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Magnesium-catalyzed stereoselective transformations – A survey through recent achievements

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ABSTRACT

Magnesium (Mg) constitutes one of the most abundant metal elements in the Earth's crust. The spectacular career of magnesium in organic chemistry has been initiated at the beginning of XX century and has still been lasting today. The discovery of organomagnesium compounds by Philippe A. Barbier and Victor Grignard is commonly recognized as one of the milestones in development of (organic) chemistry. The subsequent applications of Grignard reagents as relatively easy generated synthons in enantioselective reactions have opened new possibilities for acquiring enantiomerically enriched compounds. On the other hand, asymmetric reactions in which magnesium plays a role of catalyst can be considered still limited, especially when their number is compared to the number of contributions aimed at transition metal-catalyzed or organocatalyzed stereoselective transformations. However, taking into account the current trends of replacing expensive metals with their cheaper counterparts and making catalysis more environmentally (and user) friendly, the development of new and modification of known methods, which employ Earth-abundant metals, is very advisable. In this study we intend to emphasize the role of magnesium in organic chemistry, mainly in catalytic asymmetric synthesis. Among the already reported catalytic procedures, we have discussed the most recent examples, however, we also mentioned some, the groundbreaking previous ones. An exception for the pericyclic reactions has been made, as these reactions constitute the first examples of the use of magnesium catalysis in asymmetric synthesis. An attention has been drawn to some structural aspects, associated with either experimentally-determined geometry of the catalytic species or the calculated transition state(s) for a given asymmetric transformation.

1. Introduction

Nature-inspired processes, such as chirality induction, molecular recognition and molecular (self)organization play an important role in contemporary chemistry. The first of them, namely induction (transfer) of chirality is the concept covering all the processes of the transfer of information about the three-dimensional structure of "the chirality inducer" (usually catalysts) to the substrate [1,2]. Of the many molecules that are routinely used in asymmetric synthesis as ligands/catalysts, some are referred to as *privileged* (Fig. 1) [3,4]. This privilege originates from their versatility, which is understood, *inter alia,* as the ability to catalyze more than one reaction, their availability and potentiality to fine tuning for specific applications.

Even the cursory analysis of the literature on the subject leads to the conclusion that the greatest expectations are associated with several trends (Fig. 2), from which three seemed to be the most important ones [5,6].

The first of them (it can be called "classic") is catalysis with metal complexes [7]. In the case of asymmetric catalysis, the first and, in our humble opinion, so far unbeatable example of efficient metal catalysis is

Abbreviations: BDOX, Benzo[d][1,3]dioxo Group; BINOL, 1,1′-Bi-2-naphthol; Bn, Benzyl Group; Boc, *tert*-Butyloxycarbonyl Group; Conc., Concentration; CPME, Cyclopentyl Methyl Ether; Cy, Cycloheksyl Group; DCM, Dichloromethane; DMF, Dimethylformamide; *dr*, Diastereomeric Ratio; EDG, Electron Donating Group; *ee*, Enantiomeric Excess; Et, Ethyl Group; EWG, Electron Withdrawing Group; HMPA, Hexamethylphosphoramide; HPLC, High Performance Liquid Chromatography; *i*Pr, Isopropyl Group; K-10, Montmorillonite; LHMDS, Lithium bis(trimethylsilyl)amide; MCH, Methylcyclohexane; Me, Methyl Group; MTBE, Methyl-*tert*-Buthyl Ether; Naph, Naphtyl Group; *n*Pr, *n*-Propyl Group; Ph, Phenyl Group; PMB, *para*-Methoxylbenzyl Group; PMP, *para*-Methoxyphenyl group; *rr*, Regioisomeric Ratio; RT, Room Temperature; TBS, *tert*-Butyl(dimethyl)silyl Group; TFA, Trifluoroacetic Acid; THF, Tetrahydrofurane; Thien, Thienyl Group; TMS, Trimethylsilyl Group; VB, Vinylbenzyl Group.

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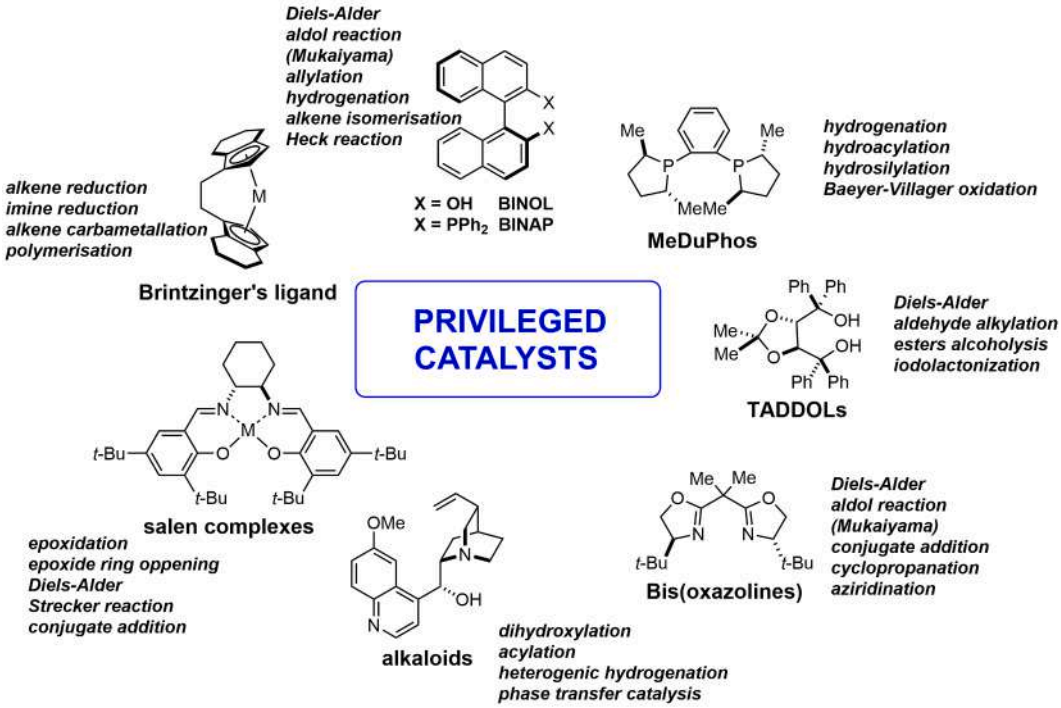


Fig. 1. Example structures of privileged ligands/catalysts.

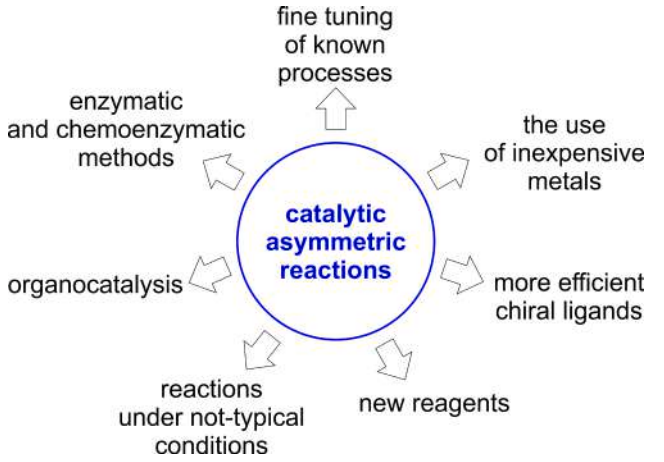


Fig. 2. Some of the current trends visible in the field of the catalytic asymmetric synthesis.

asymmetric hydrogenation with gaseous hydrogen. The known modern (transition) metal-based catalysts are prone to catalyze reaction at very low loading, with high turnover close to that reported for biocatalysts operating in living organisms. On the other hand, the high cost of metal compounds (especially of the noble metals), often difficult and laborious preparation of the complexes as well as usually very strict requirements for reaction conditions can be considered the main disadvantages of such metal-based catalysis. Which fragment, metal or ligand, is more important to the success of a given reaction constitutes a question of an academic nature. As long as metal, in elemental or ionic form, enables reaction in general, the ligand is responsible for metal activation and/or for chirality transfer [8].

The second approach, commonly referred to as "organocatalysis" assumes the use of small chiral organic molecules as catalysts [9–16]. The spectacular successes reported by several scientific groups, confirmed by the verdict of the Noble Committee (List and MacMillan were awarded in 2021), give the impression that asymmetric catalysis has gained an universal synthetic tool. The most important advantage of organocatalytic approach to catalysis relies on (rather postulated than generally accepted) overcoming inconveniences associated with metal catalysis and, above all, the lack of metal. However, having achievements of organocatalysis in mind, one should remember its shortcomings as well. First of them is the problem with the low versatility of this approach. While the successes cannot be denied, it should be pointed out that most of them concern very close reactions types. For noble metal catalysis, the catalyst loading rarely exceeds 1 mol%, while for small organic molecule catalysis is oscillated at around 10 mol% [17].

The third trend, which we want to mention here, is an attempt to replace the precious metals with their less expensive and Earth-abundant counterparts, or to merge organocatalysis with transition metal catalysis [18–25]. To the group of Earth-abundant metals belong alkaline metals, such as magnesium and calcium. However, the application of these metals in catalytic asymmetric synthesis seems to be inversely proportional to their abundance in the Earth's crust [26–28]. The observed discrepancy between abundance and applications in catalytic asymmetric synthesis has remained in contrast to, i.e. wide use of organomagnesiums in organic synthesis.

As to date, the number of reviews aiming at magnesium catalysis have been published. Some of them focused on the reactions [29,30], where others as the starting points for further elucidations take structure of the catalytic species and the methodology of obtaining them [31–33]. As the recent reviews covered the years from the 90′s of the last century up to the beginning of 2017, in this work we would focus on the most recent contributions to the field of magnesium-catalyzed asymmetric synthesis. Thus, we have limited the discussion to the last 5 years

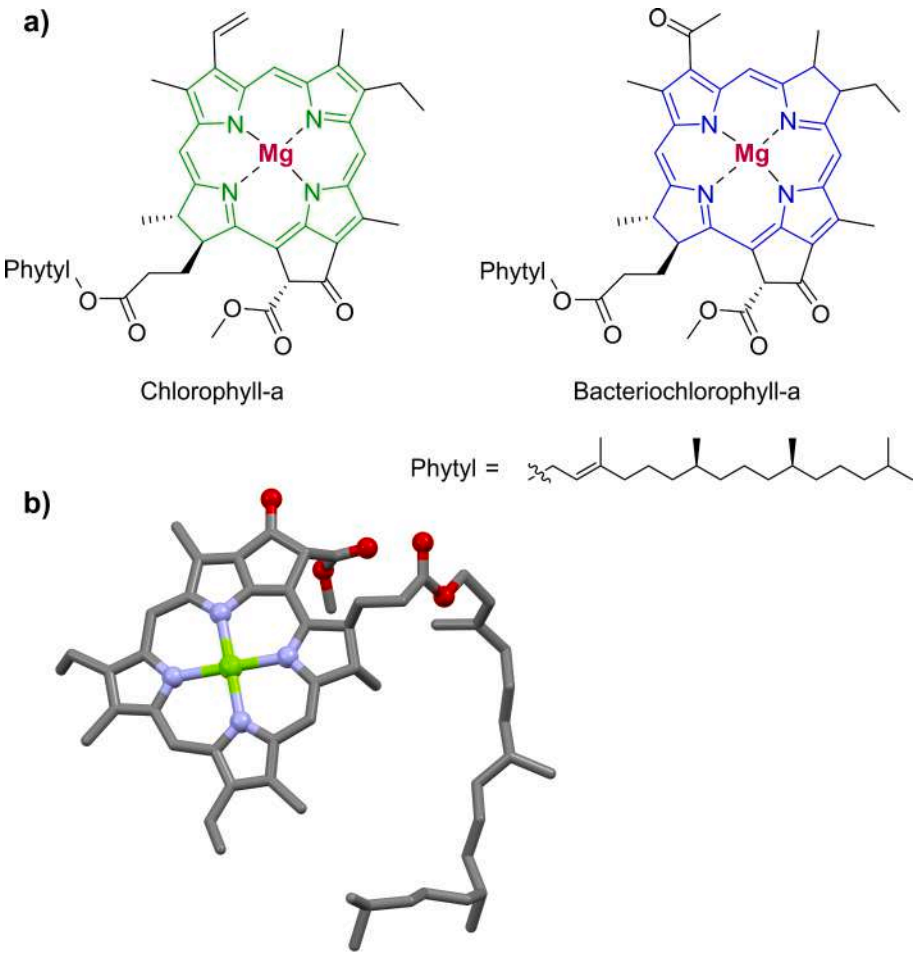


Fig. 3. a) Chemical structure of chlorophyll-a and bacteriochlorophyll-a. b) X-Ray determined structure of chlorophyll-a [41].

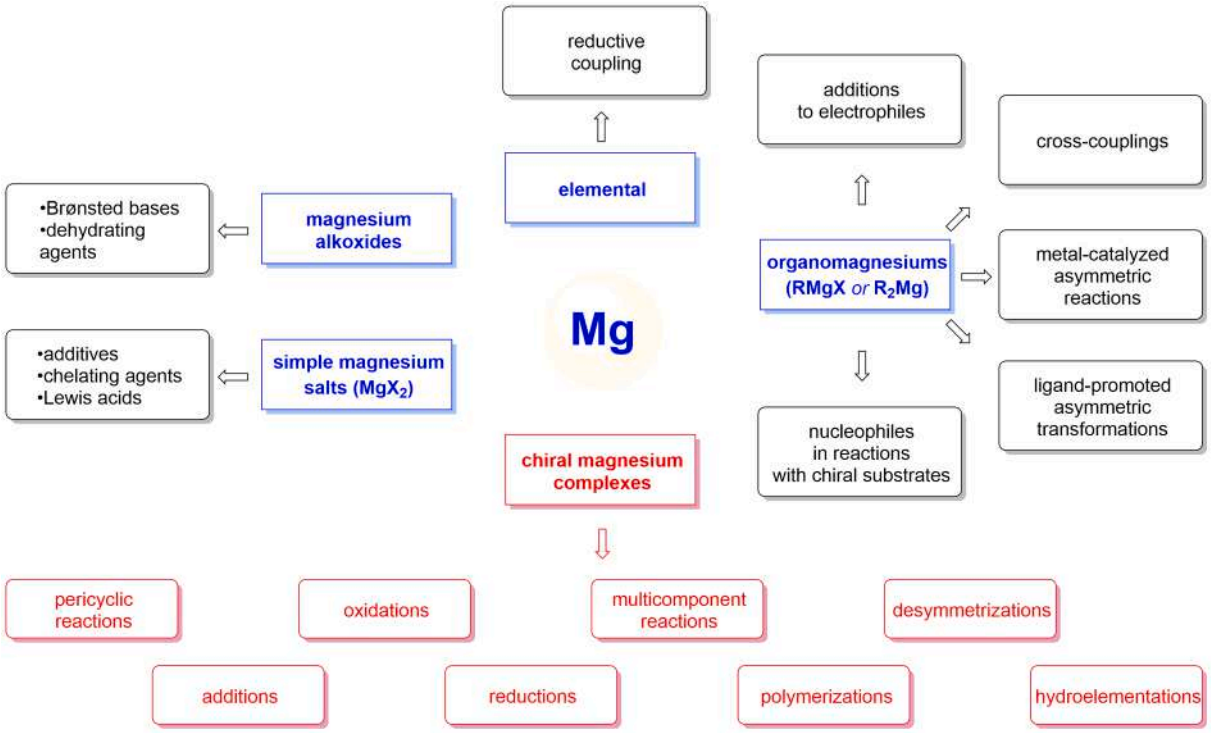
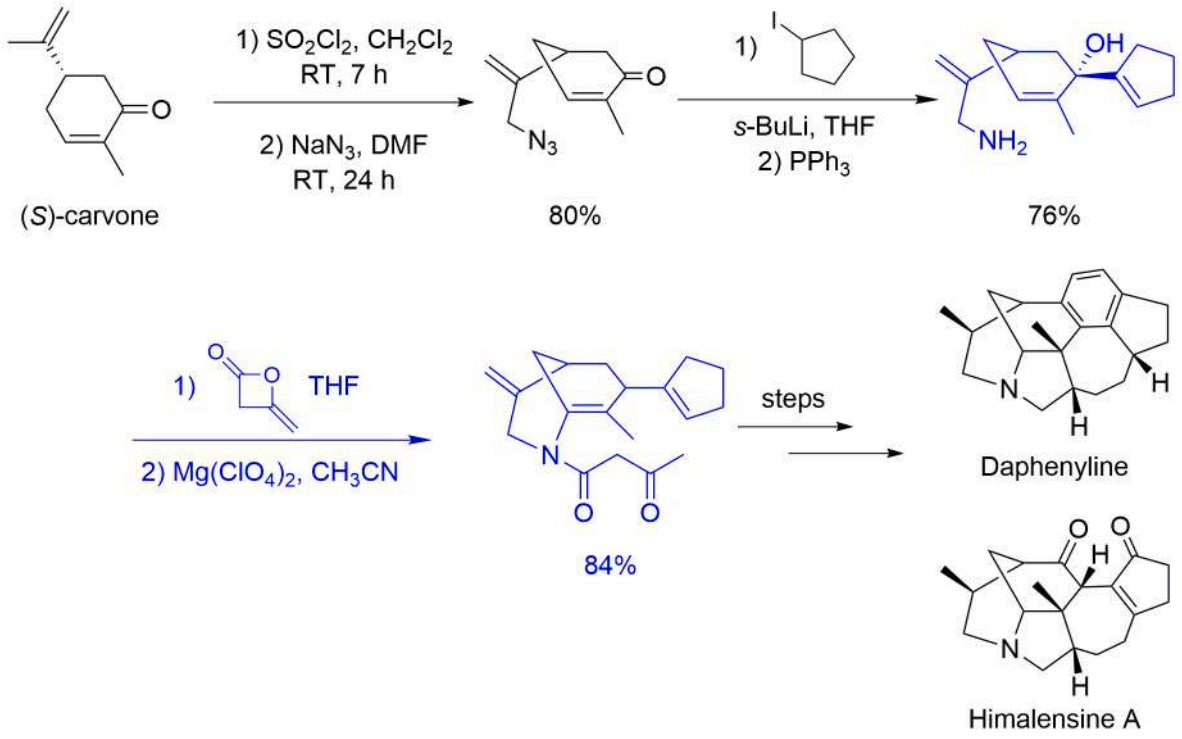


Fig. 4. Common applications of elemental magnesium, its simple compounds and chiral magnesium complexes in organic synthesis.



Scheme 1. A simplified synthetic route to (–)-daphenylline and (–)-himalensine with magnesium-catalyzed amidocyclization indicated.

(2017–2022). However, in some cases, the discussion also has touched on older literature as these achievements seemed to be important for the development of particular synthetic methodology.

We have focused on synthesis of single entities in enantioenriched forms, the applications of magnesium catalysis to, i.e. stereoselective polymerization of the *rac*-lactide, would not be discussed here [34–39].

2. A glimpse of the use of magnesium and magnesium compounds in organic synthesis

Magnesium is an element of the second group of the periodic table. Its atomic and ionic radii are both small, compared to analogous alkali metals, which results from a relatively high charge of the atomic nucleus [40].

Magnesium (like calcium) is one of the elements that are quite widespread in the Earth's crust (seventh most abundant element). It is a component of a number of silicate minerals and it is also present in some types of mineral waters.

One of the important (if not the most important one) natural pigments, namely chlorophyll (*vide infra*), contains magnesium in the complex form with porphyrin (Fig. 3) [41]. Without an exaggeration, one can venture to say that photosynthesis is a process that determines life on Earth and is critical to aerobic organisms including human beings.

In addition, magnesium ions are involved in some important processes taking place in living organisms, and the is an important component of bones [42–44]. Despite the long history of the use, magnesium and magnesium-based coordination polymers are considered as promising materials in many areas of industry, with emphasis on hydrogen and carbon dioxide storage and separation [45].

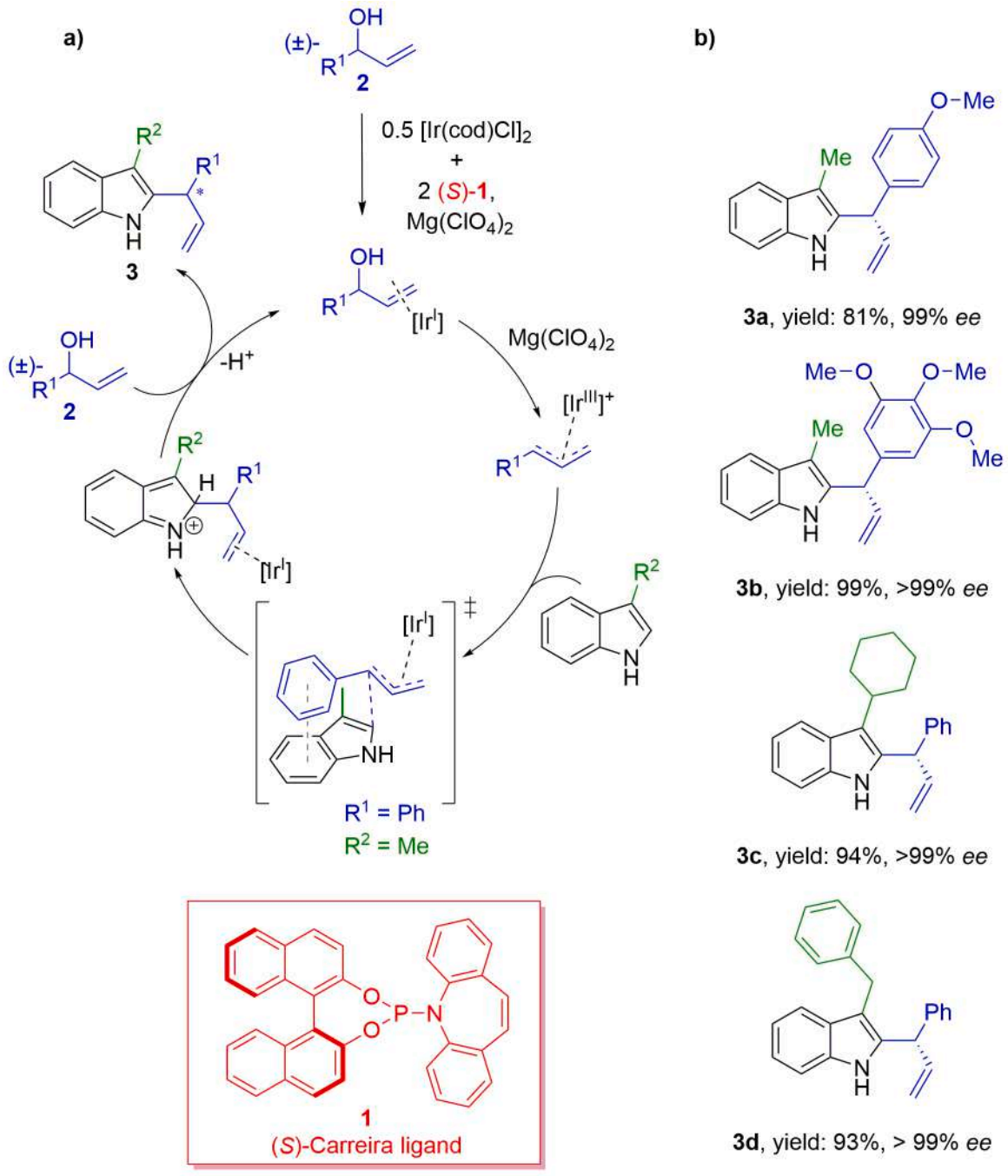
From the point of view of daily laboratory practice, the magnesium compounds are relatively non-sensitive to oxygen and moisture, with an obvious exception of organomagnesium compounds. In the Fig. 4 the most common applications of the magnesium itself and its compounds in organic synthesis have been shown.

The elemental magnesium and the magnesium amalgam have been routinely used as a reducing agent for both inorganic species like titanium(IV) chloride and for organic compounds, including reductive coupling of carbonyl compounds, selective reduction of carbonyl groups in α,β-unsaturated ketones, reductive silylation of 1,1-dibromides, chemoselective reduction of nitro group and for mild reduction of α,β-unsaturated nitriles, amides, esters, ketones, imines, halides and azides [46,47].

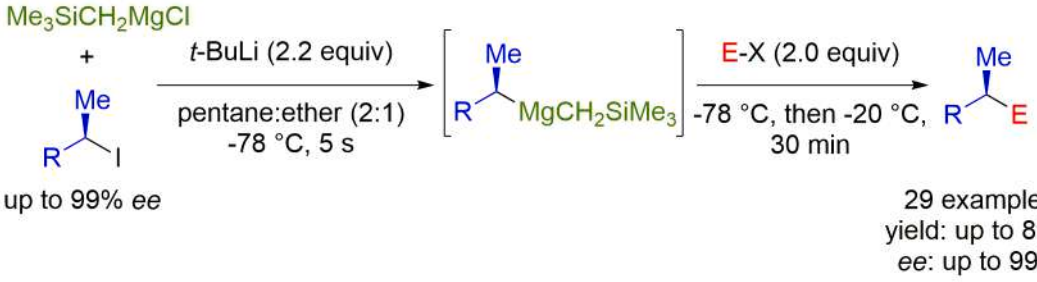
Magnesium oxide, which is easily obtainable from magnesium hydroxide, can act as a base in dehydrohalogenations and as dehydrogenation catalyst, which allows converting primary amines to nitriles [48]. It has been reported that MgO catalyze transformation of simple organic compounds present in biomass to lactic acid [49–50]. Basic magnesium methoxide forms chelates with carbonyl compounds prone to enolization [51,52], and magnesium alkoxides and aryloxides are widely used for ring-opening polymerization (ROP) of L-lactide [53].

In organic synthesis, the simple inorganic magnesium salts serve as useful Lewis acids. An addition of the magnesium bromide in pure or as etherate forms caused an increase in the yields of organometallic reactions and in nucleophilic additions and activation of dienophiles in cycloadditions. $MgBr_2$ constitutes the convenient source of bromine anion in bromination reactions [54,55].

Very recently, Qiu and co-workers have used magnesium perchlorate as a catalyst for stereoselective intramolecular amidocyclization. This reaction has been one of the key steps in the total synthesis of (–)-daphenylline and (–)-himalensine A (see Scheme 1) from (*S*)-carvone. These and other alkaloids isolated from *Daphniphyllum* genus



Scheme 2. a) Proposed mechanism of Ir-catalyzed enantioselective intermolecular indole allylation supported by magnesium perchlorate. b) Example of optically active indoles obtained by this method.



Scheme 3. Stereoselective additions of chiral mixed organomagnesiums to electrophiles.

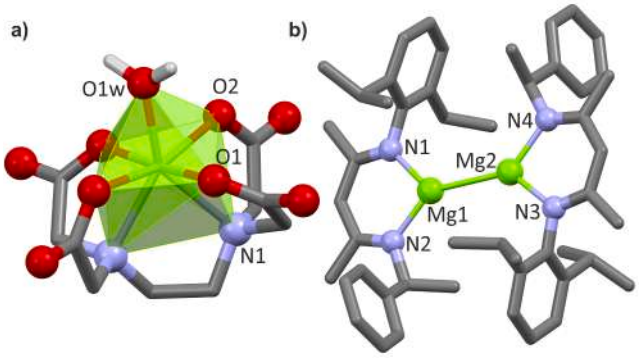


Fig. 5. a) Molecular structure of seven-coordinated magnesium(II) complex **4**. Hydrogen atoms were omitted for clarity. Selected bond lengths [Å]: Mg–O(1) 2.079; Mg–O(2) 2.269; Mg–N(1) 2.378; Mg–O(1w) 2.060. b) Molecular structure of magnesium(I) complex **5**. Hydrogen atoms omitted for clarity. Selected bond lengths [Å]: Mg(1)–Mg(2) 2.853; Mg(1)–O(1) 2.048; Mg(1)–O(2) 2.077; Mg(2)–O(3) 2.047; Mg2–O4 2.049.

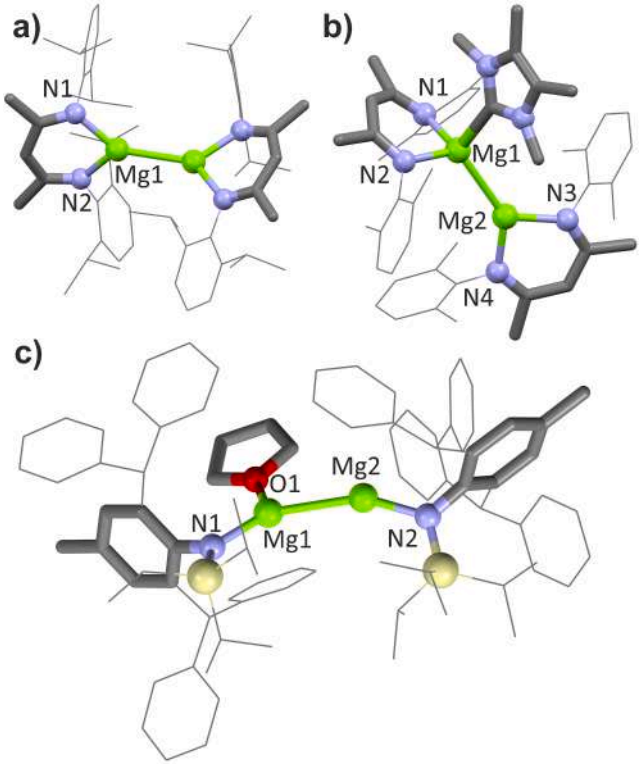


Fig. 6. Molecular structure of magnesium(I) complexes a) **6**, b) **7** and c) **8** with different coordination numbers. For clarity substituents showed as wireframe and the hydrogen atoms omitted.

exhibit broad spectrum of biological activity, i.e. anticancer, antiviral and vasorelaxant [56].

Zheng, Taylor, Unsworth, Liu and co-workers have proven usefulness of $Mg(ClO_4)_2$ in iridium-catalyzed enantioselective intermolecular indole allylation. Although the complex of iridium and optically pure (*S*)-Carreira ligand **1** controls stereoselectivity of the whole process, the reaction did not proceed without magnesium perchlorate. The established roles of the magnesium perchlorate were as follows: (i) activation of the allylic alcohol during formation of π-allyl complex of iridium; (ii) preservation against possible *N*-allylation and (iii) if needed, facilitation of the stereospecific migration of the allylic group (see Scheme 2) [57].

However, from the synthetic organic chemists' point of view, the

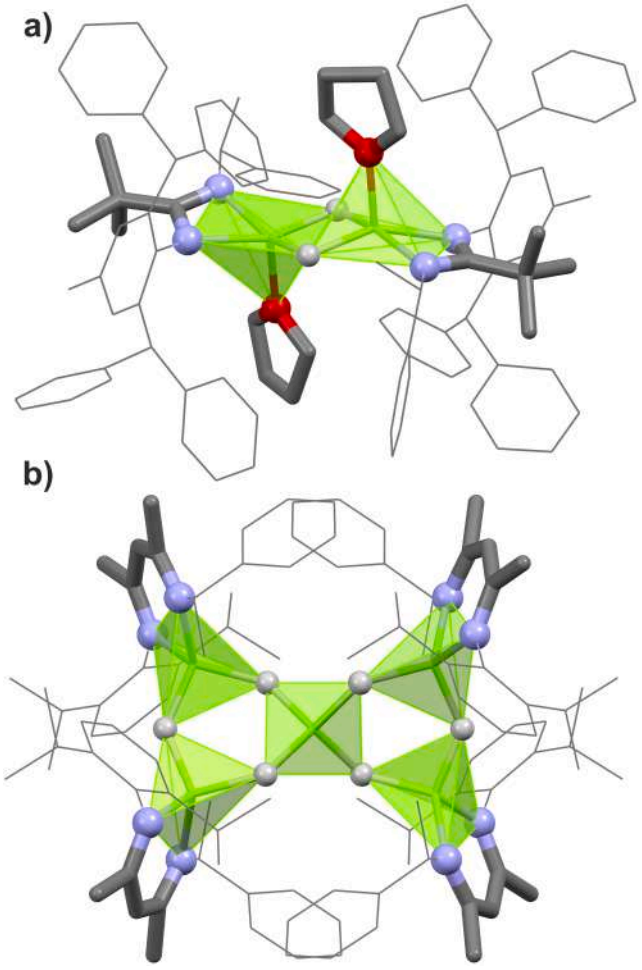


Fig. 7. Solid-state structure of a) dimeric **9** and b) multicore **10** magnesium hydride compounds. For clarity substituents were shown as wireframe and the hydrogen atoms were omitted.

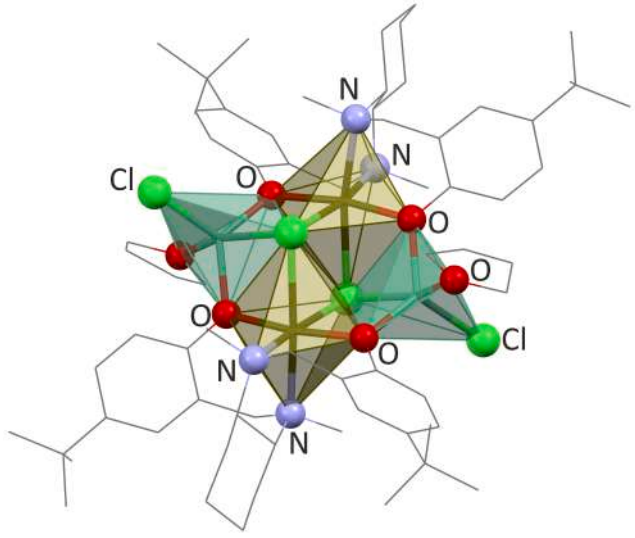


Fig. 8. Molecular structure of the magnesium salan complex **11**. Six- and five-coordinated the magnesium ions are marked with different colors of polyhedra. For clarity, substituents are shown as wireframe and the hydrogen atoms were omitted.

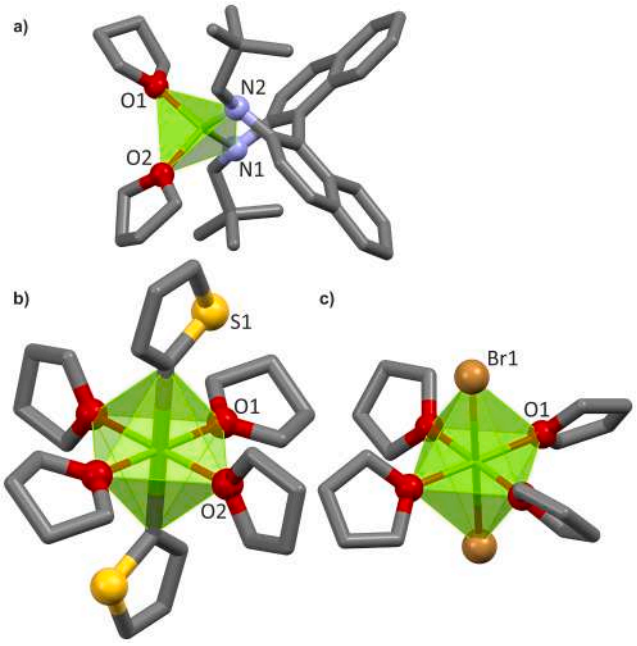


Fig. 9. a) Molecular structure of tetrahedral magnesium complex **12**. Hydrogen atoms were omitted for clarity. Selected bond lengths [Å]: Mg–N(1) 1.989; Mg–N(2) 1.990; Mg–O(1) 2.027; Mg–O(2) 2.017. Molecular structure of six-coordinated magnesium b) $Mg(thienyl)_2(THF)_4$ (**13**), selected bond lengths for asymmetric part [Å]: Mg–O(1) 2.178; Mg–O2 2.229; Mg–C 2.290; and c) $MgBr_2(THF)_4$ (**14**), selected bond lengths for asymmetric part [Å]: Mg–O(1) 2.111; Mg–Br(1) 2.652. Hydrogen atoms were omitted for clarity.

applications of magnesium and magnesium inorganic salts seems to be marginal when they are compared to universality of organometalics, mostly organomagnesium compounds discovered by Victor Grignard in 1901 [58]. After 120 years of history, Grignard reagents still play a pivotal role in organic synthesis. The so-called popularity of Grignard reagents in laboratory and industrial synthesis relies on their wide availability by insertion of magnesium into carbon-halogen bond, even in highly functionalized organohalides [59–67]. Abstracting from the main topic of this study, the usability of organomagnesium compounds in stereoselective synthesis is worth brief mentioning here. Even such a very cursory look at the Grignard reagents will help gain a full understanding of the role of magnesium in organic chemistry [68–78].

Most of enantioselective reactions employing Grignard reagents known so far, require the presence of either chiral auxiliary or stoichiometric amounts of chiral promoter. In fact, one of the very first reviews on the use of Grignard's reagents in diastereoselective synthesis is dated on 1904. In this contribution, McKenzie commented on the application of simple Grignard reagent to reaction with menthyl 2-oxophenylacetate [79].

The real difficulty in chiral ligand-mediated reactions of organomagnesiums is competitive non-catalyzed transformations that will lead to the formation of racemic mixtures. Therefore, sub-stoichiometric and stoichiometric amounts of chiral ligands are necessary [80]. On the other hand, there are number of reactions known that require only catalytical amounts of chiral inducer, usually a chiral copper complex. Among them, the (conjugate) additions are worth mentioning as they constitute one of the basic methods for the formation of C—C bonds [81–89].

One cannot forget about the potential use of chiral organomagnesiums in synthesis, however, their real applications are rather limited, due to the configurational instability. The very recent contribution from Knochel's team has described the use of optically active secondary alkylmagnesium reagents of the general formula alkyl $(Me)CHMgCH_2SiMe_3$ in reactions with various electrophiles (Scheme 3) [90].

While Grignard reagents usually play a role of nucleophiles, the discovered by Wanklyn alkylmagnesium compounds, of the general formula R_2Mg, have been recently employed as catalyst for hydrostannylation and hydrophosphination of alkynes [91,92].

3. Chiral complexes of magnesium

An ability to form stable complexes with *O*- and *N*-donor ligands is of potential use in synthetic organic chemistry and in the selective detection of magnesium ions [93]. Although most of the magnesium complexes employed in asymmetric processes are generated *in situ*, there are some known examples of chiral magnesium complexes of the structure determined by the single crystal X-ray diffraction.

A survey of the Cambridge Structural Database [94] has shown that magnesium complexes are quite popular and about 5500 structures containing magnesium have been found. As it has been evidenced by the purpose of this research, we are mainly focused on chiral complexes, therefore the search in the database has been limited to the structures crystallizing in the Sohncke groups. This decreased the number of hits to around 480. The magnesium can take a coordination number varying from 2 to as much as 7 (for example seven-coordinated magnesium(II) complex **4**, in which Mg(II) is chelated by EDTA, Fig. 5**a**) [95].

Although even greater coordination number has been found for specific cases, however, the coordination number equaling six is the most preferred (267 structures crystallizing in the Sohncke groups). In such cases of hexacoordinated complexes, it is expected that the ligands will form an octahedral environment around the magnesium ion, while the degree of distortion of the polyhedron and usually limited access to the central ion depend on the type and the size of ligands.

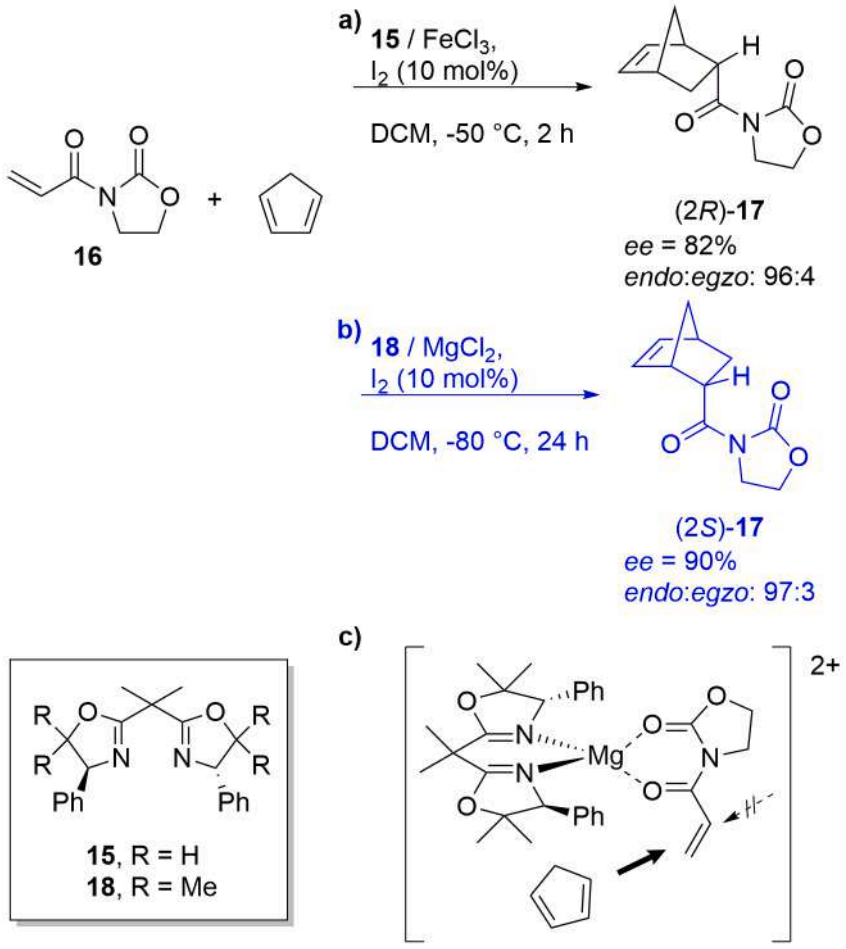
The four-coordinated magnesium complexes of often deformed tetrahedral structure have appeared less often (112 structures of four-coordinated complexes crystallizing in the Sohncke).

The characteristic five-coordinate magnesium complexes are porphyrin complexes. Mg^{2+} cation arranges itself in the center of the ring and interacts with an axially located ligand, which is in most of cases a water molecule or other small ligand. The environment of the central ion takes the form of a square pyramid. In the case of other five-coordinate complexes the coordination polyhedron is distorted.

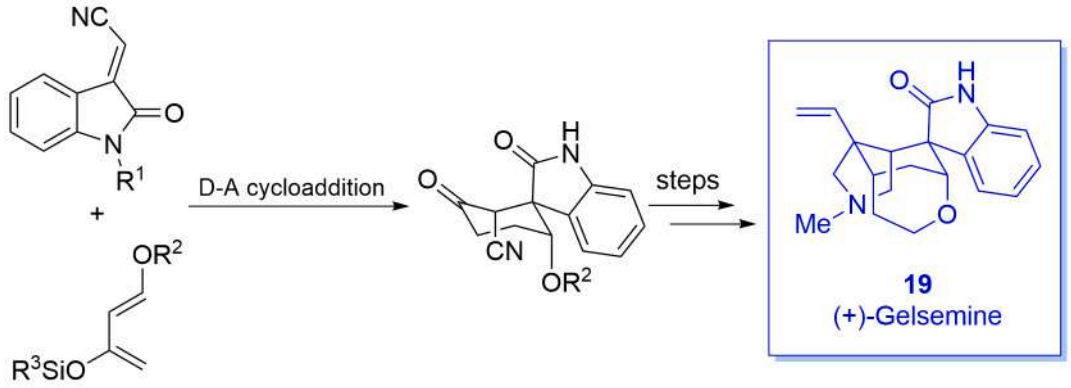
Dinuclear magnesium(I) complexes containing a covalent Mg-Mg bond and stabilized by *N*-donor bulky ligands (example structure is shown in Fig. 5**b**) are particularly interesting [96].

In the CSD database has been deposited ca. 40 such structures. The structure of a complex system, stabilized kinetically by guanidinate or *β*-diketiminate ligand, has been determined in 2007 [97], and its applicability as a reducing agent in organic and inorganic synthesis has then been demonstrated. This and similar systems may be symmetrical or not, therefore, the Mg^{2+} ions may differ in their coordination numbers, which for these systems ranges from 2 to 4, respectively for complexes **6**–**8**, Fig. 6).

The dinuclear magnesium(I) complex is easily transformed into hydride or more structurally complex systems and the hydride complexes are considered the active species in the reduction reactions [98]. During such a transformation, the Mg^{2+} cations became bridged with a hydride, and as a result, a dimer or multi-core cluster may form (Fig. 7). In multinuclear complexes **9** and **10**, the bridging of magnesium ions may



Scheme 4. a) Fe(III)-Catalyzed Diels-Alder reaction. b) The first Mg-catalyzed asymmetric D-A reaction reported by Corey. c) Proposed structure of the transition state.

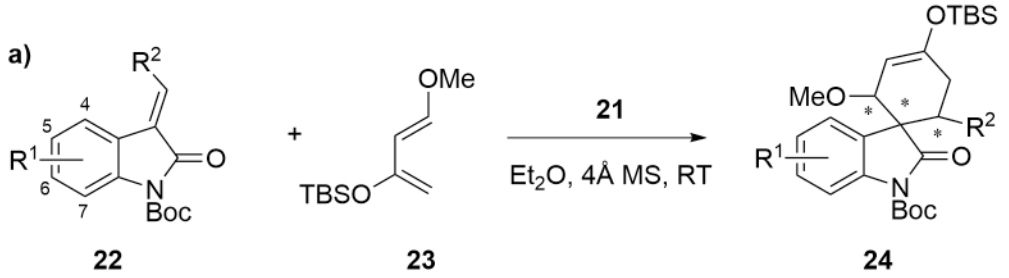


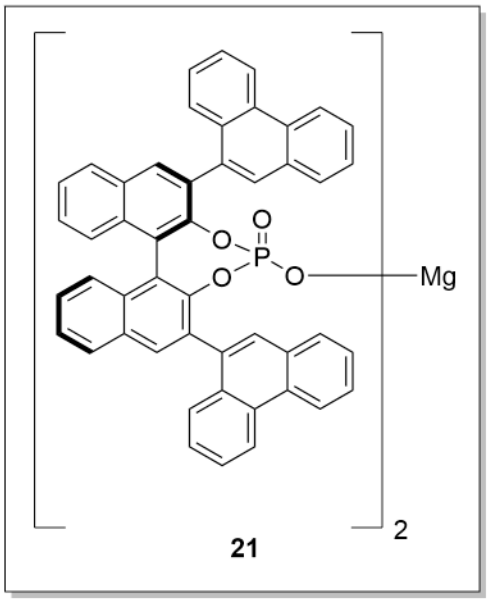
Scheme 5. Synthesis of (+)-gelsemine (**19**) precursor through cycloaddition reaction.

take place not only through hydrides, but also through oxygen [98,99] or chloride bridges [100]. Very recently Pattel *et al.* have described a structure of the complex **11**, in which two magnesium ions with an octahedral environment interact with a salan ligand and are linked to each other by a Cl bridge [100]. The additional two Mg^{2+} ions are five-coordinate and bind to the phenoxy groups on an opposite salan ligands (Fig. 8).

One has to remember that chirality of the magnesium complex may originate not only from the chirality of the ligand but also from the "chirality at the central atom". Note, this fundamentally incorrect term

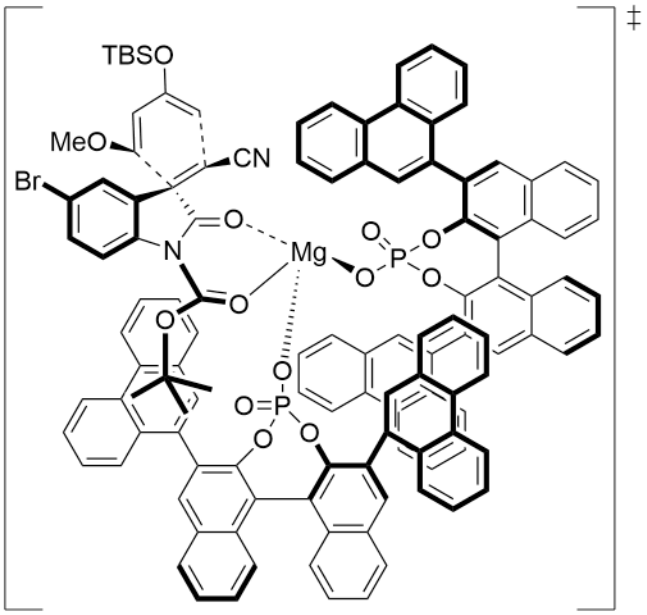
a)



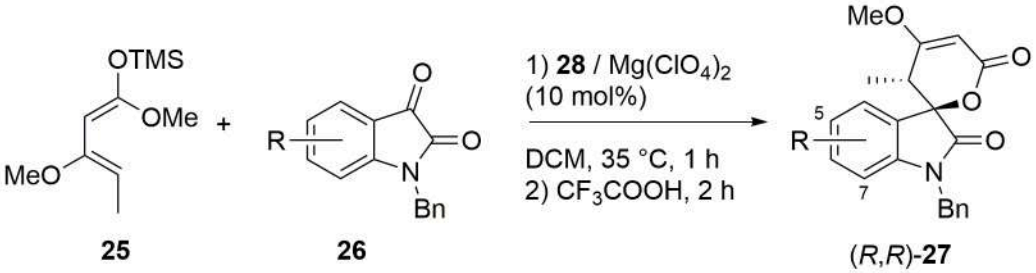


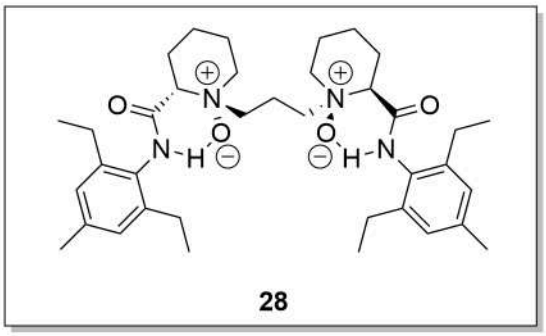
	R^1	R^2	yield [%]	ee [%]
24a	H	CN	99	99
24b	5-Me	CN	98	99
24c	5-MeO	CN	95	99
24d	5-F	CN	91	91
24e	5-Cl	CN	94	94
24f	5-Br	CN	92	98
24g	H	CO_2Me	89	98
24h	5-Me	CO_2Me	85	98

b)



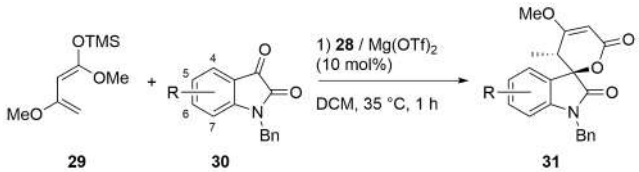
Scheme 6. a) Mg-Catalyzed cycloaddition between oxindole derivatives **22** and Danishefsky's diene **23**. b) Proposed transition state for Mg-catalyzed cycloaddition between oxidole and Danishefsky diene.





	R	yield [%]	ee [%]	dr
27a	5-F	99	96	95:5
27b	5-Cl	96	98	96:4
27c	5-Br	93	96	95:5
27d	5-I	90	96	92:8
27e	5-Me	99	98	96:4
27f	5-MeO	99	99	97:3
27g	7-F_3C	99	98	92:8

Scheme 7. Mg-Catalyzed reaction between isatins **26** and Brassard's diene providing spirolactones **27**.



	R	yield [%]	ee [%]
31a	H	82%	93%
31b	5-Me	77%	93%
31c	5,7-di-Me	85%	99%
31d	7-Me	92%	98%
31e	5-MeO	73%	93%

Scheme 8. Reaction between isatins and Brassard's type diene.

has permanently entered the jargon and is used here in the context of the chirality element generated on the metal atom, which is in fact the stereogenic center [101,102]. When the stereogenic ("chiral") central ion is surrounded by ligands specifically arranged in space, the entity becames axially chiral, as it has been seen in the well-established ruthenium complexes [103].

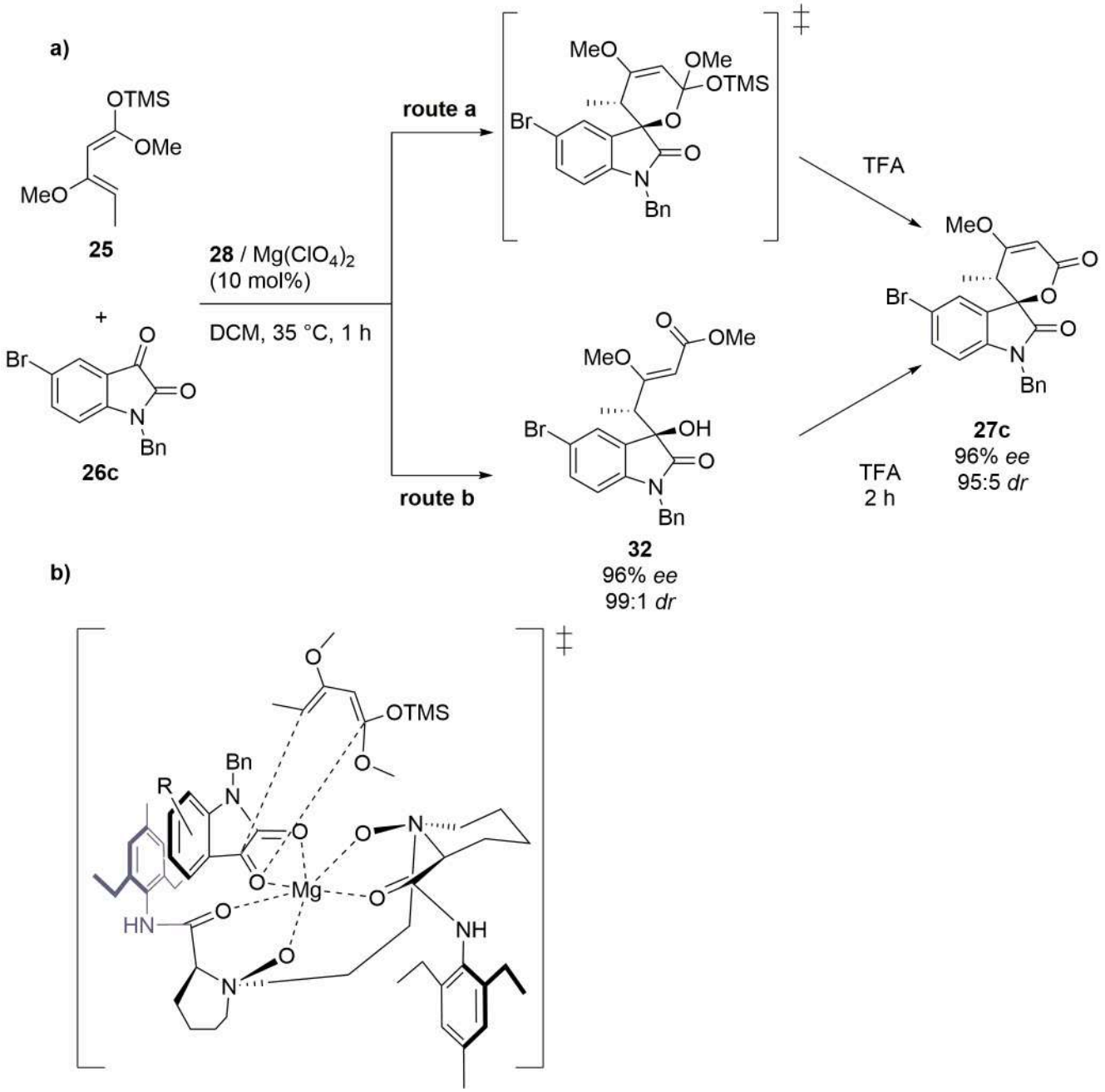
Attempts for obtaining alkaline earth metal chiral complexes (i.e. **12**), which were designed on the basis of chiral (*R*)-2,2′-diamino-1,1′-binaphthyl ((*R*)-BINAM), have been made [104]. In the crystal structure of **12**, the BINAM ligand and two THF molecules formed a tetrahedral C_2-symmetrical environment around the central ion. Due to the small size of THF molecules, the deformations of the coordination polyhedra seemed to be rather insignificant (Fig. 9**a**).

As mentioned above, six-coordinated magnesium complexes are the most commonly observed. Usually, these are formed with chelating ligands, therefore, the complex of magnesium with THF and thienyl ligands (like **13** and **14**) seems quite unusual [105]. Central magnesium ion interacts with six ligand molecules and, what seems to be more important, a stereogenic center at magnesium is generated through the appropriate arrangement of these molecules in space. (Fig. 9**b**). The compound **13** crystallizes as a racemic mixture in the $P2_1/c$ space group. In fact, a similar system, crystallizing in the $P4_22_12$ space group, was known before.

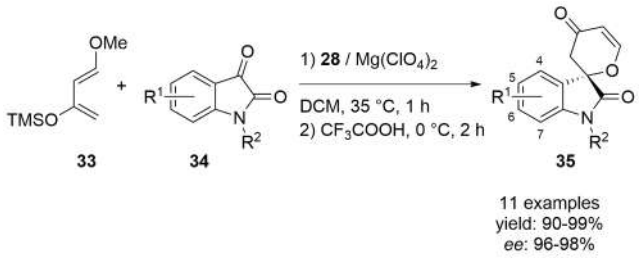
The complex **14**, in which bromine atoms are axially attached to the Mg^{2+} ion instead of thienyl, was already observed in 1966 (Fig. 9**c**) [106]. In both structures found in the crystalline phase, the THF molecules are oriented in one direction, and they resemble the blades of a propeller.

4. Magnesium-catalyzed asymmetric cycloadditions

Pericyclic reactions can be considered as one of the most powerful tools in the synthesis of carbon–carbon or carbon-heteroatom bonds. High atom efficiency makes them versatile especially in building



Scheme 9. a) Two different routes of reaction providing spirolactone **27c**. b) Proposed transition state for Mg-**28** complex-catalyzed D-A reaction.

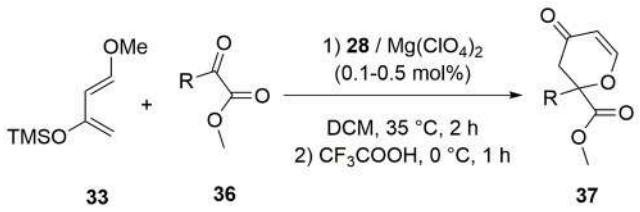


Scheme 10. Mg-Catalyzed reaction between Danishefsky's diene and isatins.

privileged structural motifs [107,108]. Among pericyclic, cycloaddition reactions occupy special position. [4 + 2] Cycloaddition, discovered in 1928 by Otto Diels and Kurt Alder (who were awarded the Nobel Prize in 1950), now commonly known as Diels-Alder (D-A) reaction, deserves special attention.

Interest in both, carbo and hetero versions of D-A reaction catalyzed by magnesium chiral complexes has been rapidly increasing from the 90 s of the XX century. Although in the previous 5 years the development in this field has slowed down a bit, however, due to the significance of D-A reactions in catalytic asymmetric synthesis, they are definitely worth describing in details.

From a historical point of view, the first Diels-Alder reaction catalyzed by a complex of magnesium and chiral ligand, was reported by Corey in 1992. However, a year earlier the same group proved that *in situ* generated Fe(III)/(*S*,*S*)-phenylbisoxazoline (**15**) chiral complex might



	R	yield [%]	ee [%]
37a	3-MeC$_6$H$_4$	99	>99
37b	3-VB	97	>99
37c	3-F$_3$CC$_6$H$_4$	96	>99
37d	3-BDOX	91	>99
37e	2-ThienC=C-	92	99

+ other examples

Scheme 11. Hetero-D-A reaction between Danishefsky's diene and ketoesters catalyzed by Mg-**28** complex.

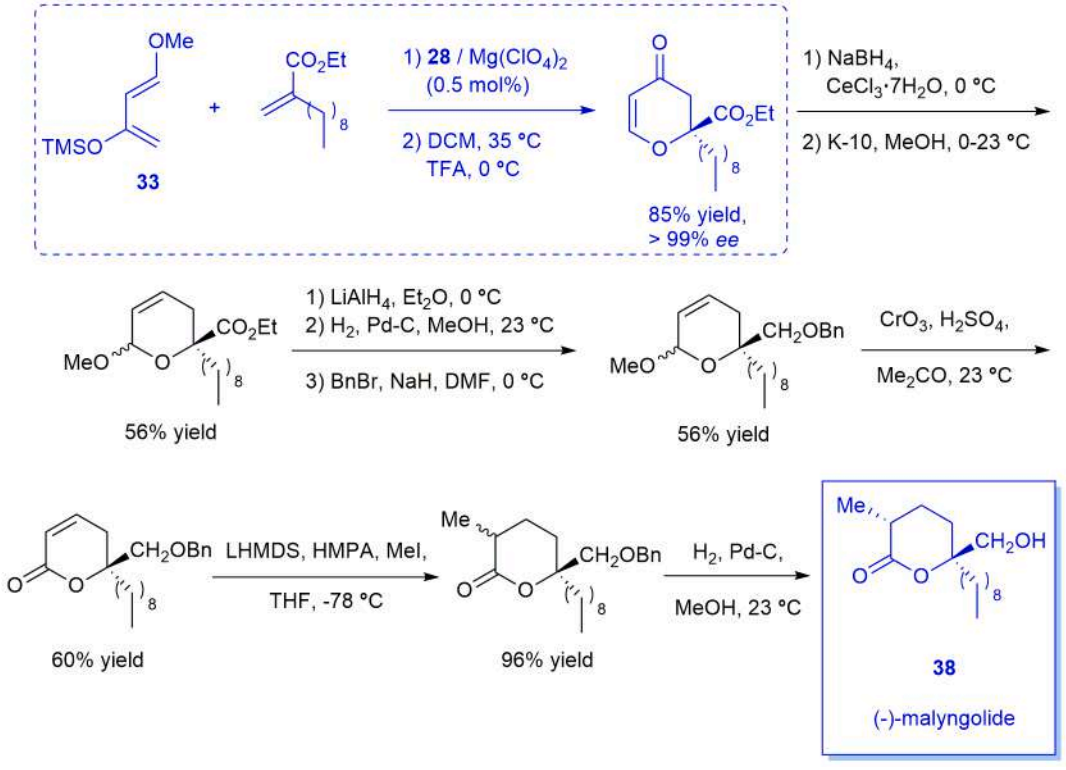
act as highly efficient catalyst of stereoselective reaction between 3-acryloyl-1,3-oxazolidine-2-one (**16**) and cyclopentadiene (Scheme 4**a**) [109,110]. The reaction led to the formation of the adduct **17** with *R* absolute configuration at *C*2 carbon atom.

By changing the cation to magnesium and ligand to a dimethyl derivative of (*S*,*S*)-phenylbisoxazoline (**18**, Scheme 4**b**), Corey and coworkers have been able to obtain adduct *ent*-**17** with a higher degree of chiral induction but of reversed stereochemistry [111].

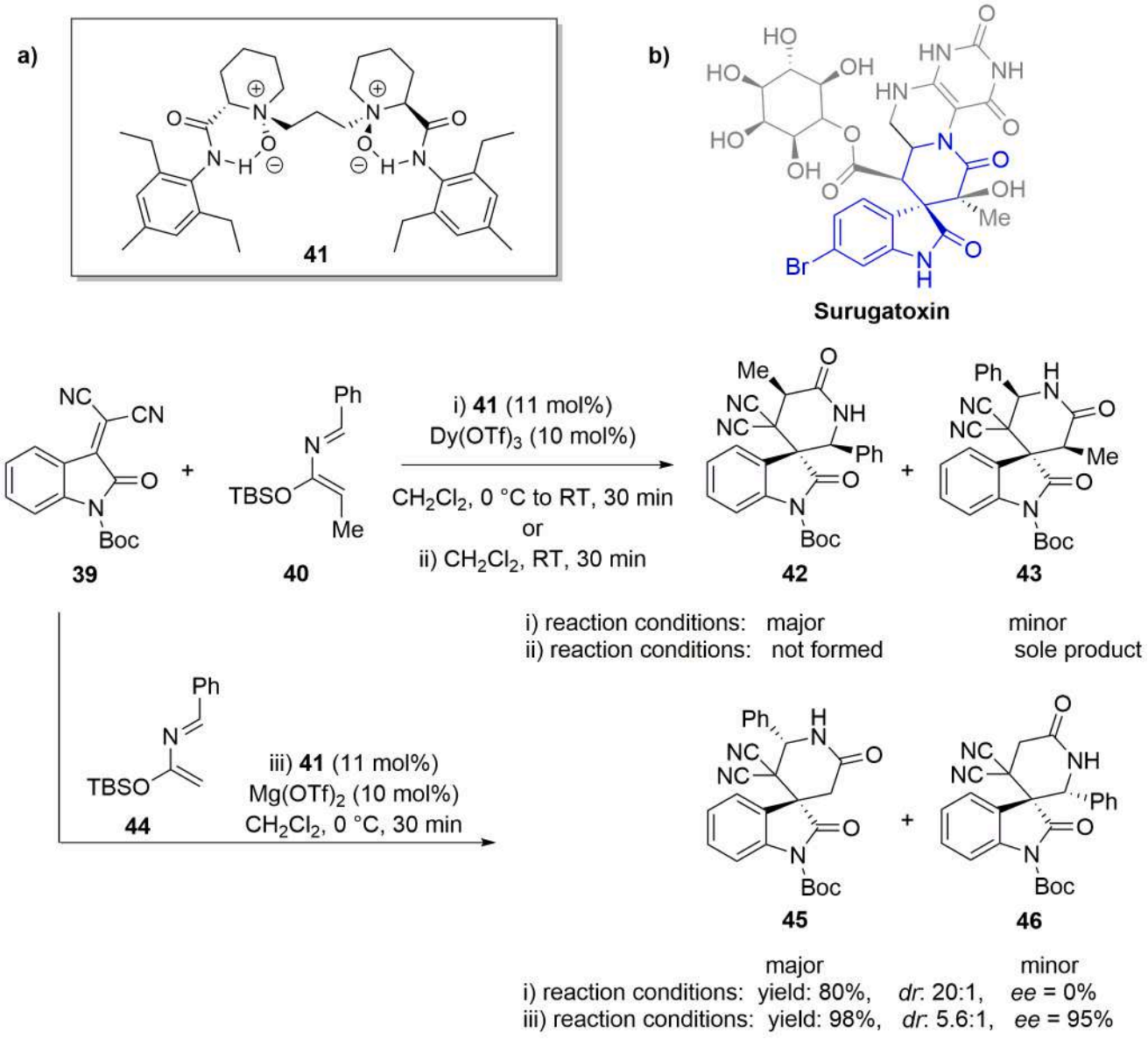
Two methyl substituents in the oxazoline rings hindered rotation of the phenyl groups and the replacement of iron cation by magnesium changed the structure of the complex which has been reflected in the degree of asymmetric induction and the configuration of the product. In the postulated transition state, magnesium catalyst-substrate complex adapts the tetrahedral geometry and this makes one of the dienophile faces less accessible (Scheme 4**c**) [112].

In 2010 Ishihara *et al.* have described chiral, based on BINOL alkaline-metal phosphates catalysts of many organic transformations [113]. The advantages of these catalytic systems have relied on the chemical neutrality, high stability and mild Lewis acidity. What is more, the catalysts have not been toxic and categorized as environmentally friendly. Antilla continued research in this field and in 2013 reported highly enantioselective synthesis of chiral spirooxindoles catalyzed by complex *in situ* generated from bulky BINOL-phosphate derivative and magnesium complex [114]. Despite the fact that six-membered spirocyclic oxindoles are important and common motifs in natural products and in pharmaceutical building blocks, only a few methods of their synthesis have been developed so far [115]. For instance, the new synthesis route enables receiving the core structure of (+)-gelsemine (**19**) – an alkaloid isolated from flowering plants of the genus *Gelsemium*, which grow in subtropical and tropical zones and is used in pharmacy (Scheme 5) [116–118].

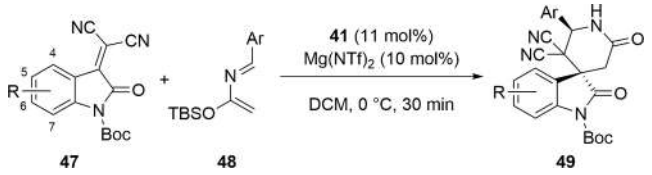
Antilla *et al.* have applied chiral 9-phenantryl BINOL phosphate derivative **20** in complex with magnesium (**21**) as a catalyst in asymmetric D-A reaction between oxindole derivatives (**22**) and Danishefsky's diene



Scheme 12. Synthesis of (–)-malyngolide with indicated hetero-D-A reaction catalyzed by Mg-**28** complex.



Scheme 13. a) Optimization of the reaction conditions. b) Structure of Surugatoxin (**47**) with 3,3′-piperidinoyl-spirooxindole core indicated.



Scheme 14. Mg-Catalyzed reaction between oxindoles and azadienes.

(**23**, Scheme 6). The electron-rich **24** molecule enables simple synthesis of unsaturated six-membered rings, which can be further easily functionalized. It is also worth adding that in the developed method, the quaternary stereocenters have been created in the product molecules.

During the optimization of the reaction conditions, the authors tested the effect of solvents, the duration of the reaction and the effect of the

Table 1
Effect of the substrates substituetns R and Ar on yield, regioisomeric ratio (*rr*) and enantiomeric excess of the products **49**.

Product	R	Ar	yield [%]	*rr*	*ee* [%]
49a	H	Ph	98	5.6:1	95
49b	5-F	Ph	99	5.4:1	96
49c	5-Cl	Ph	97	4.2:1	96
49d	5-Br	Ph	98	4.8:1	89
49e	5-I	Ph	91	5.2:1	90
49f	5-Me	Ph	90	4.5:1	94
49g	5-MeO	Ph	99	7.6:1	92
49h	5-OCF_3	Ph	96	6.5:1	90
49i	5,7-di-Me	Ph	99	4.3:1	24
49j	H	4-FC_6H_4	99	8:1	94
49k	H	2-Furyl	93	6.2:1	70

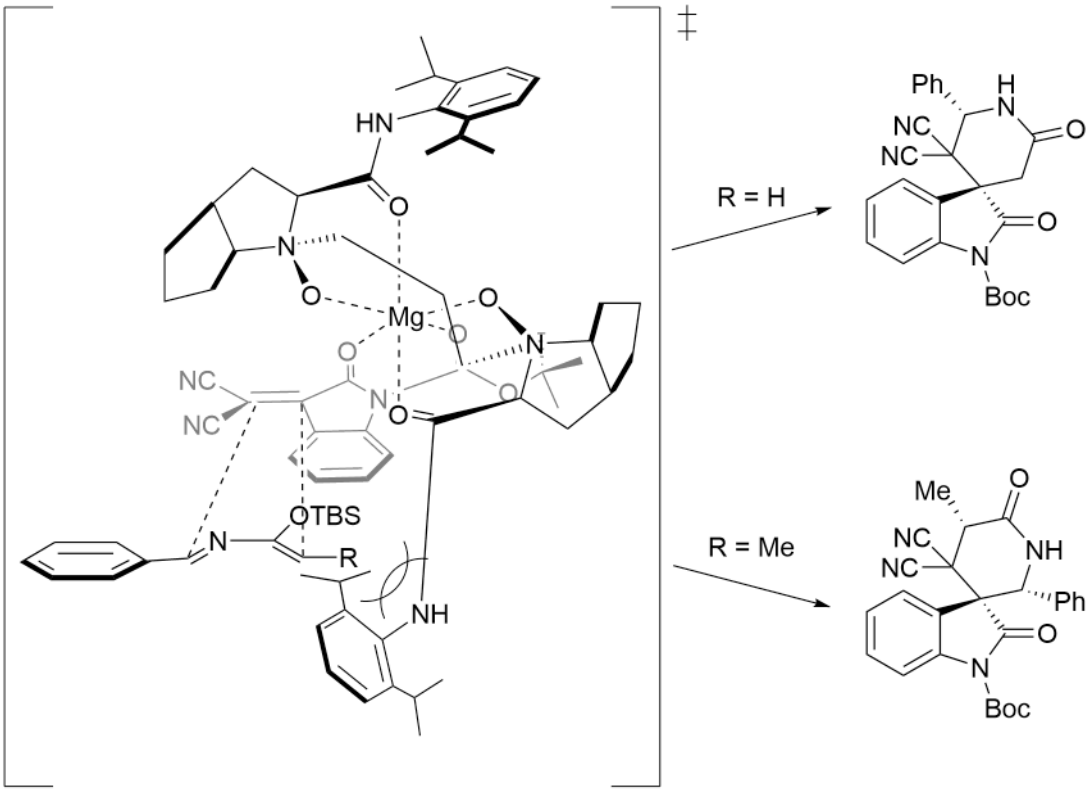


Fig. 10. Proposed transition state for Mg-**41** complex-catalyzed reaction between oxindoles and azadienes.

addition of the molecular sieves. Using tetrachloromethane, chloroform and tetrahydrofuran, the received enantiomeric excesses were moderate and, comparing to reactions which were run in toluene, hexanes and diethyl ether, the products had reversed chirality sense. In these cases, products were also not significantly enantiomerically enriched. The reaction was also conducted in dichloromethane (DCM), which resulted in the racemate. After an addition of activated 4 Å molecular sieves (MS), it was possible to shorten the reaction time from 18 h to 5 min and the enantiomeric and diastereomeric excess increased. In chloroform as the solvent, the inversed stereochemistry of the final spirooxindole was observed after MS addition. The results implied that the necessity of the presence of MS was associated with the possibility of creating tetrahedral transition state.

Although the detailed mechanism has not been known yet, it is highly likely that magnesium would coordinate two additional water molecules, which resulted in formation of catalytically inactive complex of octahedral geometry. The postulated role of MS is to remove water from the reaction environment, thus, preserve tetrahedral geometry of the complex (shown in Scheme 6**b)**. The bulky 9-phenylanthryl substituent prevents diene from coming closer to the top face of the oxindole carbon–carbon double bond. As in the transition state, only the bottom side is available, therefore, *endo* cycloadduct is obtained in great majority.

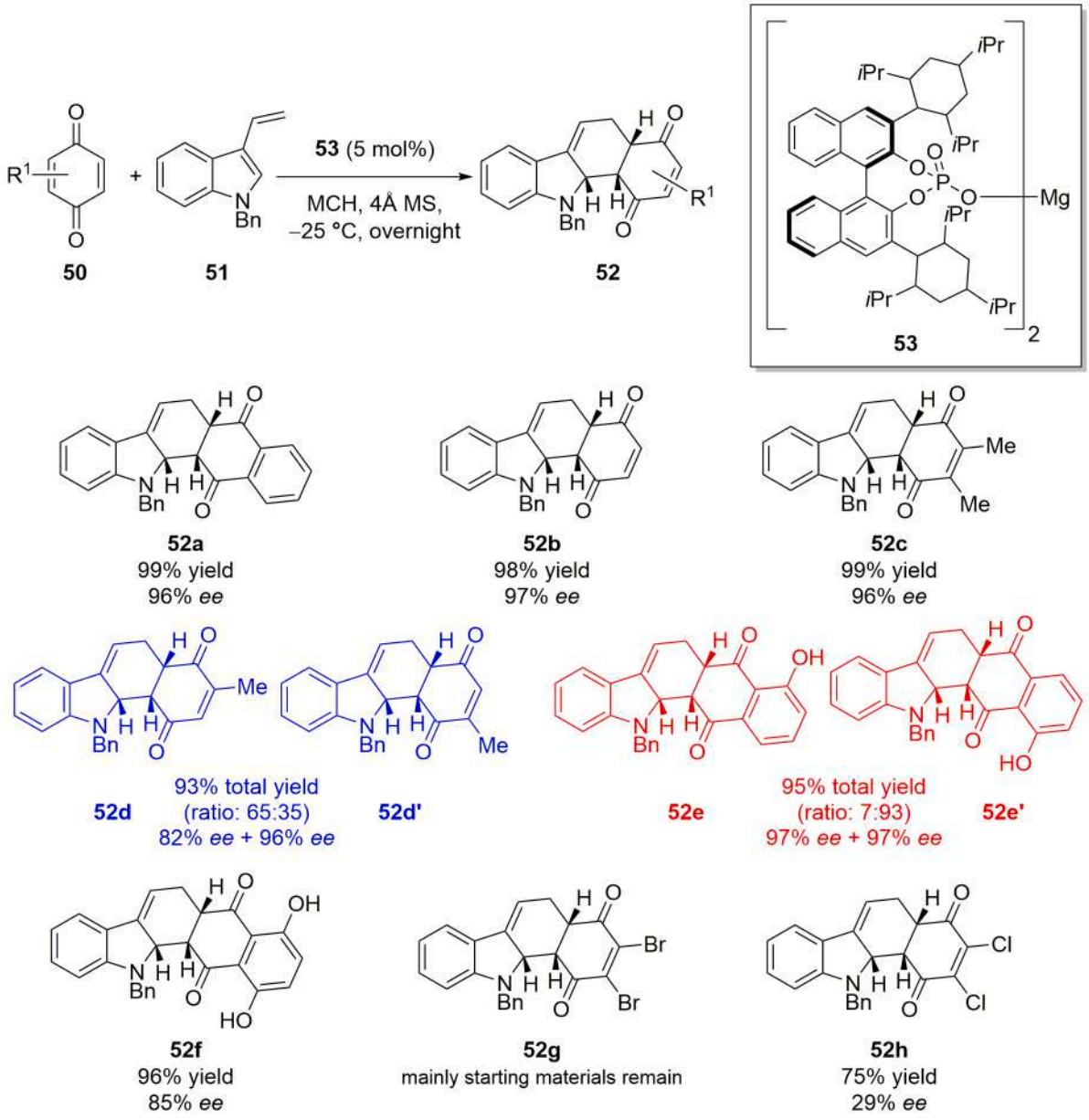
Both electron donating and electron withdrawing groups were tolerated in substrate structure. Yields of the products were rarely below 95%. The increase of the scale of the reaction did not have significant impact on the yield (96%) nor on enantiomeric excess (99%) and diastereomeric ratio (99:1).

The presence of sterically hindered amide moiety is crucial in the induction of chirality in the transition state. The magnesium cation coordinated to chiral phosphate binds oxygen atoms from the carbonyl group of the indole moiety and oxygen atom from the protecting group attached to nitrogen atom.

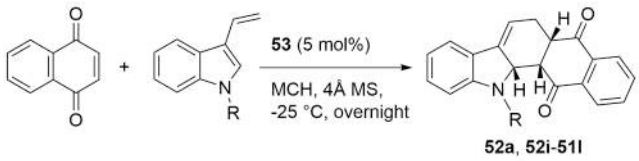
Brassard's diene (**25**) (1*E*-1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene) is often used in stereoselective D-A reactions in order to receive optically active unsaturated six-membered δ-lactones [119,120]. Apart from constituting fragments of important biologically active natural products, they can be further used as useful synthons in organic synthesis [121].

Reactions between isatins **26**, which are considered one of the most promising groups of carbonyl compounds [122], and Brassard's dienes have enabled direct receiving series of biologically active chiral spirolactones **27** [123,124]. The first catalytic asymmetric hetero-D-A reactions between Brassard's diene and isatins (**26**) were reported by Feng and co-workers in 2014 (Scheme 7) [125]. A catalyst was generated *in situ* from magnesium perchlorate and sterically hindered L-pipecolic acid derivative **28** [126,127]. The resulting spirolactones consisted of quaternary stereocenters, which belongs to desired, but difficult to stereocontrol, formation fragments in organic asymmetric synthesis. The obtained results confirmed high *enantio*- and diastereoselectivity of the process.

Similar reactions with Brassard's type diene **29** were used for testing the impact of a nitrogen protecting group. The better impact on the yield and stereoselectivity was achieved when benzyl group was used



Scheme 15. Mg-Catalyzed carbo-D-A reaction between benzoquinones and 3-vinylondoles.



	R	yield [%]	ee [%]
52a	Bn	99	96
52i	H	77	48
52j	PMP	85	5
52k	PMB	93	91
52l	4-*t*-BuBn	94	96

Scheme 16. Effect of the substituent of the nitrogen atom on the results of the Mg-catalyzed reaction between benzoquinones and 3-vinylondoles.

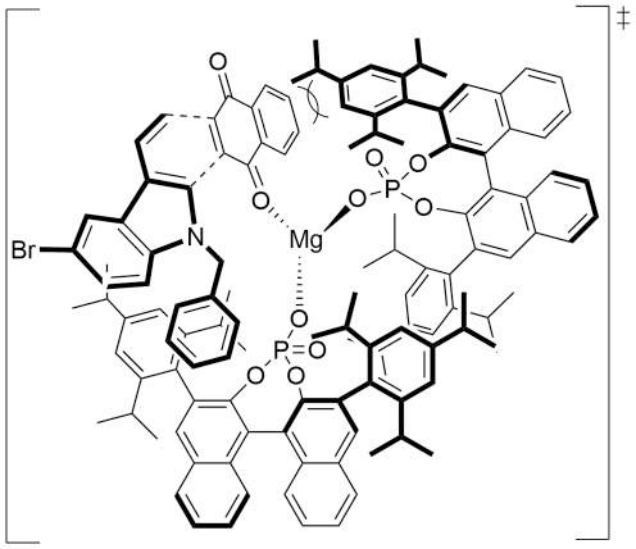


Fig. 11. Proposed transition state for the Mg-catalyzed reaction between benzoquinones and 3-vinylondoles.

(Scheme 8), despite the nature of substituent R attached to the aromatic ring of **30**.

The best results were received when the more sterically hindered ligand was used and trifluoroacetic acid was added after one hour from the start of the reaction, which implied two important facts related to the reaction mechanism. First: steric hindrance is feasible to obtain a sufficiently high level of chirality induction. Second: along with the D-A cycloadduct, a small amount of Mukaiyama reaction product **32** (Scheme 9**a**) was isolated. This indicated that the catalyst was not able to transform that by-product into D-A cycloadduct completely. Surprisingly, when trifluoroacetic acid was added, the final yield of spirocyclic product **27c** was improved up to 99%.

In the proposed transition state structure (Scheme 9**b**) the magnesium cation is coordinated by two oxygen atoms from neighbouring carbonyl groups of isatin and two *N*-oxide oxygen atoms from the ligand. In that kind of complex, *Re* face is hindered by two bulky 2,6-diethyl-4-methylphenyl groups from the ligand **28**, therefore the only possible site to attack is the *Si* face.

Feng and co-workers also faced the challenge of carrying out the hetero-D-A reaction between Danishefsky's diene (**33**) and isatins (**34**, Scheme 10), α-ketoesters and β,γ-unsaturated ketoesters (**36**, Scheme 11) [128]. In the case of β,γ-unsaturated ketoesters, hetero-D-A competes with carbo-D-A reaction [129]. Ligand **28** with magnesium perchlorate were used for *in situ* generating a catalytically active species. It is worth mentioning that in comparison with the above-described experiments, in reaction with Danishefsky's diene it was possible to significantly decrease the amount of catalyst from 10 to 0.1 mol%. The terminal methoxy substituents in Brassard's diene makes the control of stereoselectivity more difficult and a larger amount of the catalyst is needed to provide higher level of chirality induction.

Reactions carried out with α-ketoesters and β,γ-unsaturated ketoesters **36** allowed obtaining practically optically pure products **37**. The presence of electron donating or withdrawing groups in the substrate skeleton has not affected the chemical yield of the reaction.

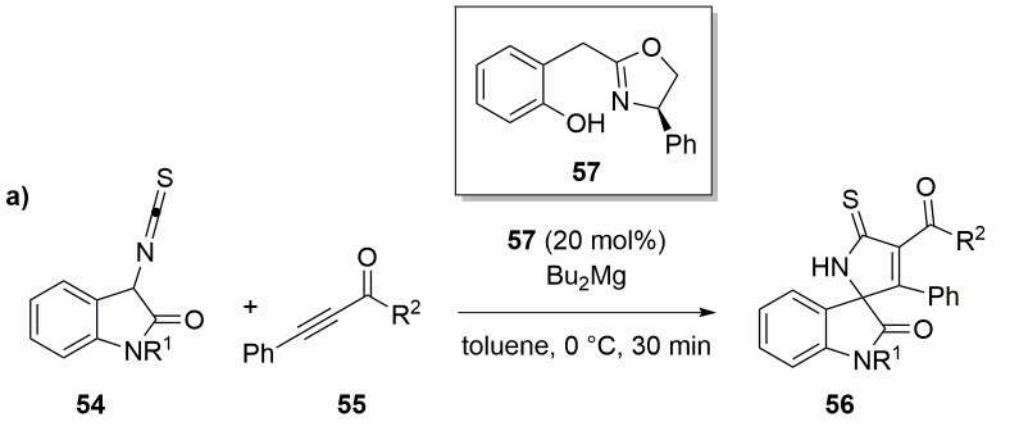
On the basis of the tested reactions, the synthetic route to (–)-malyngolide (**38**), a key intermediate of optically active algal origin antibiotic, was proposed. In this case, also a small amount of catalyst (0.5 mol%) was sufficient to obtain the satisfactory yield and excellent stereoselectivity in the first step of the synthetic route (Scheme 12) [130].

In 2017, Kumar's team presented a new oxo-D-A reaction-based method of receiving piperidinoyl spirooxindoles [131]. The reported method enables obtaining four contiguous stereocenters and two quaternary carbon atoms in just one step. These molecules are important core elements in designing new pharmaceuticals [132]. In order to obtain efficiently a 3,3′-piperidinoyl-spirooxindoles in the reaction between substituted oxindoles **39** and trimethylsiloxyazadiene (**40**) some efforts were put on the optimization of the reaction conditions (Scheme 13**a**). The choice of the appropriate ligands was based on Feng's study on asymmetric hetero-D-A. It turned out that the best enantioselectivities and yields of the products were achieved when dysprosium(III) triflate with **41** chiral ligand were used. To broaden the scope of the reaction many pairs of substrates were tested. Among the received products, one has had very similar structure to the 3,4′-piperidinoyl-spirooxindole scaffold, which is visible in Surugatoxin (Scheme 13**b**) – a carnivorous gastropod of *Babylonia japonica*'s venom. The first attempts to make this scaffold *via* the D-A reaction (**41** – 11 mol%, $Dy(OTf)_3$ 10 mol%, DCM, 0 °C – RT, 30 min) resulted in receiving predominantly 3,3′-piperidinoyl-spirooxindole **42.** In the second attempt no catalyst was used. It indisposed formatting of the 3,3′-piperidinoyl-spirooxindole and the desired one was found to be a sole, but racemic product **43**. Testing further metal complexes with ligand **41** led to conclusions that the most appropriate cation, which allows for obtaining enantiomerically enriched Surugatoxin's core with 98% yield and 95% enantiomeric excess is the magnesium ion. What is significant, after the change of the azadiene structure from **39** to **44**, reaction catalyzed by dysprosium(III) did not provide any enantioenriched product.

Further studies allowed for broadening the scope of reaction (Scheme 14 and Table 1).

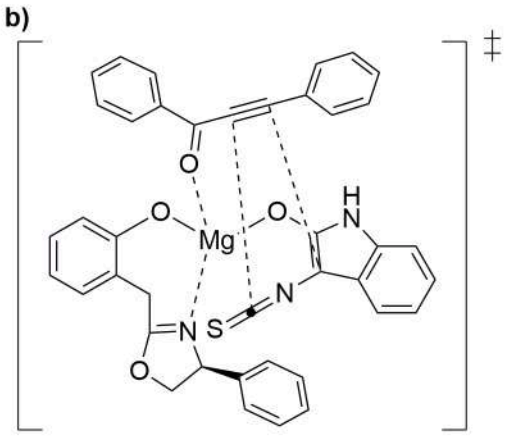
As one can see from the data collected in Table 1, in the reactions between **47** and azadienes **48** the obtained results were satisfactory in terms of enantioselectivity and regardless of the electronic nature of the substituent. An exception was product **49i**, however, the reasons why the enantioselectivity decreased in such a case are not clear.

In the proposed transition state of the octahedral structure (Fig. 10),



	R¹	R²	yield [%]	ee [%]
56a	Me	Ph	97	92
56b	Me	4-MeC$_6$H$_4$	92	86
56c	Me	4-ClC$_6$H$_4$	99	90
56d	Me	4-BrC$_6$H$_4$	94	90
56e	Bn	Ph	97	90

+ other examples



Scheme 17. a) Mg-Catalyzed reaction between 3 and isothiocyanato oxindoles and alkynyl ketones. b) Proposed transition state for Mg-catalyzed reaction between 3 and isothiocyanato oxindoles and alkynyl ketones.

ligand **41** and the oxindole block the *Si* face of the azadiene **48**. Therefore, dienophile might approach diene so only from *Re* face. For unsubstituted diene (R = H, Fig. 10), the steric repulsion did not seem to be significant enough to avoid forming of 3,4′-piperidinoyl-spirooxindole. However, a formal replacement of hydrogen atom by bulkier group, such as methyl group, has directed the reaction towards formation of a 3,3′-piperidinoyl-spirooxindole, which is received as the major product.

In the recent contribution, Antilla and co-workers have gone back to the idea of chiral magnesium BINOL-phosphate catalysis [133]. The growing role of chiral tetrahydrocarbazole in natural product chemistry was the premise to this study [134].

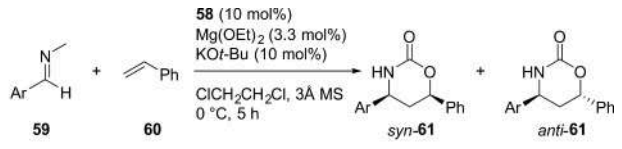
In Mg-catalyzed carbo-D-A reactions between benzoquinones **50** and 3-vinylindoles **51**, a series of substituted tetrahydrocarbazoles **52** was obtained with high yield and stereoselectivity (Scheme 15). The reactions were catalyzed by complex **53**, characterized by the presence of bulky cyclohexane-derived groups at 3 and 3′ position of BINOL skeleton. What is compelling, the developed strategy allowed for creation of three stereocenters in one step, and there has not been many similar methods before. After the optimization of the reaction conditions, it turned out that lowering the temperature to –25 °C and the addition of MS, increased the enantioselectivity significantly. The scope of both benzoquinone and 3-vinylindole substrates was further tested.

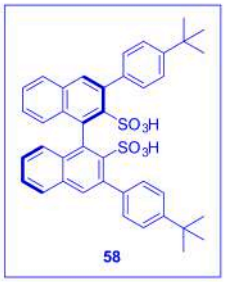
Although total yield and enantiomeric excess were satisfactory in majority of the cases, the presence of halogen atoms in vicinal position led to the synthesis of the adduct with low enantioselectivity or the reaction did not take place at all. In the case of **52d**/**52d'** and **52e**/**52e'**, the regioisomers were formed. It was visible that the structure of 3-vinylindole did not affect the results much. What is interesting, the use of *E*/*Z* diastereoisomers as respective substrates resulted in forming only one diastereomer of the product, albeit with moderate yield and enantioselectivity amounts to 83%. On the other hand, the group attached to the indole nitrogen atom significantly affected reaction outcome (Scheme 16).

The results of the reaction seemed to correlate with the steric hindrance and electronic nature of the substituent. Unprotected 3 vinylindole led to the formation of an adduct **52i** with the lowest yield and moderate enantioselectivity among all substrates tested. Sterically more hindered and electron rich *para*-methoxyphenyl group makes the vinylindole more reactive, thus, the non-catalyzed reaction would compete with the catalyzed one. As a result, product **52j** has been obtained with high yield but in almost racemic form.

The satisfactory results were achieved in the case of vinylindoles *N*-substituted by benzyl, *para*-methoxybenzyl and the *para*-*tert*-butyl-

a)

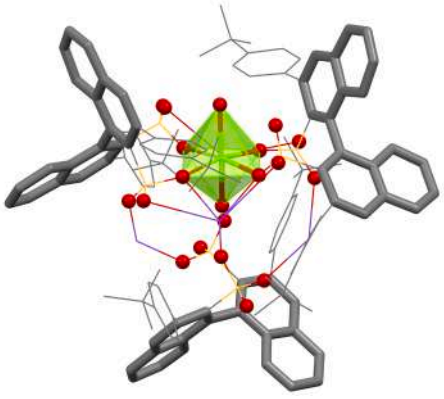




	Ar	yield [%]	syn:anti	ee_{syn} [%]
61a	Ph	91	>99:<1	96
61b	2-MeC_6H_4	80	>99:<1	98
61c	3-MeC_6H_4	98	>99:<1	94
61d	4-MeC_6H_4	96	>99:<1	96
61d	2-$F_3CC_6H_4$	100	>99:<1	99
61e	2-IC_6H_4	100	>99:<1	99

+ other examples

b)



Scheme 18. a) Mg-Catalyzed reaction between substituted styrenes and aldimines. b) X-Ray determined structure of magnesium-potassium complex **62**, formed from **58**, $Mg(OEt)_2$ and KO*t*-Bu. Hydrogen atoms were omitted for clarity.

substituted benzyl groups (products **52a**, **52 k** and **52 l**). This observation is rationalized by a greater distance of a phenyl ring attached by the methylene group to the nitrogen atom.

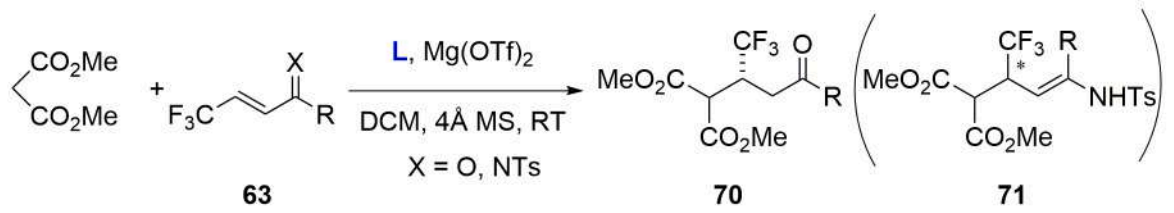
In the proposed transition state structure (Fig. 11), magnesium ion adapts the coordination number equal to three, because of the presence of the only one available oxygen donor atom in the benzoquinone molecule. The benzene ring in the benzoquinone is shielded from the upper site by 2,4,6-tri(*iso*propyl)phenyl substituent enabling the 3-vinylindole to approach from the bottom, which finally resulted in the formation of *endo* product.

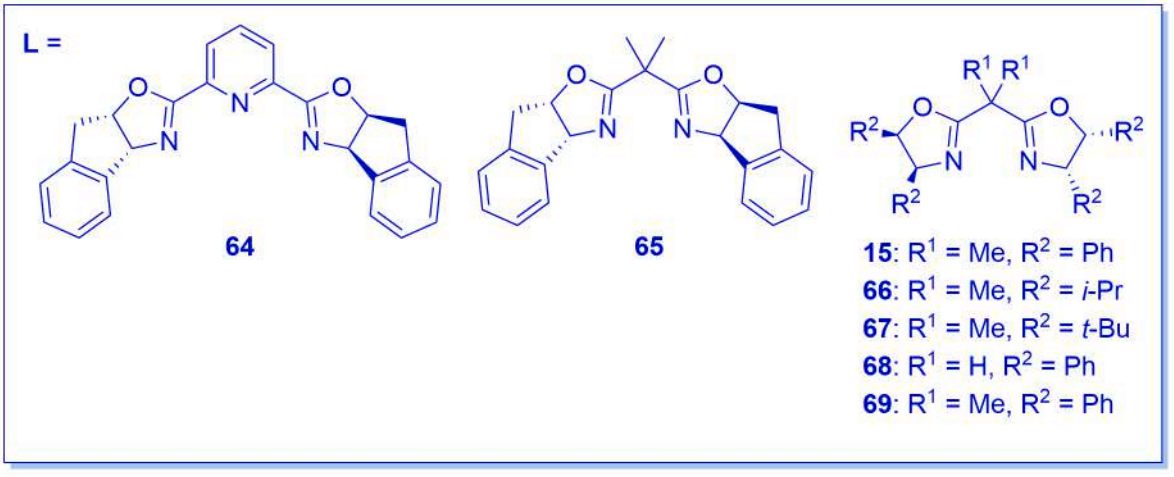
A highly enantioselective [3 + 2] cycloaddition between 3 and isothiocyanato oxindoles **54** and electron-deficient alkynyl ketones **55** has been recently developed (Scheme 17**a**) [135]. The reaction is catalyzed

Table 2
Effect of the substitution pattern, ligand (**L**) and the duration of the reaction on the yield, diasteroizomeric ratio (*dr*) and enantiomeric excess of the product.

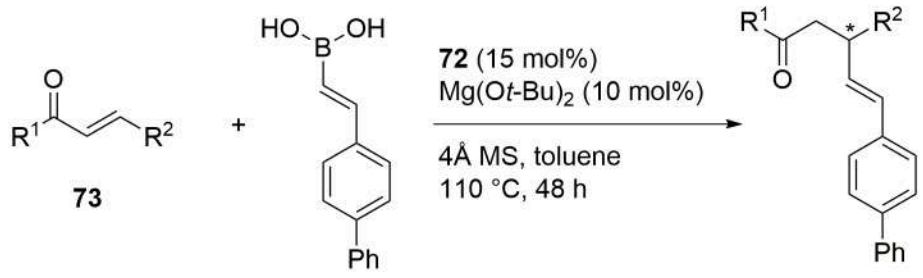
Product	X	R	L	t [h]	yield [%]	*dr* [*E*/*Z*]	*ee* [%]
70a	O	Ph	65	24	99	–	79
70a	O	Ph	15	17	99	–	–75
70a	O	Ph	66	18	99	–	–80
70a	O	Ph	67	17	35	–	rac
70a	O	Ph	68[a]	17	99	–	75
70a	O	Ph	69[a]	44	85	–	93
70b	O	4-MeC_6H_4	69[a]	48	90	–	90
70c	O	4-BrC_6H_4	69[a]	48	73	–	97
70d	O	4-$O_2NC_6H_4$	69[a]	46	96	–	96
70e	O	3-$O_2NC_6H_4$	69[a]	46	69	–	94
71a	NTs	Ph	65	20	99	92/8	86
71a	NTs	Ph	65	40	99	96/4	89
71a	NTs	Ph	65	16	98	96/4	89
71a	NTs	Ph	65	96	56	89/11	91
71a	NTs	Ph	65	41	93	96/4	91
71b	NTs	4-MeC_6H_4	65	16	96	95/5	89
71c	NTs	4-BrC_6H_4	65	17	97	84/16	89
71d	NTs	4-$O_2NC_6H_4$	65	40	92	93/7	94
71e	NTs	3-$O_2NC_6H_4$	65	16	97	78/22	83

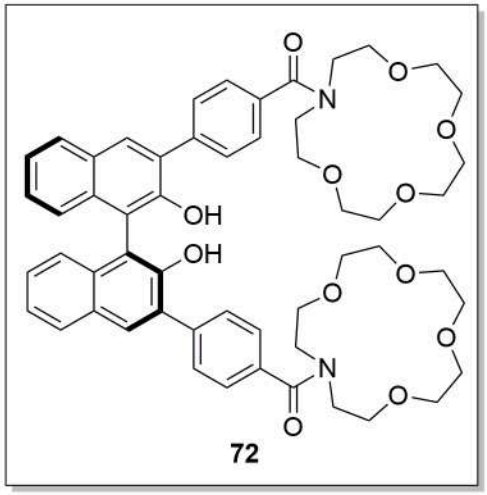
[a] An enantiomer of the ligand was used.





Scheme 19. Enantioselective conjugate addition of dimethyl malonate to enones or α,β-unsaturated imines.





	R^1	R^2	yield [%]	ee [%]
75a	Me	Me	86	81
75b	Me	Pr	83	89
75c	Ph	Ph	76	92
75d	4-FC_6H_4	Ph	77	91

+ other examples

Scheme 20. Aza-crown ether-derived BINOL **72** and magnesium-catalyzed asymmetric Michael addition of styrylboronic acids to enones.

by complex *in situ* generated from dibutyl magnesium and ligand **57**.

After optimization of the reaction conditions, the broad scope of substrates has been tested. The reactions that were carried out, involved the aromatic and aliphatic unsaturated ketones. As one can see, both chemical yields and enantiomeric excesses can be considered as high, regardless the electronic nature and steric requirements of the substituents.

In the presumed structure of the transition state (Scheme 17**b**), the magnesium ion is coordinated in the tetrahedral manner by the oxygen atom from the carbonyl group of the keto-alkyne and the oxindole, and by the two donor atoms from the ligand molecule – the oxygen atom from the hydroxyl group and the nitrogen atom from the oxazoline moiety.

In 2017, Ishihara first tested the catalytic properties of magnesium-potassium complex with 3,3′-bis(4-(*tert*-butyl)phenyl)-[1,1′-binaphthalene]-2,2′-disulfonic acid (**58**) [136]. In the highly enantioselective cycloadditions between the substituted aldimines **59** and styrenes **60**, the chiral six-membered cyclic urethanes (the oxazinanones, **61**) were obtained (see Scheme 18). The oxazinanones are known for their biological activity and for being useful as the chiral auxiliaries and as the starting materials for synthesis of chiral 1,3-amino alcohols [137,138]. Based on the X-ray analysis, the actual structure of the magnesium potassium complex **62** with the chiral ligand **58** was proposed, and the broad spectrum of substrates has been efficiently transferred into cycloadducts.

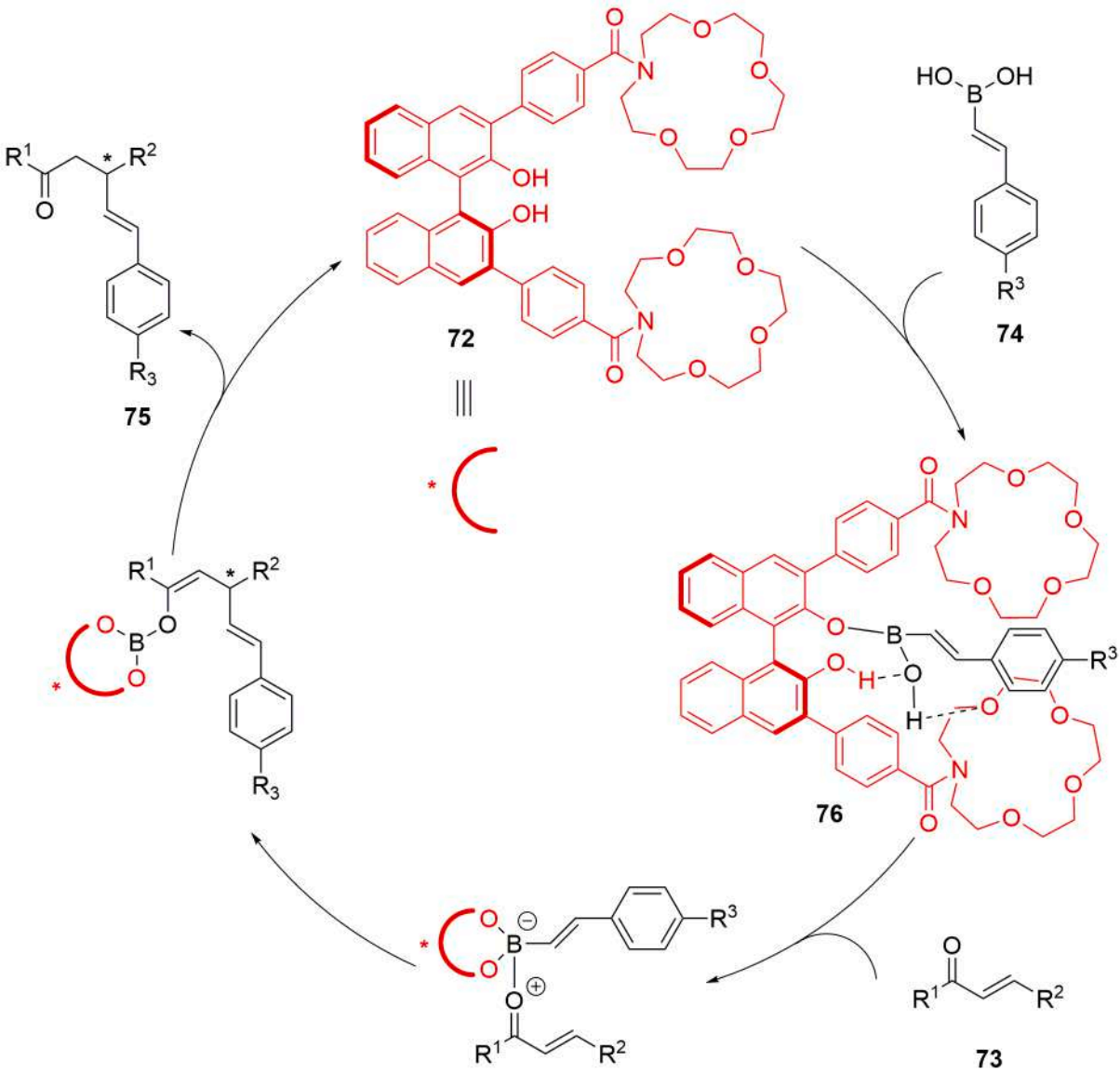
The expansion of the scale of the reactions did not affect the yield, the diastereomeric ratio (*syn*:*anti* > 99:<1) and the enantiomeric excess (96%) of the products.

5. Magnesium catalyzed asymmetric Michael additions and related reactions

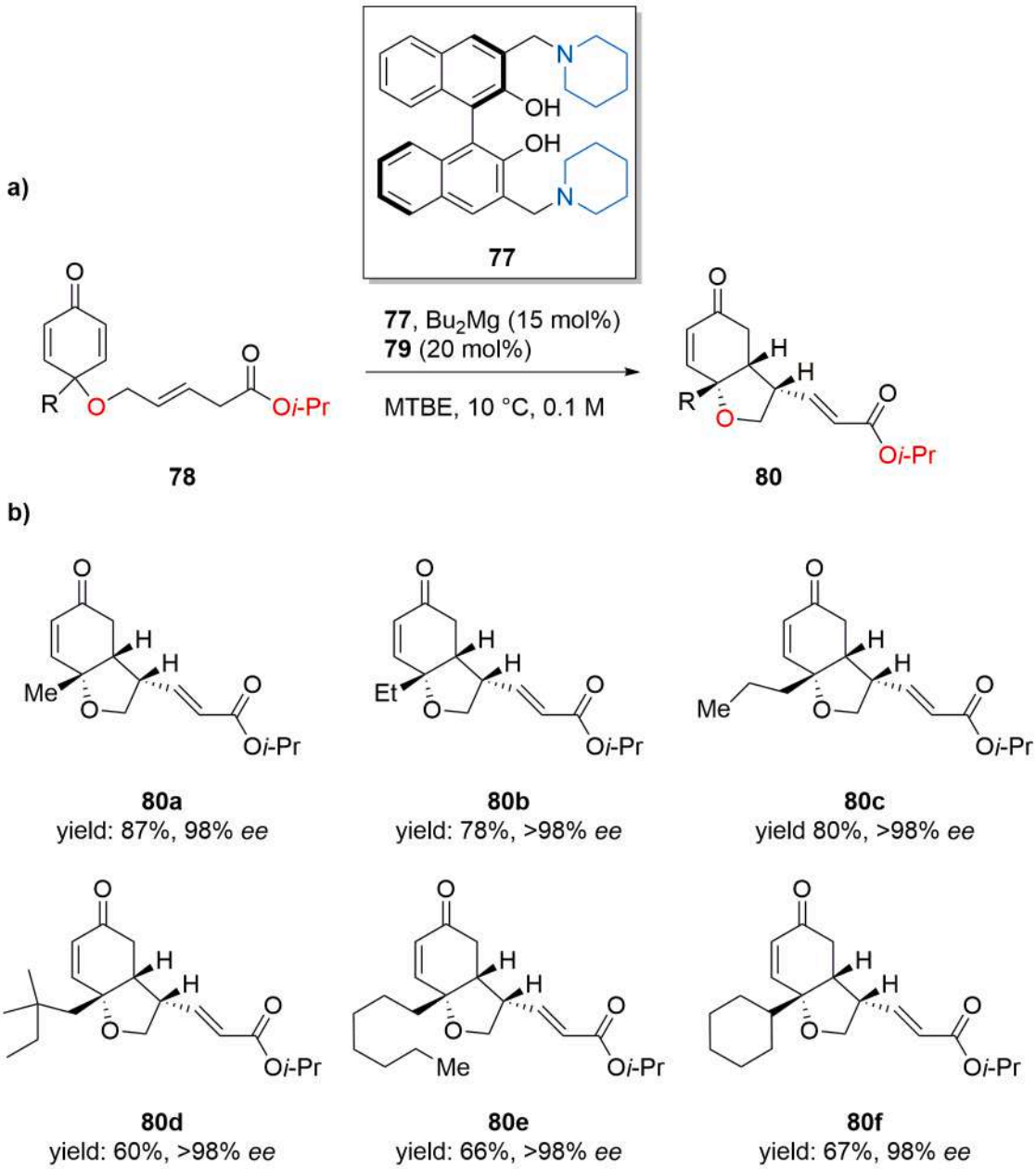
Conjugate additions represent a broad group of reactions widely used in chemistry. In so-called 'classical' Michael addition, the formation of carbon–carbon or carbon-heteroatom bond in β position to the electron withdrawing group (EWG) associated with the 'reduction' of carbon–carbon double bond began and subsequent protonation terminated the synthetic procedure. However, one has to remember that after addition of the nucleophile to the Michael acceptor, the enolate is formed at first. The enolate usually plays a role of nucleophile, which may be further used in aldol-type or Mannich reactions with various electrophiles. An alternative approach to obtaining complex molecules relies on the direct conversion of the isolated Michael adduct in subsequent reactions of various kind.

The classical Michael reaction between malonates and activated β-trifluoromethyl-α,β-unsaturated ketones and its *N*-tosyl imino derivatives **63** has been very recently reported by Blay *et al.* (Scheme 19).

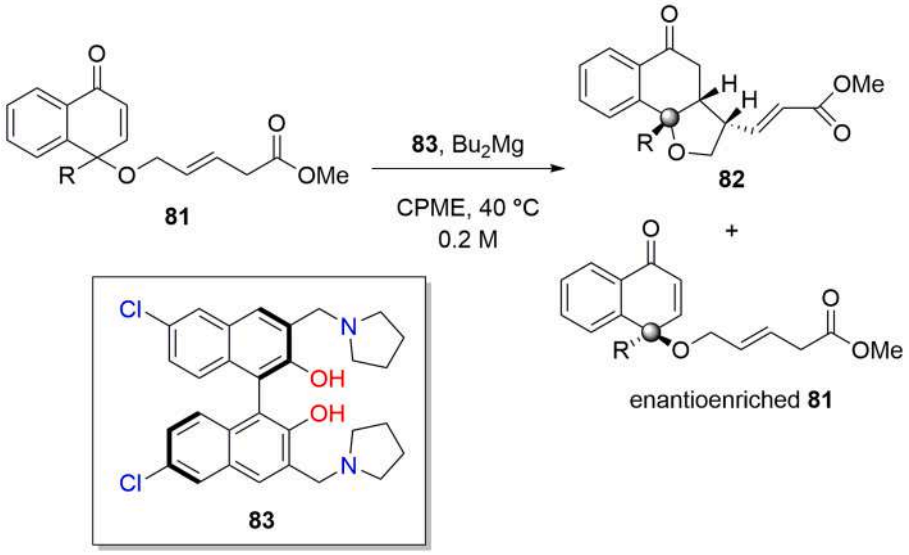
In these reactions, magnesium triflate has formed a complex with bis-



Scheme 21. Proposed catalytic cycle for aza-crown ether-derived BINOL and Mg-catalyzed asymmetric Michael addition of styrylboronic acids to enones.



Scheme 22. a) Magnesium-catalyzed desymmetrization reactions via intramolecular vinylogous Michael reactions. b) Examples of products obtained *via* desymmetrization reaction.



Scheme 23. Vinylogous kinetic resolution of racemic allylic esters catalyzed by *in situ* generated bifunctional catalyst.

Table 3
Effect of the substituent on the outcome of Mg-catalyzed vinylogous kinetic resolution of racemic allylic esters **81**.

R	product	yield [%]	*ee* [%]	product	yield [%]	*ee* [%]
Me	**81a**	45	88	**82a**	46	97
Et	**81b**	45	82	**82b**	43	93
n-Pr	**81c**	47	85	**82c**	43	96
n-Bu	**81d**	46	90	**82d**	43	91
$(CH_2)_2CH(CH_3)_2$	**81e**	45	81	**82e**	39	92
$(CH_2)_5CH_3$	**81f**	40	86	**82f**	42	91
$(CH_2)_7CH_3$	**81g**	46	84	**82g**	42	96
Bn	**81h**	46	90	**82h**	43	94
$(CH_2)_3Ph$	**81i**	42	79	**82i**	40	94
$CH_2CH(CH_2)_2$	**81j**	42	96	**82j**	44	84

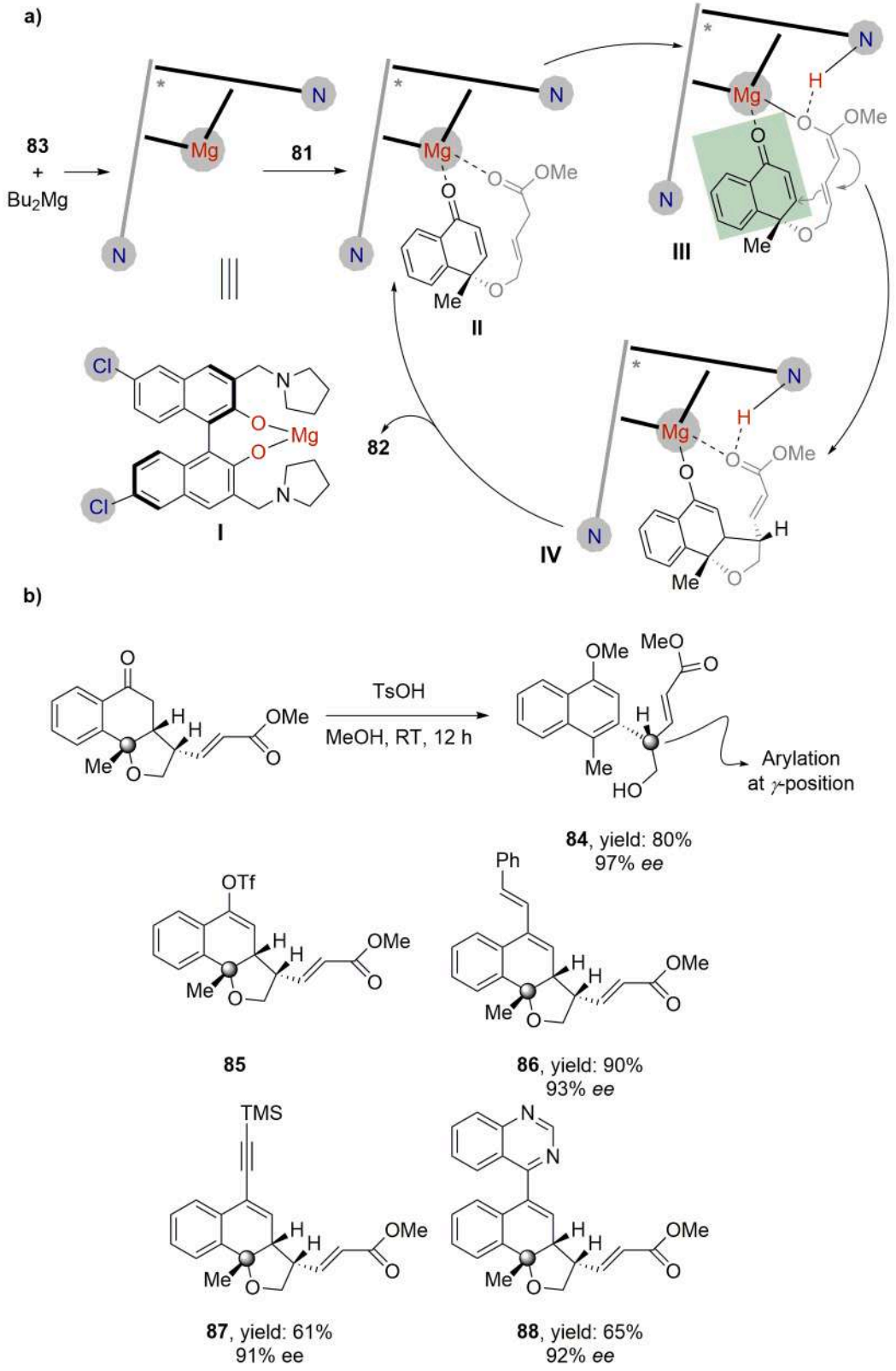
oxazoline ligands of the Py-Box (**64**) or Box (**15**, **65**–**69**) type. What is worth emphasizing is the fact that these ligands have been relatively little explored in magnesium-catalyzed asymmetric reactions, which remains in contrast to wide use of Box-ligands in copper- and zinc-catalyzed stereoselective transformations. As an outcome of the reactions, the ketones **70** bearing a stereogenic center substituted by trifluoromethyl group have been formed. The isolated yields and enatioselectivities were good. The substitution pattern in the aromatic part of the ketone has had almost no effect on the efficiency of the reaction. Both EDG and EWG groups attached to the aromatic ring were well-tolerated in this reaction (see Table 2).

When respective *N*-tosyl imines have been used as Michael acceptors, the main products were the *N*-tosylenamines, predominantly of the *E* configuration of the carbon–carbon double bond. The presence of the imino group caused little drop of enantioselectivity, however, the obtained results were still comparable to that previously reported by Espinosa for Box-Cu-catalyzed reactions [139]. The main advantage over the Cu-catalyzed reaction is associated with better *E*/*Z* diastereoizomeric ratio [140].

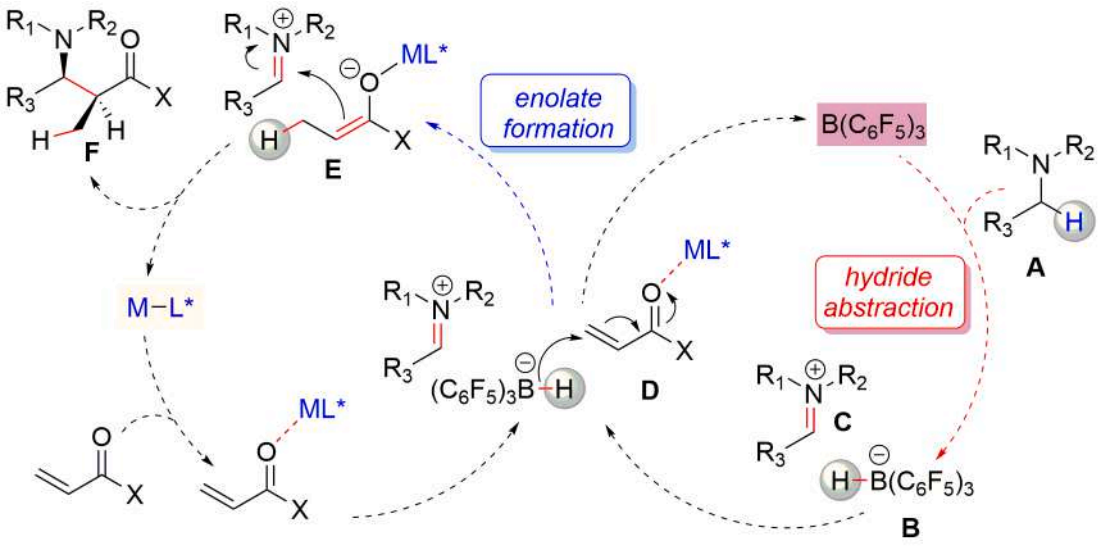
The scope of substrates, which might be used as Michael donors (nucleophiles), has been recently expanded on alkenyl boronic acids [141]. In contrast to boronic esters that are widely used in organic synthesis, boronic acids are characterized by higher stability and operational simplicity. However, the early attempts to the use of boronic acids in conjugate additions resulted in only partial success [142,143]. Especially, an addition of boronic acids to non-heteroaryl and to alkyl enones remains still problematic. By the use of catalytic system *in situ* formed from aza-crown ether-derived BINOL ligands **72** and magnesium *tert*-butoxide, Li and co-workers have overcome these obstacles. The reactions between various enones **73** and boronic acids **74**, conducted at elevated temperatures, in toluene for 48 h, provided an access to series of adducts (**75**, Scheme 20).

Yields of isolated products ranged from moderate to good and enantioselectivities were up to 95%. One of the factors that influenced the level of asymmetric induction was concentration of substrates. The optimal value was established as 0.05 M and neither increase nor decrease of the concentration improved the enantiomeric ratio. The presence of aza-crown moiety in the structure of the catalyst is essential for enantioselections. The presence of alkali metal salts improved the reaction efficiency, however, their detailed role remains unknown. It has been suggested that the most important structural features for controlling stereochemistry of the process are the formation of monoester **76** by the BINOL ligand and boronic acid and hydrogen bonding cascade $O_{BINOL}H\cdots O_{ACID}H\cdots O_{ETHER}$ involving OH phenolic group, remaining OH group from boronic acid and one of the oxygen atoms from the aza-crown ether moiety (Scheme 21) [141].

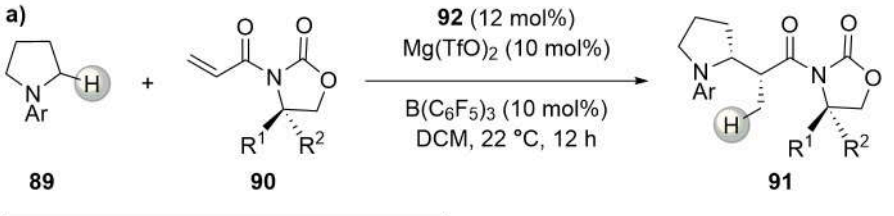
The axially chiral BINOL core is common among the ligands used in magnesium-catalyzed reactions. For example, Wang *et al.* have used amine-derived BINOL ligands (of the type **77**) for vinylogus version of Michael reaction [144]. Unlike the previously described examples, in this reaction the enatiomerically pure catalyst has enabled the desymmetrization of substrate having enantiotopic groups. In general, desymmetrization of reactions are a convenient alternative to more or less laborious construction of stereogenic center(s) step by step. The symmetrical substrates are either already available or they may be easily synthesized by well-established methods. The reaction provided in just one step compounds, which may be further used as synthons for synthesis of natural products of high biological activity, such as haterumaimide I or incarviditone. Alternatively, by simple treatment of the



Scheme 24. a) Proposed catalytic cycle. b) Possible further transformation of the tricyclic products and remaining enantioenriched substrates.



Scheme 25. The cooperative catalysis used for the synthesis of β-amino carbonyl compounds from tertiary alkyl amines and α,β-unsaturated carbonyl compounds.



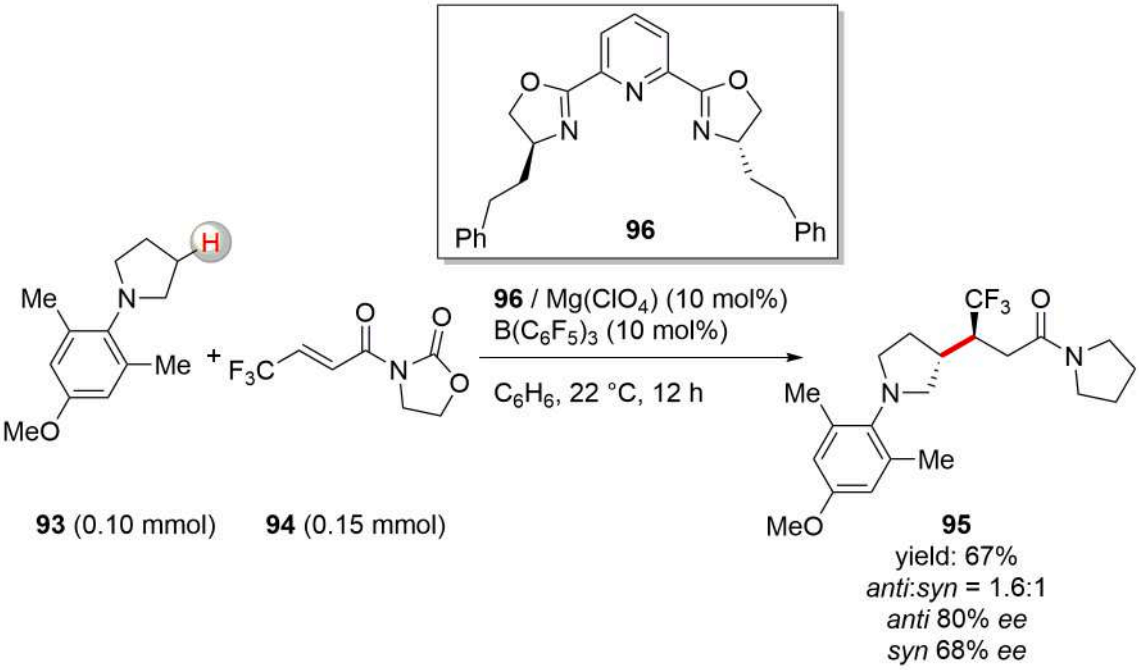
example:

	R^1	R^2	yield [%]	*anti*:*syn*	ee_{anti} [%]	ee_{syn} [%]
91a	H	H	>95	1.6:1	60	30
91b	Me	Me	88	4.3:1	94	96

Scheme 26. a) The cooperative catalysis used for the synthesis of β-amino carbonyl compounds **91** from tertiary alkyl amines and α,β-unsaturated carbonyl compounds. b) Calculated structure of the transition state, which leads to the formation of the major enantiomer.

desymmetrization product by *p*-toluenesulfonic acid, the compound is aromatized with a simultaneous ring cleavage.

In this work, *para*-substituted phenols, after oxidation in the presence of the allyl alcohol, followed by olefin metathesis catalyzed by 1st generation of Grubbs catalyst (which had provided compounds **78**), were subjected to cyclization (see Scheme 22). The catalytic system was generated *in situ* from BINOL-type ligand **77** and dibutyl magnesium. The reaction efficiency might be increased by the addition of *o*-chlorobenzamide (**79**). The role of the additive was ascribed to having a stabilizing effect through both hydrogen bonding with the ligand and by coordination of carbonyl oxygen atom to the metal center. Having developed optimized reaction conditions (0.1 mmol scale, **L**, amide and Mg_2Bn = 15 mol%, solvent – 1 mL) a library of chiral products **80**, characterized by the presence of *cis*-hydrobenzofuran motif, have been



Scheme 27. Magnesium-catalyzed stereoselective synthesis of *N*-benzylamines through *β*-amino C—H functionalization.

obtained with enantioselectivities ranging from good to excellent. The substituents attached to the cycloheksadienone skeleton did not affect the reaction significantly.

Resolution of racemates has been by far the first and still useful method of acquiring optically active compounds. The advantage of this method over others is due to the usually easier accessibility of racemates and their more convenient and 'cheaper' synthesis [145]. Racemates can be resolved on enantiomers both by physical and chemical methods. In the case of the first group, there is no necessity of chemical modification of the molecules, as the non-covalent interactions and physical forces take a decisive part in the process. The second group of methods assumes formation of the covalent bond between substrate and reactant, which may be either chiral and optically pure or achiral. In the latter case, an appropriate chiral catalyst is required, which facilitates the reaction with achiral reactant through one, preferred diastereoisomeric transition state.

Among many of resolution methods known so far, kinetic resolution is the most popular one. In this method the significant difference in the reaction rates between enantiomeric molecules of the resolving racemate and chiral reactant/catalysts seems to be crucial for achieving success. The main drawback of the classical kinetic resolution is the yield of the product of interest, which by definition should not exceed 50%.

Yang *et al.* have used the principles of kinetic resolution and applied them to intramolecular vinylogous Michael reaction taking place in racemic allylic esters **81**. The products thus formed (**82** and remaining enantioenriched **81**) contained [6.6.5]-tricyclic parallel skeletons, the structural feature often found in many natural products (Scheme 23 and Table 3).

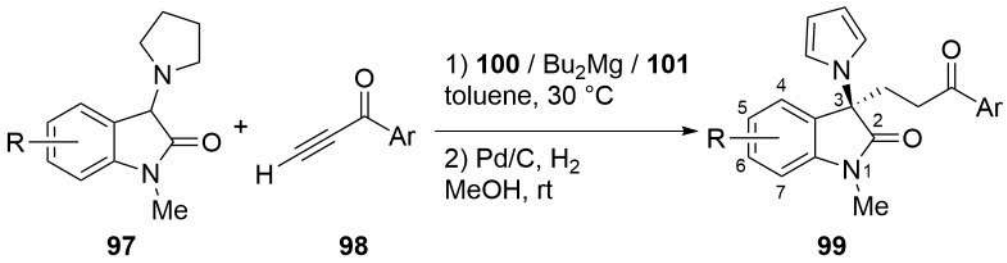
The clou of this transformation has relied on synergy in action between parts of the catalytic system. The ligand **83** used for magnesium ion complexation is based on BINOL skeleton having additional tertiary amine fragments in 3 and 3′ positions. When magnesium had been coordinated to the phenol groups of the BINOL-based ligand (**I**, Scheme 24**a**), the metal ion became then a Lewis acid center. In the next step, both carbonyl groups present in the substrate coordinated to the metal center, which was associated with assuming specific mutual orientation of reacting centers (**II**, Scheme 24**a**). Simultaneously, basic nitrogen atoms in tertiary amines had deprotonated the allylic ester fragment, which now was transformed to good Michael donor (ester enolate **III**, Scheme 24**a**). Reaction between Michael donor and acceptor parts of the molecule followed by the protonation and release of the tricyclic product (**IV**, Scheme 24**a**) has terminated the catalytic cycle. Both, the remaining substrate and the product have been characterized by high optical purity and might be used for subsequent transformations (Scheme 24**b**) [146].

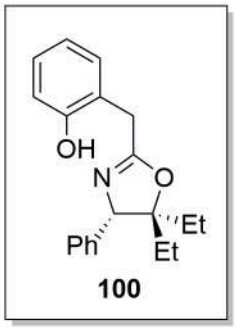
The idea of cooperative catalysis has been applied also by Wasa and co-workers to synthesize *β*-amino carbonyl compounds under redox neutral conditions. Having looked at the proposed reaction mechanism (see Scheme 25) this transformation is equally close to the Mannich and to the Michael reactions. However, taking into account that generating the enolate requires a conjugate addition of the hydride, we have decided to discuss it briefly here.

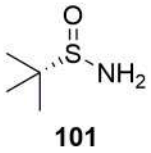
The whole process has been based on two separate tasks. In the first of them, a tertiary alkyl amine (**A**, Scheme 25) was deprotonated by strong Lewis acid of the $B(C_6F_5)_3$ type, which generated electrophilic iminium ion and borohydride (**B** and **C**, Scheme 25). Then, after coordination to the chiral Mg-Py-Box catalyst, the *α*,*β*-unsaturated carbonyl compound has been reduced (**D**, Scheme 25) by previously formed borohydride, which afforded chiral enolate (**E**, Scheme 25). After reacting with iminium ion **C**, the enolate has been transformed into enantioenriched *β*-amino carbonyl compound (**F**, Scheme 25).

N-Aryl amines of the type **89** might serve as substrates for the reaction and provided products **91** with good to excellent diastereo- and enantiomeric purity (Scheme 26**a**).

The structural feature that seemed to be important for an induction

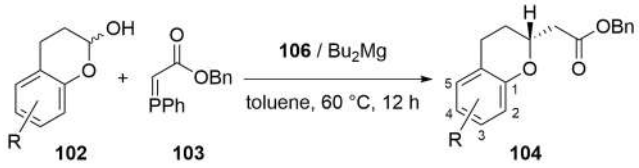


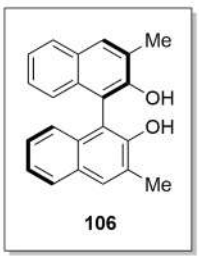




	R	Ar	yield [%]	ee [%]
99a	H	Ph	53	88
99b	5-Me	Ph	48	85
99c	6-Cl	Ph	47	70
99d	5-F_3CO	Ph	67	83
99e	H	4-FC_6H_4	53	75
99f	H	4-MeC_6H_4	67	85
99g	H	3-$MeOC_6H_4$	62	85
99h	H	2-$MeOC_6H_4$	62	85
99i	H	2,3-$(MeO)_2C_6H_3$	63	87
99j	H	2-Nph	65	77

Scheme 28. Synthesis of 3,3-disubstituted oxyindoles **99** through magnesium-oxazoline-sulfinamide-catalyzed Michael additions followed by heterogenous palladium-catalyzed hydrogenation.





	R	yield [%]	ee [%]
104a	H	92	91
104b	3-Me	89	92
104c	3-MeO	89	93
104d	3-Cl	88	74
104e	3-F	86	86

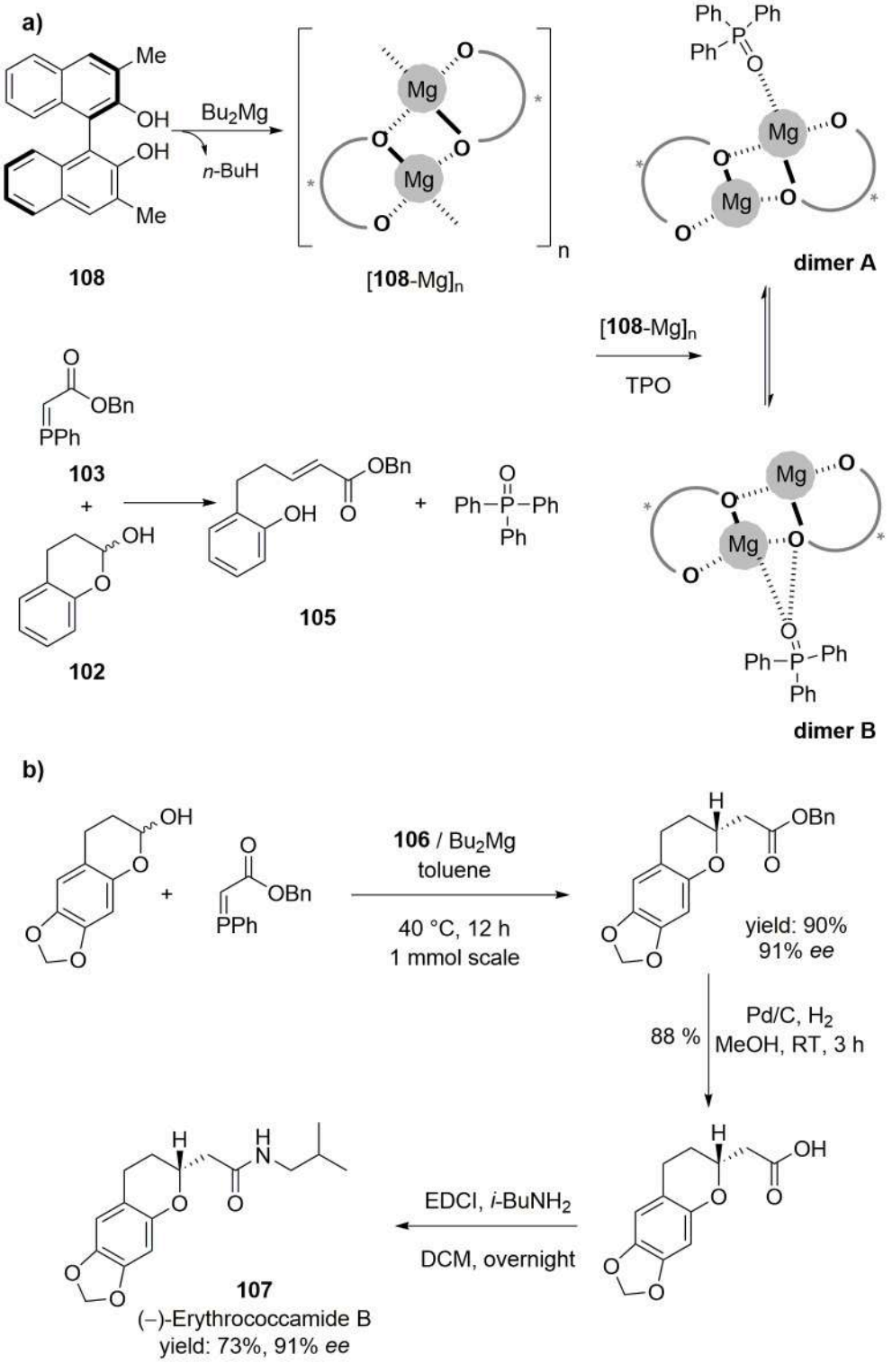
+ other examples

Scheme 29. Magnesium-BINOL complex and TPPO-catalyzed asymmetric synthesis of α-substituted cyclic ethers **104** *via* Wittig-*oxa*-Michael reaction.

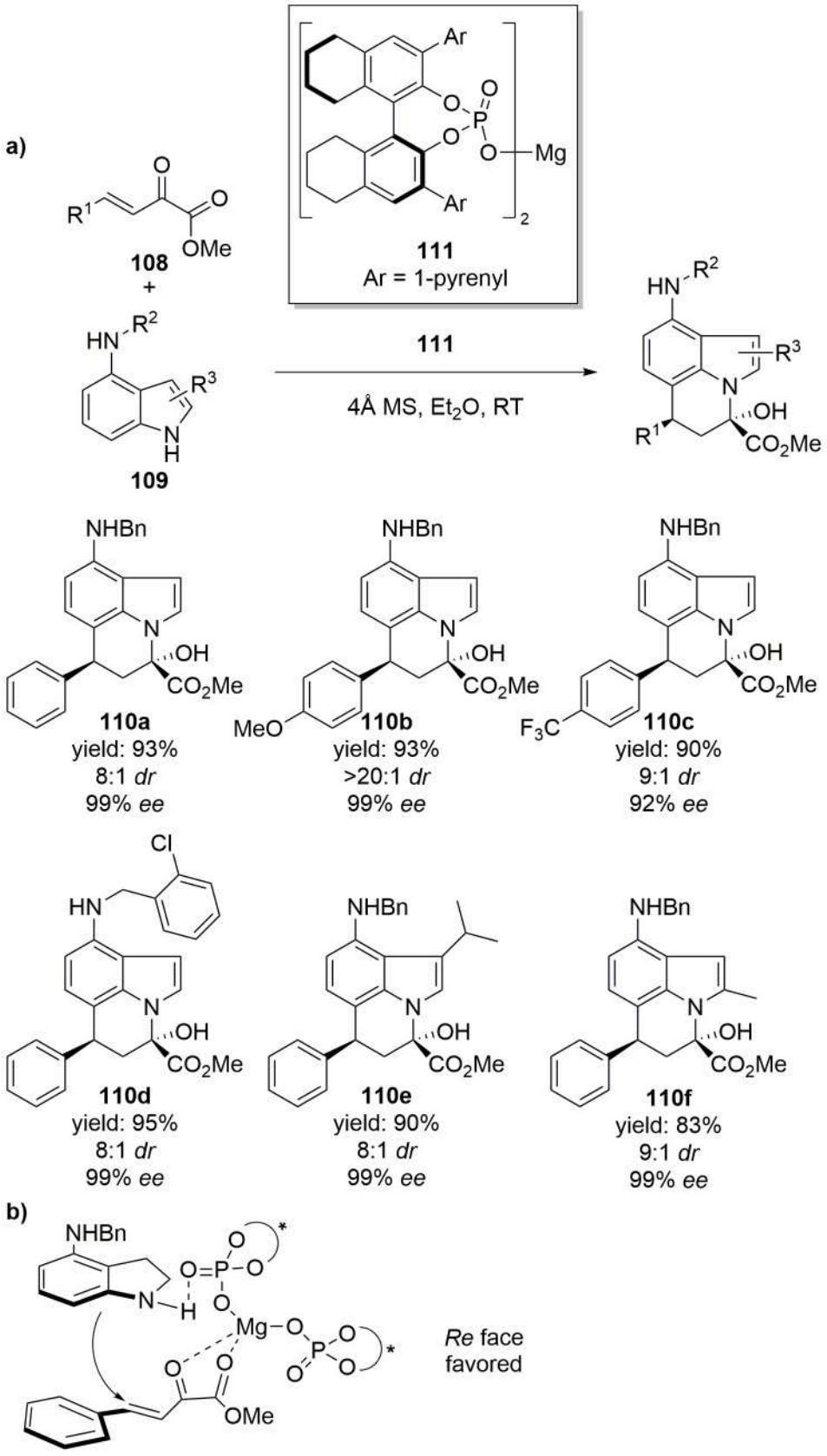
of chirality is the presence of an aryl group in each oxazoline moiety of the Py-Box ligand **92**. The role of the aryl groups was further studied by means of density functional theory. In the calculated transition state structures, the magnesium-bound enolate as well as iminium ion are oriented parallelly to one of the aryl groups. In such structures, the *Re* face of enolate is hindered, affording attack only from the *Si* face (Scheme 26**b**).

The possibility of independent tuning of both catalytic species allowed for the use of *N*-benzyl pyrrolidines **93** as substrates. In this case, the β-abstraction of hydride has taken place in the amine and then conjugate addition of the thus formed enamine to the α,β-unsaturated carbonyl compound **94** has led to the formation of a new carbon–carbon bond in the product **95** (Scheme 27). Although magnesium-Py-Box complex (Mg–**96**) would lead to the enantioenriched product, better results in terms of diastereo- and enantioselectivity were obtained with the use of scandium(III) triflate as the metal source. The subsequent mechanical considerations revealed that the metal ion should take on a coordinating number 7, which is rather rare for magnesium cation.

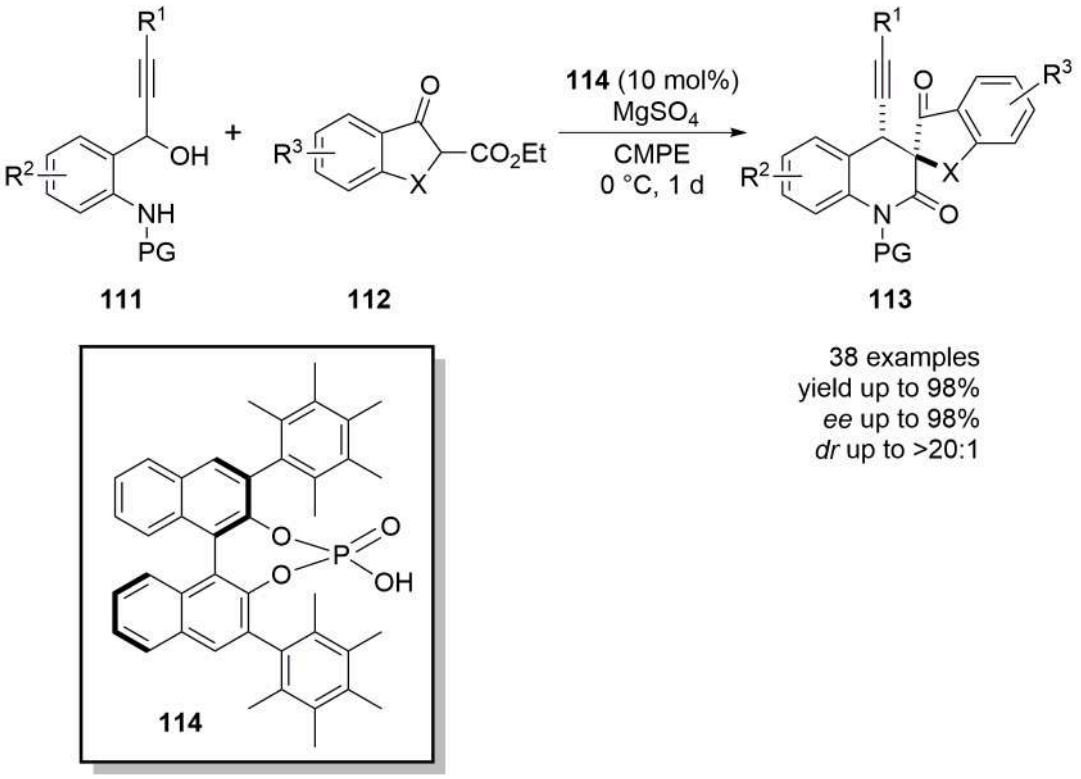
By combining Michael addition with subsequent heterogeneous palladium-catalyzed hydrogenation, Wang and co-workers have obtained a series of 3,3-disubstituted oxyindoles **99** [147]. Substrates – 3-pyrroryl-oxyindoles **97** had been at first transformed to the corresponding enolates and then reacted with Michael acceptors. In such cases, the role of Michael acceptors has fallen to aryl-propargyl ketones



Scheme 30. a) An effect of TPPO on the structure of catalytically active species. b) Synthesis of (–)-Erythrococcamide B (**107**) *via* Mg-catalyzed Wittig-*oxa*-Michael reaction.



Scheme 31. a) Magnesium-catalyzed asymmetric synthesis of 4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives from β,γ-unsaturated α-ketoesters and 4-aminoindoles. b) Proposed working mode of this reaction.



Scheme 32. Stereoselective synthesis of spirocyclic dihydroquinolones **113**.

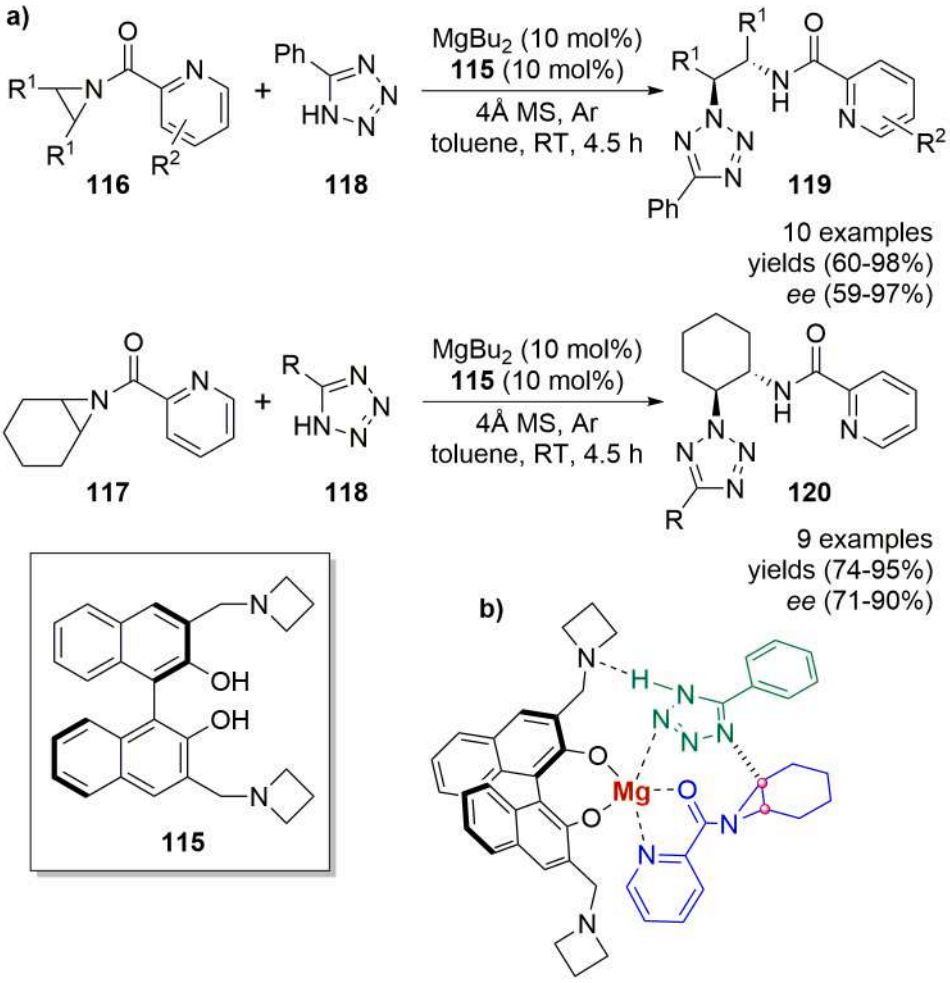
(alkynones, **98**). The reactions were catalyzed by *in situ* generated magnesium complexes and out of the ligands tested, the best performing one (**100**) has consisted of a chiral oxazoline part connected with phenol. In contrast, BINOL derivatives used as magnesium ligands have provided products with low enantiomeric purity. During the further optimization of the reaction conditions, it turned out that additive of (*R*)-*tert*-butanesulfinamide (**101**) had increased the efficiency of asymmetric induction. Although the structure of the catalytically active species has not been determined yet, it is supposed that the catalytic species contains both chiral molecules coordinating the central metal ion. Note that the additive affected only enantiomeric ratio, whereas the *E/Z* proportion of diastereoisomers of primary products remained unchanged regardless of using or not using the additive. On the other hand, the problem with separation of obtained alkenes would be solved at the next step. A subsequent reduction of carbon–carbon enone double bond *via* heterogenous palladium on charcoal hydrogenation transformed the mixture of *E/Z* enones into the same product. The final products **99** have been obtained with moderate yields but good enantioselectivities. It is worth mentioning that the substitution patterns within both components, namely oxyindole and alkynone, have almost not affected the level of asymmetric induction but influenced the chemical yields (Scheme 28) [147].

Michael addition is often a step of tandem reactions. Wang *et al.* have described Wittig-oxa-Michael reaction, which afforded enantioenriched **104** (see Scheme 29) [148]. Reactions sequence began from Wittig olefination of racemic hemiacetal **102** by stabilized ylide **103**. In this step, the α,β-unsaturated carbonyl compound **105** is formed, which would undergo subsequent intramolecular Michael addition of oxonium ion. When the reaction is run in the presence of chiral catalyst, the induction of chirality would take place during the conjugate addition step. In this particular case, an *in situ* generated from BINOL derivative **106** and dibutyl magnesium polymeric catalytic species [**106**-Mg]$_n$ has been found as the best performing one.

Despite the greater or lesser sophistication of the method, one more factor is important to the success of this reaction. After careful evaluation of the procedure, it has been turned out that *in situ* formed triphenylphosphine oxide (TPPO) is essential for achieving high level of enantioselectivity. Typically, TPPO is an unwanted and difficult to remove by-product of many reactions employing PPh_3 as a reagent, however, in this particular case TPPO has served as a full participant in the process. TPPO is known to coordinate to the metal centers, thus, blocks the catalytic site of the catalysts. The subsequent ^{13}P NMR studies have revealed that the optimal ratio TPPO:Mg catalyst was 0.5:1 and there were two possible coordination mode of TPPO to the BINOL-Mg species. What was more important was the fact that the presence of TPPO caused depolymerization of the catalyst to form dimeric species, each bound one TPPO molecule (Scheme 30**a**). Among the examples showing the scope of the reaction, its practical utility has been demonstrated, i.e., by synthesis of (–)-erythrococcamide B (Scheme 30**b**).

Antilla and co-workers have used cascade reactions for the synthesis of optically active polycyclic indoles **110** (Scheme 31**a**).

The reaction has been catalyzed by chiral BINOL-derived phosphate-magnesium complex **111** and have employed 4-aminoindole derivatives **108** and β,γ-unsaturated α-ketoesters **109** as substrates. Whereas the presence of hydrogen atom at the C4-amino group was not necessary, the NH-indole seemed to be crucial. The dual activation mode has been proposed for this reaction. The magnesium ion has acted as the Lewis



Scheme 33. a) The asymmetric ring-opening reaction in *meso*-aziridines with substituted tetrazoles catalyzed by a chiral Mg-**115** complex. b) Postulated structure of the rection intermediate.

acid center, to which both carbonyl groups from substrates have coordinated, whereas P═O moiety has served as Lewis base activating 4-aminoindole through hydrogen bonding. The electron-rich indole has attacked carbon–carbon double bond in activated carbonyl compound from unhindered *Re* face. The subsequently formed 1,4-adduct has undergone spontaneous *N*-hemiacetalization providing 4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (see Scheme 31**b**) [149]. Note, the reaction may be classified alternatively as Friedel-Crafts alkylation connected with *N*-hemiacetalization.

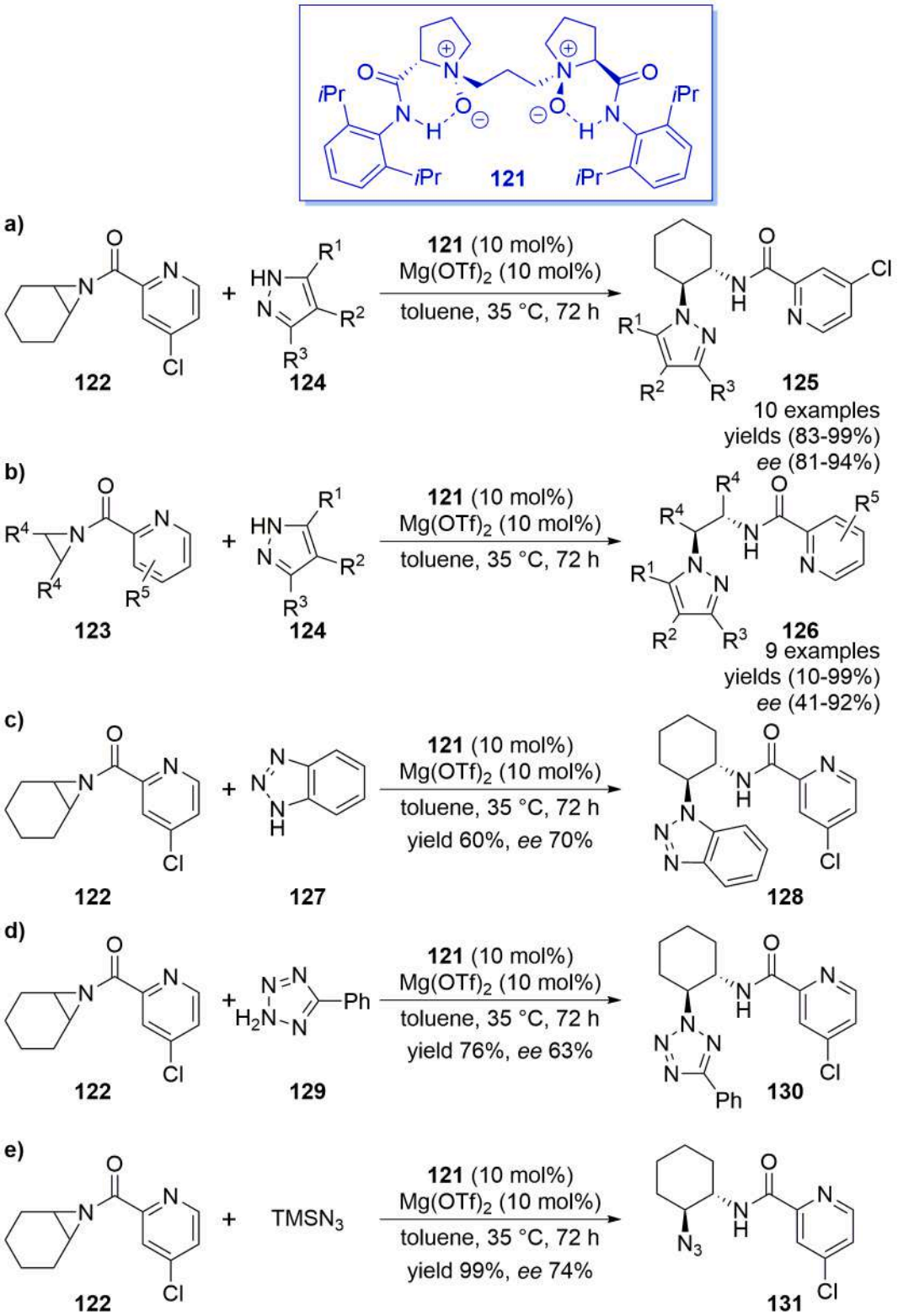
The spirocompounds **113** can be obtained through domino Michael addition-lactamization of *ortho*-quinone methide imines (Scheme 32). The reactions took place in the presence of 10 mol% of chiral, BINOL-based phosphoric acid **114** and $MgSO_4$. Although, the spectrum of tested substrates **111** and **112**, and the results can make an impression, the so far performed mechanical studies have not proven unequivocally the sole role of the *in situ* generated magnesium complex in the control of stereoselectivity. Instead, $MgSO_4$ enhanced significantly the rate of reaction, thus yield of the product, and does not affect the enantioselectivity [150].

6. Mg-Catalyzed Desymmetrization of aziridines

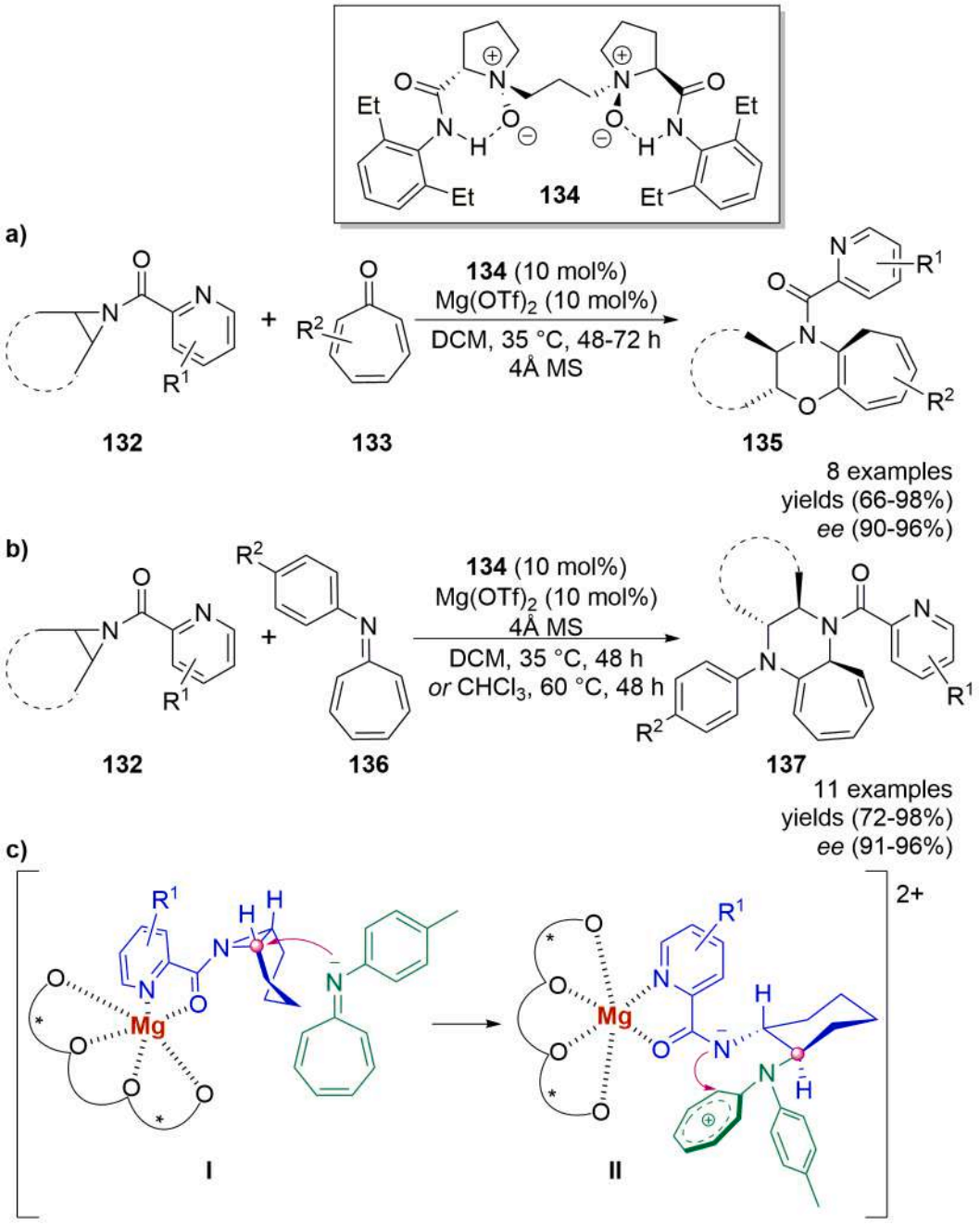
One of the most important method for one-step acquiring valuable chiral 1,2-difunctionalized compounds with neighbouring stereocenters is a nucleophilic ring-opening of epoxides and aziridines [151–159]. At the beginning of 2010 there were only a few examples known of magnesium-catalyzed asymmetric ring-opening reaction of *meso*-epoxides, which led to obtaining chiral products generating from moderate to high yields (24–92%) and enantioselectivities ranging from 56% to 94%) [160–161].

On the other hand, a ring-opening of *meso*-aziridines will allow for the synthesis of a product of significant utility [153]. Between 2014 and 2016 [162], Feng *et al.* [163] and Wang *et al.* [164–167] demonstrated first catalytic systems based on magnesium and chiral ligands such as: *N*, *N'*-dioxide, quinine, BINOL or oxazoline, for enantioselective ring-opening reaction of *meso*-aziridines with different nucleophiles such as: alcohols, amines, indoles and β-naphthols.

In the 2017, Wang's group reported one of the first examples of asymmetric ring-opening reaction in *meso*-aziridines with substituted tetrazoles catalyzed by a chiral Mg-**115** complex (Scheme 33**a**). Reactions were run in toluene, at room temperature and with the presence



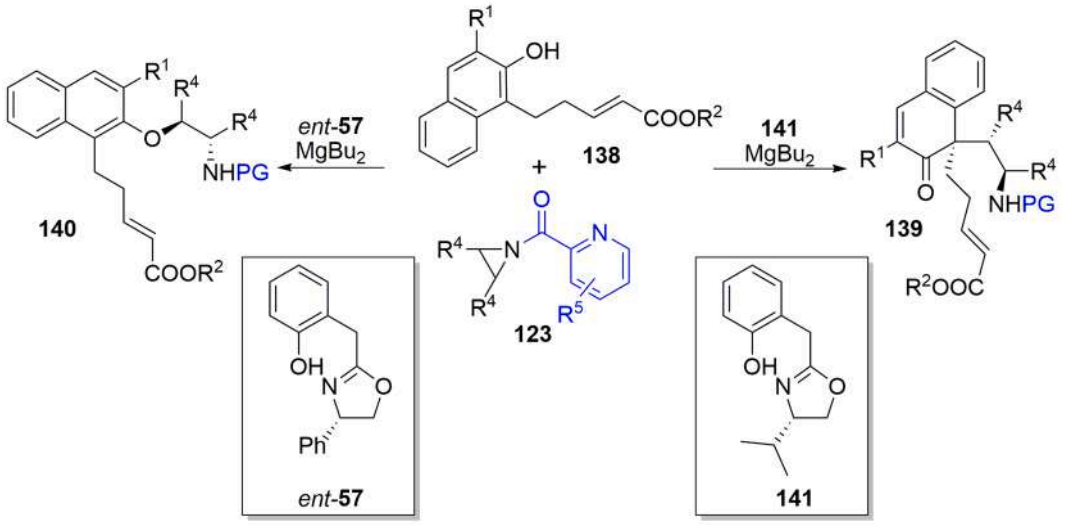
Scheme 34. Desymmetrization of *meso*-aziridines catalyzed by *N,N'*-dioxide **121**-$Mg(OTf)_2$ complex.



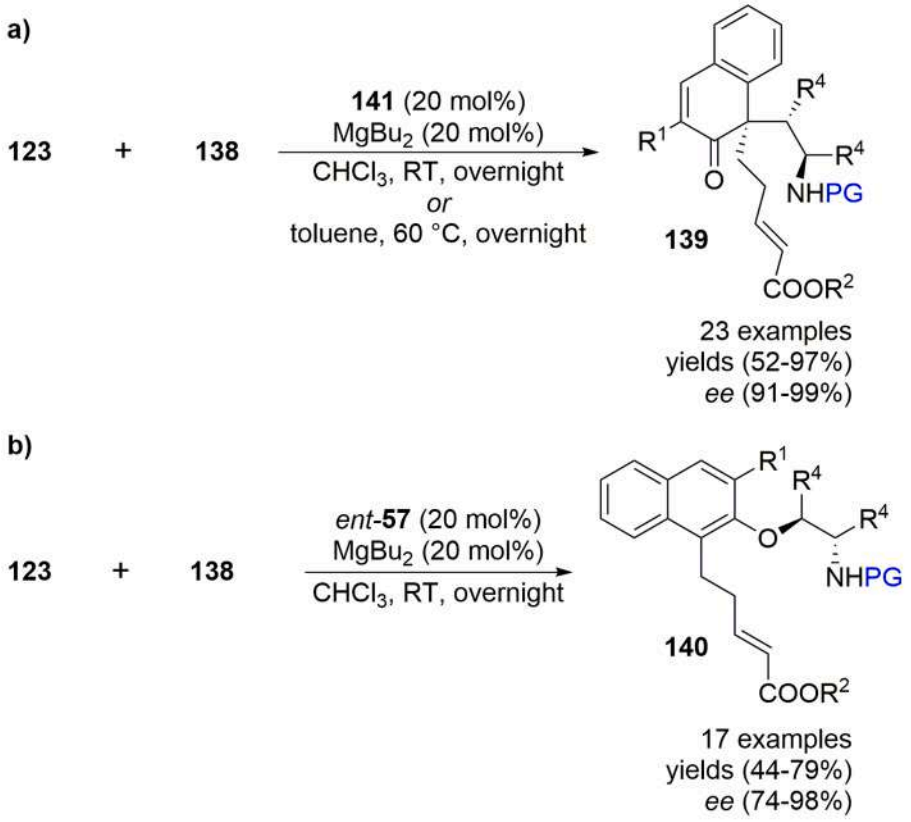
Scheme 35. Asymmetric [8 + 3] cycloadditions between a) tropones or b) azaheptafulvenes and *meso*-aziridines catalyzed by chiral $Mg(OTf)_2$/*N*,*N*'-dioxide **134** complex. c) Proposed mechanistic model.

of molecular sieves [168]. This protocol was successfully applied to desymmetrization of *meso*-aziridines **116**, **117** of cyclic and acyclic structures by substituted tetrazoles **118** as nucleophiles, which led to the enantioenriched ring-opening products **119**, **120**, respectively, with good to high yields (60–99%) and moderate to excellent *ee* values (71–99%) (Scheme 33**a**). The proposed mechanism assumes that the *N*-heterocyclic ring from phenol ligand **115** (Scheme 33**a**) is supposed to act as a C_2-symmetrical Brønsted base, which could bind tetrazoles by hydrogen bond (Scheme 33**b**). Thus, the use of *N*-heterocyclic substrates would have positive effects on chirality induction. The reaction could be scaled up and conducted in the gram scale with the same efficiency. The tetrazole protection group can be smoothly removed to generate chiral alkyl amines in almost quantitative yield.

In the same year, Feng and co-workers presented a highly enantioselective protocol for the desymmetrization of *meso*-aziridines **122**, **123** by a ring-opening with pyrazoles **124** using *N*,*N*'-dioxide **121**–$Mg(OTf)_2$ complex as catalyst [169]. The reactions were carried out in toluene under inert atmosphere, at slightly elevated temperature (35 °C), for 72

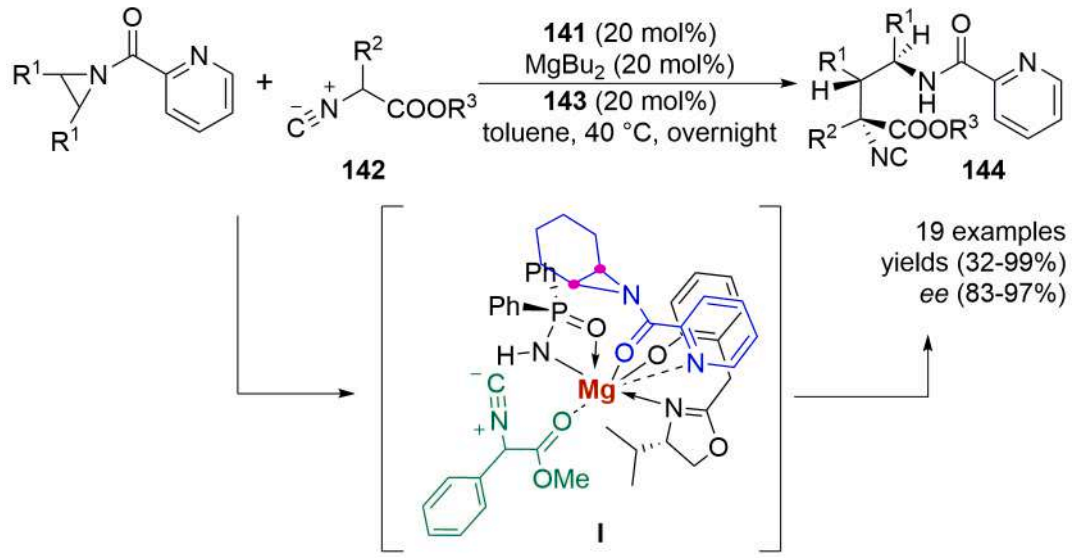


Scheme 36. Diversiform reactivity of naphthols.

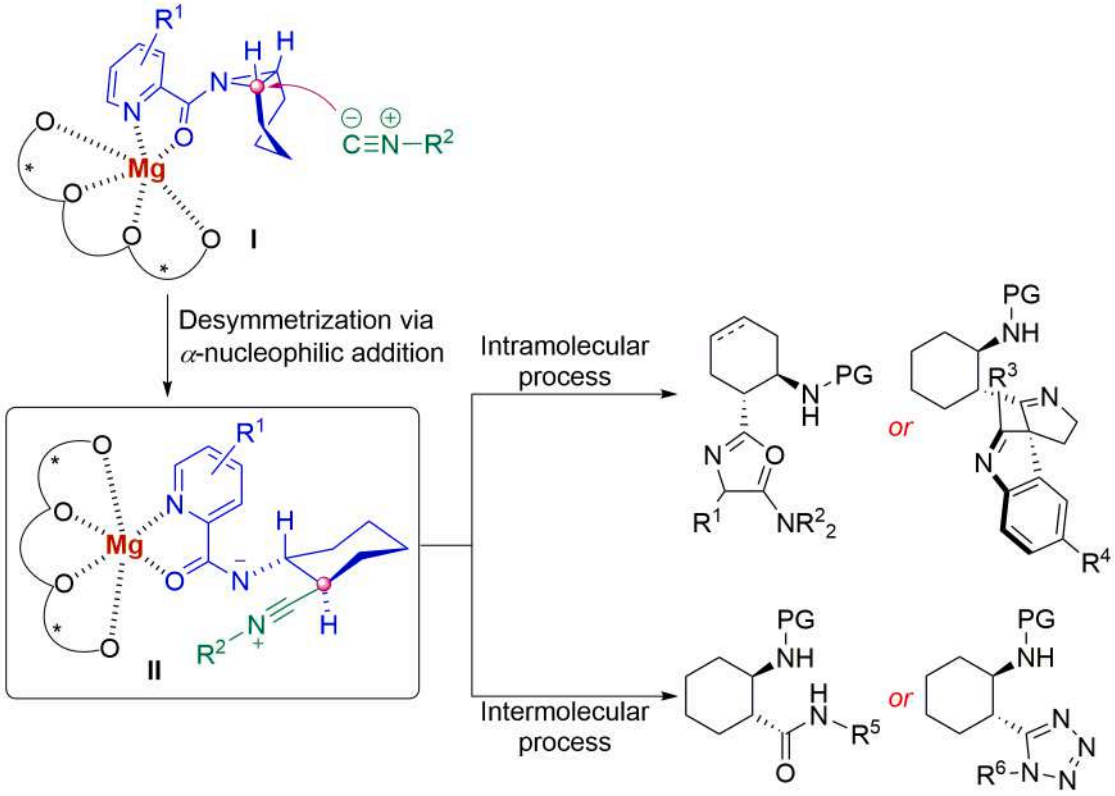


Scheme 37. a) The *C*-dearomatization reactions catalyzed by **141**-Mg complex. b) *O*-Alkylation reactions catalyzed by *ent*-**57**-Mg complex.

h and with 10 mol% of catalyst. Several *meso*-aziridines were tested, including derivatives bearing saturated and unsaturated cyclohexane or cyclopentane ring and with various protective group at nitrogen atom. Having used differently substituted pyrazoles (Scheme 34**a,b**), the corresponding products were obtained with good to excellent yields (41–99%) and enantioselectivities up to 94%. This catalytic system was also applied to the desymmetrization of the aziridines using different nucleophiles, such as triazole **127**, tetrazole **129** and trimethylsilyl azide ($TMSN_3$), providing the corresponding products with moderate yields and enantioselectivities (Scheme 34**c,e**). It is noteworthy that there was



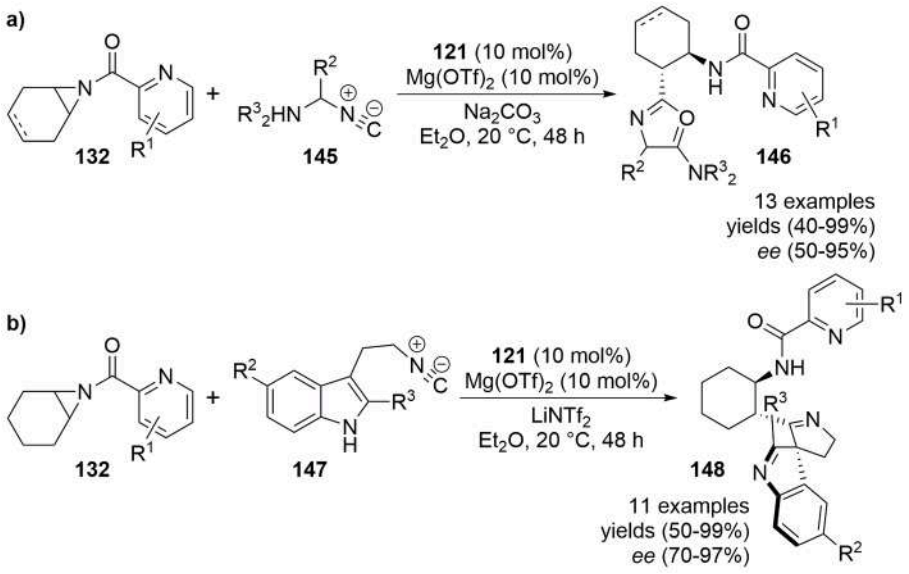
Scheme 38. Mg-Catalyzed asymmetric reactions of α-isocyanoacetates with *meso*-aziridines and pleasurable reaction intermediate **I**.



Scheme 39. Enantioselective ring-opening desymmetrization of *meso*-aziridines by isocyanides catalyzed by chiral $Mg(OTf)_2$-*N*,*N*'-dioxide **121** complex.

observed a remarkably strong positive nonlinear effect implying that the reaction took place in the presence of polymeric Mg species. The reaction could be scaled up to a gram-scale without a loss of enantioselectivity.

Asymmetric [8 + 3] cycloadditions between tropones **133** or azaheptafulvenes **135** and *meso*-aziridines **132** were described by Liu and Feng in 2018 [170]. The desymmetrization/annulation process was catalyzed by chiral $Mg(OTf)_2$/*N*,*N*'-dioxide **134** complex in DCM, at 35 °C with an addition of 4 Å MS, which afforded the wide scope of tricyclic heterocycles **136**, **137** containing functionalized



Scheme 40. a) Reactions between *meso*-aziridines having various protecting groups at nitrogen atom and α-isocyanoacetamides. b) Reactions between *meso*-aziridines and various *C*2– and C5-substituted 2-isocyanoethylindoles.

cycloheptatriene unit. The yields of the reactions were modest to high (up to 98%) but diastereo- and enantioselectivities were excellent (>19:1 *dr*, up to 96% *ee*) (Scheme 35**a**,**b**).

The proposed mechanism is based on an X-ray crystal structure of the catalyst and assumes formation in the transition state octahedral complex by magnesium ion, chiral *N*,*N*'-dioxide ligand **134** and an aziridine. The latter is coordinated through aromatic nitrogen and carbonyl oxygen atom from nitrogen atom protective group (**I**, Scheme 35**c**). Due to a steric hindrance caused by chiral ligand, cyclohexyl ring from aziridine is located downward. In such a structure, nucleophilic attack takes place from the back side of aziridine ring leading to *trans*-1,2-diaminocyclohexane zwitterionic intermediate (**II**, Scheme 35**c**), which gives the desired product after cyclization.

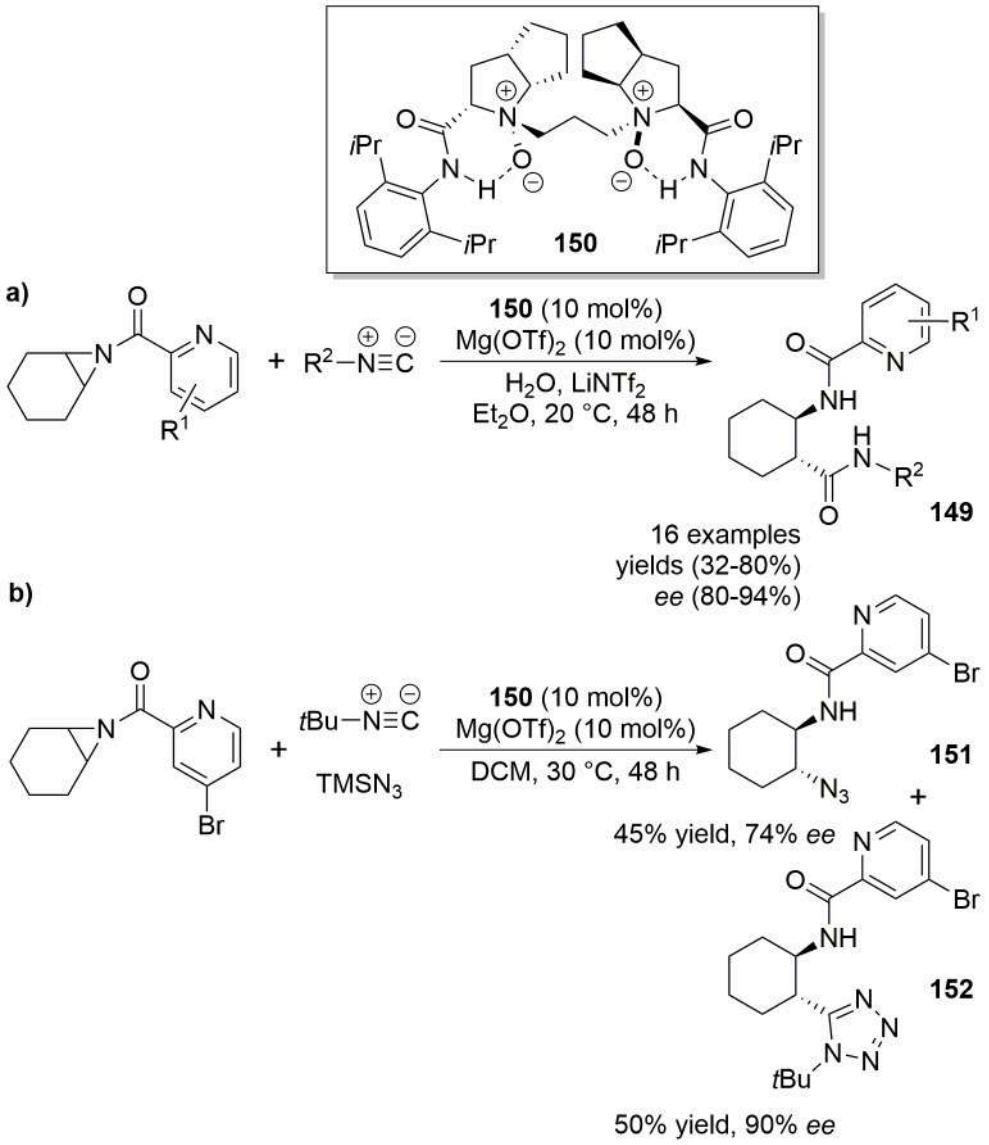
Wang *et al.* presented an extension of their previous research on asymmetric dearomatization of phenol compounds with *meso*-aziridines, catalyzed by chiral magnesium complexes [165,171,172]. The authors have focused on finding the conditions for switchable divergent reactivities of phenol compounds **138** furnishing dearomatized **139** or *O*-alkylated products **140** [173]. There have been investigated reactions between naphthols having catenulate ester group at C1-position and *meso*-aziridines, catalyzed by *in situ* generated complex Mg/oxazoline ligands **141** or *ent*-**57** (Scheme 36). It should be noted that this switchable reaction is ligand and substrate-dependent. The group at C3-position of naphthols dramatically affects the chemoselectivity of the process and the effect is considered even higher than the effect of the catalyst. In the cases discussed here, two processes may compete – *O*-alkylation and *C*-dearomatization. Although coordination of the group from C1-position (i.e., catenulate ester group) partly releases the phenolic hydroxyl group, which participates in the *O*-alkylative reaction, it has slight effects on the *C*-dearomatization/*O*-alkylation ratio.

The intermolecular asymmetric dearomatization reaction occurs when naphthols were substituted at C3-position with halogen, aryl and different alkyl groups (including long alkyl chains). The yields of the reactions as well as the *C*-dearomatization/*O*-alkylation ratios may be considered satisfactory, while diastereo- and enantioselectivities were up to 99% (Scheme 37). Various cyclic- or acyclic-*meso*-aziridines, of the general formulas **122** and **124**, were collaborated well in the Mg(II)-catalyzed asymmetric dearomatization reaction leading to a series of enantioenriched γ-amino-ketones **139** (Scheme 37**a**).

It has been found that asymmetric *O*-alkylation route is compatible with C3–(H)-naphthol and different C3-halogen substituted naphthols. In most cases, the yield of *O*-alkylated product increases while a reaction of C3-halogenated-naphthols is catalyzed by *ent*-**57**–Mg complex. In such conditions, the corresponding *O*-alkylation products were generated smoothly, with moderate to good yields and enantioselectivities up to 98% (Scheme 37**b**).

The previously discovered catalytic system based on *in situ* generated Mg/**141** complex has been applied to asymmetric reactions of α-isocyanoacetates with *meso*-aziridines [174]. The reactions were carried out in toluene, at 40 °C. An addition of an achiral ligand – diphenylphosphinamide (**143**) improved *enantio*- and diastereoselectivity of the reaction (Scheme 38). The ring-opening reaction of a wide range of *meso*-aziridines (containing five-, six-, and seven-membered rings as well as acyclic aziridines having alkyl or aryl groups) were carried out using the current catalytic system. The corresponding desymmetrization products were obtained in yields ranging from 54 to 92% and good to excellent diastereo- and enantioselectivities (*dr* up to > 20:1 and 97% *ee*, respectively). The scope of α-isocyanoacetates was also investigated in the reaction with different cyclic or acyclic *meso*-aziridines resulted in satisfied yields (32–98%) of the product and moderate to high diastereo- and enantioselectivities (*dr* up to > 20:1 and 96% *ee*) (Scheme 38). It is worth mentioning that the ring-opening products could be easily and effectively converted to the corresponding lactams or multisubstituted tetrahydropyrimidines. After a set of preliminary experiments, mechanism of this reaction has been proposed.

The most important factor for efficient diastereo- and enantiodiscrimination is the presence of an achiral ligand coordinated to the magnesium ion as it ensures a sufficient hindrance effect. This resulted in the formation of specific chiral environment determining the coordination direction of isocyanoacetates and the C—C bond formation occurring at the outside carbon atom of the aziridine (Structure **I** in Scheme 38).



Scheme 41. a) Reactions between *meso*-aziridines and *N*-Boc- or *N*-Ts-protected 2-isocyanoethylindoles in the presence of H_2O. b) Reactions between *meso*-aziridines, *α*-isocyantes and $TMSN_3$.

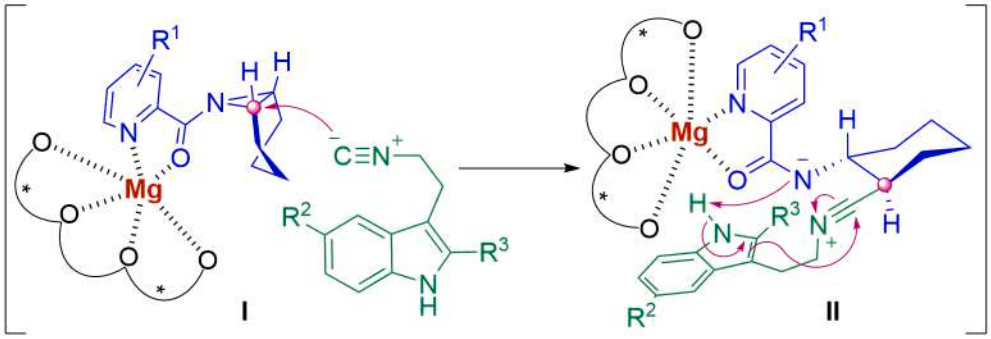
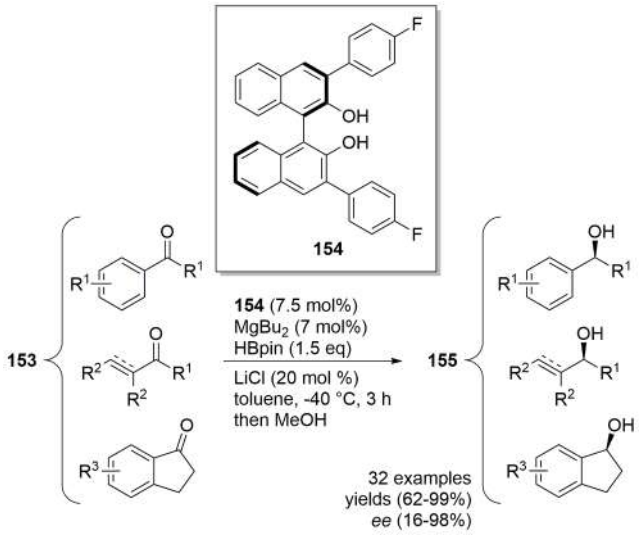


Fig. 12. Proposed mechanistic model.



Scheme 42. Asymmetric magnesium-catalyzed hydroboration of ketones.

In 2019, Feng *et al.* proposed an extension to the previously reported method for asymmetric dearomatization of indoles through Michael-Friedel–Crafts reactions cascade, which allowed for constructing polycyclic spiroindolines [175]. Such a highly efficient enantioselective ring-opening desymmetrization of *meso*-aziridines by isocyanides catalyzed by chiral Mg(OTf)$_2$-*N*,*N*'-dioxide **121** complex **I** (Scheme 39), started from *in situ* generated chiral 1,4-zwitterionic intermediates **II** (Scheme 39). Then, **II** would react with nucleophile in an intramolecular (oxygen or carbon-based nucleophiles) and in an intermolecular (H_2O or $TMSN_3$ nucleophiles) manner (Scheme 39) [176]. A range of chiral, vicinal amino oxazoles, spiroindolines, β-amino amides and tetrazoles have been obtained in moderate to good yields and with high level of asymmetric induction. For the synthesis of chiral vicinal amino-oxazoles **146**, the reactions need to be carried out with 10 mol% of *in situ* generated Mg(OTf)$_2$–**121** complex, in Et_2O, at room temperature and with Na_2CO_3 as an additive. A reaction between a series of *meso*-aziridines **132** having various protecting groups at nitrogen atom and α-isocyanoacetamides **145** led to the formation of amino-oxazoles **146** with moderate to excellent yields (40–99%) and characterized by enantiomeric excess range 50–95% (Scheme 40**a**).

Additionally, when the same catalytic system has been used for reactions between *meso*-aziridines and various *C*2– and C5-substituted 2-isocyanoethylindoles **147** as nucleophiles, with a presence of $LiNTf_2$, the vicinal amino spiroindoline **148** products were successfully formed with good to excellent yields (56–99%) and high diastereo- and enantioselectivities (*dr* up to > 19:1 and 97% *ee*, respectively) (Scheme 40**b**).

Interestingly, when *N*-Boc- or *N*-Ts-protected 2-isocyanoethylindole were used as substrates, and reaction was carried out in the presence of H_2O, the vicinal amino-amides **149** were afforded with high yields and enantioselectivities up to 94% instead of the expected spiroindoline products (Scheme 41**a**). The expansion of substrates scope led to obtaining β-amino-amides with good yields and enantiomeric excesses up to 90%. It has been found that $TMSN_3$ could serve as a second nucleophile reacting with the zwitterionic intermediate to form corresponding tetrazole **152** with 50% yield and 90% *ee*, along with the product **151**, which is the result of aziridine ring-opening by the azide anion (Scheme 41**b**). Reactions were catalyzed by *in situ* generated complex Mg(OTf)$_2$ with ligand **150**.

In the proposed mechanism (Fig. 12), aziridine was bound to the metal centre in a bidentate manner with the cyclohexyl ring located downward due to steric hindrance caused by the chiral ligand (**I**, Fig. 12). The isocyanide attack took place from the back side of aziridine ring furnishing the nitrilium intermediate **II**. Then intramolecular proton migration has occurred with a ring closure and creation of a new stereogenic centre.

7. Magnesium-catalyzed asymmetric reductions and oxidations

Although it is not defined as strictly as in inorganic chemistry, the oxidation and reduction reactions are one of the most important groups of transformation in organic chemistry, also catalyzed by magnesium complexes [177,178]. To be precise – there are no reaction in organic chemistry, in which the oxidation number of a given carbon (reaction center) atom remains unchanged. However, in the common sense, the oxidation reactions are usually connected with addition of an oxygen(s) atom(s) to the olefine or with increasing the multiplicity of the bond between the carbon and oxygen atoms. Looking at the (relatively short) history of catalytic asymmetric synthesis the development of reduction and oxidation reactions can be recognized as the milestones in such a field.

Despite the fact that over the last 5 years many new catalysts based on alkaline-earth abundant metals used for reduction of carbonyl group have appeared [28,31,179–193], there are only a few examples of magnesium-catalysed enantioselective ketone reduction [194,195].

The first example of enantioselective hydroboration of prochiral ketones **153** using BINOLate **154**–Mg catalyst, was presented in 2019 by the Rueping's group (Scheme 42) [194].

The best results were achieved when reactions were catalyzed by *in situ* generated **154**-Mg complex and carried out in toluene, at –40 °C, with HBpin as hydrogen source and LiCl as an additive. The catalytic system allowed for obtaining a wide range of chiral alcohols **155** deriving from acetophenone and 1-indanone, in excellent yields and enantioselectivities up to 98%. It is worth emphasizing that the method performed very well also for more challenging α,β-unsaturated ketones, thus selectively allylic alcohols and alkynols with good to high enantioselectivities could be obtained.

Based on a series of preliminary mechanistic studies and DFT calculations, it has been claimed that the reaction did not involve a magnesium hydride intermediate, as one could expect. Instead, the activation of HBpin is probably due to a dual Mg-O and O-B coordination

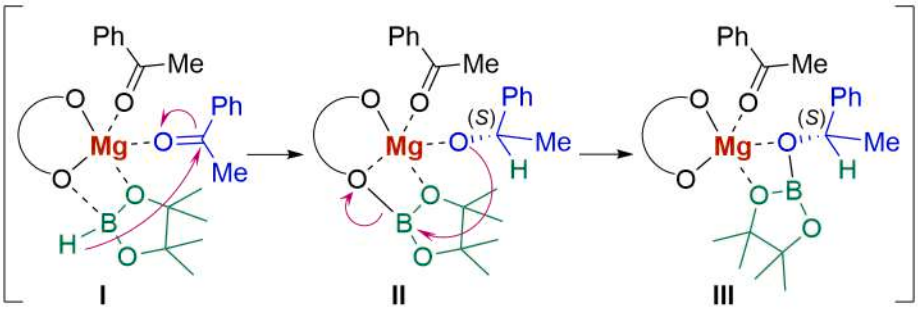
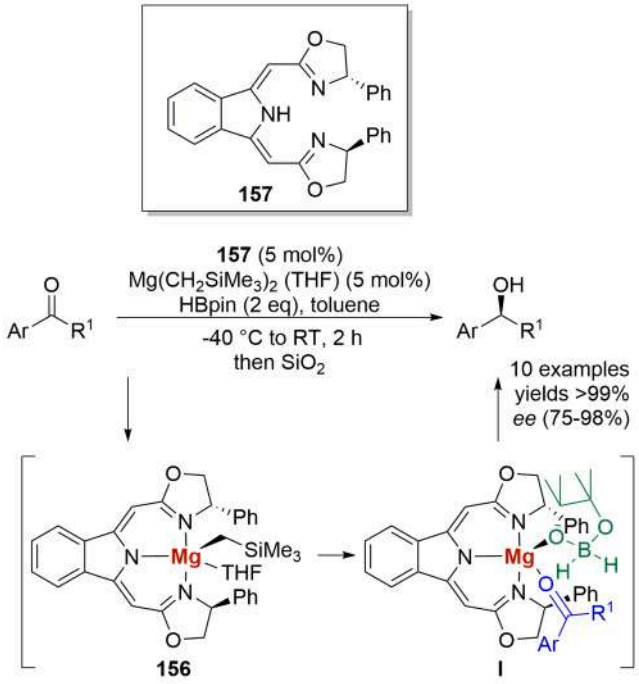


Fig. 13. Proposed mechanistic model.



Scheme 43. The ^{Ph}boxmi-Mg(CH_2SiMe_3)$_2$-catalyzed asymmetric hydroboration of functionalized ketones and proposed structure of the reaction intermediate.

to a BINOL/Mg complex (Fig. 13). According to the results of DFT calculations, the hydride transfer to the carbonyl group occurs in a well-controlled chiral environment (**I**, Fig. 13) providing an intermediate product **II**. In the next step, an alkoxide migration from magnesium to boron (structure **III**, Fig. 13) is followed by the release of the (*S*)-product with simultaneous regeneration of BINOL–Mg complex, which terminates the catalytic cycle.

In 2020, Gade and co-workers reported boximi-magnesium alkyl complex [^{Ph}boximi-Mg(CH_2SiMe_3)$_2$THF] (**156**), generated from ligand **157**, which was efficiently used in an enantioselective reduction of various prochiral ketones including diaryl, aryl–alkyl and dialkyl ketones (Scheme 43) [195]. The (*S*)-alcohols were obtained quantitatively and with a high degree of asymmetric induction (enantiomeric excesses were up to 98%). It is worth mentioning, that the catalyst used, did not show any reactivity in relation to epoxides, imines and alkenes, which highlights the functional group tolerance and selectivity towards carbonyl groups of this catalytically active species. Both hydrogen source and no-coordinating environment (solvent) are crucial in achieving high reactivity. Surprisingly, safe and (relatively) non-expensive hydrosilanes, currently widely used for reduction, did not provide any reduced products.

To gain more insight into the reaction mechanism, a series of experimental (isolation of proposed catalytic intermediates, NMR spectroscopy) and DFT computational studies have been performed. As an outcome, the zwitterionic structure **II**, formed from a cationic [boximi-Mg]$^+$ and an anionic [pinBH$_2$]$^-$, has been indicated as far more stable than magnesium hydride species and responsible for preferential formation of (*S*)-product (Scheme 43).

The discovery of asymmetric epoxidation of allyl alcohol by Sharpless [196,197] allowed for the wide use of oxiranes in stereoselective synthesis and made them as the member of "a new chiral pool". However, the main drawback of this and other common methods of asymmetric epoxidation relies on specific substrate requirements. For example, oxidation of electron-rich alkenes precede smoothly, whereas electron withdrawing groups usually hamper an addition of an electrophile.

In the recent work, Młynarski and Jaszczewska-Adamczak have reported an efficient asymmetric epoxidation of enones **158** catalyzed by magnesium-ProPhenol (**159**) [198] complex with the use of TBHP as an oxidation reagent (Scheme 44) [199]. Dibutyl magnesium was the metal source for the generation of catalytically active complex. Whereas the nature of the aryl groups attached to the sp^3 carbon atom had only little influence, the presence of OH phenolic group in ligand structure was crucial for the reaction efficiency. In contrast, the character and sterical requirements of substituent at the C4 position of the central aromatic ring have not significantly affected the reaction.

The scope of tested substrates was broad, thus, some general trends were visible. The substitution pattern in the 'benzene' part of the chalcone determines both yield and enantioselectivity. As one could expect less sterically congested *para*-substituted substrates provided products **160** with the highest yields and enantioselectivities. The electronic nature of the substituent seems to be less important. In general, the reaction is more sensitive to the steric hindrance within substrate skeleton than to an electronic character of the substituent of the double bond. (*E*)-4,4,4-Trifluoro-1-phenylbut-2-en-1-one compound, which is oxidated but provides racemate, is an exception.

To be catalytically active, the *in situ* prepared catalyst (**I**, Scheme 45) needs to be oxygenated with O_2. According to the proposed tentative catalytic cycle, the oxygenation step is crucial for initiation of the cycle. Thus, preformed 'oxy' species **II** is further regenerated with TBHP during next catalytic cycles. The molecular oxygen is inserted between the magnesium-carbon bond to form peroxide. Then, the substrate is coordinated by means Lewis acid–Lewis base interactions (structure **III**, Scheme 45) and the oxygen is transferred to the *Re* face of the enone. Dissociation of the epoxide and re-oxygenation of the reduced species finishes the catalytic cycle [199].

8. Cyclization reactions

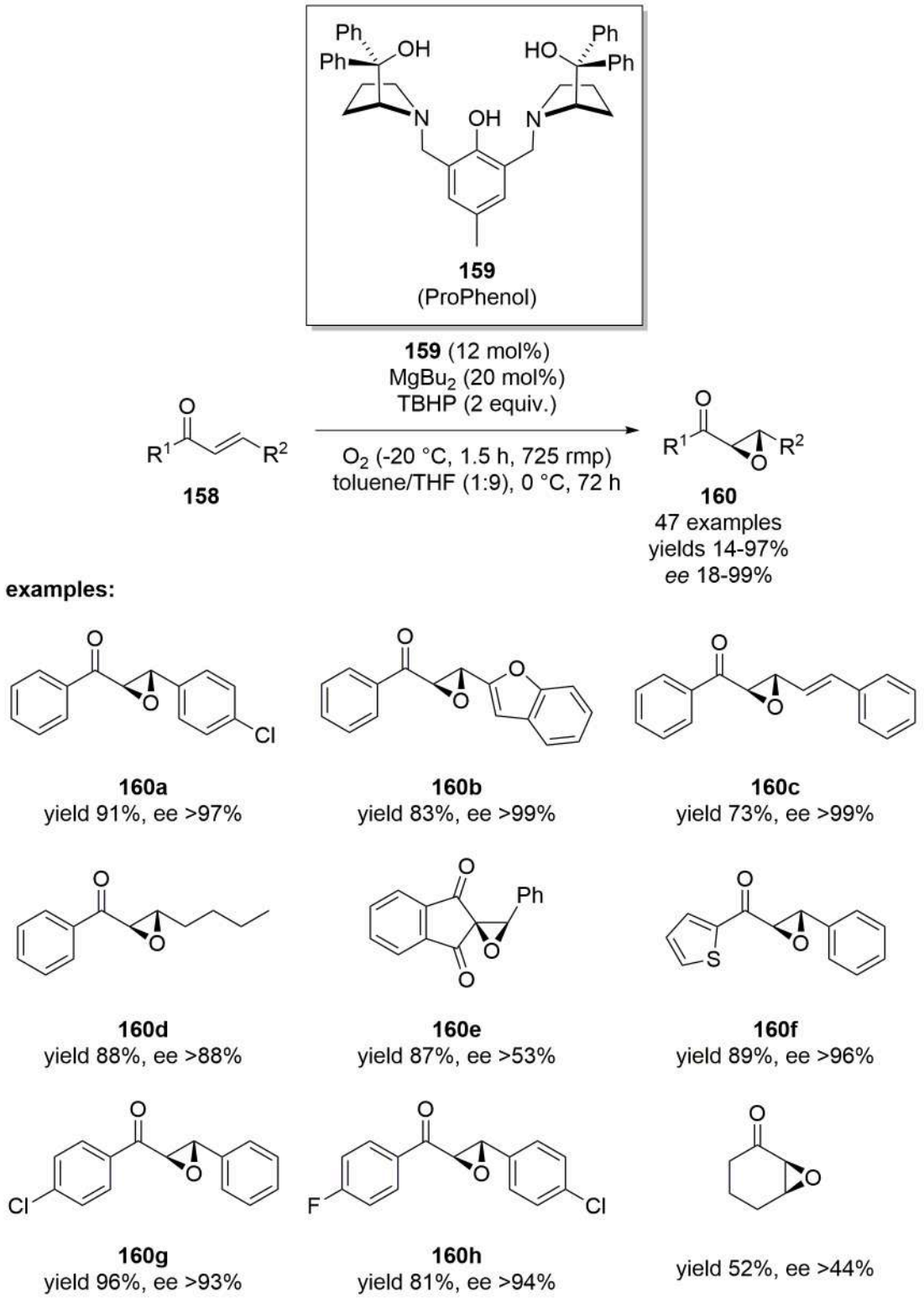
Asymmetric cyclization reactions may be considered a powerful tool for acquiring optically active heterocyclic products. Such a structural feature is common in natural products, agrochemicals, pharmaceuticals, synthetic intermediates and materials [200–209].

9. Isocyanide-based multicomponent reactions (IMCRs)

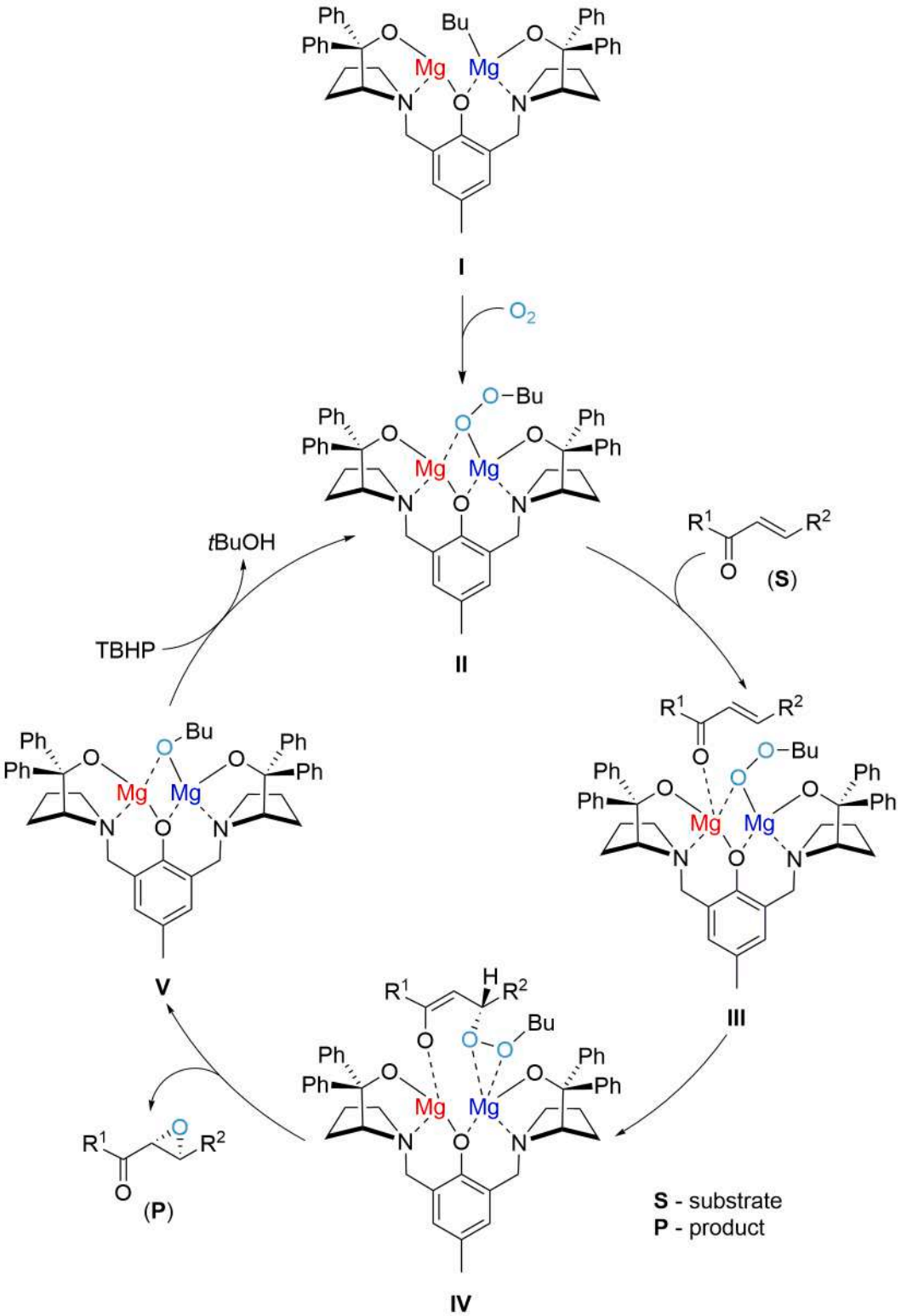
Over the last decade, various isocyanide-based multicomponent reactions have been developed. These reactions represent one of most efficient and rapid methods for *one pot* synthesis of heterocyclic complex molecules from commercially available substrates [210–217]. However, the asymmetric versions of IMCRs remain still elusive [210,218], and among the reactions reported so far, there have only been a few examples of IMCRs catalyzed by magnesium complexes [219–221].

In 2016 Feng's group [219] presented the first example of a highly efficient enantioselective α-addition of isocyanides **162** to alkylidene malonates **161** leading to a range of 2-alkyl-5-aminoaxazoles **163** with moderate to excellent yields (up to 99%) and enantioselectivities up to 96% (Scheme 46**a**). The reactions were catalyzed by *in situ* generated chiral Mg(OTf)$_2$-*N*,*N*'-dioxide **150** complex characterized by tetradentate manner coordination of the ligand.

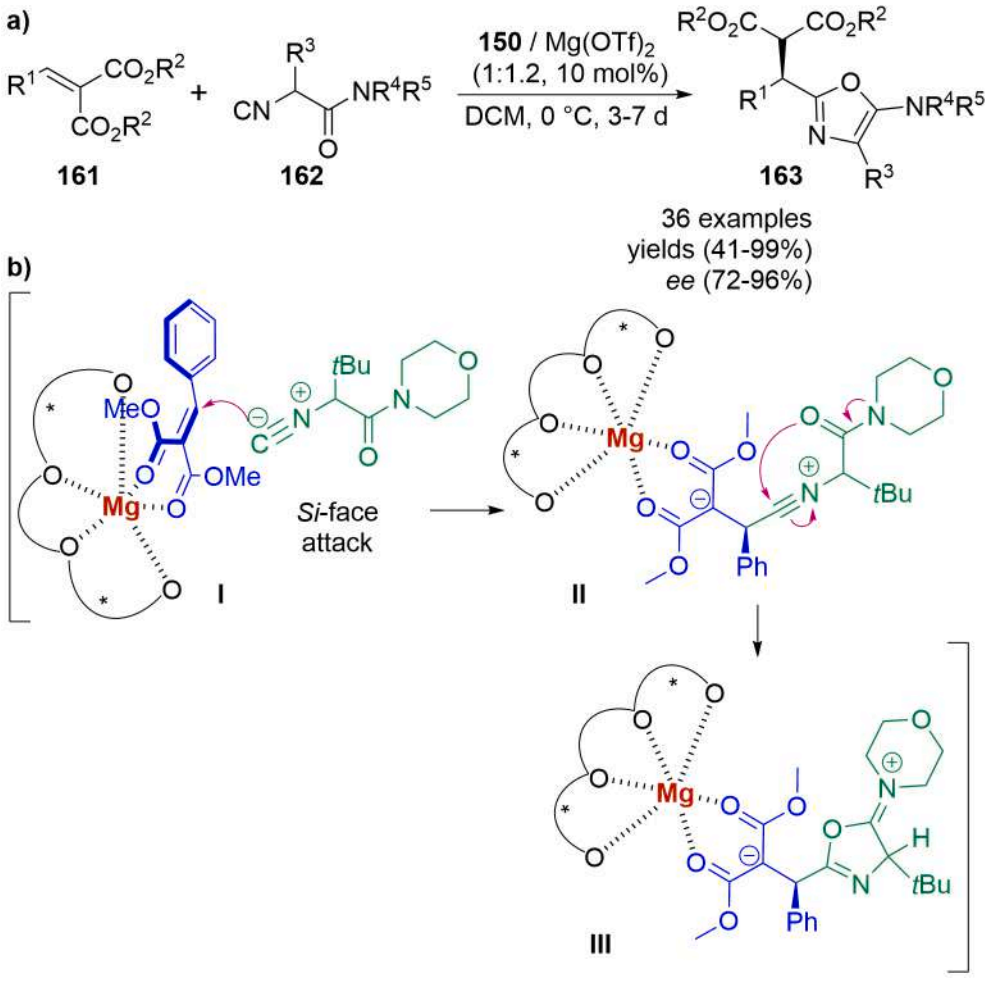
The alkylidene malonate was activated by coordination to the magnesium centre with the *Re* face blocked by chiral ligand (**I**). The



Scheme 44. Mg-ProPhenol-catalyzed epoxidation of enones.



Scheme 45. Proposed catalytic cycle.

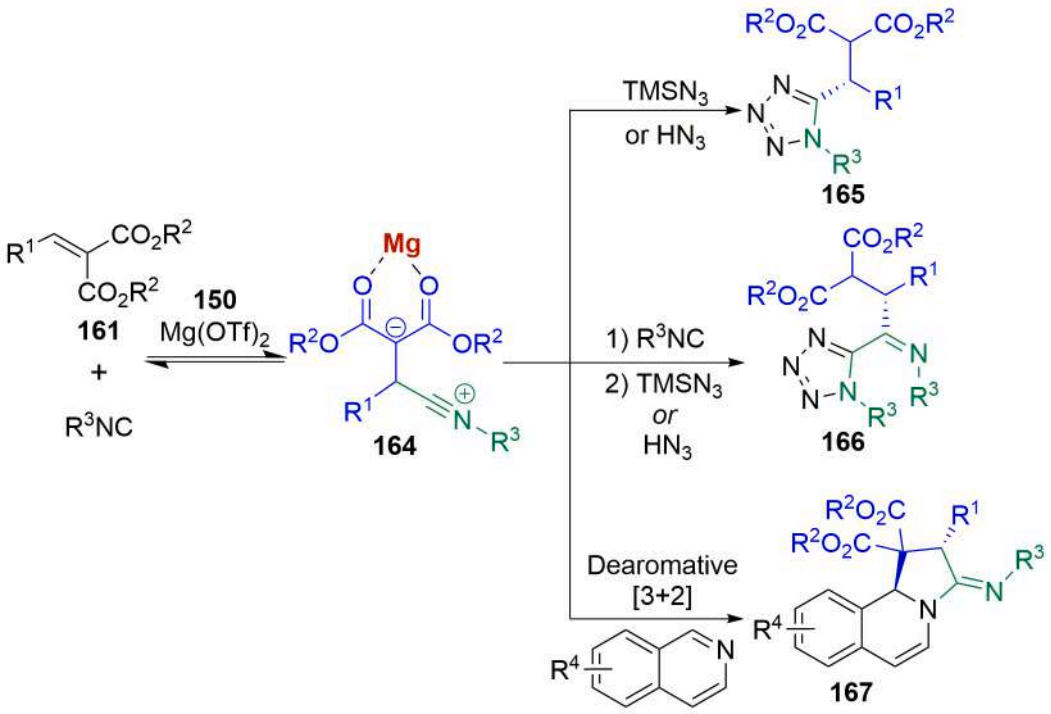


Scheme 46. a) Enantioselective α-addition of isocyanides to alkylidene malonates. b) Proposed mechanism of enantioselective α-addition of isocyanides to alkylidene malonates.

nucleophile has then approached the isocyanate from *Si* face to form nitrilium intermediate (**II**), which has undergone subsequent cyclization (**III**) and deprotonation providing desired product (Scheme 46**b**). It is noteworthy that the oxazole products could be synthetised in a gram scale and easily transferred into chiral dipeptide and imide.

Highly enantioselective isocyanide-based multicomponent reactions that are based on the addition of isocyanides to activated alkenyl bond have been catalyzed by chiral Mg(OTf)$_2$-*N*,*N*'-dioxide (**150**) catalyst. Feng *et al.* has proposed modification of such a reaction towards a precise synthesis of enantioenriched 1,5-disubstituted tetrazoles **165**, **166**, or polycyclic 1,2-dihydroisoquinoline-based amidine derivatives (**167**, Scheme 47) [220]. When reactions were carried out in DCM at –40 °C for 2 days, then the temperature was raised to –20 °C and reactions were kept at that temperature for 3 days, three-component tetrazoles **165** were selectively formed with good yields and high enantioselectivities up to 94% (Scheme 48**a**). Typically, the reactions required 10 mol% of Mg(OTf)$_2$–**150** catalyst, isocyanide, alkylidene malonate, $TMSN_3$, 5 Å MS and H_2O as an additive. Modification of the reaction conditions by changing the substrates ratio, solvent and rising the temperature up to 30 °C, led to the formation of four-component tetrazoles in very high, one can say even quantitative yields (up to 99%) and enantiomeric excess up to 91% (Scheme 48**b**). It has been assumed that the zwitterionic intermediate could be captured by imine to form another heterocyclic amidine-type of product. Under the optimized conditions, a broad range of alkylidene malonates were tested leading to the formation of corresponding products with good yields and high enantioselectivities. Additionally, with the use of various substituted isoquinolines and isocyanides, the products **167** were obtained effectively and with excellent enantiomeric excesses (up to 98%) (Scheme 48**c**). It is worth noticing that a drop of enantioselectivity was observed when aromatic isocyanide or less bulky aliphatic isocyanide were used.

Based on the previous works and the control experiments mechanism of reaction has been proposed (Scheme 49) [175,219,222]. In the beginning, both the chiral ligand and the malonate coordinate to the magnesium ion to form an octahedral complex **I**. In the complex, the *Re* face of the alkylidene malonate has been blocked by the bulky groups from the ligand, therefore the isocyanide has been able to attack only the exposed *Si* face (**II**). After it has been formed, the zwitterionic intermediate (**III**) could undergo two different transformations. One of them, leading to three-component tetrazoles when intermediate (**III**) has trapped HN_3 and formed species (**IV**), which having undergone subsequent cyclization, led to the formation of desired product $\boldsymbol{P_1}$. The second



Scheme 47. Synthesis of enantioenriched 1,5-disubstituted tetrazoles, or polycyclic 1,2-dihydroisoquinoline-based amidine derivatives.

pathway included a reaction between (**III**) and another isocyanide to form the zwitterionic intermediate (**VI**), which then reacted with $TMSN_3$ or HN_3 to give a corresponding four-component tetrazole product (***P*$_2$**). Several factors have been found to be crucial. One of them was an electronic nature of isocyanides – electron-rich isocyanides have been prone to undergo four-component reaction, whereas for electron-deficient isocyanides preferential for three-component reaction has been noticed. Secondly, the three-component reaction took place when another equivalent of the chiral ligand or water was added.

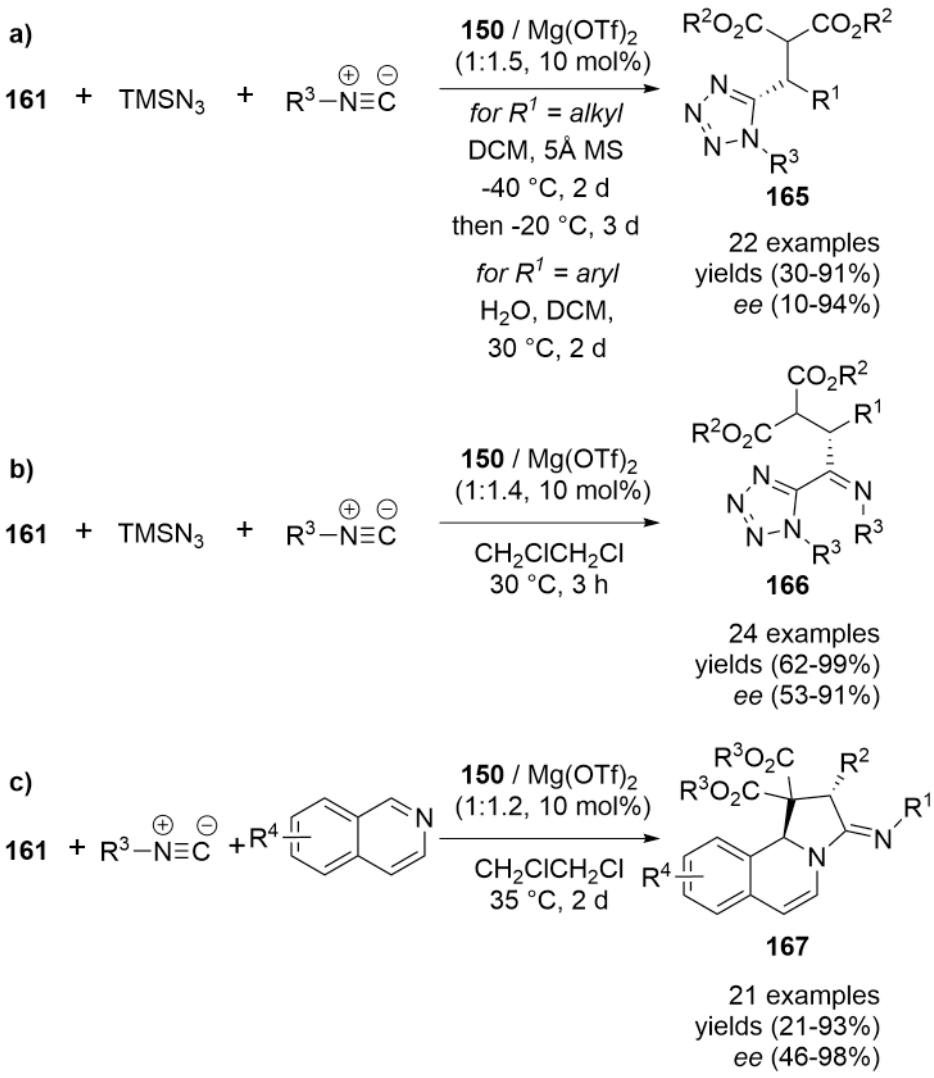
Both, the idea of asymmetric addition of isocyanide to alkylidene malonate with a subsequent nucleophilic addition of benzothiazoles and the catalytic system have been used by Feng *et al.* for the enantioselective [2 + 1 + 2] cycloadditions leading to a range of chiral hydrothiazole **168** and other heteroaromatic **169** derivatives. The reactions catalyzed by chiral $Mg(OTf)_2$/*N*,*N*'-dioxide **150** complex, have provided respective products with good yields (up to 98 %) and very high diastereo- and enantioselectivities (*dr* > 19:1 up to 97% *ee*, respectively) (Scheme 50) [221]. Similarly to the previous findings [175,219], the first step of the catalytic cycle is the coordination of malonate to the magnesium ion followed by the isocyanide attack from the *Si* face of the substrate (**I**, Scheme 51) with a subsequent formation of a zwitterionic intermediate **II**. In the next step, the nucleophilic addition of benzothiazole to **II** took place to generate another zwitterionic intermediate **III**, which underwent intramolecular nucleophilic addition from the *Si* face of the imine cation (Scheme 51).

Very recently Feng *et al.* have published a new version of a highly enantioselective isocyanide-based multicomponent reaction, which is $Mg(OTf)_2$-*N*,*N*'-dioxide **150** complex-catalyzed. Starting from alkylidene malonates and phenols **170** various phenoxyimidate products (**171**, Scheme 52**a**) have been obtained in good to high yields (up to 94%) and excellent enantioselectivities (up to 91%) [223]. The wide range of substrates including alkyl- and aryl-substituted isocyanides were smoothly transformed into corresponding products when alkylidene malonates and various phenols were used and reactions were carried out in $PhCF_3$ at 0 °C, for 48 h, with an addition of a catalytic amount of $NaBAr^F_4$ and tri(*n*-pentyl)amine as a base. It is noteworthy that the reaction proceeded without typically observed Smiles rearrangement and the presence of *N*,*N*'-dioxide ligand and a base have turned to be crucial. The proposed catalytic cycle (Scheme 52**b**) has shown a large degree of similarity to the previously proposed ones [218–221]. In the first step, the complex **I** contained a chiral ligand, magnesium and malonate was formed. Then after isocyanide attack from the *Si* face of malonate (**I**), the zwitterionic intermediate **II** was trapped by phenol (*β*-naphthol in this case) in the presence of a base, to form complex **III**. After the protonation, the product was released and the next cycle started.

Wang *et al.* have developed a catalytic method for construction of enantioenriched 2*H*– and 3*H*-pyrroles **174** through the reaction between readily available *α*-isocyanoacetates **172** and alkynyl ketones **173** [224]. The cyclization reactions were carried out in toluene, at 40 °C for 12 h and in the presence of *in situ* generated from Bu_2Mg and chiral prolinol derivative **175** catalyst. Polyfunctionalized 2*H*-pyrroles have been obtained with moderate to good yields (46–78 %) and enantiomeric excesses up to 96% (Scheme 53**a**). In addition, 2*H*-pyrroles could be smoothly transferred into functionalized 3*H*-pyrroles **176** by the aluminium mediated and chirality maintaining 1,5-ester shift reaction (Scheme 53**b**).

10. Miscellaneous cyclization reactions

An asymmetric double C(sp^3)-H bond functionalization involving a sequential hydride shift/cyclization process was presented by Mori and Akiyama in 2018 [225]. In fact, this reaction can be considered a domino process started from a highly stereoselective C(sp^3)-H bond



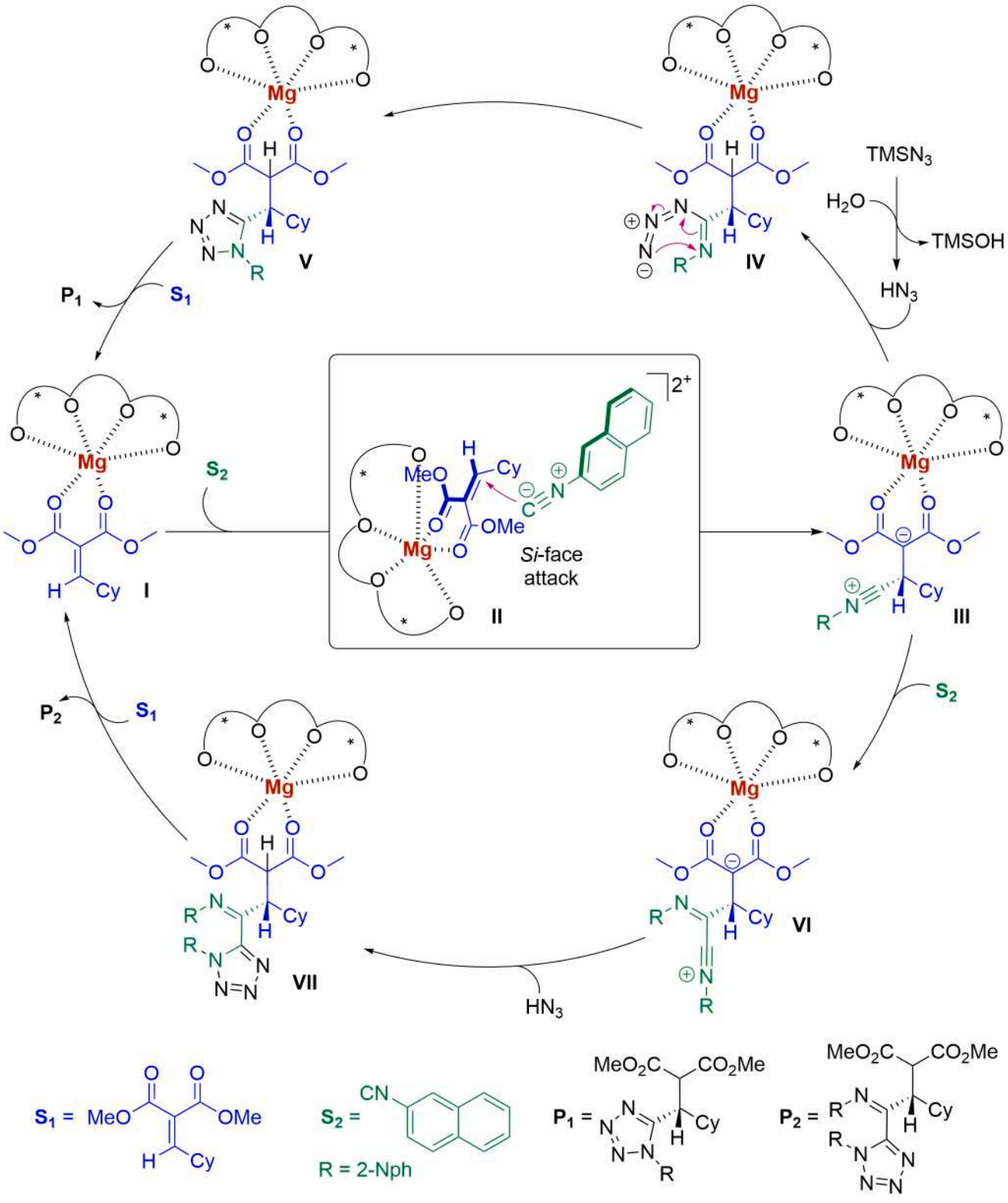
Scheme 48. a) Asymmetric synthesis of three-component alkyl- or aryl-substituted tetrazoles. b) Asymmetric synthesis of four-component alkyl- or aryl-substituted tetrazoles. c) Asymmetric synthesis of 1,2-dihydroisoquinoline derivatives.

functionalization catalyzed by magnesium phosphate complex **179** (10 mol%). Various cinnamylidene malonates **177** can be transferred into bicyclic products **178** in good yields by [1,5]-hydride shift/cyclization (Scheme 54**a**). For a suppressing of the second hydride shift, a presence of a *p*-bromobenzyl group attached to the nitrogen atom was crucial. After an isolation and purification of the initial product **178**, the second [1,5]-hydride shift/cyclization took place in a presence of catalytic amount of $Yb(OTf)_2$ in 1,2-dichloroethane, at 60 °C for 0.5 h. This second process has led to the formation of tricyclic piperidine products **180** with good yields (63–80%) and high to excellent diastereo- and enantioselectivities (*dr* 10:1->20:1, 91–96% *ee*, respectively).

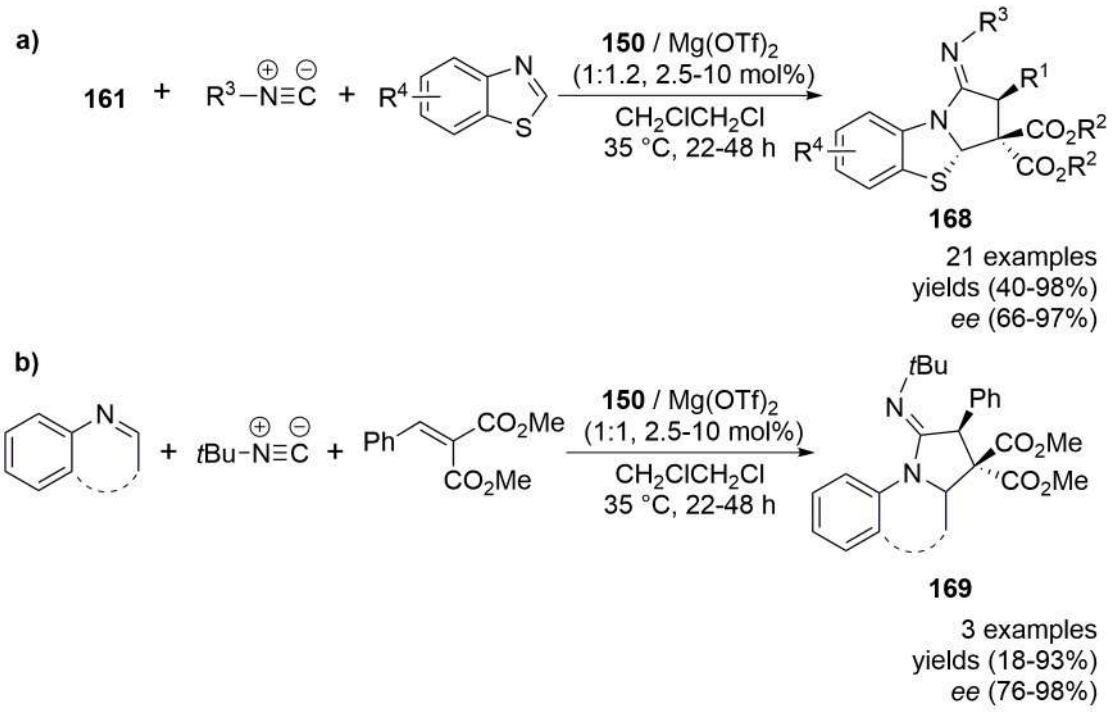
Based on the results of DFT calculations, attempts to explain stereochemistry of the reaction have been made. The presence of bulky 2,4,6-tricyclohexylphenyl groups in the ligand structure enforces the malonate to adapt the position in the centre of the chiral space (Scheme 54**b**). The formation of hydrogen bond between the phosphoryl oxygen and the *N*-benzyl group from the substrate is crucial for keeping the amine moiety at the right place for the sequential [1,5]-hydride shift/cyclization process.

The new protocol for effective synthesis of highly functionalized tetrahydroisoquinoline derivatives has been recently presented by Kim *et al* [226]. In reactions of *N*,*N*-dialkyl-3-vinylanilines with various donor–acceptor *N*-tosylaziridines **181**, catalyzed by *in situ* generated Mg $(OTf)_2$/bisoxazoline **182** complex, a series of tetraisoquinolines **183** has been obtained (Scheme 55**a**). The products of [3 + 3] cycloadditions were characterized by high values of diastereo- and enantiomeric excesses (*dr* up to > 30:1, 90% *ee*, respectively). In the proposed catalytic cycle the aziridine coordinates to the Mg/bisoxazoline complex *via* two dicarboxylate groups to generate activated azomethine ylide intermediate (**I**, Scheme 55**b**). Then the nucleophilic attack of *N*,*N*-dialkyl-3-vinylanilines *via* a typical Friedel-Crafts reaction on the exposed *Re* face took place to form a zwitterionic intermediate **II**. After a diastereoselective intramolecular Michael reaction and subsequent rearomatization, the desired product is released and the whole cycle may start again.

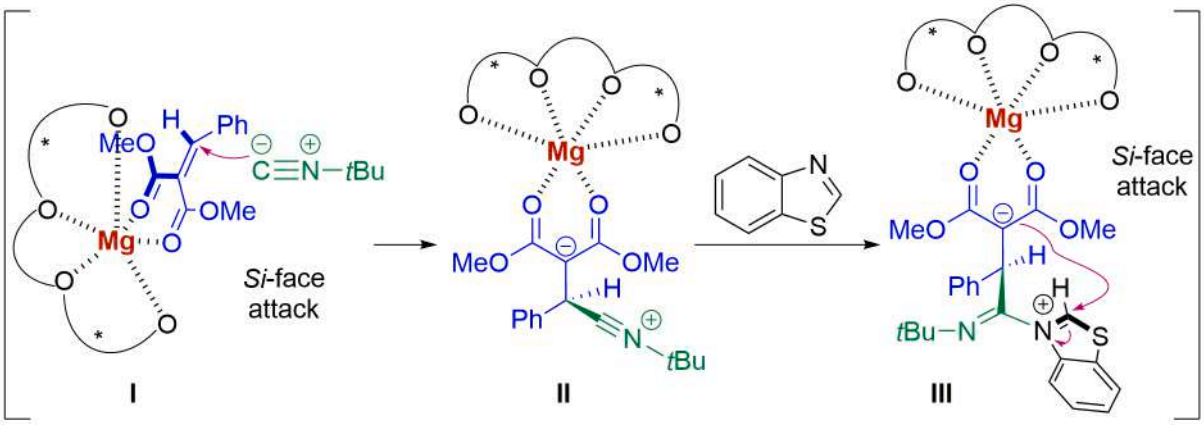
Yoda has recently reported a ring opening-asymmetric reclosure of



Scheme 49. Proposed catalytic cycle for IMCRs.



Scheme 50. Formal [2 + 1 + 2] cycloaddition reactions of isocyanides, alkylidene malonates and: a) benzothiazoles; b) other heteroaromatic compounds.



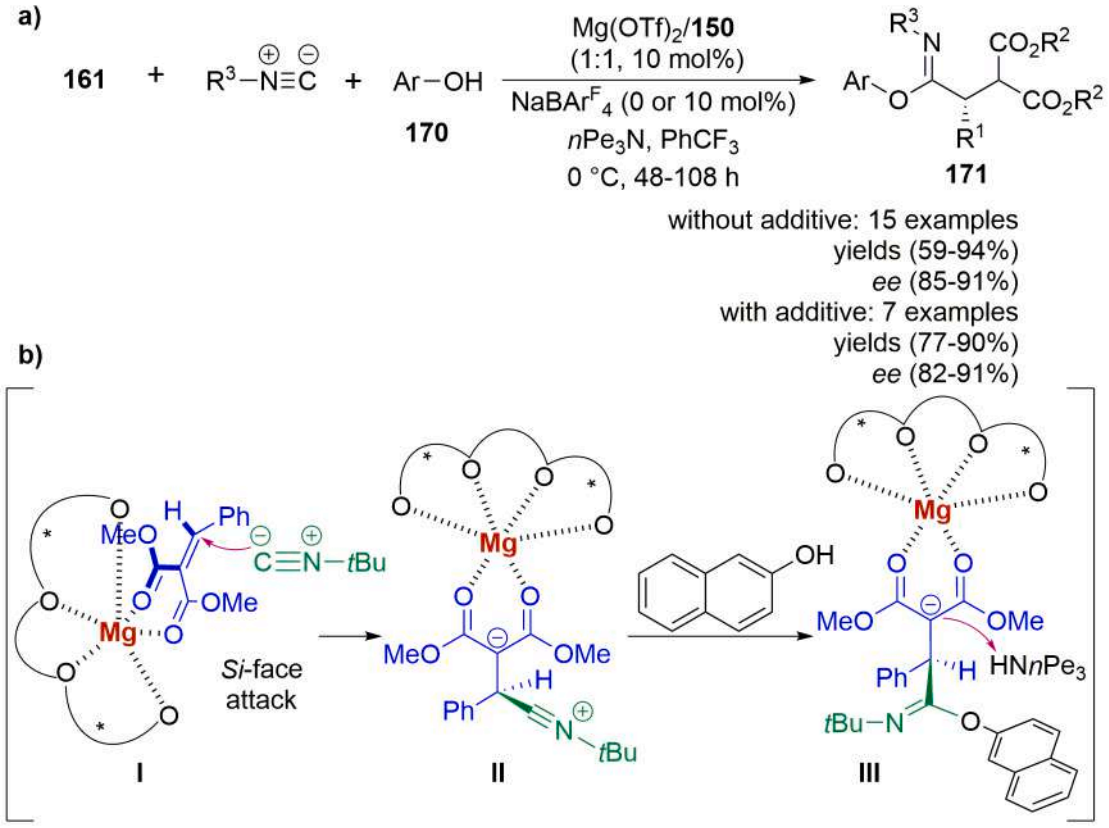
Scheme 51. Proposed mechanistic model.

hydroxylactams **184**, which have been prepared from *N*-carbonyl phthalimides and *β*-amido functionalized allylboronates. The reactions have been catalyzed by $MgBr_2$/aminophenol **185** complex and have led to formation of the *N*,*O*-spirocyclic compounds **186**, through intermediate **185**, with good to high yields (20–99%) and enantiomeric excesses ranging from 57 to 93% (Scheme 56**a**) [227]. The enantioselectivity was strongly dependent on the steric hindrance around the phenylamide group of the chiral aminophenol ligand. In the proposed structure of the transition state, the *Re* face of the keto group is obscured, therefore, the attack on the *Si* face is preferred (Scheme 56**b**). Unfortunately, to date, only a small number of compounds has been tested in this reaction.

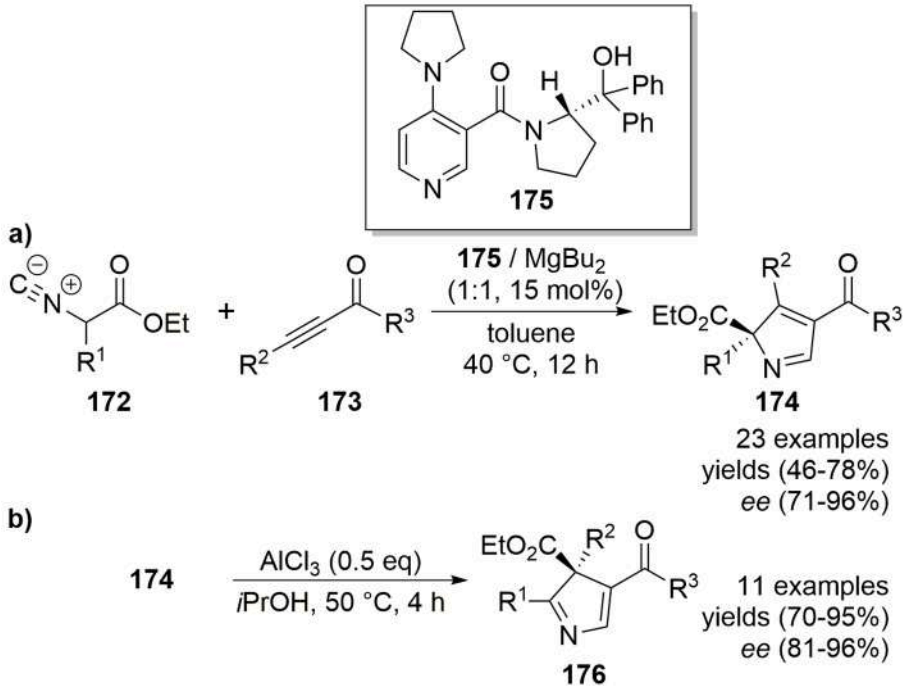
11. Miscellaneous reactions

While the synthesis of tertiary stereocenters (where one of the substituents with the lowest priority is hydrogen atom) seems to be well-recognized, the construction of quaternary stereocenters is still a demanding task. The successful magnesium-catalyzed amination of *β*-ketoesters by nitrosocarbonyl compounds was one of the first examples of the formation of chiral molecules containing quaternary stereocenters [228].

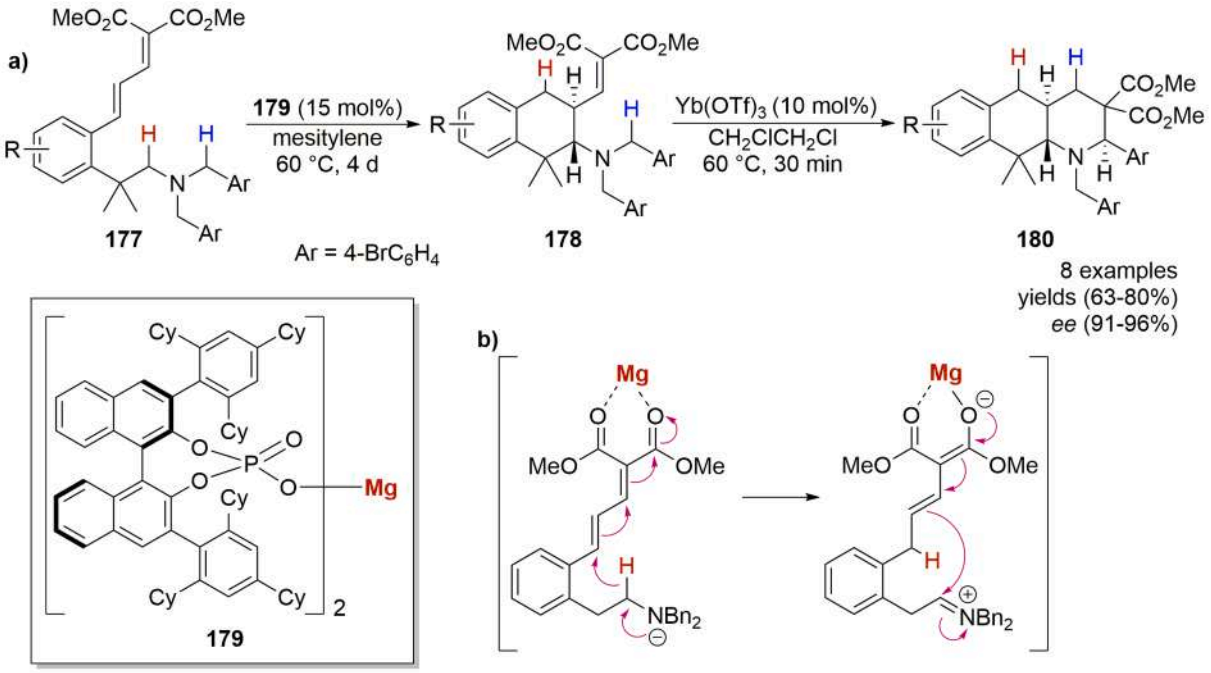
The synthesis of unnatural amino acids **191** was also the subject of interests of the Feng, Liu and co-workers [229]. In the recent contribution, these authors have described magnesium-catalyzed asymmetric [2,3]-rearrangement taking place in ammonium salts *in situ* generated



Scheme 52. a) Enantioselective IMCRs with various alkylidene malonates, phenols and isocyanides. b) Proposed mechanistic model.



Scheme 53. a) Synthesis of polyfunctionalized 2*H*-pyrroles. b) Transformation of 2*H*-pyrroles into functionalized 3*H*-pyrroles.



Scheme 54. a) Magnesium bisphosphate-catalyzed asymmetric double $C(_{sp}^{3})$ – H bond functionalization based on sequential hydride shift/cyclization process. b) Proposed mechanistic model.

from **187** and allyl bromides **188**. The catalytic system consists of magnesium triflate and respective *N*,*N*'-dioxide ligand.

During the optimization of the reaction conditions, the authors found that the best combination of ingredients was: (i) the catalytic species made of sterically congested ligand **189** and $Mg(OTf)_2$; (ii) acetonitrile as the solvent and (iii) {NaB[3,5-$(F_3C)_2C_6H_3)_4$} as an additive. The reactions were conducted at —20 °C for 24 h and led to the formation of primary products **190** (Scheme 57 and Table 4).

The whole processes began with the formation of quaternary ammonium salt in the reaction of *N*,*N*-dialkylglycine pyrazoleamide with respective allyl bromides, which are aryl-substituted at the vinyl position. The salt **I** (Scheme 58) has been transformed into allylic ammonium ylide **II** upon bidentate coordination with the magnesium complex and by treatment with an external base – diisopropyl amine.

Due to the sterical interactions between the aryl group from the substrate and octahydrocyclopenta[*b*]pyrrole unit in the proposed transition state (***TS***), the rearrangement is highly stereoselective and has led to the preferential formation of *anti*-products. It is worth mentioning that **190** can be easily converted to respective amino acid methyl esters **191** through simple heating in methanol for 16 h. This reaction is an elegant route to the unnatural amino acids methyl esters (or amino-alcohols after reduction of the COOMe group), however, currently limited to the *β*-aryl-substituted ones [229].

The different approach to the formation of quaternary stereogenic centers has been recently described by Katayev *et al.* [230]. In the magnesium-catalyzed enantioselective trifluoromethylation of oxindoles **192**, the trifluoromethyl group has been transferred through SET-induced pathway from hypervalent iodine reagent **193** to the substrate, which led to the formation of product **194**. The catalytic system is based on simple Lewis's acid magnesium bromine etherate and Py-Box-type ligands **195**–**204** (Scheme 59**a**).

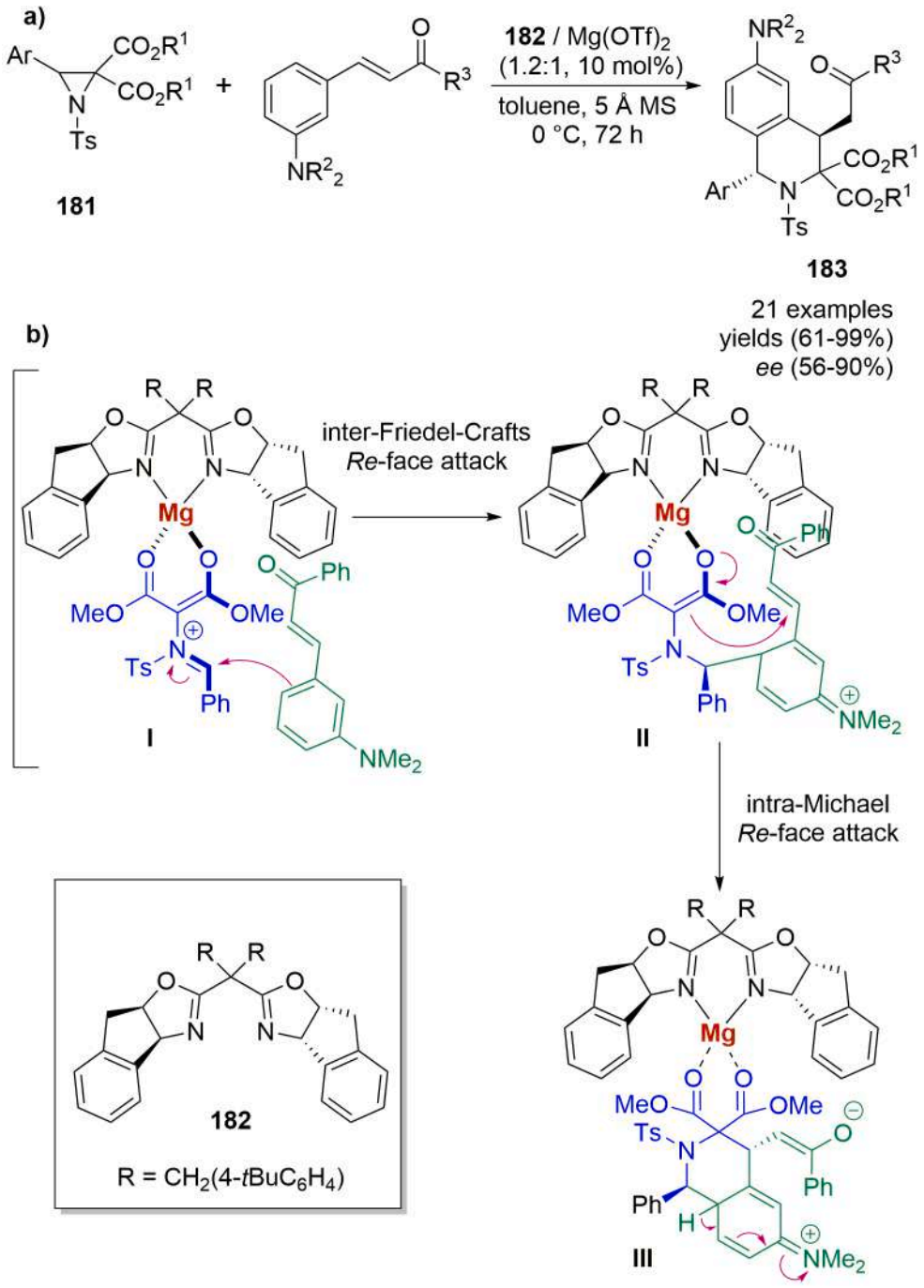
Although even with the basic and commercially available **195** ligand the results were promising in terms of both enantioselectivity and stereoselectivity, ligand **198** turned out to be the best performed ligand. However, for oxyindoles having CH_2Ar substituents at the C3 position, better results were obtained for tetralin containing ligand **204** (Scheme 60).

The mechanism of the reaction has been established by means of experimental and theoretical methods. An addition of the radical scavengers inhibited the reaction completely. Bearing in mind that selectivity, including stereoselectivity, of such radical reactions is difficult to control, Kotayev has postulated additional interactions as the key factors responsible for a high level of asymmetric induction. Introduction of more bulky alkyl groups to the trifluoromethylation reagent caused a significant decrease in enantioselectivity. Based on theoretical calculations at the DFT level (SMD/PW6B95-D3/def2-TZVPP method), one can conclude that the coordination of the substrate to the metal center of the catalyst is the rate-determining step of the reaction. After proton transfer from the substrate to the reagent, an enolate intermediate is formed, which may exist in both open- and closed-shell form. The more energetically favorable path has been found for the open-shell species, and due to the π···π stacking interactions between the substrate and the aromatic group from the chiral ligand, a transfer of the CF_3 radical is possible only from *Re* face. As the calculated structure of CF_3 radical is unexpectedly planar and the transition state (shown in Scheme 59**b**) resembles that of nucleophilic substitution reaction, namely of the S_N2 type, the whole reaction can be considered a SET induced S_N2-type [230].

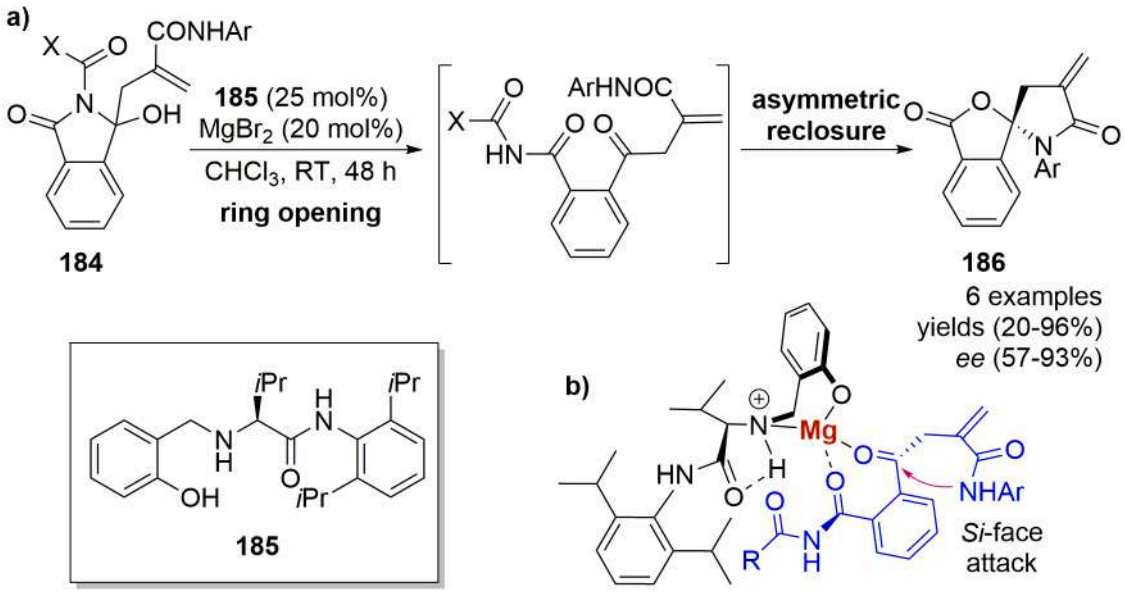
The obtained optically active 3-trifluoromethylated oxindoles constituted valuable synthons for further transformations to pyrroloindolines and α-trifluoromethylated esters.

12. Summary and outlook

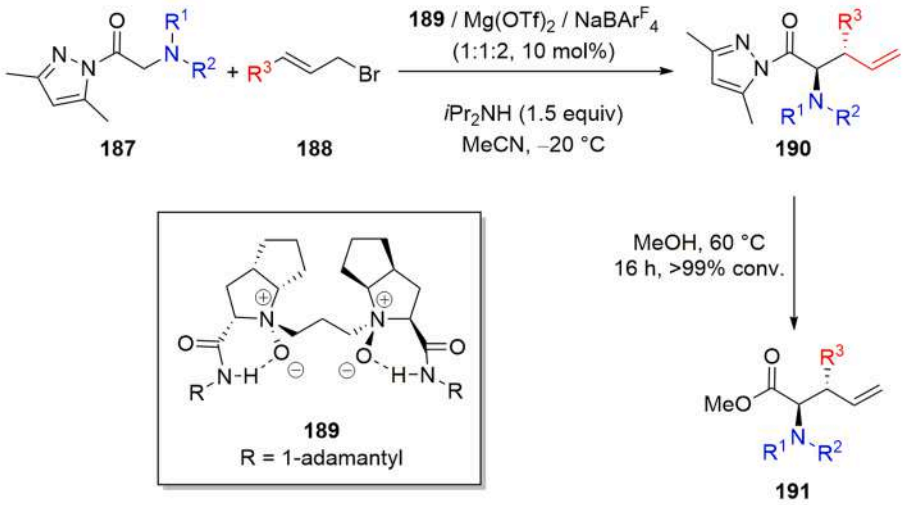
In the light of dwindling resources of precious metals, searching for methods which are capable of replacing transition metal-based catalysis will be one of the primary tasks of contemporary organic synthesis. Catalysis by Earth-abundant metals might constitute complementary approach to organocatalysis or resolution of racemates in synthesis of chiral enantioenriched molecules. Despite recent achievements, often spectacular magnesium catalysis is still restricted to limited number of reactions. Some of them, like Diels-Alder and Michael additions are well-established, others not. Magnesium catalysis is still lacking generality and versatility of noble metal-catalysis and is not as convincingly



Scheme 55. a) Asymmetric [3 + 3] cycloaddition of donor–acceptor aziridines with *N*,*N*-dialkyl-3-vinylanilines. b) Plausible mechanistic model.



Scheme 56. a) Synthesis of the *N*,*O*-spirocyclic compounds via ring opening-asymmetric reclosure of hydroxylactams. b) The proposed structure of the transition state.



Scheme 57. Mg-Catalyzed asymmetric [2,3]-rearrangement.

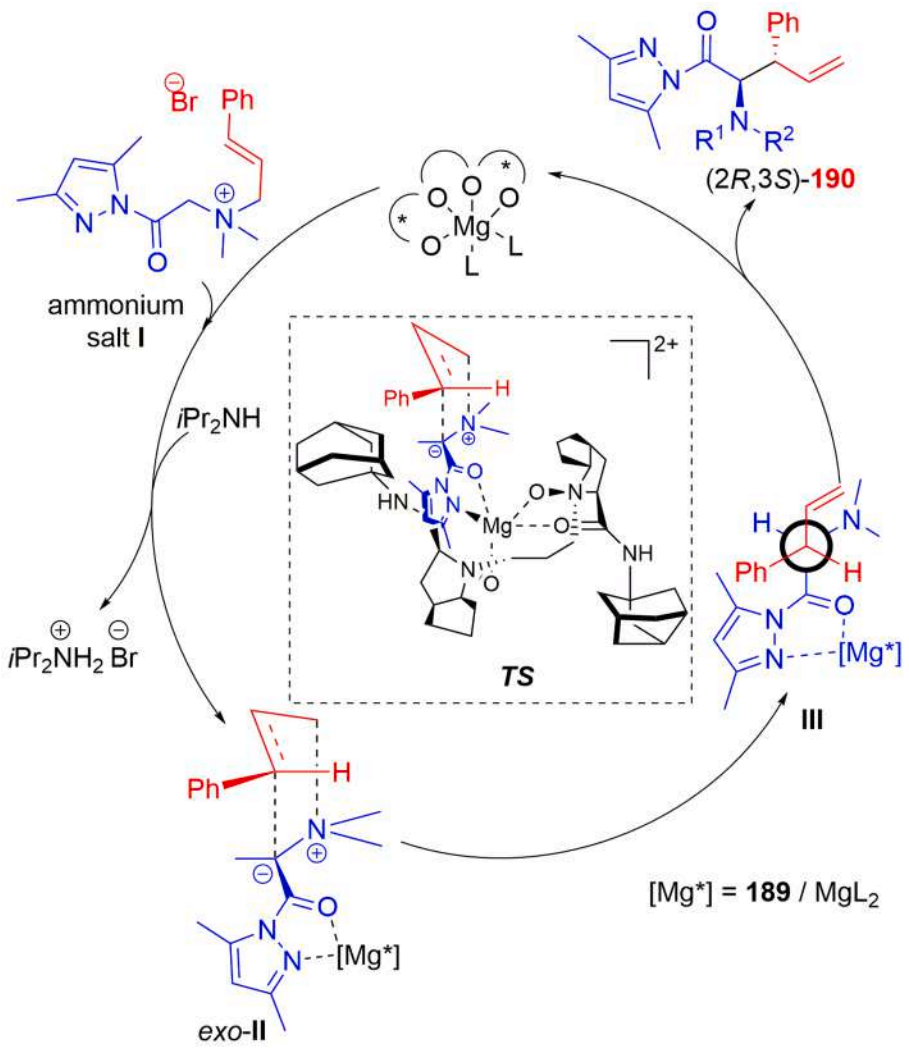
Table 4
Effect of the substituents and the duration of the reactions on the yield, diastereo- and enantioselectivity of Mg-catalyzed asymmetric [2,3]-rearangement.

Product	R^1	R^2	R^3	time	yield [%]	*anti:syn*	*ee* [%]
190a	Me	Me	Ph	24 h	94	>19:1	94
190b	Et	Et	Ph	168 h	64	>19:1	99
190c	Me	Me	3-ClC_6H_4	24 h	88	>19:1	99
190d	Me	Me	3-MeC_6H_4	72 h	83	>19:1	92
190e	Me	Me	4-MeC_6H_4	48 h	85	14:1	85

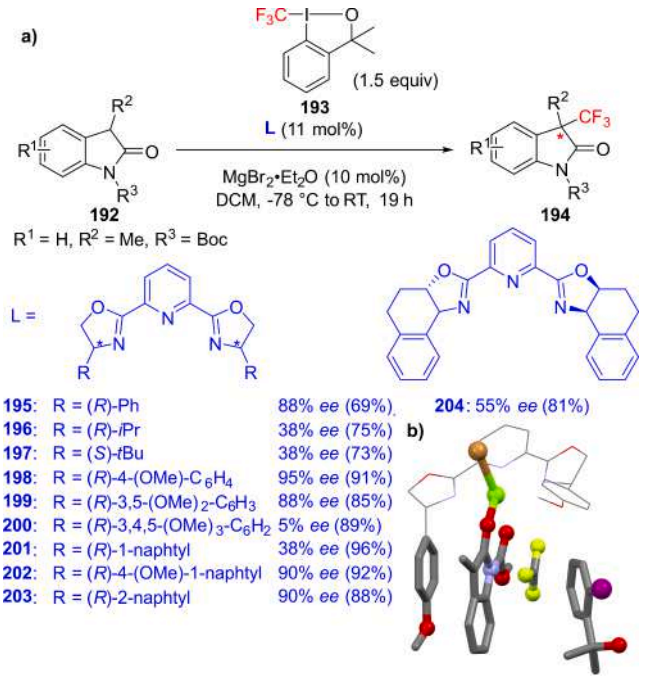
recognized as environmental-friendly as the organocatalysis is. On the other hand, it is worth adding that intensively studied Cu(II)-catalyzed asymmetric transformations have been also investigated with Mg(II) catalysis. This is the case of i.e., the asymmetric hydrazinations with diazodicarboxylates first reported by Evans in the late 90′s [231] . The reactions, which are still waiting for their chance to be catalyzed by magnesium complexes are photochemical reactions. This remains surprising, bearing in mind universality of photochemical reactions of nature origin. From the technical point of view, the relatively high loading of catalyst, necessary for efficient conduction of a given reaction is an on-going problem.

On the other hand, to date only limited number of chiral ligands has been tested. Even if the question regarding the importance of metal and ligand in asymmetric catalysis sounds naive, without chiral ligand, it is not possible to obtain chiral product even with the most active metals (with exception of autocatalytic and catalyzed by “chiral-at-metal” complexes) [101,102,232,233]. Therefore, there is a plenty of room for improvements in this field.

Finally, an additional aspect of magnesium chemistry needs to be mentioned. The location of magnesium in the periodic table makes it less “problematic” in advanced quantum-chemical calculations. Thus, interest in learning the mechanistic details is currently observed. For example, apart from the formation of six-membered ring, it has been proven that magnesium complexes have been able to catalyze



Scheme 58. Proposed catalytic cycle for Mg-catalyzed asymmetric [2,3]-rearangement.

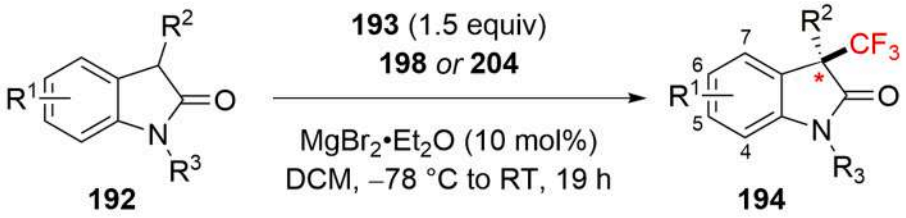


Scheme 59. a) Ligand screening for enantioselective trifluoromethylation of oxyindole **192** (in parentheses yields of the reactions were given). b) Calculated at the SMD/PW6B95-D3/def2-TZVPP level structure of transitions state in Mg-catalyzed enantioselective trifluoromethylation of oxindoles.

cyclopropanation reactions between 3-alkenyl oxindoles and stabilized sulfoxonium ylides. These reactions are catalyzed by tetra-coordinated chiral magnesium(II) complexes, and provided products with good yields and diastereo- and enantioselectivities. Very recently, Su *et al.* have studied in details mechanism of this reaction by means of DFT methods and established factors responsible for a high level of asymmetric induction. Without going into all the details, the appropriate magnesium metal ion-ligand matching has been indicated as the prerequisite for efficiency of the process. In complexes characterized by larger cavity, such a zinc(II) complexes, the shielding effects of the ligand is less visible, which resulted in the decrease of the level of chirality induction [234]. By means of DFT calculations, Simón and Paton have revealed the real, catalytically active species in Mg- and Ca-catalyzed Mannich reaction [235].

Mechanism of one of the first magnesium-catalyzed asymmetric reaction, namely Mg-Box-catalyzed D-A reaction, has been re-investigated very recently by Casali and co-workers. The aim of this study was to verify the models, which had been proposed previously to rationalize the experimental observations. Having taken as a model the reaction between 3-acryloyl-1,3-oxazilidin-2-one and pentadiene, catalyzed by complexes of (*R*,*R*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) and various Mg(II) salts, the mechanistic problems have been approached. On the basis on DFT computation, the role of counterion in determining stereoselectivity of the reaction has been established [236].

To sum up – the use of complementary experimental and theoretical approaches will allow for better understanding the mechanical aspects of a given transformation and above all more rational planning of future studies.



	R1	R2	R3	yield [%]	ee [%]
194a	H	Me	Boc	91	95
194b	H	Me	Cbz	94	98
194c	6-F3CO	Me	Cbz	99	91
194d	6-F	Me	Cbz	97	95
194e	6-MeO	Me	Cbz	96	97
194f	H	C≡CTMS	Boc	81	90
194g	H	4-MeOC6H4	Boc	96	97
194h	H	2-FC6H4	Boc	87	94
194i	H	1-Nph	Boc	91	97

Scheme 60. Example of Mg-catalyzed enantioselective trifluoromethylation of oxindoles **192**.

CRediT authorship contribution statement

Anna M. Czombik: Writing – original draft, Visualization. **Jadwiga Gajewy:** Writing – original draft, Visualization. **Agnieszka Czapik:** Writing – original draft, Visualization. **Marcin Kwit:** Conceptualization, Supervision, Writing – review & editing, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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