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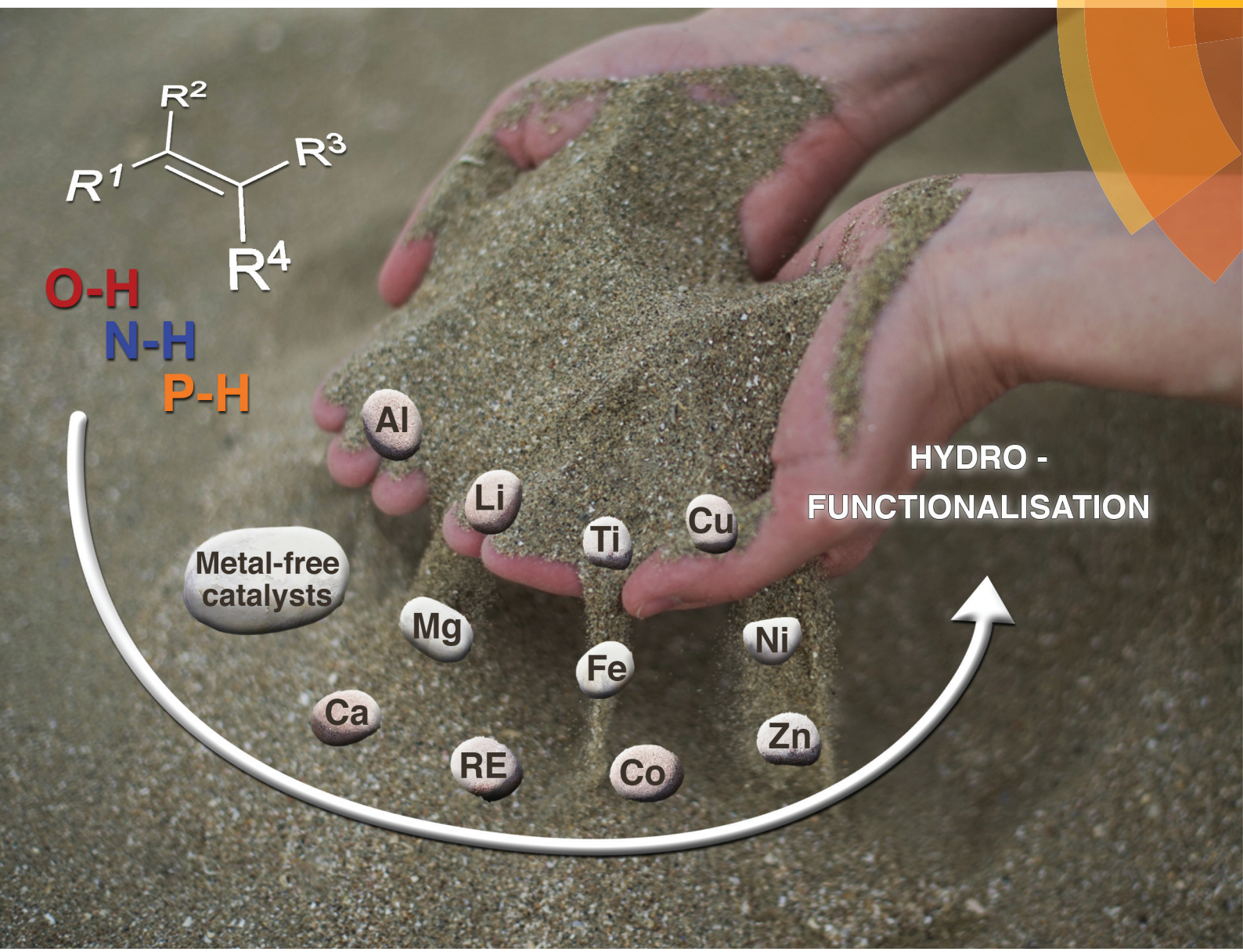

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PERSPECTIVE

Jérôme Hannedouche *et al.*

Recent developments in alkene hydro-functionalisation promoted by homogeneous catalysts based on earth abundant elements: formation of C–N, C–O and C–P bond

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Recent developments in alkene hydrofunctionalisation promoted by homogeneous catalysts based on earth abundant elements: formation of C–N, C–O and C–P bond

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This Perspective article provides an overview of the recent advancements in the field of intra- and intermolecular C–N, C–O and C–P bond formation by hydroamination, hydroalkoxylation, hydrophosphination, hydrophosphonylation or hydrophosphinylation of unactivated alkenes, including allenes, 1,3-dienes and strained alkenes, promoted by (chiral) homogeneous catalysts based on earth abundant elements of the s and p blocks, the first row transition metals and the rare-earth metals. The relevant literature from 2009 until late 2014 has been covered.

1. Introduction

The wide applications of nitrogen-, oxygen- and phosphorus-based organic compounds in various domains such as pharmaceuticals, fine and bulk chemicals, agrochemicals, biological and coordination chemistry or catalysis amongst others have driven the interest of the scientific community with a strong demand for the development of sustainable, more selective and efficient processes for their syntheses. Among the plethora of synthesis routes, the addition of E–H (E = N, O, P) across an unactivated carbon–carbon double bond, the more generally called hydrofunctionalisation (or hydroelementation)[1] reaction of unactivated alkene, promoted by a metal or metal-free catalyst is a very promising field of research towards

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Violeta Rodriguez-Ruiz

Violeta Rodriguez-Ruiz received her B.Sc. in Pharmacy at the University of Valencia, Spain. She got her M.Sc. in Chemistry at the Technical Institute of Chemistry (ITQ, UPV-CSIC), where she carried out her Ph.D. at Prof. Corma's group. In 2011, she obtained a Marie Curie-ITN Experienced Researcher fellowship to work at the "Institut Galien Paris-Sud" (Faculty of Pharmacy, CNRS-Université Paris-Sud). In 2012, she joined the "Laboratory of Molecular Catalysis" (ICMMO, Faculty of Sciences, CNRS-Université Paris-Sud) as a Post-Doctoral Fellow. Since 2014, she works at the "Laboratory for Vascular Translational Science" (Institut Galilée, Université Paris13-INSERM) as Temporary Lecturer and Research Assistant.

Romain Carlino

Romain Carlino was born in 1988 in Monaco. He obtained his diploma from Ecole Nationale Supérieure de Chimie de Clermont-Ferrand and his master degree at Université Blaise Pascal in 2013. He is currently a PhD student at ICMMO (Université Paris-Sud) working on rare-earth complexes for catalytic applications in hydroalkoxylation reaction under the supervision of Dr Sophie Bezzenine-Lafollée and Dr Richard Gil.

the development of an economic and environmentally friendly synthetic methodology. Indeed, the hydrofunctionalisation reaction provides a 100% atom efficiency and waste-free process from relatively low-cost and ubiquitous starting materials. Furthermore, catalysis brings the opportunity to fine-tune the regio-, chemo- and stereoselectivity of the overall transformation by a perfect synergy between the metal and the ligand(s) or by the direct design of a metal-free system. However, despite the inherent interesting features of the transformation, it is very challenging to control the regioselectivity of this reaction providing exclusively the Markovnikov or the *anti*-Markovnikov adduct. As a general trend, Markovnikov selectivity is the most common selectivity noticed in the addition reactions of N–H and O–H onto unactivated alkenes while the addition of P–H provides usually the *anti*-Markovnikov product. For the corresponding addition reaction, few contributions exhibit the opposite regioselectivity.[2–4] These features highlight the challenges to access both regioisomeric products which are all of synthetic value. Additionally to the regioselectivity, the control of stereoselectivity of the newly generated stereogenic carbon of the branched product is also an important issue of this process. For example, the intermolecular and highly enantio- and regioselective addition of amines to simple aliphatic alkenes still remains one of the most unresolved problems in alkene hydroamination[5] as is the control of the enantioselectivity in alkene hydroalkoxylation.[3d–e,6] The last decades have witnessed an intensive research activity focusing on the development of metal-based and metal-free catalysts to promote the addition of E–H across an unactivated carbon–carbon double bond intra- and intermolecularly. Although tremendous progresses have been gained from the study of precious metal catalysts,[1] the growing request for novel, more economical and eco-friendly catalytic systems has stimulated the exploration of earth abundant elements as alternatives to address some of the issues.

This Perspective article will outline some of the recent advancements in the field of intra- and inter-molecular C–N, C–O and C–P bond formation by hydroamination, hydroalkoxylation, hydrophosphination, hydro-phosphonylation or hydrophosphinylation of unactivated alkenes, including allenes, 1,3-dienes and strained alkenes, promoted by (chiral) catalytic systems based on earth abundant elements. The hydration of alkenes is not included and the reader should refer to reported reviews on the topic.[7] This article will focus on systems based on Group 1–3 elements, the most relevant first-row transition metal elements of the field (titanium, iron, cobalt, nickel, copper and zinc) and also the block p element aluminum. It is beyond the scope of this article to comprehensively review all the research activity of this broad field and literature coverage has been mainly limited from 2009 until 2014, even if a few representative reports appeared earlier are included. This article has been divided according to the Group, the element within the Group and the type of C–E (E = N, O, P) bond formed in the transformation. For a broader overview, the latest developments in metal free-catalysed C–E (E = N, O, P) bond formation by alkene hydrofunctionalisation have also been included and will start this Perspective.

2. Metal-free catalysts

2.1 C–N bond formation

2.1.1 Brønsted acid catalysts. Over the years, alkene hydroamination promoted by Brønsted acid catalysts has naturally attracted the attention of the scientific community as an eco-friendly methodology for metal-free C–N bond formation. Although significant developments have been gained in broadening the scope of the racemic transformation,[8] the most recent achievements have been on the challenging control of the stereoselectivity of the N–H addition on the unactivated

Sophie Bezzenine-Lafollée

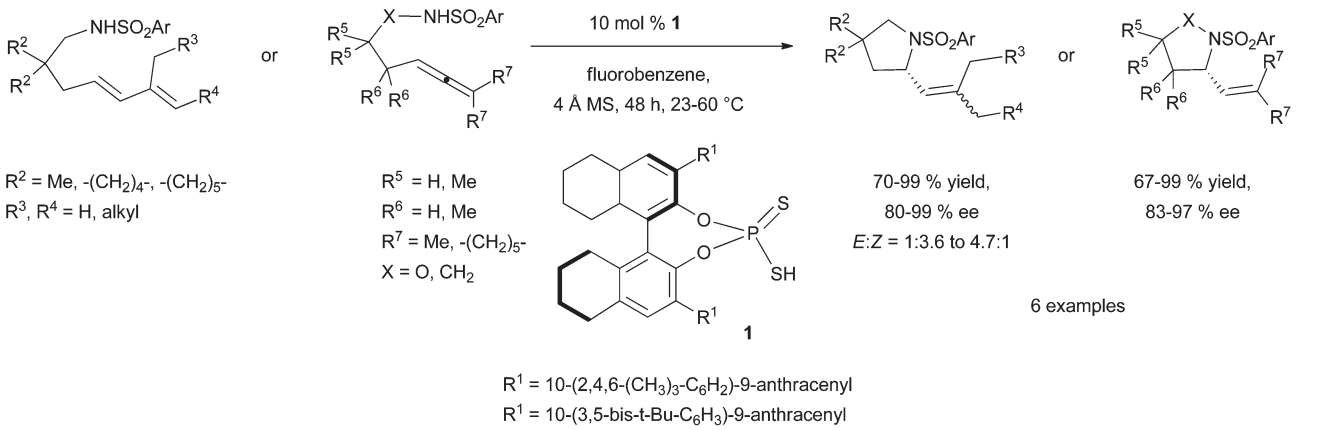
Sophie Bezzenine-Lafollée received her Ph.D. degree from Université Paris VI in 1998. After a postdoctoral stay on asymmetric synthesis with Pr. P. Müller at the University of Geneva, Switzerland, she spent two years in the laboratory of Pr. J. Ardisson at the University of Cergy-Pontoise working on total synthesis. She became Maître de Conférence in Orsay University in 2001, she firstly worked with Drs F. Guibé and J. Collin on lanthanides chemistry. Recently, she collaborated with Pr. V. Gandon on silver-free two-component approach in gold catalysis and since 2010, she works with Dr R. Gil on enantioselective catalysis with rare earths complexes.

Richard Gil

Richard Gil studied chemistry at Université Paris-Sud (Orsay, France) where he received his PhD in 1993. His thesis work was under the supervision of Professor Jean-Claude Fiaud and dealt with enantioselective palladium-catalysed reactions. He then spent one post-doctoral year (1993–1994) at Imperial College London under the group of Pr. Susan E. Gibson. In 1995, he went to Université de Cergy-Pontoise and became Maître de Conférences in 1996. In 2002, he returned to ICMMO where he joined the Dr Jacqueline Collin group in which he has been interested in lanthanide-catalysed reactions. His research interests include enantioselective reactions catalysed by rare earths.

alkene. Pioneer work in metal-free enantioselective alkene hydroamination reaction was reported in 2008 by the group of Ackermann by using an enantiomerically enriched phosphoric acid diester as Brønsted acid catalyst albeit only one example was disclosed and a poor enantioselectivity of 17% was reached.[9] In 2011, the group of Toste reported the first highly selective intramolecular hydroamination of sulfonylamines tethered to substituted 1,2- and 1,3-dienes catalysed by chiral 3,3′-bisaryl-substituted binaphthol-derived dithiophosphoric acids **1** (Scheme 1).[10] Remarkably, under the optimal mild conditions, vinyl-pyrrolidines and -oxazolidines were synthesised in high yields and with high ee values. The high regio- and enantioselectivity of the process originates from original the covalently selective addition of the dithiophosphoric acid on the diene to give an "activated" substrate and subsequent controlled S_N2'-type displacement of the dithiophosphoric acid conjugate base by the nucleophilic protected amine. The presence of the sulphur atoms on the phosphoric acid **1** was essential to reach high conversion and selectivity as the oxygenated analogues of the corresponding acid were less efficient. The substrate design was also important to control the chemo- and regioselectivity of the catalyst addition.[11]

2.1.2 Cope-type hydroamination. A complementary but mechanistically distinct approach to achieve amination of unactivated alkenes under metal-free conditions is the Cope-type hydroamination using hydroxylamines.[12] In this type of transformation which is the microscopic reverse reaction of the well-known Cope-elimination, the alkene and the hydroxylamine undergo a pericyclic reaction through a 5-membered cyclic transition state involving concerted C–N and C–H bond formations. In 2011, the group of Beauchemin described a metal-free catalytic tethered strategy to promote an enantioselective intermolecular Cope-type hydroamination reaction.[13] Building on their strong expertise on metal-free Cope type hydroamination, the group has postulated that the rate of such entropically unfavored transformation could be enhanced by



Scheme 1 Enantioselective intramolecular hydroamination of amines tethered to 1,3- and 1,2-dienes with chiral dithiophosphoric acids.

Damien Prim

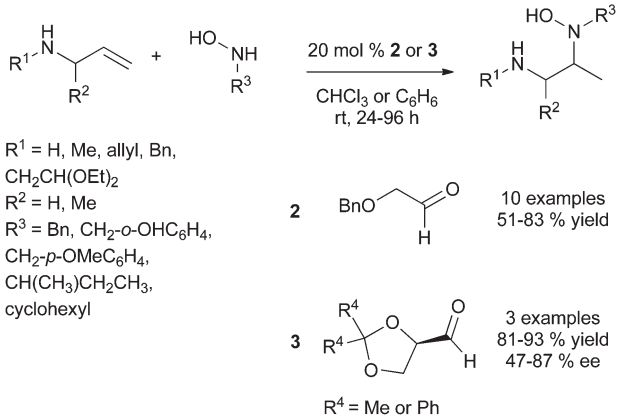
Damien Prim received his PhD at the University Paul Verlaine of Metz in 1994 under the guidance of Pr. G. Kirsch. He joined Pr. L. Ghosez group at the University Catholique de Louvain, Belgium, for a one year post-doctoral training. After four years (1995–1999) as Assistant Professor at the University Paul Verlaine, he moved to the University Pierre et Marie Curie, Paris, as CNRS research associate (1999–2001) and joined the University of Versailles in 2001. His current research interests concern homogeneous catalysis, multitask ligands and their application to the synthesis of helical, twisted and planar molecular architectures.

Emmanuelle Schulz

Emmanuelle Schulz graduated from ESCIL in Lyon and received her Ph.D. degree in 1992 for studies concerning the total synthesis of Strigol (Pr. P. Welzel, Ruhr-Universität Bochum/Université de Lyon). After a postdoc at RP Agro, she joined the group of Pr. M. Lemaire and obtained a position at the CNRS. Since 2000, she is at ICMMO (Université Paris Sud). Her research interests are mainly directed towards asymmetric catalysis. She particularly explores the enantioselective hydroamination reaction promoted by chiral rare-earth based catalysts. New procedures for the easy recovery and reuse of chiral organometallic catalysts are also developed in her group.

the use of a catalytic organic molecule, appropriately designed as tether for temporarily bringing together both reaction partners to react intramolecularly through a Cope-type reaction.

This strategy was successfully developed by the perfect match between the chiral tethering catalyst and both alkene and amine partners. Extensive screening of aldehydes and ketones have identified benzyloxyacetaldehyde **2** as the appropriate metal-free tethering catalyst for intermolecular Cope-type hydroamination of allylic amines and α-benzylhydroxylamine (20 mol%) at room temperature (Scheme 2). Mechanistic studies suggest that the hydroamination step is the rate-limiting step of the catalytic cycle and lead to the identification that paraformaldehyde (5–10 mol%) is a more efficient metal-free catalyst providing higher yields of hydroamination products.[14] The use of 20 mol% of (*R*)-glyceraldehyde **3** allowed the development of an enantioselective variant of this process to furnish enantioenriched vicinal diamine derivatives in high yields and with ee values of up to 87% after 24 h at room temperature (Scheme 2). The reaction is proposed to proceed through the formation of a mixed aminal intermediate resulting from nucleophilic attack of the nitrone (resulting from aldehyde-hydroxylamine condensation) by the allylic amine. This methodology is so far restricted to simple allylic amines as homoallylic amines and disubstituted allylic amines led to catalyst deactivation.



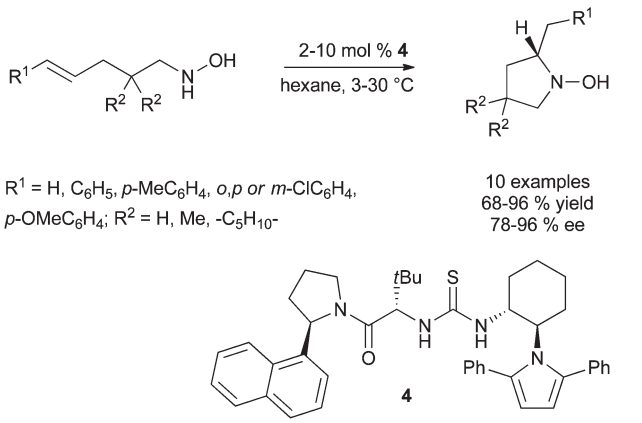
Scheme 2 Intermolecular Cope-type hydroamination catalysed by achiral and chiral aldehydes.

More recently, the group of Jacobsen has investigated the use of chiral thioureas to stabilise the polar transition state of the Cope-type intramolecular hydroamination reaction through hydrogen-bonding interactions (Scheme 3).[15] In this context, extensive screening of a variety of chiral thiourea catalysts bearing polarisable and conformationally constrained aromatic components was conducted and led to the identification of thiourea **4** as the optimal catalyst structure. Various 4-alkenyl-1-hydroxylamines bearing in some cases electronically different (*E*)-styryl moieties, cyclise in good to high yields and enantioselectivities under the optimal mild conditions displayed in Scheme 3. It is suggested that additional cation–π interactions between the cationic transition state and the arene of the catalyst occur in the process.

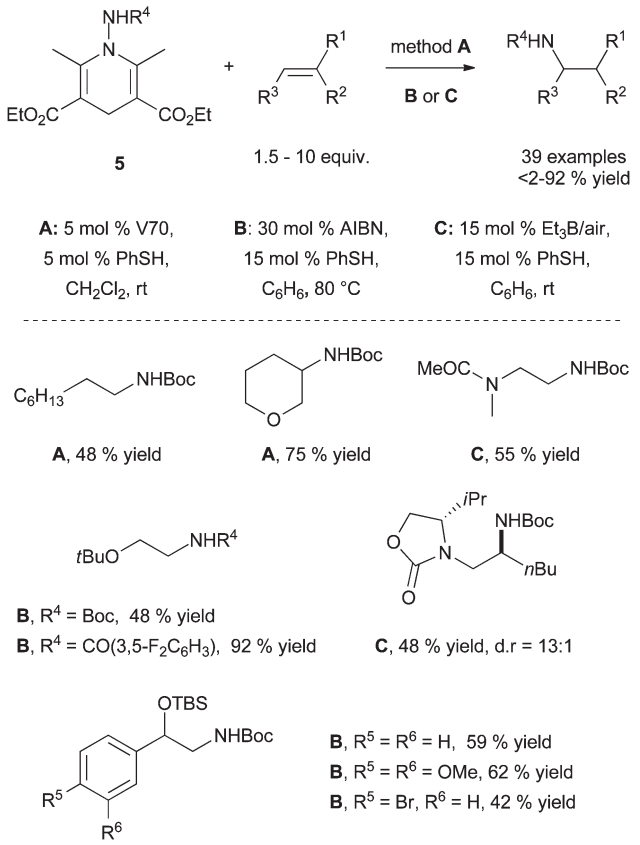
2.1.3 Radical initiator catalysts. Novel strategies relying on radical chemistry have recently been reported to tackle successfully the challenging *anti*-Markovnikov hydroamination of alkenes. The group of Studer disclosed the first report of radical transfer hydroamination of unactivated olefins[16] using 1-aminated-2,5-cyclohexadienes as stable N-radical precursors in the presence of thiols as polarity reversal catalysts.[17] The radical hydroamination process occurs with good to excellent *anti*-Markovnikov selectivity and moderate yields under harsh conditions. However, the laborious synthesis of 1-aminated-2,5-cyclohexadienes in large-scale and their instability under acid conditions encourages the search for alternative N-radical precursors. In 2008, Studer *et al.* introduced N-aminated Hantzsch ester **5** as a readily available and non-toxic radical-transfer-hydroamination reagent for the selective *anti*-Markovnikov intermolecular hydroamination of various unactivated alkenes under milder conditions (Scheme 4).[18] Initial optimi-

Jérôme Hannedouche

After completing a PhD degree under the supervision of Pr. Martin Wills (University of Warwick, UK) in 2003, Jérôme Hannedouche undertook a 2-year postdoctoral training with Pr. Olivier Riant (UCL, Belgium). In October 2006, he was appointed at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO) (Université Paris-Sud, France) as a CNRS fellow researcher. His research interests lie in the development of novel synthetic methodologies in asymmetric catalysis, mainly for C–N bond formation via *hydroamination reaction.*



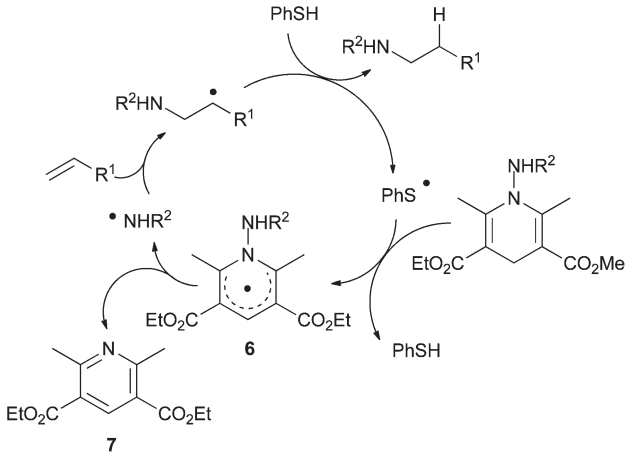
Scheme 3 Enantioselective thiourea-catalysed intramolecular Cope-type hydroamination.



Scheme 4 Intermolecular radical transfer hydroamination with N-aminated Hantzsch ester **5** using polarity-reversal catalysis.

sation studies on the radical hydroamination of **5** (R^4 = BOC) and norbornene in the presence of various polarity reversal catalysts and initiators reveal that the best results were obtained with the low-cost and commercially available PhSH as polarity reversal catalyst. Under the optimised conditions using either 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V70) (method **A**), azobisisobutyronitrile (AIBN) (method **B**) or Et_3B/air (method **C**) as initiators, a variety of aliphatic alkenes, enol ethers, enamides and enecarbamates were converted into the corresponding hydroamination products in low to moderate yields (Scheme 4). Electron-rich alkenes provide the highest yields with perfect *anti*-Markovnikov selectivity. Traces of Markovnikov product was however noticed with 1-octene. Chiral enecarbamates derived from Evans oxazolidinones could also lead to the formation of enantiomerically pure diamines with high diastereoselectivity.

The process involves a regioselective N-radical addition onto the alkene to deliver a C-radical (Scheme 5). In the presence of a catalytic amount of a thiol as polarity reversal catalyst, efficient H-transfer occurs giving the hydroamination product and forming a thiyl radical. Subsequently, the latter undergoes hydrogen abstraction from the N-aminated dihydropyridine to regenerate the thiol catalyst and form **6**. Homolytic cleavage of the weak N–N bond of **6** should regenerate the N-centered radical and liberate pyridine derivative **7**. The

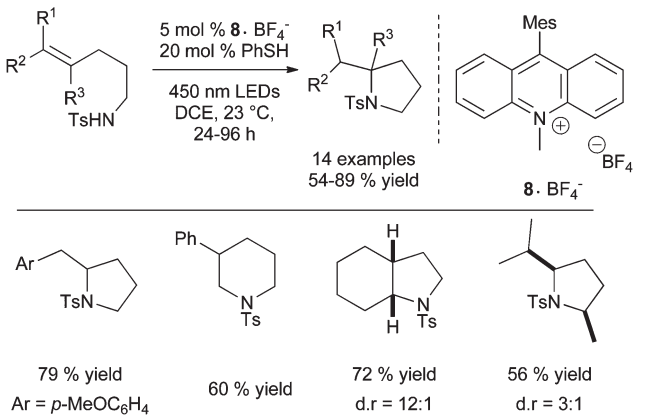


Scheme 5 Proposed mechanism for intermolecular radical transfer hydroamination with N-aminated Hantzsch ester **5** using polarity-reversal catalysis.

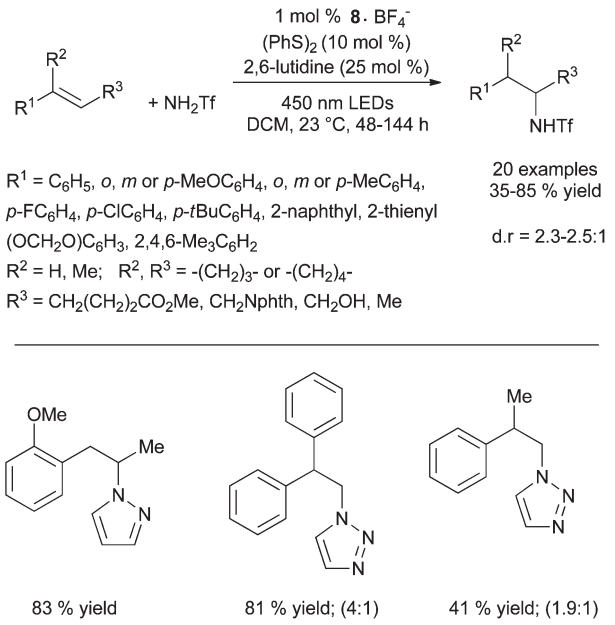
polarity reversal agent allows an efficient hydrogen-transfer reaction to the C-centered radicals.

The group of Nicewicz has also reported an alternative radical *anti*-Markovnikov intramolecular hydroamination process based on single electron oxidation of olefins using a mild two-component organic photoredox catalyst system.[19] Inspired by their previous work on direct intramolecular *anti*-Markovnikov addition of alcohols to alkenes (*vide infra*)[3a] and after optimisation studies, the group provides a very efficient metal-free method for the cyclohydroamination of electron-poor amines tethered to alkenes under mild conditions using Fukuzumi acridinium photoredox catalyst **8**·BF_4^- and phenylthiol as hydrogen-donor under irradiation (Scheme 6).

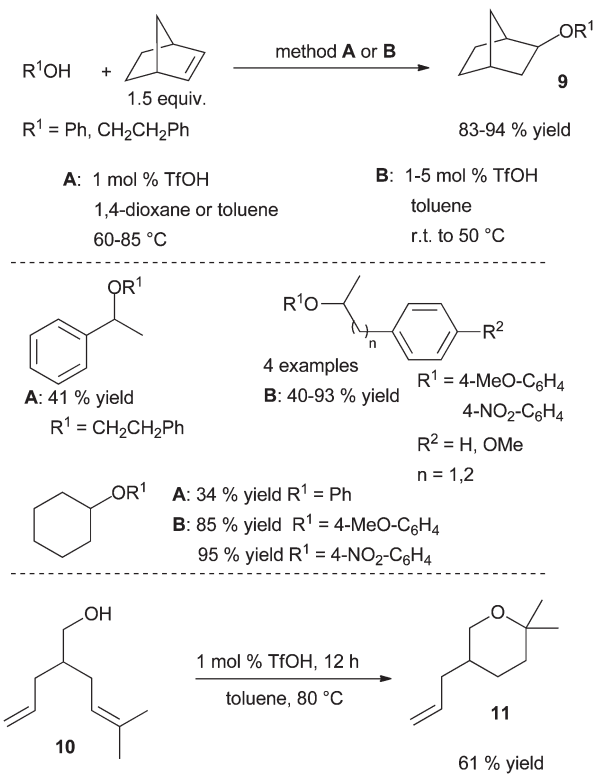
Under these conditions, electron-rich amines are prone to oxidation and are poor substrates. This method which provides exclusively the *anti*-Markovnikov product does not require *geminal* substituents on the tether to favour cyclisation. Control experiments reveal that the reaction does not proceed



Scheme 6 Intramolecular *anti*-Markovnikov hydroamination of tosylamines catalysed by Fukuzumi acridinium photoredox catalyst.



Scheme 7 Intramolecular *anti*-Markovnikov hydroamination of trifluoromethanesulfonamide, pyrazole and 1,2,3-triazole catalysed by Fukuzumi acridinium photoredox catalyst.



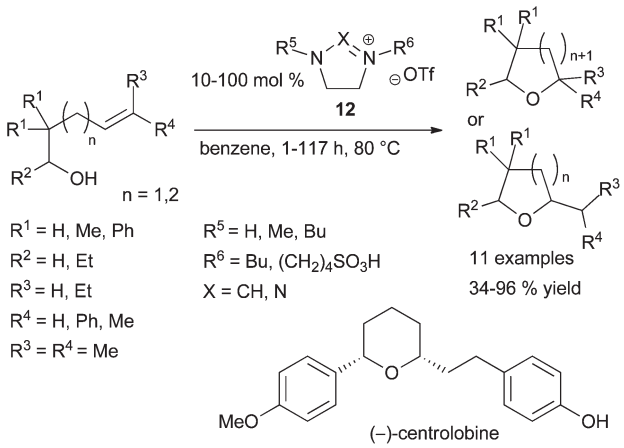
Scheme 8 Inter and intramolecular hydroalkoxylation of alkenes catalysed by TfOH.

by N-centered radical as in Studer's work (Scheme 4) or *via* a thiol–ene pathway. Furthermore, the methodology was expanded to the intermolecular *anti*-Markovnikov hydroamination of unactivated alkenes and trifluoromethanesulfonamide using **8**·BF_4^-, diphenyl disulfide instead of phenylthiol and 2,6-lutidine as catalytic additive (Scheme 7).[20] Under these modified conditions, hydroamination products are obtained in moderate to good yields with exclusive *anti*-Markovnikov selectivity. In contrast to the intramolecular version, no reactivity is observed with sulphonamides or *tert*-butyl carbamate. The use of odourless solid diphenyldisulfide offers a practical advantage over the highly toxic liquid thiophenol. The method is applicable to α- and β-substituted styrenes and di- and trisubstituted aliphatic alkenes and tolerates a variety of functional groups as illustrated in Scheme 7. Additionally, pyrazole, indazole and 1,2,3-triazole are also efficient partners for the *anti*-Markovnikov hydroamination of styrenic substrates. This photoredox process is proposed to proceed *via* an analogous mechanism as described for the hydroalkoxylation reaction (*vide infra*).

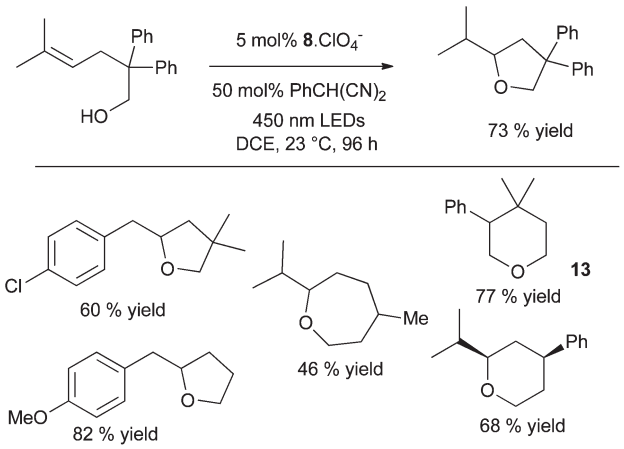
2.2 C–O bond formation

2.2.1 Brønsted acid catalysts. Hydroalkoxylation of unactivated alkenes is one of the method of choice to prepare ethers but generally needs acids or superacids in over stoichiometric amounts. Early in 2000, the first example of catalysed alkene hydroalkoxylation appears with noteworthy the use of Brønsted acids.[21] In 2004, Duñach *et al.* have shown that superacid FSO_3H (6.5 equiv.) could be substituted by triflic acid (5 mol%) in mild conditions leading for example to the cyclisation of 6-methylhept-5-en-2-ol in 2,2,6-trimethyltetrahydropyran with 100% yield.[22] In 2006, both Hartwig *et al.* (Scheme 8, method **A**)[8e] and He *et al.* (Scheme 8, method **B**)[8d] groups have independently reported an interesting intermolecular hydroalkoxylation version of various alkenes and alcohols catalysed by triflic acid (1–5 mol%) either at room temperature or at higher temperature giving the corresponding ethers with yields up to 94%. According to the nature of the substrates, an excess of alkene is often required. The addition of phenol or 2-phenylethan-1-ol to norbornene lead selectively to the *exo*-adduct **9** while styrene derivatives afford the Markovnikov product (Scheme 8). As expected for Brønsted catalysis, the more substituted double bonds have a higher reactivity than the less substituted ones as exemplified by Hartwig *et al.* for the conversion of diene **10** into **11** (Scheme 8).

In 2011, the group of Hintermann highlighted that in alkene hydroalkoxylation promoted by metal triflate catalysts under the experimental conditions studied, triflic acid is generated as the true catalyst species.[23] The same year, Ryu *et al.* showed that imidazolium and triazolium ionic liquids (IL) **12** are good promotors in intramolecular hydroalkoxylation of alcohols tethered to alkenes (Scheme 9).[24] Although the four ILs **12** tested (R^5 = H, R^6 = Bu, X = CH; R^5 = Me, R^6 = $(CH_2)_4SO_3H$, X = CH, R^5 = Bu, R^6 = $(CH_2)_4SO_3H$, X = CH, R^5 = Bu, R^6 = $(CH_2)_4SO_3H$, X = N), have shown similar efficiency in the initial NMR studies, only the two last tethered-SO_3H ILs **12** (R^5 = Bu) were more effective in large-scale reactions and led to



Scheme 9 Intramolecular hydroalkoxylation of alkenes catalysed by imidazolium and triazolium salts.



Scheme 10 *Anti*-Markovnikov organic photoredox hydroalkoxylation of alkenes.

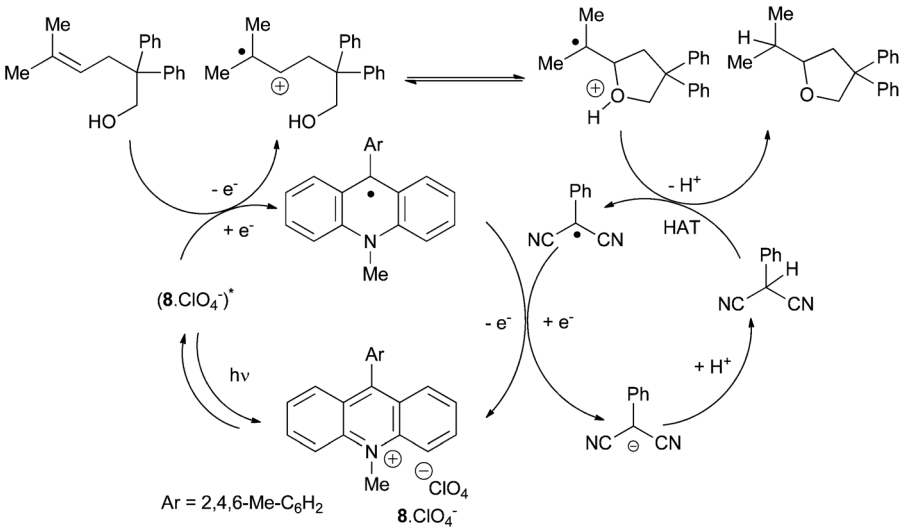
similar results. The recyclability of these functionalised ionic liquids was also demonstrated as one of them was reused in two cycles without significant loss of efficiency. Moreover, the authors described an interesting application of the methodology in the synthesis of (±)-centrolobine catalysed by **12** (R^5 = Bu, R^6 = $(CH_2)_4SO_3H$, X = CH) and by its analogue (R^5 = Bu, R^6 = $(CH_2)_4SO_3H$, X = N) giving the product of the intramolecular hydroalkylation step with 77% and 82% yields respectively. (−)-Centrolobine is an antiprotozoal natural product containing a 2,6-*cis*-disubstituted tetrahydropyran pattern and the intramolecular hydroalkoxylation catalysed by **12** gives exactly a total selectivity in favour to the *cis* stereoisomer (Scheme 9).

2.2.2 Organic photoredox catalysts. The formation of a stabilised cationic intermediate during the course of an alkene hydroalkoxylation reaction lead to the formation of the Markovnikov product which is a common feature of this transformation. The sole examples of *anti*-Markovnikov hydroalkoxylation of alkenes reported in the literature are described with organic photoredox systems. In this case the reverse selectivity could be explained by the stability of a radical species since mono-electronic transfers are generally observed in these processes. The first photoredox catalytic processes were limited to 1,1′-diarylethylene as starting materials but directly allowed total selectivity.[3b–e] It is worth noting that Inoue *et al.* described an enantioselective version in the presence of chiral naphthalene(di)carboxylates as photo-sensitizers allowing the formation of intermolecular *anti*-Markovnikov adducts with low to moderate yields and enantiomeric excesses up to 33%.[3d,e] Recently the group of Nicewicz has developed for intramolecular *anti*-Markovnikov hydroalkoxylation, a remarkable two-component organic photoredox catalyst system employing 9-mesityl-10-methylacridinium perchlorate **8**·ClO_4^- and 2-phenylmalononitrile under irradiation.[3a,25] This catalytic system was first developed and optimised by this group in hydroalkoxylation. It was later adapted and applied in hydroamination reaction as described in Scheme 6. Worth noting is that for these two reactions, the nature of **8** counter-ion is different. Moreover, in hydroamination true catalytic quantities of hydrogen atom donor are used with thiophenol in place of 2-phenylmalononitrile. However, the catalytic system developed for hydroalkoxylation can be used under mild conditions and was applied to various alkenols including di- or tri-substituted olefins and electron rich or deficient styrenes. Furthermore, a Thorpe-Ingold assistance is not necessary to reach good yields. This original methodology gives direct access to valuable cyclic ethers bearing 5- to 7-membered rings and particularly the challenging 6-*endo*-adduct **13** as illustrated in Scheme 10. The authors have also applied this catalytic system to intermolecular hydroetherification with the same total stereoselectivity.

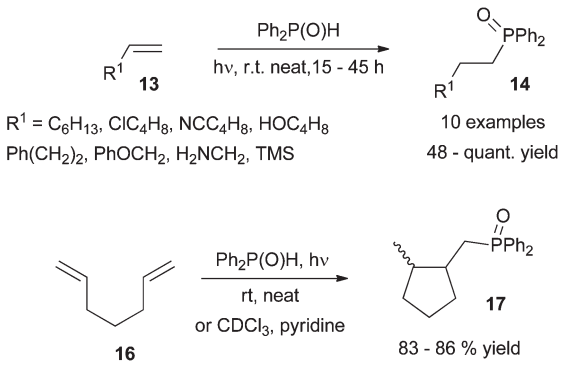
The authors are still studying the mechanism[25] but they assume that after a step of photo-activation, the mesityl acridinium catalyst oxidises the alkene in a radical cation intermediate which is cyclised to form a radical oxonium. After hydrogen atom transfer and deprotonation the desired product is obtained. The authors confirmed the link between both catalytic cycles, the photoredox one and the H atom transfer (HAT), the 2-phenylmalononitrile radical (E^{red} = +0.19 V *vs.* SCE, MeCN) oxidizing the acridinyl radical (E_1^{ox} = −0.57 V *vs.* SCE, MeCN) in a fast process. (Scheme 11).

2.3 C–P bond formation

In the context of C–P bond formation, appealing photoinduced hydrophosphinylation of alkenes has recently been described by Ogawa *et al.*[26] The former "Pudovik reaction"[27] has been successfully adapted to the addition of $R_2P(O)$–H to carbon–carbon double bonds and proceeds regioselectively under photoirradiation to cleanly afford bisarylalkylphosphine oxides. Irradiation with a xenon lamp in a 5 to 1 ratio of C=C/P reactant is required to ensure optimal results at room temperature. The transformation appears completely regioselective and affords fair to quantitative yields with an attractive functional group tolerance as shown in Scheme 12 (top, **13**→**14**). The transformation is also successful for internal alkenes or in



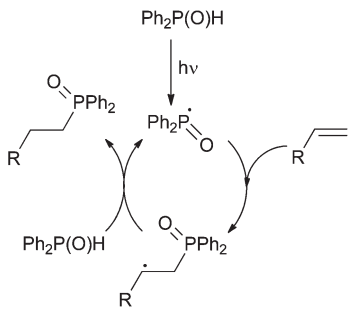
Scheme 11 Proposed mechanism of organic photoredox hydroalkoxylation of alkenes.



Scheme 12 Photoinduced hydrophosphinylation of alkenes.

the presence of bulky substituents such as cyclohexane and dihydropyran leading to the corresponding phosphine oxides in 71% to quantitative yields respectively.

The methodology allows access to cyclopentane derivatives *via* photoinduced formation of a C–P bond and subsequent *exo*-trig cyclisation from 1,6-cycloheptadiene precursor **16** (Scheme 12, bottom). Mixtures of *cis*/*trans* disubstituted cyclopentanes **17** are obtained, the former *cis* isomer being usually produced as the major one regardless of the conditions used: neat or in solution using pyridine as an additive. A possible mechanism involves the formation of key phosphinoyl radical followed by selective formation of an *exo*-C–P bond (Scheme 13). Hydrogen abstraction from a second diphenylphosphine oxide molecule affords the expected hydrophosphinylation adduct and a further phosphinoyl radical.



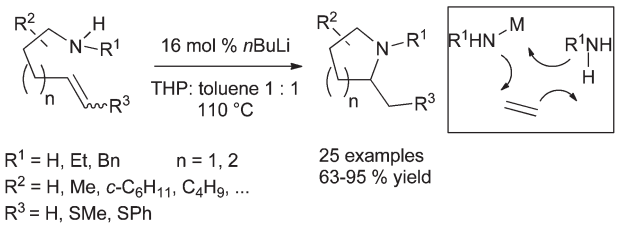
Scheme 13 Proposed mechanism for photoinduced hydrophosphinylation of alkenes.

3. Group 1-based catalysts

3.1 C–N bond formation

The hydroamination promoted by alkali metals is an old transformation[28] and numerous efforts have been drawn for developing new catalytic systems allowing mild reaction conditions.[29] Recent developments include the readily cyclohydroamination transformation of simple aminoalkene derivatives by catalytic quantities of *n*BuLi solutions, delivering the corresponding nitrogen-containing heterocycles in high yield (Scheme 14). The formation of the new C–N bond albeit requires heating the reaction mixture to 110 °C, but the scope of the reaction is wide as demonstrated by the preparation of 25 different products by this procedure.[30]

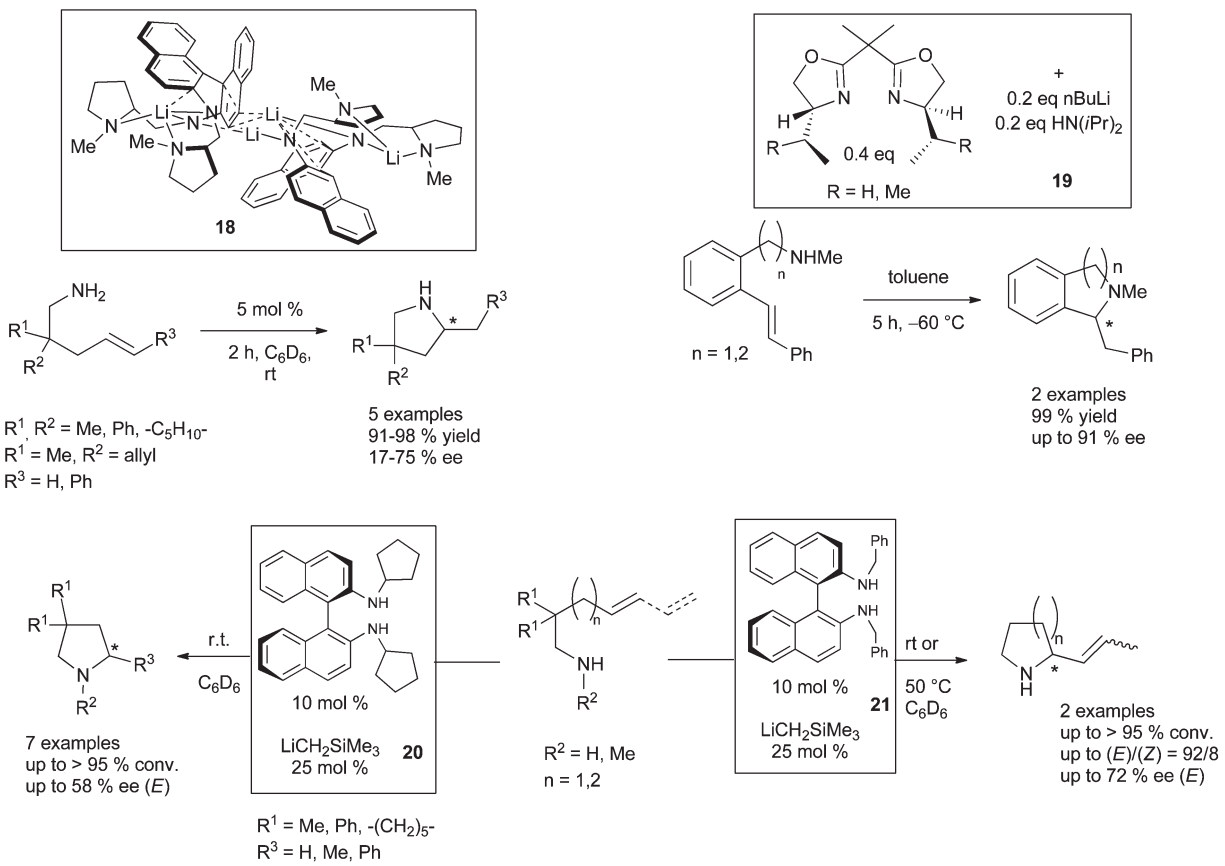
The more difficult intermolecular version was studied by the group of Hultzsch and concerned the hydroamination of vinylarenes.[31] The use of 2 mol% of $LiN(SiMe_3)_2$–TMEDA as catalytic system promoted the hydroamination of vinylarene derivatives with primary and secondary amines (1 : 1 ratio) at 120 °C and led to the *anti*-Markovnikov product with high selectivity. Attempts to perform enantioselective intermolecular hydroamination, by replacing TMEDA by (−)-sparteine and



Scheme 14 Base-catalysed cyclohydroamination reaction.

reacting α- and β-methylstyrene with benzylamines remained unfortunately unsatisfactory (≤14% ee). Jaspers and Doye have further interestingly demonstrated that KOH is also a suitable strong base to catalyse the addition of various arylamines to styrene derivatives in dry DMSO, a methodology that they could illustrate with 17 examples.[32] The challenge of introducing enantioselectivity by chiral alkali bases has until now only been successfully overcome for intramolecular transformations. Only three examples are known, with one of them involving the use of an isolated lithium-based complex. A particularly noteworthy result indeed issued from the group of Hultzsch which prepared a dilithium diamide derivative, as a dimer, from a symmetrically *N*-methylpyrrolidine-substituted binaphthylamine ligand (see **18**, Scheme 15).[33] Due to its dimeric structure, according to the authors, this catalyst promoted the cyclisation of aminopentene derivatives into the corresponding pyrrolidines with up to 75% ee. Tomioka and his group described the formation of scalemic *N*-methylisoquinoline and isoindoline by combination of the precursor aminomethylolefins with catalytic amounts of chiral bis(oxazolines) and *n*BuLi.[34] Additional diisopropylamine was necessary for the *in situ* prepared catalyst to afford a complete conversion, and the targeted products were isolated in up to 91% ee (see **19**, Scheme 15). Some of us have reported that chiral lithium salts, easily prepared by *in situ* combination of *N*-substituted (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine ligands and [(trimethylsilyl)methyl]lithium delivered efficient pre-catalytic species for the asymmetric hydroamination of amino-1,3-dienes and aminoalkenes.[35] The most efficient catalyst for the cyclohydroamination of aminoalkenes (see **20**, Scheme 15) delivered expected pyrrolidines at room temperature, in up to 58% ee. A similar catalytic system (see **21**, Scheme 15) produced 2-propenyl-pyrrolidine and -piperidine with the highest stereo- and enantioselectivities described to date.

Significant progress has therefore taken place in recent years, motivated by the use of cheap and easily available alkali bases. Their use necessary implies a reduced functional tolerance; nevertheless great advances have been reported in the area of enantioselective cyclohydroamination. The main



Scheme 15 Asymmetric cyclohydroamination of aminoalkenes and aminodienes promoted by chiral lithiated bases.

hurdle to succeed in catalysing the corresponding asymmetric intermolecular version remains still to be crossed.

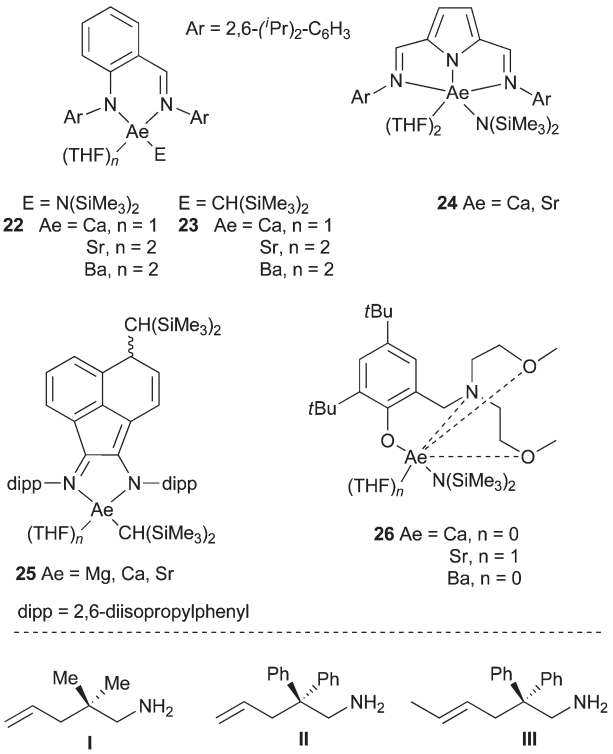
4. Group 2-based catalysts

4.1 C–N bond formation

Hydroamination reaction promoted by alkaline earth metals has been for a long time underexploited, albeit these species represent a benign series of elements and remain inexpensive. Alkaline earth metals possess indeed a great number of features common to the elements of the 4f series, long known to promote this reaction. They indeed share large radii and an important electropositive character of the cation. The group of Hill reported thus in 2005 the efficient calcium-mediated room temperature intramolecular hydroamination catalysis promoted by a synthetically easily accessible β-diketiminato calcium bis(trimethylsilyl)amide complex.[36] Since this pioneering work, various ligands have been further developed towards the synthesis of heteroleptic compounds, including aminotroponiminate complexes.[37] Comparative activity studies have been published between the different alkaline earth metals, with preliminary results indicating a decrease in the rate with increasing ion radius of the metal center, for the cyclohydroamination reaction. The main challenge that has been tackled concerns the isolation and characterisation of well-defined species for controlling the Schlenk equilibrium which often occurs, due to the labile nature of the ligands.

Focusing on the chemistry of β-diketiminate derivatives, Barrett, Hill *et al.* prepared and compared the activity of different group 2 pre-catalysts:[38] the magnesium methyl and the calcium and strontium silylamide β-diketiminate derivatives, [{ArNC(Me)CHC(Me)NAr}MX-(THF)$_n$] (M = Mg, X = CH_3, n = 0; M = Ca, X = $N(SiMe_3)_2$, n = 0 or 1; M = Sr, X = $N(SiMe_3)_2$, n = 1, Ar = 2,6-diisopropylphenyl), the bistrimethylsilylamides (THF solvated or not) and the bistrimethylsilylalkyl species (solvated) for Mg, Ca, Sr and Ba. They revealed that Ba pre-catalysts were not efficient and alkyl derivatives decomposed at high temperature and thus conclude amido species to be more valuable promoters. Although a general reactivity in the order Ca > Sr > Mg was proven, the authors noticed the important influence of the presence (or not) of THF, depending on the nature of the ligand and the substrate, for the same metal. Mechanistic studies demonstrated the tricky influence of the M^{2+} cation on both the thermodynamic and the kinetic course of the reaction, according to the ligand and the reactant structure. Trying to tame this reactivity, further development of new structurally different pre-catalysts has been more recently published.

For instance, Carpentier, Sarazin *et al.* have been able to prepare and characterise amido and alkyl iminoanilide alkaline earth complexes **22** and **23** that proved to be kinetically stable in solution (Scheme 16).[39] The hydrocarbyl complexes were very active pre-catalysts for both the cyclohydroamination of 2,2-dimethyl-pent-4-enylamine (**I**) (with a reactivity trend Ca > Sr > Ba, Table 1, entries 1–6) and intermolecular hydroami-



Scheme 16 Heteroleptic alkaline earth complexes active in the cyclo- and intermolecular hydroamination.

Table 1 Intra- and inter-molecular hydroamination reactions promoted by alkaline earth-based complexes[a]

Entry	Substrate	Catalyst (Ae) (mol%)	Time (h)	T (°C)	Conv (%)
1	**I**	**22** (Ca) (1)	4 min	25	90
2	**I**	**22** (Sr) (2)	7 min	60	97
3	**I**	**22** (Ba) (2)	1	60	96
4	**I**	**23** (Ca) (1)	<2 min	25	>99
5	**I**	**23** (Sr) (1)	<3 min	25	98
6	**I**	**23** (Ba) (1)	0.3	25	96
7	Styrene/pyrrolidine	**22** (Ca) (2)	0.5	60	65
8	Styrene/pyrrolidine	**22** (Sr) (2)	0.5	60	75
9	Styrene/pyrrolidine	**22** (Ba) (2)	0.5	60	95
10	Styrene/pyrrolidine	**23** (Ca) (2)	0.5	60	90
11	Styrene/pyrrolidine	**23** (Sr) (2)	5 min	60	85
12	Styrene/pyrrolidine	**23** (Ba) (2)	5 min	60	97
13	**I**	**24** (Ca) (5)	0.5	25	92
14	**I**	**24** (Sr) (5)	2	60	92
15	**II**	**25** (Mg) (0.5)	18	60	<5
16	**II**	**25** (Ca) (0.5)	0.25	25	>99
17	**II**	**25** (Sr) (0.5)	1	25	76
18	**III**	**25** (Ca) (5)	5	25	95
19	**II**	**26** (Ca) (1.6)	0.5	80	>99
20	**II**	**26** (Sr) (1.6)	1	80	99
21	**II**	**26** (Ba) (1.6)	1	80	10

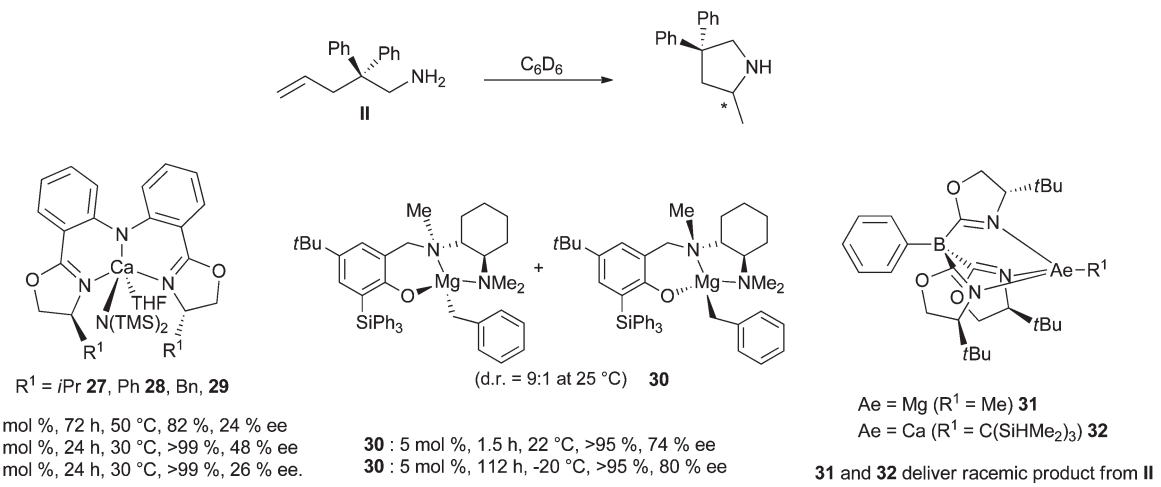
[a] All cyclohydroamination reactions are performed in C_6D_6, the intermolecular version are run in neat conditions, without additional solvents.

nation (with an interesting inverse tendency Ca < Sr < Ba, see Table 1, entries 7–12) showing no ligand redistribution. These complexes were particularly efficient for the intermolecular *anti*-Markovnikov hydroamination of alkenes, with an unprecedented huge activity for Ba derivatives, proposed to occur through a six-centered concerted mechanistic pathway. 2,5-Bis-{*N*-(2,6-diisopropylphenyl)iminomethyl} pyrrolyl amido complexes of Ca and Sr **24** were prepared from the corresponding heteroleptic iodo complexes, possessing the symmetrically κ^3-coordinated ligand in solution (Scheme 16).[40] These pre-catalysts were nevertheless less active in the cyclohydroamination reaction (Table 1, entries 13–14). Hill *et al.* described the use of sterically-hindered bis(imino)-acenaphthene ligands.[41]

They succeeded in the synthesis of alkyl derivatives, that showed enhanced stability towards Schlenk-type ligand redistribution, because of the high steric demand of the bis(trimethylsilyl)methyl substituent. These complexes proved to be highly reactive in the cyclohydroamination of aminoalkenes, as exemplified for the hydroamination of the benchmark substrate, 2,2-diphenyl-pent-4-enylamine (**II**) (Table 1, entries 15–17). The calcium complex **25** (Ae = Ca) was especially active even to promote the cyclisation of challenging substrates such as **III**, displaying a disubstituted olefin (Table 1, entry 18). Another type of ligand, based on aminophenolate backbone has also been prepared (**26**, Scheme 16),[42] and their activity in the cyclohydroamination of aminoalkenes evaluated and compared to β-diketiminato complexes. Here again the activity for Ca-, Sr- and Ba-derivatives followed the same trend but these new complexes were by far less active (Table 1, entries 19–21).

Since the Schlenk equilibrium could be controlled, efforts to perform this reaction in an enantioselective manner by using chiral ligands have been attempted. First studies in 2008 have been published by Harder *et al.*[43] who synthesised chiral heteroleptic calcium complexes from enantiopure bis-(oxazolines) or chiral β-diketimine derivatives. The corresponding amide complexes have been isolated and characterised by X-ray analysis, but they underwent to some extent Schlenk equilibrium to form catalytically inactive $[Ca(L)_2]$ complexes, and an ee lower than 10% was obtained for cyclisation of substrate **II**. Ward and his group could improve the selectivity to reach 26% ee for the same reaction, preparing calcium complexes supported by chiral diamines[44] and developing also enantiopure bisimidazoline amido derivatives.[45] A significant change in the enantioselectivity values was provided by the use of amido calcium complexes **27–29** bearing bis(oxazolinylphenyl)amine ligands, exhibiting very low ligand redistribution and affording the targeted pyrrolidine compound in up to 48% ee (Scheme 17).[46]

Accordingly, the group of Hultzsch has focused on the preparation of magnesium derivatives. They were obtained as chiral bimetallic complexes from reaction of nBu$_2$Mg using L-proline-derived diamidobinaphthyl ligands. The magnesium complexes showed moderate to high catalytic activity, but the enantioselectivity of the reaction was limited to 14% ee due to facile ligand exchange reaction and/or protolytic ligand cleavage upon addition of the substrate.[47] Furthermore, alkyl magnesium complexes containing multidentate phenoxyamine ligands delivered efficient catalysts for the cyclohydroamination reaction, showing no ligand exchange, and allowing complete conversion at room temperature for substrate **II** (2 mol% cat, 3 h).[48] They were thus structurally good candidates towards the development of chiral catalysts; chiral phenoxyamine ligands incorporating a chelating cyclohexyldiamine arm such as in complex **30** (Scheme 17) have therefore been prepared and in the presence of the bulky triphenylsilyl substituent ligand, exchange processes were eliminated.[49] This magnesium catalyst delivered the highest enantioselectivity reported to date for the alkaline earth-based hydroamination catalysis, delivering 2-methyl-4,4-diphenyl-pyrrolidine with up to 92% ee. Sadow *et al.* have discovered that To^{M}MgMe complexes (To^M = tris(4,4-dimethyl-2-oxazolinyl)phenylborate) are also active precatalysts for the cyclohydroamination reaction



Scheme 17 Enantiopure chiral heteroleptic alkaline earth complexes for promoting enantioselective cyclohydroamination.

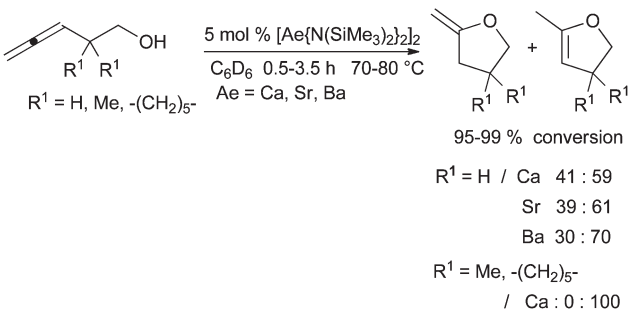
(substrate **II**, 50 °C, 10 mol%, 12 h).[50] Accordingly, chiral bulky tris(oxazolinyl)borato magnesium and calcium compounds **31–32** have been prepared (Scheme 17) but these catalysts proved however poorly enantioselective (with the analogous substrate, bearing a cyclohexyl group, the Mg complex yielded the pyrrolidine with 93% conversion and 36% ee, cat 10 mol%, 26 h, 60 °C).[51] The challenging preparation of scalemic products is still ongoing by the use of alkaline earth-based complexes, with a great demand for selective complexes, highly stable towards the Schlenk equilibrium.

4.2 C–O bond formation

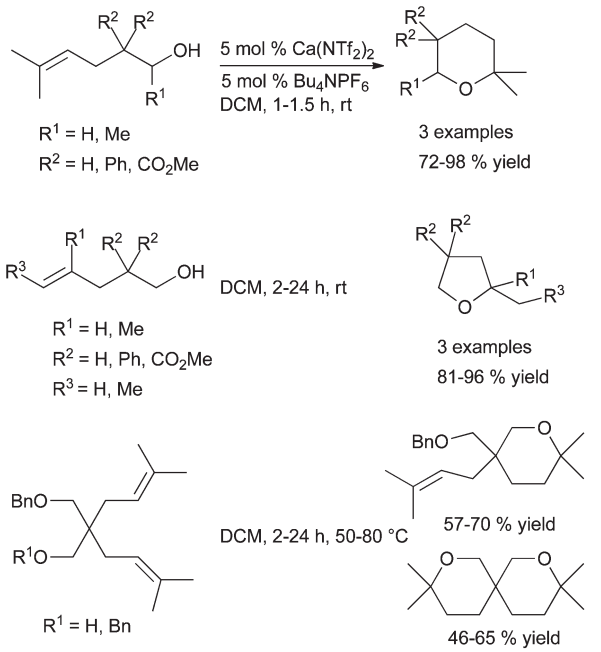
In order to develop an inexpensive and mild protocol, catalytic systems were also studied for hydroalkoxylation. Recently, two research groups have reported the efficiency of these elements for the intramolecular hydroalkoxylation of allenol and alkenol-type substrates respectively. In 2012, Barrett *et al.* described the hydroalkoxylation of allenols catalysed by alkaline earth bis(trimethylsilyl)amides (Scheme 18).[52] According to the metal and the experimental conditions, the isomerisation of the *exo*-cyclic to the *endo*-cyclic double bond occurred after the first step of hydroalkoxylation. The reaction is efficient with calcium complex on monosubstituted allenols, however with 3,5-disubstituted pent-3,4-dien-1-ol, reactions are very slow and need higher temperature (110 °C for 24–72 h with 8% conversion). No *exo*-cyclic double bond product is formed with starting allenols bearing substituents in the 2-position.

The same year, Niggemann *et al.* described the intramolecular hydroalkoxylation of alkenols catalysed by $Ca(NTf_2)_2$ (Scheme 19).[53a] The additive Bu_4NPF_6 promotes the solubility of the calcium complex $CaNTf_2PF_6$ produced after anion exchange; this complex gives higher reaction rates.[53b]

After prolonged reaction time, this catalytic system allows the deprotection of benzylether groups and in a second step the hydroalkoxylation reaction leading to the spirobicyclic ether. Except for this deprotection step, the association of $Ca(NTf_2)_2$-Bu_4NPF_6 allows very mild reaction conditions since the hydroalkoxylation is carried out at room temperature in most cases with a high yield of cycloisomerisation. An exclusive Markovnikov regioselectivity is observed with mono, 1,1-di and tri-substituted double bonds. The attack of hydroxyl group on the 1,2-disubstituted double bond occurs with lower rates and various regioselectivities. As a general trend, the reactivity of the unsaturated alcohol depends strongly on both the double bond substitution pattern and the degree of angle compression brought by the substituents.



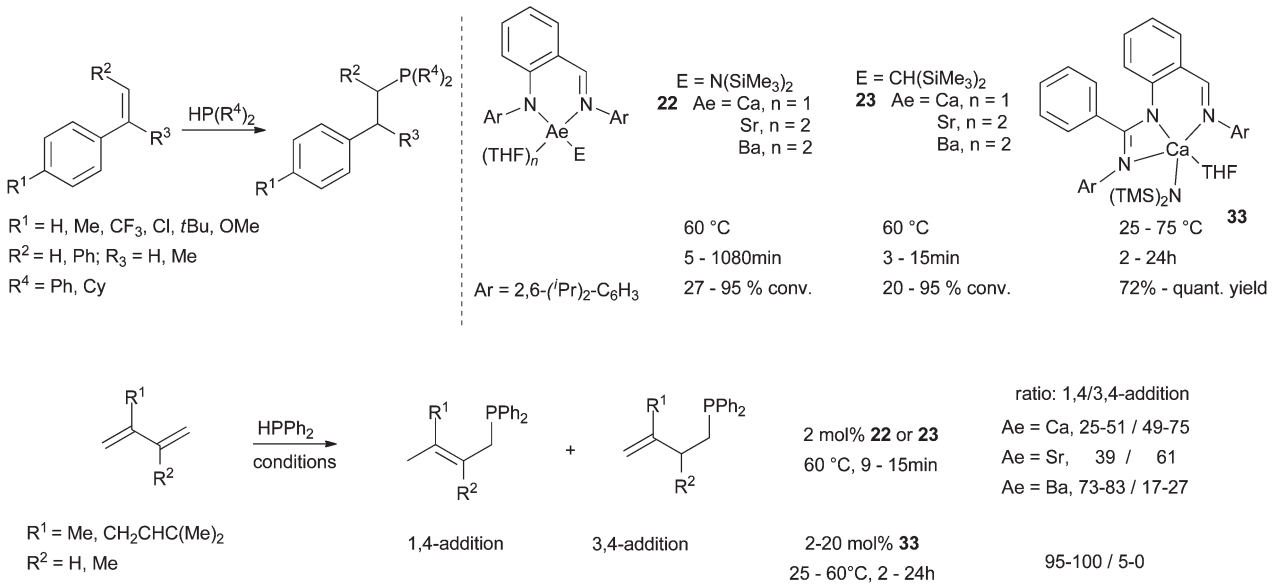
Scheme 18 Intramolecular hydroalkoxylation of allenols catalysed by alkaline earth amides.



Scheme 19 Intramolecular hydroalkoxylation of allenols catalysed by alkaline earth amides.

4.3 C–P bond formation

Alkyl and amide alkaline earth complexes (Ca, Sr, Ba) based on iminoanilide or bisiminoanilide ligands have been revealed recently to be efficient (pre)catalysts for intermolecular hydrophosphinations of styrene derivatives. Independently developed by Cui *et al.* and Carpentier *et al.*,[54,39b] both families **22–23** proved stable in solution and produced regioselectively *anti*-Markovnikov adducts in Scheme 20. Yields are impressive for both the introduction of PPh_2 and PCy_2 fragments at low catalyst loadings (1–5 mol%). Conversions are depending on the ability of styrene to bind to the metal centre and thus on the electronic contribution of substituents installed at the styrene substrate. As expected, electron-withdrawing groups are preferred, leading to the following reactivity trend: CF_3 > Cl > H > Me > *t*Bu > OMe. A second key point is the metal size. Indeed, the ionic radius deeply influences hydrophosphination within a same ligand series with the following order of reactivity Ba > Sr > Ca. A similar trend was noticed in alkene hydroamination promoted by the same series of complexes (Scheme 16). Hydrophosphination of conjugated dienes (isoprene and myrcene) were also examined (Scheme 20). In this case, the regioselectivity seems largely depending on two main factors: (i) the steric congestion imposed by the ligand, (ii) the



Scheme 20 Group 2-catalysed intermolecular hydrophosphination of styrene derivatives and conjugated dienes.

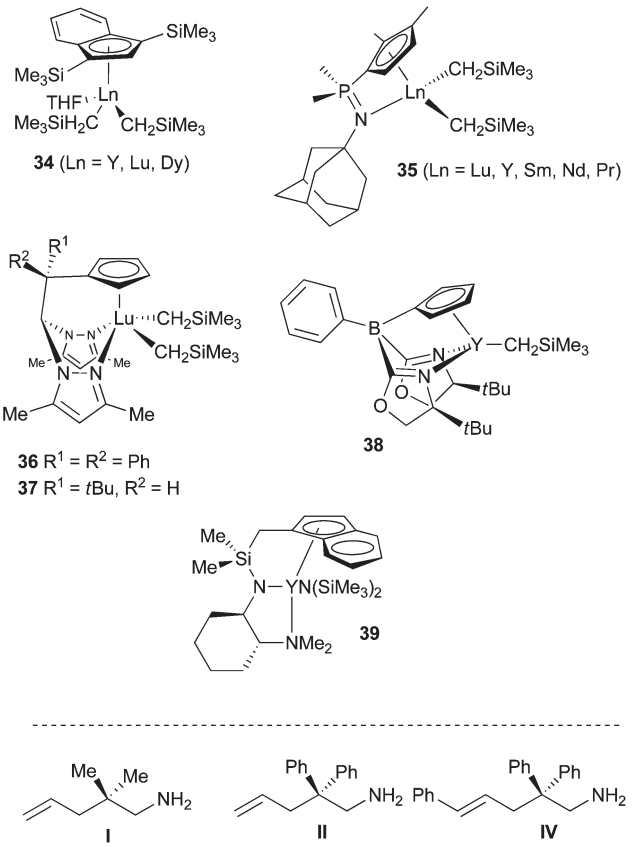
identity of the metal centre. 3,4-Addition products are favoured using iminoanilide-Ca or -Sr complexes **22–23** (Ae = Ca, Sr). In contrast, 1,4-addition adducts are obtained using more bulky iminoanilide-Ba **22–23** (Ae = Ba) or bisiminoanilide-Ca complexes **33**. Moreover, alkylcatalysts **23** are more active than the amide analogues **22** leading to faster conversions and higher yields.

5. Group 3-based catalysts

5.1 C–N bond formation

Seminal work arose from the group of Marks in the late eighties,[55] who discovered the extraordinary ability of rare-earth based complexes to promote the hydroamination of unactivated olefin with various amines. Due to their non-toxicity, their relative abundance in nature, the stereoelectronic tunability of their coordination sphere and the variation of the metal ionic radius, numerous complexes have been prepared from diverse ancillary ligands allowing large optimisation variables.[56] Metallocene and then non-metallocene complexes have been shown efficient promoters for both intra- and intermolecular hydroamination. Some challenges still exist, however, that justify the search for new catalysts; demanding substrates, possessing for instance internal non-activated olefins or lacking substituents for Thorpe-Ingold effect, are tough to cyclise; large rings are not easy to obtain; the ratio alkene/amine = 1/1 is hardly maintainable for intermolecular hydroamination; asymmetric intermolecular hydroamination is barely described. The main developments in the last past year have been devoted to the preparation of mono-cyclopentadienyl complexes, abandoning metallocenes towards an electronically less saturated and sterically less crowded metallic site. Marks *et al.* for instance prepared phenylene-bridged half-lanthanocenes as binuclear complexes for the hydroamination of various substrates. Steric contribution of the adjacent metal-containing fragment enhanced greatly the stability towards ligand redistribution, but diminished unfortunately the catalytic activity *vs.* the mononuclear analogues.[57] Chen and his group published further the synthesis and characterisation of half-sandwich indenyl rare-earth dialkyl complexes of Y, Lu and Dy **34** (Scheme 21). X-ray diffraction demonstrated η^5-hapticity of indenyl ligands in all complexes that were all active, albeit at 60 °C, for the cyclohydroamination of substrate **I** (Scheme 21, and Table 2, entries 1–3).[58] Other mono-cyclopentadienyl pre-catalysts have been targeted possessing additional coordinating elements for the rare-earth metal. Hence, Sundermeyer *et al.* synthesised cyclopentadienylphosphazene dialkyl complexes of rare-earth **35** (Scheme 21) demonstrating that the ligand could stabilise dialkyls over the full range of group 3 and lanthanide cation radii.[59] Due to the strongly chelating constrained geometry of the cyclopentadienylphosphazene ligands, only η^1,η^5-coordination was observed for all rare-earth elements used, without any additional solvent chelation. Intramolecular hydroamination of substrate **I** occurred successfully with a reactivity trend ranging in the order Lu < Y < Sm < Nd < Pr (Scheme 21, and Table 2, entries 4–8).

Neutral heteroscorpionate dialkyl lutetium complexes such as **36** have been developed by the group of Otero and Lara-Sánchez.[60] Chiral complex **37** could also be interestingly prepared as an enantioenriched species, by spontaneous resolution and preferential crystallisation of one enantiomer, due to the formation of a conglomerate by supramolecular CH–π interactions (Scheme 21). This precatalyst promoted the intramolecular hydroamination of substrate **II** at room temperature with up to 64% ee. Considering enantioselective catalysis, important results were described by Sadow *et al.* who performed the intramolecular hydroamination of substrate **II** in



Scheme 21 Cyclopentadienyl- or indenyl-based rare earth complexes for hydroamination of aminoalkenes.

Table 2 Intramolecular hydroamination promoted by monocyclopentadienyl-based rare-earth complexes

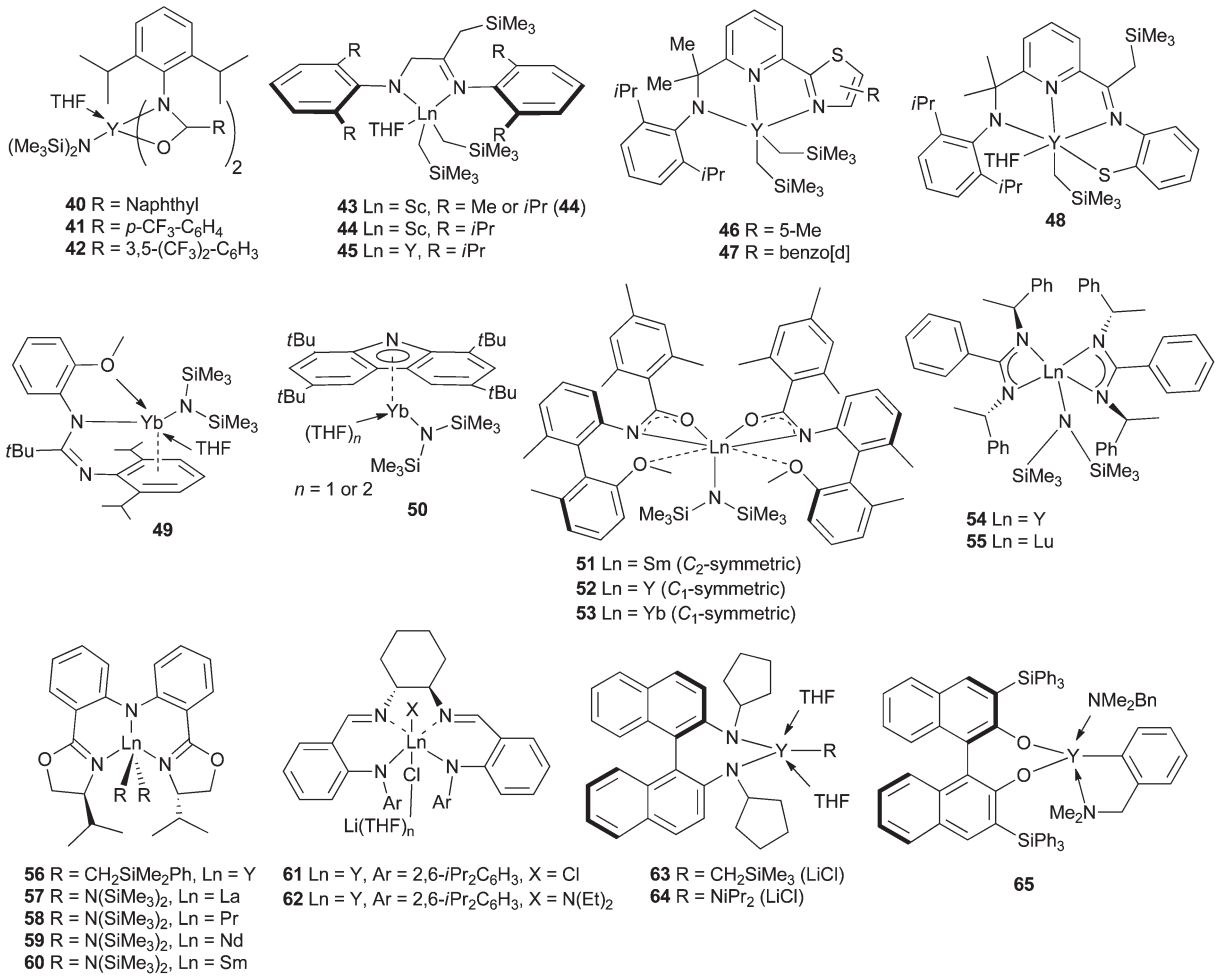
Entry	Substrate	Catalyst (Ln) (mol%)	Time (h)	*T* (°C)	Conv (%)	ee[a] (%)
1	**I**	**34** (Y) (1)	0.5	60	98	n.a.
2	**I**	**34** (Lu) (1)	0.8	60	98	n.a.
3	**I**	**34** (Dy) (1)	0.3	60	98	n.a.
4	**I**	**35** (Lu) (6)	14	60	>92	n.a.
5	**I**	**35** (Y) (5)	4.5	27	>93	n.a.
6	**I**	**35** (Sm) (5)	1	27	>93	n.a.
7	**I**	**35** (Nd) (5.3)	0.5	27	>93	n.a.
8	**I**	**35** (Pr) (5.3)	0.4	27	>93	n.a.
9	**II**	**36** (1)	1.5	20	98	n.a.
10	**II**	**37** (1)	2	20	98	n.a.
11	**II**	**38** (5)	0.2	20	>99	94
12	**II**	**39** (2)	0.8	20	98	85
13	**IV**	**39** (2)	9.6	20	99	97

[a] n.a. = non applicable.

the presence of an oxazolinylborato diamido yttrium complex **38**, to yield the product in 94% ee (*S*).[61] Remarkably, the analogous Zr-complex possessing the same ancillary ligand also delivered this high enantioselectivity but furnished the opposite enantiomer (*R*). Although a similar mechanistic route was postulated for both metals involving related transition states, the stereoinduction must be issued from dissimilar mechanisms. Very recently, tridentate amido-indenyl-based yttrium complex **39** has been reported containing enantiopure 1,2-cyclohexanediamine as chiral backbone (Scheme 21).[62] This perfectly characterised chiral catalyst afforded very high selectivities for the cyclization of both **II** (85% ee) and the di-substituted substrate **IV** (97% ee).

Non-metallocene complexes have also been the subject of much effort, in the search of activity and selectivity. Bis- and mono(amidate) complexes of yttrium **40–42** were reached by reaction of the amide proligand and $Y(N(SiMe_3)_2)_3$ (Scheme 22).[63] Specifically, in the presence of electron-withdrawing groups on the ligand, enhanced catalytic activity was observed (compare entries 1–3 in Table 3). The monoamidate derivative **40** synthesised from the naphthyl-substituted ligand, delivered the targeted pyrrolidine from **I** with analogous activity (2.5 h, 83%). Amido-imino and diamido scandium and yttrium complexes **43–45**, prepared by intramolecular alkylation of α-diimine ligands by treatment with alkyl complexes $M(CH_2SiMe_3)_3(THF)_2$ could be obtained, according to the steric bulk of the aryl-diimine ligand. The best activity in the benchmark reaction was obtained with the more sterically hindered complex (Table 3, entries 4–6).[64] N^-, *N*,*N* monoanionic dialkyl yttrium complexes **46–47** supported by thiazole-containing amidopyridinate ligands were prepared and fully characterised. Cyclohydroamination of substrate **II** was performed with these neutral and the corresponding cationic complexes, with the cationic forms showing more important activities (Table 3, entries 7–9). Generation of a monoalkyl complex interestingly occurred by metal to ligand alkyl migration and benzothiazole ring opening, resulting in a monoalkyl aryl thiolate yttrium complex **48** supported by a tetradentate N^-,*N*,*N*,S^- dianionic ligand. Unfortunately this new species revealed to be a poor catalyst.[65] Of less conventional way, divalent heteroleptic ytterbium amido complexes **49–50** supported by amidinate and 1,3,6,8-tetra-*t*Bu-carbazol-9-yl ligands respectively have been prepared by the groups of Carpentier and Trifonov.[66] The presence of an OMe group on one of the aryl substituents of the amidinate ligand led to an unprecedented κ^1-*N*,κ^2-O,η^6-arene coordination, instead of the classic κ^2-*N*,*N*′ mode in complex **49**. Similarly, replacing a simple carbazol-9-yl by the tetra *t*Bu analogue resulted in the switch of coordination mode from σ to π (**50**). These complexes were interestingly tested in the intermolecular hydroamination between styrene and pyrrolidine and were active catalysts at 60 °C, albeit with a necessary long reaction time (Table 3, entries 10–11).

Chiral biphenyl-based tridentate amidate ligands allowed the synthesis of various complexes according to the size of the lanthanide ion.[67] For Sm, the formation of a C_2-symmetric bis-ligated amidate complex **51** occurred whereas for Y and Yb, C_1-symmetric bis-ligated amidate complexes **52–53**, were privileged as demonstrated by X-ray diffraction analyses. These catalysts promoted the cyclization of **I** with up to 66% ee, at 60 °C (Table 3, entries 12–14). Chiral bis(benzamidinate)-amido complexes of yttrium **54** and lutetium **55** have been syn-



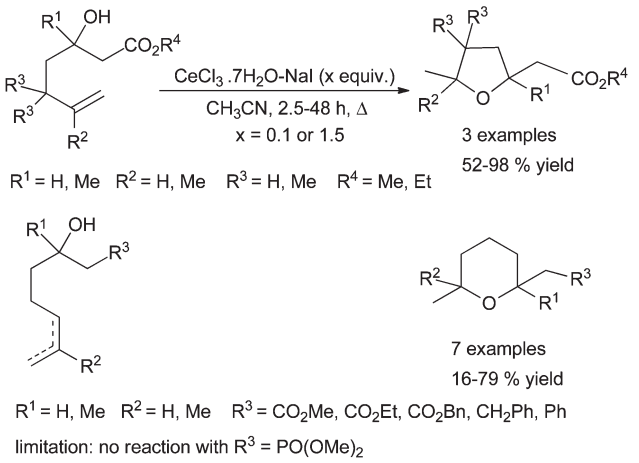
Scheme 22 Non-cyclopentadienyl based rare earth complexes for hydroamination of aminoalkenes.

thesised in one step from the corresponding Ln-amides in the group of Roesky. These complexes showed additional axial chirality and they crystallised as diastereomerically pure compounds.[68] The yttrium complex was more active but less selective than the Lu one and the pyrrolidine issued from **I** could be obtained in up to 75% ee (Table 3, entries 15 and 16). By far more active but less selective complexes have been very recently described by Ward *et al.*, through coordination chemistry of the bis(oxazolinylphenyl)amide (BOPA) ligand with lanthanide alkyl and amides (**56–60**, Ln = Y, La, Pr, Nd, Sm).[69] The yttrium alkyl derivative led to the synthesis of the pyrrolidine in 43% ee. The corresponding amido complex was not reactive, but other Ln-derived amido complexes could promote the reaction, albeit with low selectivities (Table 3, entries 18–21). Contrarily, excellent results in terms of enantioselectivities have been reported by the group of Mu, who discovered the utility of chiral tetra-azane ligands to prepare efficient scandium and yttrium complexes from salt metathesis of MCl_3. X-Ray diffraction studies showed a distorted-octahedral coordination environment, the metal centre sharing the Cl with a $LiCl(THF)_n$ moiety. From the chloride complexes, the authors could generate active hydroamination catalysts with *in situ* addition of *n*BuLi or Me_3SiCH_2Li on complex **61** (Scheme 22), and the corresponding amido complexes **62** were also catalysts for this reaction delivering up to 90% ee.[70] Some of us have discovered and studied the activity in asymmetric intramolecular hydroamination reaction, of a new family of structurally defined heterobimetallic rare earth lithium ate complexes and corresponding neutral species, based on *N*-substituted binaphthylamido ligands.[71] In the specific case of yttrium complexes, cooperative effects between Y and Li were highlighted for both alkyl and amido neutral complexes **63** and **64** delivering enhanced enantioselectivities in the presence of LiCl, for cyclohydroamination reactions (Table 3, entries 24–27).[72] The same ligand family was used for the *in situ* generation of binaphthylamido alkyl yttrium ate complexes that were interestingly demonstrated to be very active catalysts for the *anti*-Markovnikov addition between styrenyl or vinylpyridine derivatives and secondary amines.[73] The challenge for performing this reaction in an enantioselective manner has been surpassed by Hultzsch and coworkers by preparing a triphenylsilyl-substituted binaphtholate alkyl yttrium

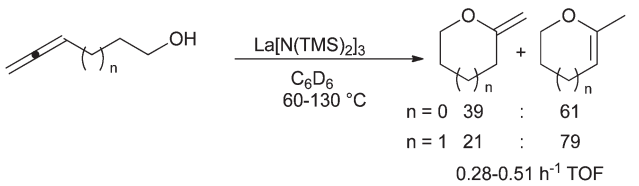
Table 3 Hydroamination promoted by noncyclopentadienyl-based rare-earth complexes

Entry	Substrate	Catalyst (mol%)	Time (h)	T (°C)	Conv (%)	ee[a] (%)
1	**I**	**40** (10)	4.5	25	88	n.a.
2	**I**	**41** (10)	2.5	25	88	n.a.
3	**I**	**42** (10)	2.5	25	93	n.a.
4	**I**	**43** (5)	5	60	53	n.a.
5	**I**	**44** (5)	5	60	>95	n.a.
6	**I**	**45** (5)	0.2	20	>95	n.a.
7	**II**	**46** (5)	1.5	40	11	n.a.
8	**II**	**46** Cationic (5)	1.5	40	97	n.a.
9	**II**	**47** Cationic (5)	0.75	80	>99	n.a.
10	Styrene/pyrrolidine	**49** (5)	31	60	85	n.a.
11	Styrene/pyrrolidine	**50** (5)	31	60	96	n.a.
12	**I**	**51** (5)	16	60	95	66
13	**I**	**52** (5)	16	60	97	54
14	**I**	**53** (5)	16	60	90	50
15	**I**	**54** (5)	6.5	60	>95	62
16	**I**	**55** (5)	35	60	92	75
17	**II**	**56** (5)	0.25	22	>99	43
18	**II**	**57** (5)	0.25	22	>99	5
19	**II**	**58** (5)	1	22	>99	16
20	**II**	**59** (5)	0.2	22	>99	12
21	**II**	**60** (5)	1	22	>99	20
22	**I**	**61**/*n*BuLi (5)	27	25	95	90
23	**I**	**62** (5)	29	25	95	90
24	**II**	**63** (6)	2.3	25	>99	66
25	**II**	**63**/LiCl (6)	1.5	25	>99	77
26	**II**	**64** (6)	2	25	>99	65
27	**II**	**64**/LiCl (6)	1	25	92	72

[a] n.a. = non applicable.



Scheme 23 Intramolecular hydroalkoxylation of alkenols catalysed by cerium(III) chloride heptahydrate in presence of sodium iodide.



Scheme 24 Intramolecular hydroalkoxylation of allenols catalysed by $La[N(TMS)_2]_3$.

complex **65**. Up to now, this is the only rare earth catalyst able to perform asymmetric intermolecular hydroamination of unactivated alkenes with simple amines following Markovnikov regioselectivity; up to 61% ee was reached for the addition of benzylamine on 1-pentene.

5.2 C–O bond formation

Lanthanide halides and triflates have been used as Lewis acids-type catalysts for the C–O bond formation by hydroalkoxylation as well as lanthanide amides as Brønsted base. In 2002, Rosini *et al.* described the use of cerium(III) chloride in the intramolecular alkene hydroalkoxylation. This methodology allows transformations of substrates bearing ester functional groups. These reactions are carried out in boiling acetonitrile giving the corresponding products in fair to good yields. It seems that CeI_3 would be the real promotor but the yields are better when 10 mol% $CeCl_3{\cdot}7H_2O$–NaI were used. Moreover, lesser yields and longer reaction times were observed when 1.5 equivalents of the promotor is used (Scheme 23). The role of water albeit crucial is not well understood.[74]

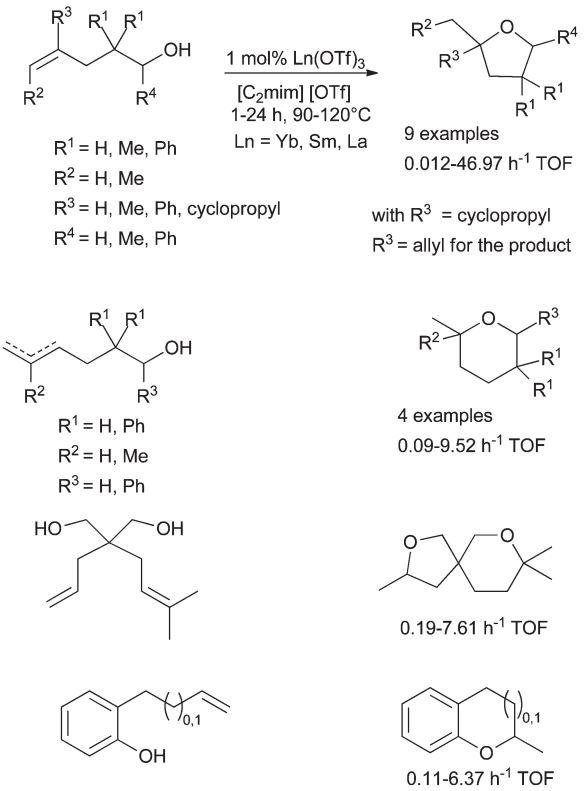
In 2007, building on its strong expertise on the application of lanthanide amides in hydroamination, the group of Marks developed the use of $La[N(TMS)_2]_3$ and $Yb(OTf)_3$ in the cyclisation of allenols and alkenols respectively with Markovnikov-type selectivity (Scheme 24).[75] Lanthanide triflates are more efficient than lanthanide amides for hydroalkoxylation. Application of $La[N(TMS)_2]_3$ have been tested by Alcaide *et al.* on chiral β,γ- and γ,δ-allendiols leading to hydroxymethylfurane unlike Pt, Pd and Au salts.[76]

In the course of studies, Dzudza and Marks *et al.* have also reported that lanthanide triflates could be associated with ionic liquid (IL) to improve the catalytic efficiency of the functionalisation of alkenes (Scheme 25).[77] ILs have been chosen for their low volatility, their high polarity and their potential environmental benefit. Various room temperature ionic liquids (RTILs) have been tested and the best results were obtained with [1-methyl-1,3-diazabicyclo-[5.4.0]undec-7-enium] [OTf] noted [C_2mim] [OTf]. The use of these conditions allows a low catalytic charge with only 1 mol% of $Ln(OTf)_3$. The catalytic activities, expressed by the turnover frequencies (h^{-1}), depend on the ionic radius of the lanthanide (Ln = Yb, Sm, La). The smaller the radius is, the higher the activity is and ytterbium triflate affords the highest activities.

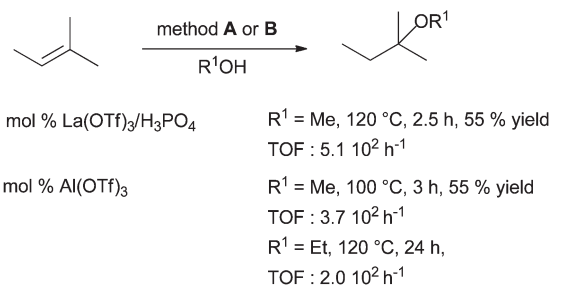
Finally, efficient methods have been developed in intermolecular hydroalkylation between isoprene and methanol using a strong association between lanthane triflate and phosphoric acid (Scheme 26, method **A**).[78]

5.3 C–P bond formation

Intermolecular hydrophosphination of styrene and phenyl- and diphenyl-phosphine was achieved using well defined Yb



Scheme 25 Intramolecular hydroalkoxylation of alkenols catalysed by lanthanide triflate in ionic liquid.



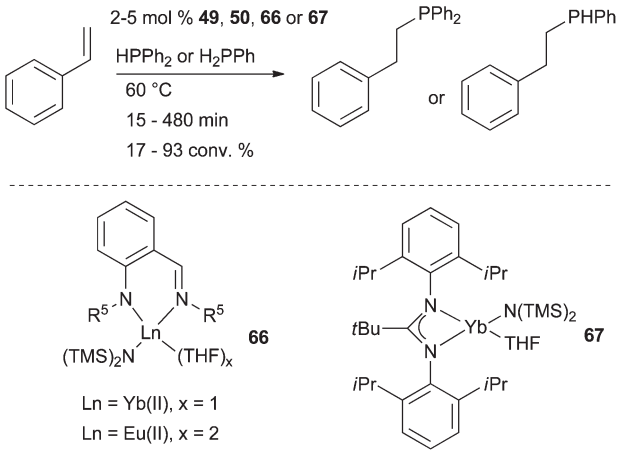
Scheme 26 Intermolecular hydroalkoxylation of isoprene with methanol catalysed by lanthanide triflate associated to phosphoric acid or aluminium triflate.

and Eu complexes **49, 50, 66** and **67** as shown in Schemes 22 and 27.[54,79] All reactions were found to be regioselective affording the *anti*-Markovnikov adducts. Noteworthy, unusual π-coordination in Yb complexes showed performance in hydrophosphination of styrene as high as more classical complexes.

6. First-row transition metal catalysts

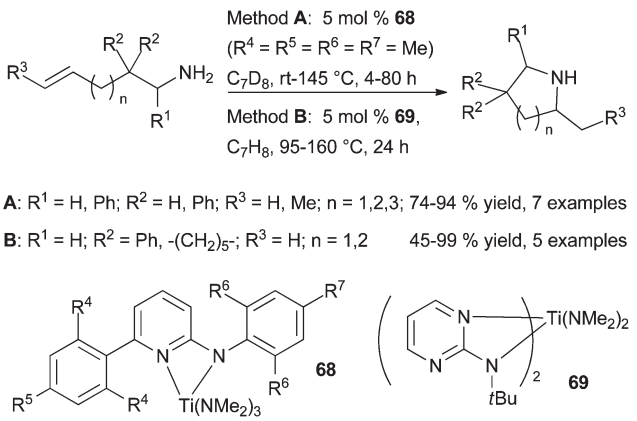
6.1 Titanium

6.1.1 C–N bond formation. The relatively low cost, low toxicity and synthetic usefulness of Group 4 metals have raised



Scheme 27 Intermolecular hydrophosphination of styrene and phenyl- and diphenyl-phosphine catalysed by ytterbium(II) and europium(II) complexes.

interest in the development of catalysts based on these metals for C–N formation by alkene hydroamination reaction. In contrast to neutral and cationic zirconium-based catalysts with which impressive breakthroughs have been made for the racemic and enantioselective cyclohydroamination of aminoalkenes,[80] titanium-based catalysts for alkene hydroamination have been less investigated. Despite significant achievements in this domain,[80a,81] titanium complexes generally display an inferior efficiency than their zirconium congeners. Recent developments have highlighted the potential utility of sterically demanding *N*,*N*-chelating ligands for the design of more efficient titanium-based catalysts in the cyclohydroamination of primary amines tethered to an alkene.[82,83] In 2013, the group of Schafer investigated the catalytic reactivity of well-defined mono(2-aminopyridinato)tris(dimethylamido) titanium complexes **68** bearing bulky aryl substituents in the cyclisation of 2,2-diphenyl-5-hexenyl-1-amine as test substrate (Scheme 28). All complexes are easily synthesised from commercially available $Ti(NMe_2)_4$ and the appropriate ligand and

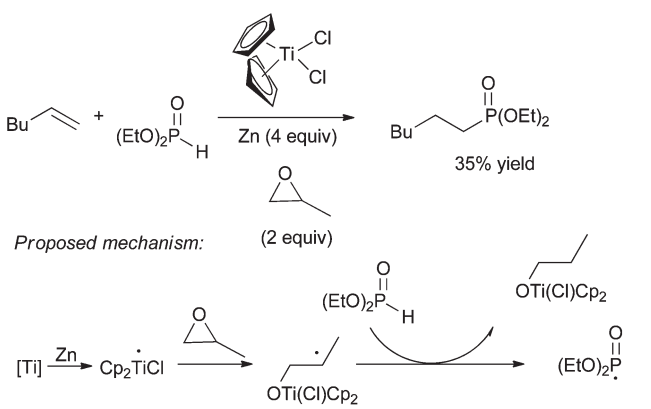


Scheme 28 Titanium-catalysed cyclohydroamination of aminoalkenes.

are isolated in high yields as monoligated compounds. From this study, it was found that the catalytic efficiency in this transformation was subtly dependent on the crowdedness around the metal with complex **68** ($R^4 = R^5 = R^6 = R^7 = Me$) affording the best yield of hydroamination product (86%) as the exclusive product at room temperature after 24 h. Complex **68** ($R^4 = R^5 = R^6 = R^7 = Me$) is more active and selective for the hydroamination reaction than $Ti(NMe_2)_4$ which gives some traces of hydroaminomethylation[84] product (10%). Interestingly, the zirconium or hafnium analogues of **68** are less efficient. The remarkable reactivity at room temperature is not a common feature for Group 4-mediated alkene hydroamination.[80i] In the presence of 5 mol% of the optimum catalyst, the process is suitable for the formation of 5-, 6- and even 7-membered rings from various primary aminoalkenes which are biased or even unbiased toward cyclisation under moderate to harsh conditions (Scheme 28). The catalyst has also the ability to convert internal alkenes which are known to be challenging substrates but is unreactive for secondary amines. In all cases, no trace of hydroaminoalkylation side product has been noticed despite the predilection of related titanium complexes to undergo hydroaminoalkylation reaction.[85]

The same year, Doye *et al.* disclosed the preparation of well-defined bis[2-(*tert*-butylamino)pyrimidine]bis(dimethylamino) titanium complex (**69**) and its application as catalyst for the hydroamination of alkynes and cyclohydroamination of primary amines tethered to simple alkenes.[83] This bis-ligated (aminopyrimidinato)titanium catalyst allows the formation of pyrrolidines and piperidines in moderate to high yields from *gem*-disubstituted aminoalkenes under however harsher conditions than **68**.

6.1.2 C–P bond formation. The use of titanocenes Cp_2TiCl_2 is also reported to promote hydrophosphonylation reactions of alkenes.[86] Fair to good yields can be obtained when Cp_2TiCl_2 (0.05–0.01 equiv.) is used in the presence of propylene oxide (2 equiv.) and Zn (4 equiv.) in THF at reflux (Scheme 29, top). The joint presence of Ti and Zn species as well as propylene oxide is mandatory. A plausible mechanism of hydrophosphorylation is supposed to go through the formation of Ti-radical intermediate followed by radical transfer to epoxide and further to diethylphosphite generating a phosphorus-centred radical as the key sequence of the transformation (Scheme 29, bottom).

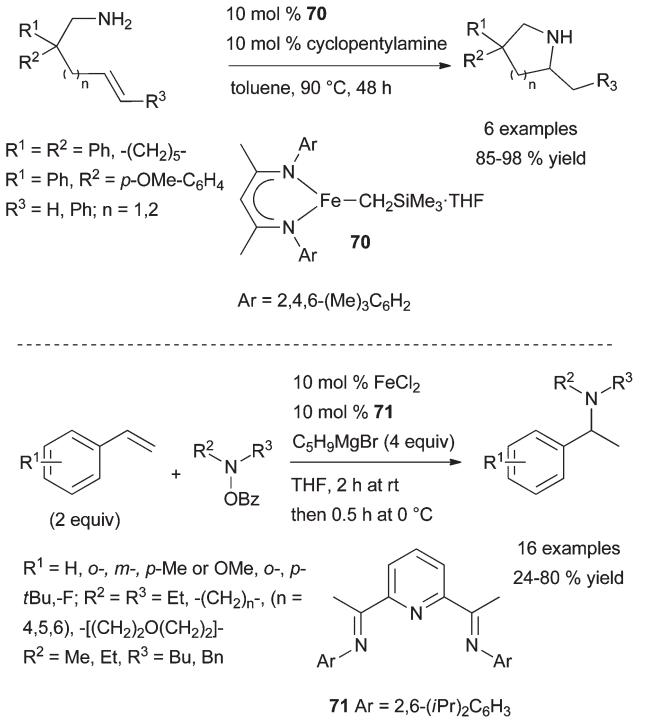


Scheme 29 Hydrophosphonylation of hex-1-ene catalysed by Cp_2TiCl_2.

6.2 Iron

6.2.1 C–N bond formation. Despite the thriving interest in catalysis promoted by iron metal, iron-based catalysts for C–N bond formation by alkene hydroamination of unactivated alkenes have been poorly explored. Early works in this field have demonstrated the advantage of $FeCl_3$ as catalyst for the intramolecular hydroamination of *N*-tosyl aminoalkenes and for the intermolecular hydroamination of styrenes and norbornene with *N*-tosylamines or electronically poor arylamines under mild to harsh conditions.[87] This methodology was more recently extended to the cyclohydroamination of *N*-tosyl aminoallenes.[88] However, some regioselectivity issues have been observed with this Lewis-acid-type methodology which is moreover restricted to electron-deficient amines. Early last year, the first example of regioselective iron-catalysed hydroamination of electronically unbiased amines was reported by Hannedouche and co-workers.[89] Building on previous reports on the reactivities of well-defined low coordinate β-diketiminatoiron(II) alkyl complexes,[90] it was hypothesised that this family of complexes could have a singular reactivity for the selective hydroamination of unprotected primary aliphatic alkenylamines. Indeed, preliminary studies have revealed the structurally-defined four-coordinate β-diketiminatoiron(II) alkyl complex **70**, in the presence of cyclopentylamine as co-catalyst, was an efficient catalyst for the selective cyclohydroamination of primary amines tethered to alkenes, giving the corresponding pyrrolidines and piperidines in good to excellent yields at 90 °C (Scheme 30, top).[89] The presence of cyclopentylamine as a noncyclisable primary amine in a catalytic amount diminishes the formation of β-H elimination products and allows a high selectivity for the hydroamination over oxidative amination pathway. However, the methodology does not proceed with aminoalkenes without a *geminal* disubstitution on the tether or with 1,2-dialkylsubstituted alkenes. Based on mechanistic studies, a stepwise σ-insertive mechanism was proposed involving a migratory insertion of the pendant alkene into an iron–amido bond and a rate determining aminolysis step.

Last year, Yang *et al.* disclosed the first report of iron-catalysed electrophilic amination of unactivated alkenes by an umpolung approach.[91] Following optimisation studies, a catalytic mixture of $FeCl_2$·**71** (10 mol%), in the presence of cyclopentylmagnesium bromide as the reducing agent were identified as optimal for the regioselective Markovnikov hydroamination of styrene with *O*-benzoyl-*N*-hydroxypiperidine as the electrophilic nitrogen source (Scheme 30, bottom). This protocol which requires the slow addition of the electrophilic amine, is applicable to a variety of electron-poor and -rich substituted styrenes and delivers the branched amines in moderate to excellent yields. However, it is inefficient for the

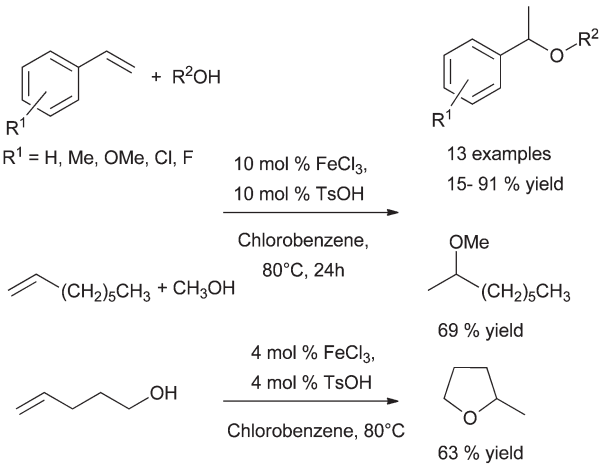


Scheme 30 Iron-catalysed intra- and intermolecular Markovnikov hydroamination of primary amines tethered to alkenes and styrenes.

transformation of styrenes bearing a chloro or a trifluoromethyl group on the aromatic ring, α- and β-methylstyrenes, and aliphatic terminal alkenes.

6.2.2 C–O bond formation. In recent years, both inter- and intramolecular hydroalkoxylation of alkenes have been described under mild conditions with efficient, inexpensive and non-toxic iron(III) chloride catalyst in the presence of different additives like silver triflate or *p*-toluenesulphonic acid. These catalytic systems are tolerant with various functional groups. In 2007, Takaki *et al.* was the first research group to show the catalytic activity of cationic iron complexes in the intramolecular hydroalkoxylation of various alkenes with $FeCl_3$–AgOTf.[92] A few years later, the group of Zhou reported the intermolecular version with aliphatic alcohols on styrene derivatives and linear alkenes displaying Markovnikov selectivity using the catalytic system $FeCl_3$–TsOH (Scheme 31).[93] It is worth noting that TsOH or $FeCl_3$ alone promotes the reaction but with very low activities, the association of both species increasing dramatically the catalytic activity. This catalytic system is also effective in the intramolecular version of this reaction.

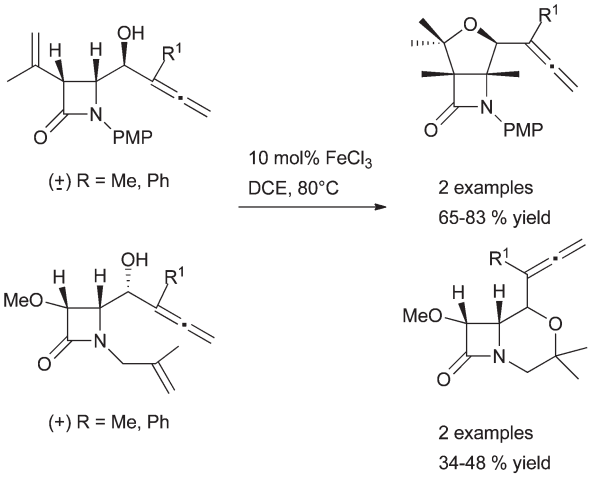
Through many transformations, the high activity and selectivity of iron have been demonstrated in the literature. In 2011, B. Alcaide and P. Almendros have illustrated an efficient chemodivergent metal-controlled methodology during the oxycyclisation study of β-lactam enallenols. The cyclisation of enallenols catalysed by precious metal salts – $[PtCl_2(CH_2{=}CH_2)]_2$ and $AuCl_3$ – affords the allene cycloisomerisation adduct whereas the chemoselectivity with $FeCl_3$ is



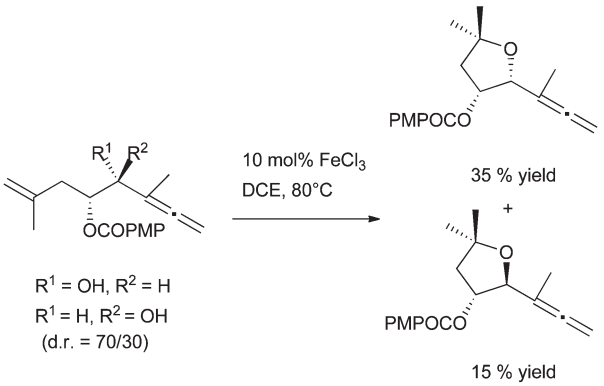
Scheme 31 Catalytic inter- and intramolecular hydroalkoxylation of alkenes by iron chloride in the presence of TsOH.

in favour of the alkenol activation. It was the first example of a total selectivity in favour of an olefin moiety *vs.* allene functionality. Moreover with $FeCl_3$, regiospecificity for five membered rings was observed affording exclusively the β-lactam-tetrahydrofuran hydride (Scheme 32). It is worth noting that complete conversions can be obtained with $BiCl_3$, $InCl_3$ or $HfCl_4$ but in these cases stoichiometric amounts of activators are needed.[94] A limitation of the system concerns β-lactam enallenols containing tetrasubstituted olefins. For these substrates, the carbonyl group becomes more electrophilic than the tetrasubstituted alkene leading to lactones instead of the hydroalkoxylation products.[95]

The chemodivergent metal-controlled methodology developed by B. Alcaide and P. Almendros was also applied to non-β-lactam enallenols. During this work, full chirality transfer from *syn* and *anti* enallenols was observed (Scheme 33).



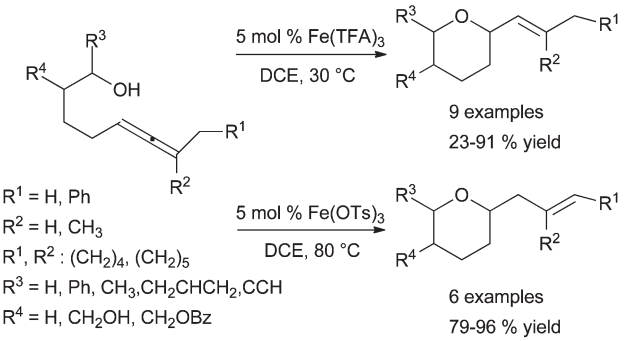
Scheme 32 $FeCl_3$-catalysed hydroalkoxylation of β-lactam enallenols.



Scheme 33 $FeCl_3$-catalysed hydroalkoxylation of non-β-lactam enallenols.

However, with an enallenol moiety tethered to an aromatic ring, a carbocylisation/dehydration sequence occurs.

However, the hydroalkoxylation of allenol catalysed by an iron catalytic system is also possible. In fact, a highly efficient catalytic system for hydrofunctionalisation of trialkylated δ-allenyl alcohols and amines was reported by Kang *et al.* in 2012.[88] The activities of the iron catalytic systems depend on their counterion and reaction conditions, and hydrofunctionalisation may be followed or not by the isomerisation of the cyclised product (Scheme 34). As indicated in section 6.2.1, this catalytic system was also applied in hydroamination of *N*-tosyl aminoallenes.[88]



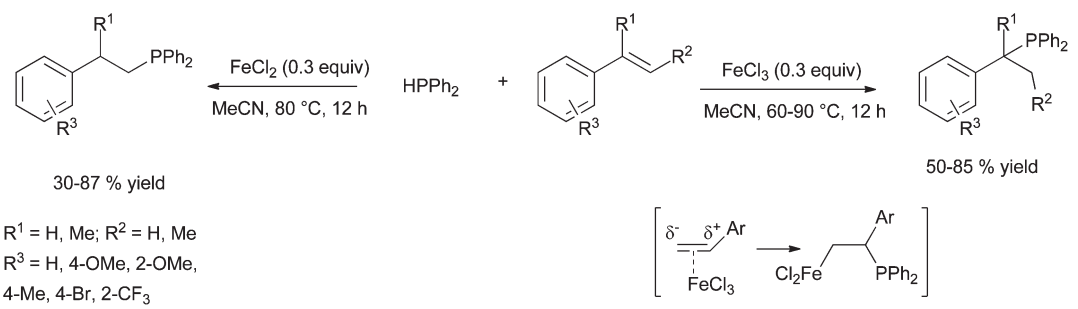
Scheme 34 Hydroalkoxylation reaction catalysed by $Fe(TFA)_3$ and $Fe(OTs)_3$ for the synthesis of tetrahydropyran.

6.2.3 C–P bond formation. More recently, Gaumont and Taillefer *et al.* have evaluated the appealing iron-assisted hydrophosphination reaction.[4c] Interestingly, α- or β-phosphinylation of styrenes can be selectively obtained depending on the metal oxidation state. If Fe(II) direct the formation of *anti*-Markovnikov adduct, whereas Fe(III) is able to switch the selectivity and mediate the formation of a benzylic stereogenic centre (Scheme 35). Again, the use of metal salts *e.g.* $FeCl_2$ and $FeCl_3$ can promote the hydrophosphination without the presence of ligands. If electronic effects only poorly affect the Fe(II)-mediated reaction, the presence of electron-withdrawing substituents at the styrene substrate appears detrimental to Fe(III) phosphination. Noteworthy, the use of strict anhydrous conditions is not required although a small erosion of yields and conversion is observed when $FeCl_3{\cdot}6H_2O$ is used instead of anhydrous $FeCl_3$. The mechanism and switch of selectivity observed is still unclear. As proposed by the authors the difference of Lewis acidity between Fe salts might explain the observed selectivity. Further, the polarized π-complex in Fe(III) promoted reactions may originate from intramolecular stabilization as stated by the authors.

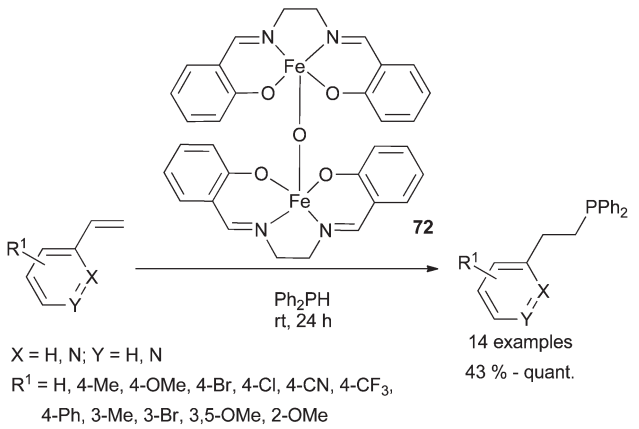
Air stable salen-capped iron catalyst **72** has recently been developed by Webster *et al.*[96] providing a new entry towards hydrophosphination reactions (Scheme 36). Indeed, hydrophosphination proceeds with low catalyst loading (0.5%) at room temperature to afford the *anti*-Markovnikov adduct. Isolated yields (from 43% to quantitative) show that the transformation appears poorly sensitive to the electronic effects of substituents installed at the styrene substrate. Preliminary mechanistic studies suggest that the reaction is unlikely to be radical mediated and rule out disproportionation of [salen-Fe]-O species into monomeric Fe(II)-based catalysts prior to substrate activation.

6.3 Cobalt

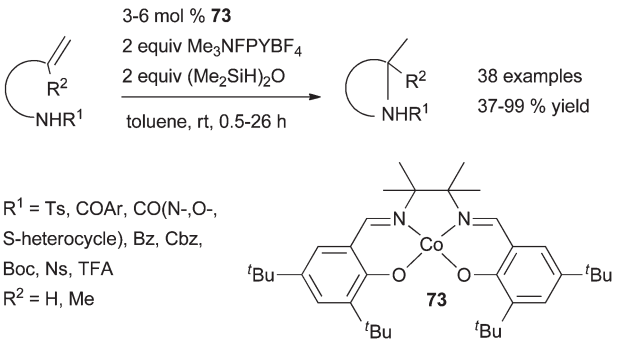
6.3.1 C–N bond formation. The first and single report of cobalt-catalysed hydroamination was disclosed in late 2014. Inspired by their remarkable achievements in catalytic, Markovnikov intermolecular alkene hydroalkoxylation using a



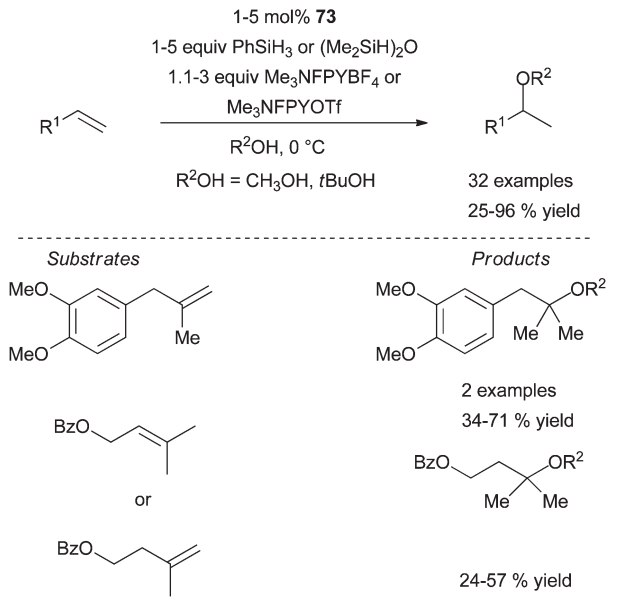
Scheme 35 $FeCl_2$- *versus* $FeCl_3$-catalysed hydrophosphination of styrene derivatives: a switchable regioselectivity.



Scheme 36 *Anti*-Markovnikov hydrophosphination of styrene and vinyl pyridine derivatives catalysed by an air stable salen-capped iron catalyst.



Scheme 37 Cobalt-catalysed intramolecular hydroamination of secondary protected amines tethered to terminal alkenes.



Scheme 38 Cobalt-catalysed intermolecular hydroalkoxylation of mono- di- and tri-substituted olefins.

cobalt(II) salen complex, silane and *N*-fluoropyridinium (*vide infra*),[97] Shigehisa and co-workers have brilliantly investigated the application of these conditions in the intramolecular hydroamination of N-protected aminoalkenes.[98] Screening and optimisation experiments led to the discovery that cobalt(II) salen complex **73** in the presence of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ($Me_3NFPYBF_4$, 2.0 equiv.) and $(Me_2SiH)_2O$, was a very efficient combination for the intramolecular hydroamination of various functionalised N-protected aminoalkenes, giving the corresponding adducts in moderate to high yields at room temperature (Scheme 37).

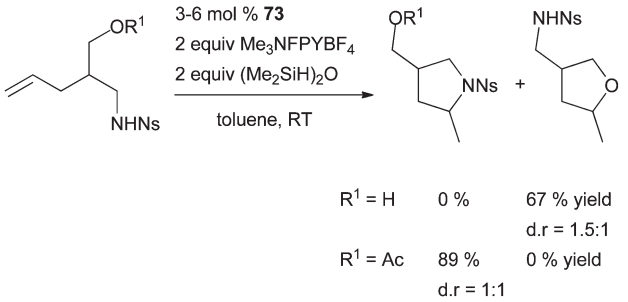
This protocol has a high functional group tolerance and impressively broad scope allowing the formation of 3-, 5-, 6- and even 7-membered heterocycles from various N-protected aminoalkenes, biased or unbiased toward cyclisation. Nevertheless, the methodology is unsuitable for the reaction of *N*-benzyl or free amines as well as internal olefins. From the work on cobalt-catalysed hydroalkoxylation, it might be speculated that the reaction proceeds through the formation of a carbocation intermediate, arising from oxidation of a carbon radical intermediate by a cobalt(III) species. The carbon radical results from a homolytic cleavage of a cobalt(III) alkyl species. The latter is generated by regioselective migratory insertion of the alkene moiety into the Co–H bond of a Co(III) hydride.

6.3.2 C–O bond formation. In 2013, Shigehisa and Hiroya *et al.* have shown that a cobalt complex, silane and *N*-fluoropyridinium salt, the similar catalytic system employed for the cyclohydroamination of alkenes displayed in Scheme 37, could also catalyse efficiently the hydroalkoxylation of unactivated alkenes (Scheme 38).[97] After the optimisation of the salen type cobalt complex and the fluoride source, various hydroxylated products were obtained in moderate to high yields from terminal olefins that present fluoroanion-sensitive silyl ethers (TBS), acid sensitive groups (PMB, acetal), esters, amides, bromo, nitro, tosylates, heterocycles, including sulphur atoms, and amino surrogates. Disubstituted and trisubstituted olefins also furnished the hydroalkoxylated products (Scheme 38). The mechanism of cobalt-catalysed hydroalkoxylation is similar to that involved for hydroamination which is discussed in section 6.3.1.

It is interesting to note that under these catalytic conditions, the selectivity is in favour of the hydroalkoxylation *versus* hydroamination as represented in Scheme 39.[98] However, a switch of selectivity can be achieved by the appropriate choice of the alcohol protecting group.

6.4 Nickel

6.4.1 C–N bond formation. To the best of our knowledge and despite the seminal work[99] of the group of Hartwig in 2002 which has demonstrated that the combination of $Ni(COD)_2$, 1,1′-bis(diphenylphosphino)ferrocene (DPPF) ligand and an acid is highly active for the hydroamination of dienes and alkylamines, nickel-based catalysts have not been used since for the hydroamination of unactivated alkenes.



Scheme 39 O- *versus* N-selectivity in the cobalt-catalysed intramolecular hydroamination of protected aminoalkenes.

6.4.2 C–O bond formation. In 2013, the sole example employing a nickel catalyst was reported by Suisse and Sauthier *et al*. They have shown that alkylbutenyl ethers could be obtained with high selectivity by hydroalkoxylation of the 1,3-butadiene with methanol, ethanol or benzylic alcohol. The catalyst is generated by reaction of $Ni(acac)_2$ and a bis(diphenylphosphino)ligand in particular 1,4-bis(diphenylphosphino)-butane (dppb), in the presence of sodium borohydride.[100]

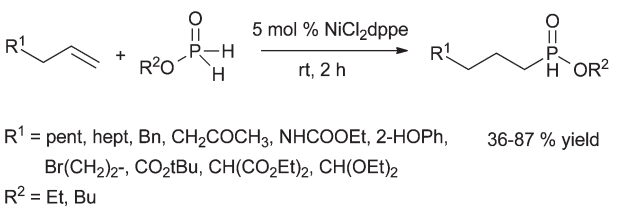
6.4.3 C–P bond formation. It has recently been shown that hydrophosphinylation of alkenes can be readily achieved using $NiCl_2$-1,2-bis(diphenylphosphino)ethane (dppe) as the catalytic system.[101] Montchamp *et al.* successfully applied the formation of C–P bonds to a large panel of terminal, internal and functionalised alkenes (Scheme 40). Selective mono- or bisphosphinylation can be obtained when 1,5-hexadiene is used as the substrate. The methodology described affords H-phosphinate fragments. Interestingly, such P–H bonds can further be arylated through a classical Pd-catalysed process, broadening the scope of the reaction and suggesting further potential applications within this series of organophosphorus compounds.[102] Attempts to develop chiral products using Josiphos or Chiraphos ligands associated to $NiCl_2$ of this reaction led to poor results (17–18% ee).

6.5 Copper

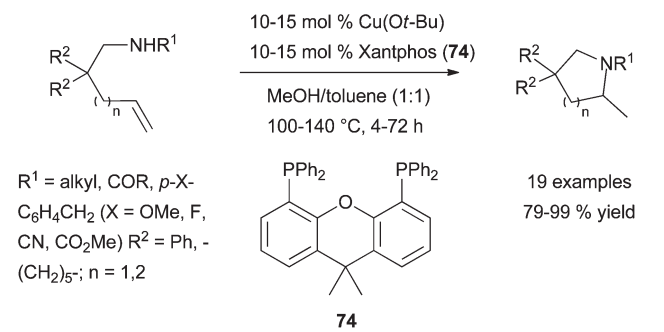
6.5.1 C–N bond formation. Encouraged by earlier studies on copper-promoted intermolecular Markovnikov and *anti*-Markovnikov hydroamination reactions of protected amines on vinylarenes,[103,104] some recent reports have arisen and have strongly emphasised the valuable use of copper-based catalysts for selective inter and intramolecular C–N bond formation. In 2009, Sawamura *et al.* reported the first example of a copper(I)-catalysed intramolecular hydroamination of electronically unbiased amines.[105] The reported Cu(O*t*-Bu)-Xantphos (**74**) system catalyses the intermolecular hydroamination of primary and secondary unprotected amines tethered to terminal alkenes, affording the corresponding pyrrolidines and piperidines in excellent yields (Scheme 41). This protecting-group free methodology represents a significant achievement as an alcoholic media and various functional groups on the aminoalkenes are tolerated. This reaction is proposed to occur by migratory insertion of the alkene into a Cu(I)–amido bond (formed by σ-bond metathesis between a alkoxycopper species and the N–H bond of the aminoalkene) to generate an copper alkyl intermediate. Subsequent alcoholysis of the copper alkyl bond would liberate the hydroamination product. No traces of β-H elimination products are noticed during the process. The methodology practicability was illustrated in the synthesis of *N*-alkylated aza-sugars without any protection of the free hydroxyl groups of the tethering chain.[106]

More recently, a convenient copper(II)-catalysed synthesis of chiral 2-methylindoles using a $Cu(OTf)_2$·(*R*,*R*)-Ph-Box catalyst was disclosed as the first report of enantioselective copper-catalysed alkene hydroamination.[107] Despite the moderate to high level of enantioinduction (72–90% ee), this methodology affords the corresponding *N*-sulfonyl-2-methylindolines in low to moderate yields (37–70%) and requires the stoichiometric use of co-reagents (H-atom donor, oxidant and base). Further mechanistic investigations of alkene hydroamination catalysed by the combination of a copper halide, a diphosphine ligand and a silver salt underlines that a Brønsted acid might be the prominent catalytic species under these reaction conditions.[108] This study brought to light that the development of truly copper-catalysed hydroamination processes are challenging, mainly for asymmetric applications.

Recently, the groups of Hirano, Miura[109a] and Buchwald[109b] have independently reported a highly regio- and enantioselective copper-catalysed intermolecular hydroamination of styrenes under very mild reaction conditions and with exclusive Markovnikov regioselectivity. These reports exploit an alternative umpolung electrophilic amination approach[110,111]



Scheme 40 Nickel-catalysed intermolecular hydrophosphinylation of linear unactivated alkenes (dppe = 1,2-bis(diphenylphosphino)ethane).



Scheme 41 Copper(I)-catalysed intramolecular hydroamination of aminoalkenes.

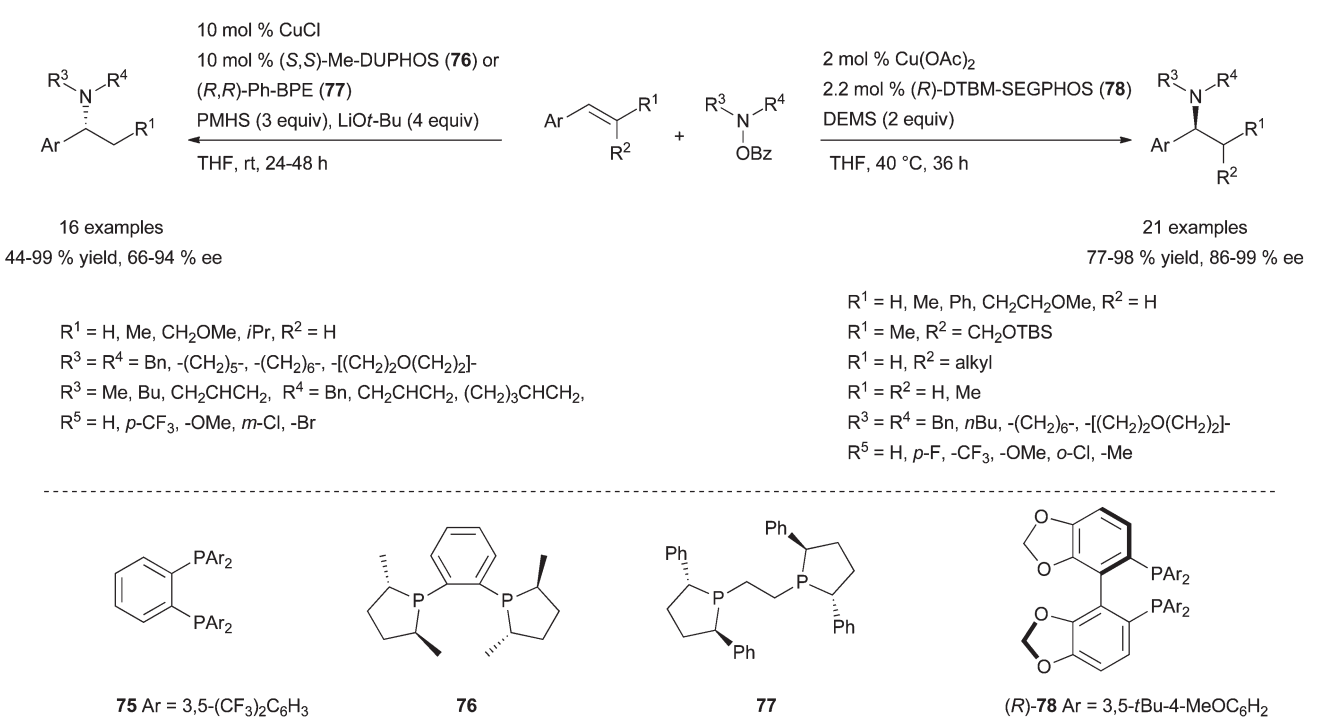
to classical alkene hydroamination using easily accessible *O*-benzoylhydroxylamines as electrophilic amination reagents and led to a remarkable breakthrough in the field. Building on their previous work on regio- and stereo-specific copper-catalysed aminoboration of styrenes,[112] Hirano, Miura *et al.* have screened several copper salts/mono-and bidentate ligand combinations in the presence of various hydride sources and base for the hydroamination of styrene with *O*-benzoyl-*N*,*N*-diethylhydroxylamine.[109a]

It was identified that the combination $Cu(OAc)_2$·**75** (Scheme 42) (10 mol%) in the presence of polymethylhydrosiloxane (PMHS) and LiO^tBu was optimal and could be applied to the regioselective Markovnikov hydroamination of functionalised styrenes and *trans*-β-substituted styrenes with *O*-benzoylhydroxylamines, affording the corresponding racemic amines in good to excellent yields at room temperature. Impressively, a slightly modified catalytic system (CuCl·(*S*,*S*)-Me-Duphos (**76**) or CuCl·(*R*,*R*)-Ph-BPE (**77**)) furnishes chiral amines with enantiomeric excesses ranging from 66 to 94% ee (Scheme 42, left). Unfortunately, these copper-based systems reported by Hirano, Miura and co-workers are not effective for the electrophilic amination of *cis*-β-substituted styrenes and, more importantly of terminal aliphatic alkenes.

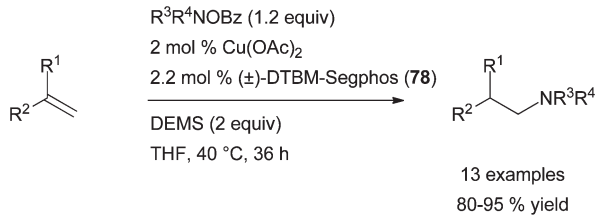
Exploiting an analogue umpolung strategy, the group of Buchwald has brilliantly published a highly efficient and related chiral system for the regio- and enantioselective copper-catalysed electrophilic amination of various aromatic alkenes.[109b] The reported $Cu(OAc)_2$·(*R*)-DTBM-Segphos (**78**) system, in the presence of diethoxymethylsilane (DEMS) as hydride source, has a broader scope than Hirano and Miura's catalytic system with similar Markovnikov selectivity and level of enantioinduction (Scheme 42, right). In addition to styrenes, β,β-disubstituted styrenes or β-substituted styrenes featuring a *trans* or a *cis* configuration are elegantly converted into the branched amines with high enantioinduction, under the described reaction conditions.

Furthermore, the reported $Cu(OAc)_2$·(±)-DTBM-Segphos (**78**) system has the exclusive ability to provide linear tertiary amines in high yields from the *anti*-Markovnikov electrophilic amination of terminal aliphatic alkenes with *O*-benzoyl hydroxylamines, (Scheme 43).[109b] Only a few metal systems have demonstrated such a regioselectivity with the scope of alkenes often limited to vinylarene derivatives, highlighting the achievement made by Buchwald's group. More recently, the group has expanded the methodology to the synthesis of a range of functionalised β-chiral amines in excellent yields with high enantioselectivities as the first report of enantioselective *anti*-Markovnikov hydroamination.[113] These reactions are proposed to occur by a regio- and stereo-selective *syn*-migratory alkene insertion into the Cu–H bond of a Cu–H intermediate. The subsequent C–N bond formation might occur with retention of stereochemistry.

6.5.2 C–O bond formation. In 2005, the group of Hii demonstrated the usefulness of a copper catalytic system in the regioselective addition of ROH to norbornene.[114] Since this work, to the best of our knowledge no other publication dedicated to the intermolecular hydroalkoxylation of olefin, allene or diene was reported using a copper catalyst. Only one



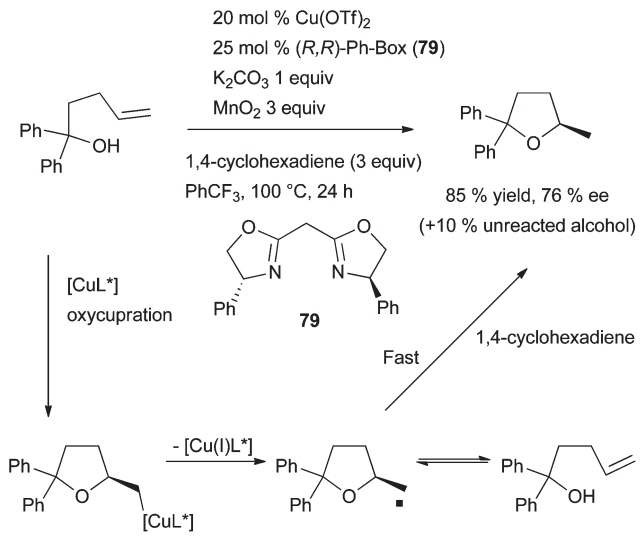
Scheme 42 Regio- and enantioselective intermolecular copper-catalysed electrophilic amination of styrenes with *O*-benzoyl hydroxylamines.



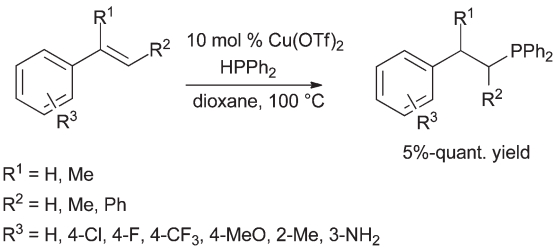
Scheme 43 Copper(II)-catalysed *anti*-Markovnikov electrophilic amination of terminal aliphatic alkenes with *O*-benzoyl hydroxylamines.

example was depicted by Chemler *et al.* in 2012 during a study on the intramolecular carboetherification of alkenes.[6] Despite the fact that only hydroalkoxylation of 1,1-diphenylpentenol was reported, this is the sole example of asymmetric Markovnikov hydroalkoxylation of an unactivated alkene (Scheme 44). The enantioselective transannular hydroetherification *vs.* carboetherification depends on the presence or not of 1,4-cyclohexadiene in the reactional medium.

6.5.3 C–P bond formation. Hydrophosphination has been realised using metal salts. As reported by Corma (Scheme 45)[115] $Cu(OTf)_2$ reacts almost as efficient as elaborated transition metal complexes, in contrast to other catalytic systems (Fe(II), Fe(III), Cu(II), Ag(I), Mn(II)). The *anti*-Markovnikov adduct is exclusively produced from the various substituted styrenes. In contrast, stilbene or 1-octene afforded poor yields of hydrophosphination. Phosphineoxides together with other oxidized adducts can be obtained under O_2 atmosphere.



Scheme 44 Enantioselective intramolecular hydroalkylation of alkenes catalysed by a copper complex.

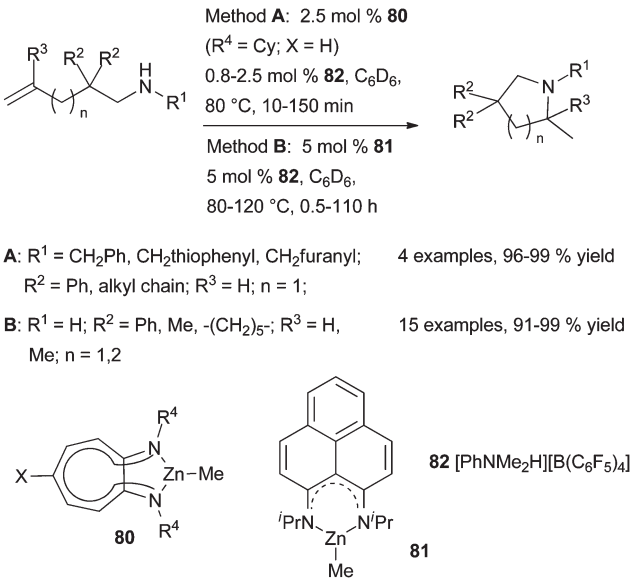


Scheme 45 Copper-catalysed intermolecular hydrophosphination of styrene derivatives.

6.6 Zinc

6.6.1 C–N bond formation. Despite the biological application of zinc in nature, zinc has been poorly investigated as a metal catalyst for the formation of C–N bonds by alkene hydroamination. In 2005, the group of Roesky disclosed the first application of a homogeneous zinc catalyst for the hydroamination of primary amines tethered to unactivated alkenes using the air- and moisture-stable [*N*-isopropyl-2-(isopropylamino)troponiminato] methylzinc **80** (R^4 = iPr, X = H,) catalyst (Scheme 46).[116] This well-defined compound, which is easily synthesised from Me_2Zn and the corresponding ligand, is monomeric in the solid state. The zinc centre is three-coordinate and adopts a trigonal planar geometry. In the presence of $[PhNMe_2H][B(C_6F_5)_4]$ (**82**) as a cocatalyst, complex **80** exhibits good catalytic activities at high temperature for the formation of 5-membered ring systems. Stimulated by early findings,[117] the group has investigated in detail the influence of structural modifications of the aminotroponiminate ligand on the catalytic reactivity.[118,119] For this purpose, a series of modified zinc catalysts **80** were prepared and evaluated in the intramolecular hydroamination of secondary aminoalkenes (Scheme 46). It was demonstrated that the steric and electronic modifications of the aminotroponiminate ligand have a strong impact on the stability and reactivity of the corresponding complexes. Regrettably, the remarkable catalytic activity noticed with the previously reported catalyst **80** (R^4 = Cy, X = H)[117a] was not improved. A very convenient ligand-free methodology for the organozinc(II)-catalysed cyclohydroamination of secondary aminoalkenes was also reported by Roesky *et al.*[120] In the presence of 2.5 mol% of $[PhNMe_2H][B(C_6F_5)_4]$ (**82**) as activator, the addition of 2.5 mol% of $ZnEt_2$ provides a very efficient cationic species for the formation of pyrrolidines in high yields at room temperature. The reactivity of this ligand-free system, which is the highest reactivity displayed so far for a zinc system, is strongly influenced by the coordination ability of the activator anion.

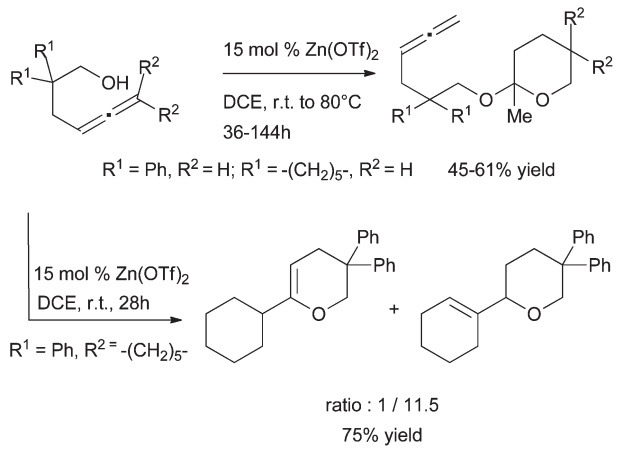
More recently, Mandal *et al.* have reported the synthesis, characterisation and catalytic application of two organozinc complexes that contain symmetrical phenalenyl-based *N*,*N*-ligands such as **81** (Scheme 46).[121] Both three-coordinate complexes have a well-defined structure with a zinc atom having a trigonal-planar coordination sphere. Nevertheless, catalyst **81** displays similar catalytic activity to that of **80** for the cyclo-



Scheme 46 Zinc(II)-catalysed cyclohydroamination of amines tethered to alkenes.

hydroamination of functionalised primary and secondary aminoalkenes.

6.6.2 C–O bond formation. To the best of our knowledge, zinc has only been investigated as a metal catalyst for hydroalkoxylation of allenols. In 2009, in the intramolecular hydroalkylation of γ-allenols which can afford 5- or 6-membered O-heterocycles, Hii *et al.* observed a regiodivergence depending on the metal catalyst used. They have described that 6-*exo*-dig cyclisation occurs predominantly when the reaction is catalysed by $Zn(OTf)_2$ (or $Sn(OTf)_2$) whereas in the presence of AgOTf, catalysis proceed by 5-*exo*-trig cyclisation (Scheme 47). Depending on the substrate structure, (for example when R^1 = Ph or $-(CH_2)_5-$ and R^2 = H), the hydroalkoxylation step resulting in the formation of a 6-membered ring cyclic ether intermediate could be trapped by another molecule of substrate to give an acetal. It was noted that the 6-*exo*-dig cyclisation was previously reported only with lanthanides (section 5.2) whereas the more common 5-*exo*-trig selectivity was also observed with Au and Pt catalysts.[122]



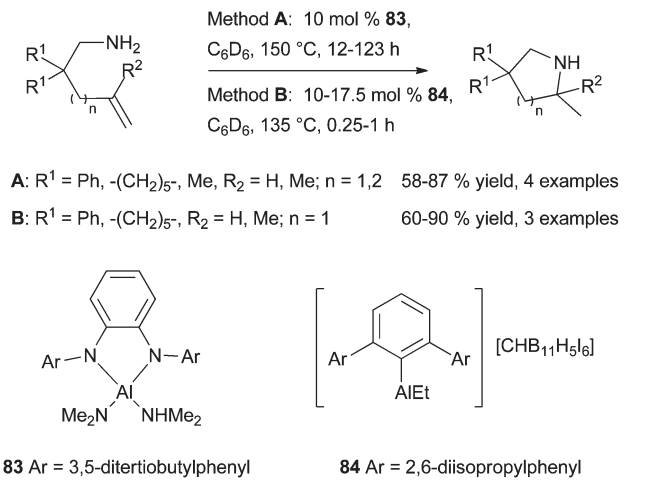
Scheme 47 6-*exo*-dig cyclisation of γ-allenols in the presence of $Zn(OTf)_2$.

7. Aluminium catalysts

Despite being the most abundant metal and the third most abundant element, after oxygen and silicon in the Earth's crust, aluminium has been poorly explored as a catalyst for alkene hydrofunctionalisation. Only a few examples have been reported for the formation of C–N and C–O bonds for specific applications.

7.1 C–N bond formation

In 2010, the group of Bergman disclosed the first report of aluminium-catalysed hydroamination of unactivated alkenes using the structurally well-defined four-coordinate aluminium complex **83** bearing a dianionic phenyl-diamine based ligand (Scheme 48).[123] The latter is synthesised from commercially available $[Al(NMe_2)_3]_2$ as a monomer thanks to the bulky aryl groups on the amine functions. The structurally-defined complex **83** (10 mol%) has the ability to promote the cyclohydroamination of primary aminoalkenes bearing *geminal* substituents on the backbone to form 5- and 6-membered rings in moderate to good yield under harsh conditions. Control experiments reveal that an acid catalysis was not operating in the process. From a stoichiometric reaction between **83** and 2,2-diphenylpent-4-ene-1-amine, the resting state of the catalyst is proposed to bear an aluminium-amide species resulting from loss of two molecules of $HNMe_2$. More recently, Wehmschulte *et al.* have evaluated the catalytic activity of cationic four-coordinate dialkylaluminum and *m*-terphenylalkylaluminum compounds in the cyclohydroamination of primary amines

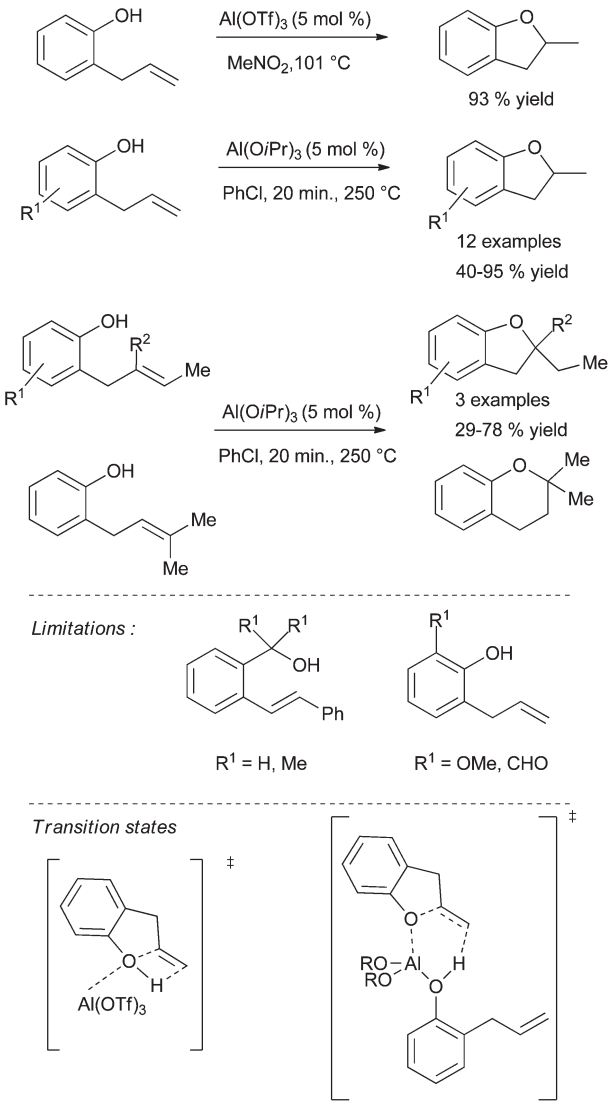


Scheme 48 Aluminium-catalysed cyclohydroamination of aminoalkenes.

tethered to alkenes.[124] It was found that the most sterically crowded compound **84** was the most active of the series for the cyclisation of primary aminoalkenes, leading to the formation of pyrrolidines in moderate to high yields at 130 °C (Scheme 48). The cationic nature of these compounds is primordial for an efficient reactivity. A secondary amine tethered to alkene could also be cyclised under analogous conditions.

7.2 C–O bond formation

Aluminium(III) derivatives are also able to catalyse the cyclisation of unsaturated alcohols. The pioneering work of Pons and Duñach *et al.* in this field have shown that $Al(OTf)_3$ is the more efficient of all of them.[22a,125,126] A large number of cyclic ethers were obtained with this metal triflate in high yields with Markovnikov regioselectivity (one example is depicted in Scheme 49). Theoretical calculations support the hypothesis of Lewis superacid type catalysis. The key step for the activation of the unactivated double bond should be the increased acidity of the hydroxyl proton. The intermolecular hydroalkoxylation of alkenes and catalysed by $Al(OTf)_3$ was also reported by the group of Williams in 2012 (Scheme 26, method **B**).[78] More recently, Hintermann *et al.* have disclosed that $Al(OiPr)_3$ is also a powerful catalyst for the cyclisation of 2-allylphenols.[127] However, these fast transformations require higher temperatures than the conditions described early on by Pons and Duñach *et al.* With $Al(OiPr)_3$, hidden Brønsted acid catalysis can be definitely eliminated. A mechanism similar to metal-catalysed hydroamination reactions can be considered. In their study, the authors clearly reported the limitations of the $Al(OiPr)_3$ catalyst in this type of cyclisation. The substrates form stable chelates with Al(III) and benzylic alcohol could not be cyclised (Scheme 49).



Scheme 49 Hydroalkoxylation of 2-allylphenol catalysed by $Al(OTf)_3$ and $Al(OiPr)_3$.

8. Conclusion and outlook

This article has reviewed some of the most recent results for performing the hydrofunctionalisation of alkenes with cheap, non-toxic, abundant and readily available catalytic species. The number of cited articles, and their diversity, is particularly revealing of the awareness of the need for elegant, inexpensive and direct methods to create these new carbon–heteroatom connections. New C–N, C–O or C–P bonds can be formed starting from various precursors able to add to carbon–carbon double bonds. By far, many more examples illustrate the C–N bond formation which is probably due to several reasons; nitrogen-containing compounds are valuable scaffolds towards the preparation of biologically active products, which substantiate an active search to find effective and green synthetic procedures. Furthermore, the nitrogen-starting compounds capable of reacting with olefins are actually diverse in their structure, and may be easily modulated, for instance, to tame their basicity. This is much less obvious, of course, if one refers to alcohols, and to a lesser extent, to phosphorus-containing derivatives. The hydrofunctionalisation reaction is concerned with notions of chemoselectivity, regioselectivity and enantioselectivity. Variable responses have been made, according to both the bond to be formed and the catalyst used, but comparison of the successes and shortcomings can be drawn.

The construction of a new carbon–heteroatom link tolerates a wide range of functional groups as long as the promoters belong to the "organocatalysts" series or to the first-row transition metals. This is not accurate anymore if metals of Groups 1, 2 or 3 are concerned. In these cases, indeed, the associated metal-acidic site is too much sensitive to stand the presence of diverse functionalities and the substrates are almost exclusively carbon-containing compounds. Some exceptions can be found for the hydroalkoxylation reaction which can be performed on substrates bearing for instance ester groups, if the catalyst is a non-sensitive lanthanide halide or $Ca(NTf_2)_2$.

Some interesting chemoselective reactions have been reported, for the catalysts issued from the first-row. For

instance, the copper-catalysed intramolecular hydroamination of alkenes has been performed on substrates containing hydroxyl groups, and the desired hydroxylated pyrrolidine and piperidine derivatives were obtained in high yield, without it being necessary to protect the OH groups. In a less straightforward way, but following nevertheless a simple procedure, the cobalt-catalysis (associated with a silane derivative and *N*-fluoropyridinium salt), of an olefin bearing a free hydroxyl group and a deactivated amine, delivers exclusively the hydroalkoxylation product. If an acetyl moiety is introduced as hydroxyl protecting group, the reactivity is interestingly reversed towards the sole formation of the hydroamination product. Iron catalysis led also to exciting results in terms of chemoselectivity. The oxycyclisation of β-lactam enallenols has been indeed demonstrated to occur entirely on the alkene group. This reactivity completes remarkably the catalysis described in the presence of noble metals (platinum or gold salts) which promote the allene cycloisomerisation.

An important point that governs the hydrofunctionalisation reaction is its selectivity towards a regioselective Markovnikov or an *anti*-Markovnikov addition. The control of this selectivity is tricky and is mainly governed by the structure of the catalyst but also the substrate backbone. Overwhelmingly, the formation of new C–P bonds has been demonstrated to follow an *anti*-Markovnikov pathway. Indeed photoinduced catalysis, and alkaline earth-, rare earth-, first row (Ti, Ni, Cu) metal-based complexes delivered the linear products from terminal olefins (mainly styrene derivatives). One example challenges this list, since iron-catalysis was demonstrated to allow providing a choice of one or the other regioisomer, according to the oxidation state of the iron centre, as chloride salts, devoid of any ligand. In contrast, the hydroalkoxylation delivers mainly products resulting from Markovnikov addition. Unique examples of *anti*-Markovnikov addition of an alcohol onto an olefin arose from photoredox catalysis, with the reverse selectivity being explained by the stability of intermediary radical species. A much more mixed state of the art issued from the results described for the hydroamination reaction. The well-studied intramolecular version of this reaction delivers, in the presence of the presented catalytic systems, exclusively products with Markovnikov selectivity. In the case of the intermolecular transformation, the selectivity of the reaction is highly related to both the structure of the involved olefinic substrate and the catalytic species. For instance, the rare-earth catalysed intermolecular hydroamination of styrene delivers the linear *anti*-Markovnikov product, whereas the same reaction performed with simple alkenyl derivatives lead to the branched Markovnikov compound. This is due to an aryl directing interaction of the weakly coordinating arene π-system and the electrophilic lanthanide centre, in the first case. Another example may be found in the copper-catalysed hydroamination reaction, in the presence of electrophilic amines, which occurs through Markovnikov or *anti*-Markovnikov selectivity, according to the structure of the engaged substrate.

Introducing enantioselectivity through formation of new carbon–heteroatom bonds is highly desirable and it has been the subject of numerous efforts with varying success. Research dedicated to performing asymmetric hydroamination reactions are already longstanding, and one may state that the control of enantioselectivity in cyclohydroamination transformations has already found numerous solutions. Indeed, in the case of alkenes tethered to simple primary or secondary amines, a large variety of examples are summarised in this article, implying catalysts with a great diversity in their structure and in the involved mechanistic pathway, which lead to nitrogen-containing heterocycles with very high enantiopurity. The use of chiral organic Brønsted acids is much more in its infancy for this reaction, but according to the huge development of such species for other reactions, one may expect future interesting advances in this reactivity. For the related intermolecular version, control of the enantioselectivity remains challenging, at least for alkali, alkaline earth and rare earth-based catalysts. In this context, nice recent examples involving the use of cheap and abundant copper catalysts have brought interesting answers, even if it must be specified that the reaction is in this case based on the use of electrophilic amines, in an umpolung-type transformation. For both of the other reactions, the formation of new C–O or C–P bonds, the state of the art really differs from what is known in the related C–N bond formation. As far as we know, only one recent example of intramolecular enantioselective hydroalkoxylation has been reported with a copper-bisoxazoline catalyst. The formation of scalemic phosphorus-containing products by such hydrofunctionalisation reaction is not known, probably in close connection to the preferred *anti*-Markovnikov regioselectivity. Such transformations could thus be studied with specific styrenyl-derived substrates, but a jump in reactivity must be found. The search for enantioselective formation of C–O or C–P bonds is still highly challenging.

Some catalytic systems have already been studied for promoting the three different hydrofunctionalisation reactions; this is the case for some group 2 and group 3 elements. Iron- and copper-promoted catalysis has also found successful solutions in each case. Some examples of nickel-catalysis show that this metal can promote the three reactions, albeit it has been hardly investigated. On the other hand, some catalysts used for one transformation may be promising to promote the other bond formations. This is probably the case for the less sensitive species, which can accommodate the presence of all the reactive functional groups present in the different substrates. There is still place for the search for the universal catalyst, but this review article already demonstrated that earth abundant elements are highly efficient for these valuable transformations, as direct addition reactions, allowing for the direct introduction of heteroelements into carbon compounds for various applications.

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