-5 hydrogens (H_{C4} and H_{C5}) and the allyl hydrogens (H_t and H_c) was registered, contrarily to that observed with the alkyl-substituted PHIM ligands; *ii*) a NOE interaction between one of the methylene hydrogens ($H_{b'}$) in the triazolylmethyl substituent and the allyl terminal hydrogen in position *trans* to phosphorus (H_t) was observed, which would be impossible if the imidazoline was coordinated in the *normal* form through the N-3 position. On the other hand, previously observed NOE interactions between the hydrogen *ortho* to the imidazoline in the phenylene bridge (H_a) and the two methylene hydrogens of the triazolylmethyl unit (H_b and $H_{b'}$) were conserved in this complex (strong for H_a-H_b and weak for H_a-$H_{b'}$). A careful comparison of these observations with the structures predicted by computational means (Table 7) makes apparent that the structures most consistent with the experimental data are the type C ones, with the triazole coordinating the palladium instead of the imidazoline. Remarkably, these structures are also the ones for which the lowest energy was predicted (see above).

CONCLUSIONS

A new family of enantiopure phosphino-imidazoline ligands (PHIM) has been synthesized, and its ability to facilitate the palladium catalyzed asymmetric allylic substitution reactions has been examined. The PHIM ligands have been modularly optimized at three different sites: The chiral diamine at the imidazoline backbone, the sp^3 nitrogen atom in the imidazoline ring, and the R_2P- moiety. The presence of a 1,2,3-triazolyl unit linked by a methylene group to the N-1 nitrogen atom of the imidazoline ring leads to highly improved catalytic activities and enantioselectivities (up to 99%) in the allylic amination reaction with respect to analogous ligands lacking the remote triazolyl unit. The CuAAC reaction has been used to support the PHIM ligands onto azide-functionalized polymers, and the resulting resins have shown to keep much of the performance of the monomeric triazolyl-substituted ligands. A change in the coordination mode of the imidazoline unit to palladium that would allow the interaction between the metal and the remote triazolyl unit has been proposed to explain the catalytic behavior of our *second-generation* PHIM ligands and of their polymer-supported congeners. Theoretical calculations and NMR studies in support of this hypothesis have been presented.

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Supporting Information Available. General experimental procedures for the synthesis of ligands, complexes, homogeneous and heterogeneous catalytic procedures, product characterization data and Cartesian coordinates of the computed structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) The employed amount of dichloromethane (7 equiv.) is that required for the optimal swelling of the polymer beads.

(30) To avoid temperature peaks that could be deleterious for the stability of the palladium complex, the reactions under microwave irradiation were performed in power control mode.

(31) Loss of catalytic activity due to leaching in supported metal complexes where the ligand is covalently bound to the support can be normally remediated by treatment with an appropriate metal source. See, for instance: Michalek, F.; Lagunas, A.; Jimeno, C.; Pericàs, M. A. *J. Mater. Chem.* **2008**, *18*, 4692-4697.

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Supporting Information

Homogeneous and Polymer-Supported Phosphinoimidazoline Ligands for Asymmetric Catalysis. Alteration of the Palladium Coordination Mode Triggered by a Remote Triazole Substituent

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1-Experimental details

1.- Experimental details.

General Remarks. All compounds were prepared under argon atmosphere using standard vacuum-line and Schlenk techniques. Tetrahydrofuran, dichloromethane, toluene, dimethylformamide and hexane were dried and deoxygenated by using a Solvent Purification System (SPS) and ethanol was deoxygenated with two freeze-thaw cycles.

All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. The experiments under microwave irradiation were carried out in a CEM discover microwave reactor (the temperature is automatically controlled by a non-contact infrared sensor that monitors and controls the temperature conditions of the reaction vessel).

NMR spectra were recorded on Varian Gemini 300 and 400 spectrometers in $CDCl_3$ at room temperature unless otherwise cited operating at 400.13 MHz (1H), 100.63 MHz ($^{13}C\{1H\}$), 161.98 MHz ($^{31}P\{1H\}$) and 282 MHz ($^{19}F\{1H\}$). ^{1}H NMR chemical shifts are quoted in ppm relative to internal TMS and ^{13}C NMR spectra to $CDCl^3$ whereas ^{31}P NMR chemical shifts are quoted in ppm relative to 85% phosphoric acid in water and ^{19}F NMR relative to $CFCl_3$. ^{1}H and ^{13}C NMR experiments of resins **35/36/37** and **41/42/43** were performed with a Bruker Avance spectrometer operating at a frequency of 500.13 MHz using a Bruker 4 mm $^{1}H/^{13}C/^{2}H$ gradient HR-MAS probe. IR spectra were recorded on a Bruker Tensor 27 spectrometer in Fourier transform mode. FAB mass spectra were obtained on a VG-Autospect instrument, EI mass spectra were obtained on a HP 5989 A spectrometer at an ionizing voltage of 70 eV. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Enantiomeric excesses were determined by HPLC on Agilent 1100 Series chromatograph with a UV detector. Elemental analyses (C; H; N; Cl) were performed by Servei de Microanalisi, Consell Superior d'Investigacions Cientifiques, Barcelona, Spain, by Centro de Microanálisis Elemental in Facultad de Farmacia, Universidad Complutense, Madrid, Spain, and by Carlo Erba Microanalyser EA 1108.

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was purchased from Alpha Aesar and $KPPh_2$ from Aldrich and were used without any further purification. Merrifield resin (1% DVB, f = 0.53 mmol Cl g–1 resin) and Wang resin (2% DVB, f_0 = 1.50 mmol Cl g^{-1}) was obtained from Novabiochem.

Synthesis of (4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-1-propyl-4,5-dihydro-1H-imidazole (12). A solution of (4*R*,5*R*)-2-(2-fluoro-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole (**4**) (170 mg, 0.54 mmol) in anhydrous THF (1 mL) was added under argon to a suspension of sodium hydride (60% in mineral oil, 23.57 mg, 0.59 mmol) in anhydrous THF (0.5 mL) previously cooled at 0 ºC. The mixture was stirred for 30 min and then propyl bromide (0.0492 mL, 0.54 mmol) was added dropwise. The reaction was stirred at this temperature for 3 h. The reaction was quenched with MeOH (0.5 mL). The purification of the product was carried out by flash chromatography (hexanes/EtOAc 1:1 (5% NEt_3)) to give compound **12** as a pale yellow oil; yield: 100 mg (52%). $[\alpha]_D^{20}$: -61.86 (*c* 1.01 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 8.31 (m, 1H, arom); 7.70 (m, 1H, arom); 7.50-7.17 (m, 12H, arom); 5.02 (d, ^3J=8.8Hz, 1H, CH); 4.55 (d, ^3J=7.2 Hz, 1H, CH); 3.04-2.88 (m, 2H, CH_2); 1.41-1.22 (m, 2H, CH_2); 0.65 (t, ^3J=7.6Hz, CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 162.2 (C=N), 144.6-116.1 (arom); 78.5 (CH); 73.5 (CH); 47.1 (CH_2); 20.9 (CH_2); 11.3 (CH_3); ^{19}F ($CDCl_3$, 376.5 MHz): δ = -113.9 (m); HRMS (ESI+): *m/z* = 359.1928, calcd. for $[M]^+$: 359.1924. Analysis calcd. for $C_{24}H_{23}FN_2$: C, 80.42; H, 6.47; F, 5.30; N, 7.82; found: C, 80.38; H, 6.56; N, 7.85.

Synthesis of (4*R*,5*R*)-2-(2-diphenylphosphanyl-phenyl)-4,5-diphenyl-1-propyl-4,5-dihydro-1H-imidazole (13). A solution of $KPPh_2$ (0.61 mL, 0.307 mmol, 0.5M in THF) was added dropwise under argon at room temperature to an oven-dried Schlenk flask contained the compound **12** (100 mg, 0.279 mmol). The resulting mixture was stirred overnight at this temperature. The reaction crude was then poured into water and extracted twice with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent was removed under argon. The final product was purified by flash chromatography under nitrogen (hexanes/EtOAc 1:1(5% NEt_3)) to give compound **13** as a white solid; yield: 111 mg (76%). $[\alpha]_D^{20}$: -22.77 (*c* 0.60 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 8.31 (m, 1H, arom); 7.64 (m, 1H, arom); 7.48-7.12 (m, 22H, arom); 4.94 (d, ^3J=9.6 Hz, 1H, CH); 4.47 (d, ^3J=10 Hz, 1H, CH); 2.85-2.68 (m, 2H, CH_2); 1.31-1.14 (m, 2H, CH_2); 0.59 (t, ^3J=7.2Hz, CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 162.2 (C=N), 144.4-126.9 (arom); 79.1 (CH); 74.4 (CH); 47.8 (CH_2); 21.1 (CH_2); 11.3 (CH_3); ^{31}P NMR ($CDCl_3$): δ = -12.7 (s); HRMS (ESI+): *m/z* = 525.2464, calcd. for $[M]^+$: 525.2460; Analysis calcd. for $C_{36}H_{33}N_2P$: C, 82.42; H, 6.34; N, 5.34; P, 5.90; found: C, 82.37; H, 6.41; N, 7.95.

Synthesis of (4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (14). To a solution of compound (4*R*,5*R*)-2-(2-fluoro-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole (**4**) (300 mg, 0.54 mmol) and DMAP (120.5 mg, 0.98 mmol) in CH_2Cl_2 (2 mL) at 0 ºC, a solution of tosyl chloride (125.1 mg, 0.65 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and further stirred for 5 h. The solvent was removed under reduced pressure and the yellow residue was purified by flash chromatography (hexanes/EtOAc 6:4 (5% NEt_3)) to obtain the final product **14** as a white foam; yield: 290 mg (65%). $[\alpha]_D^{20}$: -59.66 (*c* 1.02 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 7.60 (m, 1H, arom); 7.47-6.81 (m, 17H, arom); 5.02 (d, ^3J=4.9 Hz, 1H, CH); 4.99 (d, ^3J=4.9 Hz, 1H, CH); 2.31 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 162.2 (C=N), 144.6-116.1 (arom); 78.2

(CH); 72.5 (CH); 21.3 (CH_3); ^{19}F ($CDCl_3$, 376.5 MHz): δ = -114.7 (m); HRMS (ESI+): *m/z* = 471.1545, calcd. for $[M]^+$: 471.1543; Analysis calcd. for $C_{28}H_{23}FN_2O_2S$: C, 71.47; H, 4.93; F, 4.04; N, 5.95; O, 6.80; S, 6.81; found: C, 71.43; H, 5.01; N, 5.98; S, 6.86.

Synthesis of (4*R*,5*R*)-2-(2-diphenylphosphanyl-phenyl)-4,5-diphenyl-1-tosyl-4,5-dihydro-1H-imidazole (15) Following the general method from compound from compound **14** (102 mg, 0.217 mmol) and $KPPh_2$ (0.48 mL, 0.238 mmol, 0.5M in THF). White solid; yield: 104 mg (76%). $[\alpha]_D^{20}$: -35.72 (*c* 1.01 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 8.43 (m, 1H, arom); 7.70-6.88 (m, 27H, arom); 5.10 (d, ^3J=4.8 Hz, 1H, CH); 5.07 (d, ^3J=4.8 Hz, 1H, CH); 2.40 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 162.2 (C=N), 144.7-115.9 (arom); 78.4 (CH); 72.0 (CH); 21.8 (CH_3); ^{31}P NMR ($CDCl_3$): δ = -10.4 (s); HRMS (ESI+): *m/z* = 637.2073, calcd. for $[M]^+$: 637.2079; Analysis calcd. for $C_{40}H_{33}N_2O_2PS$: C, 75.45; H, 5.22; N, 4.40; O, 5.03; P, 4.86; S, 5.04; found: C, 75.39; H, 5.28; N, 4.45; S, 5.07.

Synthesis of (4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-4,5-dihydro-1H-imidazole (21). A solution of (4*R*,5*R*)-2-(2-fluoro-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole (**4**) (500 mg, 1.59 mmol) in anhydrous THF (2 mL) was added under argon to a suspension of sodium hydride (60% in mineral oil, 142.85 mg, 3.57 mmol) in anhydrous THF (1 mL) previously cooled at 0 ºC. The mixture was stirred for 30 min and then propargyl bromide (0.247 mL, 2.78 mmol) was added dropwise. The reaction was stirred at 0 ºC for 30 min, then allowed to reach room temperature and further stirred for 48 h. The reaction was quenched with MeOH (0.5 mL) and filtered through celite. The purification of the product was carried out by flash chromatography (hexanes/EtOAc 3:1 (5% NEt_3)) to give final product **21** as a pale yellow oil; yield: 327 mg (58%). $[\alpha]_D^{20}$: -90.73 (*c* 1.00 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 7.75 (m, 1H, arom); 7.59-7.18 (m, 13H, arom); 4.60 (d, ^3J=9.2 Hz, 1H, CH); 4.73 (d, ^3J=9.2 Hz, 1H, CH); 3.95 (dd, ^2J=18.4 Hz, ^3J=2.0 Hz, 1H, CH_2); 3.50 (dd, ^2J=18.4 Hz, ^3J=2.0 Hz, 1H, CH_2); 2.55 (s, 1H, CH); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 161.9 (d, ^3J=65.7 Hz, C=N), 159.1 (C, arom.); 143.6-116.8 (C, arom); 78.7 (C); 78.3 (CH); 74.1 (CH); 73.6 (CH); 36.2 (CH_3); ^{19}F ($CDCl_3$, 376.5 MHz): δ = -114.1 (m); HRMS (ESI+): *m/z* = 355.1613, calcd. for $[M]^+$: 355.1611. Analysis calcd. for $C_{24}H_{19}FN_2$: C, 81.33; H, 5.40; F, 5.36; N, 7.90; found: C, 81.28; H, 5.42; N, 7.96.

Synthesis of 2-(2-fluorophenyl)-1-(prop-2-yn-1-yl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[*d*]imidazole (22). Following the general method from compound **5** (425 mg, 1.95 mmol), NaH (60% in oil suspension, 175.2 mg, 4.38 mmol) and propargyl bromide (0.304 mL, 3.4 mmol). Yellow oil; yield: 309 mg (62%). $[\alpha]_D^{20}$: +23.72 (*c* 0.71 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 7.49 (m, 1H, arom); 7.40 (m, 1H, arom); 7.20-7.08 (m, 2H, arom); 3.84 (dd, ^3J= 18.4Hz, ^4J= 2.4 Hz 1H, CH); 3.73 (dd, ^3J= 18.4Hz, ^4J= 2.4 Hz, 1H, CH); 3.17 (m, 1H, CH_2); 2.97 (m, 1H, CH_2); 2.39 (br, 1H, CH); 2.14 (m, 2H, CH_2); 1.87 (m, 2H, CH_2); 1.59-1.23 (m, 4H, CH_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 164.4 (C=N); 160.8 (C, arom); 158.1 (C, arom); 131.7 (d, ^3J=8.15 Hz, C arom), 131. 1 (C, arom); 124. 6 (C, arom); 116.0 (d, ^3J=8.15 Hz, C arom); 78.0 (C); 73.2 (CH); 71.4 (CH); 68.9 (CH); 36.1 (CH_2); 31.2 (CH_2); 29.0 (CH_2);

25.8 (CH_2); 24.7 (CH_2); ^{19}F ($CDCl_3$, 376.5 MHz): δ = -113.5 (m); HRMS (ESI+): *m/z* = 257.1459, calcd. for $[M]^+$: 257.1454; Analysis calcd. for $C_{16}H_{17}FN_2$: C, 74.97; H, 6.69; F, 7.41; N, 10.93; found: C, 74.95; H, 6.75; N, 10.99.

Synthesis of 1-benzyl-5-((2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (23). Benzyl bromide (0.128 mL, 1.15 mmol) was added to a mixture of fluoroimidazoline **21** (400 mg, 1.15 mmol), sodium azide (156.8 mg, 2.45 mmol), $CuSO_4{\cdot}5H_2O$ (5.6 mg, 0.002 mol) and L-ascorbic acid (46.56 mg, 0.24 mmol) in *tert*-butyl alcohol: water (1:1) (3 mL). The reaction mixture was stirred at 40ºC for 12 h. The crude reaction product was extracted with CH_2Cl_2 (3x15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes:EtOAc from 60:40 to 0:100 (5% NEt_3)) to give final product **23** as a yellow foam; yield: 206 mg (60%). $[\alpha]_D^{20}$: -28.11 (*c* 0.53 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.69 (m, 1H, arom); 7.48-7.11 (m, 18H, arom); 6.87 (s, CH); 5.40 (d, ^2J=16 Hz, 1H, CH_2); 5.34 (d, ^2J=16 Hz, 1H, CH_2); 5.00 (d, ^3J=8 Hz, 1H, CH); 4.47 (d, ^3J=8 Hz, 1H, CH); 4.38 (d, ^2J=16 Hz, 1H, CH_2); 4.14 (d, ^2J=16 Hz, 1H, CH_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 161.5 (d, *J*=57.7 Hz, C arom); 158.7 (C, arom); 143.8-116.1 (C, arom); 78.3 (s, CH); 73.71 (s, CH); 54.2 (s, CH_2); 41.3 (s, CH_2); ^{19}F ($CDCl_3$, 376.5 MHz): δ = -113.28 (m); HRMS (ESI+): *m/z* =488.2256, calcd. for $[M]^+$: 488.2250. Analysis calcd. for $C_{31}H_{26}FN_5$: C, 76.36; H, 5.37; F, 3.90; N, 14.36; found: C, 76.29; H, 5.43; N, 14.42.

Synthesis of (3a*R*,7a*R*)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(2-fluorophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[*d*]imidazole (24). Following the general method from compound **22** (250 mg, 0.71 mmol), benzyl bromide (0.116 mL, 0.71 mmol), sodium azide (135 mg, 1.17 mmol), $CuSO_4{\cdot}5H_2O$ (4.86 mg, 0.0019 mol) and L-ascorbic acid (40.3 mg, 0.20 mmol). Yellow foam; yield: 281 mg (59%). $[\alpha]_D^{20}$: +37.15 (*c* 0.81 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.36-6.9 (m, 9H, arom); 5.44 (br, 2H, CH); 4.4 (d, ^3J=16 Hz, 1H, CH); 4.07 (d, ^3J=16 Hz, 1H, CH_2; 3.12 (m, 1H, CH_2); 2.78 (m, 1H, CH_2); 2.32 (m ,1H, CH_2); 2-1.2 (m, 7H, CH_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 164.1 (s, C=N); 160.5 (C=N); 159-115 (C, arom); 71.1 (s, CH); 54.2 (s, CH); 42.9 (s, CH_2); 32.1 (s, CH_2); 29.9 (s, CH_2); 29.8 (s, CH_2); 25.6 (s, CH_2); 24.6 (s, CH_2); ^{19}F ($CDCl_3$, 376.5 MHz): δ = -113.28 (m); HRMS (ESI+): *m/z* =390.2094, calcd. for $[M]^+$: 390.2084; Analysis calcd. for $C_{31}H_{26}FN_5$: C, 70.93; H, 6.21; F, 4.88; N, 17.98; found: C, 70.89; H, 6.35; N, 17.65.

Synthesis of 1-benzyl-5-((2-(2-(diphenyl-phosphino)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (25). Following the general method from compound **23** (150 mg, 0.31 mmol) and $KPPh_2$ (0.48 mL, 0.38 mmol, 0.5M in THF). White solid; yield: 141 mg (70%). $[\alpha]_D^{20}$: -23.41 (*c* 0.34 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.69 (m, 1H, arom); 7.48-7.11 (m, 18H, arom); 6.87 (s, CH); 5.40 (d, ^{2}J=16 Hz, 1H, CH_2); 5.34 (d, ^2J=16 Hz, 1H, CH_2); 5.00 (d, ^3J=8 Hz, 1H, CH); 4.47 (d, ^3J=8 Hz, 1H, CH); 4.38 (d, ^2J=16 Hz, 1H, CH_2); 4.14 (d, ^2J=16 Hz, 1H, CH_2);

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 161.5 (d, J=57.7 Hz, C arom); 158.7 (C, arom); 143.8-116.1 (C, arom); 78.3 (s, CH); 73.71 (s, CH); 54.2 (s, CH_2); 41.3 (s, CH_2); ^{31}P NMR ($CDCl_3$): δ = -11.4 (s); HRMS (ESI+): *m/z* =654.2793, calcd. for $[M]^+$: 654.2787; Analysis calcd for $C_{43}H_{36}N_5P$: C, 79.00; H, 5.55; N, 10.71; P, 4.74; found: C, 79.02; H, 5.67; N, 10.76.

Synthesis of (3a*R*,7a*R*)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(2-(diphenylphosphino)phenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[*d*]imidazole (26). Following the general method from compound **24** (150 mg, 0.31 mmol) and $KPPh_2$ (0.48 mL, 0.38 mmol, 0.5M in THF). White solid; yield: 83 mg (68%). $[\alpha]_D^{20}$: +32.47 (*c* 0.30 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 7.39-6.92 (m, 19H, arom,1H CH); 5.36 (br, 2H, CH_2); 4.18 (d, ^3J=15.6 Hz, 1H, CH); 3.83 (d, ^3J=15.6 Hz, 1H, CH); 2.70 (m, 1H, CH_2); 2.46 (m, 1H, CH_2); 2.13 (m, 1H, CH_2); 1.66-1.5 (m, 3H, CH_2); 1.2-1 (m, 4H, CH_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 167.5 (d, J=57.7 Hz, C arom); 134.9-122.3 (C, arom); 74.2 (s, CH); 54.2 (s, CH); 43.6 (s, CH_2); 31.1 (s, CH_2); 30.2 (s, CH_2); 25.7 (s, CH_2); 24.7 (s, CH_2); 21.2 (s, CH_2); ^{31}P NMR ($CDCl_3$): δ = -11.4 (s); HRMS (ESI+): *m/z* =556.2643, calcd. for $[M]^+$: 556.2630; Analysis calcd. for $C_{43}H_{36}N_5P$: C, 77.65; H, 6.17; N, 12.60; P, 5.57; found: C, 77.60; H, 6.29; N, 12.64.

Synthesis of di-μ-chloro-bis-(η^3-1,3-diphenylallyl)palladium (II) To an oven-dried Schlenk flask containing palladium dichloride (0.450 g, 2.56 mmol) under nitrogen atmosphere was added a solution of lithium chloride (0.450 g, 10.72 mmol) in deoxygenated water (30 mL). The reaction mixture was stirred for 30 minutes. Then, a solution of deoxygenated ethanol (5 mL) and rac-1,3-diphenyl-3-acetoxyprop-1-ene (1.7 g, 6.74 mmol) in THF (15 mL) were introduced via syringe to the oven-dried Schlenk. The temperature was decrease to 0 ºC and HCl conc. (1mL) was added and the resulting solution was stirred. Carbon monoxide was bubbled into solution for 5 min and HCl conc. (1mL) was added again to the solution. This procedure should repeat until the apparition of orange precipitate. The mixture was stirred overnight under 1 atmosphere of carbon monoxide. The crude water solution was extracted with CH_2Cl_2 (3x15 mL). The organic phases were washed with brine (15 mL) and dried ($MgSO_4$). The drying agent was filtered off and the solvent was removed under reduced pressure. The Palladium complexes precipitated were filtered off, washed with cold mixture of CH_2Cl_2 and hexanes and dried in vacuum.

General procedure for the preparation of [Pd(ŋ^3-diphenylallyl)(L)]PF_6 complexes. (L = 6,13,25). The corresponding ligand **6/13/25** (0.05 mmol) and the complex [Pd(μ-Cl)(ŋ^3-1,3-diphenylallyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) for 30 min. under nitrogen at room temperature. Then, NH_4PF_6 (0.5 mmol) was added and further stirred for 30 min. The resulting crude solution was then filtered over celite under nitrogen. The Palladium complexes precipitated were filtered off, washed with cold hexanes and dried *in vacuum.*

Complex [Pd(ŋ^3-diphenylallyl)(6)]PF_6. Major diastereoisomer: ^1H NMR ($CDCl_3$): δ = 8.75 (m, 1H, arom); 7.79-6.11 (m, 34H, arom); 6.09 (m, 1H, H allyl central); 5.77 (m, 1H, H allyl terminal trans to phosphorous); 4.46 (d, ^3J=6.4 Hz, 1H, CH); 3.80 (d, ^3J=6.4 Hz, 1H, CH); 3.78 (br, 1H, H allyl terminal cis to phosphorous). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ = 165.1 (C=N); 140.2-126.3 (C, arom); 111.3 (C allyl central); 102.3 (d, *J*=25.1 Hz, C allyl terminal trans to P); 77.8 (CH); 66.4 (CH); 66.2 (br, C allyl terminal cis to P); ^{31}P NMR ($CDCl_3$): δ = 21.46 (s); Minor diastereoisomer: ^1H NMR ($CDCl_3$): δ = 8.65 (m, 1H, arom); 7.78-6.29 (m, 34H, arom); 6.21 (m, 1H, H allyl central); 4.47 (br, 1H, CH); 4.40 (br, 1H, H allyl terminal trans to phosphorous); 4.28 (d, ^3J=6.8 Hz, 1H, H allyl terminal cis to phosphorous); 3.81 (br, 1H, CH); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 165.2 (C=N); 140.2-126.3 (C, arom); 108.1 (C allyl central); 88.1 (d, *J*=25.1 Hz, C allyl terminal trans to P); 78.3 (CH); 74.2 (br, C allyl terminal cis to P); 76.3 (CH); ^{31}P NMR ($CDCl_3$): δ = 26.17 (s); HRMS (ESI+): *m/z* = 781.1969, calcd. for $[M]^+$: 781.1964; Analysis calcd. for $C_{48}H_{40}F_6N_2P_2Pd$: C, 62.18; H, 4.35; F, 12.29; N, 3.02; P, 6.68; Pd, 11.48; found: C, 61.97; H, 4.42; N, 3.07.

Complex [Pd(η^3-diphenylallyl)(13)]PF$_6$. Major diastereoisomer: ^1H NMR ($CDCl_3$): δ = 7.93-6.51 (m, 33H, arom); 6.37 (d, *J*=7.6 Hz, 1H, arom); 6.11 (d, ^2J=6.8 Hz, 1H, H terminal trans to phosphorous); 5.85 (dd, *J*=13.6 Hz, *J*=10 Hz, 1H, H allyl central); 4.15 (d, *J*=6.4 Hz, 1H, H allyl terminal cis to phosphorous); 4.01 (d, ^3J=10 Hz, 1H, CH); 3.83 (d, ^3J=10 Hz, 1H, CH); 3.0-3.11 (m, 2H, CH_2); 1.28 (m, 2H, CH_2); 0.57 (m, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ = 165.3 (C=N); 140.9-126.0 (C, arom); 111.1 (C allyl central); 103.4 (d, *J*=21.03 Hz, C allyl terminal trans to P); 75.2 (CH); 72.2 (br, C allyl terminal cis to P); 66.7 (CH); 50.5 (CH_2); 21.3 (CH_2); 10.7 (CH_3); ^{31}P NMR ($CDCl_3$): δ = 17.74 (s); HRMS (ESI+): *m/z* = 823.2442, calcd. for $[M]^+$: 823.2433; Analysis calcd. for $C_{51}H_{46}F_6N_2P_2Pd$: C, 63.20; H, 4.78; F, 11.76; N, 2.89; P, 6.39; Pd, 10.98; found: C, 63.14; H, 4.87; N, 2.97.

Complex [Pd(η^3-diphenylallyl)(25)]PF$_6$. Major diastereoisomer: ^1H NMR ($CDCl_3$): δ = 8.38 (m, 1H, arom); 7.93-6.86 (m, 33H, arom); 6.47 (m, 1H, arom); 6.39 (br, 2H, arom); 6.14 (m, 1H, H terminal trans to phosphorous); 6.00 (d, *J*=7.2 Hz, 2H, arom); 5.87 (m, 1H, H allyl central); 5.34 (br, CH_2); 4.59 (br, CH_2); 4.08 (m, 1H, CH); 3.92 (d, *J*=9.6 Hz, 1H, H allyl terminal cis to phosphorous); 3.75 (d, ^3J=6.2 Hz, 1H, CH); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 163.3 (C=N); 140.4-122.7 (C, arom); 110.5 (br, C allyl central); 102.5 (d, J=24.11 Hz, C allyl terminal trans to P); 74.6 (CH); 71.9 (CH); 65.8 (br, C allyl terminal cis to P); 53.1 (CH_2); 43.2 (CH_2); ^{31}P NMR ($CDCl_3$): δ = 20.4 (s); HRMS (ESI+): *m/z* =952.2745, calcd. for $[M]^+$: 952.2760; Analysis calcd. for $C_{58}H_{50}F_6N_5P_2Pd$: C, 63.42; H, 4.50; F, 10.38; N, 6.38; P, 5.64; Pd, 9.69; found: C, 63.36; H, 4.63; N, 6.42.

Synthesis of the click-resins 35/36/37: The N_3-functionalized resin[1] (0.75 g, f = 0.53 mmol g^{-1}) was reacted with the corresponding alkynyloxymethyl imidazoline **21/22** (0.59 mmol), CuI (2 mg, 0.01mmol) and DIPEA (0.08 mL, 0.47 mmol) in a 1:1 mixture of DMF and THF (5 mL) at 45 ºC. The progression of the reaction was monitored by IR spectroscopy. After disappearance of the azide signal (16 h) the resin was collected by filtration and sequentially washed with water (250 mL), DMF (250 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL). The solid was dried *in vacuo* overnight at 40 ºC.

Resin 35: ^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.25-6.77 (m, polymer), 6.75-6.05 (m, polymer), 5.33-5.24 (m, 1H), 5.20 (m, 2H), 4.60-4.25 (m, 1H), 3.65 (m, 2H), 2.13-1.72 (m, polymer); 1.70-1.20 (m, polymer); ^{13}C NMR (HRMAS, CD_2Cl_2): δ = 161.8 (m, CF), 159.0 (C=N), 146.5-145.5 (m, polymer), 129.3-128.0 (CH), 127.8-126.8 (CH), 126.4 (CH), 124.1 (CH), 113.4-108.5 (m, polymer), 105.2 (CH), 85.4 (CH), 78.2 (CH), 67.9 (CH_2), 41.8-40.7 (m, polymer), 40.6-39.6 (m, polymer), 25.7 (CH_2); ^{19}F NMR (CD_2Cl_2): δ = –111.6 (s, F); IR (ATR): ν = 3058, 3025, 2922, 2850, 1665, 1598, 1492, 1452, 1385, 1255, 1215, 1092, 1049, 1028, 758, 698, 659 cm^{-1}. A 100 % yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 3.17; found: C 86.91, H 7.25, N 2.86; f = 0.41 mmol g^{-1}.

Resin 36: ^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.40-6.89 (m, polymer), 6.75-6.22 (m, polymer), 5.44-5.20 (m, 2H), 5.16 (m, 1H), 4.55-3.93 (m, 1H), 3.65 (m, 2H), 2.34-1.68 (m, polymer); 1.63-1.18 (m, polymer); ^{13}C NMR (HRMAS, CD_2Cl_2): δ = 161.8 (m, CF), 159.8 (C=N), 147.2-145.8 (m, polymer), 134.7-130.8 (CH), 129.3-126.9 (CH), 126.3-125.5 (CH), 122.3-119.2 (CH), 116.0-106.9 (m, polymer), 105.2 (CH), 85.3 (CH), 77.6 (CH), 67.9 (CH_2), 53.7 (CH_2), 47.0-42.3 (m, polymer), 40.5-39.6 (m, polymer), 29.6 (CH_2), 25.7 (CH_2); ^{19}F NMR (CD_2Cl_2): δ = -112.8 (s, F); IR (ATR): ν = 3058, 3024, 2920, 2849, 1600, 1491, 1450, 1330, 1218, 1154, 1067, 1027, 906, 754, 696 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 3.32; found: C 85.02, H 7.65, N 2.79; f = 0.40 mmol g^{-1}.

Resin 37: ^{1}H NMR (HRMAS, CD_2Cl_2): δ = 8.50-6.13 (m, polymer), 5.62-5.49 (m, polymer), 5.48-5.25 (m, 1H), 5.24-4.96 (m, 2H), 4.89-4.46 (m, 1H), 4.07-3.74 (m, 2H), 2.76-1.22 (m, polymer); ^{13}C NMR (HRMAS, CD_2Cl_2): δ = 161.8 (m, CF), 158.9 (C=N), 148.3-142.6 (m, polymer), 141.3 (CH), 135.6 (CH), 133.3-123.1 (m, polymer), 119.4 (CH), 112.3-109.5 (m, polymer), 105.9 (CH), 85.2 (CH), 78.1 (CH), 67.9 (CH_2), 53.7 (CH_2), 42.5-36.2 (m, polymer), 25.8 (CH_2); ^{19}F NMR (CD_2Cl_2): δ = -113.2 (s, F); IR (ATR): ν = 3057, 3025, 2920, 2848, 1626, 1600, 1492, 1452, 1328, 1216, 1154, 1065, 1028, 906, 755, 696 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 7.31; found: C 79.59, H 6.41, N 6.36; f = 0.91 mmol g^{-1}.

Synthesis of the polymer-supported phosphinooxazolines 38/39/40: A solution of $KPPh_2$ (0.41 mmol, 0.82 mL of 0.5M solution in THF) was added dropwise under argon at 0 ºC to an oven-dried Schlenk flask which contained the corresponding resin **35-37** (0.29 mmol) previously swollen with anhydrous and degassed THF (5 mL). The reaction mixture was shaken at 0 ºC for 2 h, allowed then to reach room temperature and further shaken for 12 h at this temperature. The solution was removed under argon *via cannula* and the resin was washed with anhydrous and degassed CH_2Cl_2 (7 x 10 mL) and dried *in vacuo* for 10 h. Resins **38/39/40** were not fully characterized (only ^{31}P NMR in gel-phase was recorded) and were immediately transformed into the corresponding palladium complexes **41/42/43**. Resin **38**: ^{31}P NMR (CD_2Cl_2): δ = –9.5 (s, PPh_2). Resin **39**: ^{31}P NMR (CD_2Cl_2): δ = –7.6 (s, PPh_2). Resin **40**: ^{31}P NMR (CD_2Cl_2): δ = –10.2 (s, PPh_2).

Synthesis of the polymer-supported phosphinooxazoline allylpalladium complexes 41/42/43: A solution of $[Pd(C_3H_5)Cl]_2$ (0.014 mmol, 50 mg) in anhydrous and deoxygenated toluene (1 mL) was added to an oven-dried Schlenk flask which contained the corresponding resin **38/39/40** (0.26 mmol) previously swollen with anhydrous and degassed toluene (4 mL). The reaction mixture was shaken for 1 h. The resin was filtered, rinsed with toluene (10 mL) and CH_2Cl_2 (200 mL) and dried *in vacuo* for 12 h.

Resin 41: ^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.87-6.73 (m, polymer), 6.70-5.85 (m, polymer), 5.24 (m, 1H), 5.13 (m, 2H), 4.84-3.88 (m, 2H), 2.24 (m, 2H), 1.99 (m, 2H), 1.95-0.86 (m, polymer); ^{13}C NMR (HRMAS, CD_2Cl_2): δ= 146.5-144.3 (m, polymer), 141.3 (CH), 138.1 (CH), 135.5-131.1 (m, CH), 130.2-126.6 (m, CH), 126.5-124.1 (m, CH), 119.8 (m, CH), 116.0-105.8 (m, polymer), 85.2 (CH), 76.4 (CH), 73.2 (CH_2), 53.6 (m, CH_2), 47.2-42.7 (m, polymer), 41.5-39.4 (m, polymer), 29.8 (CH_2), 25.6 (CH_2); ^{31}P NMR (CD_2Cl_2): δ = 28.24 (s, PPh_2); IR (ATR): ν = 3024, 2920, 1630, 1591, 1542, 1492, 1451, 1435, 1341, 1277, 1181, 1122, 1100, 1041, 1020, 998, 910, 749, 695 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 2.48; found: C 76.86, H 6.47, N 2.28; f = 0.33 mmol g^{-1}.

Resin 42: ^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.63-7.28 (m, polymer), 7.25-6.82 (m, polymer), 6.73-6.17 (m, polymer), 5.29 (m, 1H), 5.17 (m, 2H), 4.77-4.16 (m, 2H), 2.28 (m, 2H), 2.05 (m, 2H), 2.25-1.68 (m, polymer) 1.66-0.87 (m, polymer); ^{13}C NMR (HRMAS, CD_2Cl_2): δ = 146.6-144.8 (m, polymer), 138.1 (CH), 135.5-131.4 (m, CH), 129.1-128.0 (m, CH), 127.9-126.8 (m, CH), 126.6-126.1 (m, CH), 126.0-125.5 (m, CH), 125.5-124.6 (m, CH), 114.5-106.0 (m, polymer), 85.4 (CH), 79.6 (CH), 73.5 (CH_2), 53.7 (m, CH_2), 47.8-42.4 (m, polymer), 41.9-40.8 (m, polymer), 40.7-39.8 (m, polymer), 29.8 (CH_2), 24.7 (CH_2); ^{31}P NMR (CD_2Cl_2): δ= 31.2 (s, PPh_2); IR (ATR): ν= 3055, 3024, 2921, 1633, 1598, 1492, 1451, 1354, 1169, 1125, 1035, 1008, 831, 755, 725, 696 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 2.43; found: C 75.85, H 6.55, N 2.19; f = 0.31 mmol g^{-1}.

Resin 43: ^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.97-5.90 (m, polymer), 5.27-5.20 (m, 2H), 5.17-4.28 (m, 2H), 3.64-3.56 (m, polymer), 3.55-3.41 (m, polymer), 2.24 (m, 2H), 2.17 (m, 2H), 1.80-1.68 (m, polymer), 1.68-1.50 (m, polymer); ^{13}C NMR (HRMAS, CD_2Cl_2): δ = 145.0-140.0 (m, polymer), 134.6-123.6 (m, CH), 119.9 (CH), 114.9-107.6 (m, polymer), 67.7 (CH_2), 53.9 (CH_2), 53.6 (CH_2), 25.6 (CH_2), 25.5 (CH_2); ^{31}P NMR (CD_2Cl_2): δ= 27.5 (s, PPh_2, *exo*), 17.3 (s, PPh_2, *endo*); IR (ATR): ν= 3025, 2920, 1625, 1598, 1491, 1452, 1339, 1214, 1180, 1122, 1047, 1028, 999, 909, 755, 695 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 4.77; found: C 67.73, H 6.03, N 4.83; f = 0.69 mmol g^{-1}.

General Procedure for Palladium-Catalyzed Allylic Alkylation: Thermal Conditions Allylic alkylation.[2] In an oven-dried Schlenk tube containing [Pd(η^3-C_3H_5)Cl]$_2$ (7.32 mg, 0.02 mmol) was added a solution of the corresponding phosphino-imidazoline ligand (0.044 mmol) in CH_2Cl_2 (2 mL) under argon, and stirred for 30 min to prepare the palladium complexes. Then, (*E*)-3-acetoxy-1,3-diphenyl-1-propene **18** (250 mg, 1.0 mmol), dimethyl malonate (0.350 mL, 3.0 mmol), BSA (0.740 mL, 3.0 mmol) and a catalytic amount of KOAc (0.02 mmol) were successively added to the solution mixture. The mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with diethyl ether, filtered over celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure. The crude mixture was filtered through a short SiO_2 pad eluting with ethyl acetate. The conversion of the reaction was measured after removing the solvent by ^{1}H NMR of the crude mixture. Enantiomeric excesses were determined from the residue by HPLC[2] on a OD-H column (0.5 mL/min, hexanes/isopropyl alcohol, 99:1, 254 nm): (*R*)-**19** Rt = 23 min, (*S*)-**19** Rt = 25 min.

General Procedure for Palladium-Catalyzed Allylic Alkylation: Microwave-Assisted Conditions.[2] In an oven-dried Schlenk tube containing [Pd(η^3-C_3H_5)Cl]$_2$ (7.32 mg, 0.02 mmol) was added a solution of the corresponding phosphino-imidazoline ligand (0.044 mmol) in CH_2Cl_2 (2 mL) under argon, and stirred for 30 min to prepare the palladium complexes. Then, (*E*)-3-acetoxy-1,3-diphenyl-1-propene **18** (250 mg, 1.0 mmol), dimethyl malonate (0.350 mL, 3mmol), BSA (0.740 mL, 3.0 mmol) and a catalytic amount of KOAc (0.02 mmol) were successively added to the solution mixture. The resulting solution was heated under microwave reactor in power control mode (8 W) for 3 h. Isolation of compounds was performed as stated before (*vide supra*).

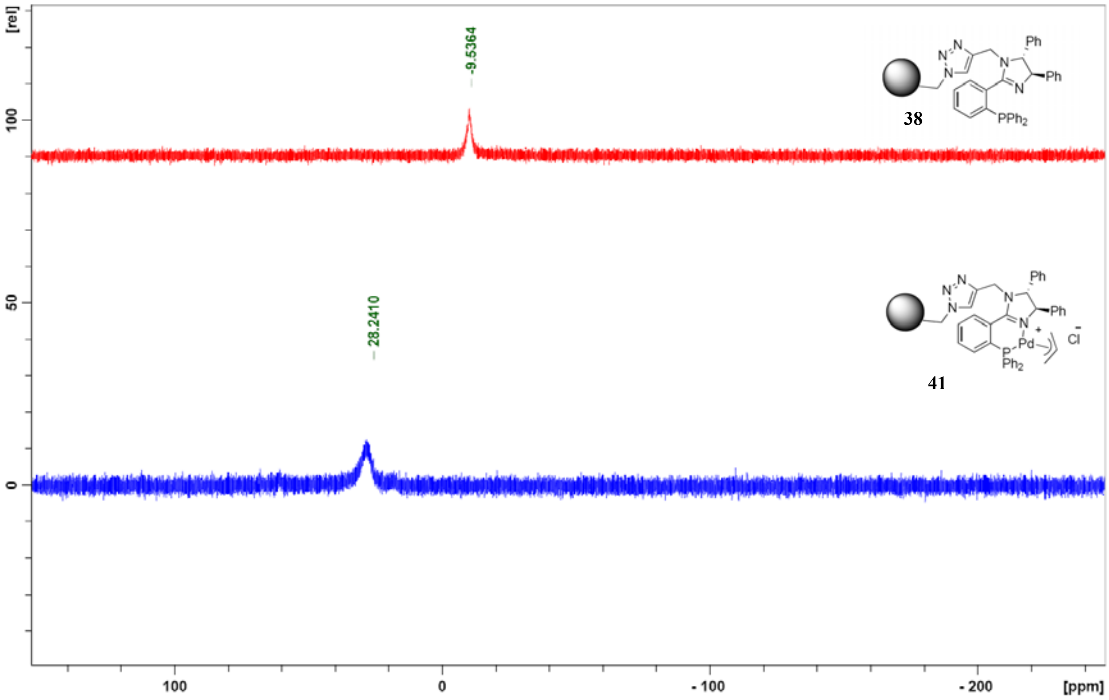
General Procedure for Palladium-Catalyzed Allylic Alkylation of Substrate 27.[2] The procedure was analogous to the general previous procedure for allylic alkylation, but using instead of (*E*)-3-acetoxy-1,3-diphenyl-1-propene **18**, the substrate (*E*)-3-acetoxy-1,1,3-triphenyl-1-propene **27**. The enantiomeric excesses were determined by HPLC[2] on a AD-H column (0.3 mL/min, *n*-hexane/isopropyl alcohol, 97:3): (*R*)-**28** Rt = 49.4 min, (*S*)-**28** Rt = 51.6 min.

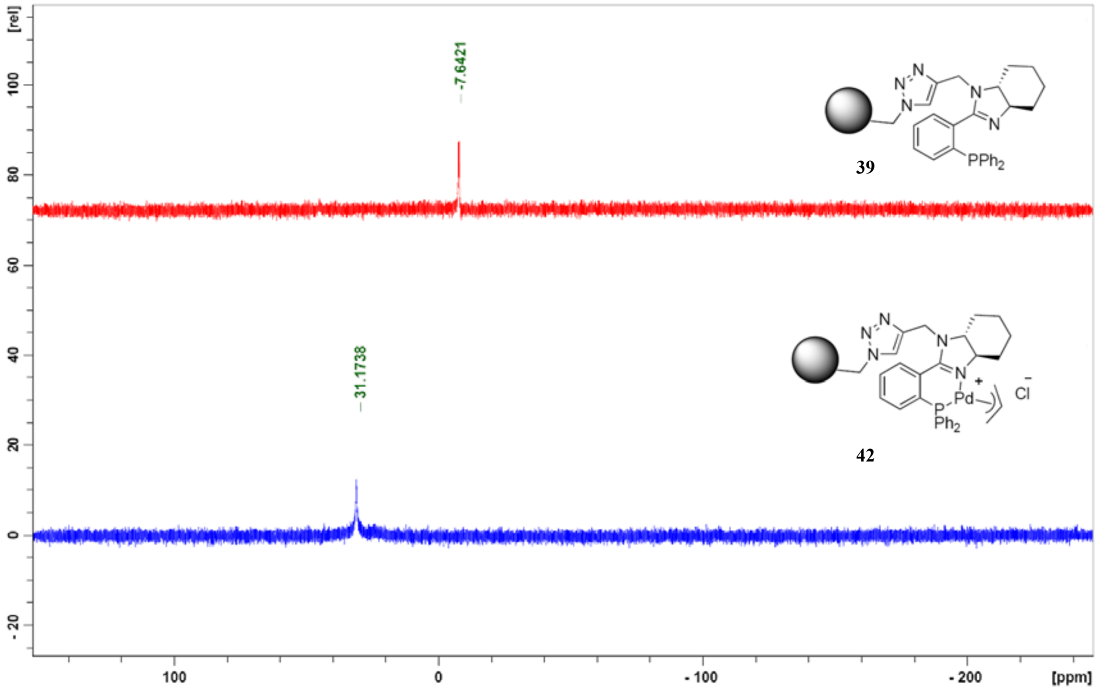
General Procedure for the Palladium-Catalyzed Allylic Amination with different Nitrogen Nucleophiles.[1c] In an oven-dried Schlenk tube containing [Pd(η^3-C_3H_5)Cl]$_2$ (1.84 mg, 0.005 mmol) was added a solution of the corresponding phosphino-imidazoline ligand (0.011 mmol) in CH_2Cl_2 (2 mL) under argon, and stirred for 30 min to prepare the palladium complexes. Then, (*E*)-3-acetoxy-1,3-diphenyl-1-propene **18** (62.5 mg, 0.250 mmol), the nitrogen nucleophile **29-34** (0.750 mmol), BSA (0.185 mL, 0.750 mmol) and catalytic amount of KOAc (0.005 mmol) were successively introduced. The mixture was stirred at room temperature for 24-48 h. The reaction mixture was then diluted with diethyl ether, filtered over celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous $MgSO_4$. The residue was purified through a short SiO_2 pad eluting with (hexanes/EtOAc from 100:0 to 80:20). The conversion of the reaction was measured after removing the solvent by ^{1}H NMR of the crude mixture. The enantiomeric excess was determined by HPLC[1c] on the corresponding column and method.

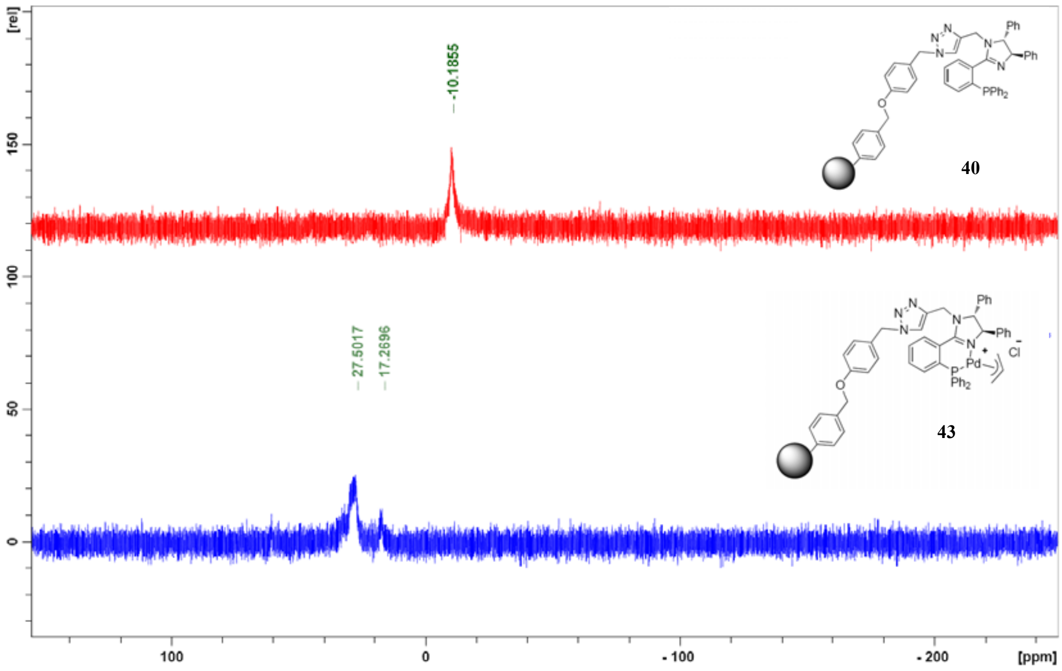
General Procedure for the Palladium-Catalyzed Allylic Amination with different Nitrogen Nucleophiles using Polymer Complexes.[1c] To an oven-dried vial for microwave reactor containing the corresponding polymer complexes (0.015 mmol), previously swollen with anhydrous and degassed CH_2Cl_2 (0.05 mL) under argon, were successfully added (*E*)-3-acetoxy-1,3-diphenyl-1-propene **18** (35 mg, 0.158 mmol), the corresponding nitrogen nucleophile **29-34** (0.474 mmol) and BSA (0.103 mL, 0.416 mmol). The reaction mixture was heated in a microwave reactor in power control mode (8 W) for 3h (unless stated otherwise, see Table 6). Then the resin was filtered off and rinsed with anhydrous CH_2Cl_2 (3x0.5 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20). The enantiomeric excess was determined by HPLC[1c] on the corresponding column and method.

General Procedure for the Recycling Experiments. (*E*)-3-acetoxy-1,3-diphenyl-1-propene **18** (35 mg, 0.138 mmol), benzylamine **29** (0.045 mL, 0.416 mmol) and BSA (0.103 mL, 0.416 mmol) were added *via* syringe to an oven-dried vial for microwave reactor containing the polymer complex **43** (22 mg, 0.015 mmol), previously swollen with anhydrous and degassed CH_2Cl_2 (0.05 mL) under argon. The reaction mixture was heated in a microwave reactor in power control mode (8 W) for 3h. The temperature of the reaction mixture, measure with an internal, Teflon-coated Pt-100 probe, was 40ºC. Then, the solution was removed under argon *via* cannula and the resin was rinsed with dichoromethane (3x0.5 mL) and dried under argon for 10 min. The resin was pre-swollen again with CH_2Cl_2 (0.05 mL), the reactants were added and the mixture was reacted as indicated before. The same resin was used for each cycle and no further Pd source was added. Isolation of compounds was performed as stated before (*vide supra*).

^{31}P NMR spectra of resins 38/39/40 and 41/42/43







2 - References

[1] K. Harju, M. Vahermo, I. Mutikainen, J. Yli-Kauhaluoma, *J. Comb. Chem.* **2003**, *5*, 826; b) S. Löber, P. Gmeiner, *Tetrahedron* **2004**, *60*, 8699; c) D. Popa, R. Marcos, S. Sayalero, A. Vidal-Ferran, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 1539.

[2] D. Popa; C. Puigjaner; M. Gómez; J. Benet-Buchholz; A. Vidal-Ferran; M. A. Pericàs, *Adv. Synth. Catal.* **2007**, *349*, 2265-2278.

CHAPTER 4

IMMOBILIZATION OF *N,N*-LIGANDS AND THEIR USE IN RU-CATALYZED ASYMMETRIC TRANSFER HYDROGENATION REACTION

4.1 INTRODUCTION

4.1.1 METAL-CATALYZED ASYMMETRIC TRANSFER HYDROGENATION OF KETONES

Enantioselective reduction of prochiral ketones to yield enantiopure secondary alcohols is a reaction of great interest, due to the importance of these alcohols as intermediates in the production of pharmaceuticals and advanced materials.[1]

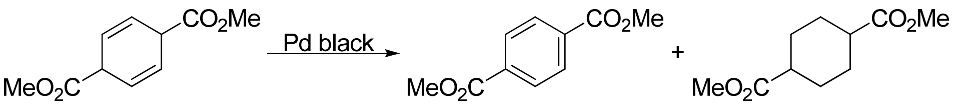
For more than half a century, stereoselective reduction of simple ketones relied heavily on the stoichiometric metal chemisty developed largely by H. C. Brown.[2] Chemoselective reduction of a C=O function has been best effected by the use of reagents such as $NaBH_4$ or $LiAlH_4$ in stoichiometric amounts.[3] Diastereoselctive reduction of ketones has frequently been achieved by Selectrides,[4] or other commercially available chiral complex metallic hydrides like BINAL-H.[5] In a similar way, enantioselective reduction of achiral ketones has been effected by the use of stoichiometric amounts of chiral boron-containing reagents, like DIP chloride[6] and Alpine-borane,[7] or by the Corey-Bakshi-Shibata (CBS) method combining B_2H_6 or catecholborane and a chiral oxazaborolidine catalyst.[8]

Homogeneous catalytic asymmetric hydrogenation of ketones, using chiral metal complexes, has also been extensively studied. It is the simplest, but one of the most powerful ways to produce a wide array of important compounds in large quantities using inexpensive, clean hydrogen gas without forming any waste. Catalytic hydrogenation was initiated at the end of the 19th century by P. Sabatier,[9] who used fine metal particles as heterogeneous catalysts.[10] Until very recently, these types of selective C=O reductions were not generally achievable by catalytic hydrogenation.[11] Nowadays, some metal complexes have been successfully used for this process, like BINAP-Ru(II),[12,13] which have proved extremely efficient for the asymmetric hydrogenation of functionalized ketones. This has led to the industrial production of synthetically important pharmaceutical intermediates like Levofloxacin and carbapenem antibiotics.[14]

In addition to the different methods explained herein, the Asymmetric Transfer Hydrogenation (ATH) represents an extremely practical alternative since it exhibits the main advantages of hydrogenation while avoiding the use of flammable hydrogen gas as a reducing agent, as well as the necessity of pressure vessels. Taking into account the versatility and practical simplicity of ATH it can be considered as a powerful alternative to asymmetric hydrogenation for catalytic reduction. Transfer hydrogenation (or hydrogen transfer reduction) has been defined as the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst. The process entails hydrogen abstraction from the donor (reagent) followed by, or in concert with, hydrogen addition to the acceptor (substrate). It can be generalized as shown in equation 1 (DH_2 = hydrogen donor, A = hydrogen acceptor).[15,16]

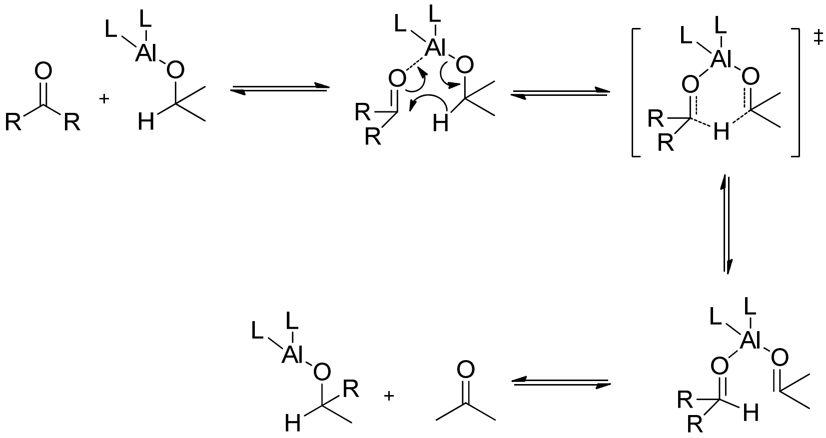
$$DH_2 + A \xrightleftharpoons{\text{cat.}} D + AH_2 \qquad \text{Eq. 1}$$

Knowledge of this process goes back to Knoevenagel, who in 1903 observed that dimethyl 1,4-dihydroterephtalate disproportionated in the presence of palladium black to dimethyl terephtalate and hexahydroterephtalate[17] (Scheme 1). Several years later, Wieland observed the same behaviour with dihydronaphthalene.[18]



Scheme 1: Disproportionation of dimethyl 1,4-dihydroterephthalate, catalyzed by palladium.

The first known examples of ATH of ketones were observed in 1925, when Meerwein and Schmidt performed the reduction of an aldehyde with aluminium ethoxide in ethanol.[19a] The same year Verley reported the reduction of butyraldehyde in the presence of aluminium triethoxide using geraniol as a hydrogen donor.[19b-c] Almost simultaneously, Ponndorf extended the scope to the reduction of ketones with aluminium isopropoxide in isopropanol.[19d] This reaction proceeds through a concerted mechanism involving a six-membered cyclic transition state[20] (Scheme 2).



Scheme 2: Meerwein–Pondorf–Verley (MPV) Mechanism.

Twelve years later, Oppenauer reported also the reverse process (i.e. hydrogen transfer oxidation of alcohols to ketones).[21] This finding demonstrated that hydrogen transfer reactions are reversible and the equilibrium can be shifted towards one way or the other by using an excess of alcohol (reductant) or ketone (oxidant).

Although the MPV reaction and its reverse, the Oppenauer oxidation, were considered from their discovery useful for synthesis of steroids and vitamins,[22,23] other applications were scarce.[24] Moreover, just some catalysts were known for the process, the most important being the original aluminium alkoxides, but also sodium,[25] potassium[23] and zirconium[26] alkoxides.

In the 80's and 90's some improvements were achieved by the introduction of lanthanides like samarium[24,27] and transition metals (Rh(I), Ir, Ru(II))[16] as catalysts.[1]

From then on, transfer hydrogenation has developed enormously, mainly relying on ruthenium catalysts introduced first by Bäckvall,[28] and developed by Noyori[29] into asymmetric versions (see below). In this context, the most

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[1] In fact, though the process is theoretically catalytic, long time passed before the discovery of catalysts being active enough to use them in substoichiometric amounts. In MPV reaction a large excess of the metal alkoxide was used.

popular hydrogen donors include formic acid/triethylamine and isopropyl alcohol (IPA), although some alkenes have also been used as donors. Several catalysts have been reported to be efficient in the asymmetric transfer hydrogenation of carbonyl compounds, nitriles, imines, and activated olefins like conjugated carboxylic acid and amino acid derivatives, azo compounds, nitro compounds and even halides and other hydrogenolysis substrates. The enantiomeric excess (ee) of the product depends on the substrate type, the catalyst and the reaction conditions.[15]

In this work, attention will be focused on transfer hydrogenation involving the formation of a metal (ruthenium) hydride intermediate by interaction of the hydrogen donor with the catalyst, which subsequently transfers the hydride to the substrate.

4.1.1.1 Mechanism

Generally, there are two mechanisms of the metal-hydride mediated transfer hydrogenation. The first one involves direct coordination of the substrate to the metal centre (*inner sphere mechanism*). The second mechanism implies hydrogen bonding and dipolar interactions of the substrate with two different sites of the catalyst (metal-ligand bifunctional catalysis, *outer sphere mechanism*) depending on the nature of the catalyst. In inner sphere mechanisms, a monohydride (MH) or dihydride (MH_2) species may be formed depending on the metal.[15,16,20, 30, 31]

Until 2001, an inner sphere, monohydride mechanism for transfer hydrogenation as outlined in Figure 2 was accepted for Ru catalysts. Base is required to generate the isopropoxide ion, which coordinates to the metal and then β-eliminates forming an M-H reducing species and acetone. Coordination of the ketone, which, in this example, occurs through the carbonyl group, followed by insertion into the M–H bond gives the metal alkoxide intermediate. Alcoholysis of the M-O linkage gives an alcoholic product while regenerating the initial metal alcoxy complex. Coordination of a chiral organic ligand to M results in asymmetric induction.[15,16,20,30,32]

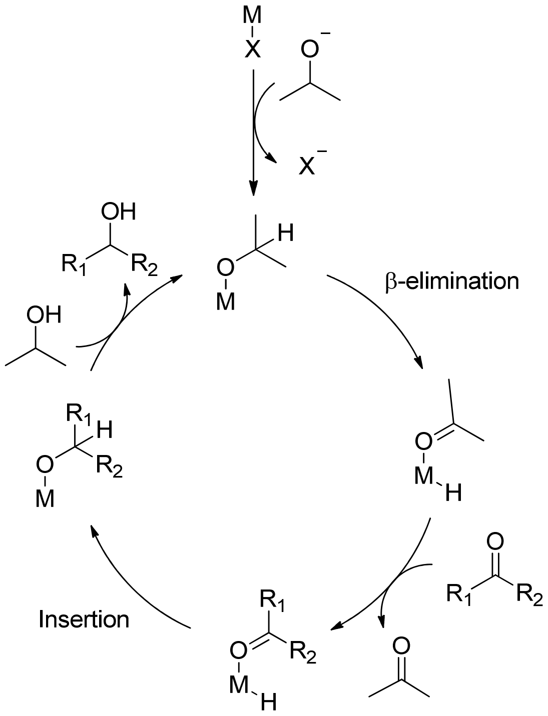


Figure 1**:** Monohydride Inner sphere hydridic mechanism for TH. (X = anionic ligand, typically a halide).

However the non-classical outer sphere mechanism is much more important for the present topic. It occurs mainly with diamine-metal complexes which Noyori terms metal ligand bifunctional catalysts.[31,33] This is the mechanism that the vast majority of the successful systems for ATH work by.

This mechanism was first proposed by Noyori for the [Ru(TsDPEN)(η^6–arene)X] system. In this kind of catalytic systems neither the ketone nor the alcohol coordinate directly the metal centre, but the hydride is transferred in concert with a proton from the ligand, (the carbonyl reduction occurs in the outer sphere of the metal hydride complex). Theoretical calculations along with experimental findings support this mechanism, suggesting the hydrogen transfer takes place *via* the six-membered pericyclic transition state.[31,34,35] (Figure 2).

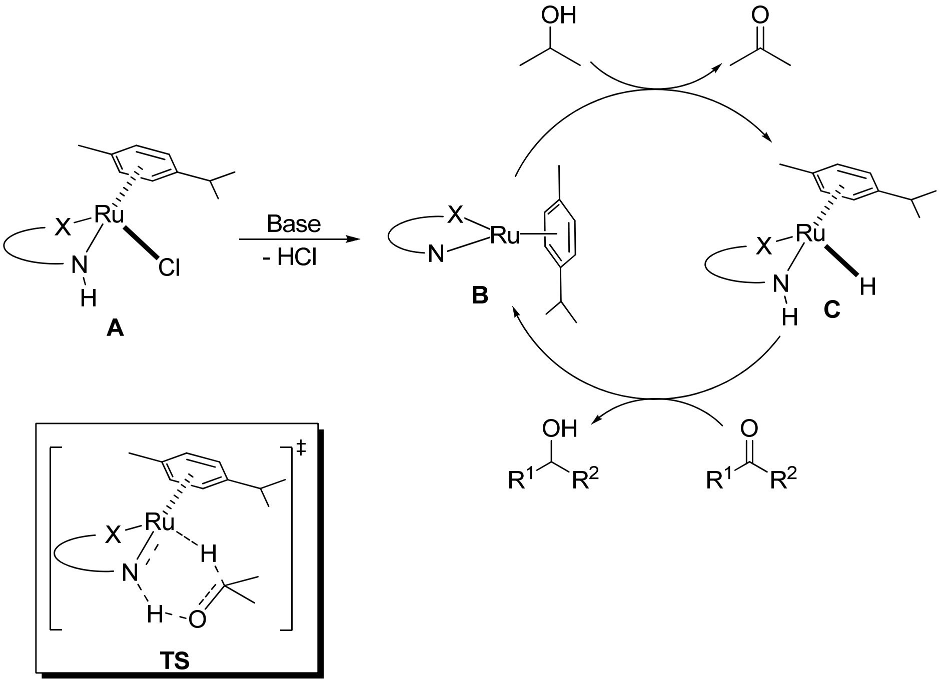


Figure 2**:** Outer sphere, metal–ligand bifunctional mechanism of ATH.

In 1997 the three key complexes in the process with the TsDPEN ligand were isolated and characterized by X-ray crystallography:[36] the precatalyst (**A**), together with the two intermediates of the catalytic cycle, the 16–electron planar complex **B** and the 18–electron octahedral monohydride **C**.

KOH or other base is necessary for the generation of Ru-complex **B** from the precatalyst **A** by elimination of HCl. It can be transformed back to **A** by treatment with triethylammonium chloride. **B** reacted readily with primary and secondary alcohols (hydrogen donor) to afford **C**. On the other hand, **C** reacted with ketones (substrates) to afford **B**. Most significantly, both **B** and **C** catalyzed the transfer hydrogenation of ketones without base, with identical results, at the same rate and with the same enantioselectivity, and identical also to those obtained with the *in situ* formed catalyst. A kinetic study of the catalytic cycle showed that the interconversion between **B** and **C** takes place either directly or *via* a very short-lived intermediate and that no other complexes limiting the catalytic turnover are involved. There is no evidence that other ruthenium complexes were involved in these processes.

4.1.2 NITROGEN-CONTAINING LIGANDS IN METAL-CATALYZED ASYMMETRIC TRANSFER HYDROGENATION OF KETONES

Chiral phosphines are surely the most popular ligands in asymmetric catalysis, and they have indeed been employed in transfer hydrogenation since the very beginning, but without much success.[16] However, it should be noted that the most used chiral ligands in ATH contain nitrogen as the donor atom. A brief summary of the most notable nitrogen-containing ligands and their performance is described below.

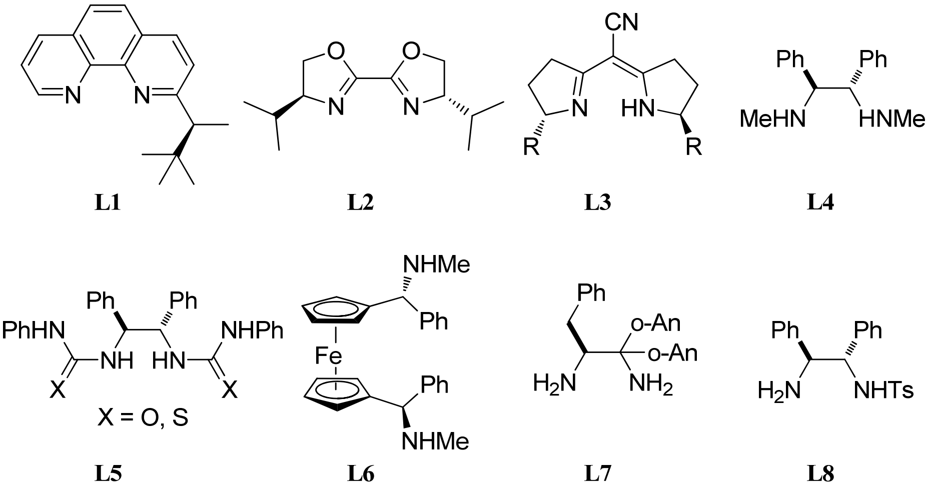
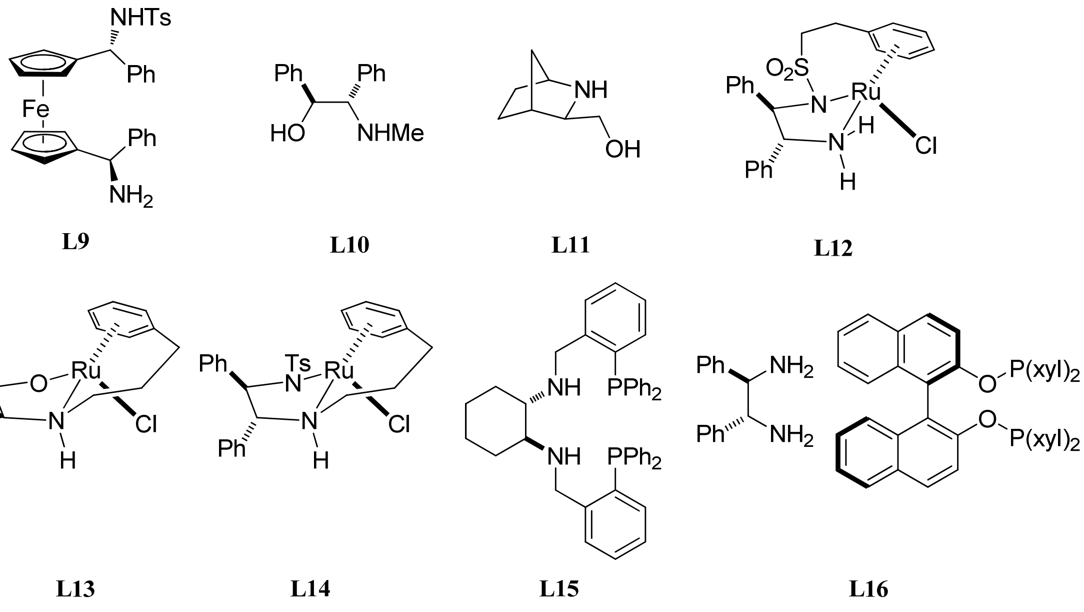


Figure 3**:** Nitrogen-containing ligands used in asymmetric transfer hydrogenation

Some of the earliest catalytic systems disclosed using nitrogen-containing ligands were bipyridine and phenanthroline rhodium and iridium complexes. In 1990, Gladiali *et al*. used chiral phenanthrolines of the type **L1**[37] and chiral imines as ligands in the reduction of acetophenone. Although the enantioselectivities were modest (60% ee), they showed very high activity in the transfer hydrogenation. In contrast, Pfaltz *et al.* reported the use of C_2-symmetric bisoxazoline **L2**[38] with iridium, which furnishes reduction products in excellent enantioselectivity (90% ee) and moderate activities. Semicorrins **L3** did not produce similar results when they were used in this reaction (no significant catalytic activity).

Rh complexes of C_2-symmetric chiral diamines **L4** have been studied by Lemaire *et al.*,[39] obtaining modest results in terms of enantioselectivity. However better results (91% ee) were achieved using the bis(urea) and the bis(thiurea) **L5** (X = O, S respectively) with ruthenium.[40] Knochel has also utilized C_2-symmetric diamines, typified by **L6**, to give products of up to 90% ee. In this case with the additional advantage that the reduction can be carried out at temperatures as low as –30 ºC.[41] On the other hand, Noyori reported the combination of iridium with the diamine **L7**, which is excellent for reduction of a wide range of ketones.[42]

Of all the developments in this area in recent years perhaps the most important and significant one is the rise in status of monotosylated 1,2-diamines. This work has been led by Noyori,[29] who has reported the use of ruthenium complexes containing an spectator arene ligand in combination with TsDPEN **L8** and other chiral amino sulphonamides as ligands.[43] These catalytic system works in the presence of a strong base, with IPA or formic acid:triethylamine azeotrope as hydrogen donor. The latter system has generally afforded excellent enantioselectivities for a wide array of substrates because of the irreversible nature of the transfer. The choice of the arene ligand is also important; complexes of either *p*-cymene or mesitylene give as a rule better selectivities than those of benzene alone.



L9 **L10** **L11** **L12**

L13 **L14** **L15** **L16**

Figure 4: Nitrogen-containing ligands used in asymmetric transfer hydrogenation

After this ground-breaking work by Noyory, other ligands mimicking the behaviour of mono *N*-tosyl diamines have been studied. Attending to the mechanism (see above, Figure 2), ligands containing a free amine NH moiety together with an acidic group have been successfully tested. In this context, Knochel has reported some monoarylsulfonylated ligands **L9** derived from diaminoferrocene.[41] These complexes afforded good levels of enantioselectivity, some of which were close to those obtained using **L8**.

Moreover, β-amino alcohols, like **L10** and **L11** introduced by Noyori *et al*.[44] in 1996 and by Andersson *et al*.[45] in 1999, respectively, showed in general higher activities with similarly good enantioselectivities.[46]

The attempts to use ligands with other coordinating groups besides amine, like phosphine oxides,[47] carboxylates,[48] amides,[49] thiols,[50] triazoles,[51] or even aromatic carbon atoms have been less successful.[52]

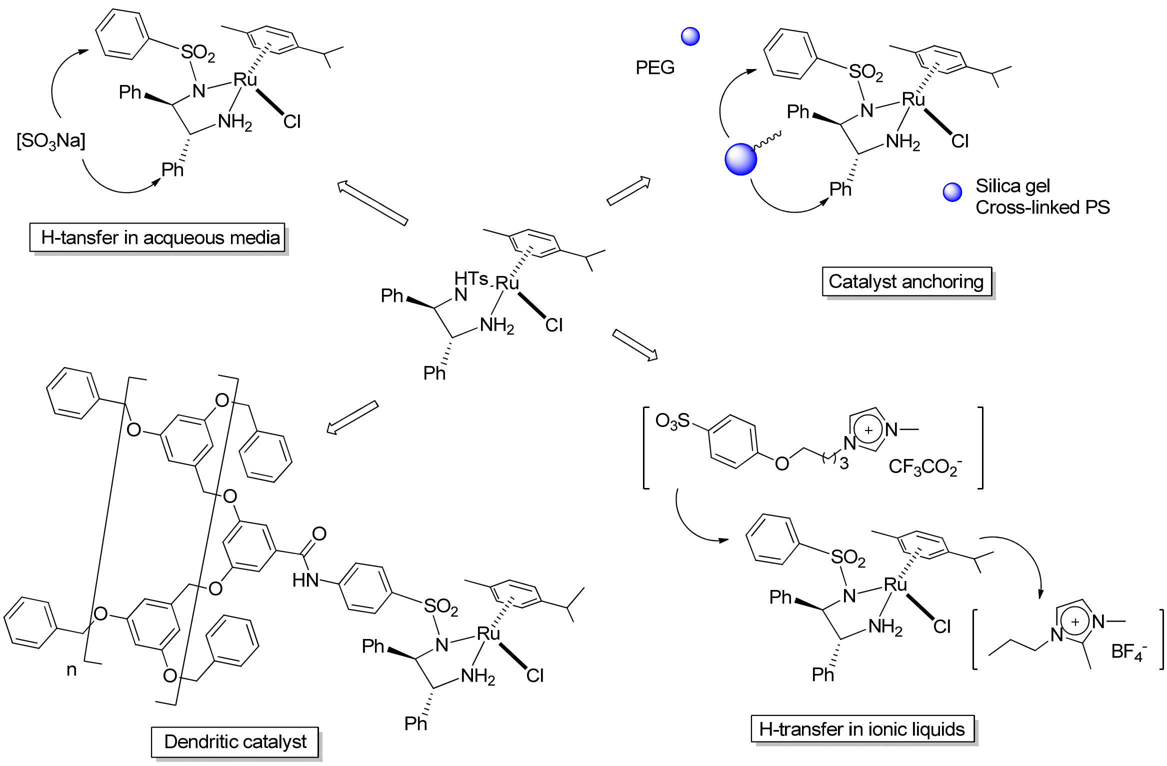
Some of the most flourishing contributions after Noyori's ligands were done by Wills *et al.*, who introduced modifications to the amino sulfonamide and amino alcohol ligands by linking the arene and the amine moieties together by a tether. (Figure 4 Ligands **L12-L14**).[53] This strategy afforded more rigid and stable catalysts resulting enhanced activity while preserving high enantioselectivity.

On the other hand, Ru(II) complexes containing tetradentate bis(amino phosphine) ligand **L15** described by Noyori, has been applied in the transfer hydrogenation of aromatic ketones. Although it offered good enantioselectivities, it was far less effective.[31,34,54] Similarly, Morris *et al.*[55] developed a catalytic system formed by (*R*,*R*)–DPEN together with a BINOL-derived diphosphinite (**L16)** which achieved slightly better reaction rates maintaining enantioselectivities. Another series of nitrogen-containing phosphine ligands like phosphinooxazolines[56] and pyridine-based diphosphine[57] have been tested with different results.

4.1.3 SUPPORTED LIGANDS IN RU-CATALYZED ASYMMETRIC TRANSFER HYDROGENATION OF KETONES

Despite the great practical advantages of ATH over other methods for industrially obtaining enantiopure chiral alcohols, the process can still be improved. In this context, use of heterogenized catalysts would be extremely useful due to the easy recovery and subsequent recycling of the catalytic species. It is also important that heterogenization allows suppressing metal contamination in the reaction products. Product contamination by metal leaching is particularly unacceptable for the production of fine chemicals and pharmaceuticals.

Scheme 3 summarizes some elaborations of TsDPEN catalyst in this direction. Analogous modifications have been carried out on other successful catalytic systems, like aminoalcohols[58] or diaminophosphines.[59]



Scheme 3: Modifications of Noyori-Ikariya's catalysts aimed towards recyclable catalyst and *green* hydrogen transfer processes.

Deng and coworkers reported the first syntheses and application of chiral TsDPEN analogues enclosed in dendritic ligands by attaching the monomeric ligand onto the focal point of the Fréchet-type dendrimers.[60] High catalytic activity and enantioselectivity were observed in the ATH of acetophenone. Such immobilized catalyst could be reused with slight loss of activity in consecutive runs, resulting from the decomposition of the dendritic ligand. Recently, dendrimers containing peripherally linked chiral diamines were synthesized but showed reduced recyclability compared to the TsDPEN-cored ones.[61]

Interestingly, Noyori's ligand can be modified by introduction of imidazolium tags either at the complexed arene, at the tosyl group or simply using the ligand in an ionic liquid, [bdmin][PF_6].[62] In spite of the positive effects (excellent ee values) arising from the imidazolium salt, asymmetric transfer hydrogenations of acetophenone in an ionic liquid showed that the reusability of the catalysts was largely dependent on the reaction conditions (formic acid/triethylamine versus iPrOH/KOH as donor).

With the aim of developing catalytic systems with tunable solubility in the reaction medium, heterogeneization and aqueous-switching of asymmetric catalysis has been performed *via* immobilization of the TsDPEN unit onto silica or polymeric supports. The silica-supported TsDPEN ligands were developed with amorphous silica gel and mesopores (MCM-41 and SBA-15).[63] Although all of them were tested in the Ru-catalyzed asymmetric transfer hydrogenation of ketones in water with sodium formate with different surfactants, only the amorphous silica gel one exhibited high catalytic activity and enantioselectivity. However the reactivity decreased markedly in the recycling experiments.

The first study on the polymer-supported version of the Noyori-Ikariya's ligand was reported by Lemaire.[64] Although first recycling results were poor, this approach was successfully followed by other groups.[65] The water-soluble polymers involving MeO-PEG-functionalized ligands represent some of the most efficient ligands for ATH in water using HCOONa as the hydrogen source. High rates and excellent recyclability (14 runs) were obtained with Xiao's catalytic system, but the enantioselectivities were moderate (93% ee).[65] Better enantioselectivity (95-96% ee) was achieved by Li, Chan *et al.*[67] in eight runs using PEG-BsDPEN.

On the other hand, water solubility can be achieved by sulfonylation of either the phenyl substituents of the diamine ligand or the tosyl group. Itsuno and coworkers[68] have developed a series of PS-supported TsDPEN ligands, consisting of a polystyrene main chain and highly hydrophilic sulfonylated pendant groups, for use in water. Hydrophilicity-hydrophobicity balance of the polymer-support can be readily controlled by changing the salt (from Na^+ to quaternary ammonium). These polymer catalysts exhibited a high catalytic performance (3h, 100% conversion) to afford 98% ee. However these supported complexes were reused just 5 times.

4.1.4 AIMS

All of these approaches of immobilization of Noyori's ligand are of interest but mainly require the use of additional additives or deep catalyst modifications. These syntheses are thus normally tedious and time-consuming. In most of the cases they try to develop systems able to work in water. Therefore, avoiding the catalyst complexity required to work in water, we conceived the plan of developing a simple yet efficient and robust polymer-supported version of TsDPEN that could work under highly concentrated reaction conditions in the ATH.

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4.2 PAPER C

POLYSTYRENE-SUPPORTED DPEN: A MOST PRACTICAL REAGENT FOR THE ENANTIOSELECTIVE TRANSFER HYDROGENATION OF KETONES

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Polystyrene-Supported Enantiopure 1,2-Diamines: Development of a Most Practical Catalyst for the Asymmetric Transfer Hydrogenation of Ketones

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Dedicated to the memory of Professor Rafael Suau

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Abstract. Chlorosulfonylated polystyrene, a commodity resin, reacts with enantiopure 1,2-diamines to afford, in a single step, high loading catalytic resins involving monosulfonylated 1,2-diamino moieties. These functional polymers forms stable RuCl(*p*-cymene) complexes that efficiently catalyze (down to S/C = 150) the asymmetric transfer hydrogenation (ATH) of alkyl aryl ketones with formic acid-triethylamine under essentially solvent-free (down to 0.25 mL/mmol) reaction conditions. Among these resins, the immobilized version of TsDPEN stands as a most practical catalyst for ATH: Uniformly high enantioselectivities are achieved with its use at low catalyst loading, and the resin can be recycled with virtually no limits.

Keywords: asymmetric catalysis; hydrogen transfer; N,N-ligands; ruthenium; ketones; polymer supporting

Introduction

The Ru-catalyzed asymmetric transfer hydrogenation (ATH) of prochiral ketones is one of the most attractive methods for the production of ubiquitous secondary alcohols in enantiopure form.[1] The main advantages of the method lie on the very efficient control of enantioselectivi-ty through the use of the Noyori-Ikariya catalyst,[2] the use of cheap and safe reducing agents (isopropyl alcohol, sodium formate, formic acid-triethylamine[2c]) and the possibility of employing energetically and environmentally benign reaction conditions.

Although the reaction can be normally carried out at high substrate/catalyst ratios, the use of ruthenium species in the process is the only important negative factor in view of its possible implementation at the production level.

Probably for this reason, a very important effort has been devoted to the development of immobilized versions of the Noyori-Ikariya and other well established catalysts.[3,4] Immobilization should not only allow the easy recovery and recycling of the expensive catalytic species, but also mitigate or suppress metal contamination in the reaction products.

The different strategies reported up to date for the immobilization of the Noyori-Ikariya catalyst include: (a) the interaction of monomeric TsDPEN with a polymeric ruthenium complex,[5] (b) the development of soluble polymers involving MeO-PEG-functionalized 1,2-diaryl-1,2-ethylenediamine,[6] (c) the reaction of DPEN with chlorosulfonylated matrices such as ionic liquids,[7] dendrimers,[8] silica,[9] or complex PS-derived resins,[10] and (d) the copolymerization of *N*-(*p*-vinylbenzenesulfonyl)-PEG with styrene, divinylbenzene, and other co-monomers involving polar, hydrophilic groups.[11]

The design of these supported ligands has been generally guided by the goal of developing catalytic systems that work in water; probably for this reason, an important price of catalyst complexity has been paid.

While water presents obvious advantages as a solvent with respect to cost and availability, its decontamination can be more problematic than that of low boiling point organic solvents.[12] With this idea in mind, we conceived the plan of developing a polymer-supported version of Noyori-Ikariya catalyst showing good compatibility with the formic acid-triethylamine reagent that could minimize or even suppress the use of additional solvents. This could be achieved through the use of highly functionalized polystyrene resins that would be used in minute amounts in pre-swollen form.

We wish to report here the development of a polystyrene-supported TsDPEN ligand that can be prepared in one step from commercial reagents and whose Ru complex efficiently catalyzes the highly enantioselective transfer hydrogenation of alkyl aryl ketones with formic acid/triethylamine in the presence of a small amount of dichloromethane.[13]

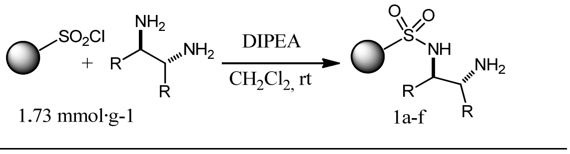
Results and Discussion

Preparation of catalytic resins.

As a preliminary stage in this study, a set of enantiomerically pure, C_2 symmetrical 1,2-diamines was selected, and the corresponding catalytic resins **1a-f** were prepared. We reasoned that the polymeric nature of the sulfonylating reagent and the presence of an excess of diamine would efficiently control the sulfonylation level, and that the process would preferentially lead to monosulfonylation.

Very gratifyingly, the supporting process could be per-formed in a single step from commercial chlorosufonyl-ated polystyrene (PS-1%DVB, 100-200 mesh, nominal loading: 1.0-1.5 mmol/g) and the corresponding 1,2-diamine (2 equiv) in dichloromethane at room temperature in the presence of DIPEA (Scheme 1). The exact functionalization of the starting resin (f_0 = 1.73 mmol.g^{-1}, corresponding to 22% chlorosulfonylated phenyl rings in the polymer chains) was determined (see Supporting Information for details) by elemental analysis either directly (S) or by conversion into the corresponding sulfonamide with *N*-methylpiperazine (N).

Table 1. Preparation of catalytic resins **1a-f**.



Resin	R or R-R	Mono [%]	*f* [mmol.g^{-1}]
1a	phenyl	86	1.01
1b	cyclohexane-1,2-diyl	94	1.09
1c	2-naphthyl	85	0.86
1d	cyclohexyl	96	1.20
1e	2,4,6-trimethoxyphenyl	60	0.45
1f	2,4,6-trimethylphenyl	100	1.19

Elemental analysis of resins **1a-f** (N) allowed us to establish the proportions of mono- and bis(sulfonylated) diamine present on the different polymers and, therefrom, the effective functionalization in monosulfonylated diamine (*f*) of the polymers (Table 1). In this manner, for example, it was determined that 86% of the DPEN molecules were anchored through a single nitrogen atom in **1a** (Figure 1), corresponding to an effective functionalization of *f* = 1.01 mmol.g^{-1}; for the rest of the diamines similar or higher levels of monosulfonylation were recorded, and only in the case of resin **1e** a high level of doubly linked diamine (leading to a rather low effective functionalization) was observed. In any case, it is important to recall here that macrocyclic or cross-linked structures involving *N*,*N'*-bis(sulfonylated) diamines would be inert in front of $[RuCl_2(p\text{-cymene})]_2$ and, accordingly, would not interfere with the planned reaction (Figure 1).

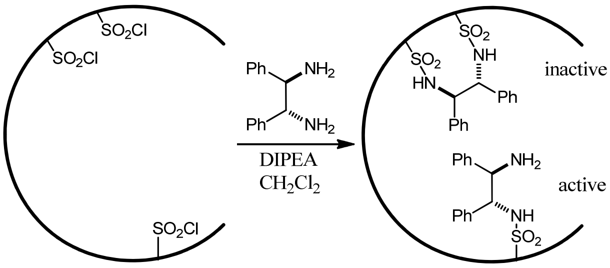


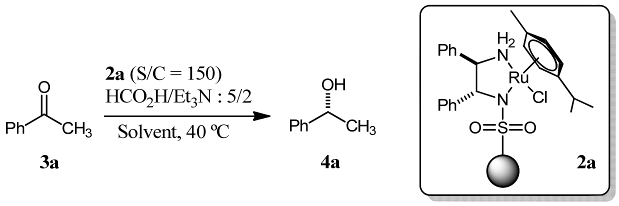
Figure 1. Schematic representation of the reaction of highly loaded chlorosulfonylated PS (1.73 mmol.g^{-1}) with (*R*,*R*)-DPEN leading to bis-sulfonylated (inactive) and monosulfonylated (active) DPEN units.

Functional resins **1a-f** could be converted to the corresponding Ru(II) complexes (**2a-f**) by treatment with $[RuCl_2(p\text{-cymene})_2]_2$ in dichloromethane at 40 ºC for 1 h. Both the supporting and the complexation processes could be assessed by gel-phase NMR.[11c] This is illustrated in the Supporting Information for the case of **1a**.

Determining the optimal catalytic resin and the optimal reaction conditions.

With catalytic resins **2a-f** in hands, optimal conditions for use (reducing agent, solvent, temperature) were screened in the transfer hydrogenation of acetophenone (**3a**) catalyzed by **2a**. The results of this study have been summarized in Table 2. Resin **2a** was initially tested (entry 1) in the presence of a small amount of dichloromethane (less than 1 mL per mmol of substrate), at rather high substrate to catalyst ratio (150/1), at 40 ºC. Under these conditions the resin was perfectly swollen, and reduction took place to completion in 24h, leading to (*S*)-**4a** of 97% ee. When the reaction was repeated at room temperature (entry 2), reaction rate markedly decreased. With water as the solvent (entries 3 and 4), the catalytic resin was less efficiently swollen, and conversion remained low (37%) even after 48 h. Finally, when isopropyl alcohol was tested as the solvent and the reducing agent (entry 5), both conversion and enantioselectivity were disappointingly low. Thus, the conditions of entry 1 were selected for the rest of the study.

Table 2. Optimization of reaction conditions for the ATH of acetophenone catalyzed by **2a**.



Entry	Solvent	Time [h]	Conv. [%][a]	ee [%][a]
1	CH_2Cl_2	24	99	97
2[b]	CH_2Cl_2	48	20	94
3[c]	H_2O	24	22	86
4[c]	H_2O	48	37	85
5[d]	$^{i}PrOH$	96	9	6

[a] Conversion and ee were determined by GC. [b] The reaction was performed at rt, and HCO_2H/Et_3N (5:3) was used as the reducing agent. [c] $NaHCO_3$ (5 equiv) was used as the base. [d] KOH was used as the base.

To determine the optimal catalytic resin, **2b-f** were next evaluated in the same reduction process under reaction conditions identical to those previously optimized for **2a** (Table 3). Very interestingly, except for **2e** and **2f**, the other catalytic resins also exhibited high levels of catalytic activity and led to the reduction product with high enantioselectivity (>93% ee). The catalyst derived from *trans*-1,2-cyclohexanediamine (**2b**) yielded full conversion but somewhat lower ee (93% ee) than the supported Noyori-Ikariya catalyst **2a**. The 2-naphtyl derivative **2c**, in turn, led to lower conversion (71%) and no improvement in enantioselectivity (entry 3). On the other hand, the results obtained with **2d** (entry 4) are remarkable and totally comparable to those provided by **2a**. Enantiopure 1,2-dicyclohexylethylenediamine, however, is far more expensive than DPEN, and cannot compete with it in a practical sense. Finally, sterically demanding catalysts such as **2e** and **2f** showed a marked inhibition of activity, which indicates that excessive crowding around the metal prevents the fulfilment of the stereoelectronic requirements for the reaction to proceed.

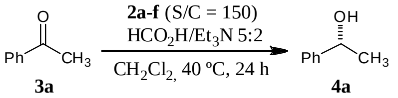
From these results, it turns out that the optimal catalyst is the one derived from the interaction of enantiopure 1,2-diphenylethylenediamine (DPEN) with chlorosulfonylated polystyrene (resin **2a)**, which combines excellent activity and enantioselectivity with easy availability. It is worth noting that the preparation of **2a** does not add any synthetic complexity or additional steps over the preparation of the homogeneous Noyori-Ikariya catalyst.

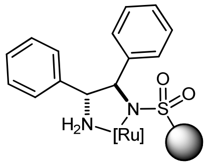
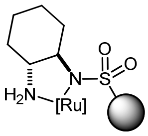
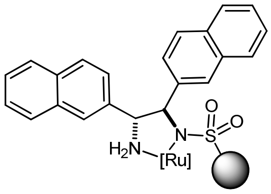
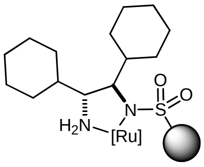
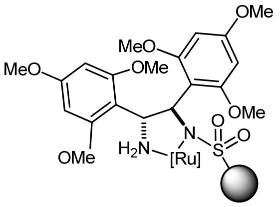
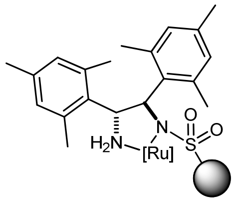
Substrate scope.

The scope of the reduction with **2a** was next tested on a representative family of alkyl aryl ketones (**3b-o**) under the optimized conditions previously developed for **3a**. Results obtained in this study have been summarized in Table 4.

As it can be seen, the studied family of substrates includes unsubstituted alkyl aryl and alkyl hetaryl ketones (**3a-d**), *o*-substituted aryl substrates, including bicyclic systems (**3e-h**), *m*-substituted substrates (**3i-k**), and *p*-substituted substrates (**3l-o**). In most cases, the reductions are complete after 24h. The reactions are in all cases very clean, and only the reduction products are formed.

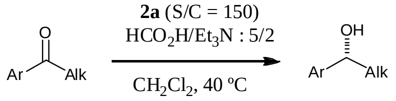
Table 3. Evaluation of resins **2a-f** in the catalytic ATH of acetophenone.



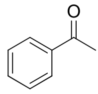
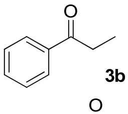
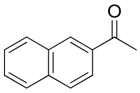
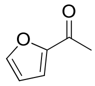
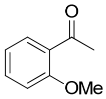
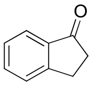
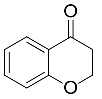
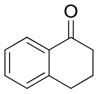
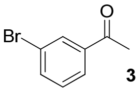
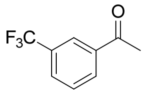
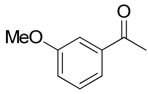
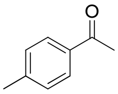
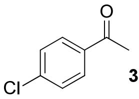
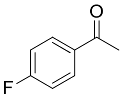
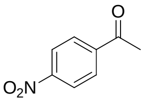
	Resin	Conv. [%][a]	ee [%][a]
2a		99	97
2b		99	93
2c		71	93
2d		99	96
2e		0	-
2f		7	n.d.

[a] Conversion and ee determined by GC on a chiral ß-DEX column.

Table 4. Scope of the ATH of alkyl aryl ketones catalyzed by **2a**.



3a-o **4a-o**

Substrate	Time [h]	Conv [%][a]	ee [%][a]
 **3a**	24	99	97
 **3b**	24	96	93
 **3c**	24	99	97
 **3d**	24	93	93
 **3e**	24	26	86
 **3f**	36	99	96
 **3g**	24	99	99[b]
 **3h**	48	86	99
 **3i**	24	99	97[c]
 **3j**	24	99	91
 **3k**	24	99	94
 **3l**	30	96	97
 **3m**	24	99	92
 **3n**	36	98	93
 **3o**	24	99	88

[a] Conversion and ee were determined by GC. [b] $[\alpha]_D^{25}$: +71.4 (*c* 0.98, $CHCl_3$). [c] $[\alpha]_D^{25}$: +31.9 (*c* 1.10, $CHCl_3$).

Simple alkyl aryl ketones **3a-d** are excellent substrates for the reaction, and only the increase of the alkyl chain size leads to a slight decrease of enantioselectivity (**3b**). Among *o*-substituted systems, the presence of a methoxy group appears to reduce reactivity and enantioselectivity. However, the integration of such a substituent into a ring (in **3h**) leads to high reactivity and virtually complete enantioselectivity. Finally, for *m*-substituted (**3i-k**) and *p*-substituted substrates (**3l-o**), where substituents covering a range of electronic characters have been explored, it becomes evident that electron-withdrawing substituents (in **3j** and **3o**) lead to slightly decreased enantioselectivities, while electron-donating ones (in **3i** and **3l**) have the opposite effect.

From a general perspective, it is also worth paying attention to the favourable reaction conditions associated to the use of catalytic resin **2a**. In a preparative experiment, the asymmetric transfer hydrogenation of 3'-bromoacetophenone (**3i**) was achieved at a 4 mmol scale using 1.6 mL of the HCO_2H/Et_3N azeotrope (the reducing agent) and only 1 ml of dichloromethane (0.25 mL/mmol substrate) as resin swelling agent. Under these conditions conversion was 85% after 20 h reaction, and 680 mg of **4i** (84% yield) with *R* configuration (97% ee) could be isolated after aqueous workup.

For some of the examples studied here (**3a-d**, **3f**, **3h**, **3k**, **3m**), a direct comparison can be made with the results obtained with the homogeneous Noyori-Ikariya catalyst with the same reducing agent.[2c] For this set of examples, the mean reaction time for complete conversion (28.5 h) and the mean ee of the resulting alcohols (95.1%) recorded with **2a** compares well with the corresponding values (38.5 h, 97.5% ee) recorded with the homogeneous catalyst (reactions at 28 ºC, with S/C = 200).

Catalyst recycling and reuse.

A further aspect in the performance of resin **2a** that also deserves comment is the possibility of its recovery and re-use. The recycling studies have been performed with acetophenone **3a** as a representative substrate, and the experiments have been planned to be performed in a single flask containing the catalyst sample, where reactants and solvents can be introduced or withdrawn *via* cannula. In a initial series of experiments, the reduction of **3a** was performed in three consecutive runs with the same sample of catalyst working at the usual substrate to catalyst ratio of 150. Following separation of the reaction crude, the resin was simply washed with dichloromethane, and the reagents for the next run were added.

Very interestingly, enantioselectivity kept constant (97%) over the three experiments; conversion, in turn, suffered some deterioration (1st cycle: >99% in 24h; 2nd cycle: 92% in 48h; 3rd cycle: 80% in 48h). We reasoned that this combined behaviour could be due to mechanical etching of the resin beads in the stirred reaction flask, which could provoke a decrease in the effective amount of catalyst after every cycle.

In order to minimize the possible effect of catalyst losses during manipulation between cycles, a second series of experiments was planned where the substrate/catalyst ratio was decreased to 12.5 and the stirring rate was fixed to 500 rpm. Under these conditions, reaction time was very substantially reduced, conversion in the first cycle being complete after 3 h. Even under these conditions, however, rate slightly decreased with every run, which made necessary to increase reaction times to achieve full conversion. In this way, almost full conversion was achieved for 5 consecutive runs, but only 62% conversion was observed after 48 h in the 6th run (Figure 2).[4b] As in the initial experiments, enantioselectivity kept constant (97%) over the whole series.

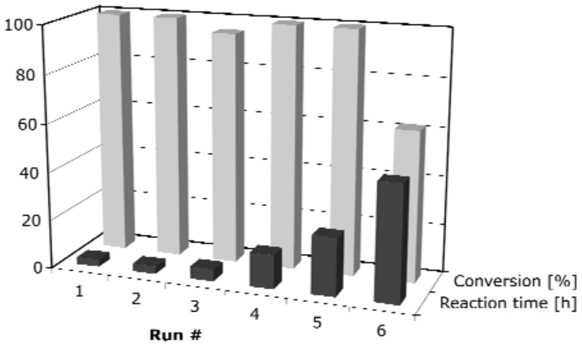


Figure 2. Recycling of catalyst **2a** in the asymmetric transfer hydrogenation of acetophenone at S/C = 12.5. Enantioselectivity (ee) was 97% in all runs. Reaction time was selected in each cycle to maximize conversion.

These results led us to speculate on alternative explanations for activity losses between consecutive reaction cycles and, more specifically, for the significant one observed between the fifth and sixth reaction cycles. As a matter of fact, we realized that important losses of catalytic activity took always place whenever resin **2a** was dried and stored before the next run, as it had happened between cycles 5 and 6 in the experiments represented in Figure 2. We reasoned that after an ATH reaction cycle, the catalytic resin would not be in the form of the stable precatalyst but, rather, in the form of a highly reactive ruthenium hydride. When stored dry, this reactive species would likely decompose to some extent, and this will result in extended reaction time for full conversion in the next reaction cycle. Most importantly, the same decomposition process could also take place during reaction cycles if ATH processes are reactions are driven to full conversion. Thus, in the final part of each cycle when conversion increases only marginally, and the ketone substrate has been essentially depleted, the catalytically active species could also suffer decomposition processes. With these observations in mind, we hypothesized that two simple measures: (a) stopping reaction cycles before full conversion, and (b) conserving resin samples wet in acetophenone between cycles could avoid the deactivation problem and thus extend catalyst life cycle.

To test this hypothesis, a new recycling experiment was planned where time length of individual cycles was fixed to a rather short value (1 h; expected conversion: 75%) and kept constant in order to allow the observation of any possible decrease in catalytic activity, while intercycle catalyst decomposition would be avoided by storing the resin wet in acetophenone. It is interesting to note that these reaction conditions represent a feasible simulation of continuous flow operation of ATH with **2a**, where the duration of individual cycles would be infinitely short.[14] We have represented in Figure 3 the performance of the reaction along the recycling experiment.

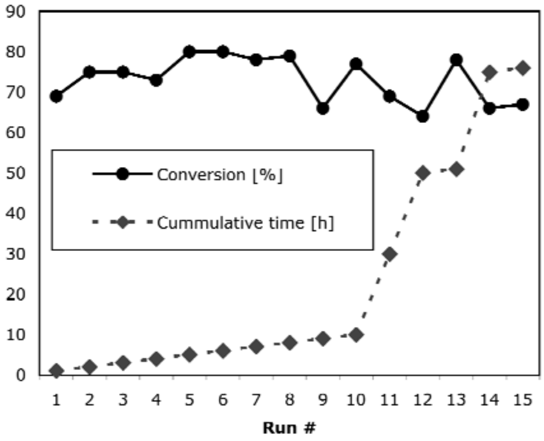


Figure 3. Recycling of catalyst **2a** in the asymmetric transfer hydrogenation of acetophenone at S/C = 12.5. Enantioselectivity (ee) was 97% in all runs. Reaction time was kept at 1 hour for each run.e resin

In an initial series of ten consecutive cycles of ATH of acetophenone (S/C = 12.5; 1 h), the catalyst was immediately reused after every run. In this manner, it was unambiguously established that the activity of the catalyst was well preserved (Figure 3). After the 10th run, resin **2a** was stored wet with neat acetophenone for 20 hours, then washed and reused. Quite interestingly, GC analysis of the acetophenone used as storage media revealed the presence of 1-phenylethanol **4a**, thus confirming that when the reaction is stopped, Ru-H groups are present on the resin.

Gratifyingly enough, conversion in cycle 11 replicated that of the first cycle. In four additional cycles, including two alternate 20 h rest periods with neat acetophenone catalytic activity was again preserved, conversion in the 15th cycle essentially replicating that of the first one.[15] In total, the same resin sample was used 15 times without significative loss of activity. It thus appears that catalytic resin **2a** can be recycled and reused with practically no limitations, provided that individual cycles are driven to incomplete conversion and that already activated resin samples are stored wet with acetophenone if recycling is temporarily paused.

Conclusions

In summary, a highly efficient yet extremely simple polymer-supported version of the Noyori-Ikariya catalyst has been developed. As an important, differential characteristic, catalytic resin **2a** is assembled in a single step from commercially available precursors. In comparison with previous supported versions of the same catalyst, **2a** presents a high functionalization level. This allows working at high substrate to catalyst ratios (up to 150/1) under essentially solventless conditions. Moreover, resin **2a** exhibits high recyclability provided that measures are taken to preserve the chemical integrity of the catalytically active Ru-H species. All together, these characteristics convert resin **2a** into an excellent catalyst for ATH reactions.

Experimental Section

Preparation of Resin 1a

To a suspension of chlorosulfonyl polystyrene (0.4 g, f = 1.73 mmol g^{-1}) in anhydrous CH_2Cl_2 (14 mL) under nitrogen, DIPEA (0.24 mL, 1.4 mmol) and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (0.29 g, 1.4 mmol) were sequentially added. The reaction mixture was shaken under nitrogen at room temperature for 24 h. The resin was collected by filtration, sequentially washed with CH_2Cl_2, THF, MeOH, MeOH:water 1:1, MeOH, THF, and CH_2Cl_2. and dried *in vacuo* overnight at 40 ºC. ^1H NMR (HRMAS, $CDCl_3$): δ = 5.14-4.82 (m, CHNH-$CHNH_2$) ppm. IR (ATR): ν 1318, 1152 cm^{-1}. An effective functionalization of monosulfonylated DPEN, f_{Mono} = 1.01 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis; found: N, 3.34% (see Supporting Information for details).

Preparation of Resin 1b

The same procedure for resin **1a** was followed, using (1*R*,2*R*)-1,2-diaminocyclohexane (237 mg, 2.08 mmol) as the 1,2-diamine reactant. IR (ATR): ν 1310, 1151 cm^{-1}. An effective functionalization of monosulfonylated (1*R*,2*R*)-1,2-diaminocyclohexane, f_{Mono} = 1.09 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis; found: N, 3.71%.

Preparation of Resin 1c

The same procedure for resin **1a** was followed, using (1*S*,2*S*)-1,2-bis(2-naphtyl)ethylen-1,2-diamine (475 mg, 1.52 mmol) as the 1,2-diamine reactant. IR (ATR): ν 1326, 1153 cm^{-1}. An effective functionalization of monosulfonylated (1*S*,2*S*)-1,2-bis(2-naphtyl) ethylen-1,2-diamine, f_{Mono} = 0.86 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis; found: N, 2.94%.

Preparation of Resin 1d

The same procedure for resin **1a** was followed, using (1*S*,2*S*)-1,2-bis(cyclohexyl)ethylen-1,2-diamine (342 mg, 1.52 mmol) as the 1,2-diamine reactant. IR (ATR): ν 1323, 1153 cm^{-1}. An effective functionalization of monosulfonylated (1*S*,2*S*)-1,2-bis(cyclo-hexyl)ethylen-1,2-diamine, f_{Mono} = 1.20 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis; found: N, 3.53%.

Preparation of Resin 1e

The same procedure for resin **1a** was followed, using (1*S*,2*S*)-1,2-bis(2,4,6-trimethoxyphenyl)ethylen-1,2-diamine (596 mg, 1.52 mmol) as the 1,2-diamine reactant. IR (ATR): ν 1307, 1153 cm^{-1}. An effective functionalization of monosulfonylated (1*S*,2*S*)-1,2-bis(2,4,6-trimethoxyphenyl)ethylen-1,2-diamine, f_{Mono} = 0.45 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis; found: N, 2.35%.

Preparation of Resin 1f

The same procedure for resin **1a** was followed, using (1*S*,2*S*)-1,2-bis(2,4,6-trimethylphenyl)ethylen-1,2-diamine (450 mg, 1.52 mmol) as the 1,2-diamine reactant. IR (ATR): ν 1327, 1148 cm^{-1}. An effective functionalization of monosulfonylated (1*S*,2*S*)-1,2-bis(2,4,6-trimethylphenyl)ethylen-1,2-diamine, f_{Mono} = 1.19 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis; found: N, 3.33%.

Preparation of the Catalytic Resins 2a-2f. Typical experimental procedure (2a)

Resin **1a** (0.032 g, $f_{MonoDPEN}$ = 1.01 mmol g^{-1}, 0.032 mmol) was swollen in anhydrous, dichloromethane (5 mL). $[RuCl_2(p\text{-cymene})]_2$ (0.030 g, 0.0122 mmol) was added, and the mixture was stirred at 40ºC for 1 h. Resin **2a** was then collected by filtration and washed with anhydrous dichloromethane (3x5 mL). ^1H NMR (HRMAS, $CDCl_3$): δ = 5.27-5.23 (m, 1H), 5.16-5.10 (m, 1H) (CHNH-CHNH2), 2.00 (s, 3H, Me).

Typical Procedure for ATH with Resin 2a

The catalytic resin **2a** was prepared in situ from resin **1a** (0.0120 g, f_{Mono} = 1.01 mmol g^{-1}, 0.0121 mmol), swollen in anhydrous dichloromethane (1 mL) and $[RuCl_2(p\text{-cymene})]_2$ (0.0025 g, 0.0041 mmol). The mixture was stirred at 40ºC for 1 h under argon, and then the ketone substrate **3** (1.25 mmol) was added, followed by formic acid (0.24 mL, 6.25 mmol) and triethylamine (0.35 mL, 2.5 mmol) . The mixture was stirred at 40ºC for 24-48 h (see Table 2) as dictated by GC analysis of aliquots taken at different reaction times. After cooling to room temperature, the reaction mixture was filtered through a pad of celite. GC analysis at this point allowed determination of conversion and enantioselectivity. In preparative experiments, the filtrate was diluted with CH_2Cl_2 and washed with aq. sat. $NaHCO_3$ and brine. After concentration, the corresponding alcohol was isolated in pure form. In recycling experiments, the reaction mixture was transferred through a filtering cannula, the catalytic resin was washed with anhydrous, degassed dichloromethane (2x1 mL), and the reaction process was immediately repeated by addition of the same amounts of solvent, substrate, and reducing agent employed in the first cycle.

Acknowledgements

We thank MICINN (grant CTQ2008-00947/BQU and Consolider Ingenio 2010 grant CSD2006-0003), DURSI (grant 2009SGR623), and the ICIQ Foundation for financial support. R. M. thanks MICINN for a predoctoral fellowship.

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[14] Carbon dioxide evolution during reduction hampers the implementation of experimental set-up's for the real continuous flow asymmetric ATH reduction of ketones with **2a** in packed columns.

[15] Rest periods appear to provoke a temporary decrease in catalytic activity, but this is recovered in the next consecutive cycle.

Supporting Information

Polystyrene-Supported Enantiopure 1,2-Diamines: Development of a Most Practical Catalyst for the Asymmetric Transfer Hydrogenation of Ketones

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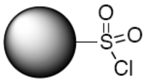
Table of Contents

i) Calculation of the functionalization of the commercial chlorosulfonyl resin by elemental analysis

The degree of functionalization of a resin can be calculated from the results of elemental analysis with the formulas:

$f_N = (0.714/n_N)\%N$, where n_N is the number of nitrogen atoms in the functional unit and %N is the percent of nitrogen provided by the elemental analysis, and

$f_S = (0.3125/n_S)\%S$, where n_S is the number of sulfur atoms in the functional unit and %S is the percent of sulfur provided by the elemental analysis



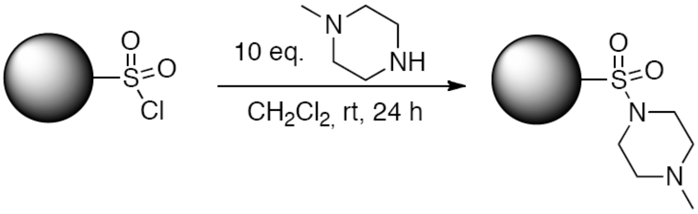
The commercial resin employed in this study gave the following elemental analysis

EA: 75.67% C, 6.28% H, 0.09% N, 5.51% S

Thus, the functionalization calculated from the sulfur elemental analysis is:

$f_S = (0.3125)5.51 = 1.722\ \text{mmol.g}^{-1}$

To obtain an independent estimate of the reactive groups in the starting polymer, the commercial resin was reacted with *N*-methylpiperazine, and the functionalization of the new resin f_N' was calculated by nitrogen elemental analysis:



EA: 76.46% C, 7.23% H, 4.38% N.

$f_N' = (0.714/2)4.38 = 1.564$

To obtain an independent estimate of the functionalization of the initial resin, the following formula can be used:

$f_{\text{chlorosulfonylated}} = f_N'/[1 + f_N'(\Delta M_w)10^{-3}]$, where ΔM_w represents the difference in molecular weight between the final (chlorosulfonylated) and initial (sulfonamide) functional fragments (-63.71 mu)

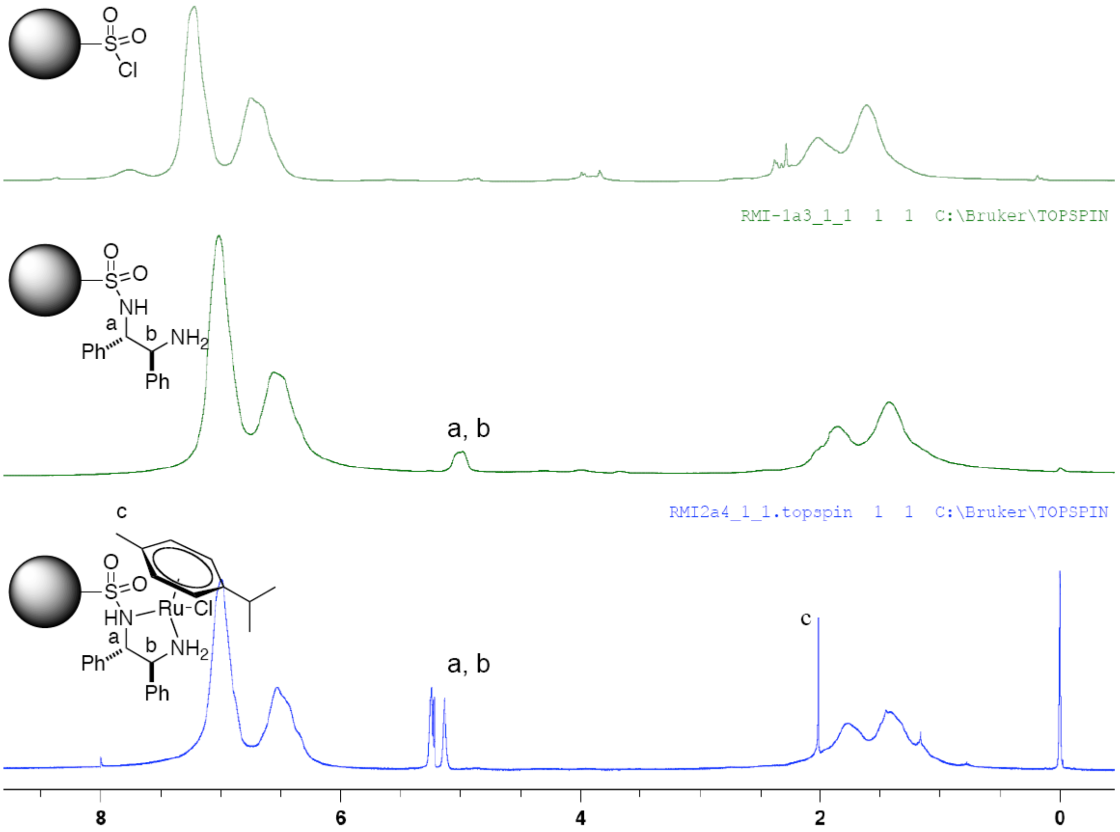
$f_{\text{chlorosulfonylated}} = f_N'/[1 + f_N'(\Delta M_w)10^{-3}] = 1.564/[1 + 1.564(-63.71)10^{-3}] = 1.737\ \text{mmol.g}^{-1}$

The functionalization of the starting resin has been taken as **1.73** mmol.g^{-1}, the mean value of the two independent determinations.

For a reference to the formulas employed here, see: A. Bastero, D. Font, M. A. Pericàs, *J. Org. Chem.* **2007**, *72*, 2460-2468.

ii) Monitoring the conversion of the commercial chlorosulfonyl resin into PS-supported DPEN (1a) and its Ru complex (2a) by gel-phase ^{1}H NMR

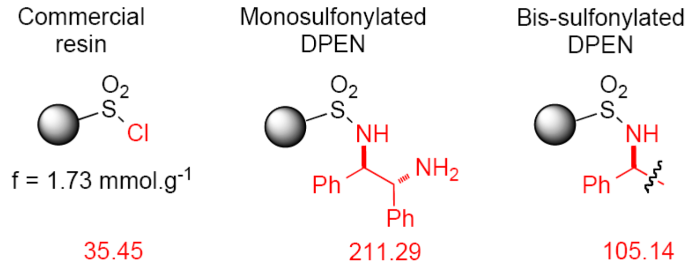
^{1}H-NMR spectra of the catalytic resin ($CDCl_3$, 400 MHz):



iii) Estimation of the effective functionalization of resin 1a in monosulfonylated DPEN by elemental analysis

Functionalization of resin 1a:

Resin **1a** gave the following elemental analysis: 78.31% C, 6.61% H, 3.34% N, 4.62% S.



Taking into account that we know the functionalization of the starting resin, the theoretical value of the N percent in resins where all the supported DPEN was monosulfonylated or bis-sulfonylated can be calculated with the formulas given in i).

Thus, for a resin where all DPEN was monosulfonylated, the maximal functionalization f_{Mono} and the nitrogen percent $\%N_{\mathrm{Mono}}$ can be calculated as:

$f_{\mathrm{Mono}} = 1.73/[1 + 1.73(175.84)10^{-3}] = 1.326$
$\%N_{\mathrm{Mono}} = 1.4nf_{\mathrm{Mono}} = 1.4x2x1.326 = 3.71$

In the same manner, for a resin where all DPEN was bis-sulfonylated, the maximal functionalization f_{Bis} and the nitrogen percent $\%N_{\mathrm{Bis}}$ can be calculated as

$f_{\mathrm{Bis}} = 1.73/[1 + 1.73(69.69)10^{-3}] = 1.544$
$\%N_{\mathrm{Bis}} = 1.4nf_{\mathrm{Bis}} = 1.4x1x1.544 = 2.16$

The experimentally determined %N linearly depends on the proportions of Monosulfonylated and Bis-sulfonylated DPEN in the prepared resin:

$\%N_{\mathrm{Exp}} = x\%N_{\mathrm{Mono}} + (1-x)\%N_{\mathrm{Bis}}$, where x represents the molar fraction of monosulfonylated DPEN

$3.34 = 3.71x + 2.16(1-x)$ By solving, $x = 0.76$

Accordingly, the nitrogen percent corresponding to monosulfonylated DPEN is 2.824, and the effective functionalization of resin 1 in monosulfonylated DPEN is:

$\boldsymbol{f_{\mathrm{Mono}} = (0.714/2)2.824 = 1.01\ \mathrm{mmol.g^{-1}}}$

For the calculation of the percent of monosulfonylated DPEN on the resin, it has to be taken into account that bis-sulfonylated DPEN has been counted as "half-molecules". Then the percent of monosulfonylated DPEN is given by x/x+0.5(1-x). *For x = 0.76, a 86.4% of the DPEN molecules in the resin are monosulfonylated and thus suitable for catalysis.*

CHAPTER 5

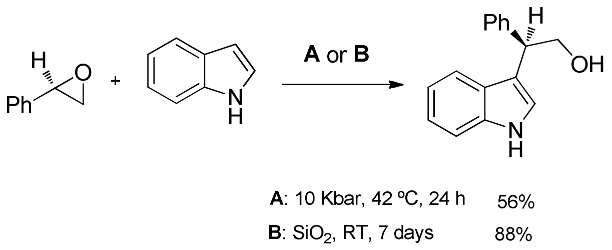
LEWIS ACID-MEDIATED STEREOSPECIFIC REARRANGEMENT OF ARYL GLYCIDY ETHERS

5.1 INTRODUCTION AND AIMS

5.1.1 CATALYTIC STEREOCONTROLLED RING-OPENING OF EPOXIDES BY AROMATIC COMPOUNDS

The ring-opening of epoxides by aromatic compounds in the presence of Lewis acids, bases, and solid acids is widely recognized as an effective methodology in the synthesis of polyfunctionalized compounds.[1] In addition, the availability of enantioenriched *cis* and *trans* epoxides by means of various stereoselective epoxidations[2-6] makes this approach an attractive candidate to use as a tool in the synthesis of optically active aromatic compounds.[7]

This strategy can also be viewed as a Friedel-Crafts β-hydroxyalkylation, and the main drawbacks associated are: i) the occurrence of polyalkylation and ii) the frequent absence of regioselectivity. To date, only a few examples involving enantiomerically enriched epoxides have been described in the literature.



Scheme 1: Stereoselective ring-opening of R-(+)-styrene oxide.

In particular, Kotsuki *et al.* reported the regio- and stereoselective alkylation of indole with (*R*)-(+)-styrene oxide promoted at high pressure or catalyzed by silica gel.[8] (Scheme 1) Recently, hymenialdisine analogues were synthesized also using silica gel as catalyst for ring-opening of epoxides with indoles.[9]

5.1.1.2 Catalytic Stereocontrolled Ring-Opening of epoxides in the presence of Lewis Acids

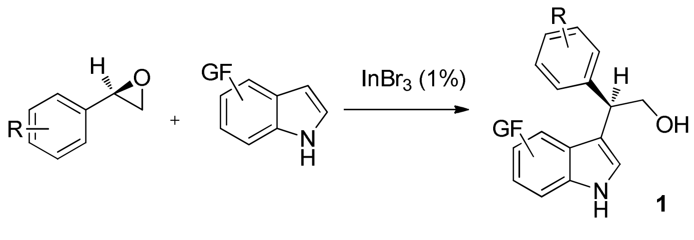
The use of Lewis acids represents a valuable way to promote and control the reactivity of oxiranes toward nucleophiles. It is known that a metal able to form a strong coordinate bond with the oxygen atom of the epoxide ring should increase the electrophilicity of the carbon atoms of the oxirane ring. This effect promotes the ring-opening of the epoxide ring by the nucleophile under mild conditions.[10] Nevertheless, in order to minimize side reactions while maintaining stereocontrol of the process, the electronic features of the Lewis acid must be considered carefully to prevent the formation of carbocation intermediates.

Herein, a brief overview of the catalytic stereocontrolled ring-opening of epoxides in the presence of Lewis acids is presented below.

Indium(III) salts

The mild Lewis acidity of Indium(III) and its relatively low heterophilicity[11] make indium (III) salts suitable candidates for the promotion of stereoselective alkylations of aromatic compounds by the ring-opening of enantiomerically pure epoxides.[12]

In 2002, Umani-Ronchi *et al.* reported an example of the use of indium(III) cations as Lewis acids. A highly stereoselective alkylation of functionalized indoles with enantiomerically pure aryl epoxides was described in the presence of anhydrous $InBr_3$.[13] The reaction, which proceeds exclusively through a regio- and stereoselective S_N2-type pathway at the benzylic position of the epoxide, allows the isolation of several β-3-indolyl alcohols **1** in high yields.[14] (Scheme 2)

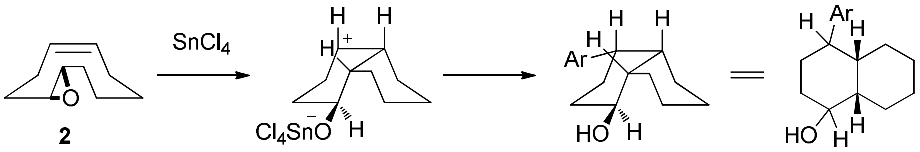


Scheme 2: Regio and stereoselective ring-opening of epoxides catalyzed by $InBr_3$.

Tin salts

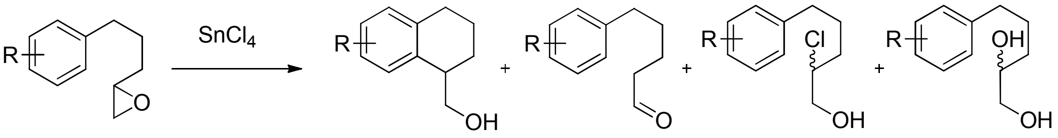
Many different examples have been reported about the use of $SnCl_4$ in reactions involving epoxides.[15] In general, Friedel-Crafts akylation reactions catalyzed by this Lewis acid have not been considered as highly selective, being usually accompanied by isomeration and disproportionation processes.[16]

Notwithstanding, some examples of interesting selective transformations do exist. Taylor *et al.,*[17] when attempting the *cis-trans* isomerisation of *trans*-5,6-epoxy-*cis*-cyclodecene by a conventional technique involving the use of $SnCl_4$,[18] discovered the extremely selective transannular ring-opening. (Scheme 3) This reaction proceeds in combination with a nucleophilic attack on the alkene. This behaviour can be attributed to significant medium-ring strain in the *trans* epoxide and through-space interaction in the transition state, which contribute to the exceptionally facile ring opening of **2**.[19]



Scheme 3: Friedel-Crafts Reactions of *trans*-5,6-epoxy-*cis*-cyclodecene.

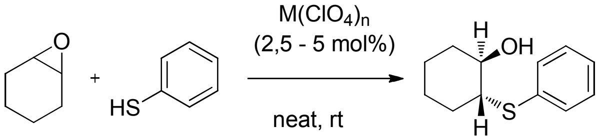
Later on, these same authors established the relative facility for the cycloalkylation of aromatic compounds through intramolecular Friedel-Crafts-type attack at the C-1 or C-2 to form five-, six- and seven-membered rings with $SnCl_4$ acting as the Lewis acid.[20] Some reports suggest that cyclialkylation[21] and other Friedel Crafts reactions developed with epoxides[17,22] were dramatically influenced by the substituents on the aromatic ring. Thus, substituent effects and the efficiency of the employed reaction procedure were investigated.[23] (Scheme 4) The yields were found to be high when the aromatic ring was activated, as expected.



Scheme 4: Epoxide-based cycloalkylation products obtained using $SnCl_4$ as catalyst.

Metal perchlorates

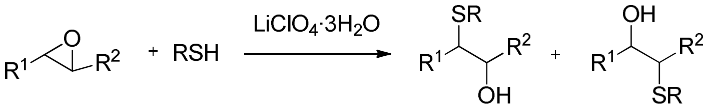
Due to their oxophilic character, groups I and II metals have the potential for being effective and not expensive catalysts. In addition, strongly electron-withdrawing counteranions can be selected in order to further increase the oxophilicity of the metal centre.[10] On this basis, the catalytic efficiency of metal perchlorates for electrophilic activation has been recently examined in the ring-opening of epoxides with thiols.[24] (Scheme 5)



Scheme 5: Ring opening of epoxides with thiols catalyzed by metal perchlorates.

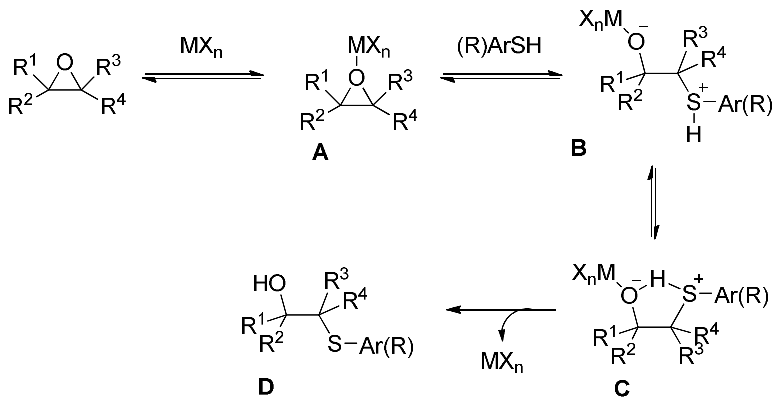
Among the different Lewis acids which have been used to perform this transformation,[25] lithium perchlorate has shown optimal performance, allowing clean reactions with high yields and without rearrangement to carbonyl compounds. In terms of activity, functional group tolerance and regioselectivity, lithium perchlorate is a significantly superior catalyst under solvent-free conditions.

In order to understand the scope and limitations of the use of lithium perchlorate for the preparation of β-hydroxy sulfides, various epoxides were treated with different thiols under solvent-free conditions at room temperature.[26] (Scheme 6) Lithium perchlorate, as a catalyst, offered higher regioselectivity for the ring-opening of styrene oxide with a variety of nucleophiles including aliphatic thiols.[27] However, in this case, high catalyst loading of $LiClO_4$ (12.5 mol%) and longer times were needed in order to complete the reactions.



Scheme 6: $LiClO_4 \cdot 3H_2O$-catalyzed thiolysis of epoxides under solvent-free conditions.

Similarly, other metal perchlorates as $Mg(ClO_4)_2$ and $Ba(ClO_4)_2$ have been shown to efficiently catalyze the nucleophilic ring opening of epoxides.[28] The relative reactivities of these alkaline and alkaline earth metals are generally explained on the bases of their charge to size ratio, metals with higher charge to size ratio being more electrophilic ($Mg(ClO_4)_2 > Ba(ClO_4)_2 > LiClO_4$). On the other hand, $Zn(ClO_4)_2 \cdot 6H_2O$ has been shown to be even more efficient, allowing very fast reactions with low catalyst loadings.[10,29] (Scheme 5).

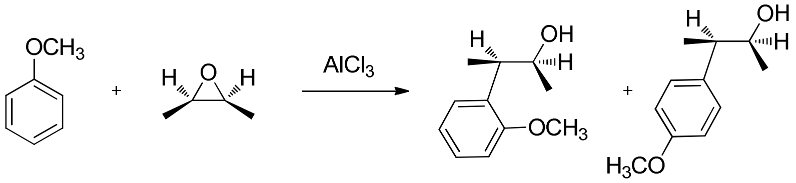


Scheme 7: Role of $Zn(ClO_4)_2{\cdot}6H_2O$ in catalyzing the opening of epoxide ring by thiols.

The lower charge to size (Z^2/r) value of Li^+ and Ba^{2+} ions compared to that of Zn^{2+} ion makes the Li^+ and Ba^{2+} ions significantly less oxophilic than Zn^{2+}. Thus, $Zn(ClO_4)_2{\cdot}6H_2O$ was more effective inducing the *electrophilic activation* of the epoxide ring. Furthermore, the strong electrophilic characteristics of the Zn^{2+} ion efficiently delocalized the negative charge of the oxygen atom and assisted the progress of the reversible reaction in the forward direction.[29] This can be explained on the basis of the mechanism depicted in Scheme 7.[10]

Aluminium(III) salts

Aluminum halides are probably the most widely used commercially available aluminium (III) Lewis acids. Thus, Friedel-Crafts-type reactions catalyzed by aluminium halides and organoaluminium chemistry are some of the most widely studied organic reactions.[16b,30-32] Twenty-seven years ago, Ichikawa described the Friedel-Crafts reaction of toluene or anisole with 2-methyloxirane or with *cis*- and *trans*-2,3-dimethyloxiranes using $AlCl_3$ as catalyst.[33]

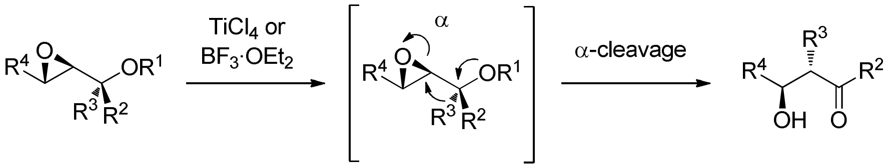


Scheme 8: Friedel-Crafts reaction of anisole with 2,3-dimethyloxirane.

The methylation of anisole can proceed by two paths: the direct alkylation of the aromatic nucleus and the alkylation of oxygen to form an oxonium ion, followed by intermolecular transalkylation.[34] (Scheme 8)

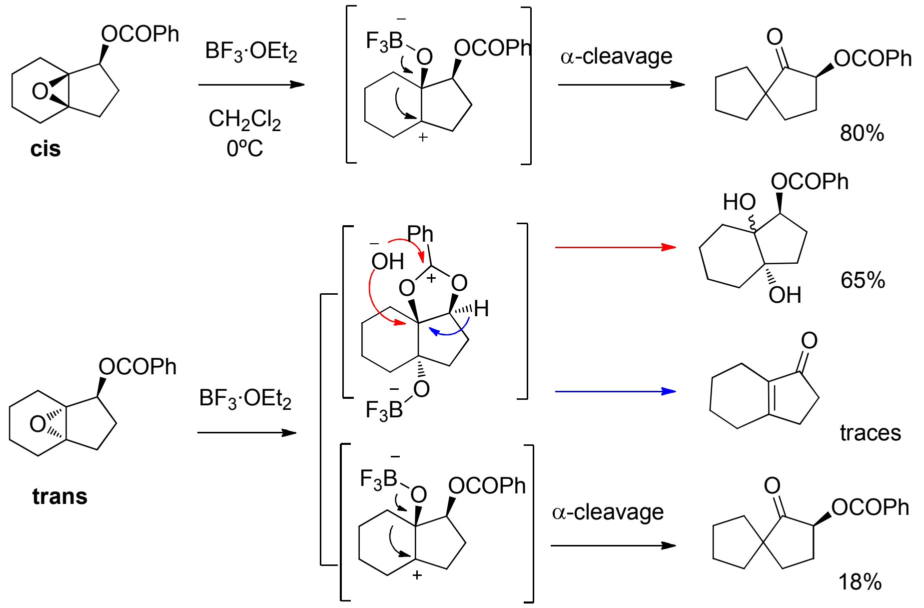
Boron(III) halides

Boron-based Lewis acids, particularly boron trifluoride or other boron halides, have been used in the last decades as catalysts for skeletal rearrangements of epoxyacylates derivatives, to form optically active carbonyl compounds.[35] (Scheme 9) Due to the electron-donating nature of R-oxy groups, the cleavage of the oxirane ring occurred preferentially at its α-position, giving place β-hydroxy carbonyl compounds.[36]



Scheme 9: Cleavage of the oxirane ring and posterior rearrangement to β-hydroxy carbonyl compounds.

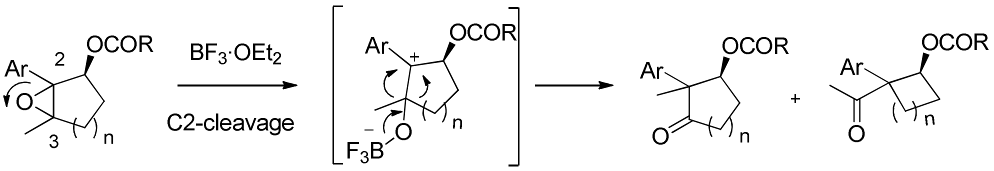
Similarly, there are some examples of the use of boron halides as catalysts for rearrangements of epoxy acylates,[37] providing access to spiro-bicyclic compounds by stereoselective formation of quaternary carbon centres. [38] (Scheme 10) Depending on the relative stereochemistry of the starting material, the reaction can proceed with or without a nucleophilic attack of the acyl group to the epoxide.



Scheme 10: Behaviour of an acyloxy group in the cis- and trans-epoxy benzoates treated with $BF_3{\cdot}OEt_2$.

Kita *et al.* studied the Lewis acid-induced rearrangement of 2,3-epoxy acylates with alkyl substitutents in the C-2 and C-3 positions. Despite the recognized ability of the aciloxy group to act intramolecularly as a nucleophile, the authors succeeded in controlling the regiochemistry of the rearrangement of alkyl substituted 2,3-epoxy acylates via the C-3 cleavage of oxiranes by tuning the bulkiness and electron-withdrawing nature of the acyloxy group.[38,39]

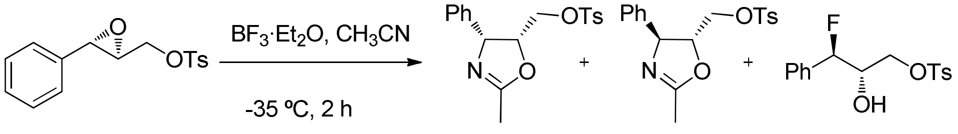
In their synthesis of fredericamycin A,[40] which contains the 2-aryl substituted 2,3-epoxy acylate moiety, the rearrangement proceeded via the C-2 cleavage of the oxirane ring. The carbocation stabilizing ability of the aryl group is stronger than the electron withdrawing nature of the acyloxy-alkyl substituent.[41] (Scheme 11)



Scheme 11: Rearrangement via C2-cleavage of the oxirane ring catalyzed by $BF_3{\cdot}OEt_2$.

In connection with our group's research on the synthesis of new modular ligands for asymmetric catalysis from synthetic epoxides,[42,43] we investigated the synthesis of oxazolines **3** under the influence of boron trifluoride.

Surprisingly, under these reaction conditions, boron trifluoride was able to induce the ring-opening of the oxirane to afford as a by-product fluorohydrin **4** in a completely regio- and stereoselective manner.[44] (Scheme 12)

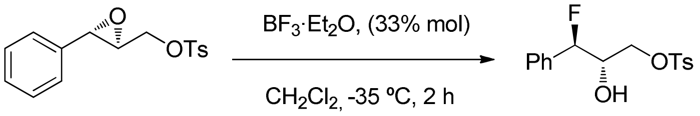


3 (52%) **4** (32%)

Scheme 12: Synthesis of oxazolines from (2*S*,3*S*)-3-phenylglycidyl *p*-toluenesulfonate

Due to the intrinsic interest of enantiopure fluoro alcohols, the observation of this behaviour prompted us to investigate the use of $BF_3 \cdot OEt_2$ as a suitable reagent for the ring-opening hydrofluorination of enantiopure epoxides.

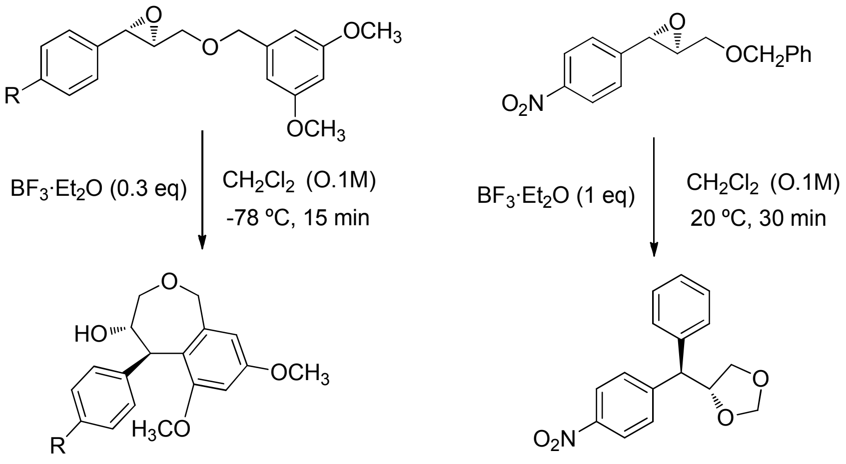
Noteworthy, enantiopure β-fluoro alcohols can be obtained in good yield and with complete regiocontrol under very mild conditions using this methodology. (Scheme 13) Thus, the fast reactions observed in this study contrast with the long reaction times required to induce analogous epoxide ring-opening with other fluoride sources.[45]



4 (71%)

Scheme 13: Ring-opening hydrofluorination of (2*S*,3*S*)-3-phenylglycidyl *p*-toluene sulfonate catalyzed by $BF_3 \cdot OEt_2$.

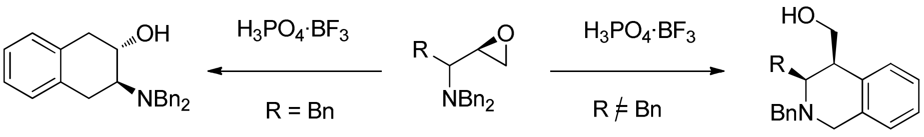
Nevertheless, when the *p*-methoxybenzyl ether of phenylglycidol was employed as a substrate, the course of the reaction was completely different, a nonfluorinated rearrangement product being obtained, without participation of the fluoride as a nucleophile.[46] The $BF_3 \cdot OEt_2$-promoted rearrangement described in Scheme 14 provides an useful and stereospecific method for the synthesis of enantiopure diarylmethane derivatives or enantiopure *trans*-4,5-disubstituted tetrahydrobenzo[*c*]oxepin-4-ols from readily available, enantiopure *O*-benzyl-protected epoxy alcohols.



Scheme 14: New stereospecific rearrangements of (2S,3S)-3-phenylglycidyl derivatives induced by boron-trifluoride.

Very interestingly, the regiochemical course of the underlying Friedel-Crafts process can be easily controlled by shifting the nucleophilic reactivity in the benzyl moiety of the substrate from the ipso to the ortho/ortho´ positions.[47]

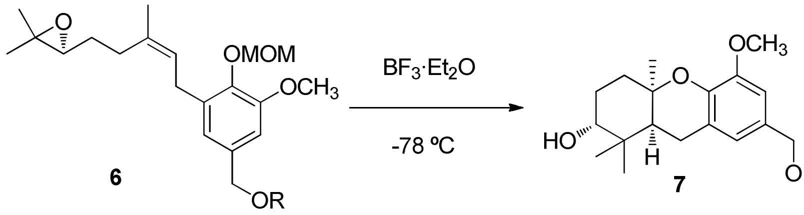
Analogous behaviour was described for *syn*-amino epoxides **5** using boron trifluoride phosphoric acid complex ($H_3PO_4 \cdot BF_3$) to obtain disubstituted tetrahydroisoquinolines or tetrahydronaphtalenes.[48] The synthesis of these enantiopure products can be explained by assuming that in both cases an intramolecular Friedel-Crafts reaction also takes place. However, in this case, the electrophilic substitution reaction takes place simply on the phenyl group oriented in a more favourable geometry respect to the oxirane ring.



5

Scheme 15: Synthesis of tetrahydroisoquinolines and tetrahydronaphtalenes promoted by boron trifluoride phosphoric acid complex.

Recently, a similar rearrangement was obtained when the aryl epoxide **6** was treated with $BF_3 \cdot OEt_2$ at –78ºC to afford the *cis*-fused hexahydroxanthene in modest yield with a considerable amount of polymeric material (Scheme 16).[49] This tricyclic alcohol **7** is an intermediate in the synthesis of schewinfurthin analogous.



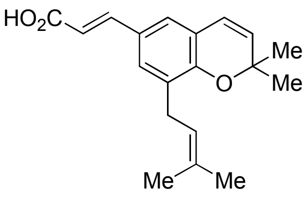
Scheme 16: Synthesis of cis-fused hexahydroxanthene induced by boron trifluoride.

These findings encourage further studies that would employ still larger isoprenoids to access systems that contain cis-fused rings.[50]

5.1.2 CHARACTERISTICS AND SYNTHESIS OF CHROMAN-3-OLS

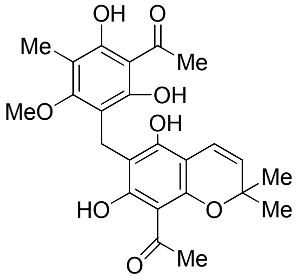
Benzopyrans (Chromenes, Chromanes and Chroman-ols)

The benzopyran core is found in a wide range of biologically and pharmacologically active compounds, including natural products.[51] In particular, 2,2-dimethylbenzopyrans are of great interest from a pharmacological point of view (see below an example of synthesis of these compounds). The benzopyran HLC-2 (**8**)[52] shows high and selective antitumor activity, while mallotochromene (**9**) is a highly potent HIV-1 reverse transcriptase inhibitor.[53]



HLC-2

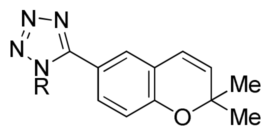
8



Mallotochromene

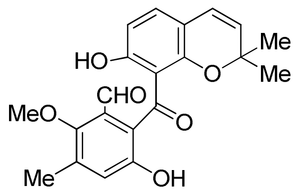
9

Other interesting examples are the potassium channel activator **10**,[54] antibiotic **11**, extracted from *Bacillus subtilis,*[55] and DNA cleaving agent **12**.[53] Also, the cannabinoid (-)-Δ^9-THC (**13**), isolated from the plant *Cannabis sativa,* which interacts with the human cannabinoid receptors CB1 and CB2.[56]



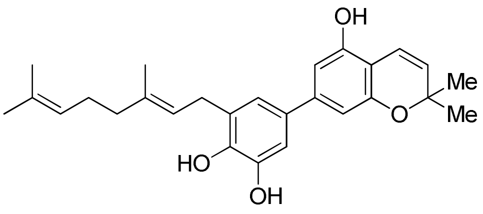
Potassium channel activator

10



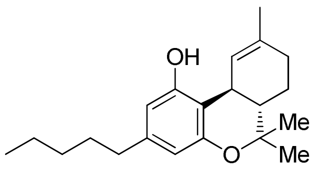
From B. Subtilis

11



DNA cleavage agent

12



(-)-Δ9-THC

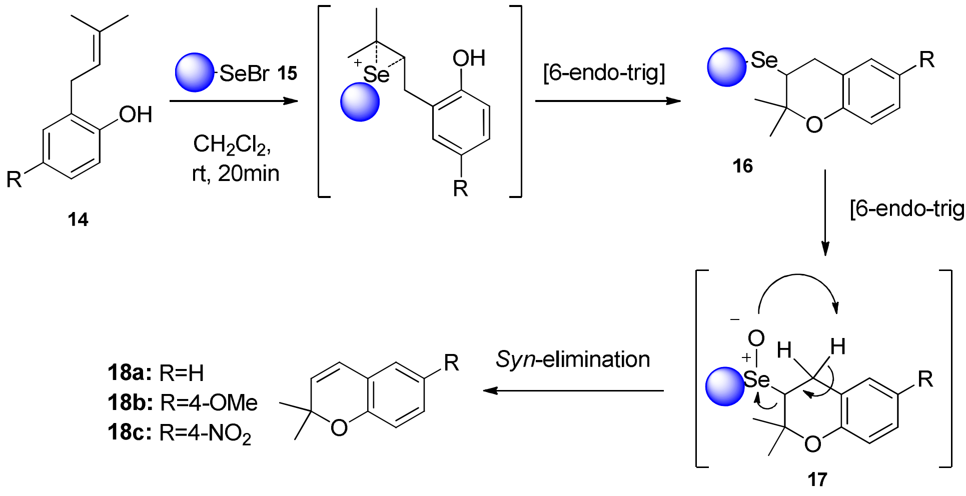
13

Chromenes

Chromenes (1-benzopyrans) constitute an important class of oxygenated heterocyclic compounds.[51a] As shown by the examples already described (**8-13**), particularly relevant the 2,2-dimethylbenzopyran motif, present in many synthetic targets.[52-56]

Among the many different syntheses that have been reported for this class of compounds, the solid-phase approach reported by Nicolaou *et al.* constitutes a good practical example.[57] (Scheme 17) In a series of preliminary studies, selenyl bromide resin **15** was treated with excess of *ortho*-prenylated phenol **14** providing resin-bound dihydro-benzopyrans **16** via a [6-endo-trig] cycloaddition.[57]

The benzopyrans **18a**-**c** were released from the solid support upon oxidation with H_2O_2 and subsequent *syn*-elimination from intermediate resin **17**. High yields (>91%) and high purities (>95%) were obtained regardless of the phenolic substrate's electronic environment (**18a**, **18b**, or **18c**).

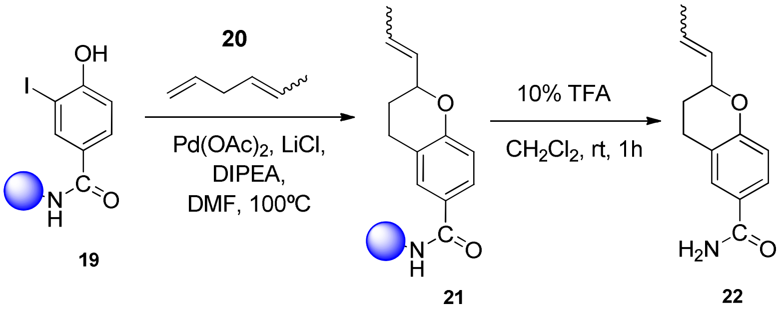


Scheme 17: Solid-phase synthesis of benzopyrans via cyclo-loading strategy.

Chromanes

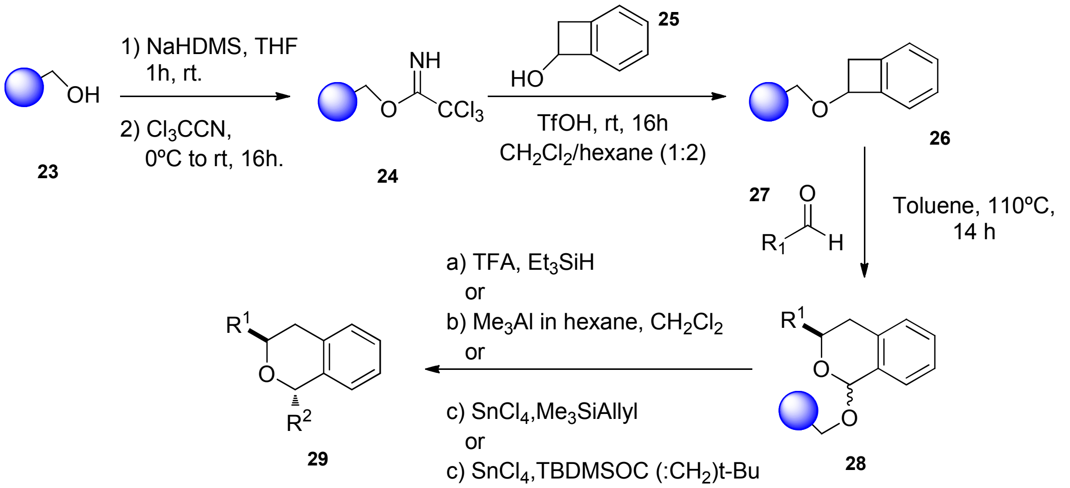
The chromane (dihydro-1-benzopyran) core structure frequently appears in natural products and is of major pharmaceutical interest.[58] Among the several strategies to construct chromane derivatives,[59] the solid-phase organic synthesis (SPOS) offers the opportunity to synthesize drug like molecules without tedious and time-consuming purification.

An approach to the SPOS of chromanes via palladium-catalyzed annulation was reported by Wang and Huang.[60] As depicted in Scheme 18, the annulation reaction was carried out by heating phenolic resin **19** with 1,4-hexadiene **20** in the presence of 10 mol% of Pd(OAc)$_2$, LiCl, and *N,N*-diisopropylethylamine in DMF at 100 °C, yielding resin-bound chromane **21**. Cleavage was effected by treatment with 10% TFA in CH$_2$Cl$_2$ and afforded the chromane **22** (*trans/cis* = 5.3:1) in good yield (84%) and good purity (88%).



Scheme 18: Solid-phase synthesis of substituted chromane **22**.

A different route toward the solid-phase synthesis of benzodihydropyrans was reported by Craig *et al.*[61] The key step in this approach was a hetero Diels-Alder reaction between benzaldehydes and a resin-bound *o*-quinodimethane.



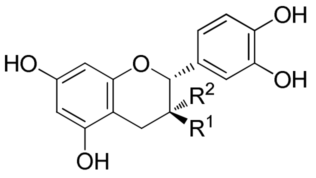
Scheme 19: Solid-phase synthesis of substituted chromanes.

Benzocyclobutenol **25** was used as the precursor for *o*-quinodimethane, as depicted in Scheme 19. Hydroxymethylpolystyrene **23** was treated with NaHMDS and trichloroacetonitrile, leading to resin **24**. Benzocyclobutenol **25** underwent reaction with resin **24** in the presence of catalytic TfOH, providing resin-bound *o*-quinodimethane **26**. Hetero Diels-Alder reactions between a variety of dienophiles **27** and resin **26** were performed at high temperature, providing resin-bound dihydrobenzopyrans **28**.

Cleavage from the polymer support **28** was performed under acidic conditions using either Brønsted or Lewis acid-nucleophile combinations, yielding the dihydrobenzopyrans **29** in moderate to good yields and with excellent stereoselectivity for the *anti*-isomer.

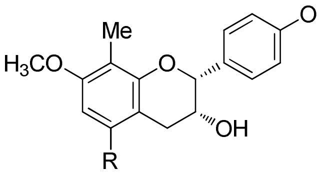
Chroman-3-ols

3-Chromanol is a structural motif found in many natural products and pharmaceutical agents. For example, this group is the core structure of catechin, epicatechin, and tupichinols, all of them bearing electron-rich substituents on the phenyl ring.[62,42h] Given that the key scaffold in these compounds remains constant, their variety of different biological activities can be attributed to the nature, pattern, and stereochemistry of substituents of the chroman core.



Catechin : R^1 = OH, R^2 = H
Epicatechin : R^1 = H, R^2 = OH

30

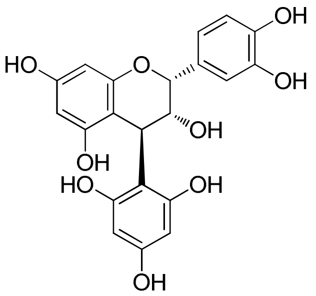


Tupichinol

31

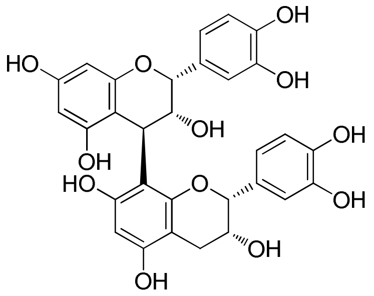
Catechins, one of the major groups of flavanoids, are widely diffused in a variety of foods and beverages such as fruits, vegetables, chocolate, tea, and wine.[63] These bioactive compounds are also present in agricultural by-products.

Catechins have been shown to be potentially beneficial to human health. Their biological activities include inhibition of platelet aggregation, anti-inflammatory action and, most notable, anticarcinogenic properties.[64] These activities have been mainly attributed to their antioxidant capacity.[65]



4-arylflavan-3-ol

32



Procyanidin B_2

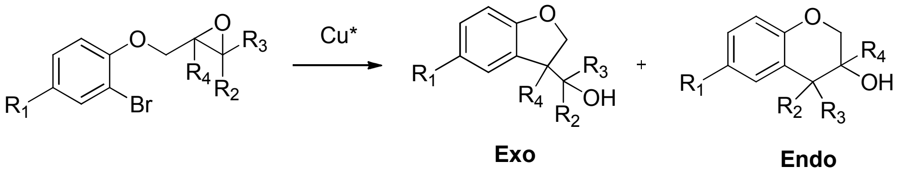
33

Neoflavens are thought to be important intermediates in the biosynthetic transformation of dalbergiquinols or dalbergiones into 4-arylcoumarins.[66] Some examples of 3-hydroxy-4-arylchroman structures are observed in the 4-aryl-flavan-3-ol **32** isolated from the South African plant *Nelia meyeri*,[67] and in the more complex proanthocyanidin dimers derived from catechin and epicatechin such as procyanidin B_2 **33**.[68] In traditional Chinese medicine, these flavan-3-ols (tupichinols) have normally been used for the treatment of rheumatic diseases and snake-bite.[62l]

5.1.2.1 Synthesis of chroman-3-ols

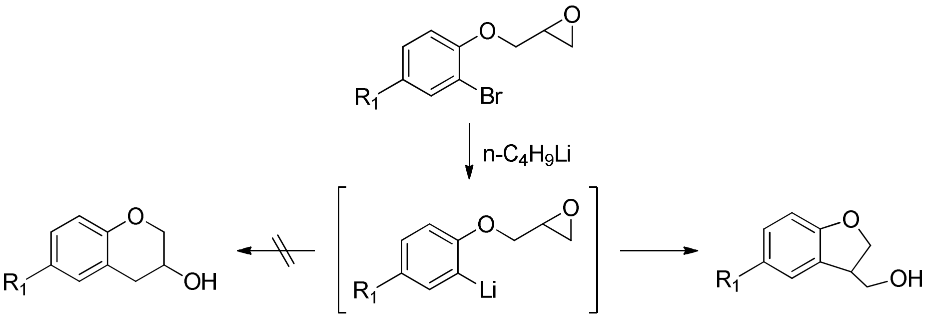
On the basis of the Lewis acid-catalyzed rearrangements of epoxides we have already mentioned (see above), we envisioned that an appropriately controlled rearrangement would provide a direct, straightforward access to chroman-3-ols. Indeed, some interesting approaches in this line of thought have been already reported.

As a part of the continuing interest in the intramolecular epoxide-opening reactions, Rieke *et al.*[36a,69] explored this type of reaction utilizing highly active copper powder (Cu*). As shown in Scheme 20, the intramolecular cyclizations of epoxy-aryl-copper compounds could evolve towards *exo* ring closure to form 2,3-dihydrobenzofuran or *endo* closure to yield 3-chromanol. The regioselectivity of these cyclizations is affected by the substitution pattern, reaction solvent, and the CuI·PR$_3$ complex used to generate the active copper. However, in general, the *exo* mode of ring closure is usually preferred for these reactions.[70]



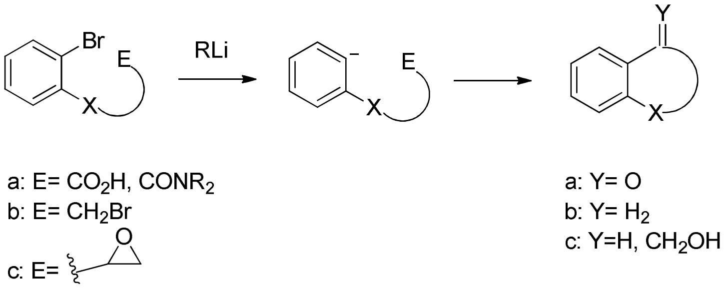
Scheme 20: Intramolecular epoxide-opening reactions of epoxy aryl halides using active copper.

Similarly, metalation of *o*-bromo-substituted (phenoxymethyl)oxiranes with butyllithium species at low temperatures (–100 °C) was reported via bromine-metal exchange.[71] (Scheme 21) The resulting organolithium reagents undergo cyclization by *exo* attack on the epoxide linkage as predicted by the Baldwin rules.[70]



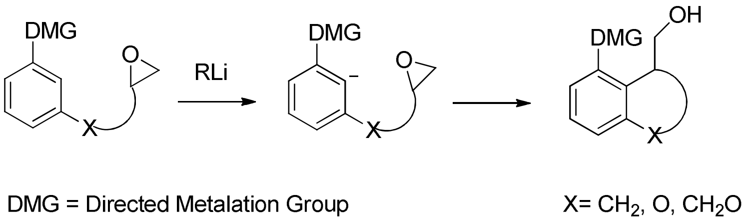
Scheme 21: Cyclization by exo attack on the epoxide linkage.

The anionic equivalent of the Friedel-Crafts and related reactions discovered by Parham[72] constitutes a methodology with high synthetic potential which, is dependent on the metal-halogen exchange process and the availability of *ortho*-bromo substituted reactants. The same issues are of applicable for the anionic epoxy cycloalkylation variant[20,21b,73] disclosed by Bradsher[71] and by Durst.[74] (Scheme 22)



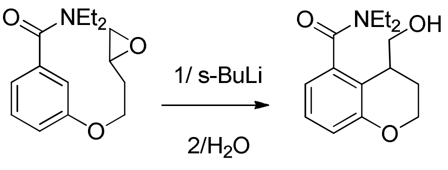
Scheme 22: Friedel-Crafts reactions of the ortho-bromo substituted reactants.

An anionic heteroring epoxy cycloalkylation has also been reported,[75] whose regiospecificity in the lithiation step is controlled by the inclusion of an appropriate directing group.[76] (Scheme 23)



Scheme 23: Directed ortho metalation induced epoxy cyclialkylations.

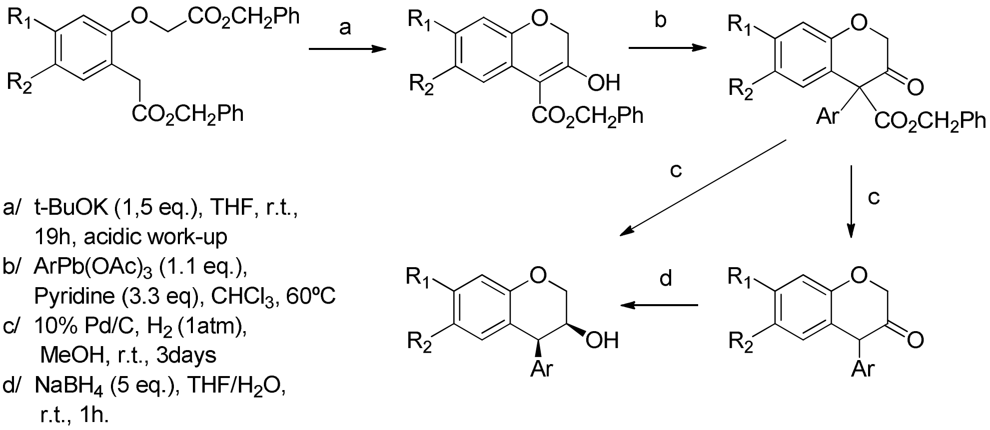
As depicted in Scheme 24, the epoxide amide **34** was subjected to the cyclization conditions to give the benzopyran derivative **35** following the preferred 6-*exo*-tet-mode.[70]



34 **35**

Scheme 24: Synthesis of benzopyran derivative **35** induced by lithium-epoxide oxygen coordination effects.

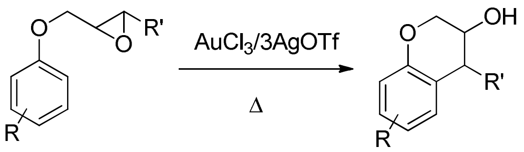
In recent years, Finnet *et al.* described the synthesis of 4-(2,4,6-trimethoxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-ol derivatives in good yields.[66] (Scheme 25) The key step is the coupling reaction between the aryllead(IV) triacetates and a suitably activated chromene-3-one moiety. This sequence should be useful for the synthesis of proanthocyanidin structures from 3-oxoflavanes although this arylations appeared to require too long reaction times.



a/ t-BuOK (1,5 eq.), THF, r.t., 19h, acidic work-up
b/ $ArPb(OAc)_3$ (1.1 eq.), Pyridine (3.3 eq), $CHCl_3$, 60ºC
c/ 10% Pd/C, H_2 (1atm), MeOH, r.t., 3days
d/ $NaBH_4$ (5 eq.), THF/H_2O, r.t., 1h.

Scheme 25: Synthesis of the 4-aryl-2*H*-1-benzopyrane derivatives.

Finally, a gold(III)-catalyzed cycloalkylation of electron-rich arenes with tethered epoxides has been reported. (Scheme 26) This system afforded good results for electron-rich substrates, which were readily transformed into the corresponding chroman-3-ols within ca. 4h at 50 ºC. However, longer reaction times and higher temperatures (ca. 48h, 83 ºC) were necessary for less electron-rich substrates.[76]



Scheme 26: Synthesis of the aryl chroman-3-ols towards gold(III)-catalyzed cylialkylation.

Although the authors claimed an unique gold-catalyze C-H activation to be taking place, the fact that gold(III) was only effective in combination with AgOTf (frequently used for removing halide ligands giving place to complexes with an enhanced cationic character), suggested that a Lewis acid-catalyzed Friedel-Crafts-type reaction could explain the transformation.

5.1.3 AIMS

Taking into account the close similarity between the previously described $BF_3\cdot OEt_2$ promoted rearrangement, leading to *trans*-4,5-disubstituted tetrahydrobenzo[*c*]oxepin-4-ols, and the Au(III) promoted cyclization of aryl glycidyl ethers leading to 3-chromanols, we considered that the same Lewis acid-mediated Friedel-Crafts-type mechanism.

Intrigued by the previously reported failure of different Lewis acids for inducing the rearrangement, as claimed by He and coworkers,[76] we decided to re-investigate thoroughly this issue, by a systematic study of different Lewis acids and reaction conditions to determine the general applicability of this methodology.

Apart of the advantages inherent to substituting the use of precious metals by cheaper ones, the discovery of an analogous reaction catalyzed by simple Lewis acids would shed light on the true mechanism of this transformation.

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5.2 PAPER D

METAL-MEDIATED CYCLIZATION OF ARYL AND BENZYL GLYCIDYL ETHERS: A COMPLETE SCENARIO

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Metal-Mediated Cyclization of Aryl and Benzyl Glycidyl Ethers: A Complete Scenario.

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Glycidyl systems, readily available in enantiomerically pure form by Sharpless epoxidation,[1] are versatile scaffolds that can be submitted to many different selective transformations.[2] Intramolecular processes involving their epoxide ring are particularly interesting, since they can provide access to a variety of substituted heterocyclic systems both in racemic and in enantiomerically pure form.[3] In this context, it has been reported that aryl glycidyl ethers **1**, when treated with a catalytic amount of $AuCl_3$ in the presence of AgOTf in 1,2-dichloroethane at high temperatures for prolonged periods of time, lead to 3-chromanols **2** as the only reaction products.[4] On the other hand, we have shown that enantiomerically pure benzyl glycidyl ethers **3**, when treated with $BF_3{\cdot}Et_2O$ in dichloromethane at low temperature for short periods of time lead to either 4,5-disubstituted tetrahydrobenzo[c]oxepin-4-ols **4** or to 4-diarylmethyl-1,3-dioxolanes **5** through stereospecific processes, depending on the substitution pattern of the benzyl residue.[5]

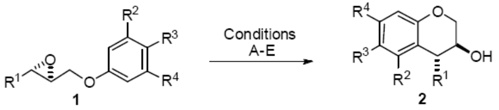
In spite of the close similarity of these reactions, it has been reported[4] that a Lewis acid such as $BF_3{\cdot}Et_2O$ fails to induce the conversion of **1** into **2**, and that the Au(III) catalyst was absolutely required for the reaction to take place. According to this, the intermediacy of an arylgold(III) species formed through an auration step[6] has been proposed as a mechanistic alternative for this transformation. We were intrigued by the possibility of this mechanistic duality, and given the interest of the considered reactions and of the products arising therefrom, we decided to reinvestigate this set of processes from the perspective of its mechanistic nature.

As the starting point of this research, we examined the Lewis acid reactivity of a family aryl glycidyl ethers **1a-i**, most of them in enantiomerically pure form (**1h** and **1i** were racemic). The results of this study have been summarized in Table 1.

In contrast with the results discussed above,[4] but in full agreement with our previous findings,[5] $BF_3{\cdot}Et_2O$ induces the high yield (79%), stereospecific cyclization of **1a** into 3-chromanol **2a** after a short treatment at –55 °C in dichloromethane (entry 1). Even more conveniently, the same reaction can be induced by $FeBr_3$ (10 mol%)[7] at 20 °C (Conditions B), **2a** being obtained in 92% yield after 30 min (entry 2). It is interesting to realize that for this particular substrate the use of $AuCl_3$/3AgOTf (2.5 mol%) in 1,2-dichloroethane, although involving harsher reaction conditions (50 °C) and more prolonged reaction time (4 h) leads to lower yields than the more conventional Lewis acids.[4]

The use of $FeBr_3$ under the same very mild conditions employed for **1a** allowed the stereospecific, high yield cyclization of aryl phenylglycidyl ethers **1b-g** to 3-chromanols **2b-g**. For substrates bearing less nucleophilic aryloxy fragments, like **1b**, increased amounts of $FeBr_3$ (30 mol%) and extended reaction times (1 h) are required for complete conversion (entry 3).

Table 1. Lewis acid-mediated cyclization of aryl glycidyl ethers **1** to 3-chromanols.



entry	product	R^1	R^2	R^3	R^4	cond[a]	yield [%]
1	**2a**	Ph	OMe	H	OMe	A	79
2	**2a**					B	92
3	**2b**	Ph	H	H	H	B[b]	61
4	**2c**	Ph	H	OMe	H	B[c]	92
5	**2d**	Ph	Me	H	Me	B	88
6	**2d**					C	97
7	**2e**	*p*-BrPh	OMe	H	OMe	B	76
8	**2f**	Ph	H	I	H	C[b]	73
9	**2g**	Ph	H	*t*-Bu	H	B	95
10	**2g**					C	99
11	**2h**	H	H	*t*-Bu	H	D	94[d]
12	**2h**	H				E	91[e]
13	**2i**	H	H	H	H	D	18
14	**2i**	H				E	17

[a] Cond. **A**: $BF_3{\cdot}Et_2O$ (30 mol%), CH_2Cl_2, –78 or –55 °C, 30 min. Cond. **B**: $FeBr_3$ (10 mol%), CH_2Cl_2, 20 °C, 30 min. Cond. **C**: $FeBr_3$/3AgOTf (10 mol%), CH_2Cl_2, 20 °C, 30 h. Cond. **D**: $FeBr_3$/3AgOTf (10 mol%), $ClCH_2CH_2Cl$, 80 °C, 48 h. Cond. **E**: $FeBr_3$/3AgOTf (10 mol%), $ClCH_2CH_2Cl$, 140 °C, microwaves, 40 min. [b] 30 mol% catalyst, 60 min. [c] Reaction time was 60 min. [d] 57% conversion. [e] 53% conversion.

The unsubstituted glycidyl ethers **1h-i**, lacking the activation of the epoxide ring towards ring-opening provided by the aryl substituent, are sensitive probes for the efficiency of the different Lewis acid types in the cyclization process. Taking **1i** as a model substrate, different Lewis acids known to induce the ring opening of epoxides [$BF_3{\cdot}Et_2O$, $FeBr_3$, $InCl_3$, $LiClO_4$, $Cu(OTf)_2$, $Cu(ClO_4)_2$, $Zn(OTf)_2$] were tested under different experimental conditions.[8] In no case the expected 3-chromanol **2i** was formed, the only identified minor reaction products being halohydrins **6i**.[9] In view of the results reported by He,[4] we decided to explore the use in the reaction of $FeBr_3$ in combination with AgOTf with the aim of increasing the electrophilicity of the iron salt. Gratifyingly enough, **2i** was obtained, albeit in a modest 18% yield, under these conditions (Conditions D, entry 13). It is worth mentioning that, in our hands, the use of the $AuCl_3$/3AgOTf catalyst (5 mol%) under identical experimental conditions afforded **2i** in 11% yield.[10] Use of Conditions D allowed the preparation of **2h** in 94% yield (57% conversion, entry 11). Interestingly, reaction times for the preparation of **2h-i** could be drastically reduced (from 48 h to 40 min) without yield decrease by performing the reactions at 140 °C with microwave irradiation (Conditions E, entries 12 and 14). The $FeBr_3$/3AgOTf reagent was subsequently tested under milder conditions (Conditions C) for substrates **1a-g**. Except for the results in entries 6 and 10, only marginal yield increases were recorded.

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The results obtained with unactivated substrates (**1h-i**) provide a clear indication that the cationic Au(III) or Fe(III) species likely generated in the presence of AgOTf can efficiently mediate the formation of **2** when halide delivery is avoided (Figure 1).

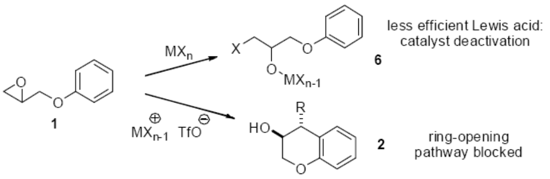
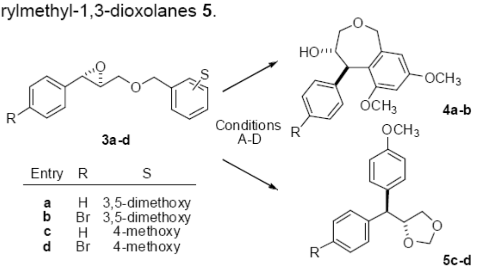


Figure 1. Reaction pathways of aryl glycidyl ethers with Lewis acids.

Once the ability of Lewis acids to induce the cyclization of aryl glycidyl ethers **1** into 3-chromanols **2** had been established, we turned our attention towards benzyl glycidyl ethers **3**, with the goal of determining whether the $FeBr_3$, $FeBr_3$/3AgOTf, and $AuCl_3$/ 3AgOTf catalysts could also induce the reactions[5] shown in Table 2. Substrates **3a-b** were selected as precursors of tetrahydrobenzo[*c*]oxepin-4-ols **4a-b** via *ortho* activation of the benzyl substituent, while **3c-d** were chosen as precursors to 4-diarylmethyl-1,3-dioxolanes **5** via *ipso* activation of the benzyl fragment. The results of the study have been summarized in Table 2 along with those obtained with $BF_3{\cdot}Et_2O$, when available.[5]

Table 2. Lewis Acid Mediated Cyclization/Rearrangement of Benzyl Glycidyl Ethers **3** to Tetrahydrobenzo[*c*]oxepin-4-ols **4** or to 4-Diarylmethyl-1,3-dioxolanes **5**.



entry	substrate	product	conditions[a]	yield [%]
1	**3a**	**4a**	A	80
2	**3a**	**4a**	B	82
3	**3a**	**4a**	C	70
4	**3a**	**4a**	D	88
5	**3b**	**4b**	B	75
6	**3b**	**4b**	C	74
7	**3b**	**4b**	D	81
8	**3c**	**5c**	A[b]	59
9	**3c**	**5c**	B	25[c]
10	**3c**	**5c**	C	72
11	**3c**	**5c**	D	82
12	**3d**	**5d**	C	89
13	**3d**	**5d**	D	96

[a] Cond. **A**: $BF_3{\cdot}Et_2O$ (30 mol%), CH_2Cl_2, –78 °C, 15 min. Cond. **B**: $FeBr_3$ (10 mol%), CH_2Cl_2, 20 °C, 60 min. Cond. **C**: $AuCl_3$/3AgOTf (2.5 mol%), $ClCH_2CH_2Cl$, 50 °C, 4 h. Cond. **D**: $FeBr_3$/3AgOTf (20 mol%), CH_2Cl_2, 20 °C, 30 min. [b] Reaction at –35 °C for 5 min. [c] 29% of the corresponding bromohydrin was also obtained. Reaction time was 90 min.

When the stereospecific cyclization of **3a** is considered (entries 1-4), it becomes clear that Au(III) is also able to induce conversion into **4a**, although $FeBr_3$/3AgOTf and the other tested Lewis acids are more efficient mediators than $AuCl_3$/3AgOTf for this process. The less reactive **3b** displayed a similar behavior.

While the cyclization of substrates **3** bearing an *ortho*-activated benzyl substituent to oxepinols **4** is normally very clean,[5] the corresponding Lewis acid-induced rearrangement of *ipso*-activated substrates to diarylmethanes is a more critical process, normally accompanied by variable degrees of halohydrin formation. According to this, the rearrangement of **3c-d** leading to **5c-d** is a more stringent test for possible mediators. With substrate **3c** (entries 8-11), it becomes clear that the ability of the four Lewis acids to induce the rearrangement varies in the order $BF_3{\cdot}Et_2O$ > $FeBr_3$/3AgOTf > $AuCl_3$/3AgOTf > $FeBr_3$. When the yield of the diarylmethane **5** is considered, the $FeBr_3$/3AgOTf reagent represents an optimal compromise (entry 11). The same trends are observed for the conversion of **3d** into **5d**.

In summary, the results reported here clearly show that the cyclization and rearrangement reactions of aryl and benzyl glycidyl ethers are Lewis acid mediated processes. While the $FeBr_3$/ 3AgOTf combination appears as the catalyst of choice for this set of processes, the cationic species presumably formed through the interaction of $AuCl_3$ with AgOTf is also able to mediate, albeit in a less efficient manner, the same reactions. From a mechanistic point of view, the observed reactivity trends clearly indicate that these cyclizations are of the Friedel-Crafts type.

From the perspective of practical use, cost and availability considerations[11] make iron bromide a most attractive alternative for these reactions and, in general, for processes where gold and other expensive metals merely act as Lewis acids.

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Supporting Information Available: Experimental details and product characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The $FeBr_3$/3AgOTf and $AuCl_3$/3AgOTf catalytic systems have also been tested in the stereospecific and regioselective intermolecular addition of 1,3,5-trimethoxybenzene to (2*S*,3*S*)-3-phenylglycidyl methyl ether. The former gave the desired product **7** in 60% yield whereas the latter was less active (ca. 40%; see SI for details). Further studies concerning related intermolecular addition are in course.
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Supporting Information

Metal-Mediated Cyclization of Aryl and Benzyl Glycidyl Ethers: A Complete Scenario.

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1. Materials and Methods: General Information.

All reagents were commercially available and used without further purification unless otherwise noted. Solvents were obtained anhydrous from a Solvent Purification System. All reactions were performed under nitrogen atmosphere. The starting materials were synthesized following previously described procedures.[1-3] 2-(Phenoxymethyl)oxirane and (4-(*tert*-butyl)-phenoxymethyl)oxirane are commercially available and were used as starting materials without further purification. Melting points have been determined on a Büchi Melting Point B-540 apparatus. Infrared (IR) spectra have been recorded with a Tensor 27 Bruker FT-IR spectrophotometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) have been measured with a Bruker Avance ultrashield spectrometer 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100.6 MHz), with TMS as internal reference. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet, m, multiplet), coupling constants (Hz), and integration. ^{13}C NMR data are reported in terms of chemical shift (δ, ppm). High-resolution mass spectra have been measured with a Waters LCT Premier instrument operated in ESI mode.

The identification of the different products prepared has been carried out through the determination of their physical and spectroscopic characteristics, and comparison with known compounds.[3-7] The compounds have been ordered according to its numbering in the main body of the manuscript.

2. General Procedure for the preparation of starting materials 1a-g.[1-3] A solution of the corresponding phenol (0.23 g, 1.49 mmol) in DMF (8 mL) was added via cannula to a suspension of sodium hydride (0.054g, 2.46 mmol) in DMF (8 mL) at 0 °C under N_2. The mixture was stirred until gas evolution ceased, and a solution of enantiomerically pure (ee > 99%) [(2*S*,3*S*)-3-phenyloxiran-2-yl]methyl 4-methylbenzenesulfonate] (0.5 g, 1.64 mmol) in DMF (8 mL) was added via cannula to the mixture. The solution was stirred for ca. 48 h at 0 ºC. The reaction mixture was suspended in MeOH (10 mL) and brine (120 mL) and extracted with Et_2O (4×15 mL). The residual oil was purified by column chromatography on silica gel using hexanes:EtOAc (90:10/80:20) as eluent.

In the case of the preparation of compound **1e,** [(2*S*,3*S*)-3-(4-bromophenyl)oxiran-2-yl]methyl 4-methylbenzenesulfonate] was used instead of [(2*S*,3*S*)-3-phenyloxiran-2-yl]methyl 4-methylbenzenesulfonate]. It was synthesized as follows: A solution of tosyl chloride (0.45 g, 2.40 mmol) in CH_2Cl_2 (10 mL) was added via cannula to a mixture of triethylamine (0.52 mL, 3.71 mmol) and DMAP (0.03 g, 0.24 mmol). The mixture was cooled at –20 °C under N_2 and a solution of enantiomerically pure (ee > 99%) [(2S,3S)-3-phenyl-2,3-epoxypropan-l-ol][3] (0.5 g, 2.18 mmol) in CH_2Cl_2 was added via cannula. The solution was stirred for ca. 16 hours at –20 ºC. The reaction mixture was washed with a solution of tartaric acid 10%, saturated aqueous $NaHCO_3$ and brine (3×4 mL) and extracted with Et_2O (4×15 mL). The residual solid was purified by column chromatography on silica gel using hexanes:EtOAc (90:10/80:20) as eluent to afford 0.80 g (96 %) of product as a colorless solid.

(2*S*,3*S*)-3-(4-Bromophenyl)oxiran-2-yl]methyl 4-methylbenzenesulfonate.
m.p. = 147–148 ºC; $[\alpha]_D^{27}$: –37.7 (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 3.17-3.20 (m, 1H), 3.73 (d, J = 1.7 Hz, 1H), 4.15 (dd, J = 5.3, 11.4 Hz, 1H), 4.31 (dd, J = 3.8, 11.4 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7 (CH_3), 55.9 (CH), 58.6 (CH), 69.0 (CH_2), 122.6 (C), 127.3 (2CH), 128.0 (2CH), 130.0 (2CH), 131.8 (2CH), 132.7 (C), 134.7 (C), 145.2 (C); HRMS (ES+): *m/z* calcd. for $C_{16}H_{15}BrNaO_4S$: 404.9772; found: 404.9770 $[M+Na]^+$.

2.1. Aryloxymethyloxiranes (1a-g) characterization data

(2*S*,3*S*)-2-((3,5-Dimethoxyphenoxy)methyl)-3-phenyloxirane (1a)[5]
The general procedure was applied to 3,5-dimethoxyphenol (0.23 g, 1.5 mmol) to afford 0.41 g (96 %) of product as a colorless oil: $[\alpha]_D^{27}$: –52.6 (*c* 1.2 in $CHCl_3$); ^1H NMR (400 MHz,

$CDCl_3$): δ = 3.37 (m, 1H), 3.74 (s, 6H), 3.88 (d, *J* = 2.1 Hz, 1H), 4.05 (dd, *J* = 5.2, 11.1 Hz, 1H), 4.26 (dd, *J* = 3.1, 11.1 Hz, 1H), 6.10-6.20 (m, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.2 ($2CH_3$), 56.2 (CH), 60.0 (CH), 67.9 (CH_2), 93.4 (CH), 93.5 (CH), 125.6 (2CH), 128.3 (CH), 128.4 (2CH), 136.4 (C), 160.2 (C), 161.5 (2C); HRMS (ES+): *m/z* calcd for $C_{17}H_{19}O_4$: 287.1283; found: 287.1264 $[M+H]^+$.

(2*S*,3*S*)-2-(Phenoxymethyl)-3-phenyloxirane (1b)[6]

The general procedure was applied to phenol (0.17 g, 1.8 mmol) to afford 0.15 g (40%) of product as a colorless solid: m.p. = 129–130 ºC; $[\alpha]_D^{24}$: –45.6 (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.39-3.42 (m, 1H), 3.91 (d, *J* = 2.0 Hz, 1H), 4.14 (dd, *J* = 5.1, 11 Hz, 1H), 4.32 (dd, *J* = 3.2, 11 Hz, 1H), 6.94-7.0 (m, 3H), 7.27-7.38 (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 56.4 (CH), 60.3 (CH), 67.9 (CH_2), 114.7 (2CH), 121.3 (CH), 125.7 (2CH), 128.4 (CH), 128.6 (2CH), 129.6 (2CH), 136.5 (C), 158.5 (C); HRMS (ES+): *m/z* calcd. for $C_{15}H_{14}NaO_2$: 249.0891; found: 249.0887 $[M+Na]^+$.

(2*S*,3*S*)-2-((4-Methoxyphenoxy)methyl)-3-phenyloxirane (1c)

The general procedure was applied to 4-methoxyphenol (0.20 g, 1.64 mmol) to afford 0.37 g (88 %) of product as a colorless solid: m.p. = 142–143 ºC; $[\alpha]_D^{25}$: –48.3 (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.35-3.39 (m, 1H), 3.76 (s, 3H), 3.88-3.90 (m, 1H), 4.08 (dd, *J* = 5.1, 11.2 Hz, 1H), 4.26 (dd, *J* = 3.1, 11.2 Hz, 1H), 6.81-6.91 (m, 4H), 7.26-7.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.7 (CH_3), 56.4 (CH), 60.4 (CH), 68.7 (CH_2), 114.7 (2CH), 115.8 (2CH), 125.7 (2CH), 128.4 (CH), 128.6 (2CH), 136.6 (C), 152.7 (C), 154.3 (C); HRMS (ES+): *m/z* calcd. for $C_{16}H_{16}NaO_3$: 279.0997; found: 279.0984 $[M+Na]^+$.

(2*S*,3*S*)-2-((3,5-Dimethylphenoxy)methyl)-3-phenyloxirane (1d)

The general procedure was applied to 3,5-dimethylphenol (0.20 g, 1.64 mmol) to afford 0.40 g (97 %) of product as a colorless oil: $[\alpha]_D^{27}$: –56.9 (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 6H), 3.30-3.33 (m, 1H), 3.84 (d, *J* = 2.0 Hz, 1H), 4.03 (dd, *J* = 5.3, 11.2 Hz, 1H), 4.21 (dd, *J* = 3.1, 11.2 Hz, 1H), 6.51-6.60 (m, 3H), 7.21-7.33 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.6 ($2CH_3$), 56.4 (CH), 60.4 (CH), 67.9 (CH_2), 112.6 (2CH), 123.2 (CH), 125.9 (2CH), 128.5 (CH), 128.7 (2CH), 136.8 (C), 139.4 (2C), 158.7 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{19}O_2$: 255.1385; found: 255.376 $[M+H]^+$.

(2*S*,3*S*)-2-(4-Bromophenyl)-((3,5-dimethoxyphenoxy)methyl)-3-phenyloxirane (1e) The general procedure was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-3-(4-bromophenyl)oxiran-2-yl]methyl 4-methylbenzenesulfonate (0.62 g, 1.62 mmol) and 3,5-

dimethoxyphenol (0.25 g, 1.62 mmol) to afford 0.49 g (82%) of product as a colorless solid: m.p. = 73–74 ºC; $[\alpha]_D^{25}$: –53.7 (*c* 0.9 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.30-3.40 (m, 1H), 3.76 (s, 6H), 3.88 (d, *J* = 1.7 Hz, 1H), 4.09 (dd, *J* = 5.1, 11.2 Hz, 1H), 4.27 (dd, *J* = 3.2, 11.2 Hz, 1H), 6.12 (s, 3H), 7.17 (d, *J* = 8.4 Hz, 2H) 7.48 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.4 ($2CH_3$), 55.7 (CH), 60.1 (CH), 67.6 (CH_2), 93.5 (CH), 93.6 (CH), 122.3 (CH), 127.3 (2CH), 131.7 (2CH), 135.6 (C), 160.2 (C), 161.5 (2C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{18}O_4Br$: 365.0388; found: 365.0374 $[M+H]^+$.

(2*S*,3*S*)-2-((4-Iodophenoxy)methyl)-3-phenyloxirane (1f)

The general procedure was applied to 4-iodophenol (0.33 g, 1.5 mmol) to afford 0.42 g (80%) of product as a colorless solid: m.p. = 117–118 ºC; $[\alpha]_D^{27}$: –41.1 (*c* 1.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.37 (m, 1H), 3.89 (d, *J* = 2.0 Hz, 1H), 4.07 (dd, *J* = 5.2, 11.2 Hz, 1H), 4.29 (dd, *J* = 3.0, 11.2 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 7.20-7.40 (m, 5H) 7.56 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 56.3 (CH), 60.0 (CH), 68.0 (CH_2), 83.5 (C), 117.1 (2CH), 125.7 (2CH), 128.5 (CH), 128.6 (2CH), 136.3 (C), 138.3 (2CH), 158.3 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{17}INO_2$: 394.0304; found: 394.0296 $[M+CH_3CN+H]^+$.

(2*S*,3*S*)-2-((4-*tert*-Butylphenoxy)methyl)-3-phenyloxirane (1g)

The general procedure was applied to 4-*tert*-butylphenol (0.22 g, 1.5 mmol) to afford 0.35 g (83%) of product as a colorless solid: m.p. = 152–153 ºC; $[\alpha]_D^{27}$: –54.2 (*c* 0.8 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 3.37-3.40 (m, 1H), 3.89 (d, *J* = 2.0 Hz, 1H), 4.12 (dd, *J* = 5.1, 11.2 Hz, 1H), 4.29 (dd, *J* = 3.3, 11.2 Hz, 1H), 6.87-6.90 (m, 2H), 7.27-7.38 (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 31.6 ($3CH_3$), 34.1 (C), 56.4 (CH), 60.4 (CH), 68.0 (CH_2), 114.2 (CH), 125.8 (CH), 126.4 (2CH), 128.4 (CH), 128.6 (2CH), 136.6 (C), 144.1 (C), 156.3 (C); HRMS (ES+): *m/z* calcd. for $C_{19}H_{22}NaO_2$: 305.1517; found: 305.1511 $[M+Na]^+$.

3. General Procedure for the preparation of starting materials 3a-d.[4] A solution of enantiomerically pure (ee > 99%) [(2S,3S)-3-phenyl-2,3-epoxypropan-l-ol] (0.33 g, 2.20 mmol) or [(2S,3S)-3-(4-bromophenyl)-2,3-epoxypropan-l-ol] (0.505 g, 2.20 mmol) in DMF (3 mL) was added via cannula to a suspension of sodium hydride (0.074 g, 3.07 mmol) in DMF (10 mL) at –20 °C under N_2. The mixture was stirred for 20 min, and the corresponding benzylic bromide (0.48 g, 2.10 mmol) in DMF (5 mL) was added via cannula to the mixture. After 3 h of stirring at –20 ºC and 48 h of stiring at 0 ºC, the reaction mixture was suspended in MeOH (10 mL) and brine (100 mL) and extracted with Et_2O (4×10 mL). The residual oil was purified by column chromatography on silica gel using hexanes:EtOAc (96:4) as eluent.

3.1. Benzyl glycidyl ethers (3a-d) characterization data

(2*S*,3*S*)-3-Phenyl-2-((3,5-dimethoxy)benzyloxymethyl)oxirane (3a)[4]

The general procedure was applied to enantiomerically pure (ee > 99%) [(2S,3S)-3-phenyl-2,3-epoxypropan-l-ol] (0.33 g, 2.20 mmol) and 3,5-dimethoxybenzyl bromide (0.48 g, 2.1 mmol) to afford 0.50 g (77 %) of product as a colorless oil: $[\alpha]_D^{20}$: –27.0 (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.25 (bs, 1H), 3.61 (dd, *J* = 5.2, 11.6 Hz 1H), 3.78 (s, 6H), 3.85 (dd, *J* = 2.8, 11.6 Hz, 1H), 4.56 (d, *J* = 5.2 Hz, 1H), 6.39 (t, *J* = 2.4 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 2H), 7.25-7.36 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.3 (2CH_3), 55.8 (CH), 61.1 (CH), 69.8 (CH_2), 73.3 (CH_2), 92.8 (CH), 105.4 (2CH), 125.7 (2CH), 128.2 (CH), 128.4 (2CH), 136.8 (C), 140.2 (C), 160.9 (2C); HRMS (ES+): *m/z* calcd. for $C_{18}H_{21}O_4$: 301.1440; found: 301.1425 $[M+H]^+$.

(2*S*,3*S*)-3-(4-Bromophenyl)-2-((3,5-dimethoxy)benzyloxymethyl)oxirane (3b)

The general procedure was applied to enantiomerically pure (ee > 99%) [(2S,3S)-3-(4-bromophenyl)-2,3-epoxypropan-l-ol] (0.505 g, 2.20 mmol) and 3,5-dimethoxybenzyl bromide (0.48 g, 2.1 mmol) to afford 0.78 g (94 %) of product as a colorless oil: $[\alpha]_D^{26}$: –26.4 (*c* 1.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.17-3.20 (m, 1H), 3.62 (dd, *J* = 5.2, 11.6 Hz 1H), 3.78 (s, 6H), 3.82 (dd, *J* = 3.1, 11.6 Hz, 1H), 4.55 (dd, *J* = 4.6, 16.7 Hz, 2H), 6.39 (t, *J* = 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.3 (2CH_3), 55.4 (CH), 61.2 (CH), 69.6 (CH_2), 73.4 (CH_2), 99.8 (CH), 105.5 (2CH), 122.1 (C), 127.4 (2CH), 131.6 (2CH), 136.0 (C), 140.2 (C), 161.0 (2C); HRMS (ES+): *m/z* calcd. for $C_{18}H_{20}BrO_4$: 379.0545; found: 379.0529 $[M+H]^+$.

(2*S*,3*S*)-3-Phenyl-2-((4-methoxy)benzyloxymethyl)oxirane (3c)[4]

The general procedure was applied to enantiomerically pure (ee > 99%) [(2S,3S)-3-phenyl-2,3-epoxypropan-l-ol] (0.33 g, 2.20 mmol) and 4-methoxybenzyl bromide (0.30 mL, 2.1 mmol) to afford 0.50 g (84 %) of product as a colorless oil: $[\alpha]_D^{20}$: –35.0 (*c* 1.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.20 (bs, 1H), 3.60 (dd, J = 5.2, 11.6 Hz 1H), 3.79 (dd, J = 2.0, 13 Hz, 1H), 3.81 (s, 3H), 3.83 (d, J = 2.8 Hz, 1H), 4.56 (d, J = 4.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.25-7.34 (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.2 (CH_3), 55.8 (CH), 61.1 (CH), 69.5 (CH_2), 73.0 (CH_2), 113.8 (2CH), 125.6 (2CH), 128.2 (CH), 128.4 (2CH), 129.4 (2CH), 129.9 (C), 136.8 (C), 159.3 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{19}O_3$: 271.1334; found: 271.1324 $[M+H]^+$.

(2*S*,3*S*)-3-(4-Bromophenyl)-2-((4-methoxy)benzyloxymethyl)oxirane (3d)

The general procedure was applied to enantiomerically pure (ee > 99%) [(2S,3S)-3-(4-bromophenyl)-2,3-epoxypropan-l-ol] (0.505 g, 2.20 mmol) and 4-methoxybenzyl bromide (0.30 mL, 2.1 mmol) to afford 0.66 g (86 %) of product as a colorless solid: m.p. = 86–87 ºC; $[\alpha]_D^{26}$: –27.2 (*c* 1.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.14-17 (m, 1H), 3.59 (dd, J = 5.1, 11.5 Hz 1H), 3.73 (d, J = 2.0 Hz, 1H), 3.78 (s, 3H), 3.76-3.80 (m, 1H), 4.53 (d, J = 3.9, 15.4 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.3 (CH_3), 55.3 (CH), 61.3 (CH), 69.3 (CH_2), 73.2 (CH_2), 113.8 (CH), 113.8 (CH), 122.1 (C), 127.4 (2CH), 129.4 (2CH), 129.9 (C), 131.6 (2CH), 136.1 (C), 159.4 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{18}BrO_3$: 349.0439; found: 349.0433 $[M+H]^+$.

4. General Procedure for the preparation of chroman-3-ols 2a-i.

Method A: Boron trifluoride-mediated rearrangement[4]

A solution of the corresponding aryloxymethyl oxirane (0.28 mmol) and $BF_3{\cdot}Et_2O$ (0.084 mmol) in anhydrous CH_2Cl_2 (3 mL) under N_2 was stirred for 30 min at –78 °C. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (3 mL) and then it was extracted with CH_2Cl_2 (3×3 mL). The combined organic extracts were dried and concentrated *in vacuum*, and the crude product was purified by column chromatography on silica gel using hexanes:EtOAc (80:20) as the eluent.[4]

Method A.1: Boron trifluoride-mediated rearrangement

The general procedure for boron trifluoride was followed changing the temperature to –55 ºC.

Method B: Iron tribromide-mediated rearrangement

A solution of the corresponding aryloxymethyl oxirane (0.078 mmol) and $FeBr_3$ (0.002 g, 0.0078 mmol) in anhydrous CH_2Cl_2 (2 mL) under N_2 was stirred for 30 min at 20 °C. The reaction mixture was filtered through a pad of silica gel using ether. The organic extracts were dried and concentrated *in vacuum*, and the crude product was purified by column chromatography on silica gel using hexanes:EtOAc (90:10/80:20) as the eluent.

Method C: Iron tribromide-silver salt mediated rearrangement

A solution of the corresponding aryloxymethyl oxirane (0.506 mmol), $FeBr_3$ (0.015 g, 0.051 mmol) and AgOTf (0.039 g, 0.152 mmol) in anhydrous CH_2Cl_2 (2 mL) under N_2 was stirred for 30 min at 20 °C. The reaction mixture was then treated as described in method B.

Method D: Iron tribromide-silver salt mediated rearrangement

A solution of the corresponding aryloxymethyl oxirane (0.516 mmol), $FeBr_3$ (0.015 g, 0.052 mmol) and AgOTf (0.040 g, 0.155 mmol) in $ClCH_2CH_2Cl$ (2 mL) under N_2 was stirred for 48 h at 80 °C. The reaction mixture was then treated as described in method B.

Method E: Microwave-assisted iron tribromide-silver salt mediated rearrangement

A solution of the corresponding aryloxymethyl oxirane (0.369 mmol), $FeBr_3$ (0.011 g, 0.037 mmol) and AgOTf (0.028 g, 0.111 mmol) in $ClCH_2CH_2Cl$ (2 mL) under N_2 was stirred for 40 min at 140 °C under irradiation with microwaves in a CEM reactor. The reaction mixture was then treated as described in method B.

Method F: Rearrangement mediated by other Lewis acids

A solution of the 2-(phenoxymethyl)oxirane **1i** (0.078 g, 0.28 mmol) and Lewis acid (see Table below) in anhydrous solvent (3 mL) under N_2 was stirred. The reaction mixture was then treated as described in method A.

Entry	Lewis Acid	Cat. loading	T[a]	Solvents	Yield
(1)	$InCl_3$	0.05 eq.	20 °C.	CH_2Cl_2	-
(2)	$InCl_3$ 4 Å MS	0.01 eq	20 °C	CH_2Cl_2	-
(3)	$LiClO_4$	2 eq	55 °C	CH_3CN	-
(4)	$LiClO_4$	3 eq	80 °C	CH_3CN	-
(5)	$Cu(OTf)_2$	0.1 eq	0 °C	CH_2Cl_2	-
(6)	$Cu(OTf)_2$	0.1 eq	20 °C	CH_2Cl_2	-
(7)	$Cu(ClO_4)_2$	0.02 eq.	20 °C.	-	-
(8)	$Cu(ClO_4)_2$	0.1 eq	20 °C	-	-
(9)	$Cu(ClO_4)_2$	0.02 eq	20 °C	-	-
(10)	$Cu(ClO_4)_2$	0.1 eq	80 °C	-	-
(11)	$Zn(OTf)_2$	0.05 eq	20 °C	-	-
(12)	$Zn(OTf)_2$	0.1 eq	20 °C	CH_2Cl_2	-

4.1. Chroman-3-ols (2a-i) characterization data

(3*S*,4*R*)-5,7-Dimethoxy-4-phenylchroman-3-ol (2a)[5]

Method C was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-2-((3,5-dimethoxyphenoxy)methyl)-3-phenyloxirane] (0.145 g, 0.506 mmol) at 20 ºC for 30 min to afford 0.136 g (94 %) of product as a colorless solid: m.p. = 100–101 ºC; $[\alpha]_D^{27}$: +52.3 (*c* 1.1 in $CHCl_3$); IR (ATR): 3336, 2920, 2851, 1615, 1589, 1493, 1451, 1201, 1144, 1122, 1076, 811, 749, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.20 (bs, 1H), 3.57 (s, 3H), 3.79 (s, 3H), 3.97 (d, *J* = 10.9 Hz, 1H), 4.01 (m, *J* = 2.3 Hz, 1H), 4.02 (d, *J* = 2.3 Hz, 1H), 4.24 (m, 1H), 6.10 (d, *J* = 2.4 Hz, 1H), 6.16 (d, *J* = 2.4 Hz, 1H), 7.09 (d, *J* = 7.3 Hz), 7.20 (t, *J* = 7.3 Hz, 1H), 7.25-7.29 (m, *J* = 7.3, 2.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 43.4 (CH), 55.3 (CH_3), 55.5 (CH_3), 65.1 (CH_2), 69.3 (CH), 92.5 (CH), 93.0 (CH), 101.8 (C), 126.4 (CH), 128.1 (2CH), 128.4 (2CH), 143.4 (C), 155.1 (C), 159.8 (C), 160.3 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{18}NaO_4$: 309.1103; found: 309.1118 $[M+Na]^+$.

(3*S*,4*R*)-4-Phenylchroman-3-ol (2b)

Method C was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-2-(phenoxymethyl)-3-phenyloxirane] (0.112 g, 0.495 mmol) at 20 ºC for 60 min to afford 0.071 g (63 %) of product as a white solid: m.p. = 120–121 ºC; $[\alpha]_D^{27}$: +33.9 (*c* 0.2 in $CHCl_3$); IR (ATR): 3584, 3391, 2922, 2852, 1714, 1584, 1487, 1454, 1377, 1247, 1227, 1076, 1044, 751, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.08 (d, *J* = 6.0 Hz, 1H), 4.00-4.05 (m, 1H), 4.12 (m, 2H), 4.20 (dd, *J* = 2.1, 11.0 Hz, 1H), 6.87 (d, *J* = 4.1 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.17-7.20 (m, 1H), 7.24-7.28 (m, 1H), 7.31-7.35 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 50.2 (CH), 66.8 (CH_2), 69.8 (CH), 116.6 (CH), 121.3 (CH), 122.1 (C), 127.1 (CH), 128.2 (CH), 128.8 (2CH), 129.1 (2CH), 131.3 (CH), 142.5 (C), 154.1 (C); HRMS (ES+): *m/z* calcd. for $C_{15}H_{14}NaO_2$: 249.0891; found: 249.0898 $[M+Na]^+$.

(3*S*,4*R*)-6-Methoxy-4-phenylchroman-3-ol (2c)

Method C was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-2-((4-methoxyphenoxy)methyl)-3-phenyloxirane] (0.13 g, 0.507 mmol) at 20 ºC for 60 min to afford 0.12 g (92 %) of product as a yellowish solid: m.p. = 115–116 ºC; $[\alpha]_D^{28}$: –3.4 (*c* 1.0 in $CHCl_3$); IR (ATR): 3707, 3680, 2970, 1738, 1521, 1434, 1366, 1228, 1216, 1056, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (d, *J* = 6.5 Hz, 1H), 3.65 (s, 3H), 3.97 (ddd, *J* = 10.8, 4.5, 2.3 Hz, 1H), 4.07-4.10 (m, 2H), 4.15 (d, *J* = 10.8 Hz, 1H), 6.40 (d, *J* = 2.9 Hz, 1H), 6.76 (dd, *J* = 2.9, 9.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 7.14-7.16 (m, 2H), 7.23-7.28 (m, 1H), 7.30-7.35 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 50.5 (CH), 55.7 (CH_3), 66.6 (CH_2), 69.9 (CH), 114.8 (CH), 115.3 (CH), 117.3 (CH), 122.5 (C), 127.1 (CH), 128.7 (2CH), 129.1 (2CH), 142.5 (C), 148.2 (C), 154.1 (C); HRMS (ES+): *m/z* calcd. for $C_{16}H_{16}NaO_3$: 279.0997; found: 279.0998 $[M+Na]^+$.

(3*S*,4*R*)-5,7-Dimethyl-4-phenylchroman-3-ol (2d)

Method C was applied to enantiomerically pure [(2*S*,3*S*)-2-((3,5-dimethylphenoxy)-methyl)-3-phenyloxirane] (0.128 g, 0.503 mmol) at 20 ºC for 30 min to afford 0.121 g (94 %) of product as a white solid: m.p. = 127–128 ºC. $[\alpha]_D^{24}$: +68.2 (*c* 0.7 in $CHCl_3$); IR (ATR): 3499, 2922, 2889, 1619, 1575, 1487, 1449, 1346, 1241, 1142, 1107, 1081, 1056, 1027, 912, 880, 858, 745, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 2.29 (s, 4H), 3.96-4.01 (m, 2H), 4.05 (d, *J* = 7.4 Hz, 1H) 4.14 (m, 1H), 6.64 (s, 1H), 6.66 (s, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.25-7.30 (m, *J* = 7.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.9 (CH_3), 21.1 (CH_3), 46.5 (CH), 64.4 (CH_2), 69.9 (CH), 114.9 (CH), 116.0 (C), 124.5 (CH), 126.7 (CH), 128.5 (2CH), 128.7 (2CH), 138.0 (C), 139.2 (C), 142.6 (C), 153.8 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{18}NaO_2$: 277.1204; found: 277.1216 $[M+Na]^+$.

(3*S*,4*R*)-5,7-Dimethoxy-4-(4-bromophenyl)chroman-3-ol (2e)

Method C was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-2-(4-bromophenyl)-3-((3,5-dimethoxyphenoxy)methyl)oxirane] (0.185 g, 0.506 mmol) at 20 ºC for 60 min to afford 0.143 g (77 %) of product as a white solid: m.p. = 77–78 ºC; $[\alpha]_D^{27}$: +35.2 (*c* 0.5 in $CHCl_3$); IR (ATR): 3276, 2919, 2849, 1616, 1590, 1488, 1461, 1262, 1145, 1125, 1072, 1004, 856, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.19 (bs, 1H), 3.58 (s, 3H), 3.80 (s, 3H), 3.91 (d, *J* = 11.3 Hz, 1H), 3.98 (m, 2H), 4.00-4.05 (m, *J* = 11.3 Hz, 1H), 4.17 (m, 1H), 6.09 (d, *J* = 2.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 43.0 (CH), 55.3 (CH_3), 55.5 (CH_3), 65.0 (CH_2), 69.1 (CH), 92.6 (CH), 93.0 (CH), 101.3 (C), 120.3 (C), 129.8 (2CH), 131.5 (2CH), 142.5 (C), 155.1 (C), 159.7 (C), 160.6 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{17}BrNaO_4$: 387.0208; found: 387.0217 $[M+Na]^+$.

(3*S*,4*R*)-6-Iodo-4-phenylchroman-3-ol (2f)

Method C was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-2-((4-iodophenoxy)methyl)-3-phenyloxirane] (0.178 g, 0.506 mmol) at 20 ºC for 60 min to afford 0.13 g (73 %) of product as a white solid: m.p. = 107–108 ºC; $[\alpha]_D^{25}$: –15.04 (*c* 0.9 in $CHCl_3$); IR (ATR): 3570, 3345, 3019, 2338, 1725, 1534, 1480, 1215, 1118, 1048, 891, 752, 670, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00 (d, *J* = 8.8 Hz, 1H), 3.99-4.11 (m, 3H), 4.17 (d, *J* = 2.1, 11.0 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 7.10-7.50 (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 49.8 (CH), 66.7 (CH_2), 69.3 (CH), 83.4 (C), 119.0 (CH), 124.8 (C), 127.4 (CH), 128.9

(2CH), 129.0 (2CH), 137.1 (CH), 139.7 (CH), 141.8 (C), 154.1 (C); HRMS (ES+): *m/z* calcd. for $C_{15}H_{13}INaO_2$: 374.9858; found: 374.9850 $[M+Na]^+$.

(3*S*,4*R*)-6-*tert*-Butyl-4-phenylchroman-3-ol (2g)

Method C was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-2-((4-*tert*-butylphenoxy)methyl)-3-phenyloxirane] (0.142 g, 0.503 mmol) at 20 ºC for 30 min to afford 0.141 g (99 %) of product as a white solid: m.p. = 110–111 ºC. $[\alpha]_D^{26}$:–204.2 (*c* 0.2 in $CHCl_3$); IR (ATR): 3379, 2920, 2851, 1708, 1587, 1504, 1452, 1343, 1246, 1132, 1076, 1014, 964, 908, 836, 819, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9H), 2.13 (bs, 1H), 4.00 (ddd, *J* = 1.5, 5.2, 10.7 Hz, 1H), 4.09-4.15 (m, 3H), 6,86-6.88 (m, *J* = 8.5 Hz, 2H), 7,13-7.15 (m, *J* = 8.5 Hz, 2H), 7.21 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.23-7.27 (m, 1H), 7.31-7.35 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 31.14 ($3CH_3$), 34.1 (C), 50.2 (CH), 66.5 (CH_2), 70.1 (CH), 116.0 (CH), 120.8 (C), 125.3 (CH), 127.9 (CH), 128.1 (CH), 128.7 (2CH), 129.1 (2CH), 142.9 (C), 144.1 (C), 151.8 (C); HRMS (ES+): *m/z* calcd. for $C_{19}H_{22}O_2$: 282.1620; found: 282.1629 [M].

6-*tert*-Butyl-chroman-3-ol (2h)[5]

Method E was applied to [2-((4-(*tert*-butylphenoxy)methyl)oxirane] (0.14 g, 0.679 mmol) at 140 ºC for 40 min to afford 0.069 g of product (91 % yield based on recovered starting material, with 53 % conversion) as a yellowish solid: m.p. = 79–80 ºC; IR (ATR): 3246, 2953, 2864, 1616, 1585, 1497, 1361, 1299, 1260, 1180, 1073, 1002, 964, 894, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9H), 1.99 (d, 1H), 2.80 (dd, *J* = 4.5, 16.5 Hz, 1H), 3.10 (dd, *J* = 4.5, 16.5 Hz, 1H), 4.02-4.14 (m, 2H), 4.26 (m, 1H), 6.79 (d, *J* = 8.5, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.15 (dd, *J* = 8.5, 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 31.5 ($3CH_3$), 33.8 (CH_2), 34.1 (C), 63.5 (CH), 69.7 (CH_2), 116.1 (CH), 118.4 (C), 124.8 (CH), 127.2 (CH), 143.9 (C), 151.5 (C); HRMS (ES+): *m/z* calcd. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1299 [M].

Chroman-3-ol (2i)[5,7]

Method E was applied to [2-(phenoxymethyl)oxirane] (0.10 g, 0.666 mmol) at 140 ºC for 40 min to afford 0.017 g of product (17 %) as a white solid: m.p. = 76–77 ºC; IR (ATR): 3351, 2961, 2922, 1718, 1489, 1258, 1078, 1012, 864, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00 (d, 1H), 2.82 (dd, *J* = 4.5, 16.6 Hz, 1H), 3.11 (dd, *J* = 4.8, 16.6 Hz, 1H), 4.05-4.14 (m, 2H), 4.25-4.27 (m, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.89 (dt, *J* = 7.2 Hz), 7.06 (dd, *J* = 7.2 Hz, 1H), 7.12 (dt, *J* = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 33.6 (CH_2), 63.3 (CH_2), 69.7 (CH), 116.6 (CH), 119.3 (C), 121.2 (CH), 127.7 (CH), 130.5 (CH), 153.8 (C); HRMS (ES+): *m/z* calcd. for $C_9H_{10}NaO_2$: 173.0578; found: 173.0601 $[M+Na]^+$.

5. General Procedure for the preparation of tetrahydrobenzo[c]oxepin-4-ols (4a-b) or 4-diarylmethyl-1,3-dioxolanes (5a-b).

Method A: Boron trifluoride-mediated rearrangement[4]

A solution of the corresponding benzyl glycidyl ether (0.35 mmol) and $BF_3 \cdot Et_2O$ (0.104 mmol) in anhydrous CH_2Cl_2 (3 mL) under N_2 was stirred for 15 min at –78 °C. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (3 mL) and then it was extracted with CH_2Cl_2 (3×3 mL). The combined organic extracts were dried and concentrated *in vacuum*, and the crude product was purified by column chromatography using hexanes:EtOAc (90:10/80:20) as the eluent.[4]

Method A.1: Boron trifluoride-mediated rearrangement

The general procedure for boron trifluoride was followed changing the temperature to –35 ºC for 5 min. The reaction mixture was treated as described in the general procedure.

Method B: Iron tribromide-mediated rearrangement

A solution of the corresponding benzyl glycidyl ether (0.066 mmol) and $FeBr_3$ (0.002 g, 0.007 mmol) in anhydrous CH_2Cl_2 (1 mL) under N_2 was stirred for 60 min at 20 °C. The reaction mixture was filtered through a pad of silica gel using ether. The organic extracts were dried and concentrated *in vacuum*, and the crude product was purified by column chromatography on silica gel using hexanes:EtOAc (90:10/80:20) as the eluent.

Method C: Gold trichloride-silver salt mediated rearrangement[5]

A solution of the corresponding benzyl glycidyl ether (0.066 mmol), $AuCl_3$ (0.0005 g, 0.002 mmol) and AgOTf (0.0013 g, 0.005 mmol) in $ClCH_2CH_2Cl$ (2 mL) under N_2 was stirred for 4 h at 50 °C. The reaction mixture was then treated as described in method B.[5]

Method D: Iron tribromide-silver salt mediated rearrangement

A solution of the corresponding benzyl glycidyl ether (0.506 mmol), $FeBr_3$ (0.030 g, 0.101 mmol) and AgOTf (0.078 g, 0.304 mmol) in anhydrous CH_2Cl_2 (1 mL) under N_2 was stirred for 30 min at 20 °C. The reaction mixture was then treated as described in method B.

5.1. Tetrahydrobenzo[*c*]oxepin-4-ols (4a-b) characterization data

(4*S*,5*R*)-6,8-Dimethoxy-5-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-4-ol (4a)[4]

Method D was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-3-Phenyl-2-((3,5-dimethoxy)benzyloxymethyl)oxirane] (0.152 g, 0.506 mmol) at 20 ºC for 30 min to afford 0.134 g (88 %) of product as a white solid: m.p. = 113–114 ºC. $[\alpha]_D^{20}$: –29.6 (c 1.0 in $CHCl_3$); IR (ATR): 3352, 2918, 2850, 1603, 1490, 1314, 1151, 1088, 1044, 959, 809, 737, 700, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (bs, 1H), 3.66 (d, *J* = 12.5 Hz, 1H), 3.74 (s, 3H), 3.85 (s, 3H), 3.96 (dd, *J* = 2.9, 12.4 Hz, 1H), 4.39-4.41 (m, 1H), 4.51 (dd, *J* = 13.7 Hz, 2H), 5.39 (d, *J* = 5.8 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.25-7.28 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 46.1 (CH), 55.3 (CH_3), 56.1 (CH_3), 71.6 (CH), 73.3 (CH_2), 76.0 (CH_2), 98.3 (CH), 106.2 (CH), 117.4 (C), 126.2 (CH), 127.7 (2CH), 128.6 (2CH), 139.9 (C), 142.3 (C), 159.6 (C), 160.6 (C). HRMS (ES+): *m/z* calcd. for $C_{18}H_{20}NaO_4$: 323.1259; found: 323.1264 $[M+Na]^+$.

(4*S*,5*R*)-5-(4-Bromophenyl)-6,8-dimethoxy-1,3,4,5-tetrahydrobenzo[c]oxepin-4-ol (4b)

Method D was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-3-(4-bromophenyl)-2-((3,5-dimethoxy)benzyloxymethyl)oxirane] (0.190 g, 0.501 mmol) at 20 ºC for 30 min to afford 0.154 g (81 %) of product as a white solid: m.p. = 137–138 ºC. $[\alpha]_D^{27}$: 8.7 (*c* 1.2 in $CHCl_3$); IR (ATR): 3353, 2917, 2851, 1709, 1603, 1586, 1484, 1452, 1343, 1274, 1176, 1090, 1011, 953, 855, 796, 757, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (bs, 1H), 3.63 (d, *J* = 12.6 Hz, 1H), 3.73 (s, 3H), 3.84 (s, 3H), 3.96 (dd, *J* = 2.9, 12.5 Hz, 1H), 4.35 (m, 1H), 4.50 (dd, *J* = 13.7 Hz, 2H), 5.29 (d, *J* = 5.7 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 45.8 (CH), 55.4 (CH_3), 56.0 (CH_3), 71.5 (CH), 73.2 (CH_2), 75.9 (CH_2), 98.3 (CH), 106.1 (CH), 116.9 (C), 120.1 (C), 129.5 (2CH), 131.7 (2CH), 139.1 (C), 142.1 (C), 159.7 (C), 160.5 (C); HRMS (ES+): *m/z* calcd. for $C_{18}H_{19}BrNaO_4$: 401.0364; found: 401.0372 $[M+Na]^+$.

5.2. 4-Diarylmethyl-1,3-dioxolanes (5c-d) characterization data

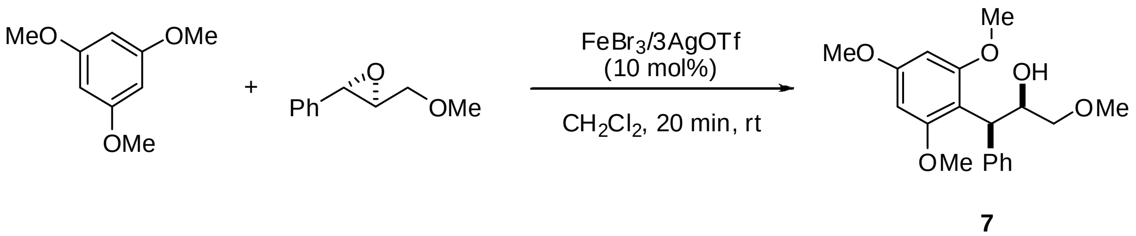
(4*R*)-[(4-Methoxyphenyl)-(*R*)-(4-phenyl)methyl]-1,3-dioxolane (5c)[4]

Method D was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-3-Phenyl-2-((4-methoxy)benzyloxymethyl)oxirane] (0.136 g, 0.501 mmol) at 20 ºC for 30 min to afford 0.112 g (82 %) of product as a white solid: m.p. = 113 ºC. $[\alpha]_D^{20}$: –7.0 (*c* 0.98 in $CHCl_3$); IR (ATR): 2928, 1719, 1607, 1509, 1454, 1301, 1244, 1177, 1086, 1030, 937, 808, 752, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.57 (dd, *J* = 6.9, 8.3 Hz, 1H), 3.77 (s, 3H), 3.88 (dd, *J* = 6.4, 8.3 Hz, 1H), 3.98 (d, *J* = 9.5 Hz, 1H), 4.70-4.76 (m, 1H), 4.94 (s, 1H), 5.05 (s, 1H), 6.83 (dd, *J* = 2.0, 6.6 Hz, 2H), 7.16 (dd, *J* = 2.0, 6.6 Hz, 2H), 7.20-7.22 (m, 1H) 7.28-7.35 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.9 (CH), 55.2 (CH_3), 69.1 (CH_2), 78.3 (CH), 95.6 (CH_2), 114.2 (2CH), 126.6 (CH), 128.2 (2CH), 128.5 (2CH), 129.2 (2CH), 133.5 (C), 142.1 (C), 158.5 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{18}NaO_3$: 293.1154; found: 293.1160 $[M+Na]^+$.

(4*R*)-[(4-Methoxyphenyl)-(*R*)-(4-bromophenyl)methyl]-1,3-dioxolane (5d)

Method D was applied to enantiomerically pure (ee > 99%) [(2*S*,3*S*)-3-(4-bromophenyl)-2-((4-methoxy)benzyloxymethyl)oxirane] (0.175 g, 0.501 mmol) at 20 ºC for 30 min to afford 0.168 g (96 %) of product as a colorless oil: $[\alpha]_D^{20}$: –2.0 (*c* 0.5 in $CHCl_3$); IR (film): 2836, 1609, 1582, 1510, 1488, 1302, 1247, 1177, 1085, 1031, 1009, 936, 804 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (dd, *J* = 6.7, 8.4 Hz, 1H), 3.77 (s, 3H), 3.87 (dd, *J* = 6.4, 8.4 Hz, 1H), 3.93 (d, *J* = 9.5 Hz, 1H), 4.64-4.69 (m, 1H), 4.93 (s, 1H), 5.05 (s, 1H), 6.83 (dd, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz): δ = 53.3 (CH), 55.2 (CH_3), 69.1 (CH_2), 78.1 (CH), 95.6 (CH_2), 114.3 (2CH), 120.6 (C), 129.1 (2CH), 130.0 (2CH), 131.5 (2CH), 132.8 (C), 141.2 (C), 158.7 (C); HRMS (ES+): *m/z* calcd. for $C_{17}H_{17}BrNaO_3$: 371.0259; found: 371.0259 $[M+Na]^+$.

6. Intermolecular addition of 1,3,5-trimethoxybenzene to (2*S*,3*S*)-3-phenylglycidyl methyl ether leading to 7 ((1*S*,2*R*)-3-methoxy-1-phenyl-1-(2,4,6-tri-methoxyphenyl)propan-2-ol)



7

A solution of enantiomerically pure (2*S*,3*S*)-3-phenylglycidyl methyl ether[8] (0.051 g, 0.309 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added to a solution of trimethoxybenzene (0.26 g, 1.55 mmol), $FeBr_3$ (0.0091 g, 0.0309 mmol) and AgOTf (0.024 g, 0.093 mmol) in anhydrous CH_2Cl_2 (0.5 mL). This mixture was stirred for 20 min at 20 °C and then it was filtered through a short plug of silica gel (CH_2Cl_2/EtOAc 8:2) and concentrated *in vacuum*. The residue obtained was purified by column chromatography on silica gel using hexanes:EtOAc (from 8:2 to 6:4) as the eluent to give 62 mg of (1*S*,2*R*)-3-methoxy-1-phenyl-1-(2,4,6-trimethoxyphenyl)propan-2-ol (0.187 mmol, 60% yield) as a white solid.

(1*S*,2*R*)-3-methoxy-1-phenyl-1-(2,4,6-trimethoxyphenyl)propan-2-ol (7)

m.p. = 68-69 ºC; $[\alpha]_D^{23}$: –65.9 (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 7.6 Hz, 2H), 7.3-7.2 (m, 2H), 7.2-7.1 (m, 1H), 6.09 (s, 2H), 5.02 (ddd, J = 10.0, 7.8, 2.6 Hz, 1H), 4.62 (d, J = 10.0 Hz, 1H), 3.76 (s, 9H), 3.35 (dd, J = 9.6, 2.6 Hz, 1H), 3.31 (s, 3H), 3.21 (dd, J = 9.6, 7.8 Hz, 1H), 2.41 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.9 (C), 158.7 (2C), 142.6 (C), 128.7 (2CH), 127.9 (2CH), 125.8 (CH), 111.4 (C), 91.1 (2CH), 75.7 (CH), 70.3 (CH_2), 58.9 (CH_3), 55.6 ($2CH_3$), 55.2 (CH_3), 44.2 (CH); HRMS (ES+): *m/z* calcd. for $C_{19}H_{24}NaO_5$: 355.1521; found: 355.1526 $[M+Na]^+$.

7. References for the supporting information

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CHAPTER 6

CONCLUSIONS

6.1 CONCLUSIONS

In summary, in the present thesis, the initial aims are satisfactorily achieved. The syntheses of different supported ligands are described and their application for metal catalyzed reactions discussed. The efficiency of these polymer complexes in catalysis is rationalized in terms of activity, and selectivity as well as the possibility to recover and reuse them. The understanding of how to develop heterogenized ligands will provide a better and more rational way of immobilizing other successful homogeneous ligands in the future.

In the second part of this work, the application of several Lewis acids catalysts for the aryl glycidyl ether rearrangement is discussed, paying attention to its mechanistic implications.

The main findings can be summarized as follows:

- Different approaches for the immobilization of successful homogeneous ligands, diphenylphosphinooxazolines (PHOX), diphenylphosphinoimidazolines (PHIM) and mono-N-tosyl-1,2-diamines, onto polymers have been described.

-Effects of the spacer, the linker, the diverse resins and the different point of anchoring of ligands onto support have been evaluated for metal-mediated reactions. The corresponding polymer-supported catalysts efficiently induce allylic amination (especially when the reactions are promoted by microwaves), and asymmetric transfer hydrogenation.

-Reactions conditions for catalyst recovery and reuse have been established using as catalysts the more active ones. High stability of the polymer-supported complexes for an extended life of the catalytic system has been demonstrated. In order to demonstrate additional utility of the heterogenized ligands, the supported PHOX system has been adapted to continuous flow operation.

- Behaviour of different Lewis acids to induce stereospecific cyclizations from enantiomerically pure aryl glicidyl ethers has been evaluated. Through the research work herein described, we have demonstrated, contrary to previous claim about only gold mediating this reaction, Lewis acids do in fact catalyze this rearrangement.

-From the perspective of practical use, cost and availability considerations, it has been considered $FeBr_3$ (alone or in combination with silver triflate) as the reagent of choice for this operation and, in general, for processes where gold and other expensive metals merely act as simple Lewis acids.

-From a mechanistic point of view, the observed reactivity trends clearly indicate that these cyclizations are of the Friedel-Crafts type.