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# Metal Promoted Diels-Alder Reactions

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502

**Abstract:** The Diels-Alder cycloaddition between a (hetero)diene and a (hetero)dienophile can be performed with metal Lewis Acids. Such activation often increases the rate of the reaction and has an influence on the observed selectivity. The most recent advances on metal promoted Diels-Alder reactions are reviewed.



**Keywords:** Diels-Alder reaction, Catalysis, Selectivity, Asymmetric synthesis.

## 1. BACKGROUND INTRODUCTION

In 1928, German chemists Otto Diels and Kurt Alder reported the reaction of *p*-quinone with cyclopentadiene to afford a bicyclic product [1]. Although this reaction proved to be highly versatile (as demonstrated by the Nobel Prize awarded to the authors), reaction between other  $2\pi$  electrons systems (dienophiles) with  $4\pi$  electrons systems (dienes) still suffers from limitations. For instance, the geometry of the cycloadduct, depends on the configuration of the dienophile (*Z* olefins would give the *cis*-substituted product, whereas *E* olefins would give the *trans* one). The conformation of the diene is also important as the *s-trans* conformation (the most

worse the reaction can occur in a stepwise manner, thus furnishing diastereoisomeric products.

The reaction is in reality governed by frontier molecular orbitals (FMO). The lowest energy difference between the HOMO and the LUMO of the reactants is usually preferred (Fig. 1). The normal electron demand is the case where the HOMO of the diene is closer in energy to the LUMO of the dienophile. The opposite (interaction between the LUMO of the diene and the HOMO of the dienophile) is called inverse electron demand (IED). When there is (almost) no energy difference, the electron demand is neutral (NED). In addition, regioselectivity can be explained by matching the orbital coef-

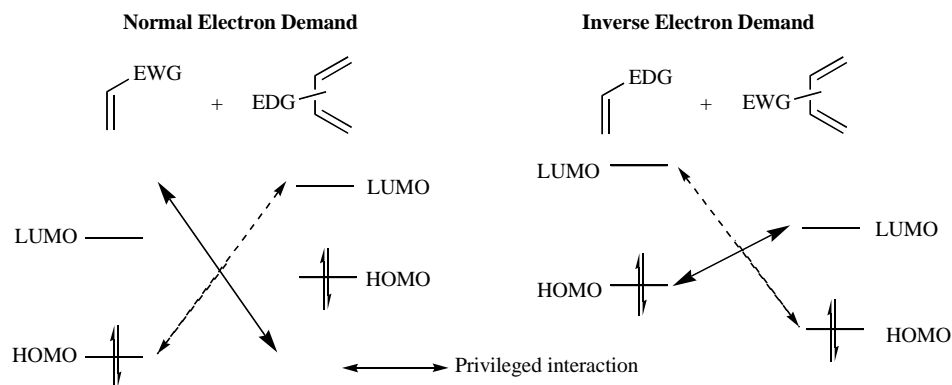


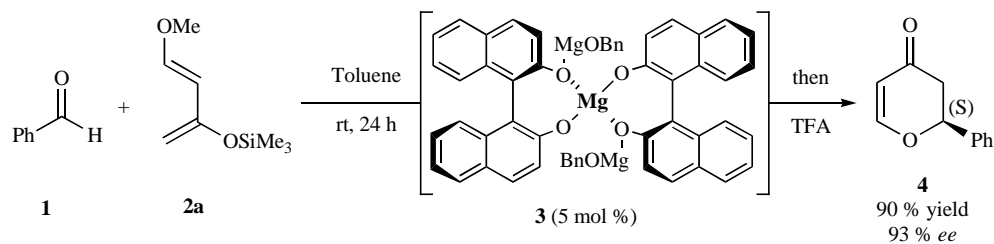
Fig. (1). FMO interactions diagram.

thermodynamically stable) is unreactive. Assuming the reaction pathway is synchronous and concerted the major product obtained is rather easily predicted. However, synchronicity can be biased or

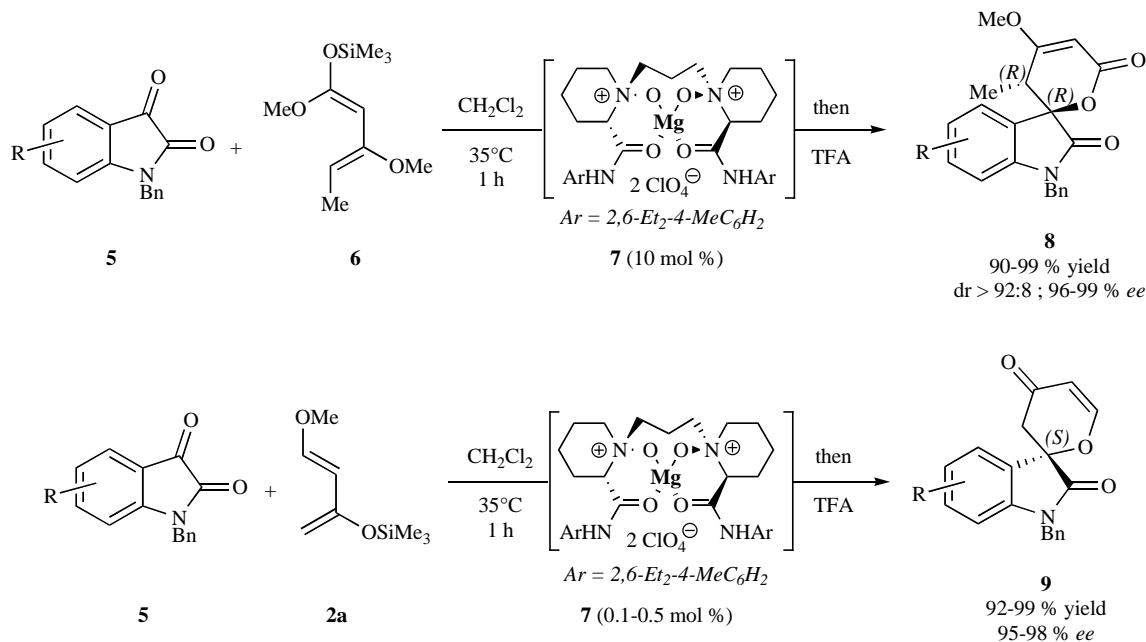
efficient of the frontier orbitals at each reactive atom. The largest lobe of the atom at the HOMO level (the most electron-rich) would preferentially react with the largest lobe of the atom at the LUMO level (the less electron-rich).

The transition state of such pericyclic reaction is usually very high in energy and often requires elevated temperature to proceed. Other modes of activation such as microwave irradiation [2-4] of

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Scheme 1.



Scheme 2.

high-pressure (1-20 kbar) [5,6] have been developed over the years to overcome such difficulties. The most reliable method is probably to reduce the energy gap between the HOMO and the LUMO. Introduction of an electron-withdrawing group on either diene or dienophile tends to deepen the orbitals energy (both the HOMO and the LUMO) whereas an electron-donating group tends to raise the energy levels of the frontier orbitals. However, introduction of such functional group is not an easy task, especially on complex molecules.

Therefore, two other strategies have been pointed out. The first one (HOMO-raising) relies on the formation of an enamine. The other one (LUMO-lowering) consists on the formation of either an iminium ion or on the complexation of a Lewis acid. The decrease in energy of the LUMO is related to the strength of the Lewis acid. From a general point of view, the Lewis acidity will increase along with the oxidation state of an element. In addition, the more dissociated the ligands are (increased cationic character), the more Lewis Acid it would be. For this reason, anions such as  $\text{BF}_4^-$ ,  $\text{SbF}_6^-$ ,  $\text{PF}_6^-$  are often used. Many Lewis acids are known and most of them are based on a central metal atom.

The aim of this review is to highlight the most recent advances (from 2009 to the end of 2014) in (Hetero-)Diels-Alder reactions promoted (or catalysed) by a metallic Lewis acid.

## 2. s-BLOCK METALS

Elements of the first two columns of the Periodic Table belong to the s-block. Alkali metals ions (group 1) are easily produced (due

to the low ionization potential of their atoms) but have not been found useful recently as cycloaddition promoter, contrary to the alkaline earth metals.

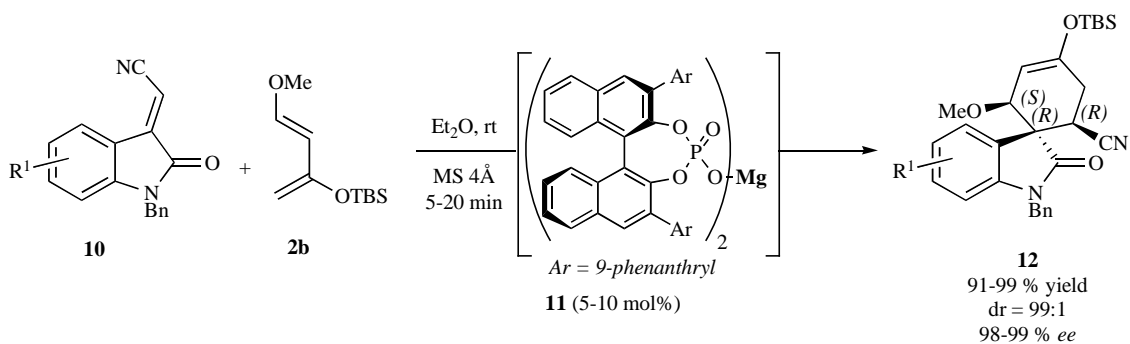
### 2.1. Group 2 (Alkaline Earth Metals)

#### 2.1.1. Magnesium (Mg)

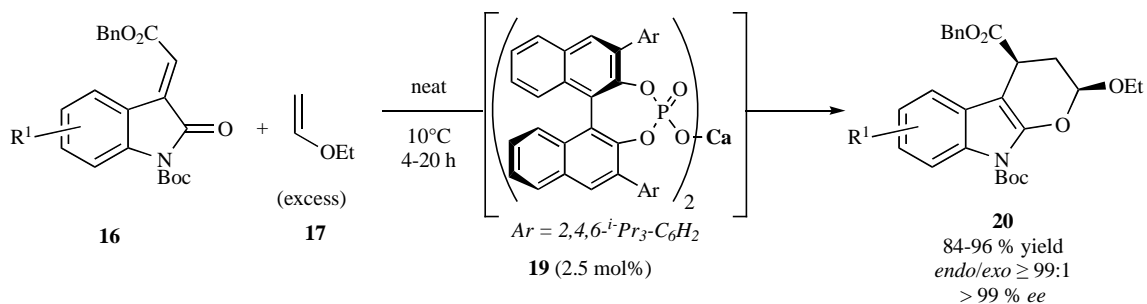
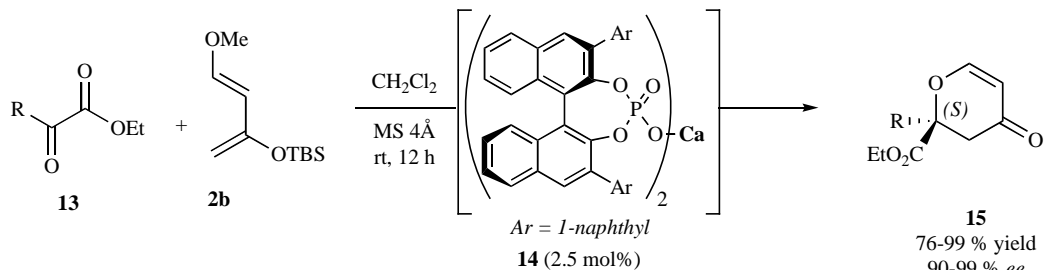
Magnesium salts have been widely used in organic synthesis because of their Lewis acidity as well as their chelating properties. However, these highly reactive species can form oligomeric structures thus decreasing their reactivity. Hatano *et al.* have shown that careful addition of an external Lewis base (benzyl alcohol) to the  $\text{Mg}^{\text{II}}$ /BINOL oligomer yields a defined trinuclear complex **3** which is able to promote the cycloaddition of benzaldehyde (**1**) with the Danishefsky's diene **2a** (Scheme 1) [7]. High enantiodiscrimination is observed and explained by preferential shielding of the BINOL aromatic rings.

*N,N'*-dioxide ligands have been efficiently employed for the cycloaddition of isatins **5** with either Danishefsky- (**2a**) or Brassard-type dienes (**6**) (Scheme 2) [8, 9]. In this reaction Mg showed superior activity or selectivity over other metals such as Sc, In or Cu.

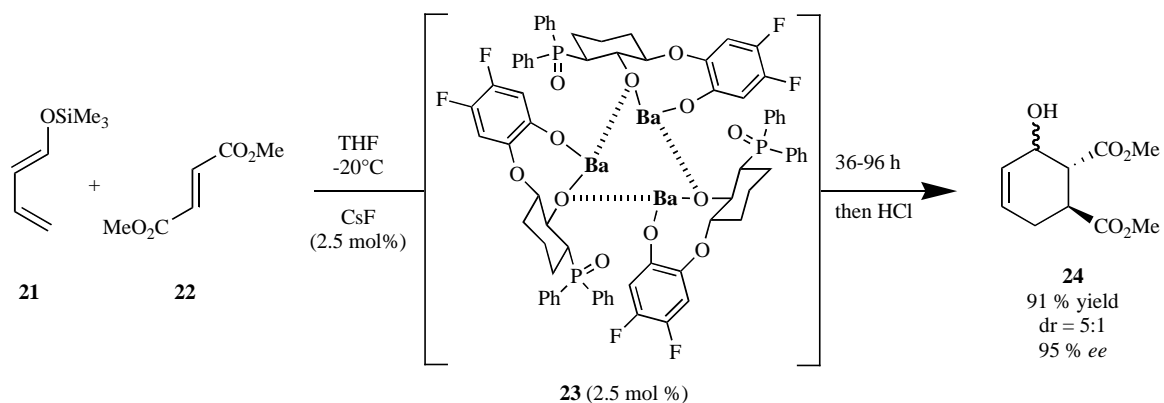
Chiral magnesium phosphates derived from BINOL (**11**) are mild Lewis, chemically neutral and rather non-toxic [10]. They were used as catalysts for the synthesis of spirooxindoles **12** with very good diastereo- and enantio-selectivities and in higher yield if molecular sieves are added (Scheme 3). Magnesium hydrates are less Lewis acidic due to an increase of donating ligands hence



Scheme 3.



Scheme 4.



Scheme 5.

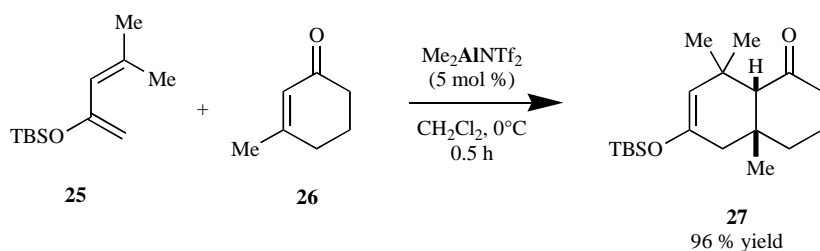
changing the coordination geometry of the metal from tetrahedral to octahedral and therefore reducing their activity.

### 2.1.2. Calcium (Ca)

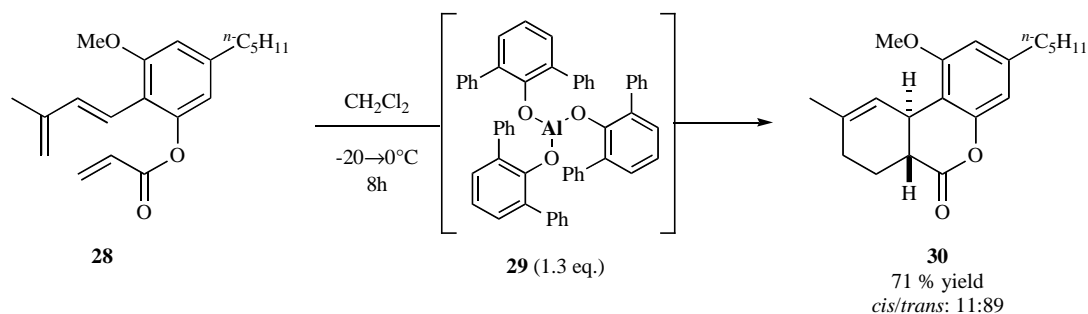
Similarly, calcium analogues (**14** and **19**) have demonstrated high activity not only with isatins **16** but also with pyruvates (**13**) (Scheme 4) [11]. These are challenging substrates due to the particular electronic and steric properties of ketones. Such catalysts are also effective to promote inverse electron demand Hetero-Diels-Alder reactions [12].

### Barium (Ba)

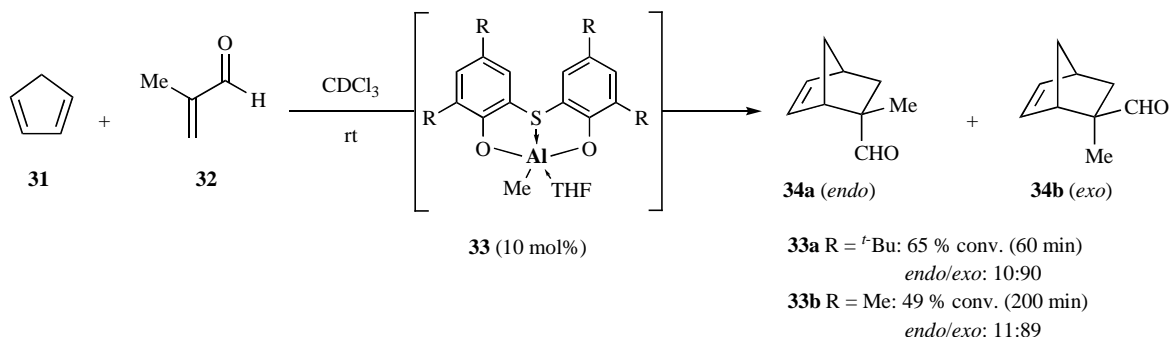
During the course of the synthesis of Tamiflu, the Shibasaki group devised the use of chiral barium complexes (Scheme 5) [13]. This reaction is supposed to occur through a HOMO-raising mechanism: the fluoride additive is believed to activate the silyl diene, facilitating transmetalation. Then, a dual activation of both diene **21** and dienophile **22** allows the formation of the desired cycloadduct **24** in high yield and enantiomeric excess, and can be performed on a 50 g scale.



Scheme 6.



Scheme 7.



Scheme 8.

### 3. P-BLOCK METALS

Located on the left-hand side of the periodic table, the *p*-block elements are the most encountered in organic chemistry. Some of them have a metallic character and are sometimes coined as *post-transition metals*.

#### 3.1. Group 13

##### 3.1.1. Aluminium (Al)

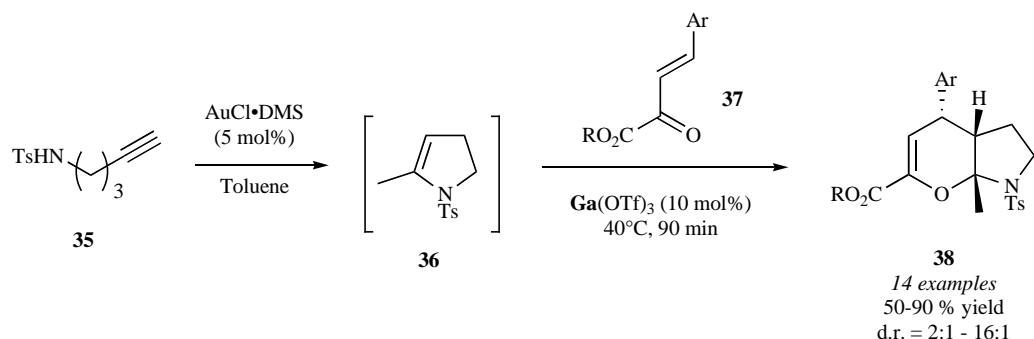
Aluminium salts are widely used as Lewis acids and  $\text{AlCl}_3$  was the first Lewis Acid to be reported as remarkably accelerating the Diels-Alder reaction [14]. It is still heavily used in total synthesis and has been shown to be compatible with a wide range of substrates. Recently, siloles have been efficiently employed furnishing 1,4-diols after Tamao-Fleming oxidation of the corresponding cycloadducts [15]. The highly electron-rich Danishefsky or Brassard-type dienes were efficient partners for the heterocycloaddition of acyl phosphonates [16]. The group of Danishefsky has also expanded the scope of dienophiles by introducing 2-halocycloalk-2-enones [17] or *N*-formyl amides [18] which is as reactive as the classical oxazolindione dienophiles.

An interesting feature of the aluminium complexes is the ease of tuning their electronic properties providing more or less reactive Lewis acids ( $\text{AlBr}_3 > \text{AlCl}_3 > \text{Me}_2\text{AlCl} > \text{Me}_3\text{Al}$ ). Mixing  $\text{Me}_3\text{Al}$  with an equimolar amount of  $\text{Tf}_2\text{NH}$  yields  $\text{Me}_2\text{AlNTf}_2$

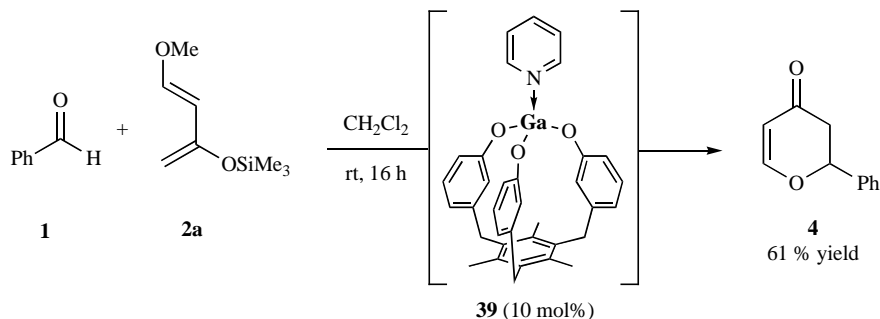
which is a very highly reactive Lewis acid, and has been especially efficient for the cycloaddition of hindered substrates (Scheme 6) [19].  $\text{MeAl}(\text{NTf}_2)_2$  is even more reactive. Interestingly, the *endo* isomer is preferentially obtained in this case. However it is known that the substitution of the terminal diene and/or dienophile yields mainly the *exo* isomer [20]. Computational investigations have put forward a twist-asynchronicity model to account for the observed selectivity [21]. Care must be taken however since these results were obtained involving the chelation of the aluminium atom with both carbonyls of the dienophile (Evans' model [22]). For low concentration of Lewis Acid (catalysis) this chelation seems unlikely and alternative mechanism should occur [23].

Sterics tuning at the aluminium atom can have interesting results on the stereochemistry of the adduct. The intramolecular cyclization of **28** usually gives the *cis* isomer predominantly with  $\text{AlCl}_3$  or under thermal conditions. Remarkably, the use of APTH (**29**) reverses the observed selectivity, due to destabilizing steric interactions in the *cis* transition state (Scheme 7) [24].

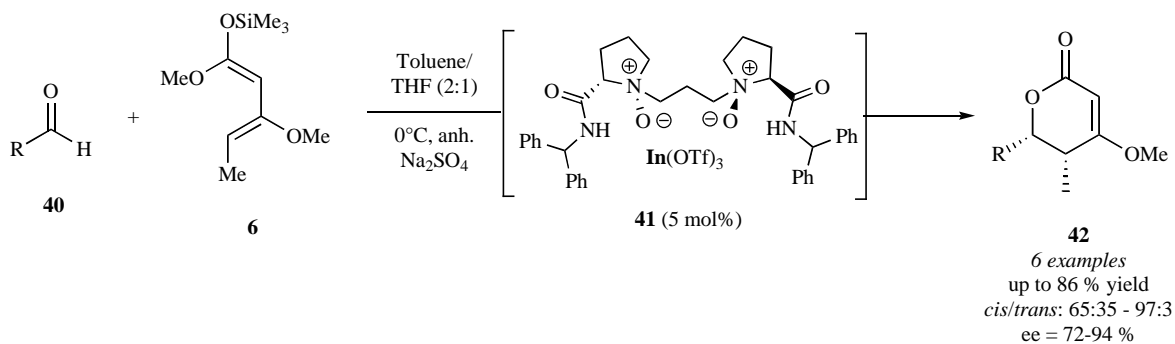
The use of the tridentate ligands 2,2'-thiobis(4,6-dimethylphenolate) (Smdiol **33b**) or 2,2'-thiobis(4,6-di-*tert*-butylphenolate) (Stdol **33a**) with  $\text{AlCl}_3$  yields defined complexes (Scheme 8) [25]. They have been found to catalyse the reaction between cyclopentadiene **31** and methacrolein **32** with moderate conversion but with good *exo* selectivity.



Scheme 9.



Scheme 10.



Scheme 11.

### 3.1.2. Gallium (Ga)

Gallium becomes increasingly used in organic synthesis. Its triflate salt  $\text{Ga}(\text{OTf})_3$  has been used for the inverse electron demand hetero-Diels-Alder of alkyl arylidene pyruvates **37** with a cyclic enamine (**36**, generated by 5-*exo*-dig gold-cyclization of aminoalkyne **35**) (Scheme 9) [26]. The bicycloaminal adducts **38** are usually obtained in high yield in favour of the *endo* isomer.

The Lewis acids from this group **13** have a vacant *p* orbital at the metal center, which can be involved in the coordination with an external ligand. As a result, the Lewis acidity is decreased. Therefore, Nakajima *et al.* have designed a caged tridentate ligand back-shielding the vacant *p* orbital from external ligands and enhancing the Lewis acidity (Scheme 10) [27]. The adduct **4** is obtained in 61% yield with such caged-shaped gallium complex instead of 34% yield with the related open-shape gallium phenoxide.

### 3.1.3. Indium (In)

Prior to the use of magnesium salts, the Feng's group employed their *N,N'*-dioxide ligands with indium(III) triflate (Scheme 11). The mechanism of the hetero-Diels-Alder reaction with butadiene with benzaldehyde has been investigated by DFT calculations [28].

The reaction seems to proceed via a concerted asynchronous mechanism through a zwitterionic transition state favouring the *endo* isomer due to less steric hinderance. Brassard-type dienes have later been found rather efficient for this kind of cycloaddition [29].

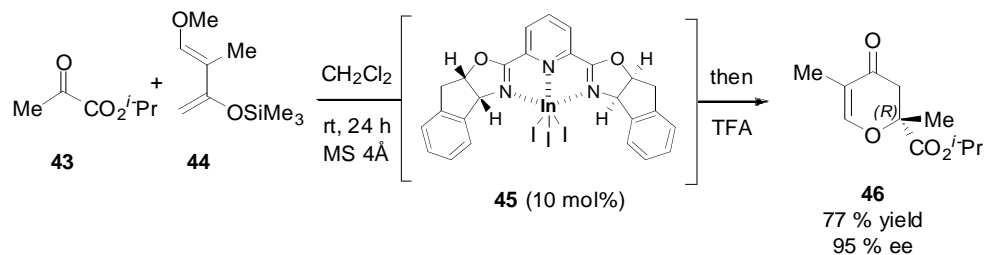
The group of Loh has explored the asymmetric hetero-Diels-Alder reaction of the Danishefsky's diene **44** with  $\alpha$ -ketoesters (**43**) using In(III)-PyBox complexes **45** (Scheme 12) [30]. The adducts **46** are obtained after TFA desilylation in moderate to high yields with usually high enantioselectivity (up to 95% *ee*).

Finally, the dual activation of  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **47** with  $\text{InBr}_3$  and a chiral phosphoric acid (**48**) can lead to either a Diels-Alder or an Hetero-Diels-Alder reaction with cyclopentadienes; the latter being favoured with cyclopentadiene itself (**31**) or disubstituted cyclopentadienes (Scheme 13) [31]. All adducts (**49** and **50**) are obtained with very high enantioselectivities.

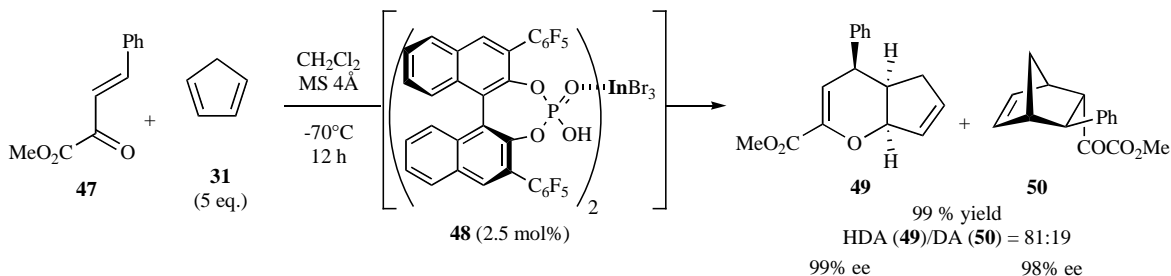
## Group 14

### 3.1.4. Tin (Sn)

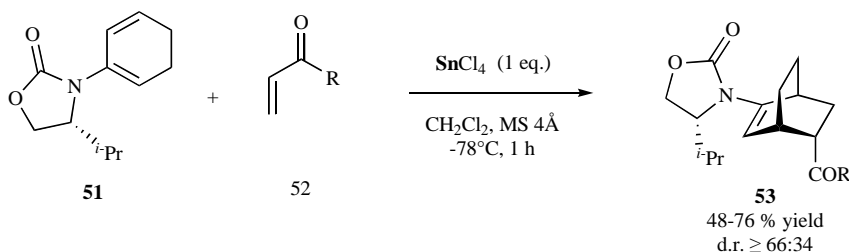
Tin halides are generally considered less Lewis acid than aluminium halides, still they are highly reactive. Cyclic 2-amidodienes



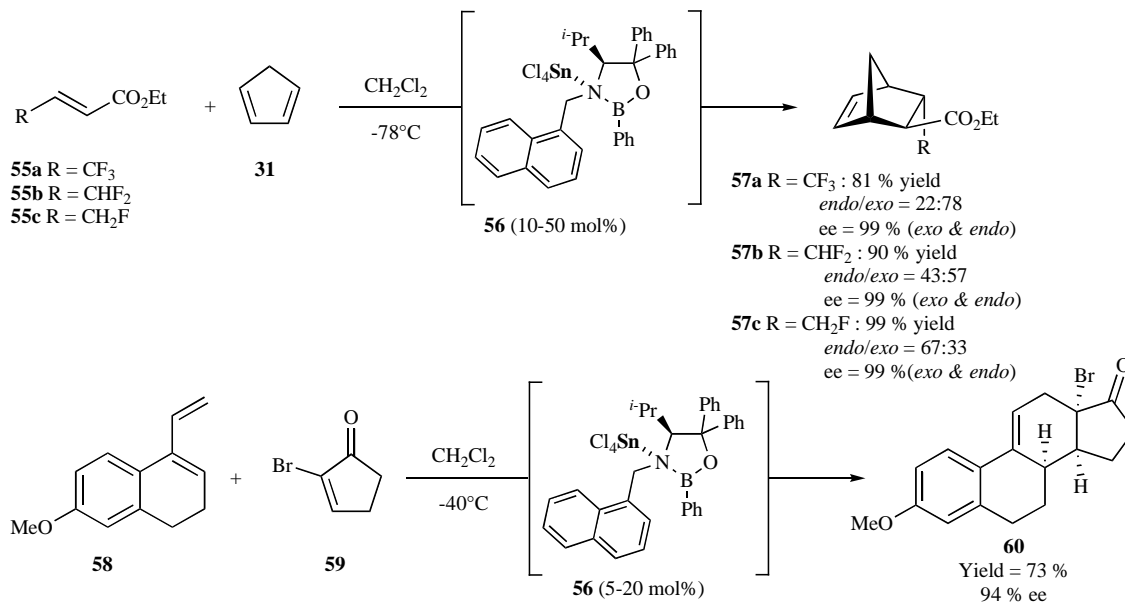
Scheme 12.



Scheme 13.



Scheme 14.

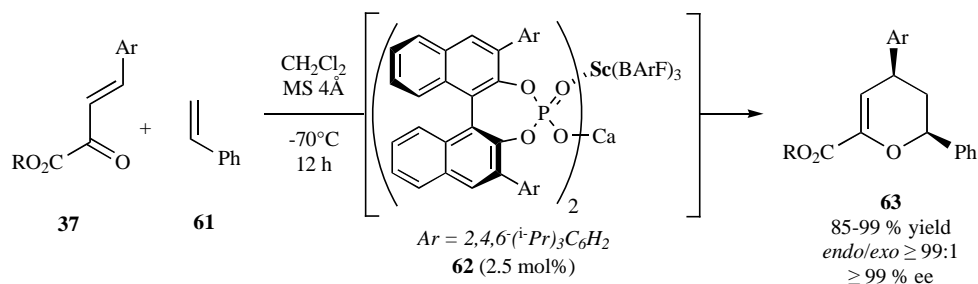


Scheme 15.

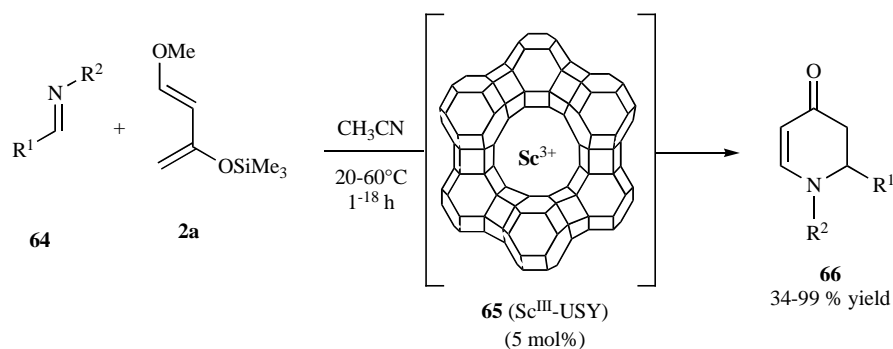
**51** are not thermodynamically stable (they tend to equilibrate to the corresponding cyclic 1-amidodiene) therefore their reaction must be performed at low temperature [32].  $\text{SnCl}_4$  proved to be the most efficient promoter for the cycloaddition with various enones **52** and the reaction can be run as low as  $-78^\circ\text{C}$  yielding the bicyclic adduct **53** with moderate (aromatic enones) to high (aliphatic enones) diastereoisomeric ratios (Scheme 14).

Chiral oxazaborolidines are highly potent Lewis acids. Their protonation or metallation ( $\text{AlBr}_3$ ) affords efficient catalysts for the Diels-Alder reactions [33,34]. Shibatomi *et al.* have demonstrated that tin(IV) chloride could also activate Corey's oxazaborolidines (**56**) and they have studied the cycloaddition of  $\alpha$ -halo enones **59** or  $\beta$ -(poly)-fluoroacrylates (**55a-c**) with various dienes in order to attain easily and selectively valuable pharmaceuticals compounds (Scheme 15) [35,36].

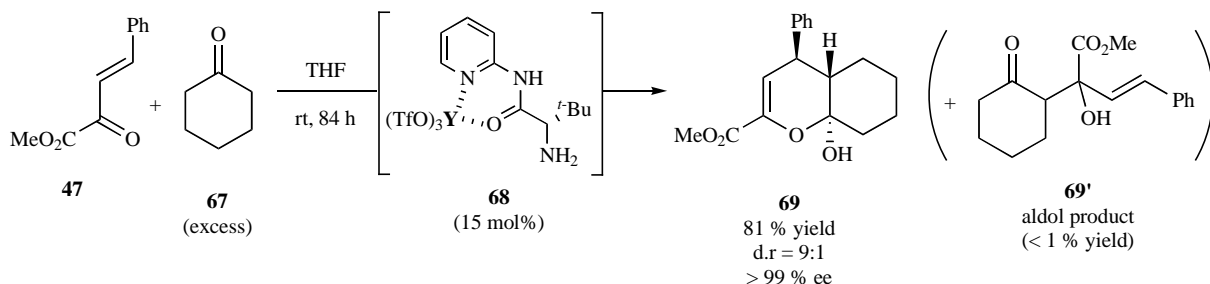




Scheme 16.



Scheme 17.



Scheme 18.

#### 4. d-BLOCK METALS (TRANSITION METALS)

The middle of the periodic table is filled with elements which have all partially or totally filled *d*-orbitals, conferring them particular reactivity.

##### 4.1. Group 3

###### 4.1.1. Scandium (Sc)

Such particular reactivity has been observed by the group of Luo [37]. The cycloaddition of  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **37** with disubstituted alkenes catalysed by indium complex yields the *exo* isomer in good yield and commonly with diastereo- and enantioselectivity. Whereas the use of a scandium complex **62** and styrene **61** yields the *endo* adduct (**63**) in very high diastereo- and enantioselectivity (Scheme 16). The rationale for this lies in a stepwise mechanism (and formation of a zwitterionic intermediate) in the case of indium while the reaction is concerted with scandium.

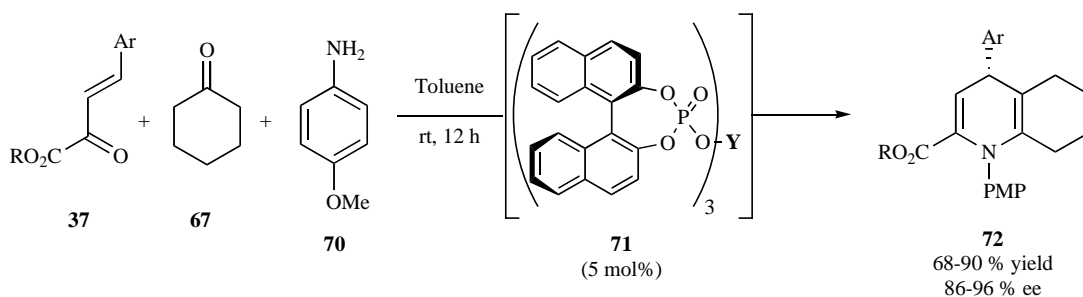
Zeolites are solid Brønsted acids but some of the protic site can be easily exchanged for a metal cation, thus conferring additional Lewis acidity to the zeolites [38]. Sc-zeolites **65** have been efficiently used for the Povarov reaction as well as for the imino-Diels-Alder reaction [39]. In this reaction the yields are often slightly higher if the imine **64** is formed prior to the cycloaddition (Scheme

17). Although the Danishefsky's diene **2a** is an efficient partner, other dienes only yields the 1,4-addition product, presumably due to the zeolite acidity. More interestingly, the heterogeneous zeolite catalyst is easily recovered and can be reused at least 10 times without any loss of reactivity.

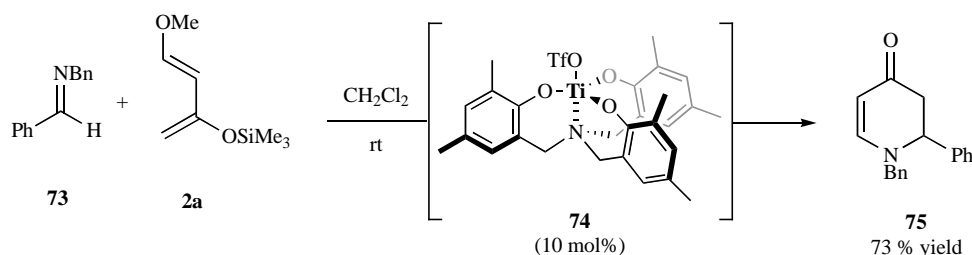
###### 4.1.2. Yttrium (Y)

The [4+2] cycloaddition of  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **47** with cyclic ketones is a challenging task mainly due to the low reactivity of the cyclic ketone. However, the group of Wang showed that the use of a chiral chelating ligand bearing a primary amine (**68**) was beneficial (Scheme 18) [40]. The amino group allows the formation of the more reactive enamine tethered to the ligand, while the chelating moiety brings the diene in close proximity to the dienophile. Several metals were screened and  $\text{Y}(\text{OTf})_3$  was the most efficient even if for some substrates the aldol product (**69'**) is unavoidable. Heteroadducts **69** are obtained in very high enantioselectivity (> 90%).

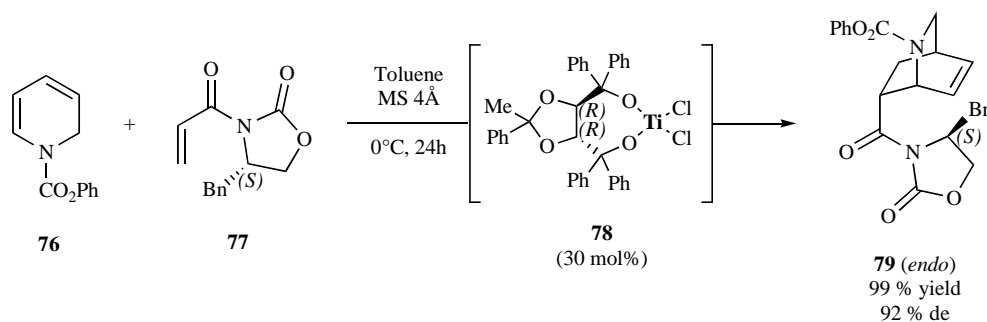
They next turned their attention to the related aza-Diels-Alder reaction by introducing an aryl amine (**70**) in the system (Scheme 19) [41]. This seems even more challenging since either the enamine or the 1-azadiene is not thermodynamically favored. In order to obtain the desired product **72** in good enantioselectivity,



Scheme 19.



Scheme 20.



Scheme 21.

the presence of a catalytic amount of chiral silver phosphate is required.

## 4.2. Group 4

### 4.2.1. Titanium (Ti)

Titanium is widely used as Lewis acid in organic reactions. Its halide salts are highly reactive and considered slightly less acid than the aluminium counterparts [42]. Titanium can also easily form stable complexes with alkoxides, lowering the overall acidity ( $\text{TiCl}_4 > \text{TiCl}_2(\text{O}^i\text{Pr})_2 > \text{Ti}(\text{O}^i\text{Pr})_4$ ). Although cheap and commercially available, these catalysts suffer from air and moisture sensitivity, as well as caustic and corrosive hazards. The group of Bull and Davidson devised the use of a propeller-type tridentate ligand that binds the titanium center (Scheme 20) [43]. The triflate salt **74** is mandatory for the activity, nevertheless the crystalline solid is bench stable for several months. This catalyst has been efficiently used for imino-Diels-Alder with the Danishefsky's diene **2a** or for homo-Diels-Alder of dienes with electron-poor dienophiles. More interestingly the ligand scaffold allows a higher *endo* selectivity than with the classical  $\text{TiCl}_4(\text{O}^i\text{Pr})_3$ .

Ligand exchange with chiral alcohols allows the formation of chiral catalysts. (*S*)-BINOL has been described for the cycloaddition of aza-chalcone with cyclopentadiene [44]. One of the best chiral ligands for titanium is TADDOL. Recently, such catalyst (**78**) has been found useful for the asymmetric synthesis of isoquinuclidines (**79**) by cycloaddition of 1-(phenoxy carbonyl)-1,2-dihydropyridine **76** with acryloyl oxazolidinone **77** (Scheme 21) [45].

In addition, theoretical studies have been carried out to identify the mechanism involved in the titanium-mediated hetero-Diels-Alder [46,47]. Both studies highlights the formation of a zwitterionic intermediate arising from a stepwise mechanism.

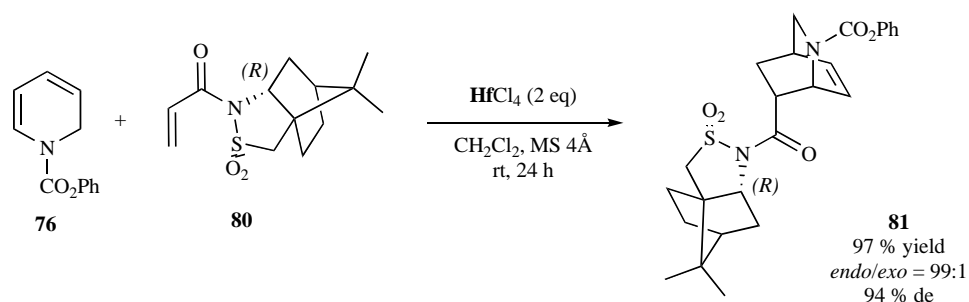
### 4.2.2. Hafnium (Hf)

In 2010, the group of Matsuyama devised a Diels-Alder route to isoquinuclidine frameworks (**81**) from 1,2-dihydropyridine (**76**) and chiral acryloyl camphorsultam **80** (Scheme 22) [48]. Interestingly, such reaction has been found effective with Ti(IV), Zr(IV) or Hf(IV) chlorides. Although less reactive (the reaction has to be performed at room temperature instead of  $-78^\circ\text{C}$ ) hafnium chloride is at least as stereoselective as titanium chloride, and excellent *endo/exo* ratios as well as *endo* diastereomeric excess are obtained. Such selectivity is accounted by intermolecular chelation of the metal between the acryloyl carbonyl and one oxygen atom of the sultam moiety.

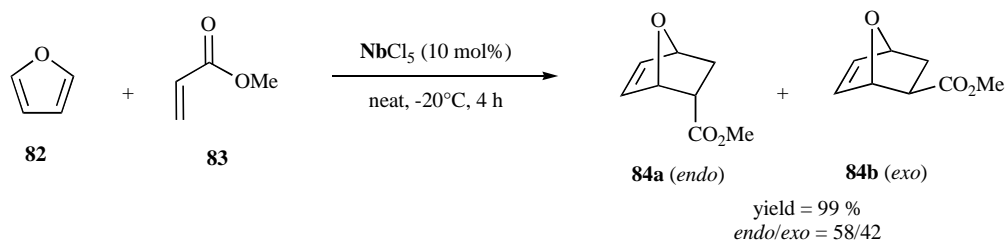
## 4.3. Group 5

### 4.3.1. Niobium (Nb)

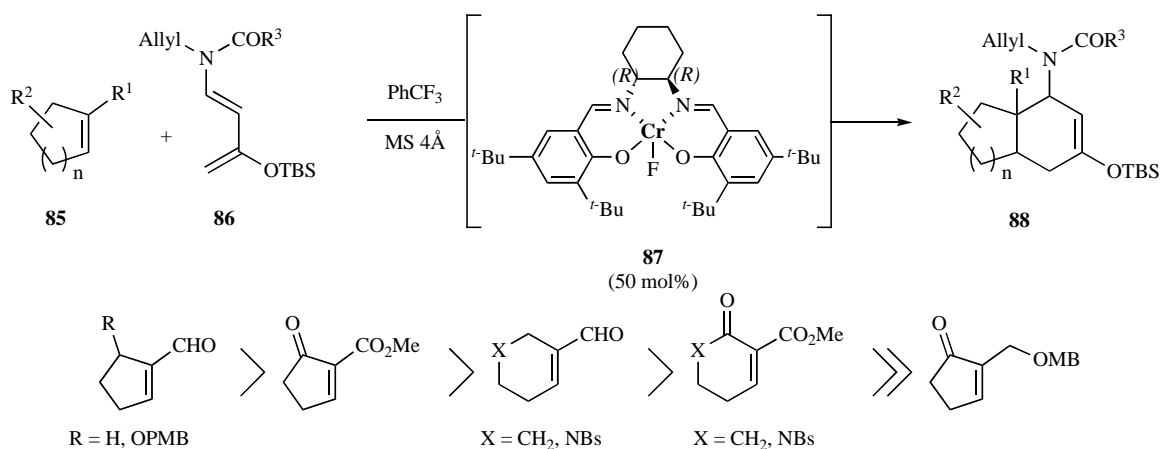
Niobium(V) chloride is highly oxophilic and highly Lewis acidic and has been used for several chemical transformations including the Diels-Alder reaction [49]. Furan **82** can be used as a



Scheme 22.



Scheme 23.



Scheme 24.

diene, however it is fairly unreactive and highly reactive dienophiles or harsh activation conditions (strong Lewis acids, elevated temperatures or high pressure) are required. In addition, its aromatic stability enables the easy retro-cycloaddition pathway. Lacerda's group found that a catalytic amount of Nb(V) chloride is highly efficient for the cycloaddition of furan with methyl acrylate **83**, yielding quantitatively the adduct (**84**) with slight *endo* selectivity (Scheme 23) [50].

#### 4.4. Group 6

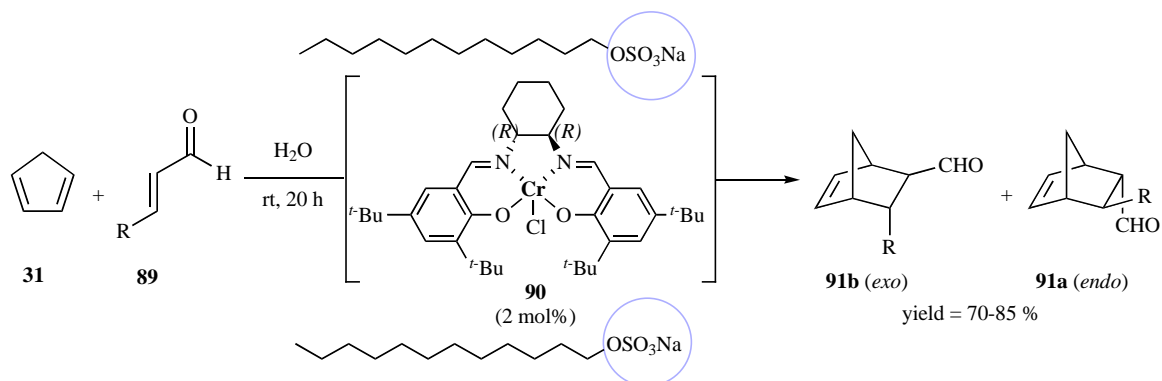
##### 4.4.1. Chromium (Cr)

The Salen ligand is one of the privileged structure (*i.e.* efficient for a wide array of reactions) [51, 52] and can accommodate several metals such as Al, Co, Mn (Jacobsen's catalyst) or Cr. The group of Nishida intensively studied the cycloaddition of the Rawal's diene **86** with cyclic dienophiles (**85**) catalysed by the Cr-Salen-F **87** (Scheme 24) [53, 54]. They have rationalized the observed selectivity of the adduct depending on the structure of the starting dienophile. The general trend in reactivity is interesting since such bicyclic adducts would be key-intermediates in the synthesis of several natural products. However, the use of trifluorotoluene and molecular sieves is required.

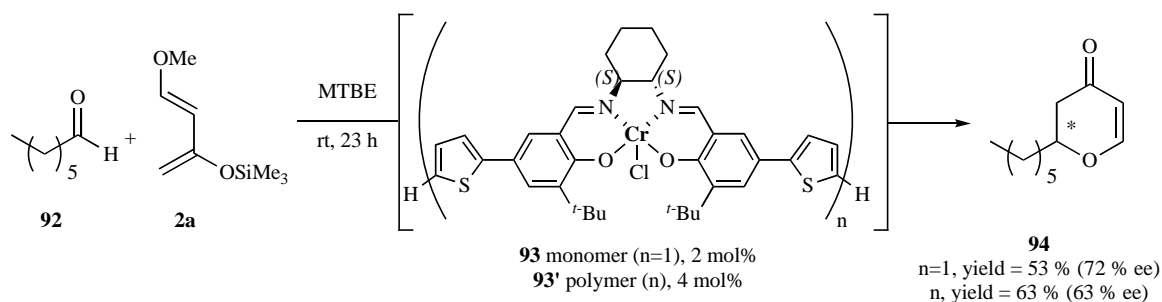
Trentin *et al.* have showed that the Cr-Salen-Cl **90** could efficiently be used for the cycloaddition of cyclopentadiene **31** and *trans*- $\alpha,\beta$ -unsaturated aldehydes **89** under micellar catalysis (Scheme 25) [55].

By introducing thiophene groups on the Salen scaffold anionic polymerization can be performed leading to an insoluble polymeric chiral catalyst **93'** [56]. Either the monomeric unit **93** or the polymer has been found useful for several transformations including the hetero-Diels-Alder reaction of heptanal **92** and the Danishefsky's diene **2a** (Scheme 26). After protic workup adduct is obtained in 53 % and 63 % respectively with an enantiomeric excess of 72 % and 63 % respectively.

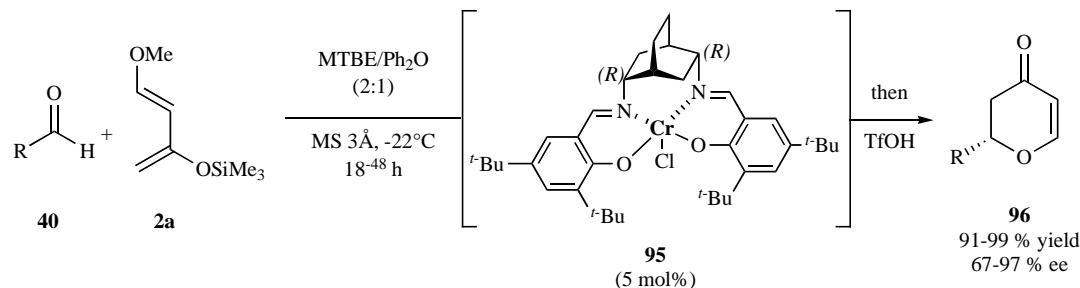
The chirality in the classical Salen ligand is ensured by the *trans*-1,2-diaminocyclohexyl moiety. The use of *cis*-2,5-diaminobicyclo[2.2.2]octane where the two nitrogen atoms are further separated would induce a larger chiral volume and could thus accommodate even more metals [57]. The cycloaddition of the Danishefsky's diene **2a** with various aromatic aldehydes **40** with this Cr(III)-Salen-Cl **95** uniformly yields the adduct in excellent yields and enantioselectivity (Scheme 27).



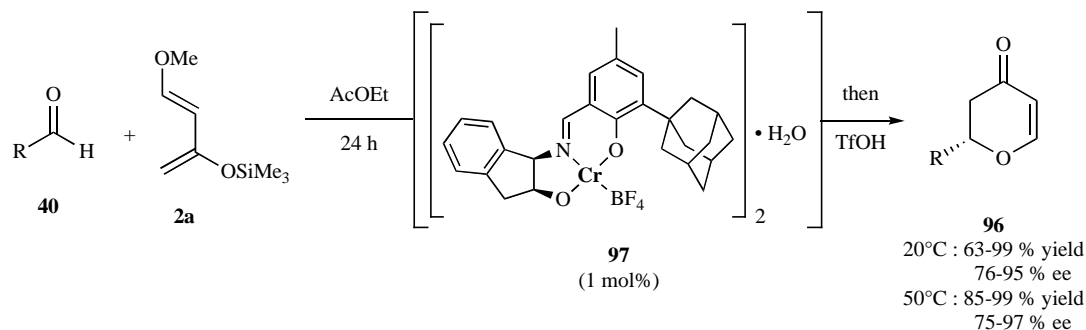
Scheme 25.



Scheme 26.



Scheme 27.



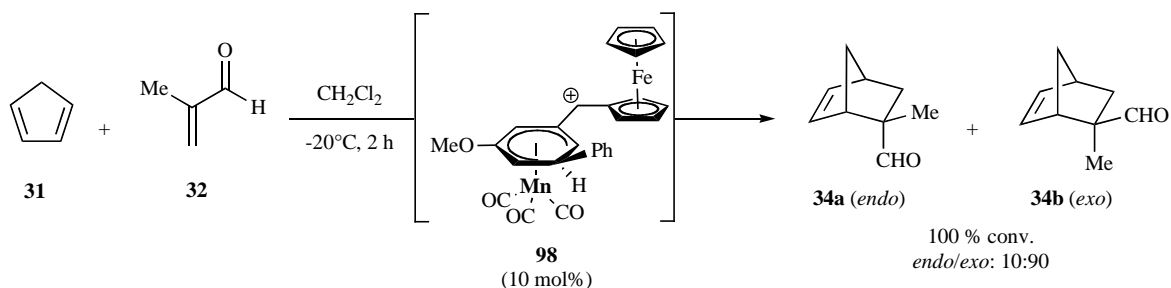
Scheme 28.

Finally, other Schiff base has been used as chiral ligand for the chromium(III) [58]. Jurczak's group demonstrated that a tridentate ligand bearing an adamantyl group (**97**) was highly efficient for the cycloaddition of the Danishefsky's diene **2a** with various aldehydes (**40**) (Scheme **28**). The authors have noticed that the enantioselectivity was slightly dependent on the temperature. In fact, a tetrameric form may be involved in the mechanism as seen by a double curved nonlinear effect.

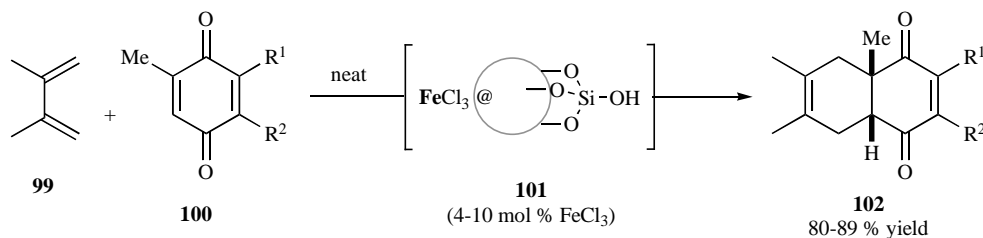
## 4.5. Group 7

### 4.5.1. Manganese (Mn)

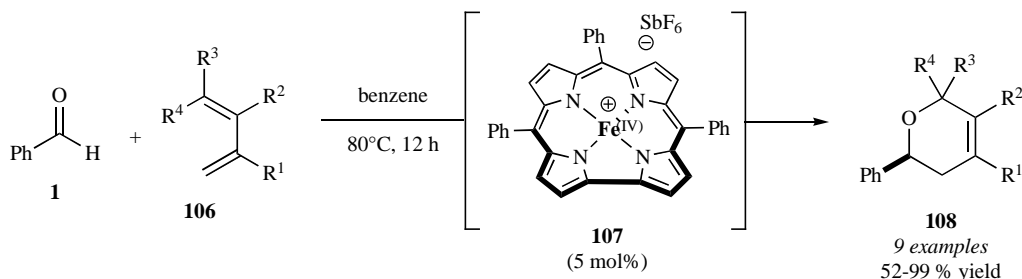
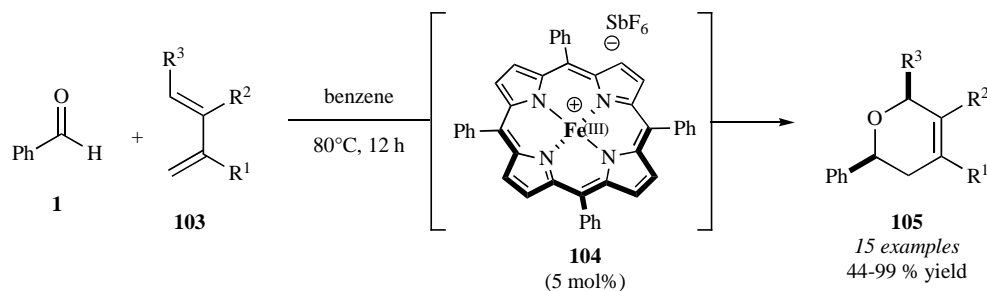
Complexation of a metal tricarbonyl to an arene ring dramatically modifies its properties. It has been shown that  $(\eta^5\text{-arene})\text{Mn}(\text{CO})_3$  is able to stabilize both negative and positive charges at the benzylic position [59]. The benzylic carbocation can be further stabilized by introduction of a ferrocenyl group to afford



Scheme 29.



Scheme 30.



Scheme 31.

a cationic complex which can be isolated. Three of these catalysts were used for the cycloaddition of cyclopentadiene **31** with methacrolein **32**. The best one (**98**) allows the complete conversion to the adducts **34** in 2 hours with 10 mol% with high *exo* selectivity (Scheme 29).

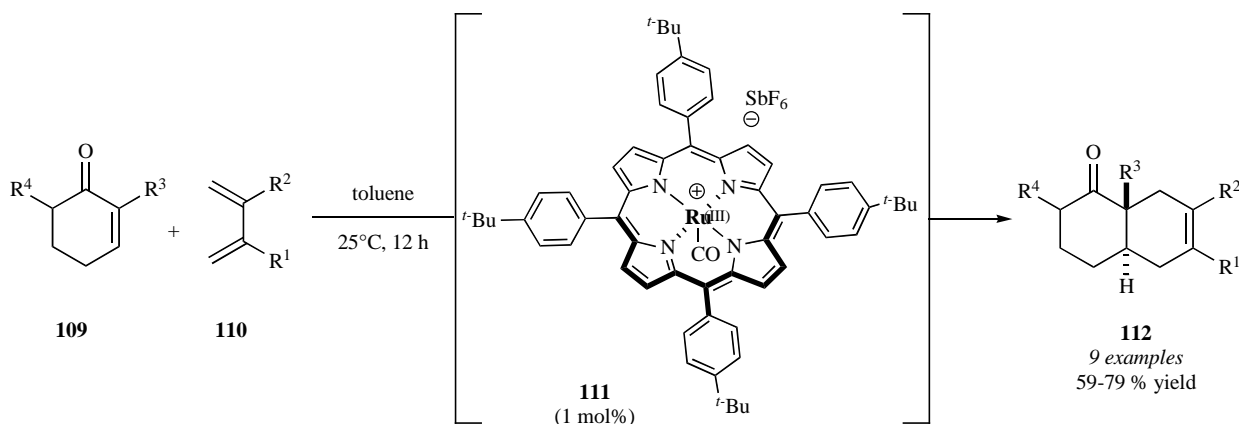
## 4.6. Group 8

### 4.6.1. Iron (Fe)

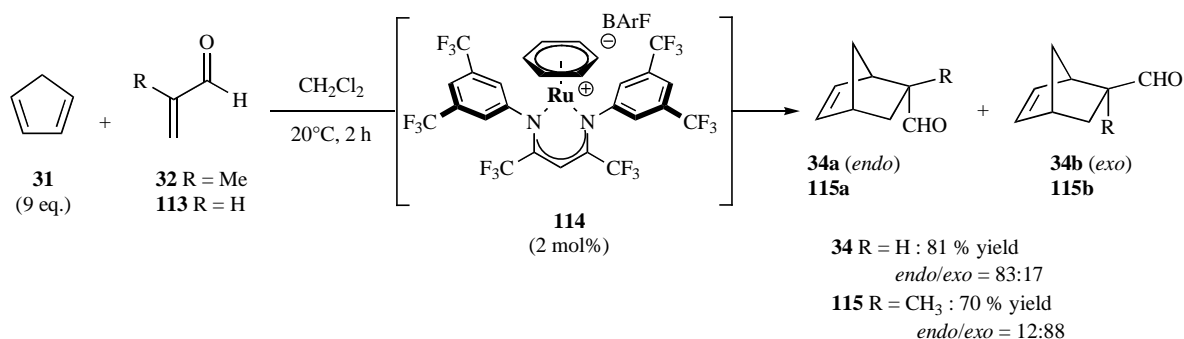
Among the most used Lewis acids is iron(III) chloride. Moreover, it is widely available and is considered as eco-compatible. Donatoni *et al.* have showed that  $\text{FeCl}_3$  can be easily adsorbed onto Aerosil<sup>®</sup> silica (**101**) [60]. Aerosil<sup>®</sup> silica is obtained by flame-pyrolysis of  $\text{SiCl}_4$  or quartz sand (thus also called fumed silica), and results 100-300  $\text{m}^2/\text{g}$  of surface area. Quinones (**100**) can efficiently react with non-activated dienes (**99**) without the need of a solvent (Scheme 30). When appropriate, the regioselectivity is governed by

the substrates. The exact nature of the catalyst cannot be determined accurately, however a change in the Raman spectrum of the adsorbed catalyst compared to  $\text{FeCl}_3$  is observed, some of the characteristic bands may be attributed to  $\text{FeCl}_4$  and  $\text{FeCl}_2$ .

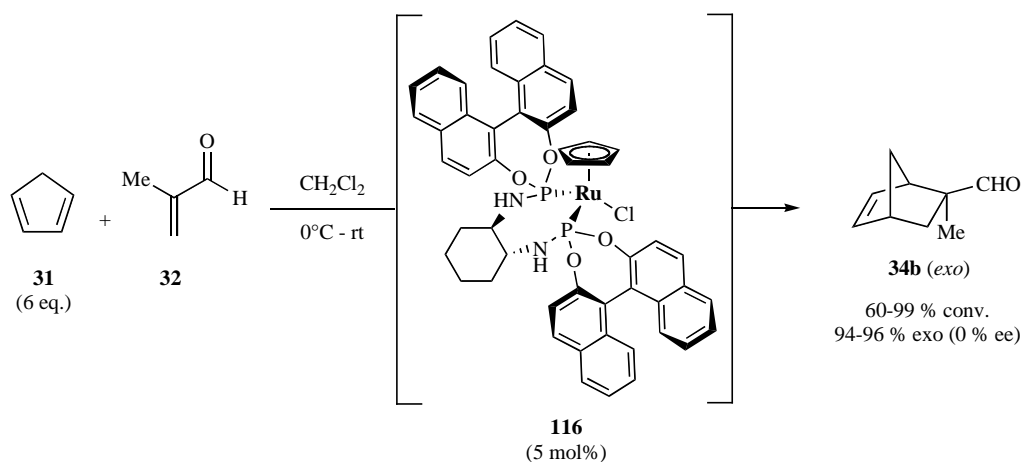
The porphyrin macrocycle is naturally occurring as metal complexes such as chlorophyll (coordinated to magnesium(II)) or heme (coordinated to iron(II)). The group of Kurahashi and Matsubara prepared the cationic complex  $[\text{Fe}^{\text{III}}(\text{TPP})]^+$  **104** and its application in the Diels-Alder reaction (Scheme 31) [61]. This catalyst is very efficient since it promotes efficiently the hetero-cycloaddition of unactivated dienes **103** and dienophiles: the corresponding adducts (**105**) are obtained usually in very high yields. It also shows a large functional group tolerance and the presence of water is tolerated. Subsequently, the authors have prepared the iron(IV) corrole analogue  $[\text{Fe}^{\text{IV}}(\text{tpc})]\text{BF}_4$  (**107**) (the corrole ring being 1 carbon atom shorter than the porphyrin ring) [62]. It appears that  $[\text{Fe}^{\text{IV}}(\text{tpc})]\text{BF}_4$



Scheme 32.



Scheme 33.



Scheme 34.

is more Lewis acidic than  $[\text{Fe}^{\text{III}}(\text{TPP})]\text{BF}_4$  yielding the desired adducts **108** in better yield albeit with a decrease in selectivity.

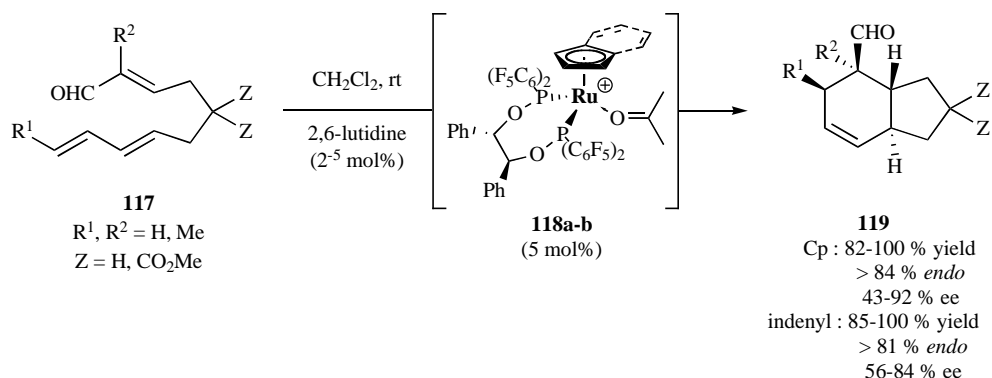
#### 4.6.2. Ruthenium (Ru)

The above-mentioned catalysts were inefficient for the formation of octalones through cycloaddition of cyclohexenones **109** with butadienes **110**. However, the  $[\text{Ru}^{\text{III}}(\text{TBPP})(\text{CO})]\text{SbF}_6$  complex (**111**) is able to perform such reaction in good yields (Scheme 32) [63]. Interestingly, the *cis*-configured octalone is formed first but gradually epimerize to the *trans* isomer **112**.

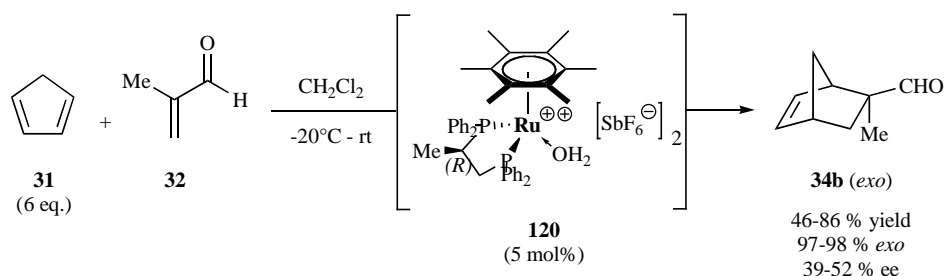
The use of ruthenium as Lewis acid is motivated by its moderate oxygen stability and its high water tolerance. In addition, compared to other strong Lewis acids, ruthenium complexes offer an increased rate of substrate-product exchange (*i.e.* better catalytic

performance) and a decreased side-product formation [64]. The “three-legged piano stool” Ru complex **114** bearing a  $\beta$ -diketiminato ligand synthesized by Schreiber *et al.* was active for the cycloaddition of cyclopentadiene **31** with acrolein (**113**) yielding mainly the *endo* isomer **115a**, while the methacrolein (**32**) furnishes predominantly the *exo* isomer **34b** (>70 % yield) (Scheme 33) [65]. The cationic character of the metal is crucial for its activity: the empty coordination site can interact with a carbonyl group and activate the substrate through a decrease of the LUMO energy.

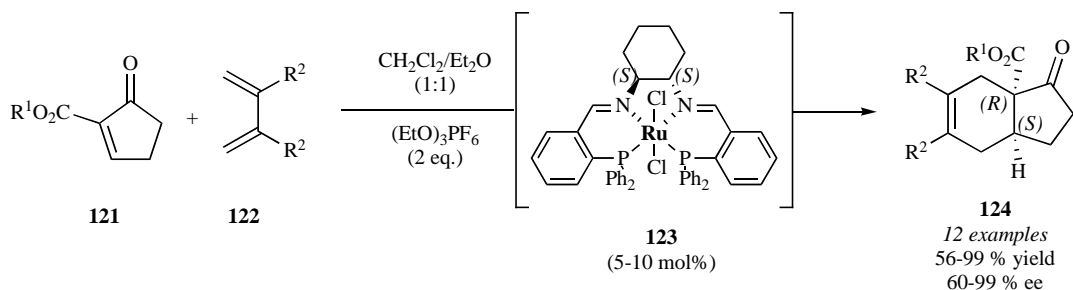
Bis(phosphoroamidite) ligands **116** can equally be used for this cycloaddition [66]. With higher catalyst loading, the *exo* adduct **34b** is formed in a better yield and with better diastereoselectivity (Scheme 34). Despite the use of a chiral ligand, asymmetric induction is seldom observed in this case.



Scheme 35.



Scheme 36.



Scheme 37.

Similar monocationic chiral Ru complexes **118** have been found useful by the group of Kündig for the intramolecular Diels-Alder (IMDA) [67,68]. These complexes are very mild Lewis acids, comparable to ZnCl<sub>2</sub>, but their electronic and steric properties can easily be tuned. For example, changing from cyclopentadienyl (**118a**) to indenyl (**118b**) ligand improves both yield and selectivity due to a looser coordination of the carbonyl to the metal (thus increasing the turnover) and to a more restricted space at the reactive site (Scheme 35).

Carmona *et al.* have prepared dicationic Ru complexes which are fairly active for the cycloaddition of methacrolein **32** and cyclopentadiene **31** (up to 86 % yield and *exo* ratio > 92 %) albeit the enantioselectivity remains low (10-52 %) probably due to a rapid interconversion of the ligands in solution (Scheme 36) [69].

Salen-type ligands (PNNP) **123** can also be useful for the cycloaddition of unsaturated β-ketoesters (**121**) [70,71]. Various dienes **122** were screened furnishing the *cis*-fused adducts **124** in 80-99 % yield with high enantioselectivity (Scheme 37).

Finally, [Ru(bpz)<sub>3</sub>]<sup>2+</sup> **127** has been described to promote a radical cation Diels-Alder reaction photocatalysis [72]. Under visible light, the Ru complex is excited and able to oxidize the dienophile

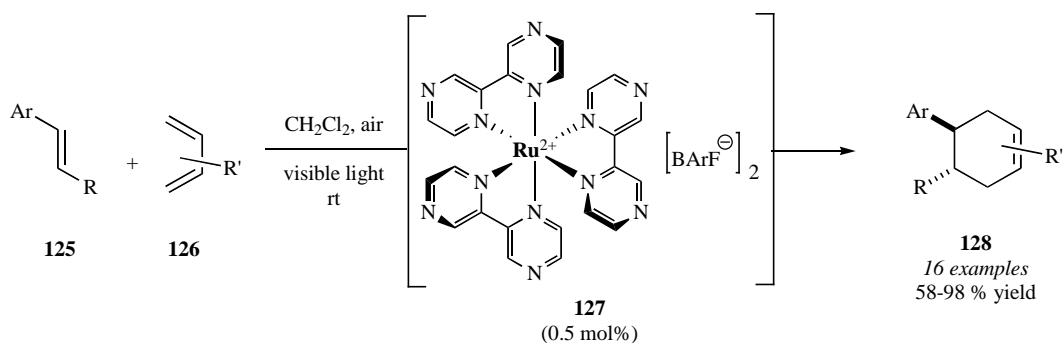
**125** to a radical cation which can subsequently react with a moderately electron-rich diene (**126**) affording the desired product **128** within a good yield (Scheme 38).

## 4.7. Group 9

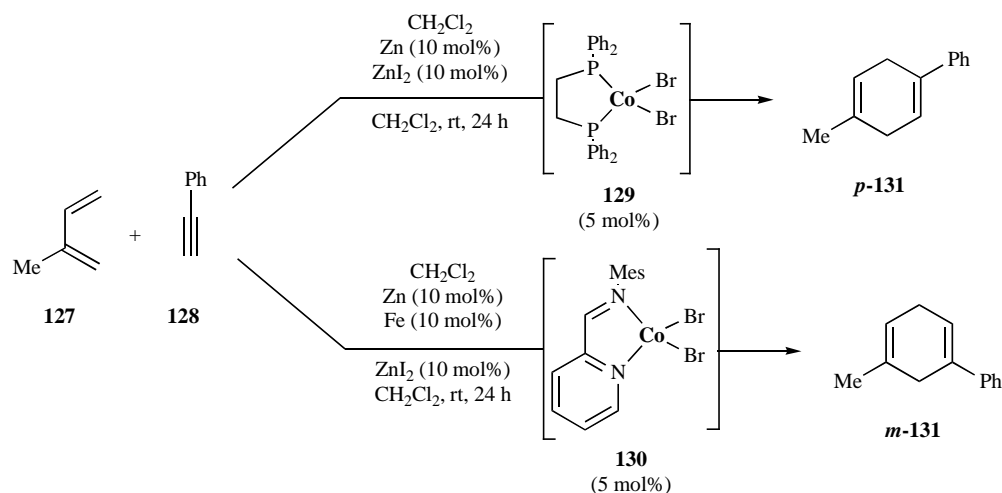
### 4.7.1. Cobalt (Co)

The group of Hilt is actively involved in the cobalt(I) 1,4-hydrovinylation. They have shown that the ligand around the cobalt has a dramatic influence on the outcome of the reaction leading either to 1,3- or 1,4-substituted cyclohexa-1,4-diene (*m*-**131** or *p*-**131**) through [4+2] cycloaddition or even cyclooctatrienes from a [4+2+2] reaction (Scheme 39) [73-75].

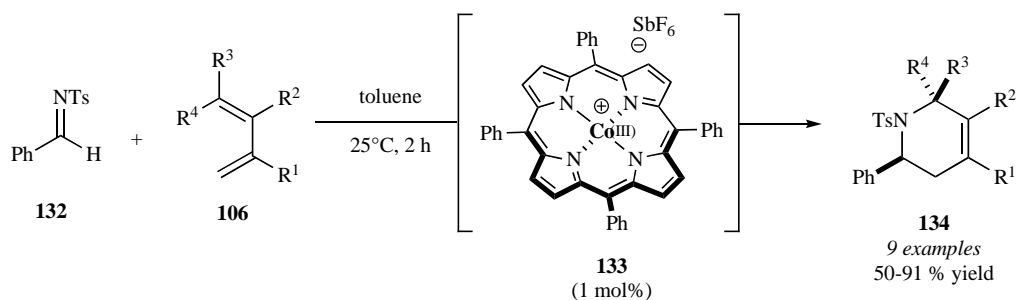
Kurahashi and Matsubara's group devised the use of [Co<sup>III</sup>(TPP)]SbF<sub>6</sub> **133** for the imino-Diels-Alder reaction of unactivated imines (**132**) and simple dienes **106** [76]. While other metallo-porphyrins (Fe or Mn) or usual cobalt Lewis acids ([Co(salen)]SbF<sub>6</sub> or CoCl<sub>2</sub>) remained inactive, the Co(III) complex is highly efficient and totally chemoselective (Scheme 40). Indeed, in the presence of other carbonyl heterodienophiles the sole imine reacts.



Scheme 38.



Scheme 39.



Scheme 40.

#### 4.7.2. Rhodium (Rh)

Chiral rhodium(II) carboxylates are widely used in organic chemistry for their facile formation of carbenoids which can in turn react with a nucleophile to yield a X-H insertion product (X = C, O, N,...). They can also be used as traditional Lewis acids for the complexation a carbonyl group in hetero-Diels-Alder reactions. Although the Rawal's diene is more reactive than the Danishefsky's one, it is also more sensitive towards moisture or (Lewis) acidity (coordination of the Lewis basic amino group would deactivate the diene). The rhodium carboxamidate  $\text{Rh}_2(\text{S-BPTPI})_4$  **136** proved to be highly efficient for the cycloaddition of Rawal type dienes with different unactivated aldehydes yielding the adducts in very high enantioselectivities [77, 78]. Using this complex, 1,3-oxazinan-4-ones **137** can be obtained from the cycloaddition of aldehydes (**40**) with 2-aza-3-siloxy-1,3-butadienes **135** (Scheme **41**) [79].

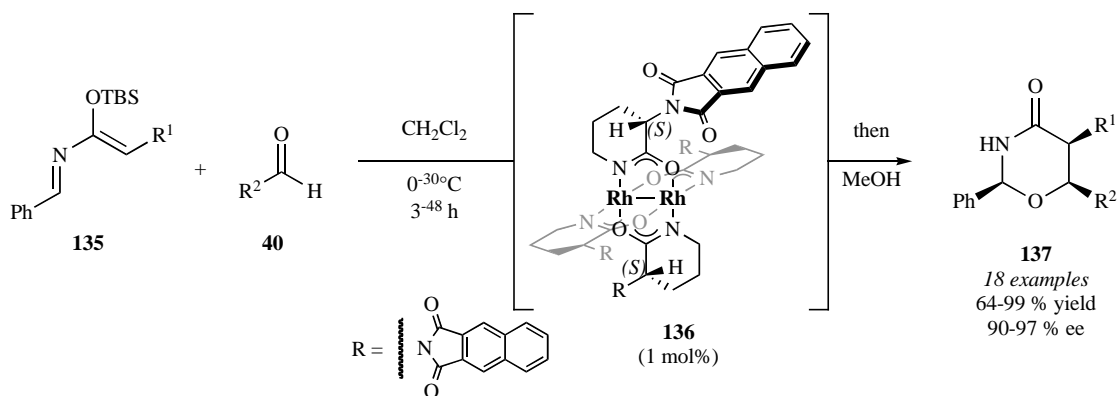
A rhodium(I) complex bearing a chiral phosphine-phosphite ligand (**140**) has been used for the intramolecular Diels-Alder reac-

tion (Scheme **42**) [80]. Although the active species has not been isolated (but supposed to be  $\text{Rh}[(\text{L}^*_2)_2]^+$ ), the catalyst preparation is crucial for the both yield and enantioselectivity and microwave-conditioning gave the best results. The mechanism for similar neutral electron demand cycloadditions has been investigated through DFT calculations [81]. The initial rhodium coordination to the diene is followed by a *cis*-coordination with the alkene. Then a *cis* oxidative cyclization and a reductive elimination yields the *cis*-configured adduct.

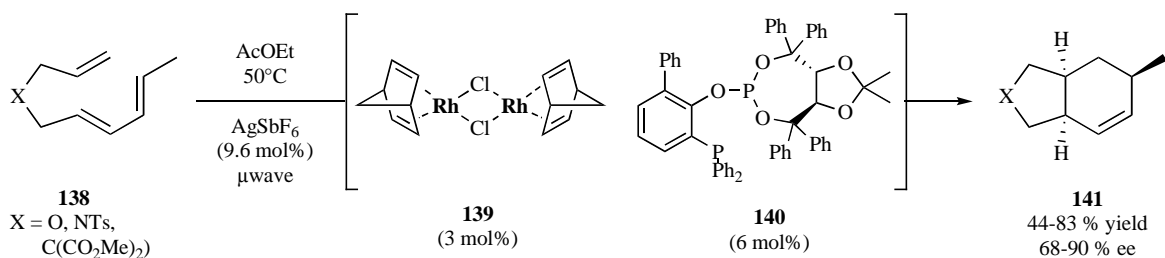
#### 4.7.3. Iridium (Ir)

Following their studies concerning the Diels-Alder reaction catalysed by  $[(\eta^6\text{-arene})\text{Ru}^{\text{II}}(\text{prophos})]^{2+}$  complexes **120**, [69] Carmona *et al.* have explored other metals such as iridium or rhodium. Although the related  $[(\eta^5\text{-C}_5\text{Me}_5)\text{Ir}^{\text{II}}(\text{prophos})]^{2+}$  **143** was moderately selective with acrolein (*exo/endo* ratio < 70 %),  $\alpha$ -substituted acroleins yields very high *exo* selectivity (enantioselect-

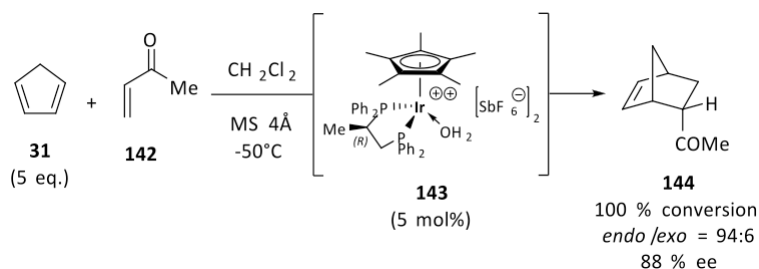




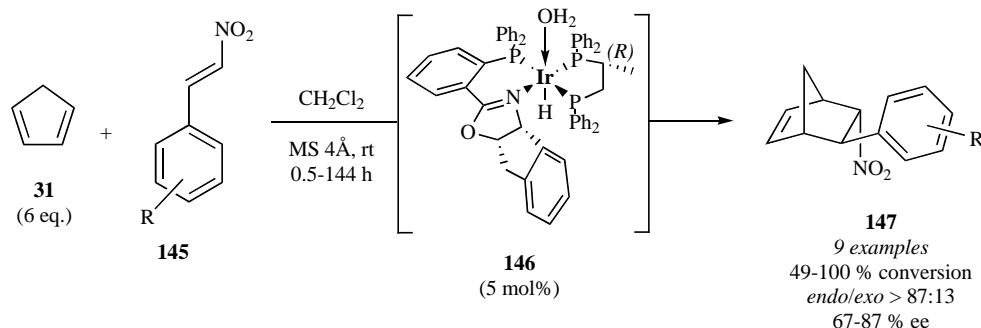
Scheme 41.



Scheme 42.



Scheme 43.



Scheme 44.

tivity was diminished by  $\beta$ -substitution) [82]. They even found that methyl (or ethyl) vinyl ketone **142** were suitable partners in this cycloaddition though with reversed facial selectivity (*endo*) (Scheme **43**) [83].

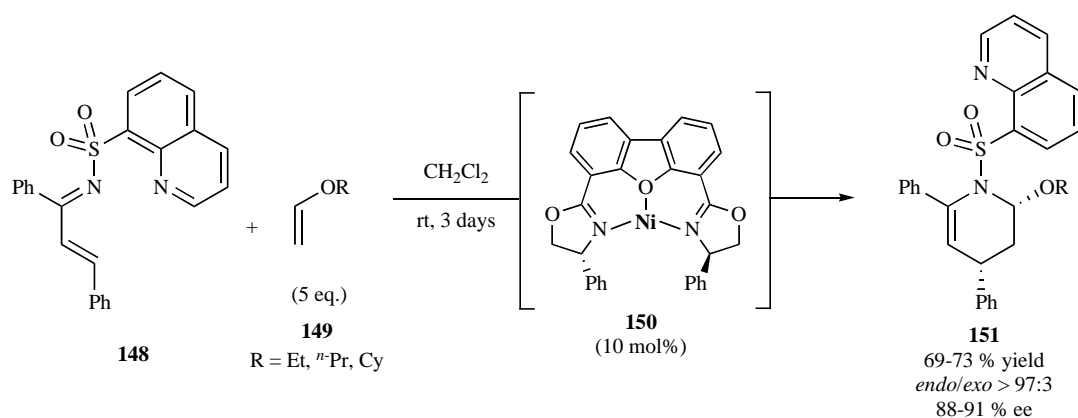
By varying the chiral phosphine ligand they managed to obtain the 5-methyl-5-formyl-2-norbornene with almost perfect *exo* ratio and very high enantioselectivity ( $> 80\%$ ) [84]. They eventually showed that chiral iridium(III) hydrides **146** were active for both 1,3-dipolar cycloaddition of nitrones or for the [4+2] cycloaddition of cyclopentadiene **31** with nitrostyrene **145** [85]. The adducts **147**

are usually obtained with almost perfect *endo* selectivity and with high enantiomeric excess (Scheme **44**).

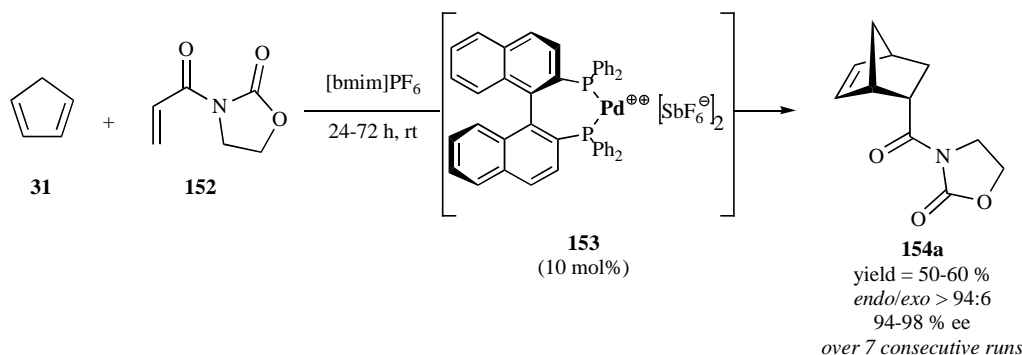
#### 4.8. Group 10

##### 4.8.1. Nickel (Ni)

The use of 1-aza-1,3-dienes in hetero-Diels-Alder allows the formation of piperidine derivatives, however these dienes have low reactivity and tend to decompose under Lewis acidic conditions. The use of a heteroarylsulfonyl protecting group on the nitrogen



Scheme 45.



Scheme 46.

gives the opportunity of another coordination site thus improving the reactivity and/or the selectivity [86]. In particular the imine **148** allows the formation of the corresponding adducts **151** in good yields and enantioselectivity (although a drop of the enantiomeric excess is observed when  $\beta$ -substituted enol ethers are used) (Scheme 45). The nickel(II) bearing a chiral bis(oxazolidine) ligand **150** has been found superior to copper(II) since a larger scope of dienophiles can be used (and in a smaller excess: 5 eq. instead of 20 eq.) and the enantiocontrol is better.

#### 4.8.2. Palladium (Pd)

Palladium is generally used for the creation of C-C bonds through a coupling reaction yet it has also been used as catalyst for the Diels-Alder cycloaddition [87]. Nishiuchi *et al.* has demonstrated that ionic liquid as solvent was important for the recycling of the  $\text{Pd}^{\text{II}}$ -BINAP catalyst **153** (Scheme 46). Although the yield is moderate it remained constant for 7 consecutive runs while the facial selectivity and the enantiomeric excess stayed very high throughout the recycling experiment.

### 4.9. Group 11 (Coinage Metals)

#### 4.9.1. Copper (Cu)

The chiral bis(oxazoline) (BOX) ligand is a  $\text{C}_2$ -symmetric and widely used scaffold for organic transformations [88]. Since the seminal report of  $\text{Cu}^{\text{II}}$ (BOX) as catalyst for the Diels-Alder reaction by Evans [89], numerous reports of such complexes are found in the literature for carbo- or hetero-Diels-Alder both normal or inverse electron demand.

For example, the group of Desimoni used a chiral aminodiol to prepare pentacoordinated copper(II) complex **155** having a square pyramidal geometry (Scheme 47) [90]. This catalyst is very active,

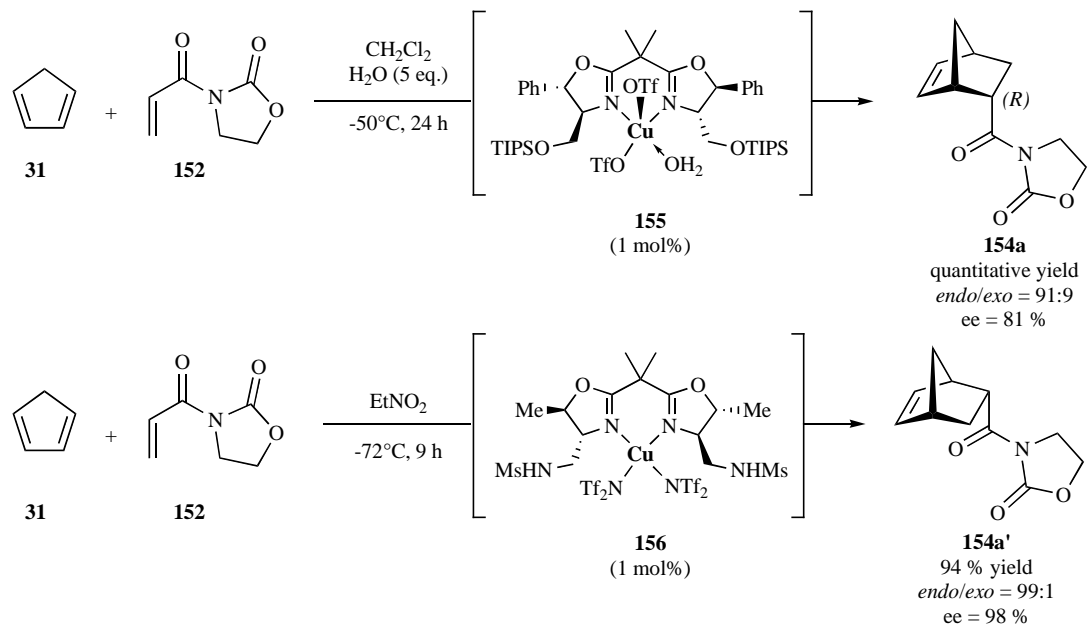
yielding quantitatively the adduct **154a** with a loading of 1 mol %, however the facial selectivity and the enantiomeric excess remains slightly lower than the original catalyst. A similar ligand design (**156**) was introduced by the group of Ishihara however the sulfonamide group provides a weak secondary interaction that increases the Lewis acidity of the copper atom (*n*-cation interaction) and induces a more rigid scaffold [91]. In turn, this catalyst provides excellent selectivity as well as activity at 1 mol % loading.

Unless the two oxazoline rings are tethered by a quaternary carbon atom, double bond isomerisation (conjugation) may occur. Therefore, O'Leary's group developed chiral oxazoline ligands derived from renewable sources, in particular arabitol (**158**) possessing the stereogenic centers on the backbone (Scheme 48) [92,93]. Despite good activity, these ligands lack selectivity with a moderate *endo* ratio (64-82%) and up to 57 % ee.

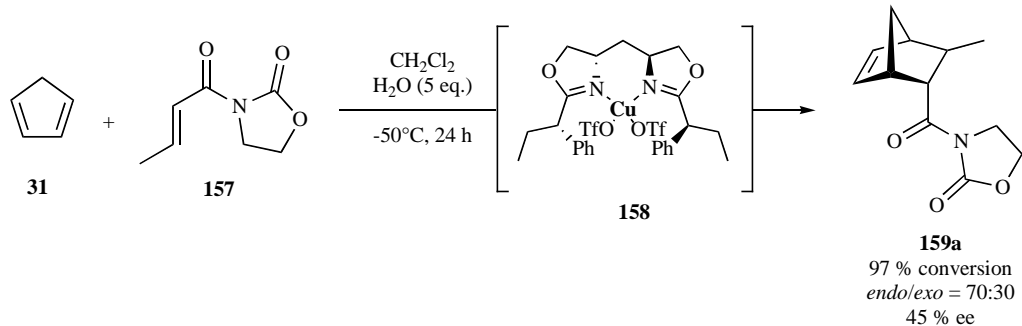
The stereochemistry of both the scaffold and the chiral oxazolines can have an influence on the selectivity of the cycloaddition. The study by Le Maux *et al.* shows that maximum enantiomeric excess is obtained with the (1*S*,12*S*)-Bis[(4'*R*)-phenyloxazoline]-9,10-dihydro-9,10-ethanoanthracene **160** (or its enantiomer) (Scheme 49) [94]. The other diastereoisomer only leads to reduced selectivity.

By analogy with the well-known Pyridine bis(oxazoline) (Py-BOX) ligands, the group of Lassaletta and Fernández synthesised chiral pyridine bis(hydrazone) frameworks (**161**) which would act as tridentate ligands [95]. In non-dried toluene up to 95% yield can be obtained with a good 92% *endo* ratio and 74 % ee (Scheme 50).

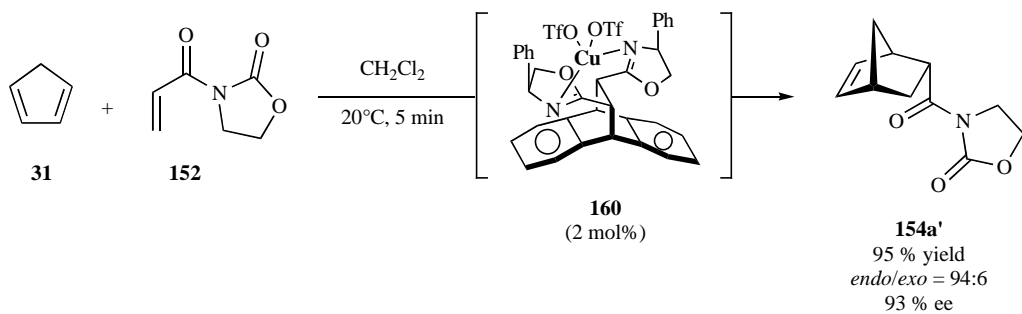
Camphor-based oxazoline ligands were used for the *exo*-selective cycloaddition of ethyl vinyl ether and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate in good yield, but with a moderate enantioselectivity [96]. The  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **162** can react with the



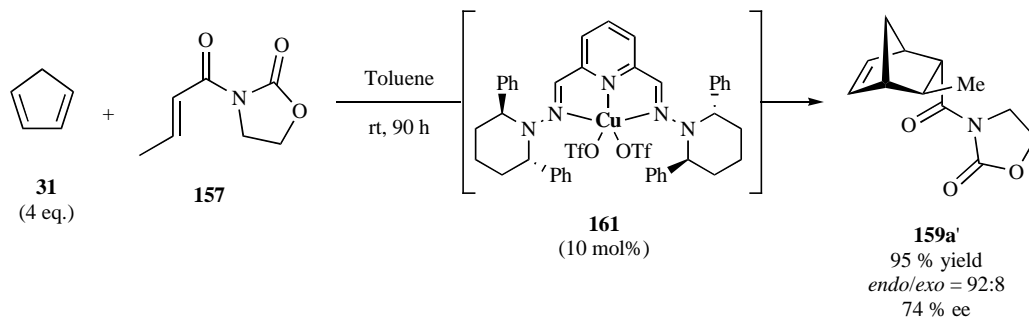
Scheme 47.



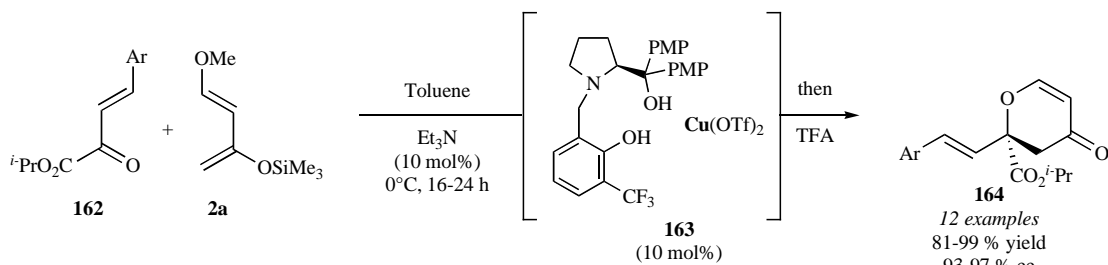
Scheme 48.



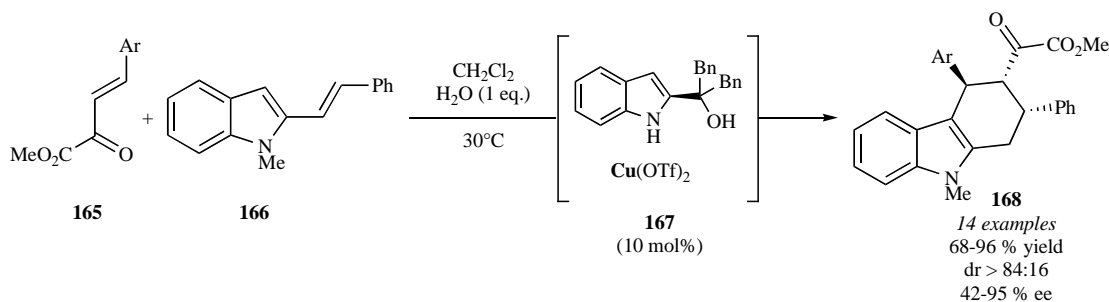
Scheme 49.



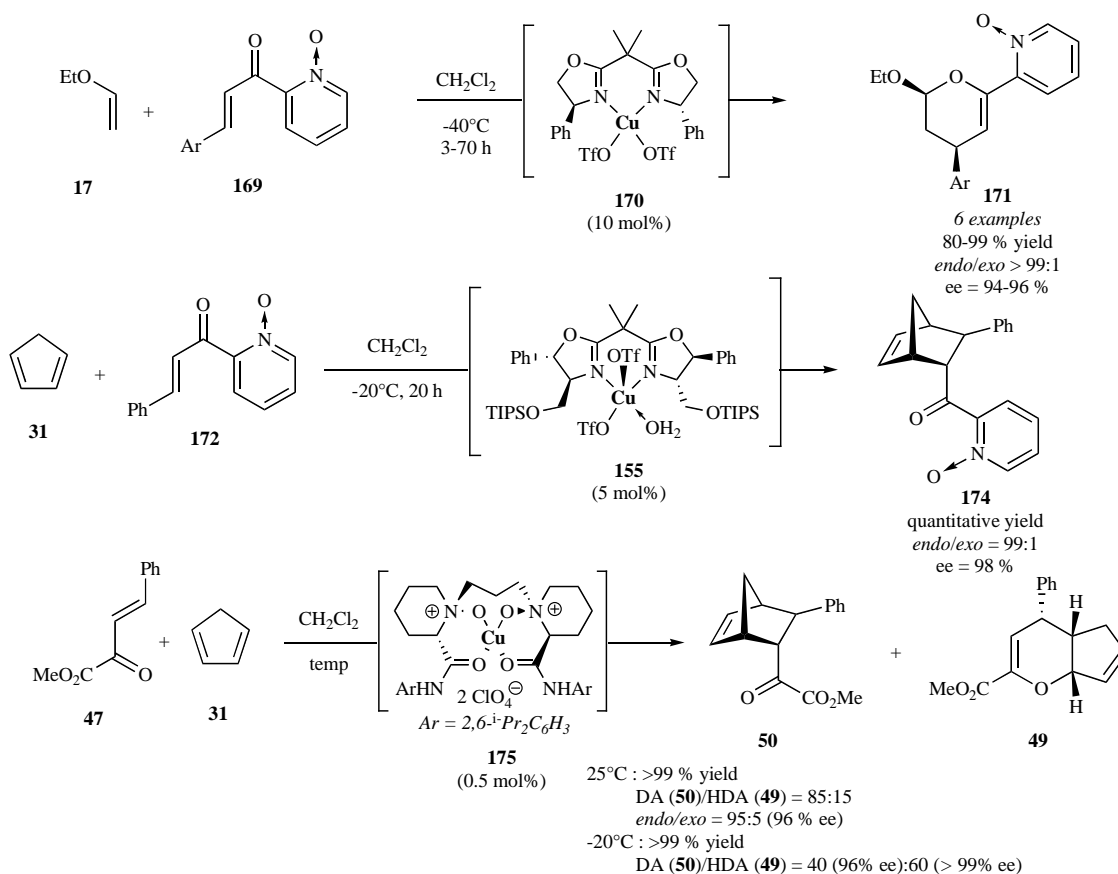
Scheme 50.



Scheme 51.



Scheme 52.



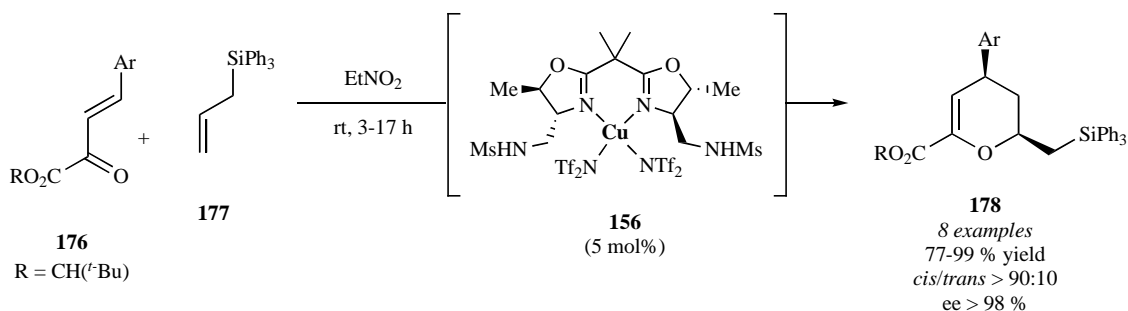
Scheme 53.

electron-rich Danishefsky's diene **2a** under the catalysis of a chiral copper-prolinol complex **163** [97]. Dihydrofurones **164** are obtained in high yields (> 80 %) with high optical purity (> 93% ee) (Scheme 51).

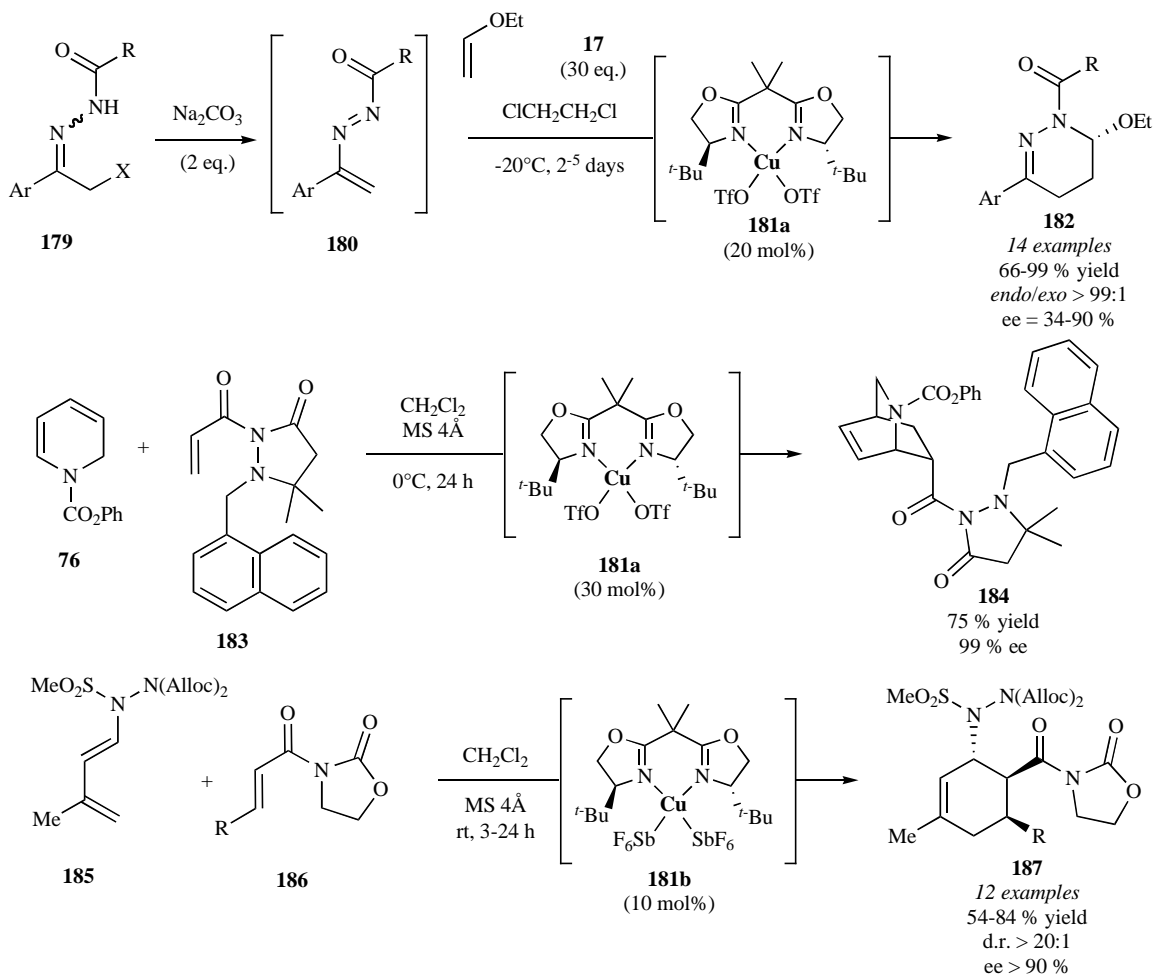
With 2-vinylindoles (**166**),  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **165** affords tetrahydrocarbazoles **168**, thus reacting as a carbadienophile

[98]. High diastereoselection and moderate to good enantiomeric excesses are obtained using a chiral indolinylmethanol ligand **167** (Scheme 52).

Having a large selection of ligands in hand, attention has also been drawn to expand the substrate scope of the Diels-Alder reaction (Scheme 53). For example 2-alkenoylpyridine-*N*-oxides (**169**,



Scheme 54.



Scheme 55.

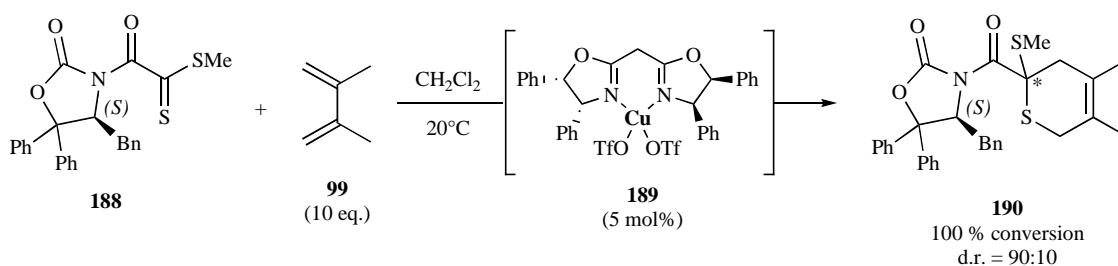
**172**) have been found useful both as heterodiene (with ethyl vinyl ether **17** at  $-40^{\circ}\text{C}$ ) [99] or as dienophile (for the cycloaddition with cyclopentadiene **31** at  $-20^{\circ}\text{C}$ ) [100] yielding the corresponding adducts in very high yield and selectivities. Similar behaviour has been observed with  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **47** and cyclopentadiene by Feng's group [101]. Keeping the same chiral catalyst **175**, the Diels-Alder pathway is favoured at room temperature while the hetero-Diels-Alder product **49** is obtained at lower temperature ( $-20^{\circ}\text{C}$ ).

Allylsilanes (**177**) are less nucleophilic than enol ethers therefore less reactive. The *n*-cation catalyst **156** developed by Ishihara's group allows the hetero-cycloaddition of allylsilanes with  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **176** with *endo/exo* ratio depending mainly on the steric hindrance of the ester moiety (Scheme 54) [102].

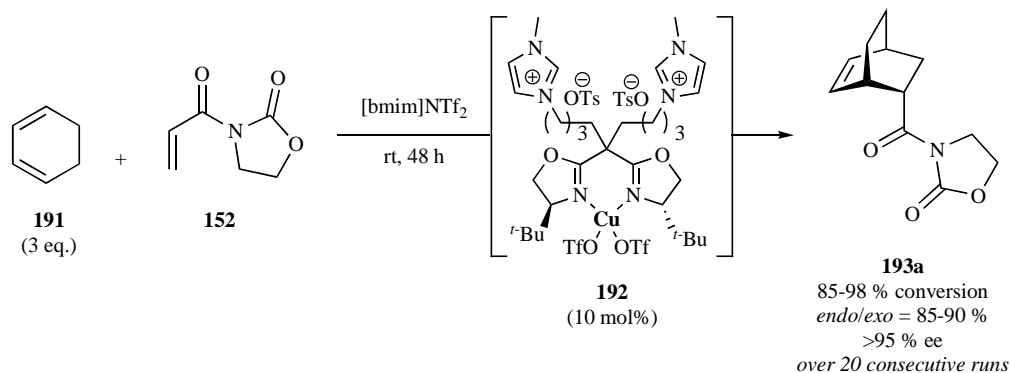
Various nitrogen heterodienes can be used in the Cu(BOX) (**181**) catalysed cycloaddition such as 1,2-diaza-1,3-dienes **180** (with ethyl vinyl ether **17**) [103], 1,2-dihydropyridine **76** with a pyrazolidinone derivative **183** [104] or 1-hydrazinodiene **185** (with *N*-acryloyloxazolidinone **186**) to afford selectively the *exo* adduct **187** (Scheme 55) [105].

Dithioesters (**188**) have also been used for the enantioselective or asymmetric diastereoselective thia-Diels-Alder cycloaddition (Scheme 56) [106,107].

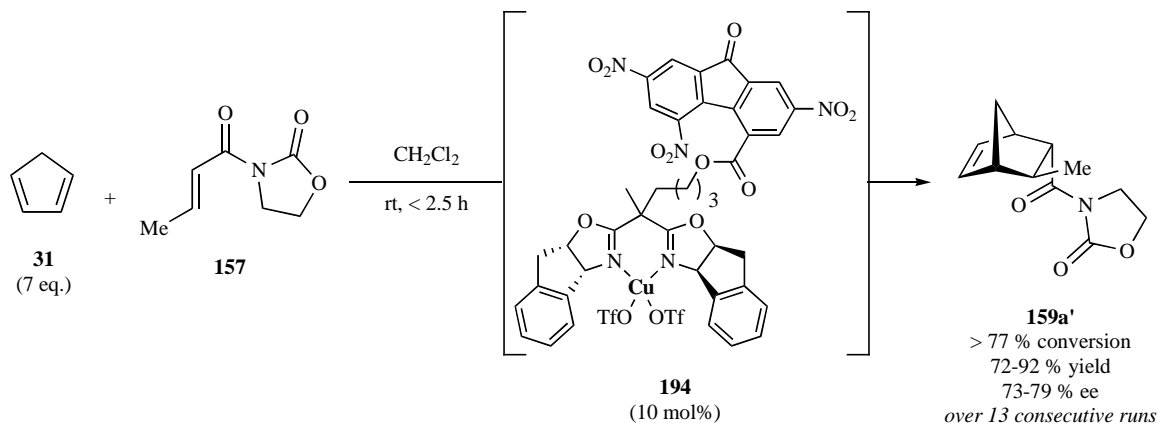
Methodological improvements have also concerned the recyclability of the chiral catalyst. To this end, two imidazolium tags can be incorporated in the ligand core of the catalyst **192** [108]. Interestingly, the cycloaddition between cyclohexadiene **191** and *N*-



Scheme 56.



Scheme 57.



Scheme 58.

acryloyloxazolidinone **152** proceeds only in hydrophobic ionic liquids ([Bmim]NTf<sub>2</sub> being the best) and gives better results than the classical CuBOX catalyst (Scheme 57). In addition, it can be reused for at least 20 times without a significant loss of yield or *endo* and enantioselectivity.

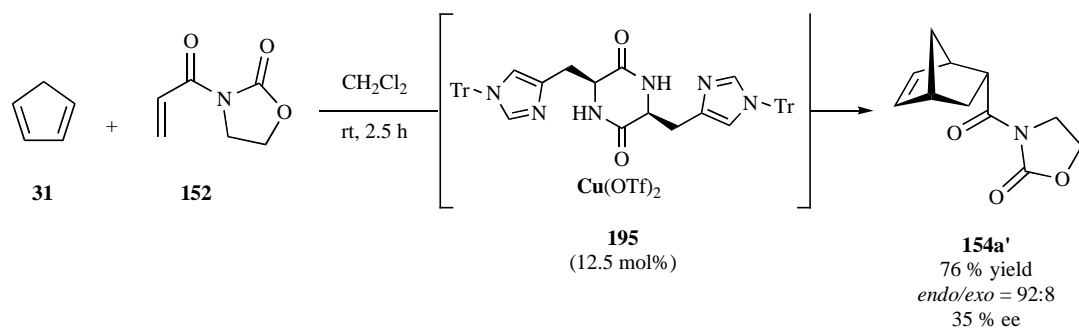
Ionic liquids can also serve to immobilize Cu(BOX) in a non-covalent fashion. The catalyst can be adsorbed on an ionic liquid film which can be used in solution (Supported Ionic Liquid Phase catalysis) or further immobilized on a solid support such as an ionic polymer (Polymer Immobilized Ionic Liquid Phase system) [109,110]. This latter system offers better enantiomeric excess and diastereoselectivity over SILP catalysis, in the detriment of the recyclability (copper leaching being the main drawback).

Another immobilization strategy is to form charge-transfer complexes (CTC) which are noncovalent interactions between an electron-rich arene (donor) and an electron-poor (receiver) arene. The group of Schulz successively investigated the incorporation of a donor and a receiver on the Cu(BOX) scaffold [111,112]. While

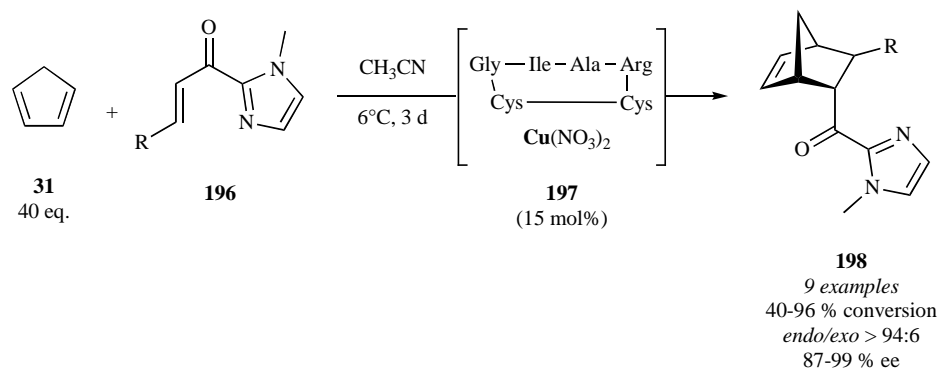
the anthracenyl ligand (donor) gave moderate results in terms of recyclability, the electron-poor ligand bearing a TNF group **194** was still affording quantitative conversion (about 90% yield) and good ee's of the *endo* adduct **159a'** after 20 different runs (Scheme 58). The catalyst can be recovered by a mere filtration after addition of anthracene and precipitation with pentane.

One important characteristic of copper(II) species is their azaphilic character. Peptides are therefore good candidates as chiral ligands. The cyclo[-His(Tr)-His(Tr)-] diketopiperazine **195** shows moderate induction (35% ee) but good facial selectivity (92% in favour of the *endo* isomer **154a'**) (Scheme 59) [113].

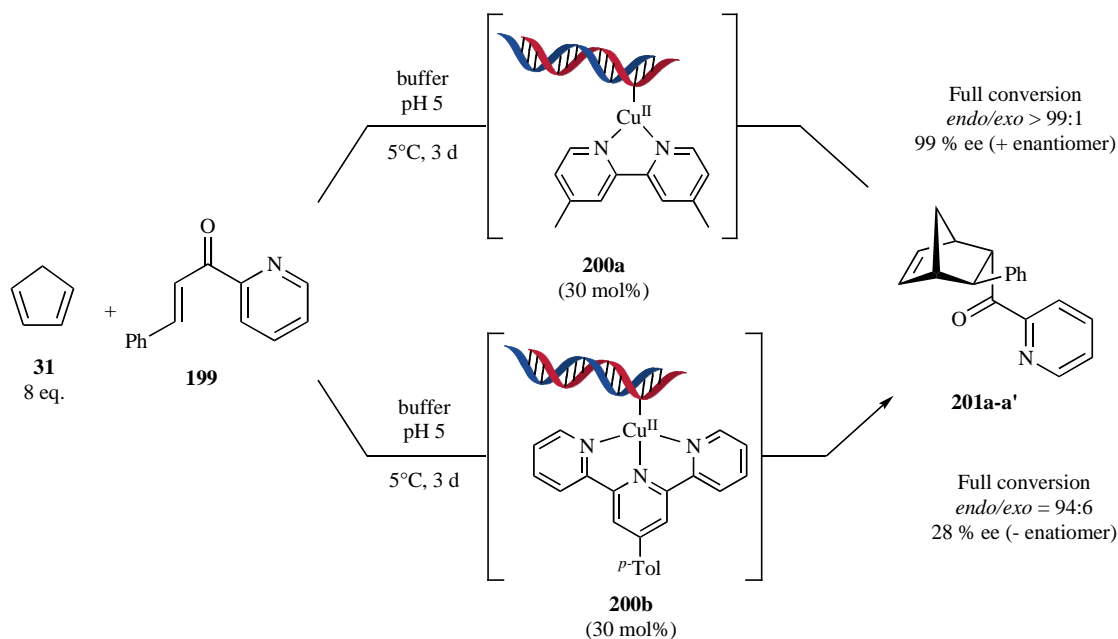
Cyclic peptides containing a disulphide bridge (**197**) have been designed and prepared by the group of Herrmann for the asymmetric copper-catalysed Diels-Alder cycloaddition (Scheme 60) [114]. They further optimised the sequence in order to obtain efficient catalysts. High *endo* selectivity (> 93%) as well as enantiomeric excess (> 88%) was obtained with acryloylimidazole dienophile **196**.



Scheme 59.



Scheme 60.



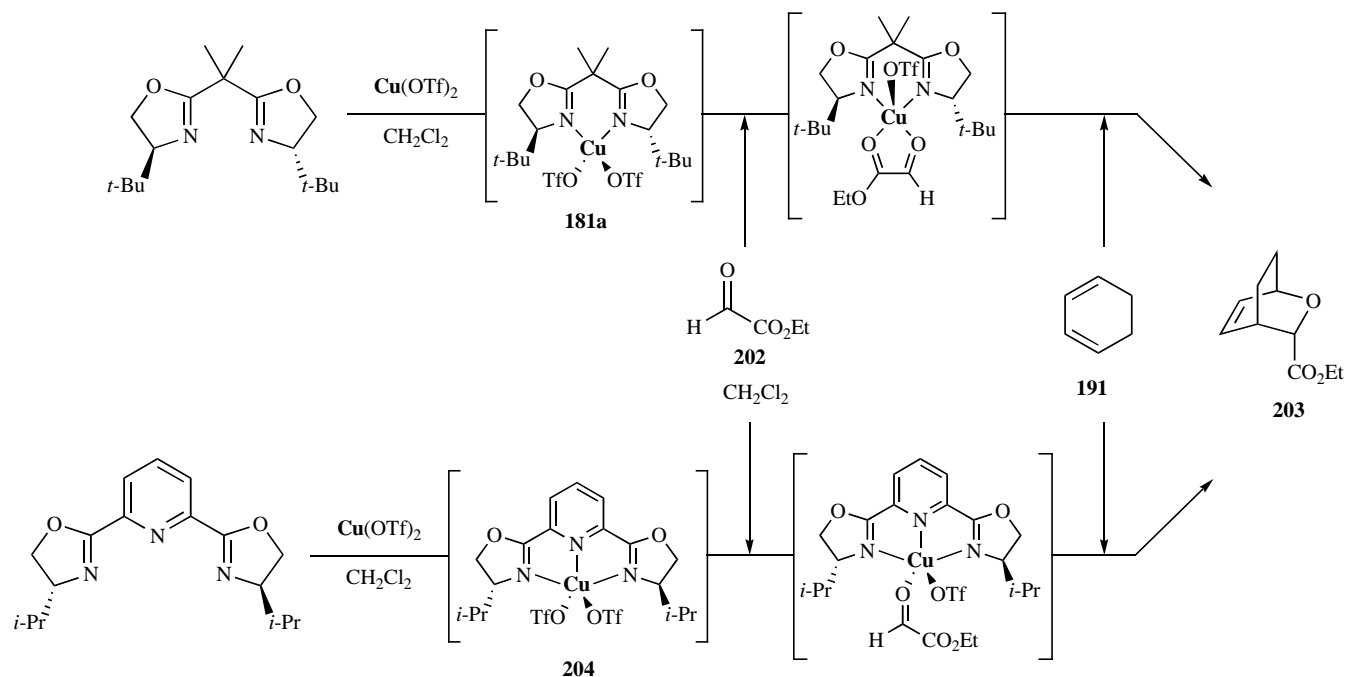
Scheme 61.

A 30-mer peptide derived from the bovine pancreatic polypeptide (bPP) in the presence of  $\text{Cu}^{2+}$  is able to catalyse the same reaction however the substrate scope is more dependent on the peptide sequence [115]. Though a maximum of 83 % ee has been obtained.

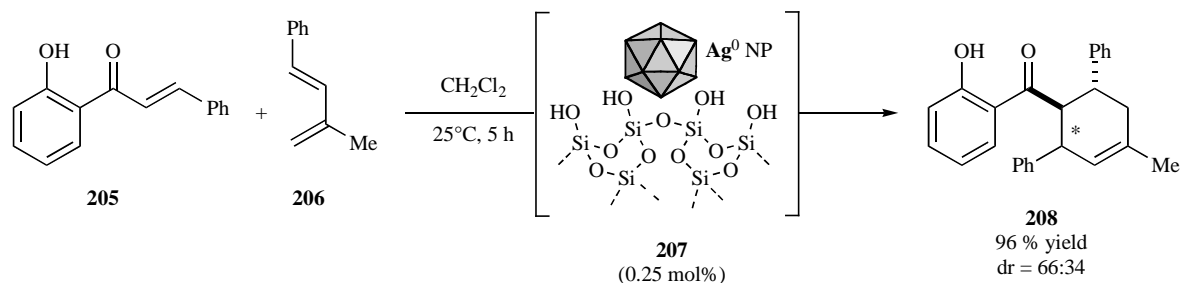
Artificial copper enzymes can also be used for the Diels-Alder reaction. Deuss *et al.* have prepared such enzymes by conjugation of sterol carrier protein type 2 like domain (SCP-2L) mutants with a tridentate copper ligand through thiol-maleimide ligation [116]. The best enantiomeric excess obtained is still limited (25 %). Feringa and Roelfes have shown that copper catalysed asymmetric Diels-

Alder reaction can be performed with salmon testes DNA (st-DNA) and a poly-pyridine ligand **200** [117]. Interestingly, the denticity of the ligand has a strong influence on the asymmetric induction (Scheme 61). The copper bound to the terpyridine ligand adopts an octahedral geometry while its geometry is a trigonal bipyramid when bound to the bipyridine ligand. The opposite enantiomer is obtained in this latter case, often with higher enantiomeric excess.

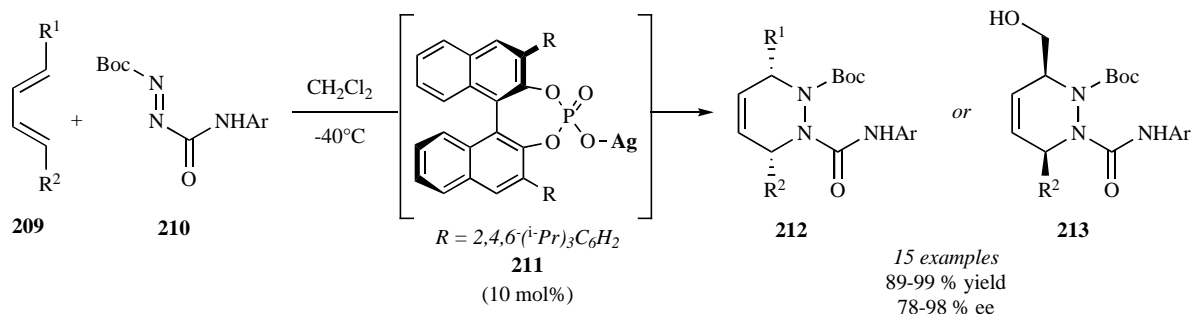
As already evoked (*vide supra*) the geometry of the copper ion in its chiral environment is important for the stereoselectivity of the reaction. EPR studies were conducted to decipher the intermediates



Scheme 62.



Scheme 63.



Scheme 64.

involved in the cycloaddition of ethyl glyoxylate **202** and cyclohexadiene **191**. Complexation of  $\text{Cu}(\text{OTf})_2$  with the (*t*-Bu)BOX ligand generates a tetrahedral intermediate (**181a**) which evolves to a penta-coordinated 18-electron complex after chelation with both carbonyls of the glyoxylate (Scheme **62**) [118]. With the (*i*-Pr)PyBOX ligand, the copper atom adopts a penta-coordinated distorted square pyramidal geometry (**204**) throughout the reaction stages [119].

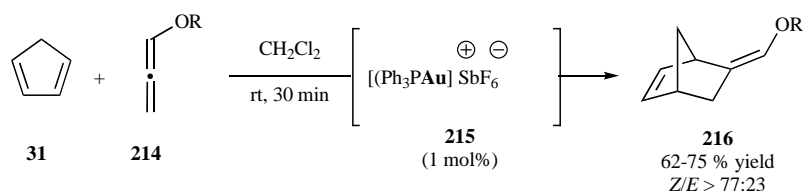
#### 4.9.2. Silver (Ag)

Silver(0) nanoparticles supported on silica (**207**) were found active in promoting the cycloaddition of hydroxychalcones **205**

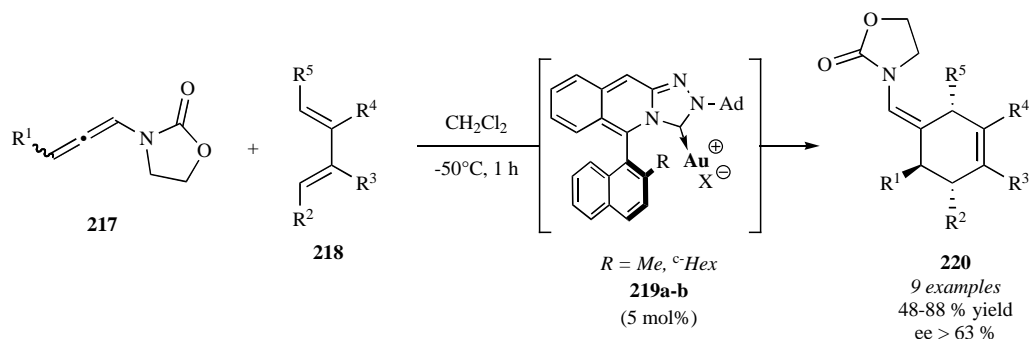
[120]. Although the *endo/exo* ratio is moderate, turnover numbers up to 8700 are achieved (Scheme **63**). The mechanism is believed to proceed through single electron transfer and generation of phenoxyl radical stabilized by the nanoparticle.

Chiral silver phosphates derived from BINOL (**211**) are able to catalyse the hetero-Diels-Alder reaction of diazenes **210** with unactivated dienes **209** with high enantiocontrol (Scheme **64**) [121]. Interestingly, the authors have noted a reversed regioselectivity if a hydrogen-bond donor was present in the diene. Indeed, a hydrogen-bond with the phosphate function and additional interaction with the silver atom (already involved in the  $\sigma$ -coordination of the urea nitrogen) has been computed.

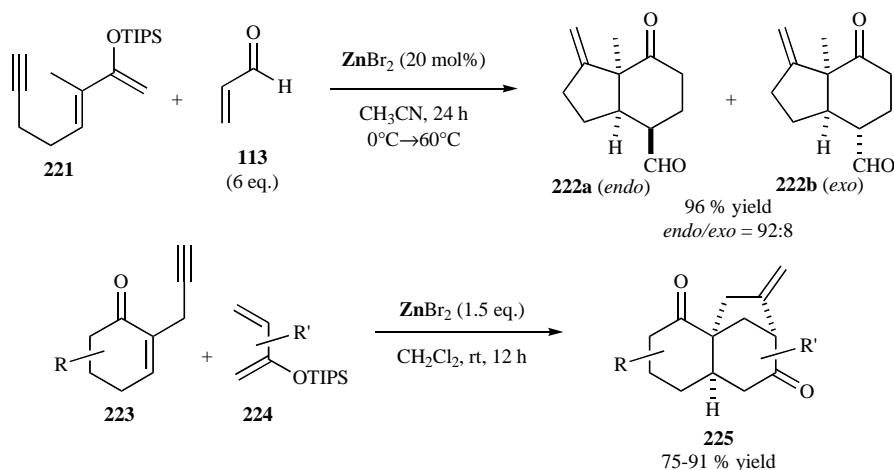




Scheme 65.



Scheme 66.



Scheme 67.

#### 4.9.3. Gold (Au)

Other metal phosphates such as magnesium, calcium or gold also allow the formation of the desired adduct, albeit in the racemic form. However gold(I) phosphoramidite ligands were found even more reactive (better yields and a reduced reaction time) and more selective [122].

Gold has recently been employed in organic transformations because of its rather unique properties of carbophilic Lewis acidity and  $\pi$ -complexation, both resulting from relativistic effects. The cycloaddition of allenyl ethers **214** is catalysed by the cationic complex  $[(\text{Ph}_3\text{P})\text{Au}]\text{SbF}_6$  (**215**) which coordinates first to the terminal allenic double bond ensued by the formation of an allylic cation intermediate (Scheme **65**) [123]. Computation shows that the transition state leading to the *Z* isomer was lower in energy, and thus confirms the experimental observations.

Similarly, the group of López and Mascareñas has shown that allenamides **217** can play the role of dienophile in the Diels-Alder reaction [124]. They have pointed out that both cationic gold complexes and neutral AuCl can catalyse this transformation, even though the neutral complex is less reactive (but more selective towards the [4+2] cyclisation). The use of atropisomeric NHC ligands

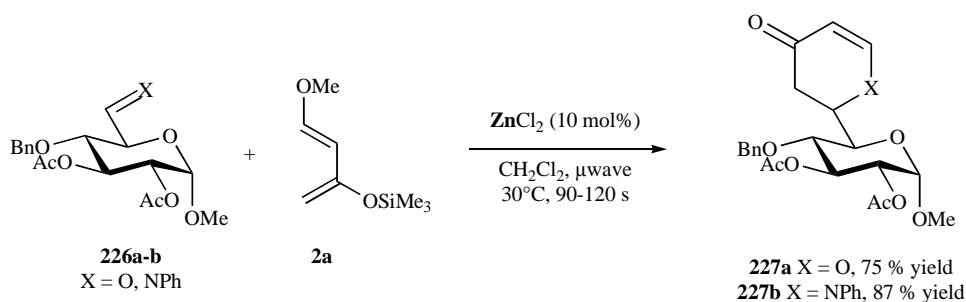
allows the formation of enantioenriched adducts **220** (> 87 % ee) with cationic gold complexes **219** (Scheme **66**) [125].

#### 4.10. Group 12

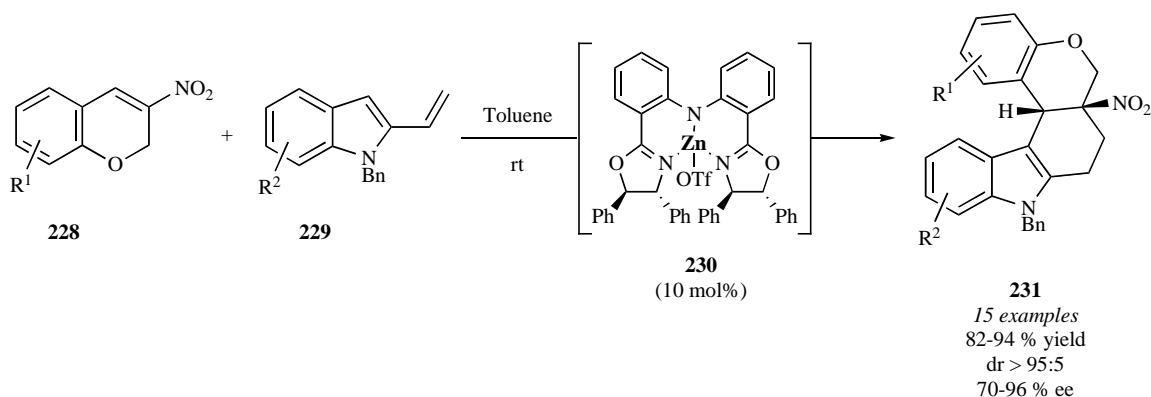
##### 4.10.1. Zinc (Zn)

With their filled valence-shell  $(n-1)d^{10} ns^2$  configuration, group 12 elements does not belong to the transition metals according to the IUPAC definition (which is an element whose atom has an incomplete *d* sub-shell, or which can give rise to cations with an incomplete *d* sub-shell). However, for the sake of convenience and since they share similar features than transition elements (as defined by the IUPAC) they will be discussed in this section.

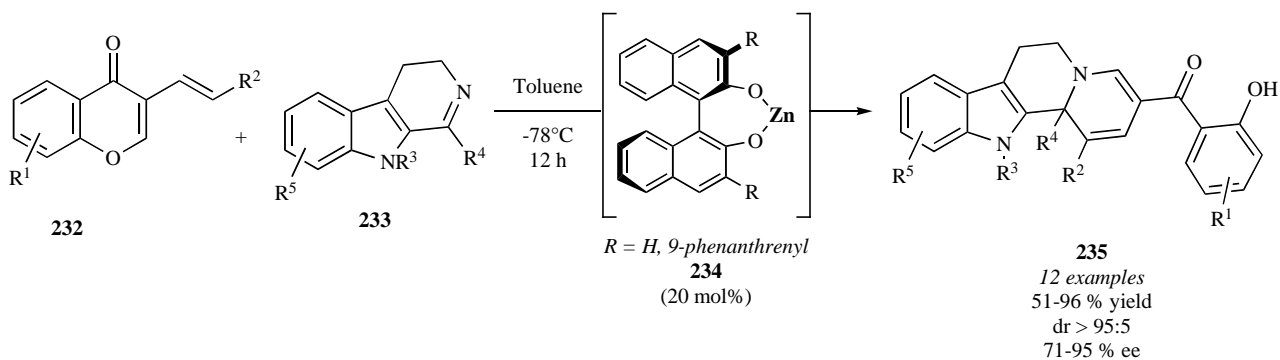
Recently, Zhu *et al.* have shown by DFT computation that  $\pi$ -binding to propene or  $\sigma$ -binding to acetaldehyde requires similar enthalpies in the case of zinc(II) salts [126]. Therefore, they are able to act as bifunctional catalysts allowing for a cascade cyclisation yielding *cis*-hydrindane cores (**222**) [127] or 6,6,5-tricyclic-fused systems (**225**) [128] (Scheme **67**). In this last example, a dimeric zinc complex is involved in a first  $\sigma$ -Lewis acid catalysed Diels-Alder reaction followed by a  $\pi$ -Lewis acid catalysed carbocyclisation.



Scheme 68.



Scheme 69.



Scheme 70.

The simultaneous use of microwave and  $\text{ZnCl}_2$  as Lewis acid has been defined as optimum conditions for the cycloadditions of the Danishefsky's diene **2a** with aldehydes (**226a**) or imines (**226b**) derived from carbohydrates (Scheme **68**) [129]. The nature of the starting sugar has an influence on the reactivity due to both steric and electronic interactions: *galacto*- and *manno*pyranoside derivatives are less reactive than glucose. In addition, electron-withdrawing protecting groups (acetates) allow better yields than electron-donating ones (benzyl).

Zinc(II) chloride has also been found valuable in the cycloaddition of unusual dienophiles such as 2-phosphono-2-alkenoates [130] or highly reactive cyclobutenones [131].

Among other metals, zinc(II) has been found the best to perform the enantioselective cycloaddition of 3-nitro-2*H*-chromenes **228** with *N*-benzyl-2-vinyl-1*H*-indoles **229** [132]. The fused heterocyclic adducts **231** were obtained with excellent diastereoisomeric ratios (> 95%) and 70-96% ee (Scheme **69**).

Although imino-Diels-Alder involving an electron-poor azadienophile and an electron-rich diene are well-known, inverse elec-

tron demand imino-Diels-Alder between an electron-poor diene (**232**) and an electron-rich imine (**233**) is seldom. Chiral indolizines **235** can be prepared in this manner by  $\text{Zn}^{\text{II}}$ -BINOL catalysis (Scheme **70**) [133]. Good yields are obtained (51-96 %) along with high optical purity (usually > 88 %).

## 5. *f*-BLOCK METALS

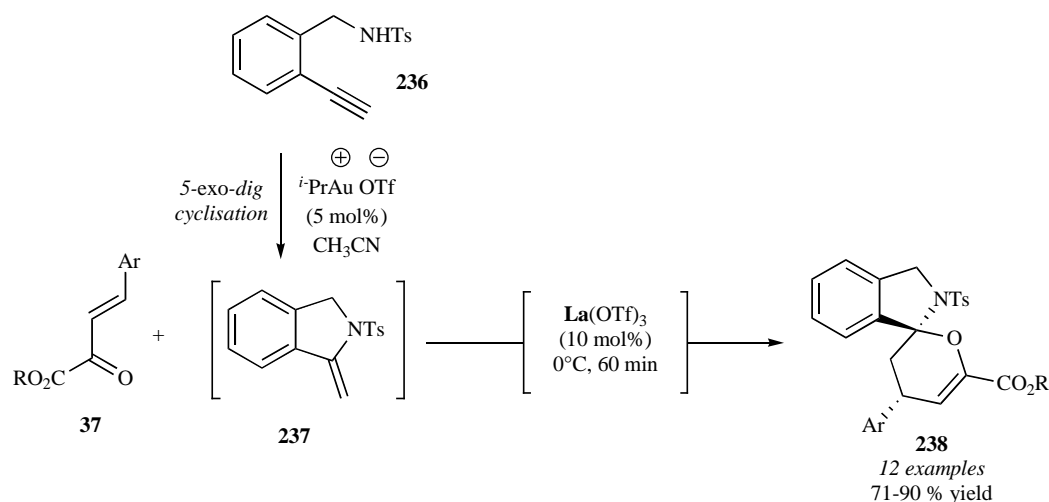
Although sometimes referred to as "inner transition metals" elements of the *f*-block possess peculiar properties (such as increased coordination number) which lead them to be treated apart.

### 5.1. Lanthanides

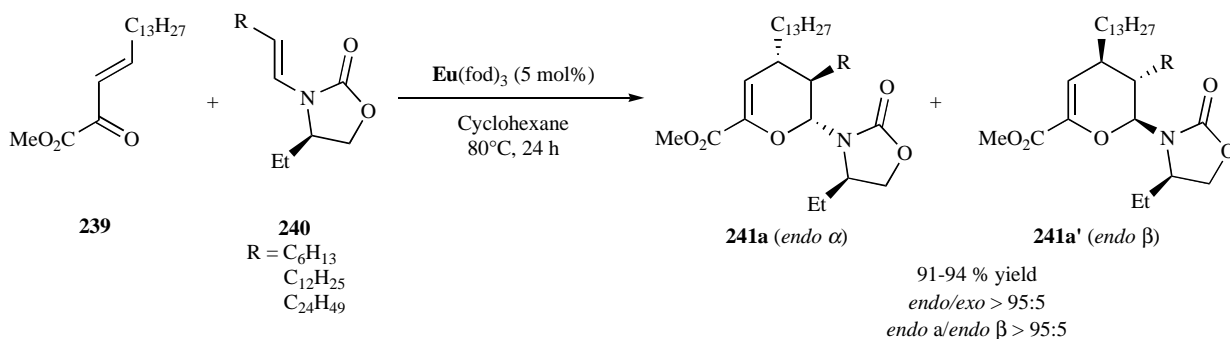
The first sub-group concerns the elements from  $Z=57$  (*La*) to  $Z=71$  (*Lu*). They mainly adopt the +3 oxidation state and basicity decreases as the atomic number increases.

#### 5.1.1. Lanthanum (*La*)

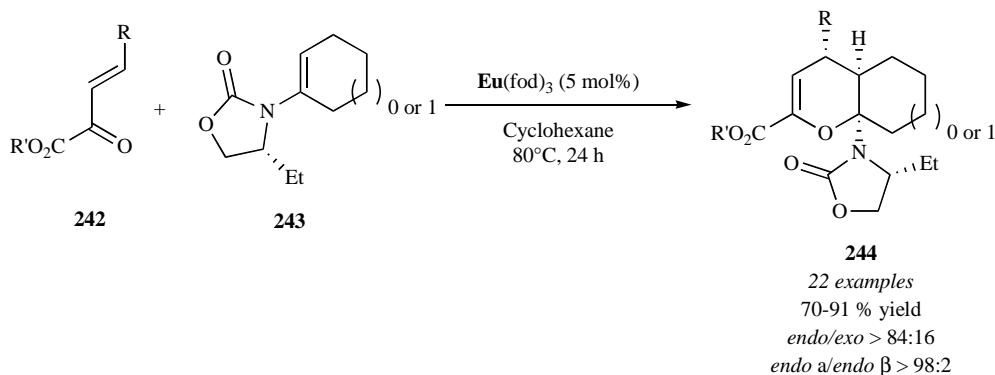
As already stated gold is a  $\pi$ -Lewis acid (*vide supra*) often used for hetero- or carbocyclisation whose resulting intermediate can



Scheme 71.



Scheme 72.



Scheme 73.

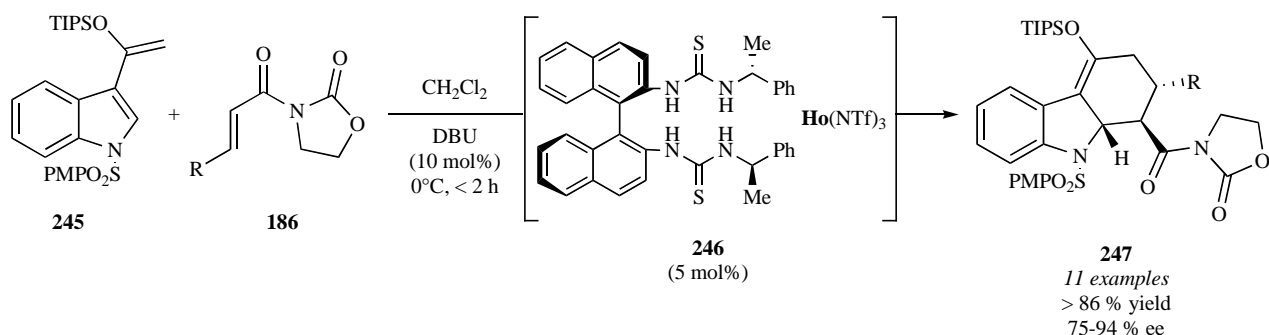
further be involved in a cycloaddition step. Xu's group has investigated the synthesis of spiroketals and spiroaminals from  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **37** [134]. The dienophile **237** is prepared by Au(I)-catalysed 5-*exo-dig* cyclisation of either benzylic alcohols or amines (**236**) (Scheme 71). Spiroketals are best prepared by Y(OTf)<sub>3</sub> cycloaddition while La(OTf)<sub>3</sub> is necessary for efficient synthesis of spiroaminals **238** (71-90 % yield).

### 5.1.2. Europium (Eu)

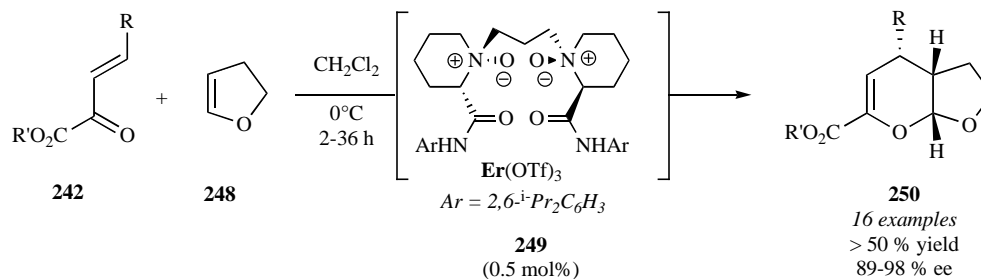
Eu(fod)<sub>3</sub> is a potent oxophilic Lewis acid which has been extensively used for inverse electron demand hetero-Diels-Alder reaction, especially by the group of Dujardin. Although very mild Lewis acid, they have shown that this catalyst can be used under hyperbaric conditions when the intrinsic reactivity of the partners is too low [135]. The reaction between  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoester

**239** and chiral *N*-alkenyloxazolidinones **240** is highly *endo* selective (Scheme 72) when catalysed by Eu(fod)<sub>3</sub> (assuming a concerted mechanism occurs) whereas a complete reversed facial selectivity is observed when SnCl<sub>4</sub> is used (explained by the formation of a zwitterionic intermediate) [136]. In addition, the yields are lower due to the high acidic character of SnCl<sub>4</sub> (partial decomposition of the heterodiene). With an appropriate dienophile, analogues of steganacin can be obtained [137].

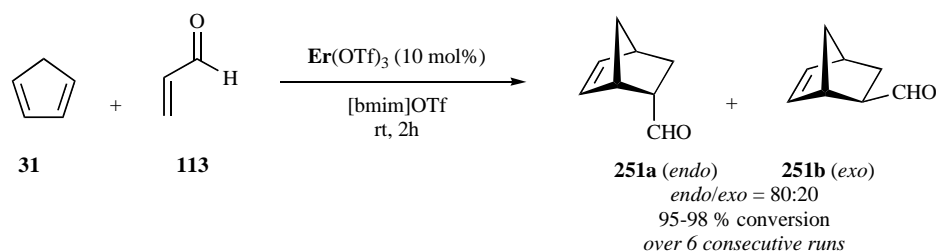
The use of dienophiles derived from ketones (cyclic in particular) is limited due to their low reactivity. Gallier *et al.* have shown that chiral cyclic enamides **243** were able to yield the bicyclic adducts **244** with high facial and *endo* selectivity (Scheme 73) [138]. This reaction has been developed as an alternative Robinson annulation.



Scheme 74.



Scheme 75.



Scheme 76.

### 5.1.3. Gadolinium (Gd)

Chiral Gd(hfc)<sub>3</sub> has been used in the cycloaddition of benzaldehyde with the Danishefsky's diene with moderate induction (35-40 % ee) slightly higher than Eu(hfc)<sub>3</sub> [139]. However, when immobilized on a polysiloxane and used as a catalytically active stationary phase in on-column reaction gas chromatography the optical purity dropped to only 12 % ee.

### 5.1.4. Holmium (Ho)

The asymmetric synthesis of highly substituted hydrocarbazoles **247** has been described by the group of Nishida using a chiral holmium(III) thiourea complex **246** [140]. Silyloxyvinylindoles **245** undergoes a complete *exo* selective cycloaddition with *N*-acyloxazolidinones **186** (Scheme 74). Ho(NTf<sub>3</sub>) has been found superior than Yb(OTf)<sub>3</sub>.

### 5.1.5. Erbium (Er)

The asymmetric inverse electron demand cycloaddition of β,γ-unsaturated-α-ketoesters **242** with electron-rich dienophiles has been performed with a chiral *N,N'*-dioxo/Er<sup>III</sup> complex **249** (Scheme 75) [141]. Erbium is superior to the other metals salts tested especially lanthanides yielding the bicyclic adduct **250** with better yields, *endo* selectivity and optical purity. Amounts of catalyst as low as 0.05 mol% can be used still giving quantitative formation of the adduct.

Natural abundance of lanthanides is rather low, so efficient way of recycling is strongly recommended. Bortolini *et al.* have demon-

strated the use of ionic liquid to perform Er(OTf)<sub>3</sub>-catalysed Diels-Alder reactions (Scheme 76) [142]. The ionic phase containing the catalyst can be reused for at least 6 times without loss of the activity (which remains higher than using CH<sub>2</sub>Cl<sub>2</sub> as solvent). Additionally, the *endo/exo* ratio has been found slightly dependent upon the ionic liquid used.

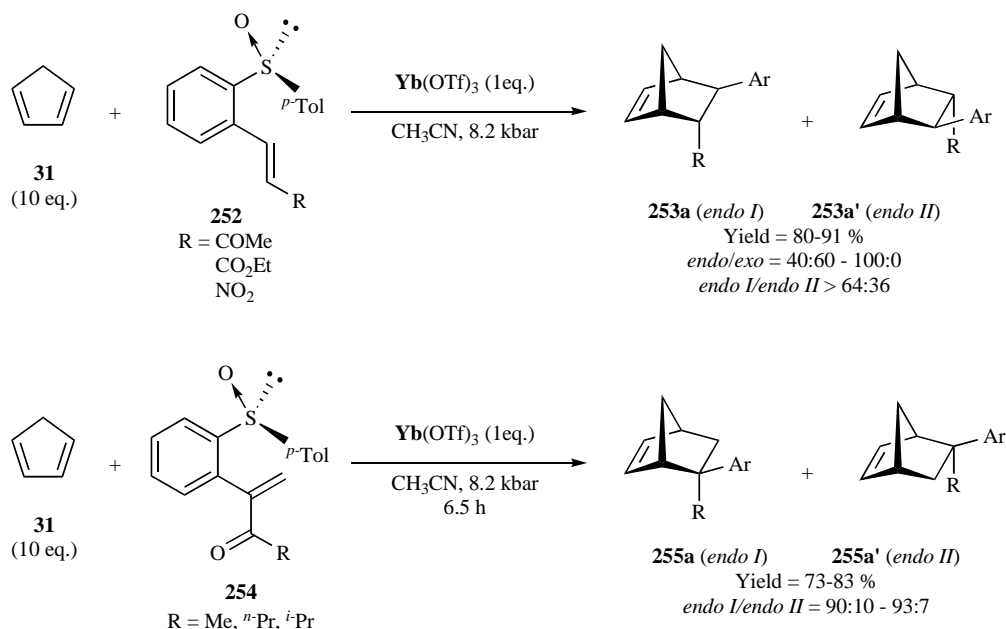
### 5.1.6. Ytterbium (Yb)

The inverse electron demand cycloaddition of vinyl ethers and α,β-unsaturated aldehydes or ketones can be performed on a wide range of substrates with Yb(fod)<sub>3</sub> upon conventional or microwave heating [143].

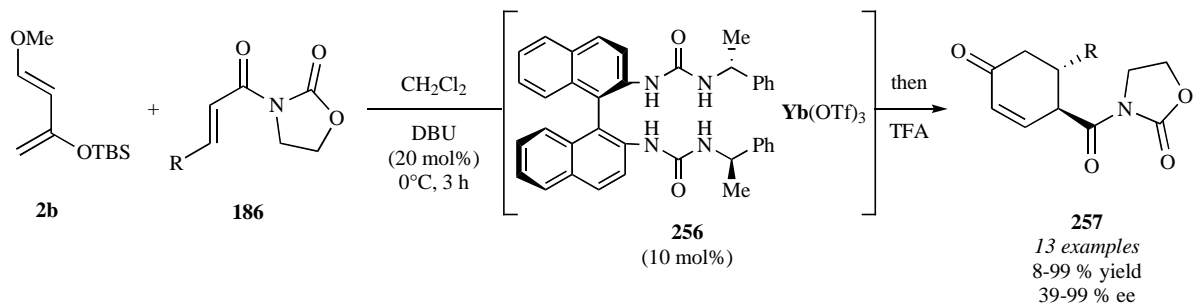
The cycloaddition of cyclopentadiene with chiral dienophiles bearing a remote *p*-tolylsulfinyl group (**252** and **254**) catalysed by Yb(OTf)<sub>3</sub> has been investigated [144]. Unless a highly reactive dienophile is used, hyperbaric conditions are required (8.2 kbar). Moderate to good diastereoselectivity was obtained albeit depending on the type of substrate used (Scheme 77).

The use of the chiral BINUREA ligand with Yb(OTf)<sub>3</sub> (**256**) allows the enantioselective cycloaddition of the Danishefsky's diene **2b** with acryloyloxazolidinones **186** [145]. The desired cyclohexenones **257** were obtained usually with very high yields and with excellent optical purity (Scheme 78).

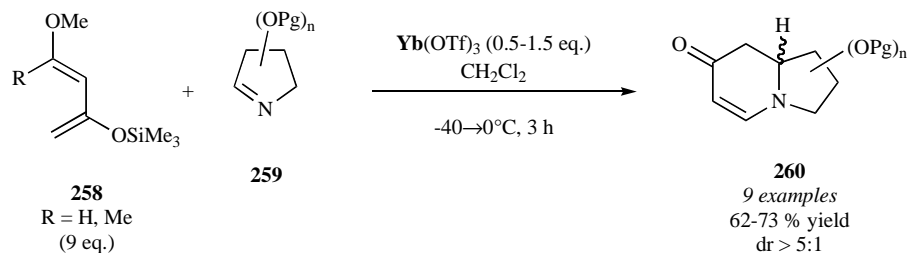
Cyclic imines **259** derived from chiral tartaric or malic acid can be transformed to indolizidinone **260** by cycloaddition with Danishefsky-type dienes **258** catalysed by Yb(OTf)<sub>3</sub> (Scheme 79) [146].



Scheme 77.



Scheme 78.



Scheme 79.

Diastereoselectivity of this reaction is governed by the configuration of the stereogenic center at C3 position of the imine as well as by the steric requirements of its protecting groups.

Imino-Diels-Alder reactions can also be achieved using polyoxometalates (POM) incorporating a metallic Lewis Acid [147]. The authors used a Dawson-type polyoxotungstate ( $[P_2W_{17}O_{61}]^{10-}$ ) and  $Yb^{III}$  (**262**) showed a better catalytic activity than  $Hf^{IV}$ ,  $Zr^{IV}$  or  $Y^{III}$  (Scheme **80**). Noteworthy, these metal POMs are organosoluble but can easily be precipitated thus allowing for recovery. This has been demonstrated in a Mannich reaction for at least ten times with  $Yb/POM$ .

## 5.2. Actinides

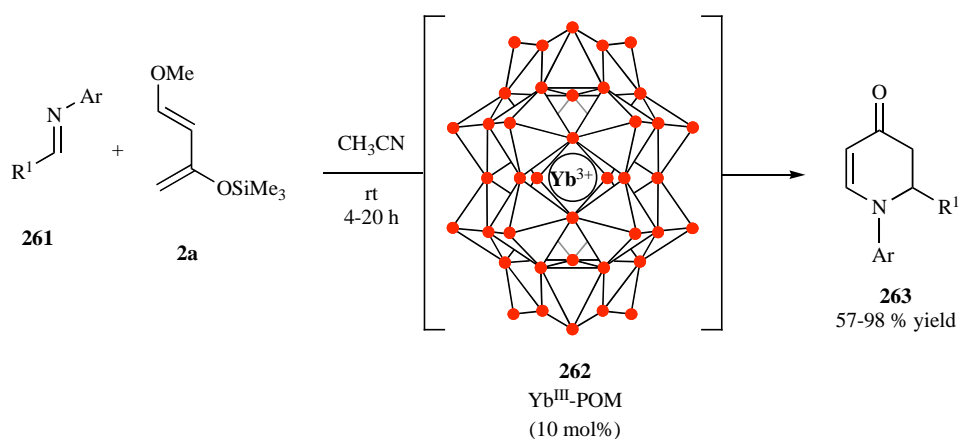
Actinides are a special group of elements since most of them are non-natural and radioactive. Therefore, their use in organic chemistry is extremely limited.

### 5.2.1. Uranium (U)

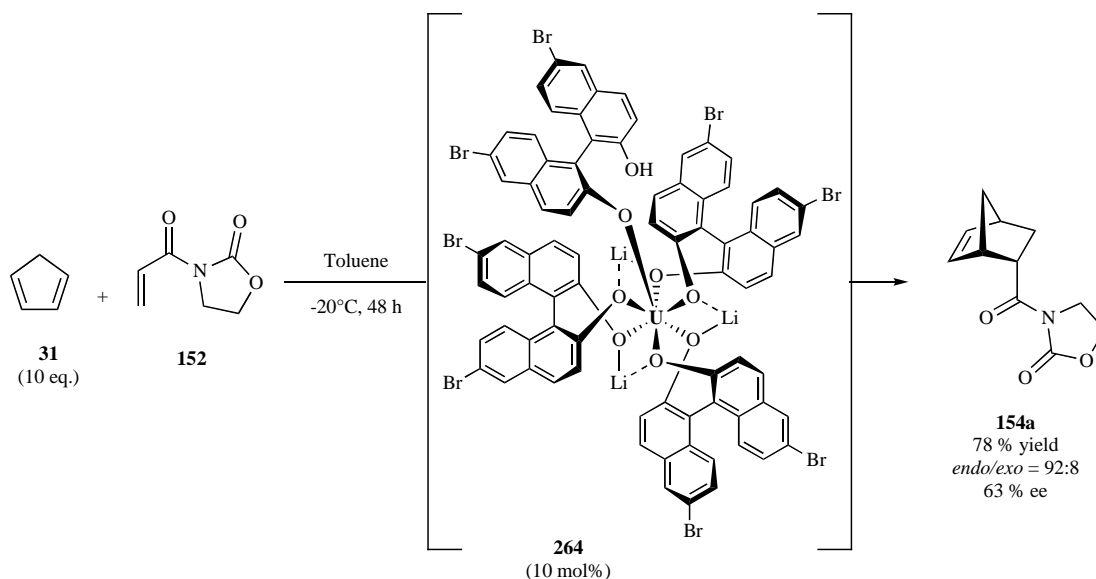
Increasing the oxidation state is expected to increase the Lewis acidity at the metal centre. Therefore, Robinson *et al.* have prepared uranium(IV) chiral heterobimetallic complexes derived from BINOL [148]. They show interesting reactivity and selectivity, only slightly lower than the  $Yb(III)$  analogue (Scheme **81**). The radioactivity in such a reaction may be a concern, however the authors have measured its intensity after filtration on a silica plug, and none of the aqueous or organic phase is contaminated with uranium.

## 6. CONCLUSION

In the past few years, numerous metal salts or catalysts have been developed for the homo- or hetero-Diels-Alder cycloadditions (either normal or inverse electron demand). These latest advances can address specific needs towards the synthesis of a desired target



Scheme 80.



Scheme 81.

or belongs to a methodological development. To this end, several compounds have been used as benchmark reagents in order to probe the reactivity/selectivity of any cycloaddition. Among the most used dienes is the Danishefsky's diene **2a**, which is very reactive (due to the two electron-donating groups) and selective (by chelation of its methoxy group with the Lewis acid) yielding (hetero)cyclic ketones. Cyclopentadiene **31** is also often used to quantify the asymmetric induction of a catalyst through the formation of known bicyclic adducts. However, its tendency to dimerize may hamper its use. Inverse electron demand hetero-Diels-Alder is performed using  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters **37** as highly regioselective diene.

Since 2009, major improvements have been described regarding the reactivity of the substrates, in particular highly congested reactants (especially those yielding adducts with a quaternary chiral center) or ketones which traditionally react sluggishly as heterodienophiles. An increasing number of catalysts is now able to promote these transformations more efficiently, but room is still available for improvement. The same remark can be formulated for diastereo- and/or enantio-selectivity. Yet, obtaining only either the *endo* or the *exo* adduct for a specific cycloaddition is not always possible. Neutral-electron-demanding Diels-Alder reactions may

undergo the most significant progress in the near future as the activation of either the diene or dienophile seems more easily feasible.

Sustainability of the whole process has become increasingly significant. Alternative solvents have emerged recently and have to be further investigated. These reactions are totally atom-economic but recyclability of the promoters (which are sometimes rather expensive) is crucial for improving their viability. Although interesting examples are already described, the selectivity or reactivity may be diminished to some extent.

Therefore, the quest for the ideal promoter is not achieved yet, and efforts are still ongoing to further improve the reactivity and selectivity issues. Finally a more in-depth understanding of the reactivity (secondary interactions, solvent effect...) would be desirable in order to design even more efficient promoters.

#### LIST OF ABBREVIATIONS

ATPH	=	Aluminium Tris(2,6-diPhenylphenoxide)
BINAP	=	2,2'-bis(diphenylphosphino)-1,1'-BINAPhtyl
BINOL	=	1,1'-BI-2-naphthOL
BOX	=	Bis(OXazoline)

Bmim	=	1-Butyl(3-Methylimidazolium)
BPTPI	=	<i>N</i> -benzene-fused-phthaloyl-piperidinonate
bpz	=	bipyrazyl
CTC	=	Charge-Transfer Complexes
EDG	=	Electron-Donating Group
ee	=	enantiomeric excess
EWG	=	Electron-Withdrawing Group
FMO	=	Frontier Molecular Orbitals
hfc	=	(1 <i>R</i> ,4 <i>S</i> )-3-heptafluorobutanoyl-camphor
HOMO	=	Highest Occupied Molecular Orbital
IED	=	Inverse Electron Demand
IMDA	=	IntraMolecular Diels-Alder
LUMO	=	Lowest Unoccupied Molecular Orbital
NED	=	Neutral Electron Demand
NHC	=	<i>N</i> -Heterocyclic Carbene
PIILP	=	Polymer Immobilized Ionic Liquid Phase
POM	=	PolyOxoMetalate
PNNP	=	(1 <i>S</i> ,2 <i>S</i> )- <i>N,N'</i> -bis[ <i>o</i> -(diphenylphosphino)benzylidene] cyclohexane-1,2-diamine
SILP	=	Supported Ionic Liquid Phase
st-DNA	=	salmon testes DNA
TADDOL	=	$\alpha,\alpha,\alpha',\alpha'$ -TetraAryl-1,3-Dioxolan-4,5-DimethanOL
TBPP	=	<i>meso</i> -Tetrakis(4- <i>tert</i> -ButylPhenyl)Porphyrinate
TPC	=	5,10,15-TriPhenylCorrole
TNF	=	2,4,7-TriNitroFluoren-9-one
TPP	=	<i>meso</i> -TetraPhenylPorphyrinate

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

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