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Homogeneous catalysis with phosphorus dendrimer complexes

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Dedicated to Prof. Armando J.L. Pombeiro on the occasion of his 70th birthday

Abstract:

Dendrimers are highly branched macromolecules, which have properties in many different fields, in particular for catalysis. This review presents an exhaustive view about complexes of phosphorus-containing dendrimers (having a phosphorus atom at each branching point), used as homogeneous catalysts in a range of reactions. First, catalysed reactions for C-C bonds formation using Pd, Rh, Ru, or Sc complexes will be displayed; then formation of C-O and C-N bonds using Cu complexes as catalysts will be shown. At the end, miscellaneous reactions catalysed without metal (organocatalysis) will be displayed. Despite their size, dendrimers are generally soluble in the reaction media, thus they afford homogeneous catalysts. However, their size is by far larger than the size of the reagents and products, thus they are generally easily separated, simply by adding a solvent in which the products are soluble, but not the dendrimers. The recovery and reuse of dendrimers (recycling) is an important advantage compared to classical monomeric catalysts, which will be emphasized in this review, together with the so-called dendrimer (or dendritic) effect, which is an enhancement of a property when the size of the dendrimer increases.

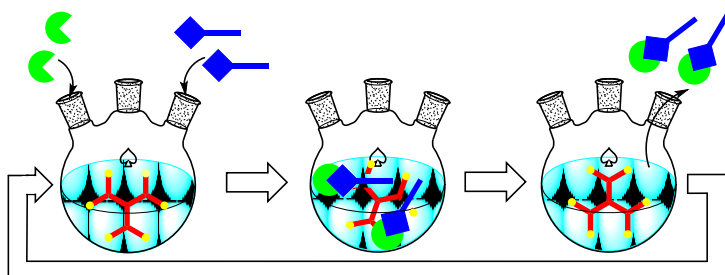
Keywords:

dendrimers; homogeneous catalysis; phosphorus; organometallic complexes; recycling; dendrimer effect

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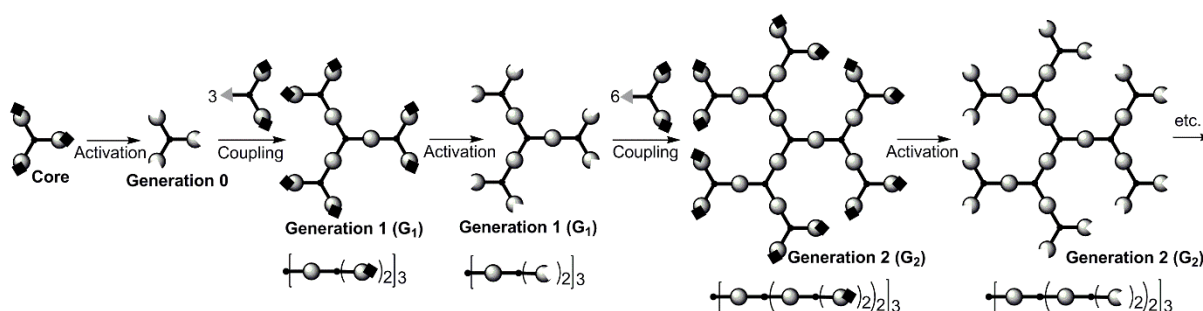


Highlights:

- Catalytic dendrimers are soluble but can be easily recovered, mainly by precipitation, and re-used
- Catalytic phosphorus dendrimers outperform the corresponding monomers in terms of yield and enantioselectivity
- The leaching of metal is drastically reduced when using phosphorus dendrimeric catalysts
- Dendrimers constitute a greener and safer alternative in homogeneous catalysis

1. Introduction

Dendrimers are highly branched macromolecules, synthesized step-by-step to ensure a highly reproducible structure [1]. They are most generally synthesized by a divergent process, starting from a multifunctional core from which branches are progressively grown. They are constituted of repetitive units, as polymers. However, they are never synthesized by polymerization reactions, but layer after layer (generation after generation), as illustrated in Scheme 1. For practical reasons, dendrimers are frequently represented in a linear form with parentheses; multiplying the numbers after the parentheses affords the number of terminal functions. Branched structures can be found at all levels in the Nature, but not at the molecular level. Thus the structure of dendrimers is unique among all the natural and synthetically produced compounds. In the early times of this topic, the name “dendrimer” was not yet fixed, and they were called “cascade” [2], or “arborol” [3], but D.A. Tomalia proposed the name dendrimer [4,5], which was then largely adopted to name these branched macromolecular structures. Most types of dendrimers have nitrogen atoms as branching points, but dendrimers based on main group elements as branching points [6] have been synthesized early, in particular for silicon [7] and phosphorus [8], and they display interesting, sometimes unique, properties [9].



Scheme 1. The principle of the divergent synthesis of dendrimers. For generations 1 and 2, both the full structures, and the linear structures with parentheses are shown.

Dendrimers have properties in many different fields [10], in particular in catalysis [11]. The very first examples of catalysis with dendrimers date back to 1994, with 3 papers published that year. A

generation 1 carbosilane dendrimer bearing nickel derivatives as terminal functions was used for the Kharash addition of polyhalogenoalkanes to carbon-carbon double bonds [12]; copper complexes of dendrimeric oxazolidine and oxazinane ligands were used in the Cu(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate [13]. Of particular interest for this review, a third paper concerns a small polyphosphine complexing palladium (Fig. 1), which was used as catalyst for the electrochemical reduction of CO₂ to CO [14]. This is the very first example of catalysis with a phosphorus-containing dendrimer (defined as dendrimers having a phosphorus atom at each branching point).

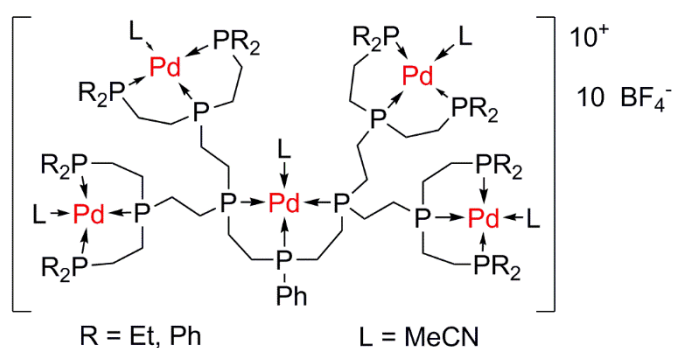
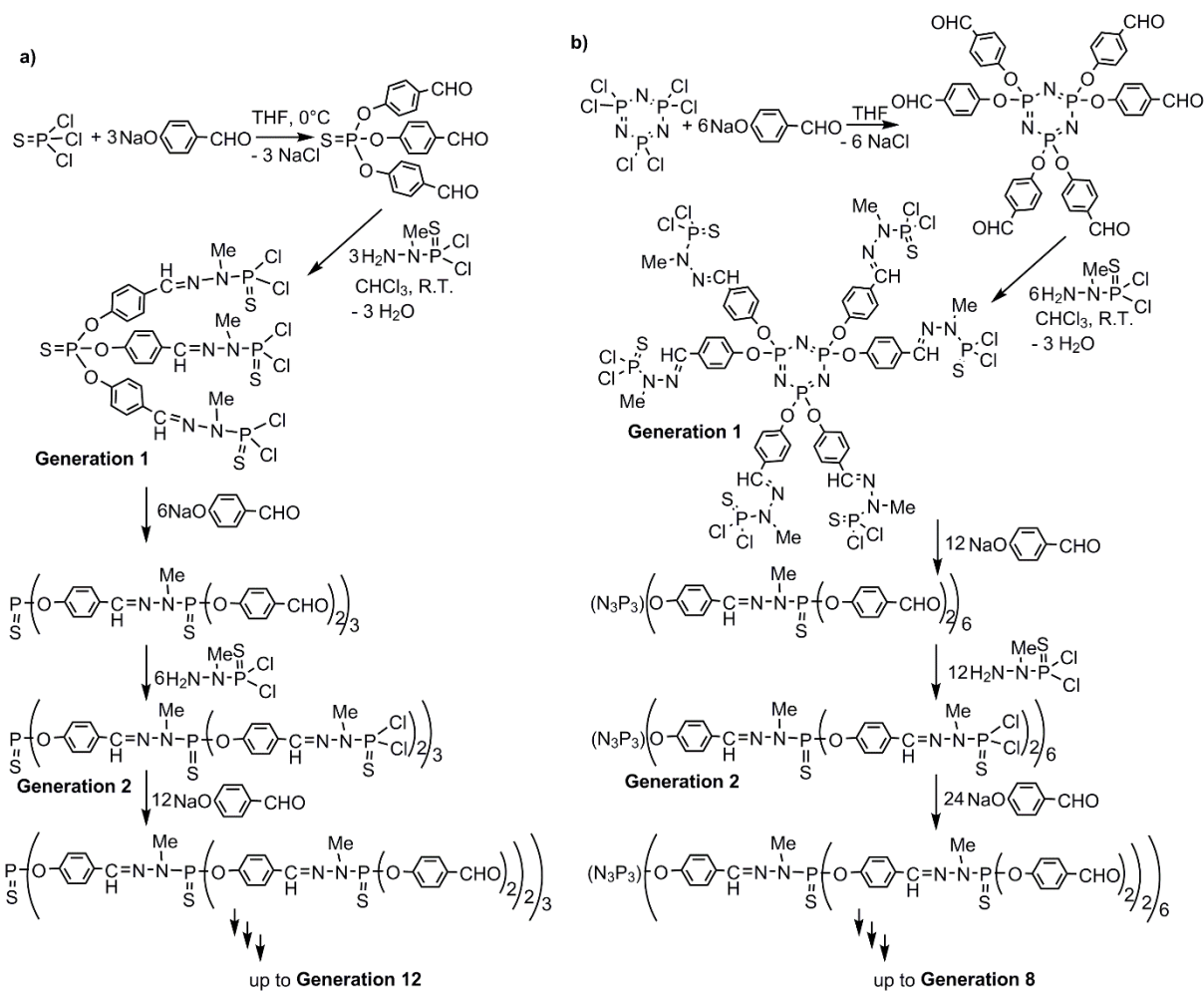


Fig. 1. Chemical structure of the first phosphorus-containing dendrimer used as catalyst.

In this review we will present an exhaustive view about complexes of phosphorus-containing dendrimers used as homogeneous catalysts in a range of reactions. First, catalysed reactions for the formation of C-C bonds using Pd, Rh, Ru, or Sc complexes will be displayed; then formation of C-O and C-N bonds using Cu complexes as catalysts will be shown; and miscellaneous reactions catalysed without metal (organocatalysis) will end this review. It is important to note that in all cases the quantity of catalytic sites is identical within a series of catalytic experiments. It means that the efficiency of a first generation dendrimer having 12 ligands/complexes as terminal functions will be compared with that of 12 equivalents of the monomer bearing the same ligand/metal. Despite their size, dendrimers are generally soluble in the reaction media, thus they afford homogeneous catalysts. However, their size is by far larger than the size of the reagents and products, thus they are generally easily separated, either using a membrane, or more simply by adding a solvent in which the

products are soluble, but not the dendrimers. The recovery and reuse of dendrimers is an important advantage compared to classical monomeric catalysts that will be emphasized in several parts of this review.

Most of the cases of phosphorus-containing catalytic dendrimers are based on phosphorhydrazone dendrimers, which are generally synthesized either from trifunctional $P(S)Cl_3$ [15] or hexafunctional $N_3P_3Cl_6$ [16] as core. The synthesis necessitates two steps for each generation. The first step is a substitution reaction of a phenol (4-hydroxybenzaldehyde) on the P-Cl functions, in basic conditions. The second step is the condensation reaction between the aldehydes generated in the previous step and the phosphorhydrazide $H_2NN(Me)P(S)Cl_2$. This condensation step affords again P-Cl functions, the number of Cl is multiplied by two compared to the previous step involving P-Cl functions, and thus a new generation is obtained. These dendrimers have been built up to generation 12 from the $(S)PCl_3$ core [17], and up to generation 8 from the $N_3P_3Cl_6$ core [18], which is presumably not the highest generation obtainable from this core (Scheme 2).



Scheme 2. Synthesis of phosphorhydrazone dendrimers, from (S)PCl₃ as core (a), and from N₃P₃Cl₆ as core (b).

2. Catalysis for C-C couplings

Cross-coupling reactions for creating carbon-carbon bonds are accessible through catalysis with a number of organometallic reagents [19]. They are particularly important, as they provide key steps in the building of complex molecules. Different metals have been used [20], but palladium complexes occupy a prominent place, in a large number of well-known cross-coupling reactions [21].

2.1. Catalysis with palladium complexes

Even if palladium complexes of NHCs (N-heterocyclic carbenes) [22,23] generally offer superior performance compared to the more traditional complexes of tertiary phosphines as catalysts in

cross-coupling reactions, many researches are still devoted to phosphine complexes [24]. The phosphorus-metal bond is generally strong with transition metals, due to the fact that the phosphine is both a strong σ -donor and a strong π -acceptor, which induces a more electrophilic character to the metal [25]. Furthermore, changing the nature of the substituents on the phosphine allows fine-tuning the steric, electronic, kinetic and thermodynamic properties of the complex, and the catalytic properties [26]. In the case of phosphorus-containing dendrimers, mainly phosphines as terminal functions [27] were used for the complexation of transition metals.

2.1.1. Suzuki couplings

The Suzuki couplings concern palladium-catalysed cross-coupling reactions between different types of organoboron compounds and various organic electrophiles including halides or triflates in the presence of a base, which provides a powerful and general methodology for the formation of carbon-carbon bonds [28]. In the case of phosphorus-containing dendrimers, three examples of Suzuki couplings have been investigated. The first one concerned dendrimers bearing azabis(methylenediphenylphosphine) terminal functions, eventually chiral on a carbon atom adjacent to the nitrogen atom. The palladium complexes of these bidentate ligands were used in Suzuki couplings of 4-bromoaniline with phenylboronic acid (Fig. 2a), using 1% loading of catalyst. These compounds were not extremely efficient, as it was needed to carry out the reaction at 120°C, and after 5.5 h, 63% of conversion was measured with the third generation G_3 ($R = H$), to be compared however with the monomer, which gave only 56% of conversion [29].

The second example concerned the comparison between phosphorhydrazone dendrimers functionalized either with triphenyl phosphine or diphenylthiazolyl phosphine. The coupling of derivatives of bromobenzene with phenyl boronic acid was carried out at 60°C in mixtures H_2O/THF (Fig. 2b). Milder conditions have been used in some cases, in pure water and at room temperature. In most cases, the dendrimers are slightly less efficient than the monomers, but contrarily to the monomers, the dendrimers could be recovered and reused, even the first generation (G_1). Recycling

of the first generations was more efficient in the case of the thiazolylphosphines than with the triphenylphosphines. Indeed, a loss of activity of the dendritic catalyst based on triphenylphosphine ligands was observed, yield decreasing from 87% in run 1 to 80% in run 2, and then to 55% in run 3, whereas the dendritic thiazolyl phosphine catalyst could be successfully recycled at least 4 times without loss of activity. This different behaviour is presumably due to a difference in the leaching of palladium, which was 173 ppm in the case of the G₁ functionalized with triphenylphosphine complexes, and <0.5 ppm (not detectable) in the case of the G₁ functionalized with thiazolylphosphine complexes [30].

In the third experiment, the activity and recyclability of pyrene-tagged dendritic Pd-phosphine catalysts immobilized by π -stacking onto cobalt magnetic nanoparticles coated by graphene layers were evaluated in Suzuki reactions (Fig. 2c). Partial desorption of the dendritic ligands from the surface of the Co-nanoparticles was observed when heating the suspension to 60°C, bridging homogeneous and heterogeneous reaction processes. The coupling of aryl boronic acids with various aryl bromides was performed in the presence of Co/C nanoparticles, Pd(OAc)₂ (0.5 mol%), phosphine dendritic ligands (1 phosphine moiety per Pd) and Na₂CO₃ in a THF/water (2:5) mixture. Good to excellent yields (70-98%) were obtained even in the case of electron-rich or bulky substrates. The catalytic system was next tested for the preparation of Felbinac, a commercial non-steroidal anti-inflammatory drug. The reaction produced quantitatively felbinac, and the catalytic system could be recovered using a magnet and reused 12 times without any loss of activity [31].

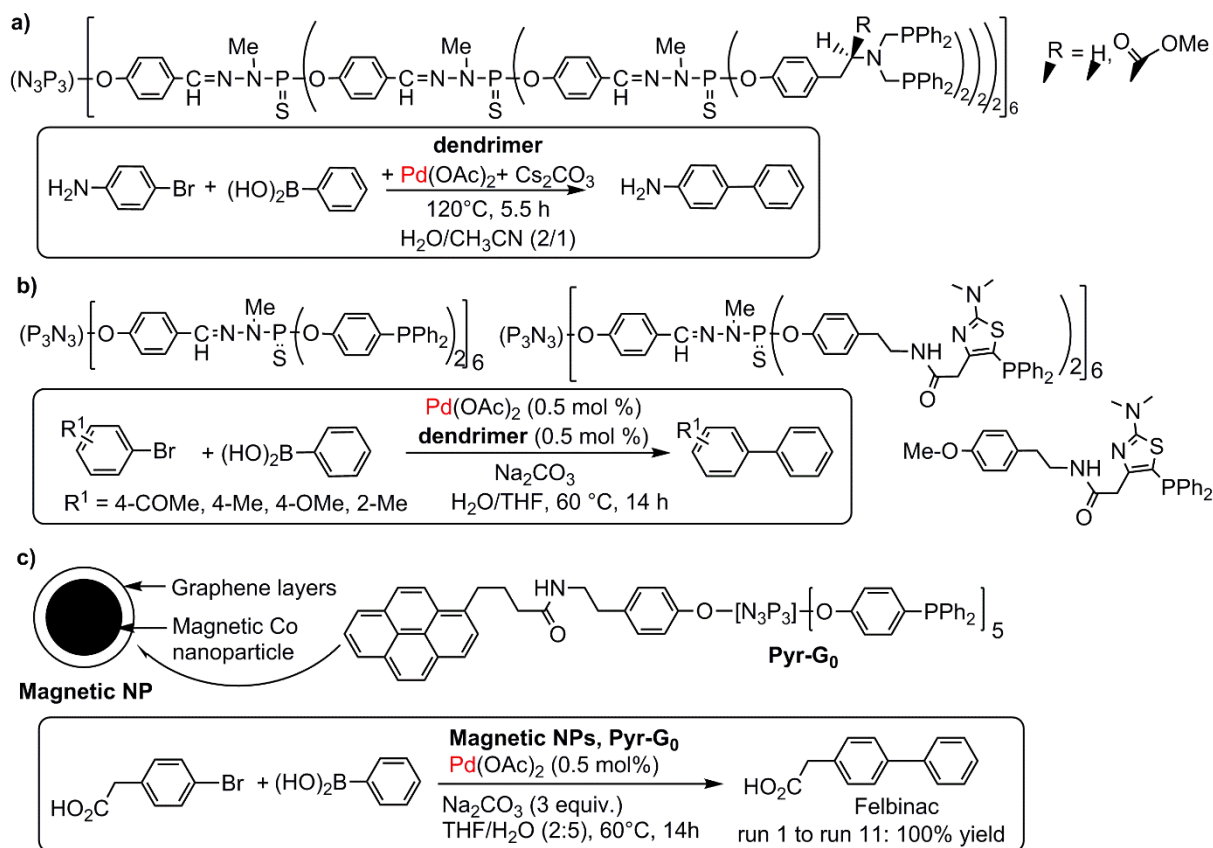


Fig. 2. Examples of Suzuki couplings using palladium complexes of phosphorhydrazone dendrimers as catalysts.

2.1.2. Stille couplings

Besides organoborons used in Suzuki couplings, the coupling of organostannanes with organic electrophiles is also a useful method for creating C-C bonds; such reactions are termed Stille couplings [32]. Two examples have been proposed using phosphorhydrazone dendrimers Pd-complexes. Dendrimers having azabis methylenediphenylphosphine terminal functions (different from those shown in Fig. 2) were synthesized from generation 1 to 4, and were used in particular for the complexation of PdCl_2 and $\text{Pd}(\text{OAc})_2$. The corresponding third generation dendrimers have been successfully used for catalysing the coupling of methyl-2-iodobenzoate with 2-(tributylstannyl)thiophene, and of iodobenzene with tributylvinyltin, respectively (Fig. 3a). In both cases the conversion was quantitative, and these dendritic catalysts could be recovered and reused two times [33].

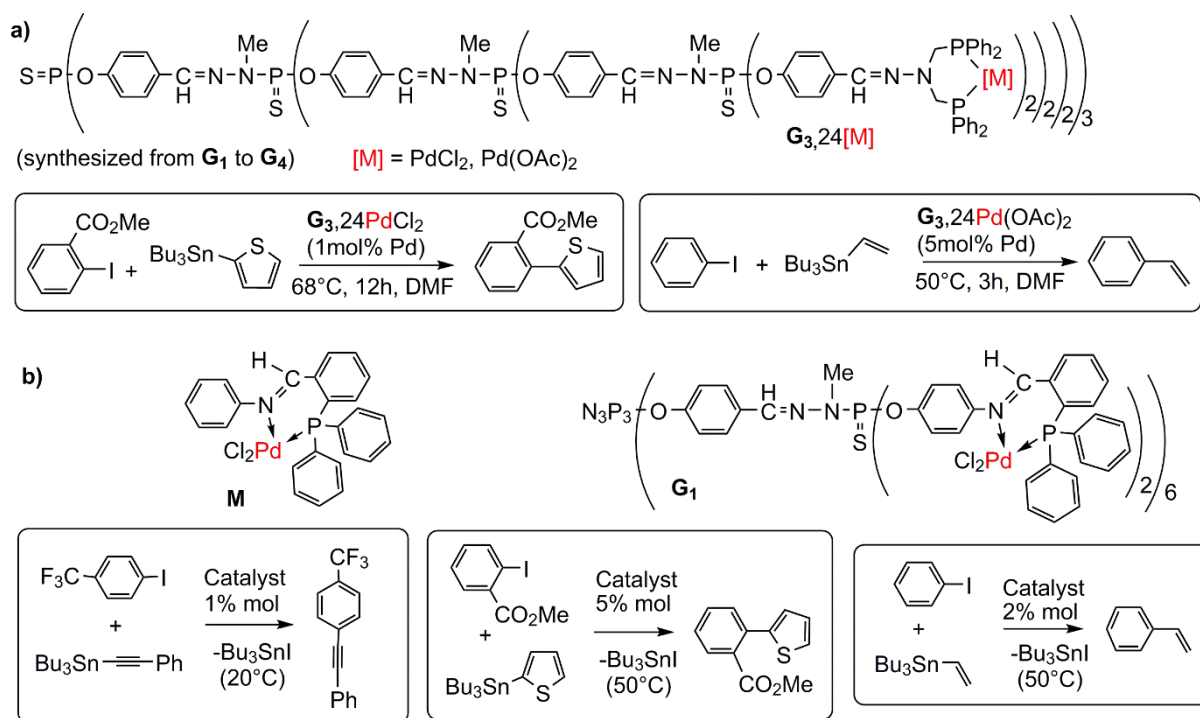


Fig. 3. Examples of Stille couplings using palladium complexes of phosphorhydrazone dendrimers as catalysts.

The second example of Stille couplings concerns dendrimers bearing P,N ligands complexing palladium. P,N ligands are an important class of ligands for asymmetric catalysis [34], but they are also useful in catalyses not involving chirality. The comparison between the efficiency of a monomeric P,N ligand and of the corresponding first generation dendrimer has been carried out in three different Stille couplings (Fig. 3b). In the Stille coupling of iodobenzene with tributylvinyltin, the dendrimer was more efficient than the monomer; in the Stille coupling of methyl-2-iodobenzoate with 2-(tributylstannyl)thiophene, the dendrimer and the monomer had the same efficiency; in the Stille coupling of 4-(trifluoromethyl)iodobenzene with phenylethynyltributyltin, the monomer was more efficient than the dendrimer. It clearly appears from these experiments that catalytic performances of the metalladendrimer depend on the reagents involved in the investigated Stille coupling reactions [35].

2.1.3. Heck reactions

The palladium-catalyzed arylation or alkenylation of alkenes is known as the Heck reaction, which has achieved the status of an indispensable tool for both common and state-of-the-art organic synthesis [36]. Three examples of Heck reactions have been carried out with phosphorhydrazone dendrimers. The first one concerns the dendrimer complexes shown in Fig. 2a for Suzuki couplings. They have been used also for Heck reactions between styrene and iodobenzene, to afford trans-stilbene, and between ethyl acetate and iodobenzene, to afford ethyl cinnamate (Fig. 4a). In the first case (styrene) the conversion is relatively low. On the contrary in the second case (ethyl acetate), the efficiency of generations 0 and 1 is more than twice the efficiency of the monomer [29].

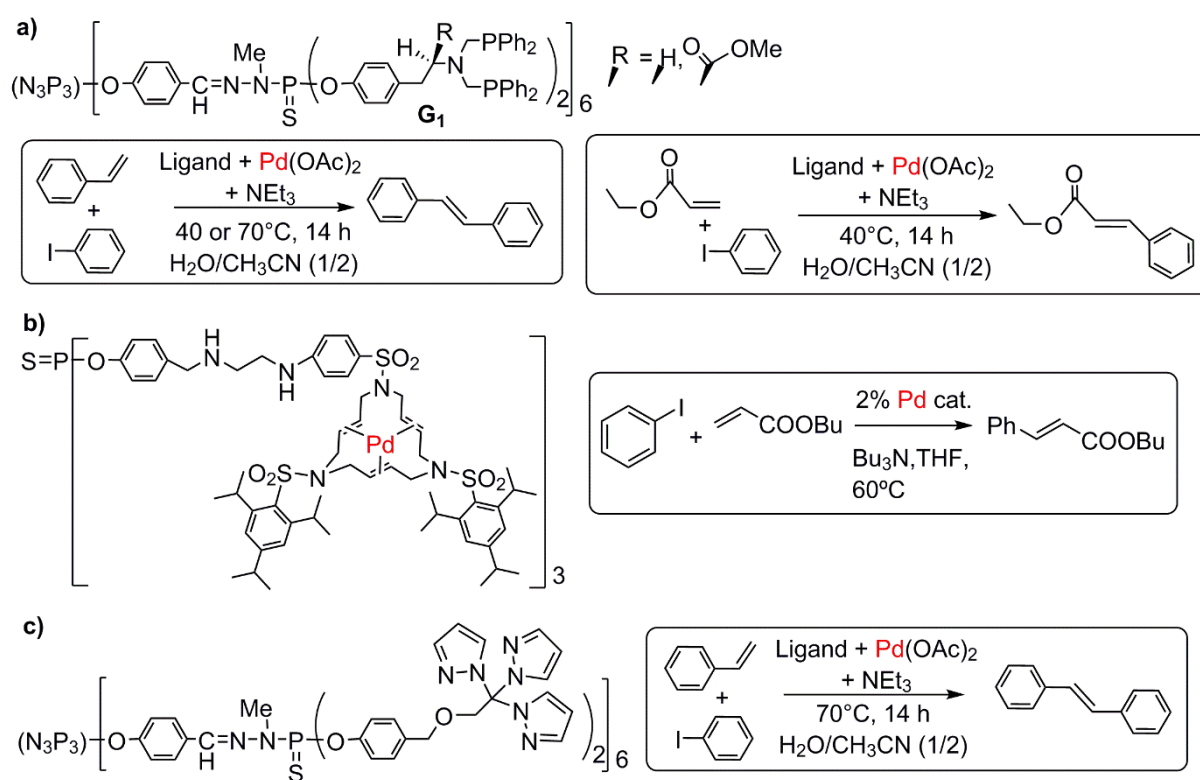


Fig. 4. Examples of Heck reactions using palladium complexes of phosphorhydrazone dendrimers as catalysts.

In the second example of Heck reactions, a family of phosphorus dendrimers containing on their surface 3, 6, 12, and 96 15-membered azamacrocycles has been synthesized, then Pd(0) has been tentatively complexed inside the macrocycles. Small dendrimers afforded discrete complexes, but high generations afforded palladium nanoparticles. Nanoparticles have been obtained also with small

dendrimers when using an excess of Pd(0). Both the discrete complexes and the Pd nanoparticles have been used for Heck reactions between iodobenzene with n-butyl acrylate in basic media (Fig. 4b). Recycling and re-use was also attempted 4 times, with the same efficiency when using the discrete complex of generation 0. Surprisingly, an increase in the catalytic efficiency was observed with the number of recycling cycles in the case of the Pd nanoparticles, in particular those obtained from small generations. This finding was ascribed to the decrease in the size of the nanoparticles when the number of recycling cycles increased [37].

Very recently, a first generation dendrimer having “scorpionate” ligands based on tris-2,2,2-(1-pyrazolyl)ethanol was used for the complexation of palladium (Fig. 4c). The complex has been used in Heck reactions between styrene and iodobenzene. The dendrimer was a more efficient catalyst (63% conversion) than the corresponding monomer (24% conversion), used in the same conditions [38].

2.1.4. Sonogashira couplings

The coupling of a terminal sp hybridized carbon atom from an alkyne with a sp² carbon of an aryl or vinyl halide (or triflate), affording a C-C bond is commonly termed as a Sonogashira coupling [39]. Experiments have been carried out, using the phosphorhydrazone dendrimers shown in Fig. 2a, Fig. 4a and Fig 4c. The catalysed reaction between phenylacetylene and iodobenzene was carried out in mild conditions (40°C), using 1 mol% of catalyst (Fig. 5). The generation 3 (Fig. 2a) was found slightly more efficient (72% conversion) than the first generation (Fig. 4a) (69%) and the monomer (66%), displaying a slightly positive dendritic effect [29]. In the case of the scorpionate derivatives (Fig. 4c), the first generation of the dendrimer and the monomer have the same efficiency [38].

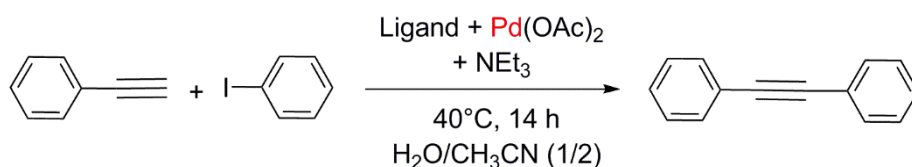


Fig. 5. Sonogashira coupling, using the dendrimers shown in Fig. 2a, Fig. 4a and Fig. 4c as ligands.

2.1.5. Allylic alkylations

Pd-catalyzed asymmetric allylic alkylation is a powerful method for simplifying the synthetic strategy towards complex molecular targets, using a wide range of classes of compounds [40]. Two families of phosphorhydrazone dendrimers bearing chiral ligands have been used as catalysts for asymmetric allylic alkylation of *rac*-(*E*)-diphenyl-2-propenyl acetate (and pivalate), affording 2-(1,3-diphenylallyl)-malonic acid dimethyl ester. In the first case, a third generation dendrimer having chiral phosphine-imine ligands as terminal functions was used in different conditions (Fig. 6a). The conversion was quantitative in all cases, and the enantiomeric excesses were found to be good to very good (ee from 90% to 95%) [41].

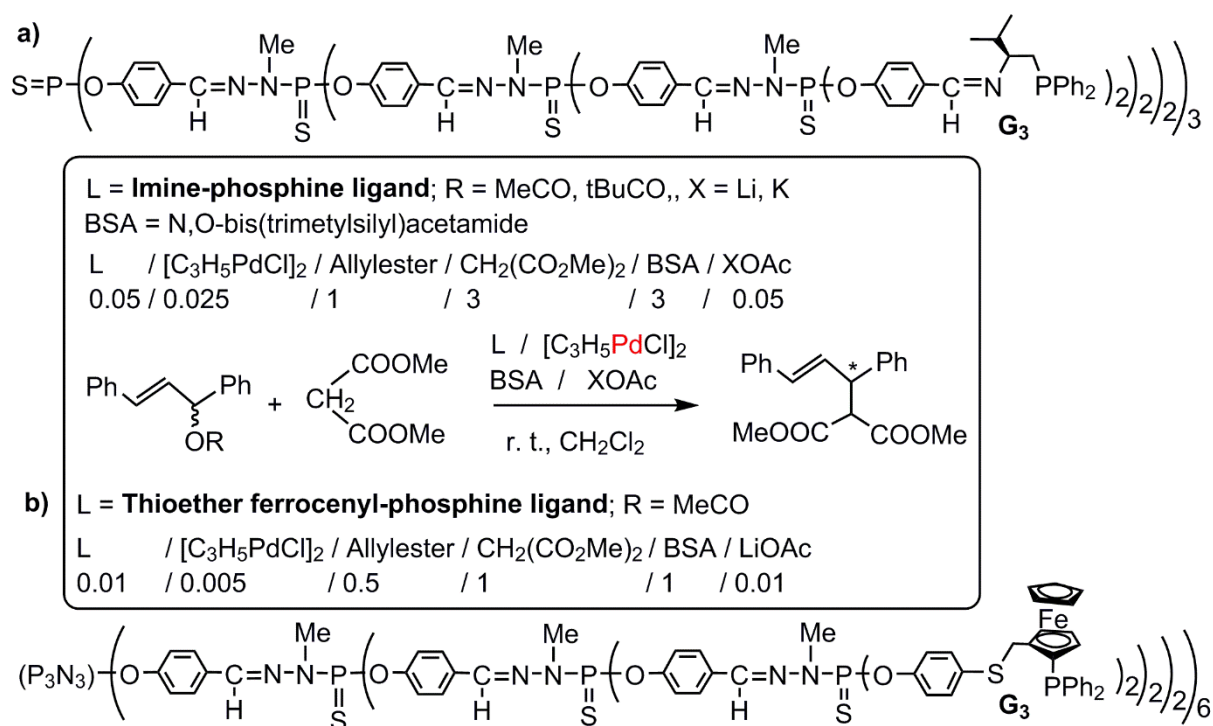


Fig. 6. Two examples of asymmetric allylic alkylations using phosphine-imine Pd-complexes (a), or thioether ferrocenyl phosphine Pd-complexes (b) as catalysts.

The same allylic alkylation reaction was carried out with a family of dendrimers having thioether ferrocenyl phosphine ligands as terminal functions, synthesized from generation 1 to generation 4 (Fig. 6b). The enantiomeric excesses are between 90 and 93%. No influence of the generation on the yield and ee has been observed [42].

2.2. Catalysis with ruthenium complexes

The use of easy-to-prepare and stable ruthenium(II) catalysts has tremendously contributed to the discovery of cheaper and efficient catalytic systems, milder reaction conditions, and new reactions in various media, in particular for the activation of C-H bonds [43]. In the case of phosphorus dendrimers, ruthenium complexes of phosphines have been used as catalysts in different types of reactions, such as Knoevenagel condensations, Michael additions, hydrogenation, hydration, and isomerisation of allylic alcohols.

2.2.1. Knoevenagel condensations

Knoevenagel-condensation reactions have emerged as a powerful protocol that not only allows the preparation of highly diverse molecules, but also permits the efficient synthesis of complex heterocyclic compounds starting from simple substrates [44]. Complexation of phosphorus dendrimers of generations 1 and 3 bearing diphosphine terminal groups with $\text{RuH}_2(\text{PPh}_3)_2$ afforded catalysts efficient for the Knoevenagel condensation involving malonitrile and cyclohexanone (Fig. 7a). Both generations are more efficient than the corresponding monomer, and they could be recovered by precipitation and reused two times without significant loss of catalytic activity. The third generation was also used for Knoevenagel condensation involving ethyl cyanoacetate and N-benzylideneaniline, and was also shown more efficient than the monomer (Fig. 7b) [33].

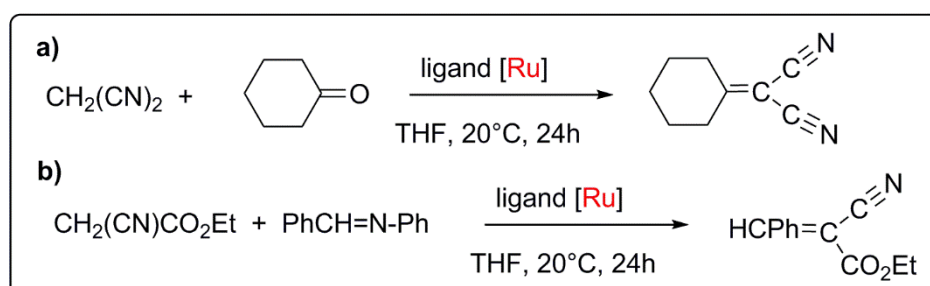
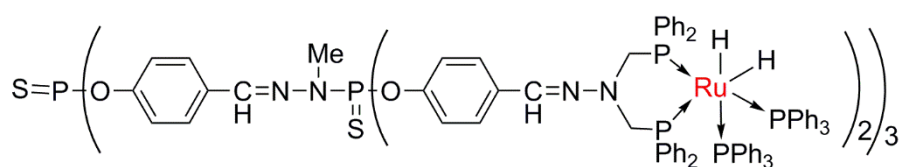


Fig. 7. Two examples of Knoevenagel condensations involving dendritic Ru complexes of diphosphines.

2.2.2. Michael additions

The catalytic asymmetric Michael reaction is among the most important organic synthetic procedures for a stereoselective C-C bond forming reaction, partly due to its high atom economy; Ru complexes are particularly efficient for catalysing such reaction [45]. In the case of phosphorus dendrimers, the third generation bearing diphosphine terminal groups complexed with $\text{RuH}_2(\text{PPh}_3)_2$, as well as a third generation dendron bearing only one diphosphine Ru complex at the core were used for catalysing the diastereoselective Michael addition involving ethyl cyanoacetate and diethylethylidene malonate (Fig. 8). Quantitative conversions were observed in both cases, with no significant difference in the diastereoisomeric ratio. Both dendritic catalysts could be recovered and reused 2 times without loss of activity or of enantioselectivity [33].

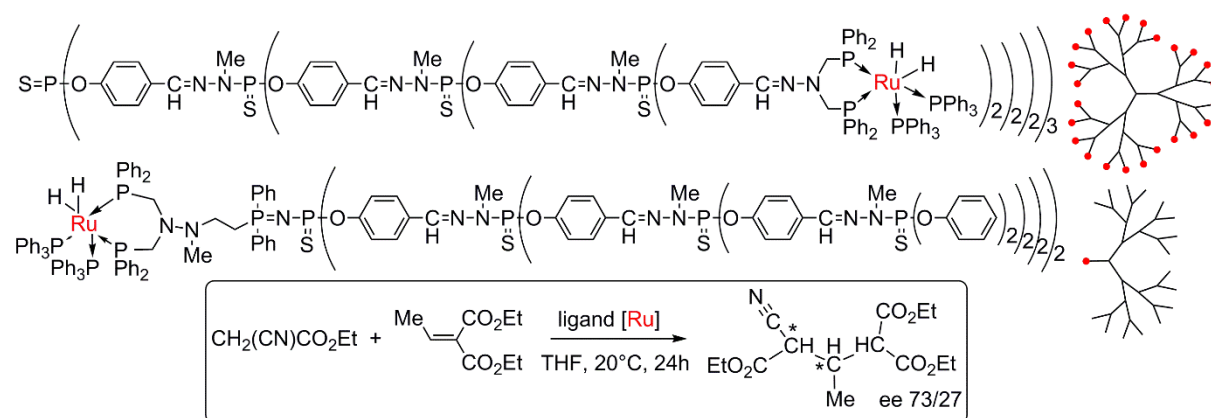


Fig. 8. Diastereoselective Michael addition catalysed by generation 3 dendrimer and dendron.

2.2.3. Hydrogenation reactions

Hydrogenation reactions catalysed by Ru (but also Rh) complexes is a core technology, which is used since a long time in academic laboratories, but also in industry [46]. A single example of such reaction has been carried out with dendritic phosphorhydrazone compounds. In fact, a series of dendrons, having a long alkyl chain at the core and phosphine terminal functions were used to generate and

stabilize Ru nanoparticles, prepared by milling under air ruthenium chloride (RuCl_3), sodium borohydride (NaBH_4) and the phosphorhydrazone dendrons of generations 0 to 2. The Ru nanoparticles were used for catalysing efficiently the hydrogenation of styrene (Fig. 9). Ethylbenzene was obtained as the almost exclusive product (yield > 99%), ethylcyclohexane being observed only in trace amounts even if the reaction time is set to 72 h and the temperature increased to 100°C . Whatever the length of the alkyl chain, the systems involving second-generation dendrons displayed higher catalytic activity compared to those involving smaller dendrons. This difference is consistent with the fact that the surface of the nanocomposite systems is less hindered when higher generation dendrons are involved, thus allowing an easier access for the substrates [47].

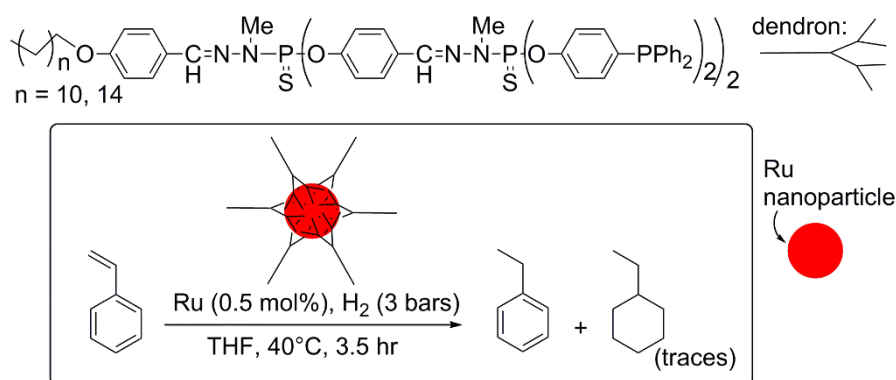


Fig. 9. Dendrons for complexing Ru nanoparticles used as catalysts for the hydrogenation of styrene.

2.2.4. Hydration of terminal alkynes

The catalytic addition of water to terminal alkynes (hydration) generates valuable carbonyl compounds from unsaturated hydrocarbon precursors. Diverse Ru complexes have been used as efficient catalysts for such purpose [48]. A series of phosphorhydrazone dendrimers (generations 1 to 3) having phosphotriaza adamantane (PTA) as terminal functions, used for complexing $\text{Ru}(p\text{-cymene})\text{Cl}_2$, was found moderately efficient catalysts for the hydration of phenylacetylene (Fig. 10a). A slight increase in the selectivity to ketone was observed from the monomer (91%) to the second and third generation dendrimers (98%), but the percentages of conversion after 48 h at 90°C is only 58% with 5% of the first generation, which is the most efficient catalyst for this series [49]. Other

conditions have been used (17h, 1% catalyst, addition of 10% H₂SO₄ as co-catalyst), and another series of PTA dendrimers, bearing twice the number of terminal functions at the same generation compared to the previous case (Fig. 10b). In these conditions, the selectivity in ketone is 100% with all dendrimers, and the dendrimer shown in Fig. 10b was shown more efficient than the first and second generation dendrimers of type shown in Fig. 10a [50]. It was shown later that the monomeric catalyst affords a larger percentage of aldehyde (up to 50% after 4h) [51].

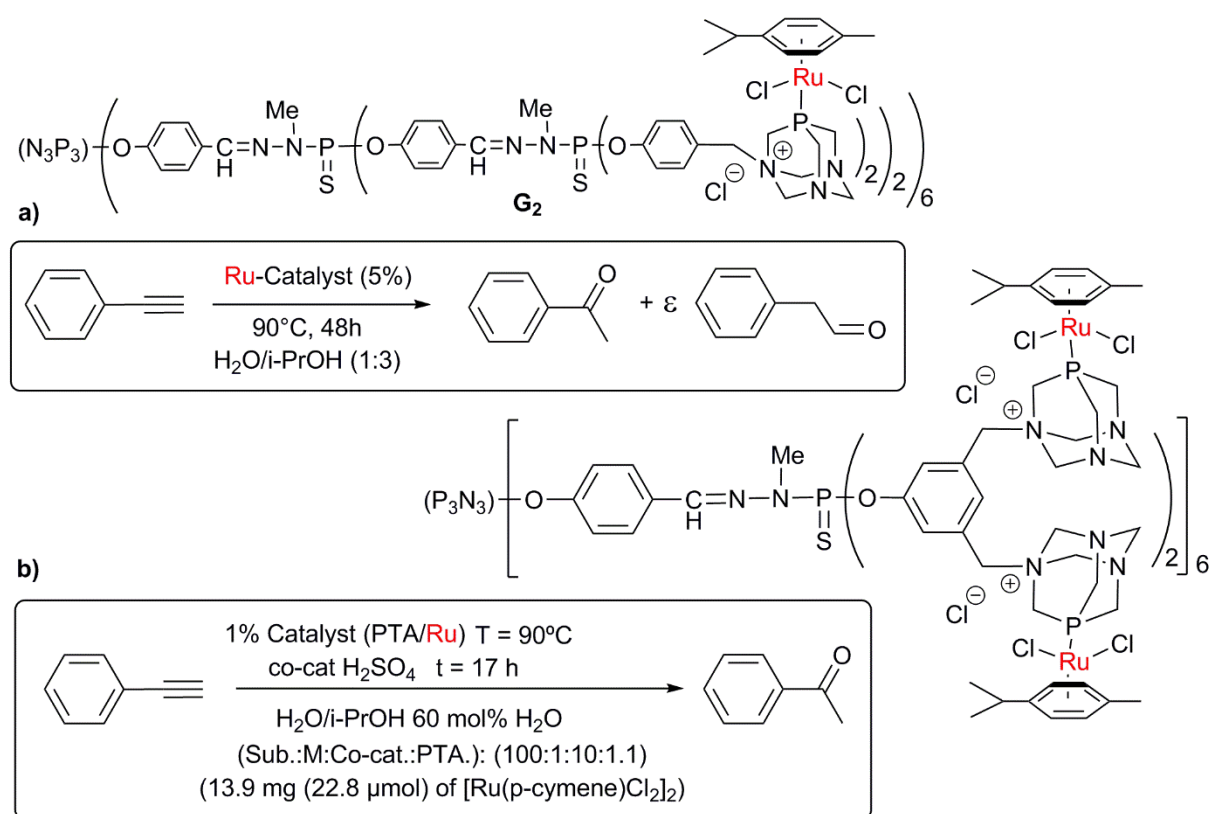


Fig. 10. Hydration of phenyl acetylene, catalysed by PTA-Ru dendritic complexes.

2.2.5. Isomerisation of allylic alcohols

The conversion of allylic alcohols to saturated carbonyl compounds is a useful synthetic process, which can be catalysed by numerous transition metal complexes [52]. Without a catalyst, this reaction necessitates two steps (reduction of alkene and oxidation of alcohol), whereas it is performed one-pot with a catalyst. In the case of phosphorhydrazone dendrimers, such reaction has been used as test for several types of complexes. All the examples concern the isomerisation of 1-

octan-3-ol to octan-3-one. The first catalytic dendrimer family was the one shown in Fig. 10a, with PTA terminal functions complexing ruthenium. A nice positive dendrimer effect [53] was observed with this family concerning the efficiency of the isomerisation, conversion after 8h being 38% (monomer), 63% (G_1), 54% (G_2), and 98% (G_3), respectively (Fig. 11a) [49]. The second family, from generation 1 to generation 3, was constituted of dendrimers having phosphine ruthenium complexes linked to the dendrimers through a linker connected to a ferrocene. The linker was either nothing, or one aromatic, or two aromatic rings (Fig. 11b). The larger complexes were poorly soluble in THF, thus the reaction was carried out in 1,2-dichloroethane (DCE). All the dendritic catalysts gave higher activities than their monomeric analogues. The family with one aromatic as linker was shown to be the most efficient catalyst, with a turn over frequency (TOF) of 267 (monomer), 400 (G_1 and G_2), and 480 (G_3), to be compared to 109, 240, 200, and 200, respectively, with no linker between the ferrocene and the phosphine. All these compounds display electrochemical properties, mainly due to the presence of the ferrocene [54].

These compounds containing a redox-active ferrocene moiety are highly suitable for redox-switchable catalysis, in which a redox-active functionality incorporated within a ligand framework allows the catalytic activity to be influenced in situ [55]. The first generation with one aromatic as linker, and the corresponding monomer were used as redox switchable catalysts in the isomerisation of 1-octan-3-ol to octan-3-one. On oxidation with $[\text{Fe}\{\eta^5\text{-C}_5\text{H}_4\text{C}(\text{O})\text{Me}\}\text{Cp}][\text{BF}_4]$ the reaction rate was markedly reduced. After reduction with $[\text{FeCp}^*_2]$ ($\text{Cp}^* = \text{C}_5\text{Me}_5$), full conversion was observed with a degree of activity similar to that of the original catalyst before oxidation. These findings clearly demonstrate an electronic effect of the redox active ligand on the catalytic efficiency. The oxidized ferrocene withdraws electron density from the phosphine, decreasing its basicity, and creating an electron-poor transition metal. The consequence is a far less active catalyst for the isomerization of allylic alcohols, as observed. This is the very first example of a catalytic dendrimer for which it is possible to reversibly tune the electronic properties, and thus the catalytic properties in situ [56].

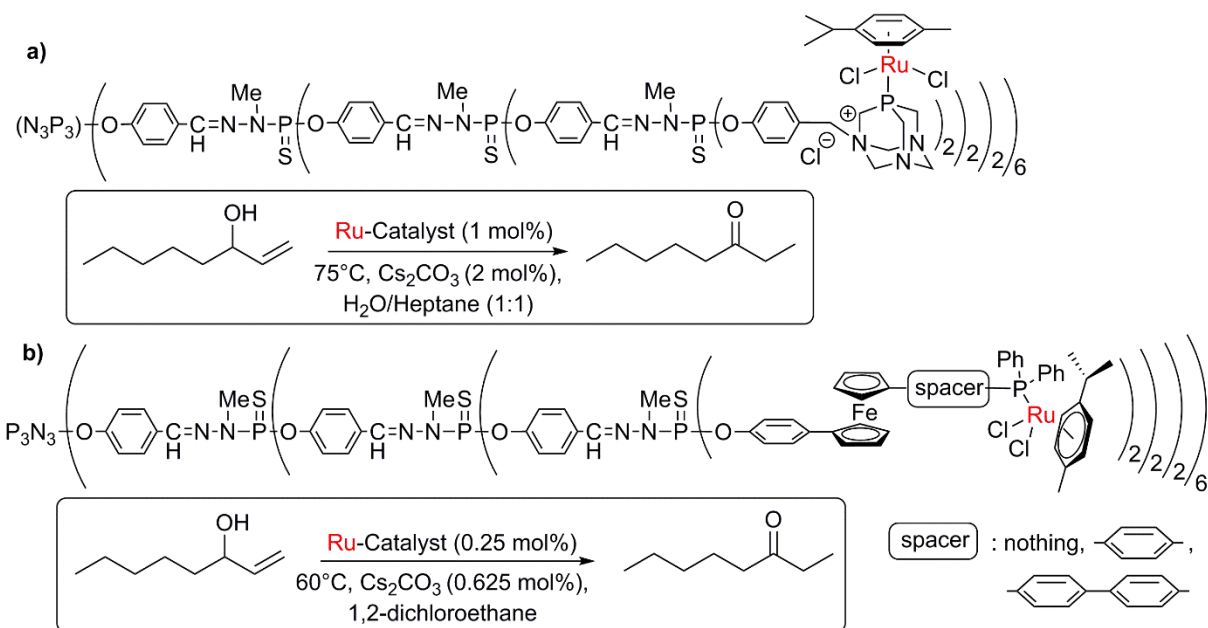


Fig. 11. Conversion of 1-octan-3-ol to octan-3-one, using dendritic ruthenium complexes of PTA (a) or of ferrocenylphosphine (b) as catalysts.

2.3. Catalysis with rhodium complexes

Rhodium catalysts in the formation of carbon-carbon bonds show complementary reactivity to other catalyst systems. Furthermore, the reactions can frequently be performed in the presence of water or even in water as the exclusive solvent [57]. In the case of phosphorus-containing dendrimers, the very first example of rhodium catalysts concerned a family of dendrimers having phosphines not only on the surface, but also at each branching points. The other cases concern phosphorhydrazone dendrimers with rhodium complexes as terminal functions.

2.3.1. Hydrogenation reactions

As indicated in part 2.2.3., hydrogenation is a very important area of chemistry, and besides ruthenium catalysts, rhodium catalysts are also extremely useful for catalysing hydrogenation reactions [46]. The family of dendrimers having rhodium catalysts at each branching point, including at the core, have been synthesized up to generation 4 (46 Rh complexes). All these dendrimers and the corresponding monomer were used as catalysts in the hydrogenation of dec-1-ene (Fig. 12). The

catalytic activity (turnover number = $\text{mol}_{\text{prod}}/\text{mol}_{\text{cat}} \approx 200$, turnover frequency = $\text{mol}_{\text{prod}}/\text{mol}_{\text{cat}}/\text{h} \approx 400$) was found to be similar in all cases. The largest dendrimer could be recovered and reused one time [58].

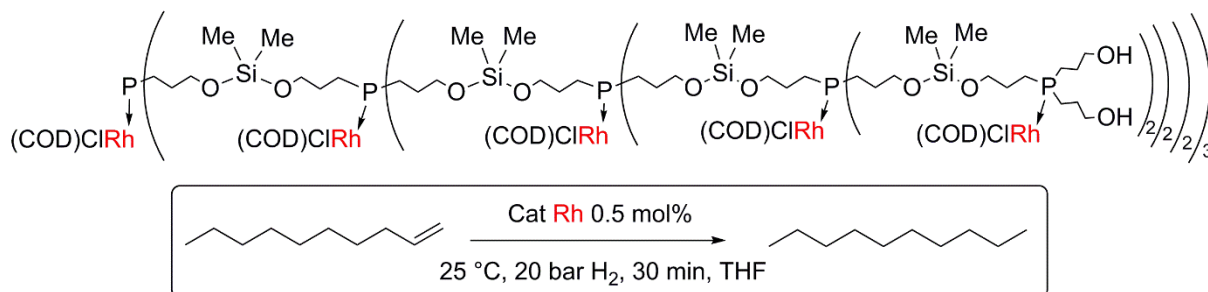


Fig. 12. Hydrogenation using a phosphorus-containing dendrimer bearing rhodium complexes at each branching point as catalysts (COD = cyclooctadiene).

2.3.2. Isomerisation of allylic alcohols

As shown in part 2.2.5., isomerisation of allylic alcohols can be catalysed by numerous transition metal complexes [52]. Besides Ru complexes, an attempt has been made using Rh complexes of PTA, in water (Fig. 13). However, the catalytic efficiency was poor, with only 11% conversion with the first generation, which was the most efficient [50].

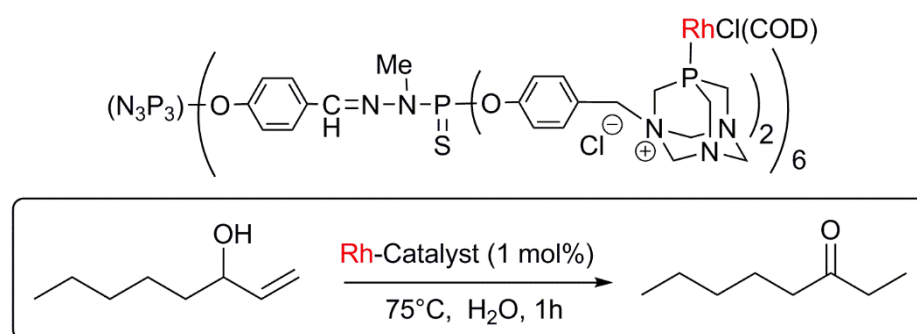


Fig. 13. Attempted isomerisation of allylic alcohol using a Rh catalyst.

2.3.3. [2+2+2] cycloadditions

Cyclotrimerisation, also named [2+2+2] cycloaddition, is an elegant and atom-efficient process for the synthesis of aromatic carbo- and heterocycles, involving the formation of several C–C bonds in a

single step. A variety of organometallic complexes can catalyse such reaction [59]. Phosphoramidite ligands immobilized on the surface of phosphorhydrazone dendrimers from generation 1 to 3 have been used to complex rhodium, and then to catalyse two examples of [2+2+2] cycloadditions. In the first case, the reaction between N-tosyl 1,6-diyne and phenylacetylene has been attempted (Fig. 14a). Considerably enhanced catalytic activity was observed when using dendrimers (G_1 – G_3) as ligands, which afforded almost quantitative yields, as compared to the model monomer (61% yield). The dendrimers could be recovered and re-used 3 times, without reduction in the yield. Then, the capacity for enantiodiscrimination of the catalytic system was checked in the reaction between N-tosyl 1,6-diyne and 2-methoxynaphthalene alkynyl derivatives. As in the previous cases, the dendrimers enabled almost quantitative conversion of the substrate into the product. Furthermore, the dendrimers induced an excellent enantioselectivity (96–98% ee when $R = P(O)(OEt)_2$, Fig. 14b), whereas the monomer gave only residual enantioselectivity (<5% ee). This was the very first example of a dendrimer displaying such an enhancement of the stereoselectivity [60].

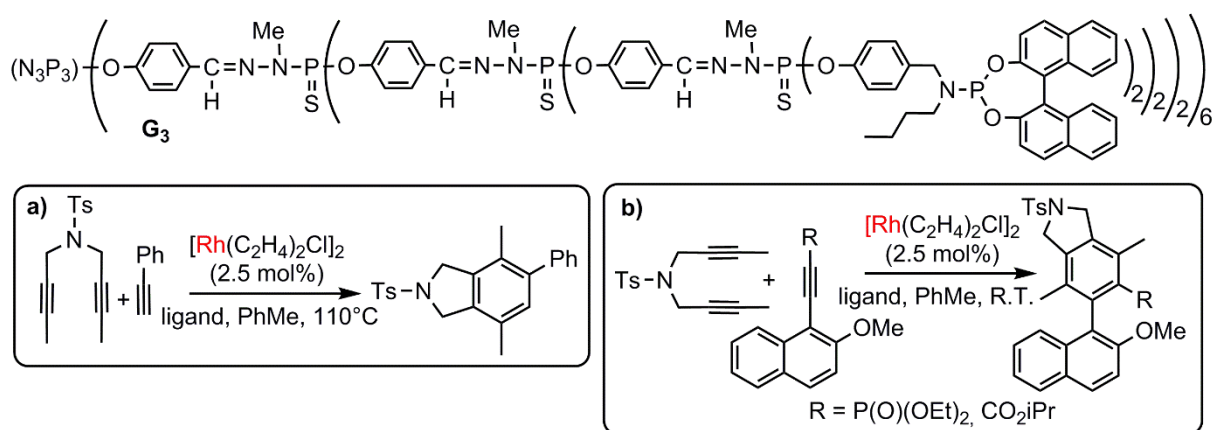


Fig. 14. Dendritic phosphoramidite ligands complexing rhodium, and used as catalysts for [2+2+2] cycloaddition reactions.

2.4. Catalysis with scandium complexes

Besides classical transition metal complexes, scandium complexes, in particular those derived from $Sc(OTf)_3$ constitute a special type of Lewis acids with a unique and extraordinary high catalytic activity in many organic reactions [61]. The Friedel–Crafts reaction of aromatic compounds with aldehydes or

ketones constitutes one of the most fundamental reactions in organic chemistry [62], which can be catalysed with scandium complexes. The grafting of terpyridine ligands as terminal functions of phosphorhydrazone dendrimers gave a family of dendrimers (generations 1 to 4) able to complex scandium triflate. These dendrimers were used as catalysts for Friedel–Crafts acylations of a wide range of aromatics (Fig. 15). The acylation of anisole with acetic anhydride was first performed. In the absence of ligand, the corresponding ketone was obtained in 60% yield. In the presence of the monomeric ligand, the catalytic activity decreased (47%), then increased with the dendrimers when the generation increased (55% for G₁, 59% for G₂, 66% for G₃, and 80% for G₄), all reactions being performed in refluxing acetonitrile. The same reaction was then attempted with a range of derivatives of benzene, but no reaction was observed with some substrates such as thioanisole or dimethylaniline, thus it was chosen to use micro-waves (MW) irradiation to try to perform these challenging reactions. Acylation of thioanisole could successfully be achieved in 80% yield and that of dimethylaniline in 95% yield under MW irradiation. In these conditions, the catalytic system was found efficient for at least four consecutive runs without loss of activity. Furthermore, the re-use was attempted when changing the substrate at each run. Twelve consecutive reaction cycles were carried out with no or little loss of activity, as shown by the comparison between the yields obtained when recycling the G₄ dendrimer catalyst or when carrying out a single run (Fig. 15). This dendritic system displays unprecedented recyclability compared to any other system known to promote Friedel–Crafts acylations [63].

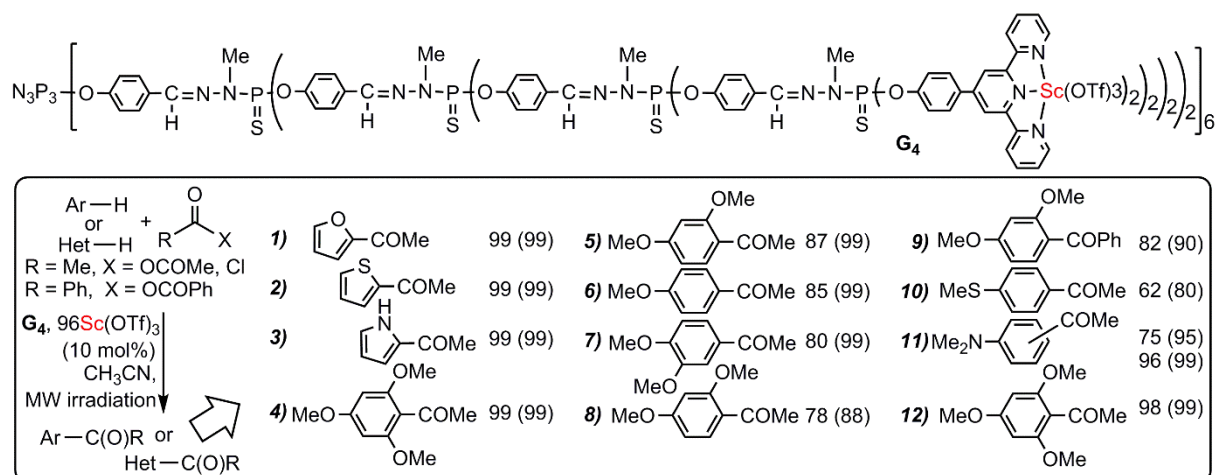


Fig. 15. Terpyridine ligands complexing scandium as terminal functions of phosphorhydrazone dendrimers, used as catalyst in Friedel–Crafts acylations. Runs 1 to 12 refer to the recycling of the dendrimer, changing the substrate at each run. The yields obtained by recycling the dendrimer are compared with the yield obtained in a single run for each product, in parenthesis.

3. Catalysis for C-O couplings with copper complexes

The copper-mediated C(aryl)-O (and C(aryl)-N) bond formation is an important transformation that has been developed to include a wide range of substrates [64]. Three examples have been carried out with phosphorhydrazone dendrimers. The first one concerned dendrimers functionalized with pyridine imine terminal functions, suitable for the complexation of CuI. The monomer and dendrimers from generation 1 to 3 were synthesized and used for catalysing the coupling of 3,5-dimethylphenol with PhI. The third generation was the most efficient. Then, the coupling of E- β -bromostyrene with 3,5-dimethylphenol was attempted (Fig. 16a). The third generation catalyst induced 91% yield after 4 days at room temperature whereas the monomer in the same conditions, induced a poor conversion of only 35% [65].

Another family of dendrimers having diketones as terminal functions was also used for the complexation of CuI, from the monomer to the fourth generation. All of them were used for arylation of 3,5-dimethylphenol by bromobenzene, eventually substituted in *para* position, in the presence of caesium carbonate at 120 °C in N,N-dimethylformamide (DMF) (Fig. 16b). Surprisingly, none of these dendrimers could be reused for another catalytic run. This is unusual, thus the composition of the filtrates was analysed. It was shown that nucleophilic substitutions onto the P–O bonds occurred fast, and that the dendrimeric diketones were quantitatively converted into monomers within 3 h. This fast degradation in the conditions used explains why this family of dendrimers could not be recovered and reused [66].

Copper-promoted arylation of aromatic amines has been known for a century as the classical Ullmann reaction, which requires harsh prolonged heating at 200°C or higher. It has been shown later that appropriate ligands can modulate the reactivity of copper to afford suitable catalysts for such reaction [68]. The copper complexes already shown in Fig. 16a have been used as catalysts in the arylation of pyrazole with aryl halides (Fig. 17). The corresponding monomeric complex has no activity in this reaction. In the case of arylation with iodobenzene, all the dendrimers enabled quantitative conversion of substrate into product within 20 h at 80°C. In the case of arylation with bromobenzene used in the same conditions, the third generation was the most efficient and afforded the product in 80% yield. The same family of copper complexes has been used also as catalyst in the N-vinylation of pyrazole. Quantitative yields in E-styrylpyrazole were obtained at 25°C within 4 days with the third generation dendrimer complex, whereas the monomeric complex afforded the same product in only 70% yield in the same conditions [65].

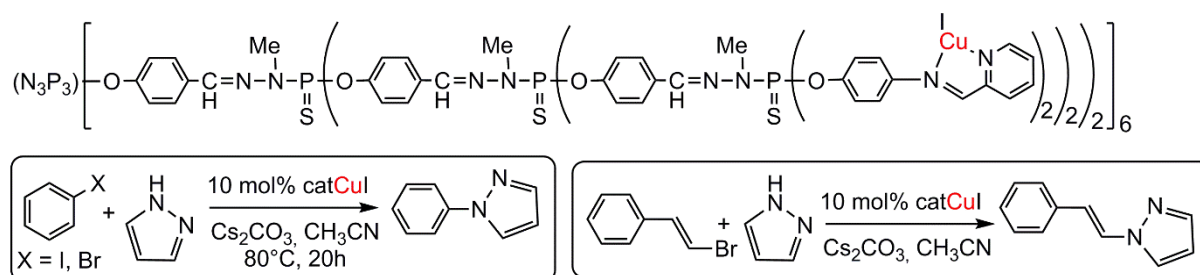


Fig. 17. Examples of copper-promoted arylation and vinylation of pyrazole.

5. Organocatalysis with phosphorus-containing dendrimers

This review has shown in the previous paragraphs the use of dendritic complexes of transition metals, then of the less common scandium, and finally of the less expensive copper. However, a large part of the future of catalysis will certainly concern catalysis without metal, also named organocatalysis [69]. The field of dendrimers used as organocatalysts has been reviewed recently [70]. In the case of phosphorhydrazone dendrimers, three examples are known. The first one concerns the Jørgensen–Hayashi catalyst ((S)- α,α -diphenylprolinol trimethylsilyl ether) linked to the surface of phosphorhydrazone dendrimers, but also on the surface of magnetic, polymer-coated

cobalt/carbon (Co/C) nanobeads. These organocatalysts displayed high activities and selectivities in the Michael additions of a wide range of aldehydes to different nitroolefins (Fig. 18). Both the yield and the ees were excellent with both types of supports. Surprisingly, the recovery was by far more efficient with the dendritic catalyst (third generation) than with the nanoparticle catalysts. Recycling tests with the G₃ dendrimer were carried out by changing the substrate at each run; Michael adducts could successfully be prepared in 7 consecutive runs with very high yields and selectivities [71].

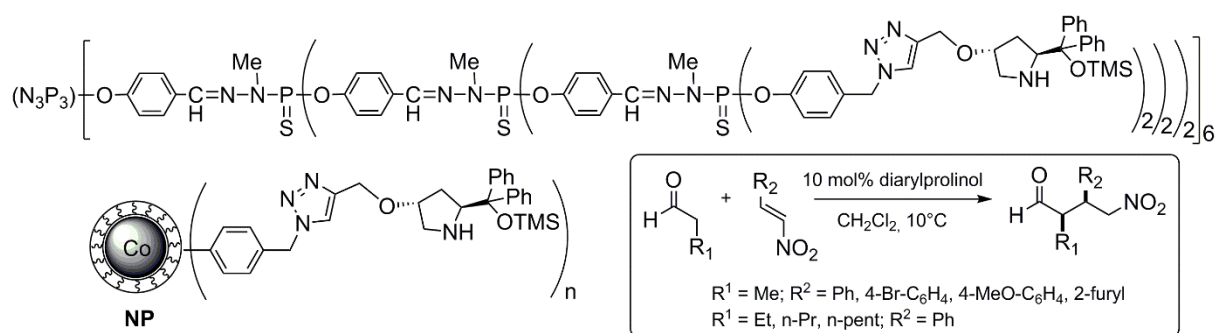


Fig. 18. (S)- α,α -diphenylprolinol trimethylsilyl ether grafted to dendrimers or to the cobalt nanoparticles, both being used as organocatalysts for Michael additions.

Numerous efforts have been devoted to the development of cinchona derivatives as catalysts for enantioselective reactions [72]. Dendritic organocatalysts based on (+)cinchonine derivatives have been synthesized (generations 1 and 4) and used in the α -amination of several β -dicarbonyl compounds, using only 4% of catalyst (instead of 20% classically) (Fig. 19a). A large number of β -dicarbonyl compounds was tested; it was shown that the enantioselectivity is better for cyclic 1,3-ketoesters. Generation 1 was found the most efficient catalyst. Its recovery and reuse over 10 cycles was demonstrated without loss of activity or enantioselectivity [73].

Cinchona derivatives have been used also as phase transfer catalysts for asymmetric synthesis [74]. (+)-cinchoninium salts on the surface of the first generation of phosphorhydrazone dendrimer have been obtained by the quaternisation of the quinuclidinic N atom of cinchonine. This dendrimer has been applied to the asymmetric alkylation of active methylene compounds, especially of a glycinate with benzyl bromide as first test (Fig. 19b). Then, the scope of the catalytic enantioselective

alkylation of the N-(diphenylmethylene)glycine tert-butyl ester with various alkylating agents was evaluated. Good yields (76–87%) and enantioselectivities (76–89%) were obtained, which showed no significant influence of the electronic effects of the substituents [75].

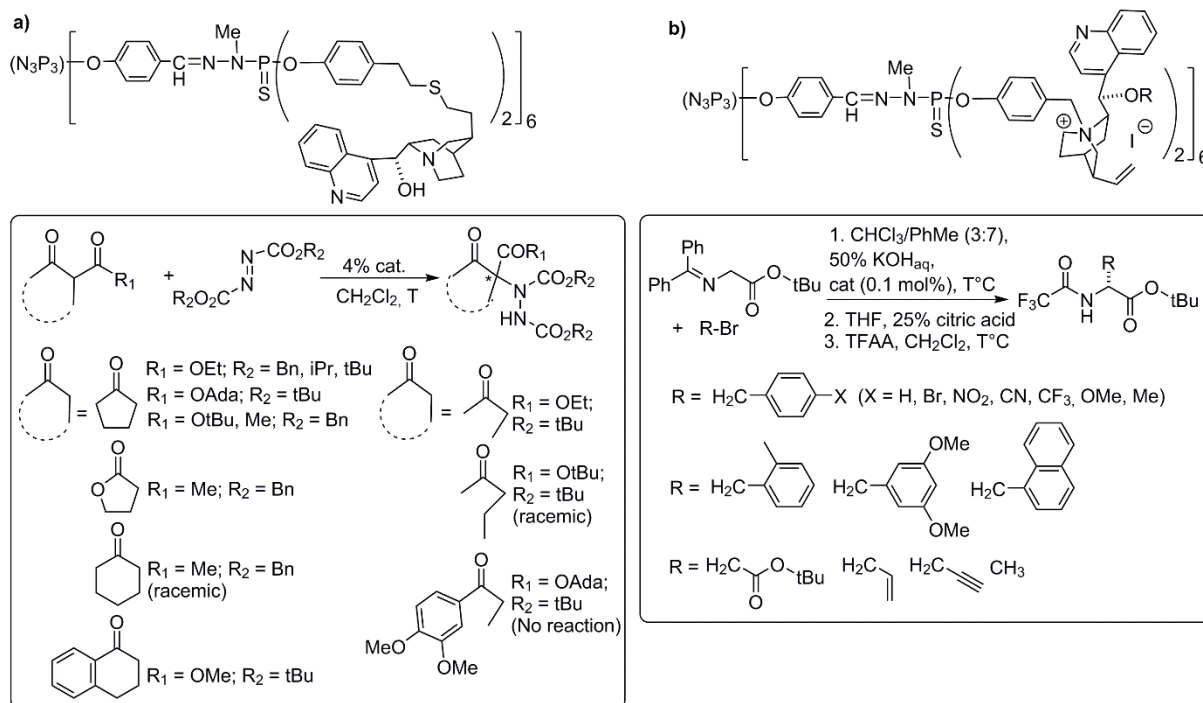


Fig. 19. Organocatalysis with dendrimers bearing cinchonine (a) and cinchoninium salts (b) as terminal functions.

6. Conclusion

Compared to classical monomeric catalysts, dendritic catalysts present in many cases two advantages: an increased efficiency, and an efficient recycling, of course considering that the quantity of catalytic sites is identical within a series of catalytic experiments. The increased efficiency is not always observed, but spectacular examples are known, such as a peptide dendrimer of generation 4 that is 140 000-fold more efficient than the reference catalyst [76]. This dendrimer effect [53] has been observed frequently with phosphorhydrazone dendrimers. For instance, an increase of the reaction yield when the generation of the dendrimer increases has been observed in the copper catalysed arylation of pyrazole with bromobenzene, in which the monomer has practically no activity (Fig. 17 [65]), or in the ruthenium catalysed isomerisation of 1-octan-3-ol to octan-3-one

(Fig. 11a [49]). Furthermore, a spectacular influence on both the yield and the enantioselectivity has been observed in the rhodium catalysed [2+2+2] cycloaddition reactions (Fig. 14 [60]). The origin of the dendrimer effect is not well understood, but it should have some connections with the multivalency (or polyvalent) effect, widely found in the Nature [77].

The other interesting point when using dendrimers is the possibility to recover and to reuse it in another catalytic run. The dendritic catalysts are generally used in solution in organic solvents or in water, but due to their large size, they can be separated from the products, eventually using a selective membrane. More frequently the recovery is carried out simply by adding a solvent in which the products are soluble, but not the catalytic dendrimer (diethylether in the case of the phosphorhydrazone dendrimers). This type of recovery can be very efficient, as illustrated by 12 runs for Friedel–Crafts acylations with scandium (Fig. 15 [63]). The use of magnetic nanoparticles as supports has also led to a very efficient recovery and reuse, also in 12 consecutive runs for Suzuki couplings with palladium (Fig. 2c [31]).

An additional advantage when using dendrimers is the decrease of wastes, for a greener chemistry. The increased efficiency compared to monomers means that less metal is needed for the catalysis. The possibility to recover easily the dendritic catalysts means that the purification of the products will be easier, as it will not be contaminated by the catalyst. Furthermore, the metal can be more firmly bound to a dendritic catalyst than to a monomeric catalyst, as illustrated by the undetectable leaching of palladium in the coupling of bromobenzene derivatives with phenyl boronic acid (Fig. 2b [30]). However, an easiest way to avoid the leaching of metal is to perform catalysis without metal, it means to perform organocatalysis. Two examples with phosphorhydrazone dendrimers has shown the pertinence of this approach (Fig. 19 [73, 75]), and recovery and reuse over 10 cycles was also demonstrated without loss of activity or enantioselectivity. Most of the work concerning catalysis with dendrimers demonstrates that the outcome of the catalytic reactions is generation dependant, but not linearly, and the “best” generation is not always the same. There is often an optimum size, which is unpredictable, as it can be the generation 0 [31, 37], or generation 1 [49, 50], or generation

2 [67], or generation 3 [65], or generation 4 [63], depending on the type of complexes and the type of catalytic experiment studied.

However, dendritic complexes are not only useful as catalysts. Indeed, the anti-cancer properties of some of them have been tested recently, and interesting results have been obtained. The generation 0 of the types of ruthenium complexes shown in Fig. 11a has been tested for its interaction with supercoiled DNA, to afford relaxed DNA, and it was shown as efficient as cisplatin [51]. Copper complexes, in particular analogous to the one shown in Fig. 17, have anti-cancer properties towards a range of solid and liquid cancer cells [78], with original mechanism of action [79], and the corresponding gold complexes are even more potent [80].

What is the future for dendrimers in catalysis? It is certainly bright in academic laboratories, as dendrimers outperform monomeric catalysts in many cases, and it is even possible to perform catalysis for which the monomer has no activity. A cheaper alternative to dendrimers are hyperbranched polymers [81]. However, relatively little research has been carried out regarding immobilisation of catalysts on hyperbranched polymers, compared to dendrimers. Indeed, the random statistical nature of hyperbranched polymers may limit any cooperativity between proximal group, thus precluding both the possibility to observe a “dendritic effect”, and a good reproducibility of the catalytic efficiency. However, hyperbranched polymers can be an interesting alternative when considering the encapsulation of metal nanoparticles having catalytic properties [82].

The question is still open concerning industrial uses of catalytic dendrimers. Indeed, catalysed industrial processes are well established and need so large investments that changes are done only when a large gap in the performances is foreseen. However, recent progresses in flow chemistry for the synthesis of molecules of industrial interest [83] may open new opportunities for dendrimers.

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