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Enantioselective magnesium-catalyzed transformations

Hélène Pellissier 

This review updates the major progress in the field of enantioselective transformations promoted by chiral magnesium catalysts, covering the literature since 2007, illustrating the power of these mild Lewis acid catalysts to provide a wide variety of novel asymmetric reactions.

1. Introduction

Developed for several decades, organometallic chemistry is even today considered to be a very dynamic discipline. In particular, asymmetric transition-metal catalysis constitutes a powerful tool to perform highly enantioselective reactions.¹ Unlike transition metals, alkaline earth metals, such as magnesium, have been well recognized owing to their vast abundance and being inexpensive and environmentally benign. Moreover, they have shown promising applications in the field of catalytic organic synthesis, due to their milder Lewis acidity in comparison with traditional transition metals. First reported in 1992 by Corey,² ecological and economical magnesium-catalyzed enantioselective transformations have attracted continu-

ous ever-growing attention in the last few decades, leading to fruitful research studies. Indeed, many chiral complexes of magnesium(II) have been designed and developed as mild Lewis acids to catalyze a wide variety of enantioselective transformations generally performed under mild reaction conditions. Among them, the first asymmetric magnesium-catalyzed domino reactions have been only recently developed besides a number of novel highly enantioselective magnesium-catalyzed cycloadditions, ring-opening reactions, Michael additions, 1,2-nucleophilic additions to carbonyl compounds and imines, α -functionalizations of carbonyl compounds, hydroaminations of alkenes, *etc.* The goal of this review is to collect the major developments in enantioselective magnesium-catalyzed transformations published since 2007, because this field was most recently reviewed in 2008 by Hatano and Ishihara in a book chapter covering the literature up to 2006.³ Prior to 2008, this field was reviewed by Nishiyama and Motoyama in a book chapter,⁴ and by Afarinkia in a review article.⁵ It must be noted that a specific book chapter was dedicated by Kantam and Chintareddy in 2011 to their works and to those of Choudary on nanocrystalline magnesium oxide for asymmetric organic reactions.⁶ In 2013, Harder edited a book dealing with alkaline-earth metal compounds but it included only one example of enantioselective magnesium-catalyzed hydroamination.⁷ Moreover, a concept review dealing with homogeneous organomagnesium catalysis was recently published by Mashima and Tsurugi, but it included only one example of enantioselective hydroamination along with racemic reactions.⁸ It must be also noted that a recent book dealing with sustainable catalysis with non-endangered metals was edited by Michael North.⁹ The present review has been divided into eight principal sections, dealing successively with enantioselective magnesium-catalyzed cycloadditions, domino and tandem reactions, ring-opening reactions, Michael reactions, 1,2-nucleophilic additions to carbonyl compounds and imines, α -functionalizations of carbonyl compounds, hydroamination reactions, and miscellaneous reactions.

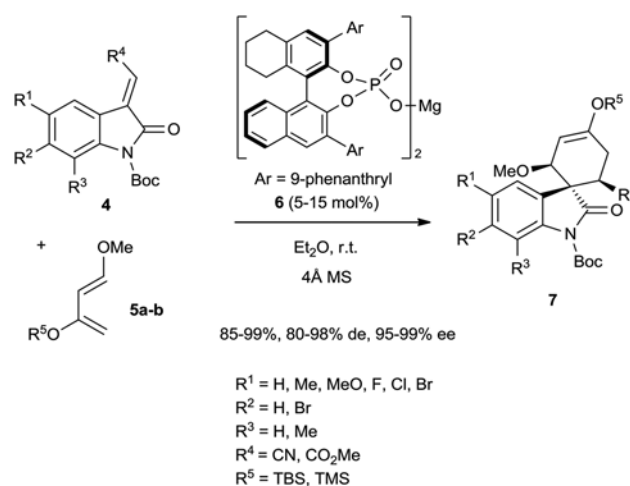
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2. Magnesium-catalyzed cycloadditions

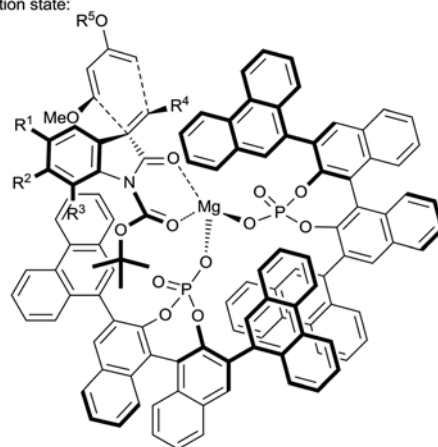
2.1. (Hetero)-Diels–Alder cycloadditions

The asymmetric Diels–Alder reaction constitutes a powerful tool to build up chiral cyclic six-membered rings.¹⁰ Since the pioneering work reported by Corey and Ishihara in 1992² dealing with the enantioselective Diels–Alder cycloaddition of *N*-acryloyloxazolidinone with cyclopentadiene catalyzed by chiral bis(oxazoline) magnesium catalysts achieved with enantioselectivities of up to 91% ee, a number of different chiral Mg(II) complexes have been successfully applied to promote this type of reaction. Even chiral magnesium complexes immobilized on silica supports have proved to be effective catalysts. Indeed, Hardacre *et al.* have developed the cycloaddition of *N*-acryloyloxazolidinone **1** with cyclopentadiene catalyzed by bis(oxazoline) magnesium complex **2** immobilized on nanoporous silica SPA-15 through ionic liquids to give the corresponding cycloadduct **3** in 72% ee with complete conversion (Scheme 1).¹¹

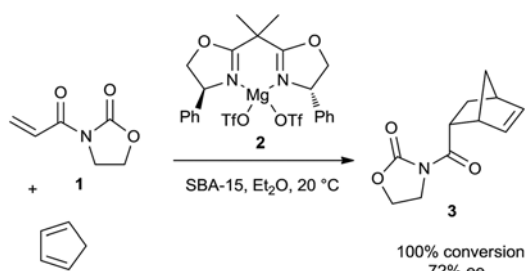
Chiral spirocyclic oxindoles are known to be pharmaceutically interesting compounds.¹² In this context, Antilla *et al.* have reported a novel rapid route to these products based on the enantioselective magnesium-catalyzed Diels–Alder reaction of variously substituted 3-methyleneoxindoles **4** with Danishefsky's diene **5a** ($R^5 = \text{TBS}$).¹³ As shown in Scheme 2, the process was promoted at room temperature by preformed the chiral magnesium phosphate complex **6** in diethyl ether as a solvent to afford the corresponding chiral six-membered spirooxindoles **7** exhibiting three contiguous stereocenters in high yields (85–99%), high diastereoselectivities (80–98% de) and remarkable enantioselectivities (95–99% ee). In addition to *tert*-butyldimethylsilyl-protected Danishefsky's diene **5a**, the smaller trimethylsilyl-protected one **5b** ($R^5 = \text{TMS}$) gave comparable results (90% yield, 98% de, 99% ee). To explain the stereochemical outcome of the cycloaddition, a plausible transition state is depicted in Scheme 2 in which the imide group of the oxindole coordinates with Mg^{2+} to form a tetrahedral intermediate in which the top face of the $\text{C}=\text{C}$ bond is blocked by the 9-phenanthryl group of the ligand, while leaving the bottom open for Danishefsky's diene to form the preferred *endo* product. On the other hand, the Boc group



proposed transition state:



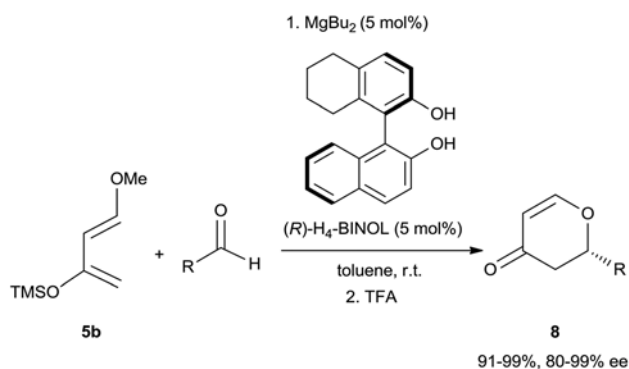
Scheme 2 Diels–Alder reaction of 3-methyleneoxindoles with Danishefsky's dienes.



Scheme 1 Diels–Alder reaction of *N*-acryloyloxazolidinone with cyclopentadiene through supported ionic liquid phase catalysis.

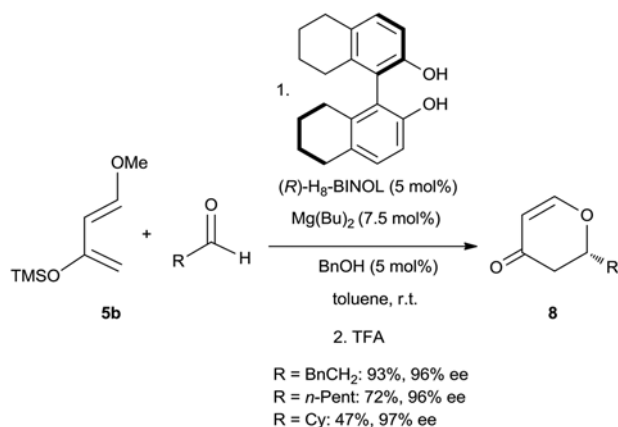
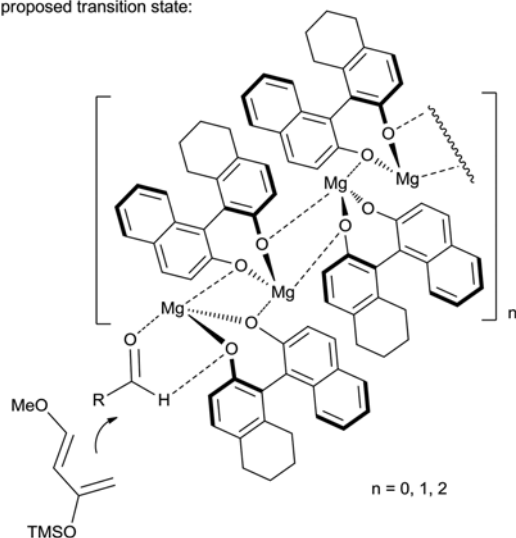
holds one of the other 9-phenanthryl groups in position by steric hindrance.

The asymmetric hetero-Diels–Alder reaction is among the most powerful methodologies available for the construction of optically active six-membered heterocycles, with extensive synthetic applications in natural or unnatural products with a wide range of biological activities.¹⁴ In 1998, Whiting *et al.* described the first enantioselective aza-Diels–Alder cycloaddition which was catalyzed by a magnesium complex derived from chiral diphenylethylenediamine as ligand.¹⁵ The reaction occurred between Danishefsky's diene and methyl glyoxylate-derived aldimine, leading to the corresponding cycloadduct in 97% ee. Later in 2008, Ding *et al.* reported the first asymmetric magnesium-catalyzed hetero-Diels–Alder reactions of aldehydes.¹⁶ Among a collection of BINOL- and TADDOL-derived ligands, (*R*)-H₄-BINOL was selected as the most efficient to give at room temperature in combination with MgBu_2 the best enantioselectivities (up to 99% ee) combined with excellent yields (91–99%) for the cycloadducts **8** arising from the reactions of a variety of aromatic as well as aliphatic aldehydes with Danishefsky's diene **5b** (Scheme 3). To



R = Ph, *p*-MeOC₆H₄, *p*-Tol, *m*-ClC₆H₄, *p*-BrC₆H₄, *p*-ClC₆H₄, *o*-BrC₆H₄, *o*-Tol, 2,6-Cl₂C₆H₃, BnCH₂, (*E*)-PhCH=CH, 2-Fu

proposed transition state:

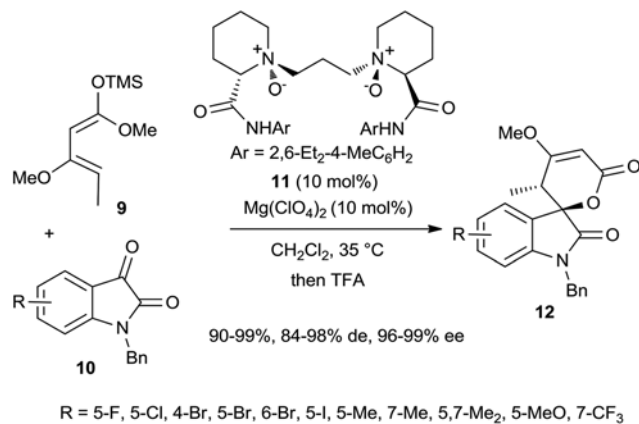


Scheme 3 Hetero-Diels-Alder reactions of aldehydes with Danishefsky's diene.

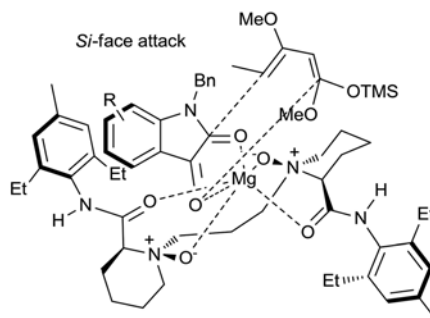
explain the stereoselectivity of the process, the authors have proposed the active catalyst species depicted in Scheme 3, possessing an oligomeric zigzag chain structure comprised of Mg_2O_2 cores from the H₄-BINOL units and magnesium centers. Although the inner magnesium centers were not accessible to the reactants owing to steric hindrance, the mag-

nesium atom situated at the end of the chain could activate the aldehyde substrate through interaction with its oxygen atom. Moreover, a hydrogen-bonding interaction between the aldehyde hydrogen atom and one of the H₄-BINOL oxygen atoms could also help in fixing the spatial position of the aldehyde. Finally, the preferential attack of the diene through the *Si* face of the aldehyde led to the formation of the (*S*)-cycloadduct. In 2013, this type of reaction was reinvestigated by Ishihara *et al.* by using (*R*)-H₈-BINOL as ligand in the presence of benzyl alcohol as an additive.¹⁷ As shown in Scheme 3, the reaction of aliphatic aldehydes with Danishefsky's diene 5b in toluene at room temperature led to the corresponding cycloadducts 8 in moderate to high yields (47–93%) and excellent enantioselectivities (96–97% ee).

The enantioselective hetero-Diels-Alder reaction of Brassard's dienes with carbonyl compounds is a classical approach to access chiral six-membered δ -lactones, which are widely found in bioactive natural products. In 2014, Feng *et al.* reported the first catalytic asymmetric hetero-Diels-Alder reaction of Brassard's type dienes, such as 9, with isatins 10.¹⁸ As shown in Scheme 4, the process was promoted by a combination of $\text{Mg}(\text{ClO}_4)_2$ with chiral *N,N'*-dioxide ligand 11 in dichloromethane at 35 °C to give the corresponding chiral spiro-lactones 12 in high to quantitative yields (90–99%), high diastereoselectivities (84–98% de) and remarkable enantioselectivities (96–99% ee). Notably, neither electron-donating



proposed transition state:



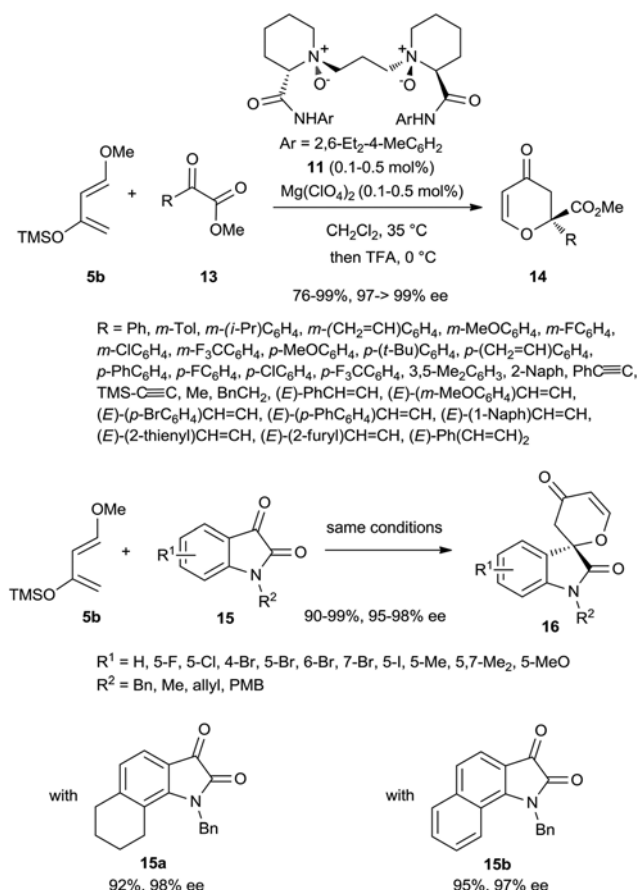
Scheme 4 Hetero-Diels-Alder reaction of isatins with Brassard's diene.

nor electron-withdrawing substituents (R) on the aromatic ring of the isatins had an obvious impact on the outcomes of the reaction. The stereoselectivity of the cycloaddition was explained by the transition state depicted in Scheme 4 in which both oxygen atoms of the amide and *N*-oxides of the ligand were coordinated with the magnesium atom. Moreover, the isatin coordinated to the Mg(II) in a bidentate fashion with its dicarbonyl groups. The *Re* face of the isatin was shielded by the neighboring 2,6-diethyl-4-methylphenyl group of the ligand, and consequently the diene attacked preferentially from the *Si* face to afford the final product.

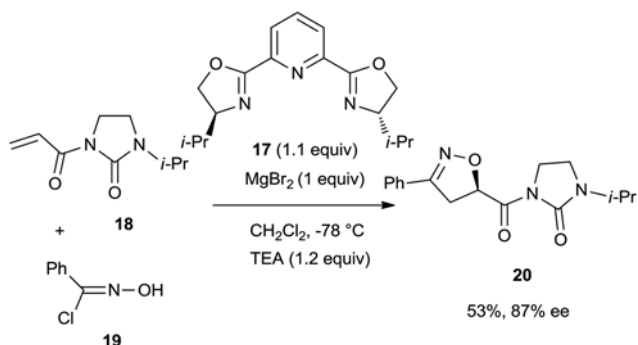
Later, these authors demonstrated that in the presence of only 0.1–0.5 mol% of the same catalyst system, a range of α -ketoesters **13** reacted with Danishefsky's diene **5b** to afford the corresponding cycloadducts **14** in good to quantitative yields (76–99%) with excellent enantioselectivities (97–>99% ee).¹⁹ Irrespective of the electron-donating or electron-withdrawing nature of the substituents on the *meta*- or *para*-position of the phenyl ring (R) of the α -ketoesters, nearly optically pure products were obtained in all cases. Furthermore, the scope of the reaction was extended to ring-fused naphthyl-substituted substrate (R = 2-Naph, 91% yield, >99% ee), as well as to α -ketoesters bearing alkynyl (79–99% yield, 97–99% ee) or alkyl (76–81% yield, >99% ee) groups. Furthermore, a range of β,γ -unsaturated α -ketoesters were proved to be excellent substrates, leading to the corresponding chiral lactones in high yields (88–98%) with remarkable enantioselectivities (97–>99% ee). Encouraged by these excellent results, the authors applied the same reaction conditions to variously substituted isatins **15** which yielded the corresponding chiral spirooxindole 2,3-dihydropyran-4-ones **16** in high to quantitative yields (90–99%) with excellent enantioselectivities (95–98% ee), as shown in Scheme 5. Even ring-fused isatins **15ab** provided excellent yields (92–95%) and enantioselectivities (97–98% ee).

2.2. 1,3-Dipolar cycloadditions

The 1,3-dipolar cycloaddition²⁰ is a classic reaction in organic chemistry consisting of the reaction of a dipolarophile with a 1,3-dipolar compound that allows the production of various five-membered heterocycles.²¹ A wide variety of chiral catalysts have been applied to promote asymmetric versions of this reaction, providing chiral proline derivatives, which are key chiral building blocks found in a number of natural products and pharmaceutically important compounds. The first example of enantioselective magnesium-catalyzed 1,3-dipolar cycloaddition was described by Jørgensen *et al.* in 1996.²² It occurred between nitrones and alkenes in the presence of a chiral bis(oxazoline) magnesium(II) catalyst with enantioselectivities of up to 82% ee. Ever since, other chiral magnesium complexes have been successfully applied to this type of reaction. For example, Yamamoto *et al.* reported the use of chiral pybox ligand **17** in combination with MgBr₂ in the asymmetric 1,3-dipolar cycloaddition of 2-imidazolidinone-derived acrylamide **18** with benzonitrile oxide precursor **19** in dichloromethane at –78 °C.²³ As shown in Scheme 6, the corresponding cycloadduct **20** was achieved in moderate yield (53%)



Scheme 5 Hetero-Diels–Alder reactions of α -ketoesters and isatins with Danishefsky's diene.



Scheme 6 1,3-Dipolar cycloaddition of a 2-imidazolidinone-derived acrylamide with benzonitrile oxide precursor.

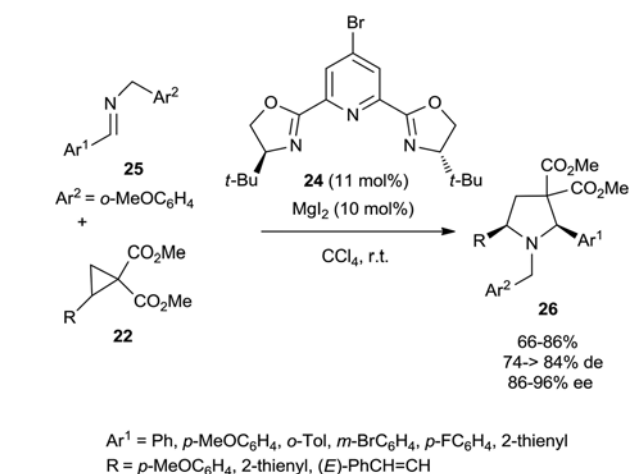
with good enantioselectivity (87% ee). It is important to note that this process employed stoichiometric amounts of the catalyst system.

On the other hand, Johnson *et al.* have developed the synthesis of chiral tetrahydrofurans on the basis of the asymmetric magnesium-catalyzed [3 + 2] cycloaddition of cyclopropanes with aldehydes occurring through dynamic kinetic resolution.²⁴ Indeed, the catalyst, *in situ* generated from MgI₂

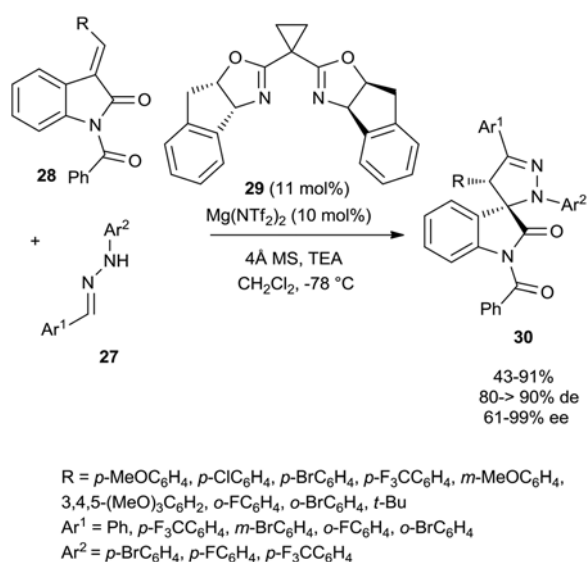
and chiral pybox ligand **21**, was found to promote the cycloaddition of aldehydes with one enantiomer of methyl malonate cyclopropanes **22** and promote the interconversion of the cyclopropane enantiomers, providing the corresponding 2,5-*cis*-disubstituted tetrahydrofurans **23** in good yields (64–92%), overall excellent diastereoselectivity (>96% de) and good to high enantioselectivities (82–94% ee). As shown in Scheme 7, aryl, cinnamyl and aliphatic aldehydes underwent cycloadditions with a variety of cyclopropanes bearing electron-rich donor groups.

A closely related chiral ligand **24** was later applied by the same authors to the 1,3-dipolar cycloaddition of methyl malonate cyclopropanes **22** with (*E*)-*N*-protected aryl aldimines **25**, yielding under comparable reaction conditions the corresponding 2,5-*cis*-disubstituted pyrrolidines **26** in good yields (66–86%) and diastereoselectivities (74–>84% de) along with high enantioselectivities (86–96% ee).²⁵ Electron-rich and neutral aryl aldimines as well as heteroaryl aldimines were compatible while aliphatic and electron-poor aryl aldimines did not react (Scheme 8).

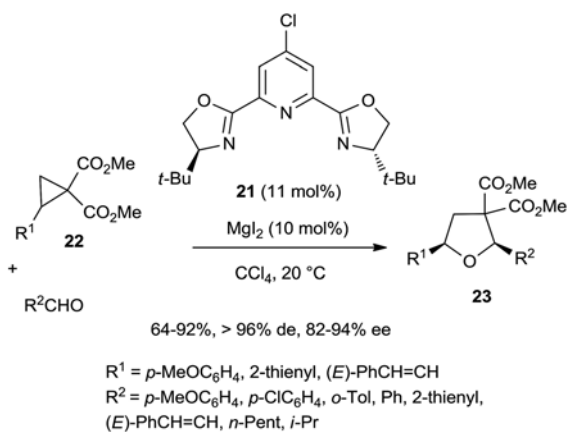
1,3-Dipolar cycloadditions of nitrile imines with alkenes represent an attractive strategy to generate pyrazolines which constitute motifs in a number of bioactive compounds. In 2013, Stanley *et al.* reported a rare example of enantioselective 1,3-dipolar cycloadditions of nitrile imines **27** with a variety of *N*-benzoyl methyleneoxindoles **28**.²⁶ As shown in Scheme 9, the reaction was performed at –78 °C in dichloromethane in the presence of a combination of Mg(NTf₂)₂ and chiral bis(oxazoline) ligand **29** to afford a range of chiral spiro[pyrazolin-3,3'-oxindoles] **30** in moderate to high yields (43–91%), good to high diastereoselectivities (80–>90% de) and moderate to excellent enantioselectivities (61–99% ee). The best enantioselectivities (92–99% ee) were generally achieved with methyleneoxindoles substituted by halogenated aromatic groups (R = *p*-ClC₆H₄, *p*-BrC₆H₄, *o*-BrC₆H₄) while an electron-deficient dipolarophile (R = *p*-F₃CC₆H₄) furnished the corresponding cycloadduct in 80% ee and 81% yield. On the other hand, the reaction of a highly electron-rich substrate (R = 3,4,5-



Scheme 8 1,3-Dipolar cycloaddition of methyl malonate cyclopropanes with aryl aldimines through dynamic kinetic resolution.



Scheme 9 1,3-Dipolar cycloaddition of (*E*)-methyleneoxindoles with nitrile imines.

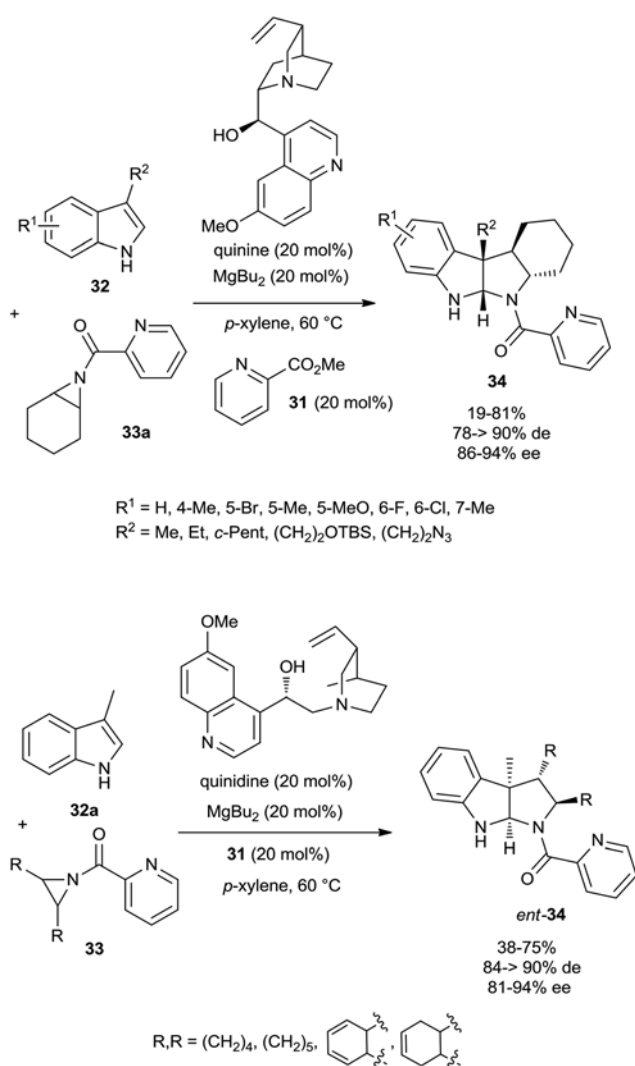


Scheme 7 1,3-Dipolar cycloaddition of methyl malonate cyclopropanes with aldehydes through dynamic kinetic resolution.

(MeO)₃C₆H₂) occurred with only 61% ee in the presence of the same conditions. Notably, a methyleneoxindole bearing a bulky *tert*-butyl substituent (R = *t*-Bu) was tolerated, leading to the corresponding product in 99% ee and 70% yield. The enantioselectivity of the cycloaddition was found to be sensitive to the geometry of the alkene unit since the reaction of a (*Z*)-methyleneoxindole (R = *t*-Bu) led to the diastereomeric cycloadduct with only 66% ee. Concerning the scope of the nitrile imines, the best enantioselectivities were generally achieved with those derived from benzaldehyde (Ar¹ = Ph) while the presence of substituents on both the aryl rings (Ar¹, Ar²) was compatible.

Besides bis(oxazoline) ligands, cinchona alkaloids have also been applied to enantioselective magnesium-catalyzed 1,3-dipolar cycloadditions. As a recent example, Wang *et al.* have

employed a chiral magnesium catalyst *in situ* generated from MgBu_2 and quinine to promote *p*-xylene at 60 °C in the presence of the achiral *N,O*-bidentate ligand **31** as an additive, the formal [3 + 2] cycloaddition between C3-alkylindoles **32** and *meso*-aziridine **33a**.²⁷ As shown in Scheme 10, the process afforded the corresponding chiral pyrroloindolines **34** in moderate to good yields (19–81%), good to high diastereoselectivities (78–>90% de) and high enantioselectivities (86–94% ee). The presence of substituents with different electronic nature located at the C4-, C5-, or C6-position of the C3-methylindole was tolerated, while a C7-substituted indole proved to be much less efficient (19% yield). Notably, some functional groups, such as silyl ether and azide, at the C3-aliphatic chain were compatible ($\text{R}^2 = (\text{CH}_2)_2\text{OTBS}, (\text{CH}_2)_2\text{N}_3$). Furthermore, the authors demonstrated that using quinidine instead of quinine as ligand under the same reaction conditions allowed the relative enantiomers of the cycloadducts to be achieved. As shown in Scheme 10, the quinidine-promoted



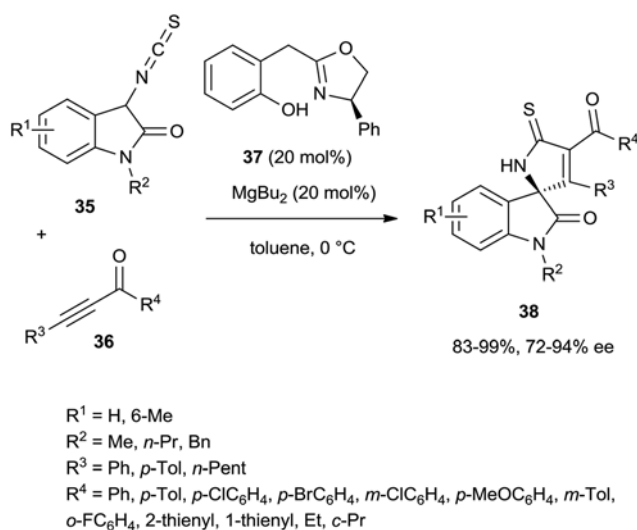
Scheme 10 1,3-Dipolar cycloadditions of C3-alkylindoles with *meso*-aziridines.

reaction of various *meso*-aziridines **33** with C3-methylindole **32a** led to the corresponding cycloadducts *ent*-**34** in moderate to good yields (38–75%), good to high diastereoselectivities (84–>90% de) and enantioselectivities (81–94% ee).

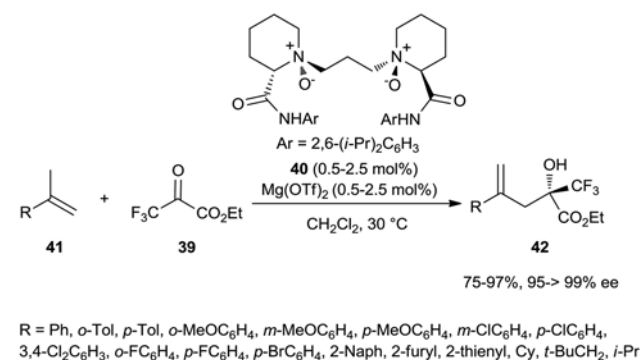
In 2015, the same authors reported the first enantioselective 1,3-dipolar cycloaddition between 3-isothiocyanato oxindoles **35** and alkynyl ketones **36**.²⁸ The process was catalyzed by a combination of MgBu_2 and chiral oxazoline ligand **37** in toluene at 0 °C, providing the corresponding chiral spiro-oxindoles **38** in high yields (83–99%) and good to high enantioselectivities (72–94% ee), as shown in Scheme 11. The scope of the reaction was wide since a range of variously substituted aromatic; heteroaromatic as well as aliphatic ketones were compatible with the catalyst system, providing comparable excellent results in reactions with differently alkyl-substituted 3-isothiocyanato oxindoles. It must be noted that chiral spirooxindole structures containing a nitrogen atom at the C-3 position represent potentially bioactive compounds.

2.3. Carbonyl ene reactions

The catalytic asymmetric carbonyl ene reaction provides a powerful tool to construct versatile and useful building blocks through atom-economical carbon–carbon bond formation.²⁹ In 2010, Feng *et al.* described highly efficient chiral magnesium complexes as catalysts for the asymmetric ketone ene reaction of trifluoropyruvate **39** by employing C_2 -symmetric N,N' -dioxide ligands for the first time.³⁰ The reactions were performed in dichloromethane at 30 °C in the presence of only 0.5–2.5 mol% of a combination of $\text{Mg}(\text{OTf})_2$ and chiral N,N' -dioxide ligand **40**. A range of alkenes **41** were tolerated, including variously substituted aromatic ones, heteroaromatic as well as aliphatic alkenes, which led to the corresponding chiral fluoromethylated α -hydroxy esters **42** in uniformly excellent enantioselectivities (95–>99% ee) along with good to excellent yields (75–97%), as shown in Scheme 12. The scope was also



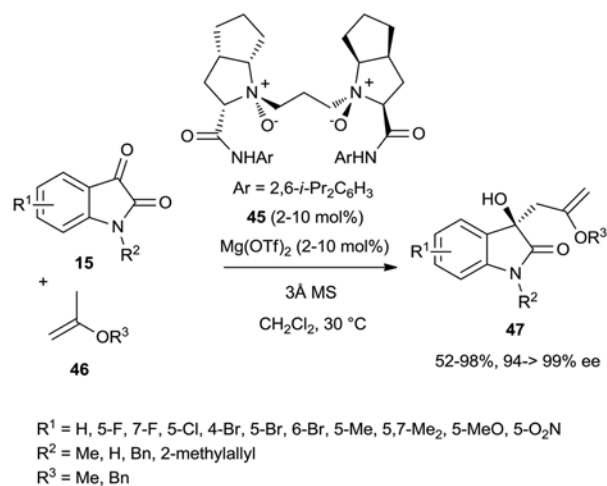
Scheme 11 1,3-Dipolar cycloaddition of 3-isothiocyanato oxindoles with alkynyl ketones.



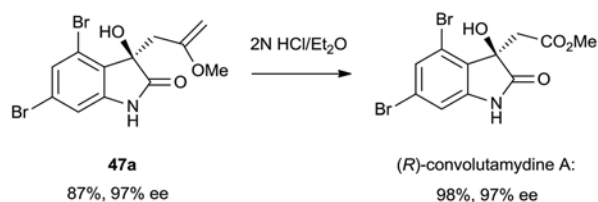
Scheme 12 Carbonyl ene reactions of trifluoropyruvate with alkenes.

extended to benzocyclic alkenes **41a** and α -substituted alkene **43** which led to the corresponding products **42a** and **44** with 96–98% ee. To further increase the synthetic utility of this novel process, the authors demonstrated that comparable enantioselectivities of 95–98% ee could be also achieved under solvent-free conditions, to meet the requirements of green chemistry.

Later in 2013, the same authors reported the first carbonyl ene reaction of 1,2-dicarbonyl compounds, such as isatins, with alkyl enol ethers.³¹ In this case, catalyst loadings of 2–10 mol% of Mg(OTf)₂ and chiral *N,N'*-dioxide ligand **45** were used to perform the reaction of various isatins **15** with alkyl enol ethers **46** to give the corresponding chiral 3-substituted 3-hydroxyindoles **47** in moderate to quantitative yields (52–98%) and uniformly excellent enantioselectivities (94–>99% ee). As shown in Scheme 13, both *N*-protected isatins and *N*-unprotected isatins reacted with high enantioselectivities. While the former gave enantioselectivities up to >99% ee, the latter proceeded with slightly decreased yields (52–92% vs.



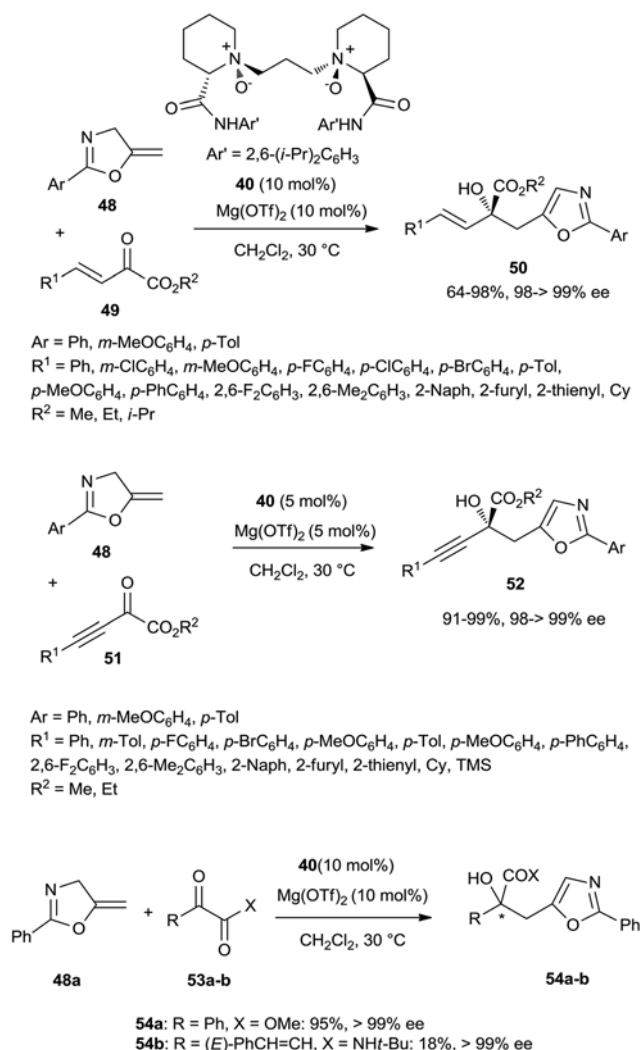
synthesis of (*R*)-convolutamydine A:



Scheme 13 Carbonyl ene reaction of isatins with alkyl enol ethers and synthesis of (*R*)-convolutamydine A.

82–98%) and enantioselectivities (94–>99% ee vs. >99% ee) as a result of their poor solubility in dichloromethane. To illustrate the synthetic utility of this novel methodology, the authors converted one of the products (**47a**) into (*R*)-convolutamydine A, which is a potent anti-leukaemia agent.

In 2015, these authors also described the first enantioselective carbonyl ene reaction of β,γ -unsaturated α -ketoesters with 5-methyleneoxazolines catalyzed by a chiral *N,N'*-dioxide magnesium(II) complex.³² As shown in Scheme 14, a catalyst system composed of Mg(OTf)₂ chiral *N,N'*-dioxide ligand **40** was successfully applied at 10 mol% catalyst loading to promote the formation of almost optically pure highly functionalized products (98–>99% ee) in all cases. Indeed, the reaction of 5-methyleneoxazolines **48** with a range of variously substituted (*E*)-2-oxo-3-enoates **49** led to the corresponding products **50** in good to quantitative yields (64–98%) combined with exceptional enantioselectivities (98–>99% ee) regardless of the nature of the substituents of each substrate. Even better results were achieved by using 2-oxo-3-ynoates **51** as substrates since the corresponding products **52** were obtained in higher yields (91–99%) with comparable excellent enantioselectivities (98–>99% ee). The catalyst system could also be applied to the ene reaction of 5-methyleneoxazoline **48a** with a simple α -ketoester **53a** (X = OMe) or a β,γ -unsaturated α -ketoamide **53b** (X = NH*t*-Bu), which provided the corresponding enantiopure products **54a–b** (>99% ee) in low to high yields (95% and 18%, respectively).



Scheme 14 Carbonyl ene reactions of β,γ -unsaturated α -ketoesters (amide) with 5-methyleneoxazolines.

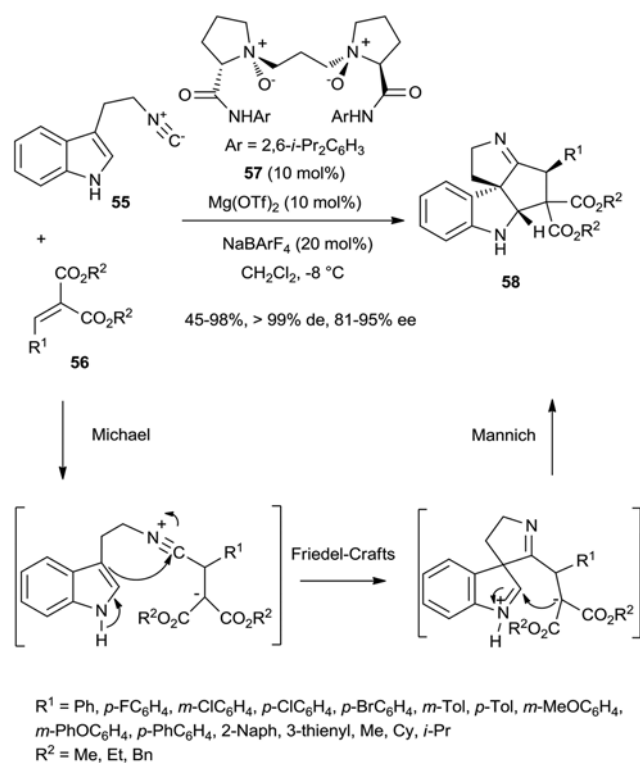
3. Magnesium-catalyzed domino and tandem reactions

3.1. Michael-initiated domino reactions

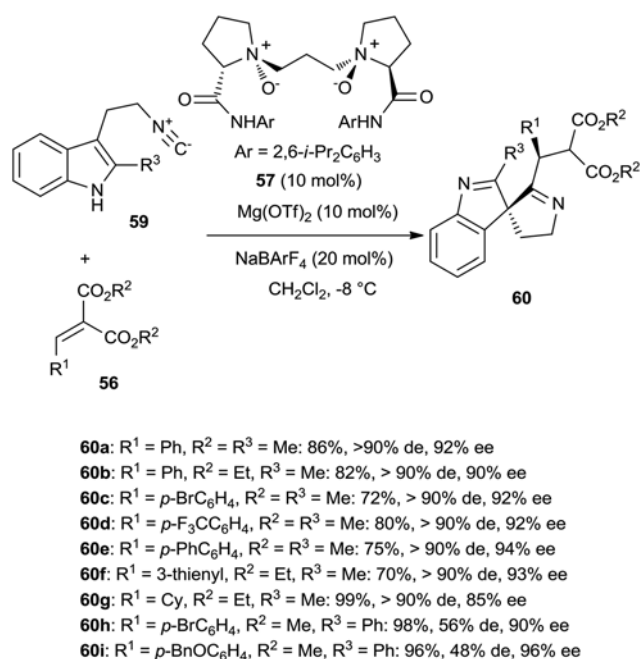
Domino reactions are processes in which two or more bond-forming transformations occur based on functionalities formed in the previous step in which no additional reagents, catalysts or additives can be added to the reaction vessel, nor can the reaction conditions be changed.³³ These fascinating reactions³⁴ allow the synthesis of a wide variety of complex molecules including natural products and biologically active compounds to be economically achieved on the basis of one-pot processes avoiding the use of costly and time-consuming protection-deprotection processes, as well as purification procedures of intermediates.^{32,35} It was only recently that the first enantioselective magnesium-catalyzed domino reactions have been developed. For example in 2015, Liu and Feng reported an asymmetric dearomatization of indoles evolving through a

domino Michael/Friedel–Crafts-type/Mannich reaction, which occurred between 2-isocyanoethylindole **55** and alkylidene malonates **56**.³⁶ This process was catalyzed with a combination of Mg(OTf)₂ and chiral *N,N'*-dioxide ligand **57** in the presence of NaBARF₄ as an additive. It provided a range of fused functionalized polycyclic chiral indolines **58** as single diastereomers (>99% de) exhibiting three stereocenters in moderate to good yields (45–98%) and high enantioselectivities (81–95% ee), as shown in Scheme 15. The best enantioselectivities (90–95% ee) were achieved in the reaction of (hetero)aryl-substituted (R¹ = (hetero)aryl) alkylidene malonates while alkyl-substituted substrates (R¹ = Cy, *i*-Pr) provided a lower enantioselectivity (81% ee).

The same authors also applied these conditions to the domino reaction of 2-isocyanoethylindoles **59** bearing a substituent at the C2-position of the indole (R³ ≠ H) with alkylidene malonates **56**.³⁵ Interestingly, a simple domino Michael/Friedel–Crafts-type reaction proceeded in this case of substrates, leading to the corresponding chiral spiroindolines **60** in good to quantitative yields (70–99%), high enantioselectivities (85–96% ee) and moderate to high diastereoselectivities (48–>90% de), as depicted in Scheme 16. Actually, in the presence of this C2-substituent, the final sequential Mannich reaction of the malonate to the imine intermediate could not occur because of steric hindrance and low electrophilicity of the C2-position of the spiroindoline. As shown in Scheme 16, regardless of the aryl substituent and heteroaromatic substitu-



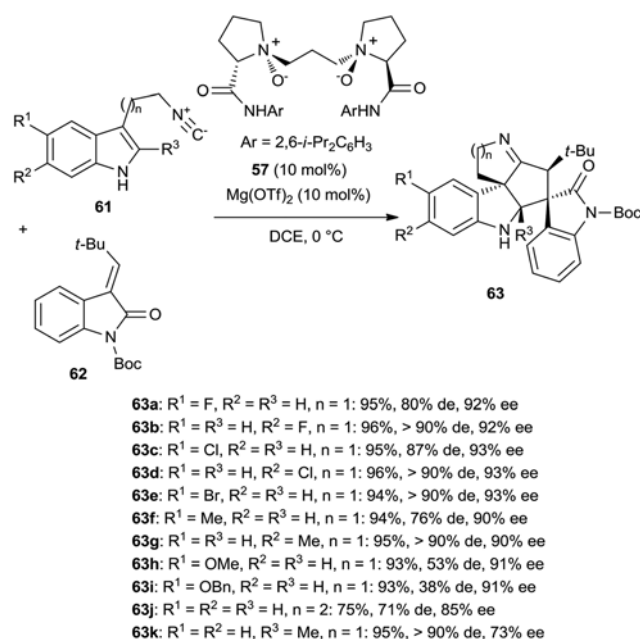
Scheme 15 Domino Michael/Friedel–Crafts/Mannich reaction of 2-isocyanoethylindole with alkylidene malonates.



Scheme 16 Domino Michael/Friedel–Crafts reaction of C2-substituted 2-isocyanoethylindoles with alkylidene malonates.

ent at the β -position (R¹) or the ester group (R²) of the alkylidene malonates, the reaction with 2-methyl-substituted 2-isocyanoethylindole (R³ = Me) proceeded with high yields (70–99%), excellent diastereoselectivity (>90% de) and high enantioselectivities (85–94% ee) to give products **60a–g**. An aliphatic alkylidene malonate (R¹ = Cy) also proved to be compatible with the reaction, yielding the corresponding product **60g** in 99% yield, >90% de and 85% ee. Furthermore, 2-phenyl-substituted 2-isocyanoethylindole (R³ = Ph) also led to the corresponding products **60h–i** in excellent yields (96–98%) and enantioselectivities (90–96% ee), although with moderate diastereoselectivities (48–56% de).

The same catalyst system was also employed to promote the asymmetric domino Michael/Friedel–Crafts/Mannich reaction of variously substituted 2-isocyanoethylindoles **61** with a 3-alkenyl-oxindole such as (*E*)-1-Boc-3-*tert*-butylideneindolinone **62**.³⁷ In this case, the reaction was performed in DCE at 0 °C to provide a straightforward route to a series of chiral polycyclic 3-spirooxindoles **63** bearing cyclopenta[*b*]indole units with four contiguous stereocenters in high yields (75–96%) and enantioselectivities of 73–93% ee, combined with moderate to high diastereoselectivities of 38–>90% de (Scheme 17). It was noteworthy that the electronic nature and position of the substituents on the indole unit of the 2-isocyanoethylindole derivative had a slight influence on the enantioselectivity of the process, while the electron-donating substituent had an obvious effect on the diastereoselectivity. Indeed in most cases, a higher diastereoselectivity was observed for the electron-withdrawing substituted compounds (R¹ or R² = F, Cl, Br) compared to the electron-donating ones (R¹ or R² = Me, OMe, OBn). Surprisingly, in contrast with the



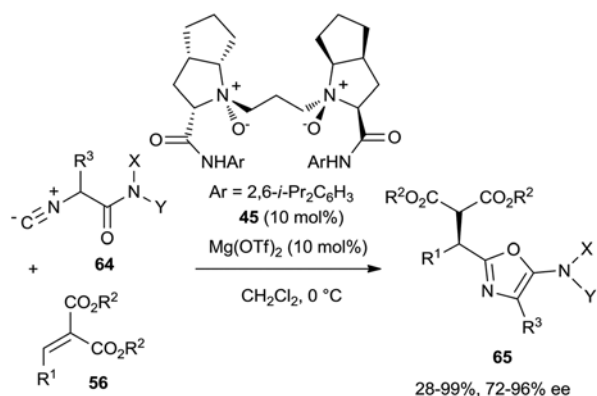
Scheme 17 Domino Michael/Friedel–Crafts/Mannich reaction of 2-isocyanoethylindoles with (*E*)-1-Boc-3-*tert*-butylideneindolinone.

previous reaction (Scheme 16) of C2-substituted 2-isocyanoethylindoles with alkylidene malonates, a substrate bearing a methyl at the C2 position of the indole (R³ = Me) led to the corresponding domino Michael/Friedel–Crafts/Mannich product **63k** in 95% yield, >90% de and 73% ee.

In 2016, the same group applied a related catalyst system composed of Mg(OTf)₂ and chiral *N,N'*-dioxide ligand **45** to promote other enantioselective domino Michael/Friedel–Crafts-type reactions of alkylidene malonates **56** involving another type of isocyanide, such as α -isocyanoacetamides **64**.³⁸ As illustrated in Scheme 18, the domino reaction allowed a range of chiral 2-alkyl-5-aminooxazoles **65** to be obtained in moderate to quantitative yields (28–99%) and good to excellent enantioselectivities (72–96% ee). Generally, the highest enantioselectivities (80–96% ee) were achieved with variously substituted (hetero)aromatic alkylidene malonates while aliphatic substrates gave moderate enantioselectivities (72–86% ee). Concerning the α -isocyanoacetamide partners, comparable high enantioselectivities were obtained regardless of the aliphatic or aromatic nature of substituent R³. To illustrate the synthetic utility of this novel methodology, the authors converted some products into a chiral imide and a dipeptide through ring-opening of their oxazole ring, both of which are important structural motifs for many biologically active compounds.

3.2. Other domino reactions

In 2007, Willis *et al.* reported the enantioselective magnesium-catalyzed domino Mannich/cyclization reaction of imide **66** with *N*-tosylimines **67**, providing the corresponding cyclized Mannich adducts **68** in good to excellent yields (63–99%) and



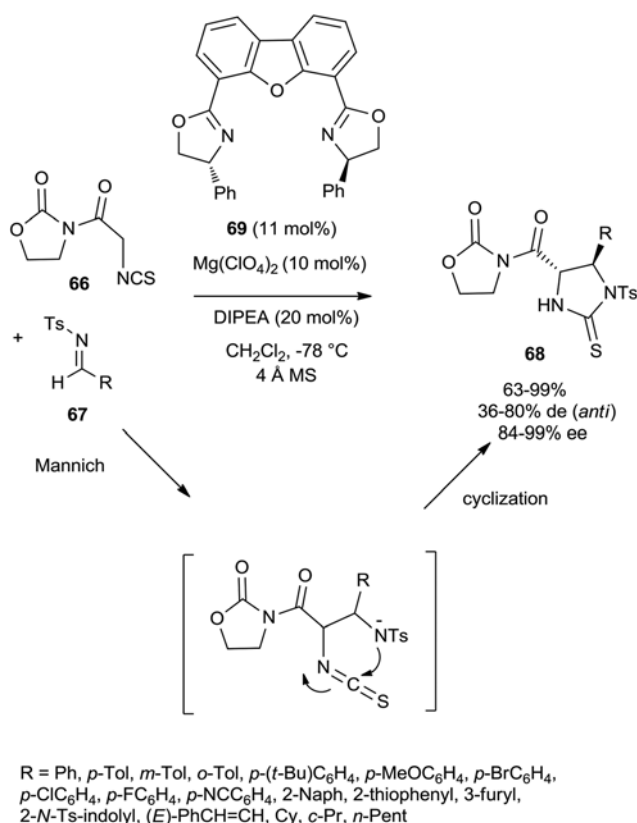
$R^1 = \text{Ph, } o\text{-FC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-Tol, } m\text{-MeOC}_6\text{H}_4, m\text{-PhOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-Tol, } p\text{-PhC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-PhOC}_6\text{H}_4, p\text{-BnOC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 2\text{-Naph, } 2\text{-thienyl, } 3\text{-furyl, Cy, Me}$
 $R^2 = \text{Me, Et, } i\text{-Pr}$
 $R^3 = t\text{-Bu, Bn, Ph, Me, } i\text{-Pr, H}$
 $X, Y = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2, (\text{CH}_2)_5, (\text{CH}_2)_4$

Scheme 18 Domino Michael/Friedel–Crafts reaction of isocyanides with alkylidene malonates.

enantioselectivities (84–99% ee) albeit with moderate to good *anti*-diastereoselectivities (36–80% de), as shown in Scheme 19.³⁹ The reaction was catalyzed by a chiral magnesium complex *in situ* generated from $\text{Mg}(\text{ClO}_4)_2$ and chiral bis(oxazoline) ligand **69**, which was selected as optimal among a series of chiral ligands tested, including other bis(oxazoline) ligands such as pybox ligands. As shown in Scheme 19, a variety of aryl-, alkenyl- and alkyl-derived imines could be employed, allowing a novel enantioselective route to *anti*-configured protected α,β -diamino acids to be achieved on the basis of a direct enantioselective Mannich reaction.

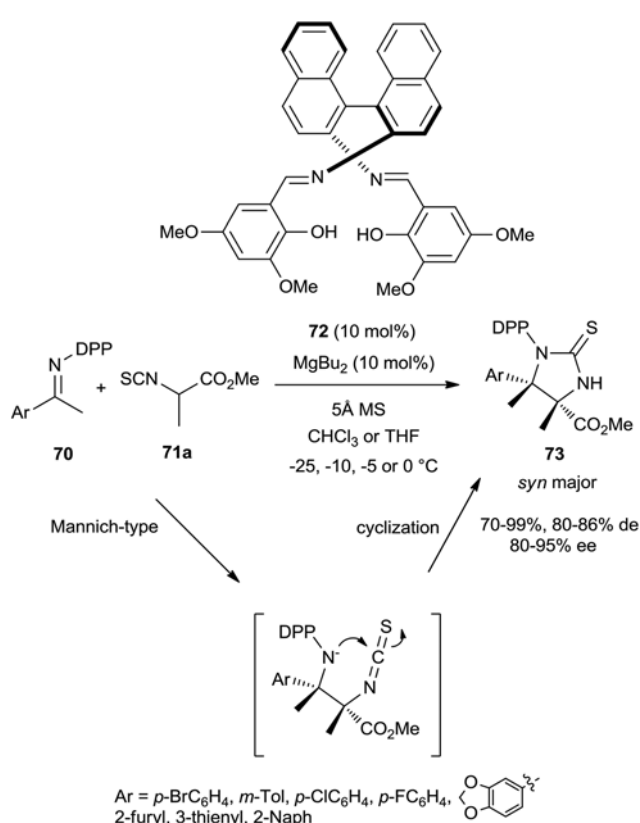
Later in 2011, Shibasaki *et al.* employed much less reactive ketimines in related enantioselective magnesium-catalyzed domino Mannich/cyclization reactions for the first time.⁴⁰ As shown in Scheme 20, the reaction of a range of *N*-diphenylphosphinoyl (DPP) aryl and heteroaryl methyl ketimines **70** with α -methyl- α -isothiocyanato methyl ester **71a** performed in the presence of MgBu_2 and the Schiff base ligand **72** yielded the corresponding chiral densely functionalized α,β -diamino esters **73** bearing two vicinal tetrasubstituted carbon stereocenters. These products were obtained in good to quantitative yields (70–99%), good *syn*-diastereoselectivities (80–86% de) and good to very high enantioselectivities (80–95% ee).

The direct catalytic asymmetric aldol reaction is a powerful and atom-economical method for synthesizing chiral



$R = \text{Ph, } p\text{-Tol, } m\text{-Tol, } o\text{-Tol, } p\text{-(}t\text{-Bu)C}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, 2\text{-Naph, } 2\text{-thiophenyl, } 3\text{-furyl, } 2\text{-}N\text{-Ts-indolyl, (}E\text{)-PhCH=CH, Cy, } c\text{-Pr, } n\text{-Pent}$

Scheme 19 Domino Mannich/cyclization reaction of an imide with *N*-tosylaldimines.



$\text{Ar} = p\text{-BrC}_6\text{H}_4, m\text{-Tol, } p\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, 2\text{-furyl, } 3\text{-thienyl, } 2\text{-Naph}$

Scheme 20 Domino Mannich/cyclization reaction of ketimines with α -methyl- α -isothiocyanato methyl ester.

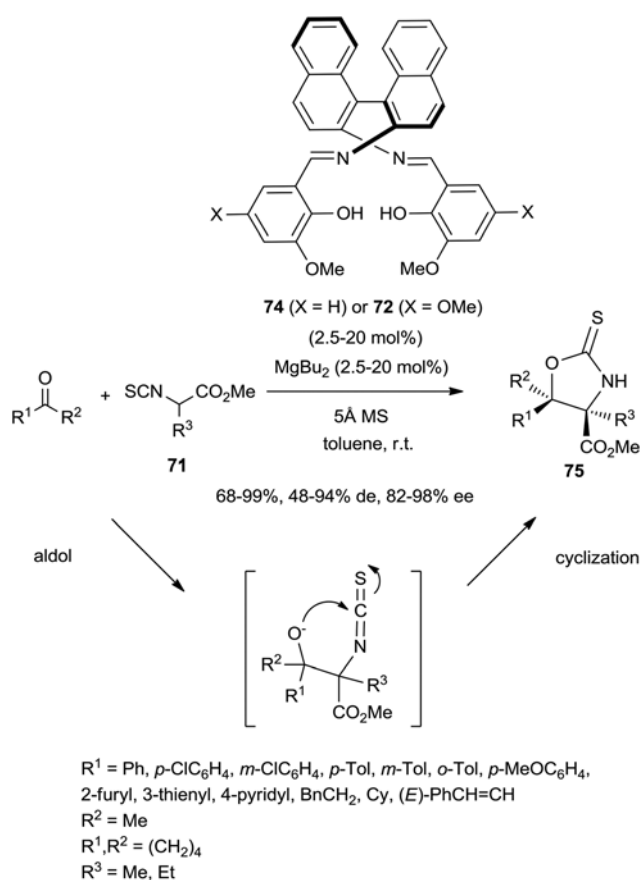
β -hydroxy carbonyl compounds. Many metals and organocatalysts for reactions of aldehyde electrophiles have been developed in the past decade.⁴¹ The use of ketone electrophiles in direct aldol reactions for the construction of a tetrasubstituted carbon stereocenter, however, is limited to either activated ketones or intramolecular reactions. In order to address this issue, Shibasaki *et al.* have employed a chiral magnesium catalyst to promote the domino aldol/cyclization reaction of α -substituted α -isothiocyanato esters **71** with aryl, heteroaryl, alkyl and alkenyl methyl ketones in addition to a cyclic ketone.⁴² The process was catalyzed by a combination of MgBu_2 with chiral Schiff bases **72** ($\text{X} = \text{OMe}$) or **74** ($\text{X} = \text{H}$), affording at room temperature the corresponding protected α -amino- β -hydroxy esters **75** bearing two contiguous tetrasubstituted carbon stereocenters in good to quantitative yields (68–99%), moderate to high diastereoselectivities (48–94% de) and high enantioselectivities (82–98% ee), as shown in Scheme 21.

In 2007, Lautens and Taillier developed the first enantioselective catalytic expansion of monoactivated methylenecyclopropanes by using a chiral magnesium catalyst, allowing direct access to chiral methylenepyrrolidines.⁴³ The reaction occurred between *N*-phenyl-*N'*-aryl methylenecyclopropane amides **76** and *N*-tosylaldimines **77** in the

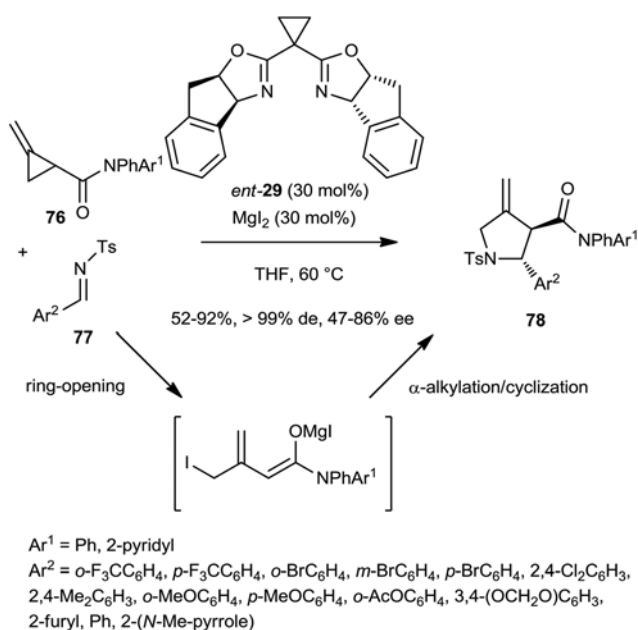
presence of a combination of MgI_2 and the chiral bis(oxazoline) ligand *ent*-**29** as the catalyst system in THF at 60 °C. As shown in Scheme 22, it afforded through a domino ring-opening/ α -alkylation/cyclization reaction the corresponding chiral ring-expanded products **78** in moderate to high yields (52–92%) and enantioselectivities (47–86% ee) as single *trans*-diastereomers. The electronic nature and position of substituents on the aryl ring (Ar^2) of the *N*-tosylaldimines seemed to have little or no influence on the yields and diastereoselectivities of the reaction while the highest enantioselectivities were obtained for aldimines bearing electron-withdrawing groups on their aromatic ring.

In another context, Seidel *et al.* described the first example of a catalytic enantioselective domino hydride shift/ring closure reaction by using a chiral magnesium catalyst.⁴⁴ Indeed, performed in dichloromethane at reflux in the presence of a catalyst *in situ* generated from $\text{Mg}(\text{OTf})_2$ and chiral bis(oxazoline) ligand *ent*-**69**, various *N*-acyl oxazolidinones **79** underwent a 1,5-hydride shift to give intermediates **80** which subsequently cyclized to afford the corresponding ring-fused chiral tetrahydroquinolines **81** (Scheme 23) in good to excellent yields (80–91%), low to moderate diastereoselectivities (up to 68% de) and moderate to high enantioselectivities (60–90% ee). The scope was extended to *N*-acyl oxazolidinones **79a–d** which afforded the corresponding products **82** and **83** in moderate to high yields (72–80% and 83–97%, respectively) with the lowest stereoselectivities obtained for substrates **79c–d** incorporating seven- and eight-membered azacycles (Scheme 23).

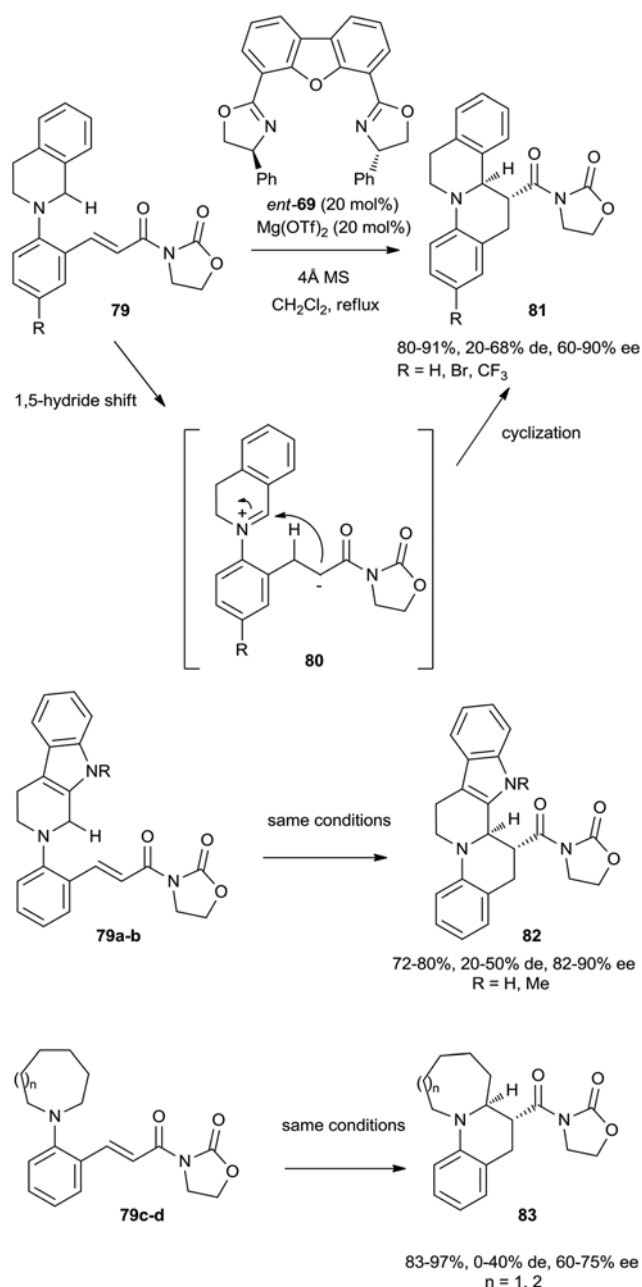
Another type of enantioselective magnesium-catalyzed domino 1,5-hydride shift/cyclization reaction was reported by



Scheme 21 Domino aldol/cyclization reaction of ketones with α -substituted α -isothiocyanato esters.

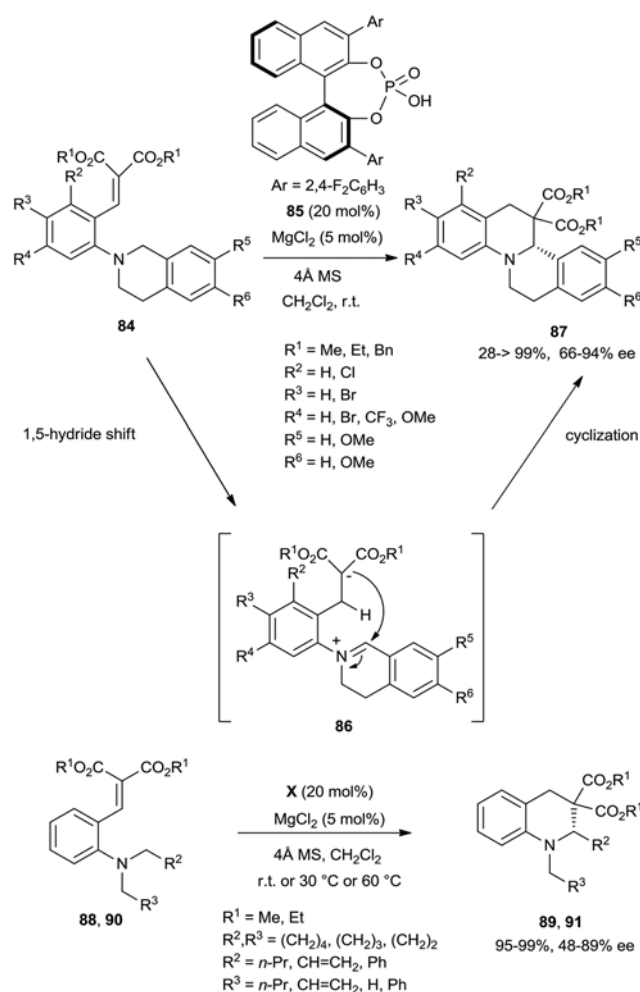


Scheme 22 Domino ring-opening/ α -alkylation/cyclization reaction of *N*-phenyl-*N'*-aryl methylenecyclopropane amides with *N*-tosylaldimines.



Scheme 23 Domino 1,5-hydride shift/cyclization reactions of *N*-acyloxazolidinones.

Luo *et al.* in 2012.⁴⁵ In this case, the substrates were cyclic tertiary amines **84** and the catalyst system a combination of MgCl_2 with chiral phosphoric acid **85** employed in dichloromethane at room temperature or 30–60 °C. As shown in Scheme 24, under these conditions a series of cyclic tertiary amines **84** underwent a 1,5-hydride shift to give intermediate **86** which then cyclized into the corresponding tetrahydroquinolines **87** in low to quantitative yields (28–>99%) and moderate to high enantioselectivities (66–94% ee). While uniformly high enantioselectivities (92–94% ee) were obtained with substrates bearing electron-withdrawing substituents (R^3 , R^4), the



Scheme 24 Domino 1,5-hydride shift/cyclization reactions of tertiary amines.

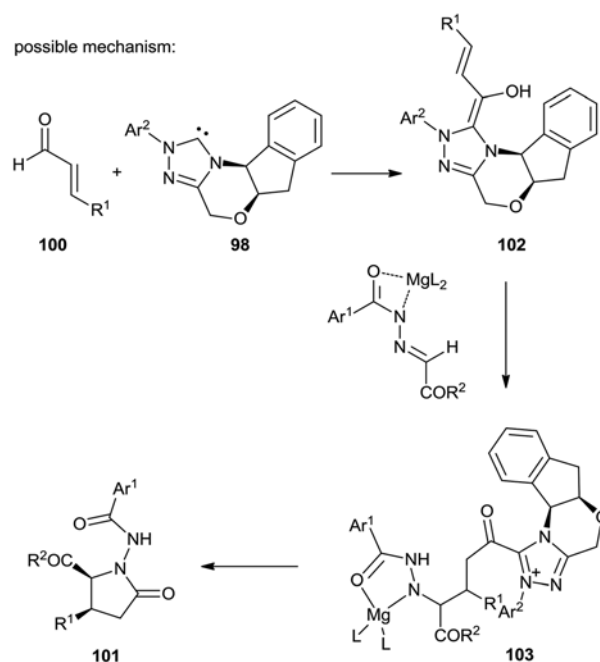
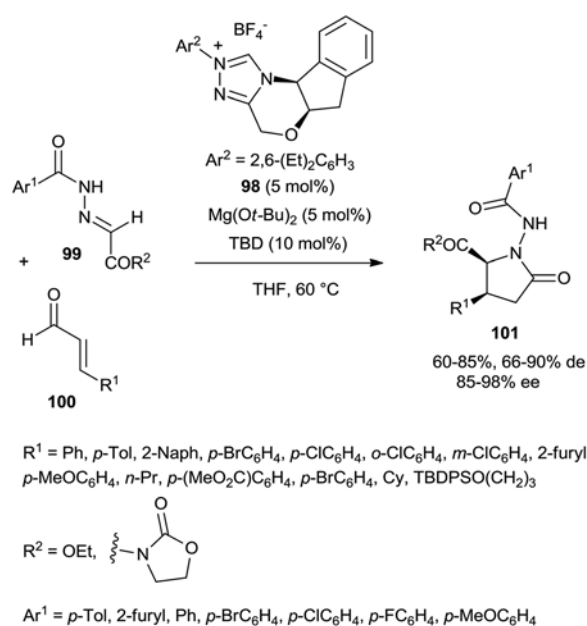
substrate with an electron-donating group (MeO) at the *meta* position (R^4) of the nitrogen atom provided the lowest activity (28% yield) and enantioselectivity (66% ee). The catalytic system was compatible with other cyclic tertiary amines **88** with five-, six-, or seven-membered rings ($\text{R}^2, \text{R}^3 = (\text{CH}_2)_2$, $(\text{CH}_2)_3$ or $(\text{CH}_2)_4$), giving the corresponding products **89** in 48–89% ee, and also to acyclic tertiary amines **90** ($\text{R}^2 = n\text{-Pr}$, CH=CH_2 or Ph , $\text{R}^3 = n\text{-Pr}$, CH=CH_2 , H or Ph) which afforded products **91** with 69–70% ee.

In 2013, Wang *et al.* reported the first examples of γ -site-specific functionalization of linear α,β -unsaturated ketones which usually act as electrophiles in Michael additions or prefer to selectively direct the reaction toward α -alkylation.⁴⁶ Indeed, in the presence of a combination of MgBu_2 and the chiral salen ligand **92** in *p*-xylene at 60 °C, linear α,β -unsaturated ketones **93** were subjected to γ -deprotonation, followed by a Michael addition of the thus-formed dienol intermediate **94** to nitroalkenes **95** to give novel intermediates **96** which then cyclized into the final densely functionalized chiral cyclohexenes **97** bearing four contiguous stereocenters

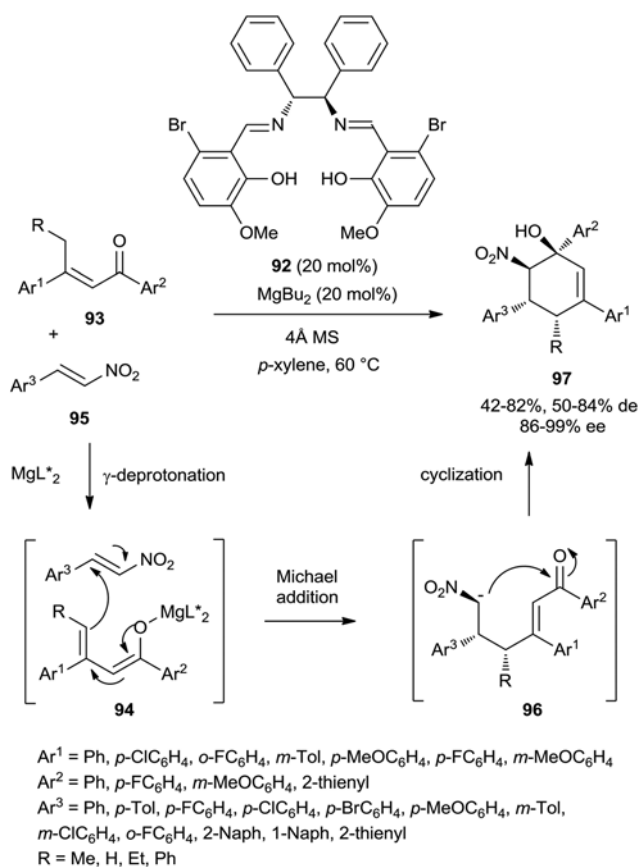
in moderate to good yields (42–82%) and diastereoselectivities (50–84% de) along with high enantioselectivities (86–99% ee), as shown in Scheme 25. Nitroalkenes bearing a variety of aryl groups with either electron-donating or electron-withdrawing substituents or heteroaryl groups were well tolerated whereas aliphatic nitroalkenes did not undergo the reaction. Furthermore, α,β -unsaturated ketones bearing different aryl groups at either the β - or the α' -positions were also compatible.

3.3. Multicatalyzed domino reactions

In the last few years, an explosive number of multiple-catalyst systems for various organic transformations have been developed.⁴⁷ This novel methodology is particularly adapted for enantioselective domino and tandem reactions.⁴⁸ In 2010, Scheidt *et al.* reported the first enantioselective cooperative catalytic system consisting of $\text{Mg}(\text{Ot-Bu})_2$ and a chiral N-heterocyclic carbene such as **98**, which was applied in the presence of a base, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), to a diastereo- and enantioselective synthesis of chiral γ -lactams from the reaction of *N*-acyl hydrazones **99** with α,β -unsaturated aldehydes **100** (Scheme 26).⁴⁹ The key behind the success was the reversible magnesium-N-heterocyclic carbene interaction, allowing the corresponding chiral γ -lactams **101** to be achieved with high levels of diastereo- and



Scheme 26 Formal [3 + 2] cycloaddition through cooperative magnesium and N-heterocyclic carbene catalysis.



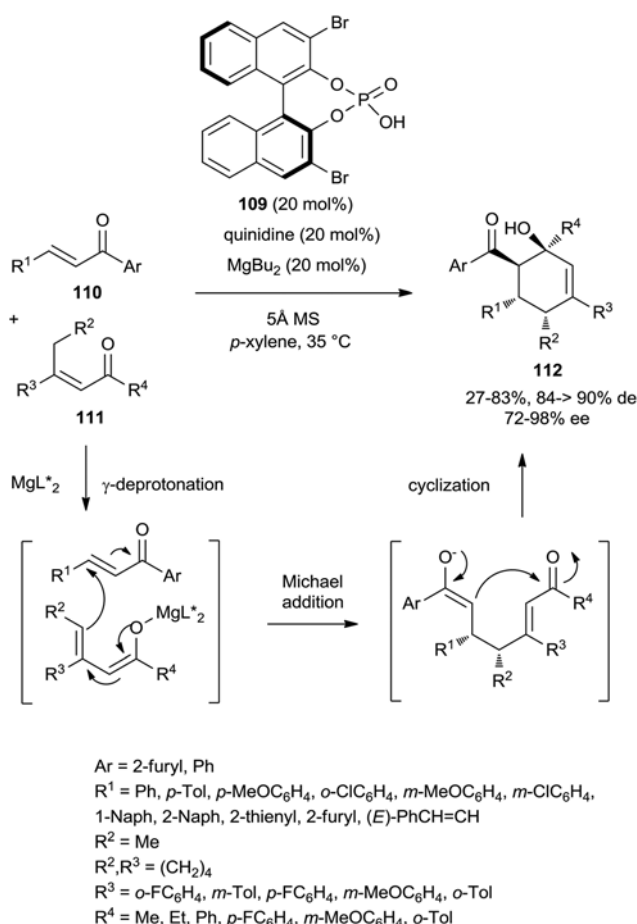
Scheme 25 Domino γ -deprotonation/Michael/cyclization reaction of linear α,β -unsaturated ketones with nitroalkenes.

enantioselectivities (up to 90% de and 98% ee, respectively), as shown in Scheme 26. The process began with the addition of the NHC catalyst previously deprotonated by the base to the α,β -unsaturated aldehyde to give the corresponding dienol intermediate **102** which further added to the *N*-acyl hydrazone activated by $\text{Mg}(\text{II})$ complex to give intermediate **103**. The latter then underwent an intramolecular acylation to afford the final formal [3 + 2] cycloadduct **101**.

In 2012, Gong *et al.* reported an enantioselective three-component reaction based on an asymmetric relay catalytic

domino Friedländer condensation/transfer hydrogenation reaction of 2-aminophenyl ketones **104**, methyl Hantzsch ester **105** and ethyl acetoacetate **106**, providing the corresponding chiral tetrahydroquinolines **107** in moderate to high yields (64–97%), diastereoselectivities of >90% de in all cases of substrates studied, combined with high to excellent enantioselectivities (85–98% ee).⁵⁰ As shown in Scheme 27, the catalyst system was constituted by a combination of $\text{Mg}(\text{OTf})_2$ and chiral phosphoric acid **108**. The authors assumed that the process could evolve through a Friedländer condensation catalyzed by either the chiral phosphoric acid or the Lewis acid, while the following asymmetric transfer hydrogenation was promoted solely by chiral Brønsted acid **108** (Scheme 27).

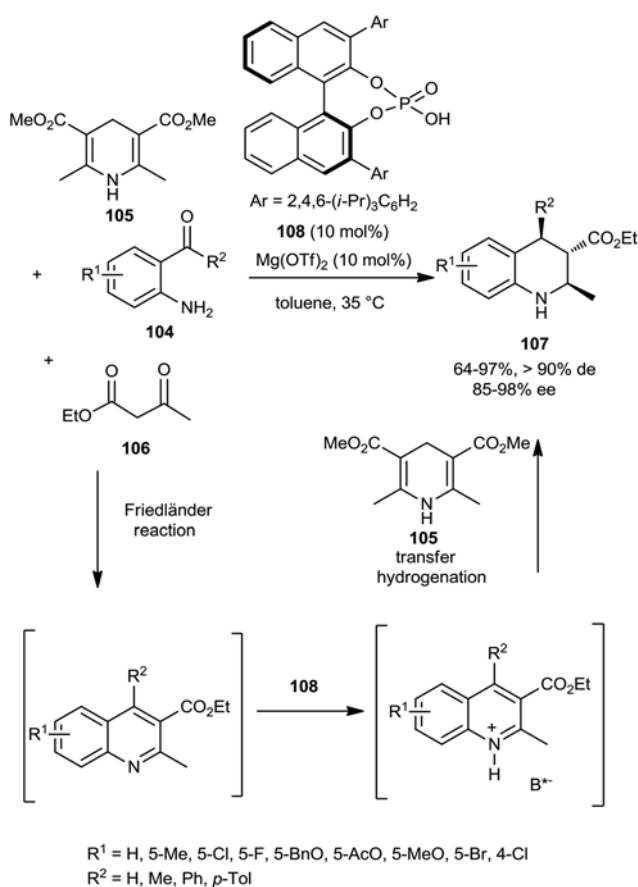
In order to extend to electrophiles other than nitroalkenes the work depicted in Scheme 25, dealing with domino γ -deprotonation/Michael/cyclization reactions of linear α,β -unsaturated ketones with nitroalkenes, the same authors later developed a more complex catalyst system composed of chiral phosphoric acid **109**, quinidine, and MgBu_2 in *p*-xylene at 35 °C.⁵¹ The domino γ -deprotonation/Michael/cyclization cross reaction of linear α,β -unsaturated ketones **110** and **111** led to the corresponding highly functionalized chiral cyclohexenes **112** in moderate to good yields (27–83%), high diastereoselectivities (84–>90% ee) and good to excellent



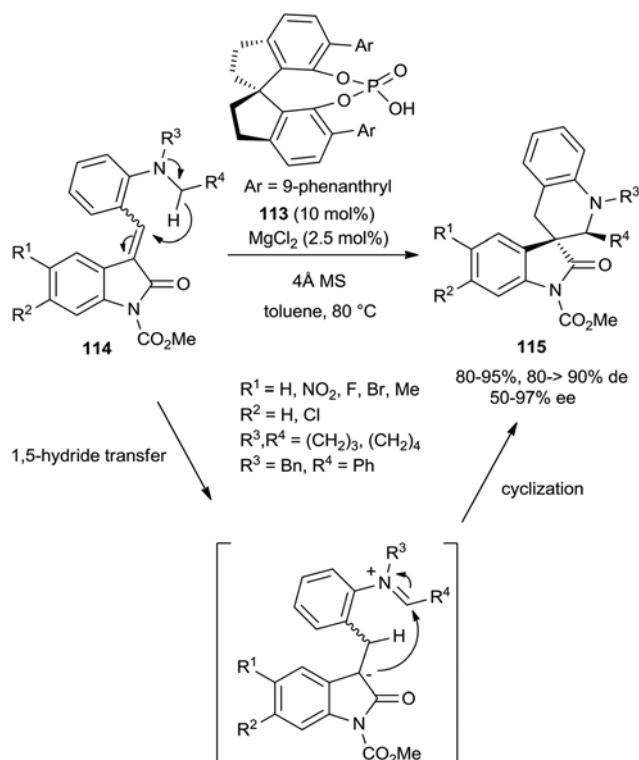
Scheme 28 Domino γ -deprotonation/Michael/cyclization reaction of linear α,β -unsaturated ketones through magnesium, cinchona alkaloid and phosphoric acid catalysis.

enantioselectivities (72–98% ee), as shown in Scheme 28. Even if the authors did not specify the exact role of each member of the catalyst system, they demonstrated that the presence of the three members was indispensable to achieve these excellent results. For example, in the absence of the acid cinchona alkaloid almost no product was generated while the absence of the chiral phosphoric acid led to the product albeit with very low stereoselectivities ($\leq 3\%$ ee). This work represented the first stereocontrolled cross reaction of linear α,β -unsaturated ketones.

In 2016, Lin *et al.* reported the use of a combination of MgCl_2 with chiral phosphoric acid **113** to promote enantioselective domino 1,5-hydride transfer/cyclization reactions of oxindole derivatives **114** performed in toluene at 80 °C.⁵² As shown in Scheme 29, the reaction led to a series of structurally diverse spirooxindole tetrahydroquinolines **115** in high yields (80–95%) and diastereoselectivities (80–>90% de) along with moderate to excellent enantioselectivities (50–97% ee). The lowest enantioselectivity of 50% ee was obtained with a substrate bearing an electron-rich substituent (R^1 = Me) on the oxindole aromatic ring whereas the highest enantioselectivities



Scheme 27 Three-component domino Friedländer/transfer hydrogenation reaction through relay magnesium and phosphoric acid catalysis.



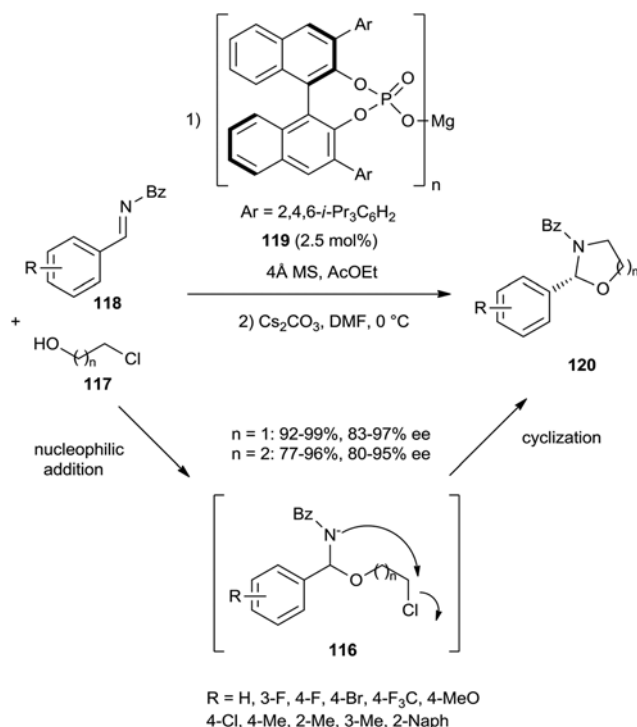
Scheme 29 Domino 1,5-hydride transfer/cyclization reaction of oxindole derivatives through magnesium and phosphoric acid catalysis.

(93–97% ee) were reached with substrates bearing a strong electron-withdrawing group such as NO₂ on this ring (R¹ = NO₂).

3.4. Tandem reactions

Tandem catalyzed reactions refer to the synthetic strategies of modular combination of catalytic reactions into one synthetic operation, occurring one after the other and working in conjunction with each other with minimum workup or change in conditions⁵³ in comparison with domino reactions defined by Tietze as strictly one-pot reactions.³³ A recent example of enantioselective magnesium-catalyzed tandem reactions was described by Antilla *et al.*, applied to the synthesis of chiral 1,3-oxazolidines and 1,3-oxazinanes under mild reaction conditions (Scheme 30).⁵⁴ The reaction began with the formation of hemiaminal intermediates **116** through enantioselective addition of the respective alcohols **117** to *N*-benzyl imines **118** catalyzed by the preformed chiral magnesium BINOL-derived phosphate catalyst **119**, followed by intramolecular cyclization to give the final products **120** in good to excellent yields (77–99%) and enantioselectivities (80–97% ee). Generally, better yields (92–99% vs. 77–96%) and slightly higher enantioselectivities (83–97% ee vs. 80–95% ee) were achieved in the formation of 1,3-oxazinanes (*n* = 2) in comparison with 1,3-oxazolidines (*n* = 1).

Another type of enantioselective magnesium-catalyzed tandem reaction was developed by Wang *et al.*, involving 3-iso-

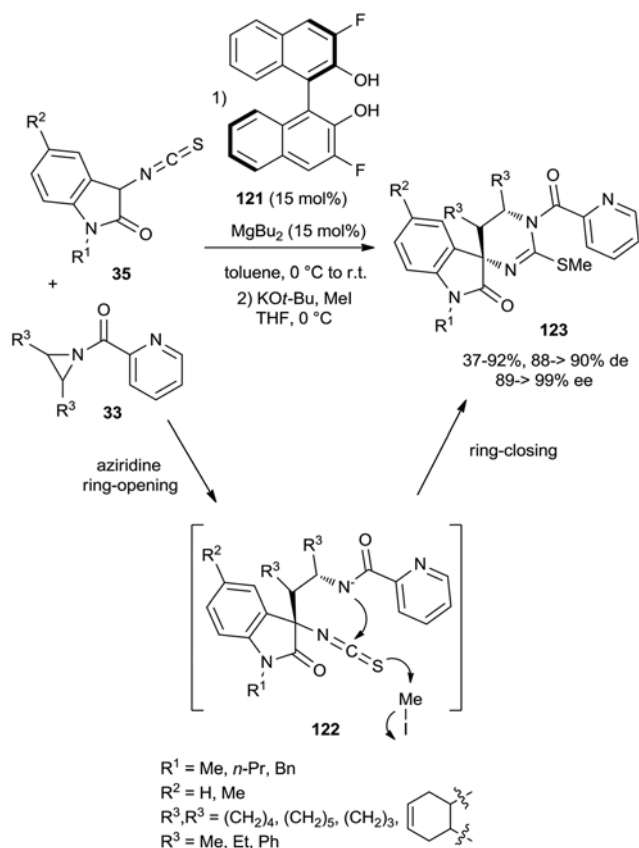


Scheme 30 Tandem nucleophilic addition/cyclization reaction of *N*-benzyl imines with alcohols.

thiocyanato oxindoles **35** and *N*-(2-picolinoyl)aziridines **33** as substrates.⁵⁵ It constituted the first asymmetric formal [3 + 3] cycloaddition with aziridines. This tandem reaction was mediated by a magnesium catalyst *in situ* generated from MgBu₂ and chiral BINOL-derived fluorinated ligand **121** in toluene at 0 °C to room temperature. It began with the ring-opening of aziridines with 3-isothiocyanato oxindoles to give intermediates **122** which subsequently cyclized into final products **123** by treatment with *t*-BuOK/MeI (Scheme 31). This novel tandem ring-opening/ring-closing reaction allowed a range of densely functionalized chiral pyrimidine derivatives **123** to be synthesized in moderate to high yields (37–92%) with uniformly high diastereo- and enantioselectivities (88–>90% de and 89–>99% ee, respectively).

4. Magnesium-catalyzed ring-opening reactions

The nucleophilic ring-opening of three-membered compounds, such as epoxides, represents an important strategy in organic synthesis because of its powerful capability of forming bonds.⁵⁶ This process leads to the possible formation of two adjacent stereocenters at the α,α'-positions of the *meso*-epoxide, allowing chiral 1,2-difunctional compounds, including 1,2-diol monoethers, 1,2-amino alcohols, or 1,2-thioalcohols, to be easily synthesized. In the past decade, magnesium complexes derived from various chiral ligands have been

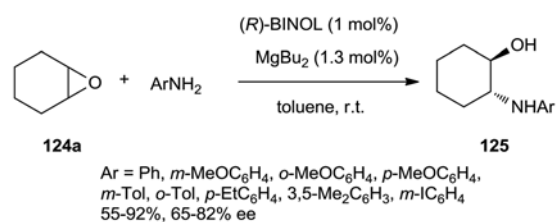


Scheme 31 Tandem ring-opening/ring-closing reaction of 3-isothiocyanato oxindoles with *N*-(2-picolinoyl)aziridines.

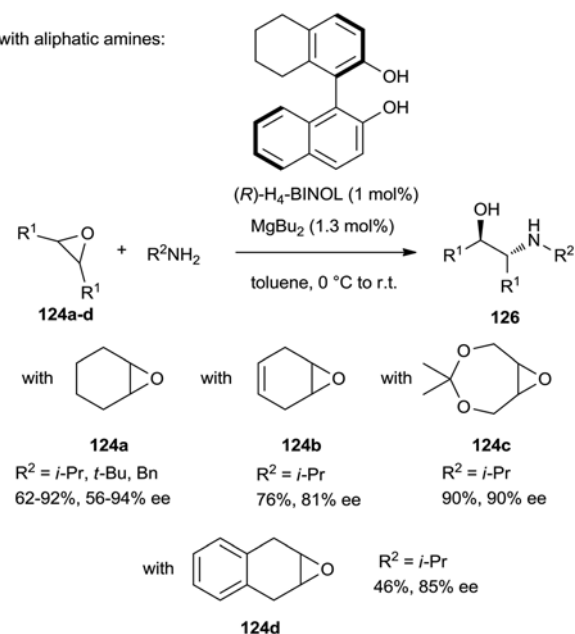
successfully applied to the ring-opening reactions of *meso*-epoxides with a variety of nucleophiles such as amines. For example, Ding *et al.* have developed enantioselective ring-opening of *meso*-cyclohexene epoxide **124a** with aromatic amines catalyzed by a low quantity (1–1.3 mol%) of a chiral magnesium complex *in situ* generated from MgBu₂ and (*R*)-BINOL as ligand in toluene at room temperature.⁵⁷ As shown in Scheme 32, the corresponding chiral β-amino alcohols **125** were obtained in moderate to high yields (55–92%) and enantioselectivities (65–82% ee). The substrate scope of the procedure was applied to more challenging aliphatic amines but in the case of substrates better yields and enantioselectivities were achieved by using the partially reduced (*R*)-BINOL derivative, (*R*)-H₄-BINOL, instead of BINOL itself as ligand. As shown in Scheme 32, the reaction of different *meso*-epoxides **124a–d** with aliphatic amines including sterically bulky isopropyl or *tert*-butylamines led to the corresponding ring-opened products **126** in moderate to high yields (46–92%) and enantioselectivities (56–94% ee).

Later, these authors reinvestigated the ring-opening reaction of *meso*-epoxides **12a–b, e–f** with aniline derivatives **127** by using another type of chiral magnesium catalyst such as that *in situ* generated from MgBu₂ and the chiral multidentate semi-azacrown ether ligand **128**.⁵⁸ As shown in Scheme 33, the process performed in pentane at room temperature afforded a

with aromatic amines:



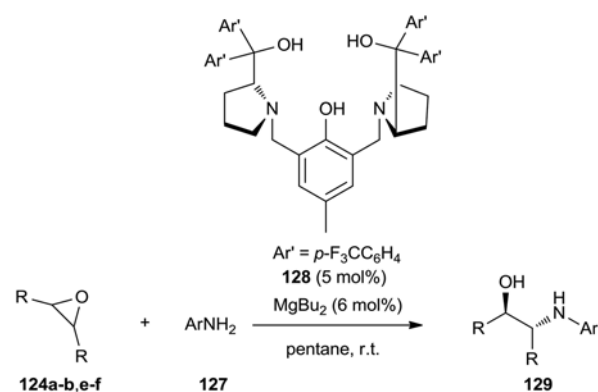
with aliphatic amines:



Scheme 32 Ring-opening reactions of *meso*-epoxides with aromatic and aliphatic amines.

series of chiral β-amino alcohols **129** in moderate to high yields (24–90%) and enantioselectivities (63–90% ee). The best results were obtained in the reaction of cyclohexene epoxide **124a** (61–90% yield and 76–90% ee). The authors have proposed a binuclear complex as the active catalyst in the process, acting as a Brønsted base–Lewis acid bifunctional catalyst for dual activation of both the amine and the epoxide, so that an oriented intramolecular delivery of the nucleophilic amine could occur with good stereochemical control at the two proximal metal centers within the chiral cavity of the complex (see the transition state in Scheme 33).

The enantioselective nucleophilic ring-opening of *meso*-aziridines has also received a large amount of attention, since it furnishes valuable nitrogen-containing products.⁵⁹ In the last decade, a range of chiral magnesium catalysts derived from different types of ligands, including *N,N'*-dioxides, cinchona alkaloids, amino alcohols, phosphates, and BINOL derivatives, have been successfully applied to ring-opening reactions of *meso*-aziridines with a variety of nucleophiles. For example, *N,N'*-dioxide ligand **45** was employed by Feng *et al.* in combination with Mg(OTf)₂ in *p*-xylene at 35 °C to promote the first enantioselective ring-opening reaction of a variety of cyclic and

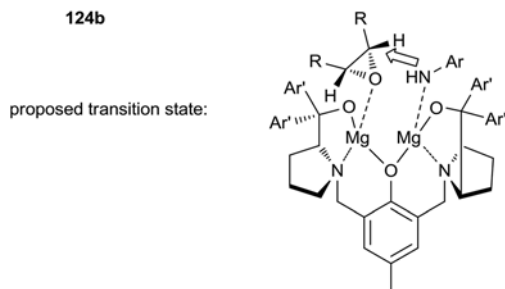


with **124f**: R = Ar = Ph: 83%, 88% ee

with **124a** Ar = Ph, *m*-MeOC₆H₄, *o*-MeOC₆H₄, *p*-MeOC₆H₄, *m*-Tol, *o*-Tol, *p*-EtC₆H₄, 3,5-Me₂C₆H₃, *m*-IC₆H₄: 61-90%, 76-90% ee

with **124e** Ar = Ph: 24%, 65% ee

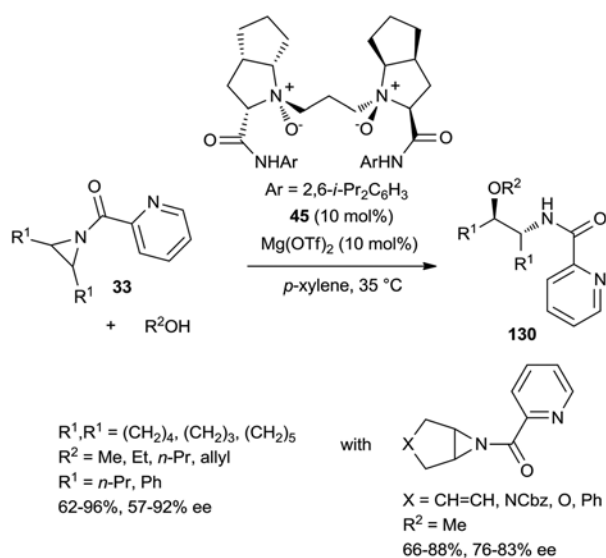
with **124b** Ar = Ph: 67%, 63% ee



Scheme 33 Ring-opening reaction of *meso*-epoxides with anilines.

acyclic *meso*-aziridines **33** with primary alcohols to give the corresponding chiral β -amino ethers **130** in moderate to high yields (62–96%) and enantioselectivities (57–92% ee), as shown in Scheme 34.⁶⁰

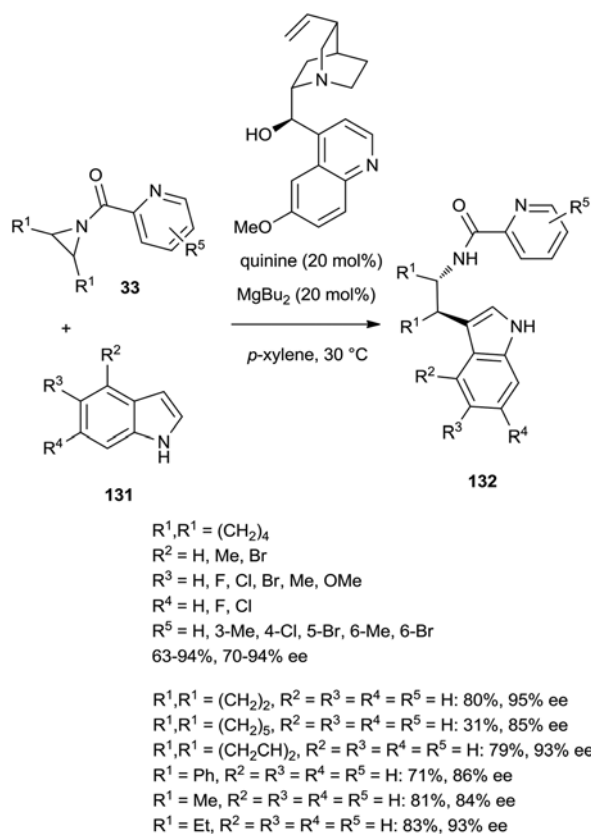
In 2014, Wang *et al.* reported the first example of an asymmetric ring-opening reaction of *meso*-aziridines **33** with C3-unsubstituted indoles **131** catalyzed by a chiral magnesium complex.⁶¹ While C3-alkylindoles **32** reacted with *meso*-aziridines **33** through 1,3-dipolar cycloadditions (Scheme 10), the reaction of *meso*-aziridines **33** with indoles **131**, promoted by a combination of MgBu_2 and quinine in *p*-xylene at 30 °C, afforded the corresponding Friedel–Crafts products **132** in moderate to high yields (31–94%) and good to high enantioselectivities (70–95% ee). In addition to various cyclic aziridines, acyclic aryl- and aliphatic aziridines were also tolerated in the reaction, providing the corresponding products in good yields (71–83%) and high enantioselectivities (84–93% ee). To illustrate the synthetic utility of this novel methodology, some of the formed products were converted into various types of



Scheme 34 Ring-opening reaction of *meso*-aziridines with primary alcohols.

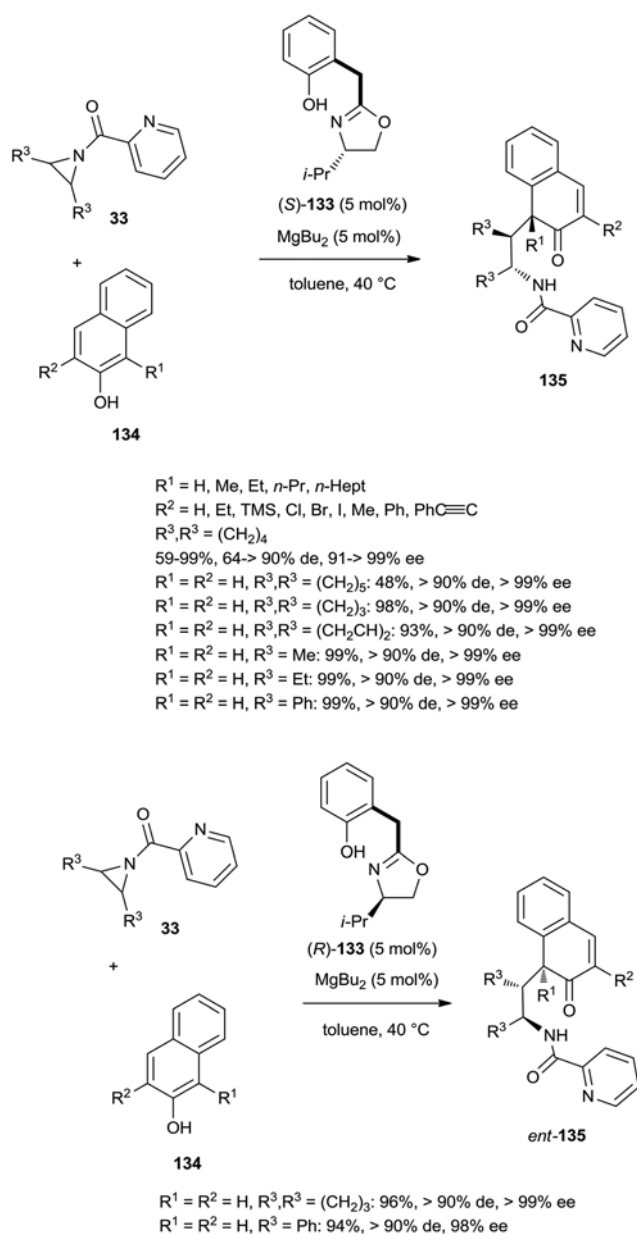
chiral C3-halogenated pyrroloindolines playing an important role in medicinal chemistry (Scheme 35).

In 2015, the same authors employed the novel chiral bis (oxazoline) ligand (*S*)-**133** to promote the first enantioselective



Scheme 35 Ring-opening reaction of *meso*-aziridines with indoles.

magnesium-catalyzed ring-opening reactions of *meso*-aziridines **33** with β -naphthols **134**.⁶² Performed in toluene at 40 °C, the process afforded the corresponding products **135** in moderate to quantitative yields (48–99%), moderate to high diastereoselectivities (64–>90% de) and high enantioselectivities (91–>99% ee), as shown in Scheme 36. The reaction constituted the first direct, facile, and highly stereoselective de-aromatization of β -naphthol derivatives. Furthermore, the enantiomeric ring-opening products *ent*-**135** could be obtained with excellent yields (94–96%), a diastereoselectivity of >90% de, and remarkable enantioselectivities (98–>99% ee) when using (*R*)-**133** as ligand (Scheme 36).

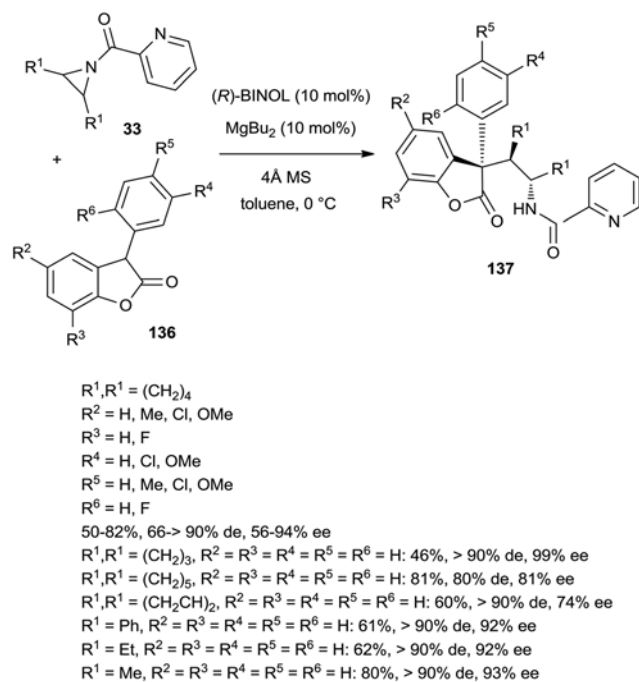


Scheme 36 Ring-opening reactions of *meso*-aziridines with β -naphthols.

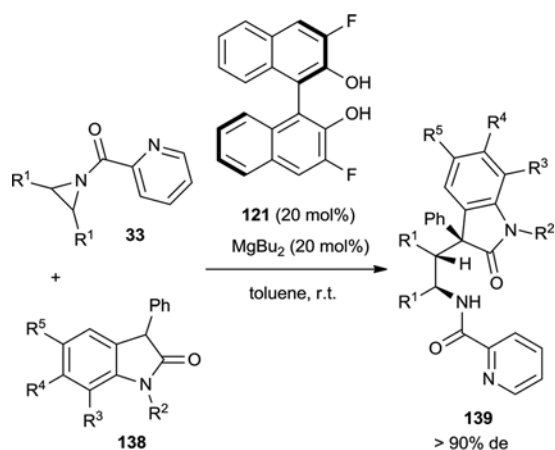
In 2015, the same authors also described the first enantioselective magnesium-catalyzed ring-opening reaction of *meso*-aziridines **33** with benzofuran-2(3*H*)-ones **136**.⁶³ In this case, (*R*)-BINOL was selected as the optimal ligand of MgBu_2 , leading to the corresponding products **137** (Scheme 37). These chiral 3,3-disubstituted benzofuran-2(3*H*)-ones bearing three contiguous stereocenters were obtained in moderate to good yields (46–92%), moderate to high diastereoselectivities (66–>90% de) and enantioselectivities (56–99% ee). The simple catalytic system was compatible with cyclic as well as acyclic *meso*-aziridines and with the presence of different substituents at the C-5 and C-7 positions of the aromatic ring of the benzofuran-2(3*H*)-ones.

In addition, the first enantioselective magnesium-catalyzed ring-opening reaction of *meso*-aziridines with 3-aryl-oxindoles was described by the same authors.⁶⁴ In this case, the BINOL fluorinated derivative **121** was selected as the optimal ligand to promote, in combination with MgBu_2 in toluene at room temperature, the reaction of a variety of cyclic and acyclic *meso*-aziridines **33** with 3-phenyl-oxindoles **138**. As shown in Scheme 38, a range of chiral 3-alkyl-3-phenyl oxindoles **139** exhibiting three contiguous stereocenters were achieved in moderate to high yields (44–94%), a uniformly high diastereoselectivity of >90% de, and good to excellent enantioselectivities (72–>99% ee). Oxindoles with different substituents at the C5-, C6-, and C7-positions were all tolerated under the catalytic system, providing comparable excellent enantioselectivities (87–>99% ee).

Finally, these authors disclosed the first enantioselective magnesium-catalyzed ring-opening reaction of *meso*-aziridines



Scheme 37 Ring-opening reaction of *meso*-aziridines with benzofuran-2(3*H*)-ones.

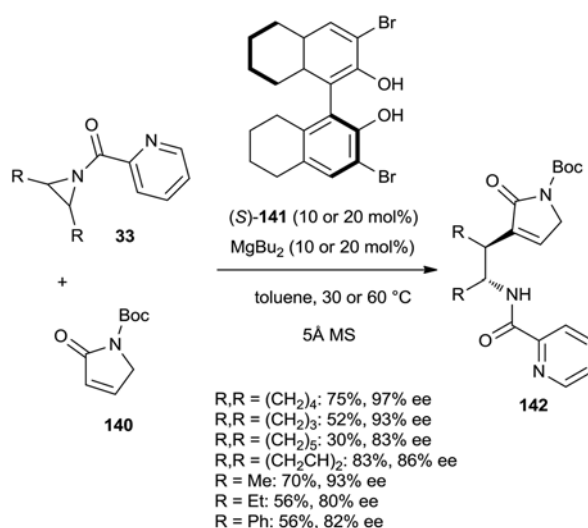


$R^1, R^1 = (CH_2)_4$
 $R^2 = \text{Me, Bn, allyl}$
 $R^3 = \text{H, Br}$
 $R^4 = \text{H, Cl}$
 $R^5 = \text{H, Me}$
 44–94%, 72- > 99% ee
 $R^1, R^1 = (CH_2)_3, R^2 = \text{Me}, R^3 = R^4 = R^5 = \text{H}$: 65%, > 99% ee
 $R^1, R^1 = (CH_2)_5, R^2 = \text{Me}, R^3 = R^4 = R^5 = \text{H}$: 63%, > 99% ee
 $R^1, R^1 = (CH_2CH)_2, R^2 = \text{Me}, R^3 = R^4 = R^5 = \text{H}$: 74%, 99% ee
 $R^1 = \text{Ph}, R^2 = \text{Me}, R^3 = R^4 = R^5 = \text{H}$: 50%, 99% ee
 $R^1 = \text{Et}, R^2 = \text{Me}, R^3 = R^4 = R^5 = \text{H}$: 70%, > 99% ee
 $R^1 = R^2 = \text{Me}, R^3 = R^4 = R^5 = \text{H}$: 87%, 99% ee

Scheme 38 Ring-opening reaction of *meso*-aziridines with 3-phenyl-oxindoles.

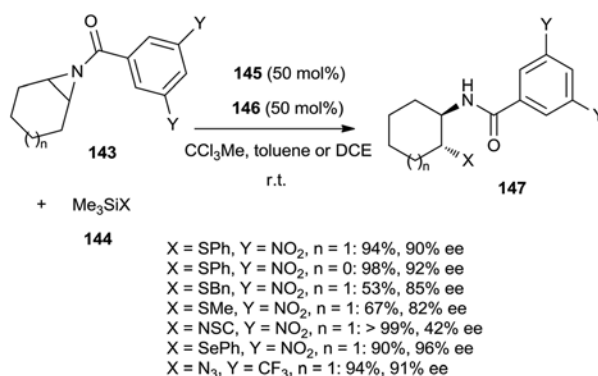
33 with α,β -unsaturated γ -butyrolactam 140.⁶⁵ Among a variety of ligands derived from (*S*)-BINOL and (*S*)-H₈-BINOL, the chiral ligand (*S*)-141 was selected as the most efficient to promote, in combination with MgBu₂ in toluene, the first α -sp²-carbon attacked catalytic asymmetric ring-opening of aziridines. As shown in Scheme 39, the process led to the formation of a series of chiral amines 142 containing aryl or alkyl groups in moderate to good yields (30–75%) with high enantioselectivities (80–97% ee). Studying different ligands, the authors demonstrated that the bromine atom of the ligand played a key role in introducing a high level of enantioselectivity and a high reaction efficiency. Moreover, the enantiomeric products could be prepared with up to 93% ee by using (*R*)-141 as ligand.

In another context, Sala has developed enantioselective ring-opening reactions of cyclic *meso*-aziridines 143 with various silylated nucleophiles 144.⁶⁶ The process was promoted by a 1:1 mixture of magnesium and calcium VAPOL-derived phosphate catalysts 145 and 146 employed at 50 mol% catalyst loading. As shown in Scheme 40, silylated sulfur nucleophiles yielded the corresponding ring-opened products 147 in moderate to quantitative yields (53–98%) with high enantioselectivities (82–92% ee) while the reaction of a thiocyanate nucleophile (X = NCS) provided only 42% ee. The best enantioselectivity of 96% ee was achieved in the reaction of a silylated selenium nucleophile (X = SePh). Moreover, a silylated azide nucleophile (X = N₃) led to the corresponding product in

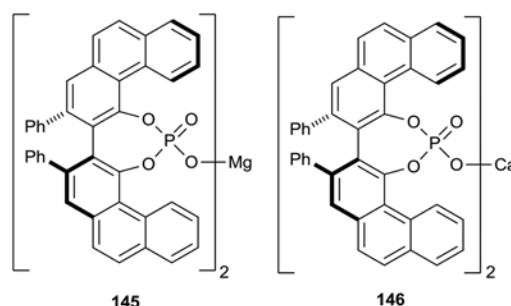


$R, R = (CH_2)_4$: 75%, 97% ee
 $R, R = (CH_2)_3$: 52%, 93% ee
 $R, R = (CH_2)_5$: 30%, 83% ee
 $R, R = (CH_2CH)_2$: 83%, 86% ee
 $R = \text{Me}$: 70%, 93% ee
 $R = \text{Et}$: 56%, 80% ee
 $R = \text{Ph}$: 56%, 82% ee

Scheme 39 Ring-opening reaction of *meso*-aziridines with a γ -butyrolactam.

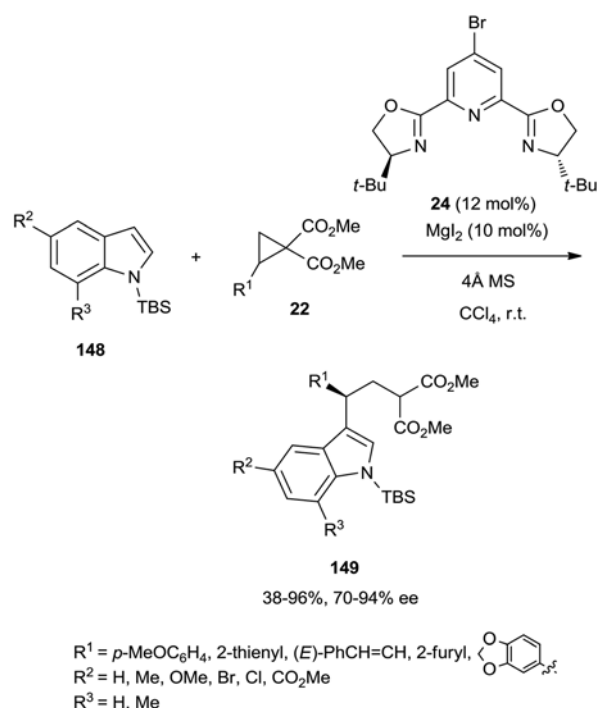


$X = \text{SPh}, Y = \text{NO}_2, n = 1$: 94%, 90% ee
 $X = \text{SPh}, Y = \text{NO}_2, n = 0$: 98%, 92% ee
 $X = \text{SBn}, Y = \text{NO}_2, n = 1$: 53%, 85% ee
 $X = \text{SMe}, Y = \text{NO}_2, n = 1$: 67%, 82% ee
 $X = \text{NSC}, Y = \text{NO}_2, n = 1$: > 99%, 42% ee
 $X = \text{SePh}, Y = \text{NO}_2, n = 1$: 90%, 96% ee
 $X = \text{N}_3, Y = \text{CF}_3, n = 1$: 94%, 91% ee



Scheme 40 Mg- and Ca-catalyzed ring-opening reaction of *meso*-aziridines with silylated nucleophiles.

91% ee. With the aim of determining the active catalyst of the process, the authors have demonstrated that the phosphoric acid alone was not able to promote efficiently the reaction and proposed that the two metals played a key role in the catalytic cycle, whether as part of a bimetallic species or as distinct monometallic molecules. One metal center could act as a Lewis acid, activating the aziridine, while the ligand attached to the other metal center generated the reactive nucleophile.



Scheme 41 Ring-opening reaction of donor-acceptor cyclopropanes with *N*-TBS indoles.

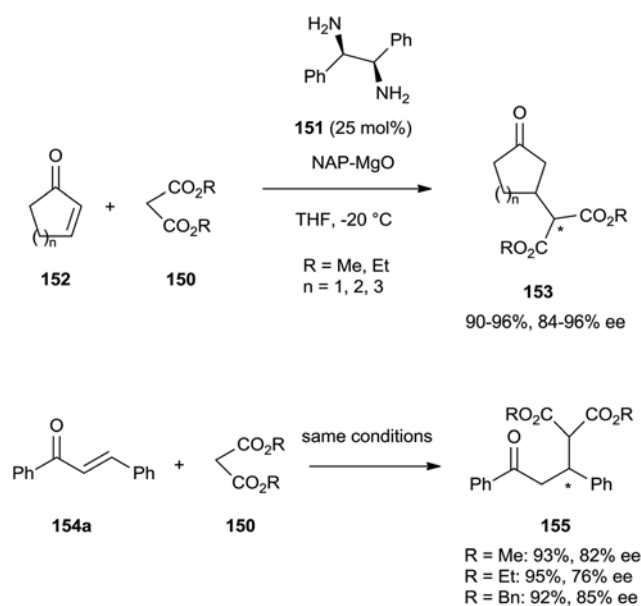
In another context, donor-acceptor cyclopropanes, especially those derived from 1,1-dicarboxylate esters, can act as homo-Michael acceptors in ring-opening reactions under Lewis acid catalysis.⁶⁷ In 2013, Johnson *et al.* investigated the asymmetric magnesium-catalyzed ring-opening of this type of cyclopropane with *N*-protected indoles.⁶⁸ In the presence of MgI_2 and chiral pybox ligand **24** as a catalyst system in CCl_4 at room temperature, *N*-TBS indoles **148** underwent a Friedel-Crafts reaction with donor-acceptor cyclopropanes **22** to give the corresponding chiral homo-Michael products **149** in moderate to high yields (38–96%) and good to high enantioselectivities (70–94% ee), as shown in Scheme 41. A range of indoles with electronically diverse substituents (R^2 , R^3) underwent the reaction with generally high yields with the exception of electron-deficient indoles bearing halo or ester substituents (38–52% yield vs. 80–96% yield). The cyclopropane partner tolerated aromatic, heteroaromatic and ethylenic substituents (R^1) which all provided high enantioselectivities with the exception of the *para*-methoxyphenyl substituent giving a lower enantioselectivity of 70% ee while the best enantioselectivity of 94% ee was achieved by using the cyclopropane bearing a thienyl group.

5. Magnesium-catalyzed Michael reactions

Michael-type reactions⁶⁹ can be considered as one of the most powerful tools for the stereocontrolled formation of carbon-

carbon as well as carbon-heteroatom bonds.⁷⁰ A range of chiral metals and chiral organocatalysts have already been applied to promote these reactions. It is only in 1997 that Sibi and Ji reported the first example of a highly enantioselective magnesium-catalyzed Michael radical addition performed in the presence of chiral bis(oxazoline) ligands, providing enantioselectivities of up to 97% ee.⁷¹ Later in 1998, a comparable catalytic system was applied by these authors to develop the first examples of highly enantioselective magnesium-catalyzed Michael additions of amines with the same enantioselectivity.⁷² In 1999, comparable excellent enantioselectivities were achieved by Ji *et al.* in asymmetric magnesium-catalyzed conjugate additions of 1,3-dicarbonyl compounds to nitroalkenes by using the same ligand in combination with $\text{Mg}(\text{OTf})_2$.⁷³ Later in 2007, Kantam *et al.* reported asymmetric Michael additions of malonates **150** to α,β -unsaturated ketones catalyzed by heterogeneous nanocrystalline MgO (NAP-MgO).⁷⁴ As shown in Scheme 42, these reactions were performed in THF at -20°C in the presence of the chiral diamine ligand **151**. When cyclic α,β -unsaturated ketones **152** were employed as substrates as electrophilic partners, the corresponding Michael products **153** were obtained in uniformly high yields (90–96%) with good to excellent enantioselectivities (84–96% ee) while acyclic α,β -unsaturated ketone **154a** provided the corresponding products **155** with slightly lower enantioselectivities (76–85% ee) with comparable high yields (92–95%).

Asymmetric conjugate additions of vinyl nucleophiles performed on α,β -unsaturated ketones appended at the β -position of an unprotected indole are still very rare. To address the lack of such methods, May *et al.* have employed a chiral magnesium catalyst *in situ* generated from $\text{Mg}(\text{Ot-Bu})_2$ and (*R*)-



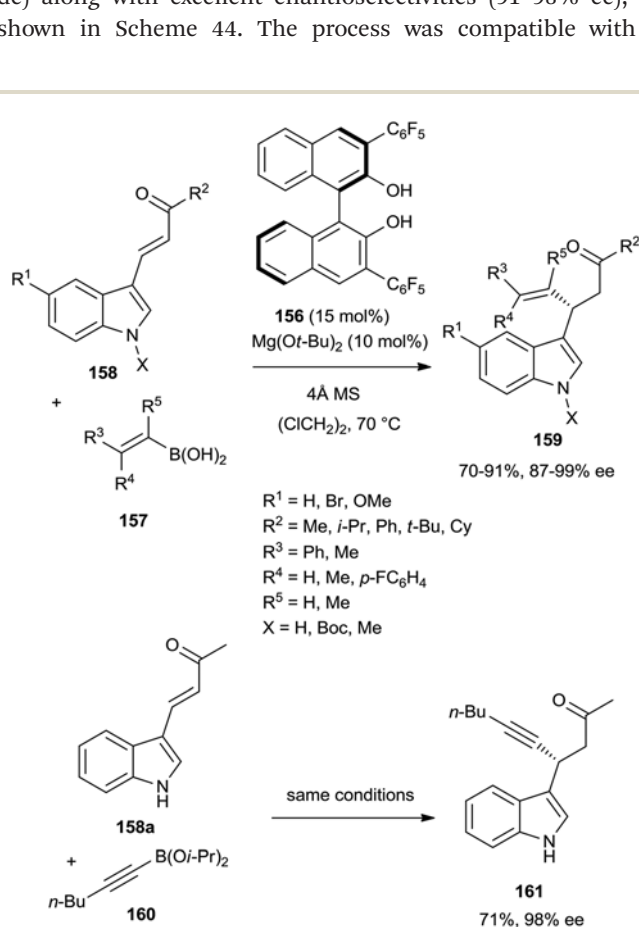
Scheme 42 Heterogeneous Michael additions of malonates to α,β -unsaturated ketones.

BINOL-derived fluorinated ligand **156** to promote the Michael addition of vinyl nucleophiles, such as (*E*)-alkenylboronic acids **157**, to indole-appended α,β -unsaturated ketones **158**.⁷⁵ As shown in Scheme 43, the reaction led to the corresponding chiral α -branched indole derivatives **159** in good to high yields (70–91%) and uniformly high enantioselectivities (87–99% ee). An unprotected indole was not necessary for the reaction, as both Boc- and methyl-protected indoles (*X* = Boc, Me) reacted smoothly with high yields (85–86%) and excellent enantioselectivities (97–98% ee). Concerning the scope of the (*E*)-alkenylboronic acids, both alkylvinylboronic acids and arylvinylboronic acids bearing electron-withdrawing or electron-donating substituents on the phenyl ring were tolerated, providing the corresponding products in comparable high enantioselectivities. Even alkynylboronic acid **160** led to the corresponding product **161** by reaction with indole **158a** in 71% yield and 98% ee.

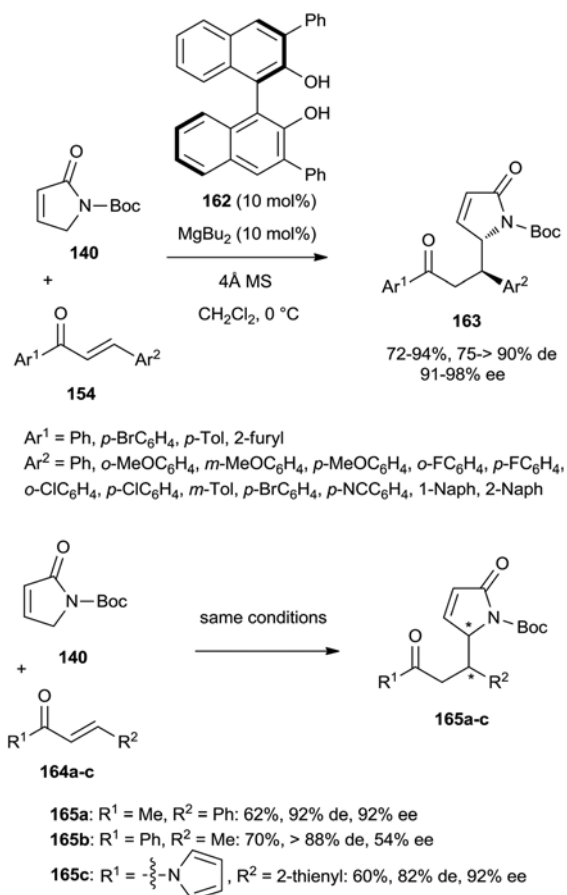
In 2011, Wang *et al.* reported enantioselective magnesium-catalyzed vinylogous Michael additions of α,β -unsaturated γ -butyrolactam **140** to α,β -unsaturated aryl ketones **154**.⁷⁶ The reaction employed a combination of MgBu_2 and the chiral BINOL derivative **162** as ligand in dichloromethane at 0 °C and afforded the corresponding Michael adducts **163** in good to high yields (72–94%) and diastereoselectivities (75–>90% de) along with excellent enantioselectivities (91–98% ee), as shown in Scheme 44. The process was compatible with a

variety of aryl enones with the enantioselectivity minimally affected by either the (hetero)aryl substituent of the carbonyl (Ar^1) or the γ -aryl substituent (Ar^2). Notably, the scope of the methodology could be extended to the less reactive β -unsaturated aliphatic ketone **164a** which afforded the corresponding product **165a** with a high enantioselectivity of 92% ee albeit combined with a moderate yield of 62% (Scheme 44). On the other hand, replacing the γ -aryl moiety (Ar^2) in enone **164b** with a methyl group resulted in the enantioselectivity of the reaction decreasing dramatically (54% ee, Scheme 44). Finally, the catalyst system was successfully applied to α,β -unsaturated *N*-acetylpyrrole **164c** to give the corresponding product **165c** with 92% ee, which constituted the first highly enantioselective direct vinylogous Michael addition of α,β -unsaturated γ -butyrolactams to α,β -unsaturated *N*-acetylpyrroles (Scheme 44).

Chiral organophosphorus compounds exhibit many biological activities and constitute important chiral ligands.⁷⁷ The catalytic asymmetric Michael addition of phosphorus nucleophiles to α,β -unsaturated carbonyl compounds constitutes one of the most powerful synthetic methodologies for the construction of these compounds.⁷⁸ In this context, Ishihara *et al.* have



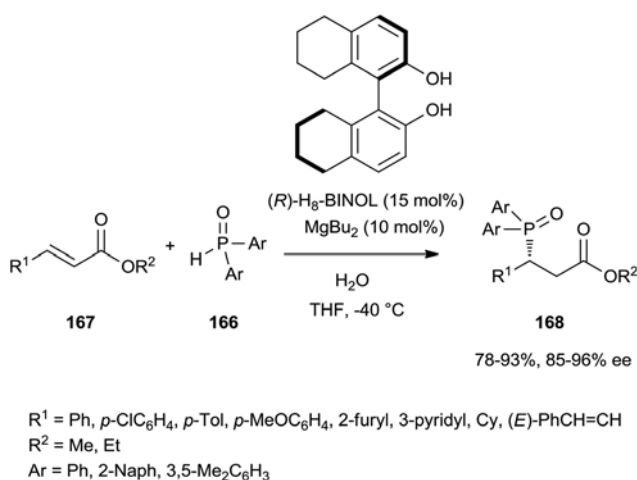
Scheme 43 Michael additions of alkenyl- and alkynylboronic acids to indole-appended α,β -unsaturated ketones.



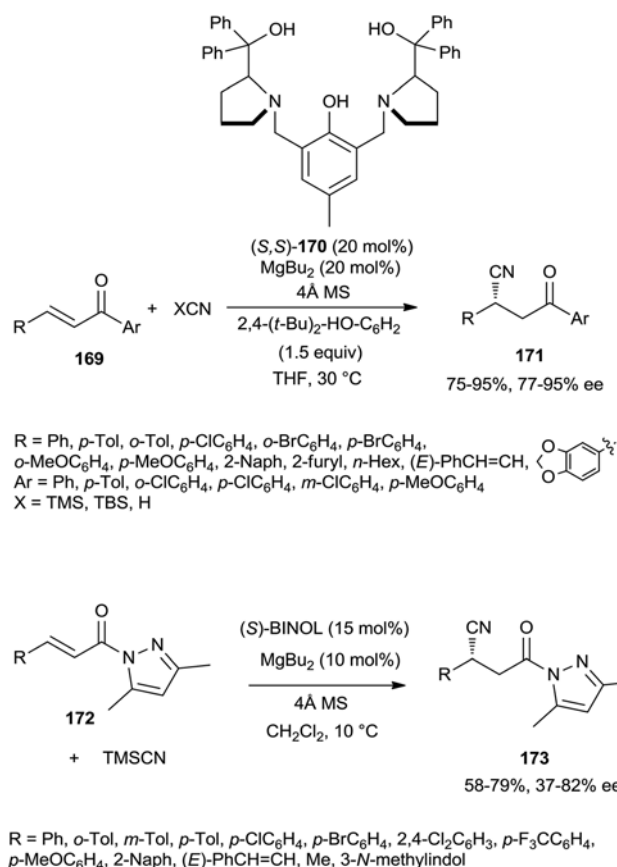
Scheme 44 Vinylogous Michael additions of an α,β -unsaturated γ -butyrolactam to α,β -unsaturated ketones and α,β -unsaturated *N*-acetylpyrrole.

developed the first highly enantioselective Michael addition of diaryl phosphine oxides **166** to α,β -unsaturated esters **167** by using a combination of MgBu_2 and (*R*)- H_8 -BINOL as chiral ligand in THF at -40°C (Scheme 45).⁷⁹ The process afforded the corresponding chiral Michael products **168** in both high yields (78–93%) and enantioselectivities (85–96% ee).

In 2014, another type of chiral magnesium complex was applied by Wang *et al.* to develop the first enantioselective magnesium-catalyzed conjugate cyanation of α,β -unsaturated compounds.⁸⁰ As shown in Scheme 46, the Michael addition of TMSCN (X = TMS) to a range of α,β -unsaturated ketones **169** performed in the presence of MgBu_2 and chiral multidentate ligand (*S,S*)-**170** afforded the corresponding chiral cyanide products **171** in good to high yields (75–95%) and enantioselectivities (77–95% ee). The enone substrates could bear aromatic substituents (R) with both electron-donating and electron-withdrawing groups, heteroaromatic substituents, and even aliphatic ones. Moreover, the cyanation also occurred by replacing TMSCN as a cyanide source with TBSCN or HCN , leading to products in 92–93% ee and 64–93% yields. The authors have proposed that the active catalyst was dinuclear with one metal coordinating the cyanide and the other metal coordinating the carbonyl group of the α,β -unsaturated ketone. With the aim of extending the scope of this methodology to other electrophilic partners, the authors found that using α,β -unsaturated amides, better results were obtained with a mononuclear magnesium catalyst derived from MgBu_2 and (*S*)-BINOL. Indeed, under these catalytic conditions, the conjugate addition of TMSCN to α,β -unsaturated *N*-acylimides **172** led to the corresponding chiral cyanides **173** in moderately good yields (58–79%) and enantioselectivities (37–82% ee), as shown in Scheme 46. The best results (up to 82% ee) were generally achieved with α,β -unsaturated *N*-acylimides bearing aromatic substituents (R) while alkyl-substituted ones provided lower enantioselectivities (37–50% ee).



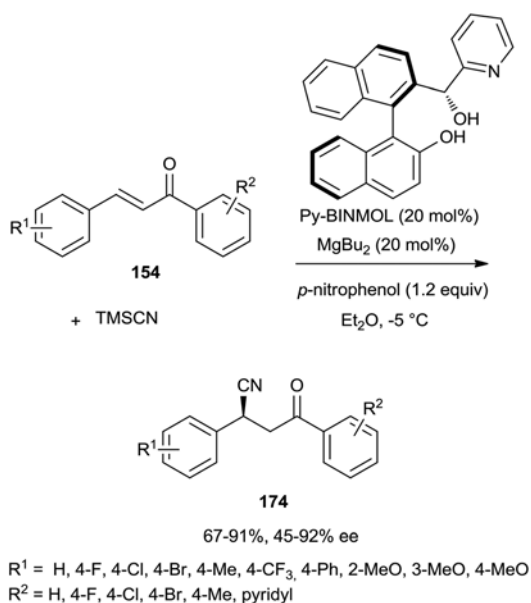
Scheme 45 Michael addition of diaryl phosphine oxides to α,β -unsaturated esters.



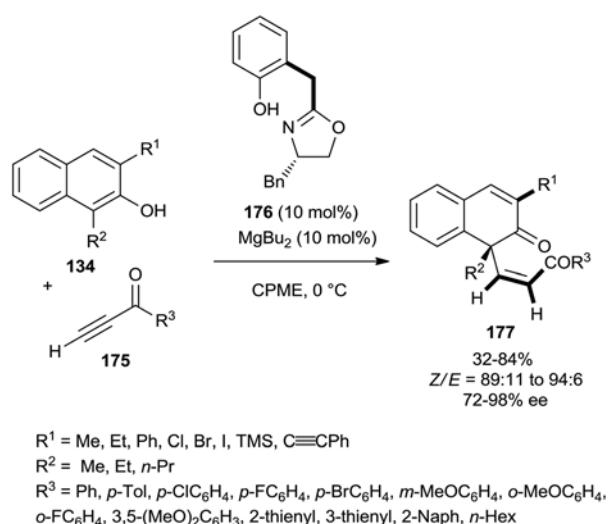
Scheme 46 Conjugate cyanations of α,β -unsaturated ketones and amides.

Later, related reactions with chalcones were developed by Xu *et al.* using Py-BINMOL as chiral magnesium ligand bearing both axial and sp^3 -central chirality.⁸¹ As shown in Scheme 47, the conjugate addition of TMSCN to a range of chalcones **154** in the presence of this chiral ligand combined with MgBu_2 in diethyl ether at -5°C afforded the corresponding chiral cyanides **174** in moderate to high yields (67–91%) and enantioselectivities (45–92% ee). It was found that the presence of *para*-nitrophenol as a stoichiometric additive was indispensable to achieve good yields and enantioselectivities. The reaction was compatible with the presence of methyl, halide, methoxy, trifluoromethyl, and phenyl groups in the chalcones while the introduction of a nitro group in chalcones led to no reaction probably because of the competing coordination to magnesium of the nitro and the carbonyl groups during the activation of the substrate with the magnesium catalyst.

In 2015, Wang *et al.* described a rare example of dearomatization of naphthols based on a catalytic asymmetric conjugate addition.⁸² Indeed, these authors developed enantioselective magnesium-catalyzed Michael additions of β -naphthols **134** to propargylic ketones **175** performed in cyclopentyl methyl ether (CPME) at 0°C in the presence of MgBu_2 and chiral oxazoline ligand **176** (Scheme 48). The process afforded the corres-



Scheme 47 Michael addition of TMS-CN to chalcones.



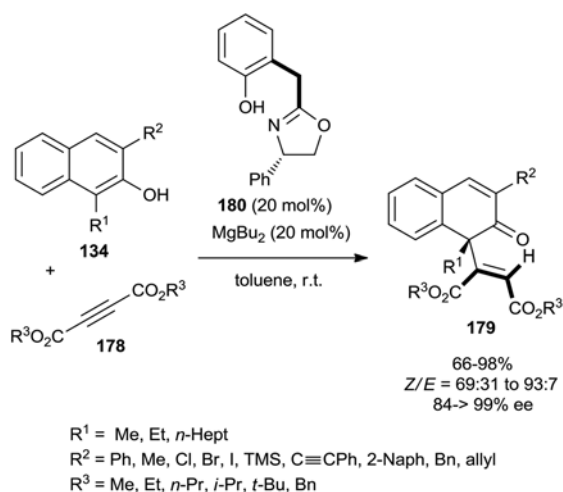
Scheme 48 Michael addition of β -naphthols to propargylic ketones.

ponding products **177** as major *Z*-diastereomers (*Z/E* = 89:11 to 94:6) in moderate to high yields (32–84%) and good to excellent enantioselectivities (72–98% ee). Excellent enantioselectivities of 92–98% ee and high yields (73–85%) were obtained in the reaction of a range of β -naphthols bearing alkyl, aryl, and halogen groups at the C-3 position (R^1) of the β -naphthols while a lower yield (32%) was observed in the reaction of a C-3-TMS-substituted β -naphthol albeit with still a high ee value (90% ee). Moreover, in addition to a methyl group, the substituent at the C-1 position (R^2) of the β -naphthol could be a bulkier group such as ethyl and *n*-propyl ones, providing moderate to high enantioselectivities (96–97% ee for $R^2 = \text{Et}$, 72% ee for $R^2 = n\text{-Pr}$). Even a phenylethynyl

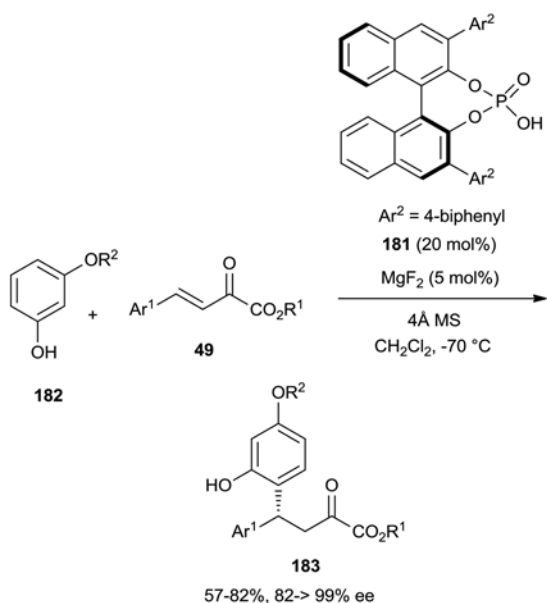
group ($R^1 = \text{C}\equiv\text{C-Ph}$) allowed the corresponding Michael product to be obtained with 84% ee. Concerning the propargylic ketone partner, (hetero)aryl-alkynyl ketones bearing various substituents all provided excellent enantioselectivities while a lower enantioselectivity (76% ee) was obtained in the reaction of an alkyl-alkynyl ketone ($R^3 = n\text{-Hex}$).

Continuing their research in this area, these authors disclosed enantioselective magnesium-catalyzed Michael additions of β -naphthols **134** to dialkyl acetylenedicarboxylates **178** to give the corresponding chiral trisubstituted olefins **179** bearing an all carbon quaternary center.⁸³ As shown in Scheme 49, in this case the oxazoline chiral ligand **180** gave the best results in combination with MgBu_2 in toluene at room temperature. The *Z*-diastereomers were generated as major products (*Z/E* = 69:31 to 93:7) in moderate to quantitative yields (66–98%) and high enantioselectivities (84–>99% ee). A wide variety of substituents at the C-3 position (R^2) of the β -naphthol was tolerated, including halogen, allyl, methyl, benzyl, phenyl, 2-naphthyl, and alkynyl groups. In addition to a methyl group at the C-1 position (R^1) of the β -naphthol, bulkier alkyl groups, such as ethyl and *n*-heptyl groups, gave generally lower yields (36–77%) albeit with high enantioselectivities (93–96% ee). Concerning the dialkyl acetylenedicarboxylates, comparable high enantioselectivities were achieved regardless of the alkyl substituent group (R^3).

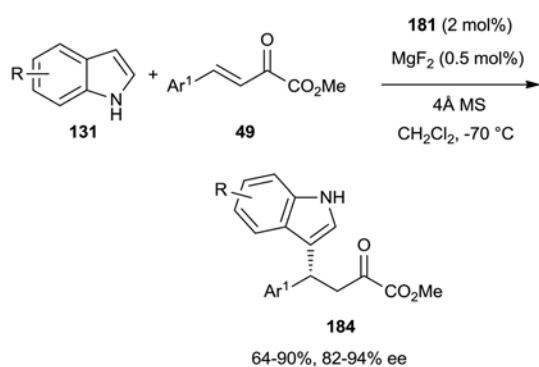
Earlier, Luo *et al.* reported the use of a combination of MgF_2 and (*S*)-BINOL-derived phosphoric acid **181** in enantioselective Friedel–Crafts reactions of phenols and indoles with β,γ -unsaturated α -ketoesters.⁸⁴ As shown in Scheme 50, in the presence of 20 mol% of this ligand and 5 mol% of MgF_2 in dichloromethane at -70°C , the reaction of phenols **182** with β,γ -unsaturated α -ketoesters **49** led to the corresponding Friedel–Crafts products **183** in moderate to good yields (57–82%) and good to excellent enantioselectivities (82–>99% ee). Notably, this constituted the first use of MgF_2 as a homogeneous Lewis acid in asymmetric catalysis. This methodology



Scheme 49 Michael addition of β -naphthols to dialkyl acetylenedicarboxylates.



$\text{Ar}^1 = \text{Ph}, p\text{-ClC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, o\text{-FC}_6\text{H}_4, p\text{-Tol}, m\text{-Tol}, p\text{-PhC}_6\text{H}_4$
 $\text{R}^1 = \text{Me}, \text{Et}$
 $\text{R}^2 = \text{Me}, \text{Et}$



$\text{Ar}^1 = \text{Ph}, o\text{-FC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, p\text{-ClC}_6\text{H}_4, p\text{-Tol}, m\text{-Tol}, p\text{-PhC}_6\text{H}_4$
 $\text{R} = \text{H}, 5\text{-MeO}, 6\text{-Cl}$

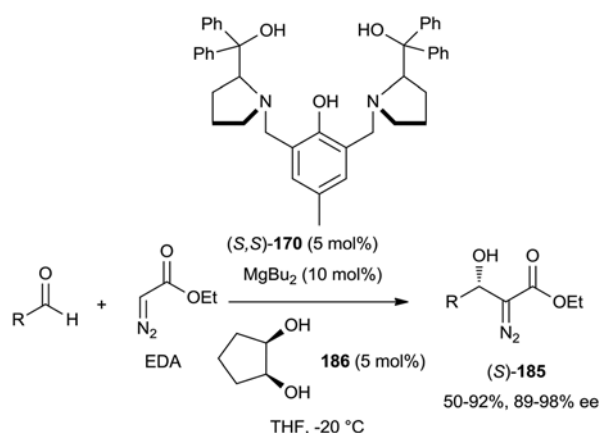
Scheme 50 Friedel–Crafts reactions of phenols and indoles with β,γ -unsaturated α -ketoesters.

was extended to other nucleophiles, such as indoles **131**, which led, through reaction with β,γ -unsaturated α -ketoesters **49**, to the corresponding chiral Friedel–Crafts products **184** in moderate to high yields (64–90%) and high enantioselectivities (82–94% ee). In this case, lower catalyst loadings were sufficient to reach these good results since 2 mol% of phosphoric acid and only 0.5 mol% of MgF_2 were used.

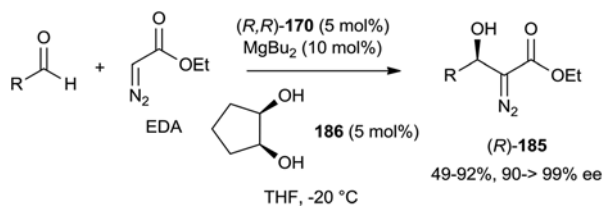
6. Magnesium-catalyzed 1,2-nucleophilic additions to carbonyl compounds and imines

In 1993, Corey and Wang reported the first enantioselective magnesium-catalyzed addition of TMSCN to aldehydes,

leading to the corresponding cyanohydrins in enantioselectivities of up to 95% ee by employing a chiral bis(oxazoline) ligand.⁸⁵ Among other asymmetric 1,2-nucleophilic additions to carbonyl compounds, the catalytic asymmetric aldol reaction is a powerful method for synthesizing chiral β -hydroxy carbonyl derivatives. A wide range of chiral catalyst systems have been successfully developed to promote this type of reaction including metals as well as organocatalysts.^{40,86} Early in 2005, Willis *et al.* reported an enantioselective direct aldol reaction for the synthesis of chiral aryl β -hydroxy- α -amino acids catalyzed by a chiral pybox $\text{Mg}(\text{II})$ complex, providing enantioselectivities of up to 95% ee.⁸⁷ Later in 2009, Trost *et al.* developed enantioselective magnesium-catalyzed direct aldol reactions between commercially available ethyl diazoacetate (EDA) and aldehydes, providing the corresponding chiral highly synthetically useful α -diazo- β -hydroxy esters **185**.⁸⁸ The process was promoted by a combination of MgBu_2 and multidentate ligand (*S,S*)-**170** in THF at -20°C in the presence of *cis*-1,2-cyclopentanediol **186** as an additive. A wide range of (hetero) aromatic aldehydes but also more challenging aliphatic ones were compatible, leading to products (*S*)-**185** in moderate to high yields (50–92%) with uniformly high enantioselectivities (89–98% ee), as shown in Scheme 51. Whereas comparable excellent enantioselectivities were obtained for these two classes of aldehydes, lower yields (50–76% vs. 70–92%) were observed in the case of aliphatic aldehydes in comparison with



$\text{R} = \text{Ph}, m\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4,$
 $m\text{-ClC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, 2\text{-furyl}, i\text{-Pr}, n\text{-Bu}, \text{BnCH}_2, (E)\text{-PhCH=CH}$



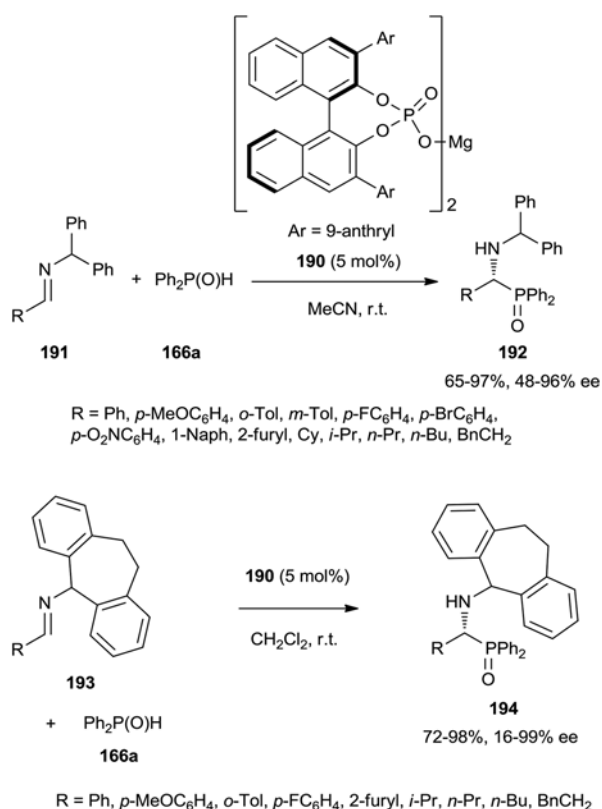
$\text{R} = \text{Ph}, m\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4,$
 $p\text{-ClC}_6\text{H}_4, 2\text{-furyl}, i\text{-Pr}, n\text{-Bu}, \text{Cy}, \text{Et}, c\text{-Pr}, \text{BnCH}_2, (E)\text{-(TBS)CH=CH}$

Scheme 51 Aldol reactions of ethyl diazoacetate to aldehydes.

aromatic ones. Using enantiomeric ligand (*R,R*)-**170** under the same conditions allowed the corresponding enantiomeric products (*R*)-**185** to be formed with comparable yields (49–92%) and enantioselectivities (90–>99% ee), as shown in Scheme 51. The synthetic utility of this methodology was demonstrated through the conversion of the products into chiral 1,2-diols bearing a tertiary alcohol through the addition of carbon nucleophiles.⁸⁹

In 2013, Ishihara *et al.* reported the use of a very simple catalyst system composed of a combination of MgBu_2 and (*R*)-BINOL in toluene at $-20\text{ }^\circ\text{C}$ to promote a highly regio- and enantioselective 1,2-hydrophosphonylation of α,β -unsaturated ketones with dialkyl phosphites.⁷⁹ As shown in Scheme 52, the reaction of variously substituted benzalacetones **187** with dimethyl and diethyl phosphites **188** led to the corresponding chiral tertiary allylic alcohols **189** in moderate to quantitative yields (59–96%) and good enantioselectivities (81–86% ee). Both aromatic and heteroaromatic moieties (Ar) in benzalacetones were tolerated. The synthetic utility of this novel practical methodology was demonstrated in the conversion of some products into chiral five-membered oxaphospholanols which are analogues of bioactive materials with anticholinesterase properties.

In addition to enantioselective magnesium-catalyzed 1,2-nucleophilic additions to carbonyl compounds, related reactions performed with imines as electrophilic partners have also been recently developed. For example, Antilla *et al.* have reported a novel methodology to add diphenylphosphine oxide **166a** to imines with generally moderate to quantitative yields (65–98%) and enantioselectivities of up to 99% ee.⁹⁰ The process was catalyzed with only 5 mol% of chiral phosphate magnesium complex **190** in acetonitrile at room temperature, as shown in Scheme 53. Two differently *N*-substituted imines were investigated under these conditions. Benzhydryl imines **191** provided the corresponding chiral α -amino phosphine oxide products **192** in moderate to excellent yields (65–97%) and enantioselectivities (48–96% ee). The best results were achieved with (hetero)aromatic imines (93–97% yield, 89–96% ee) while aliphatic imines provided lower yields (65–92%) and enantioselectivities (48–86% ee). Another class of imines **193** derived from 5*H*-dibenzo[*a,d*]cyclohepten-5-amine was also investigated under the same catalytic conditions but in di-

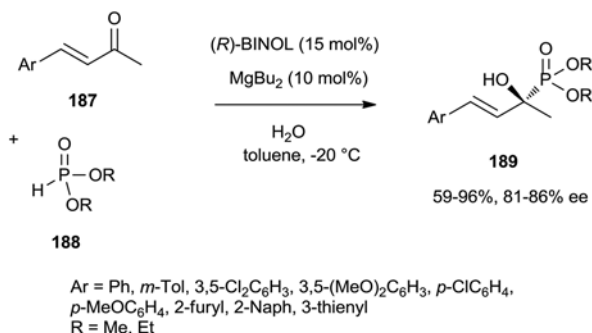


Scheme 53 Additions of diphenylphosphine oxide to aldimines.

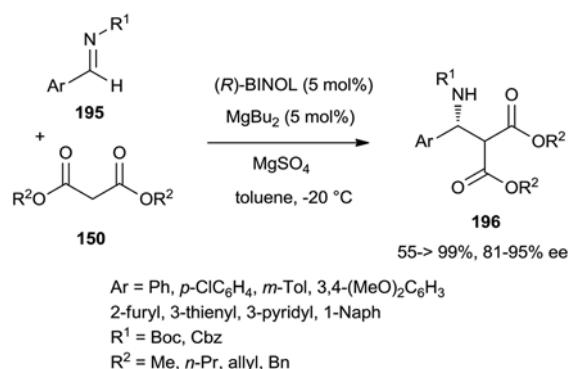
chloromethane instead of acetonitrile as solvent (Scheme 53). Most substrates led to the corresponding products **194** with comparable yields (72–98%) and slightly better enantioselectivities (74–99% ee) than those derived from benzhydryl imines with the exception of *para*-fluorophenyl-substituted imine, which afforded the corresponding product with only 16% ee.

The Mannich reaction,⁹¹ occurring between a Schiff base and a nucleophile, constitutes one of the most powerful reactions for the construction of nitrogen-containing products.⁹² Over the past two decades, the catalytic asymmetric Mannich reaction,⁹³ which allows biologically important chiral β -amino carbonyl compounds and derivatives to be easily prepared,⁹⁴ has been widely investigated on the basis of using either chiral organometallic catalysts or organocatalysts.⁹⁵ In 2010, Ishihara *et al.* developed the first enantioselective magnesium-catalyzed Mannich-type reaction of various dialkyl malonates **150** with (hetero)aryl aldimines **195**.⁹⁶ Remarkably, this very simple process employed a combination of MgBu_2 and (*R*)-BINOL as a catalyst system in toluene at $-20\text{ }^\circ\text{C}$, as shown in Scheme 54. It afforded a series of chiral amines **196** in almost quantitative yields (91–>99%) and high enantioselectivities (87–95% ee) in most cases.

The asymmetric hydrocyanation of imino compounds, known as the Strecker reaction, represents an indispensable synthetic procedure for producing chiral α -amino nitriles, which constitute highly important precursors of natural and

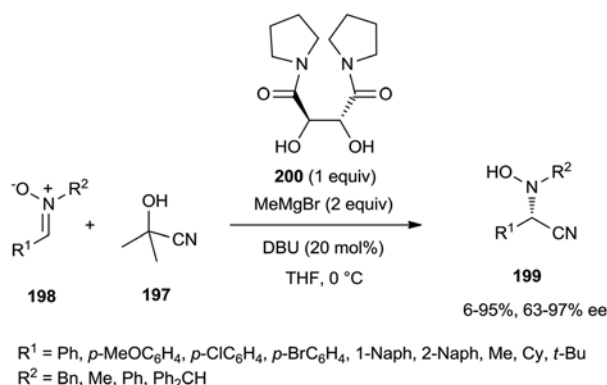


Scheme 52 1,2-Addition of dialkyl phosphites to benzalacetones.

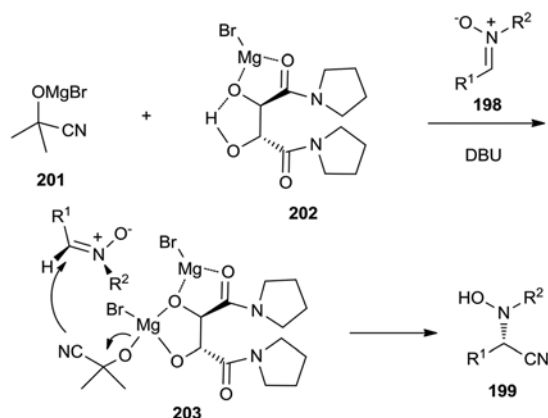


Scheme 54 Mannich-type reaction of aldimines with dialkyl malonates.

non-natural α -amino acids, as well as various useful building blocks in synthesis.⁹⁷ Numerous variants of this reaction have been reported based on the use of HCN or TMSCN as the cyanide source. Due to their toxicity, volatility and hazardous handling, alternative cyanide sources have been developed such as acetone cyanohydrin **197**. In particular, this reagent was used in magnesium-mediated asymmetric Strecker-type reactions of nitrones **198** to give the corresponding chiral α -amino nitrile derivatives **199**.⁹⁸ As shown in Scheme 55, the



possible mechanism:



Scheme 55 Strecker-type reaction of nitrones.

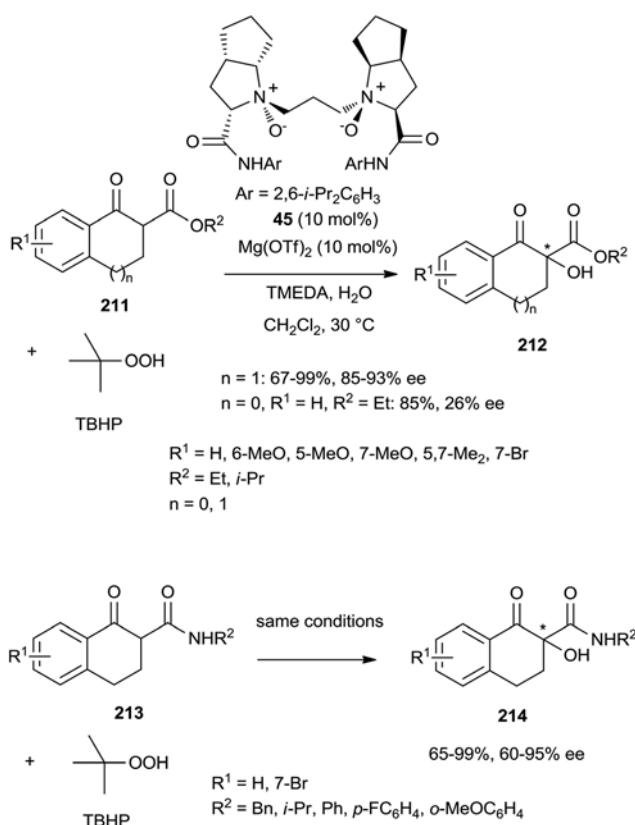
process was mediated by a magnesium complex derived from one equivalent of tartramide **200** and two equivalents of MeMgBr in THF at 0 °C in the presence of DBU as a base. Various *N*-benzyl nitrones were compatible with the process. While *N*-benzyl aryl nitrones (R¹ = aryl, R² = Bn) provided higher enantioselectivities (85–96% ee vs. 73–87% ee) than *N*-benzyl alkyl nitrones (R¹ = alkyl, R² = Bn), the latter gave higher yields than the former (90–95% vs. 63–89%). The influence of the substituents on the nitrogen of the nitrones was also investigated, showing that an *N*-benzyl nitrone (R² = Bn) led to the corresponding product in 58% yield and 96% ee whereas an *N*-methyl (R² = Me) and an *N*-phenyl (R² = Ph) nitrones reacted with lower yields (6–47%) and enantioselectivities (63–72% ee). The authors have proposed a possible mechanism depicted in Scheme 55 in which bromo-magnesium salts **201** and **202** were formed when acetone cyanohydrin **197** was treated with MeMgBr₂ and chiral tartramide **200**. In the presence of DBU, deprotonation of **202** occurred to give tartramide–magnesium ate complex **203**, to which the nitrone coordinated. A subsequent transcyanation proceeded from the *Re*-face of the nitrone to afford the final (*S*)-product **199**.

7. Magnesium-catalyzed α -functionalizations of carbonyl compounds

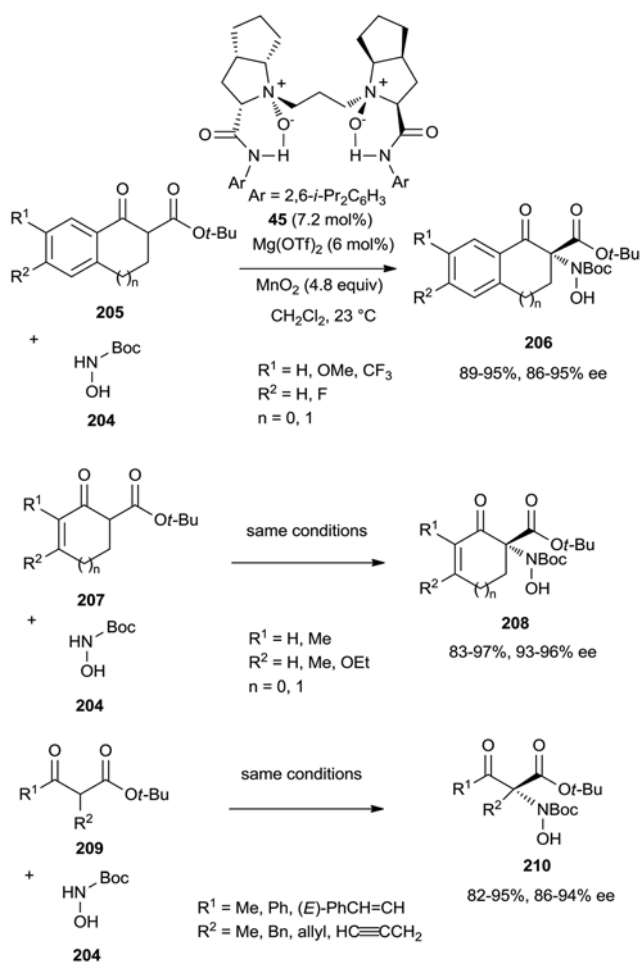
The electrophilic amination reaction constitutes a direct method to stereoselectively form C–N bonds, a fundamental process in both organic chemistry and biochemistry. In particular, the asymmetric α -amination of carbonyl compounds is an efficient route to important chiral α -amino acid derivatives.⁹⁹ Consequently, much progress has been made in the enantioselective α -amination of carbonyl compounds, such as aldehydes, ketones, α -ketoesters, α -cyano esters, and other compounds, using azodicarboxylates as the nitrogen source since the pioneering work reported by Evans and Nelson in 1997.¹⁰⁰ It dealt with the reaction between *N*-acyloxazolidinones and di-*tert*-butyl azodicarboxylate to give the corresponding chiral hydrazides in remarkable enantioselectivities (96%–99% ee) by using a chiral bis(sulfonamide) ligand. More recently, Yamamoto and Maji reported the first example of a Lewis acid-catalyzed asymmetric hydroamination of β -ketoesters with nitrosocarbonyl compounds generated *in situ*.¹⁰¹ Among the various Lewis acids investigated, including Ni(OTf)₂, Zn(OTf)₂, Ca(OTf)₂, Sr(OTf)₂, Sc(OTf)₃, Cu(OTf)₂, Mg(ClO₄)₂, Mg(NTf)₂ and Mg(OTf)₂, the latter allowed the best results to be achieved when combined with chiral *N,N'*-dioxide ligand **45** in dichloromethane at 23 °C. Under these conditions, the reaction of the nitrosocarbonyl compound, *in situ* generated from *N*-Boc-hydroxylamine **204** through oxidation with MnO₂, with cyclic β -ketoesters **205** bearing a 1-indanone (*n* = 0) or a 1-tetralone (*n* = 1) subunit led to the corresponding chiral highly substituted quaternary β -keto amino acid derivatives **206** in both high yields (89–95%) and enantioselectivities

(86–95% ee), as shown in Scheme 56. Remarkably, the regioselectivity (N- vs. O-attack) was uniformly high for all substrates (>20:1). The scope of the process was extended to cyclic β -ketoesters **207** possessing sensitive cyclohexene and cyclopentene subunits which also delivered the corresponding α -aminated products **208** in high yields (83–97%) with even higher enantioselectivities (93–96% ee). Furthermore, very good results were obtained with a range of acyclic β -ketoesters **209** which led to the corresponding amines **210** in high yields (82–95%) and enantioselectivities (86–94% ee). Even the presence of labile functionalities, such as allyl and propargyl groups, did not affect the results, thus demonstrating the mildness of the oxidation/catalytic system.

In 2013, Feng *et al.* described a rare example of asymmetric magnesium-catalyzed α -hydroxylation reactions.¹⁰² As shown in Scheme 57, the reaction involved the α -hydroxylation of β -ketoesters with *tert*-butyl hydroperoxide (TBHP) as the oxidant performed in the presence of 10 mol% of $\text{Mg}(\text{OTf})_2$ and chiral *N,N'*-dioxide ligand **45** in dichloromethane at 30 °C with TMEDA as additive. When 1-tetralone-derived β -ketoesters **211** ($n = 1$) were used, the corresponding tertiary alcohols **212** were obtained in moderate to quantitative yields (67–99%) and



Scheme 57 α -Hydroxylations of β -ketoesters and β -ketoamides with *tert*-butyl hydroperoxide.

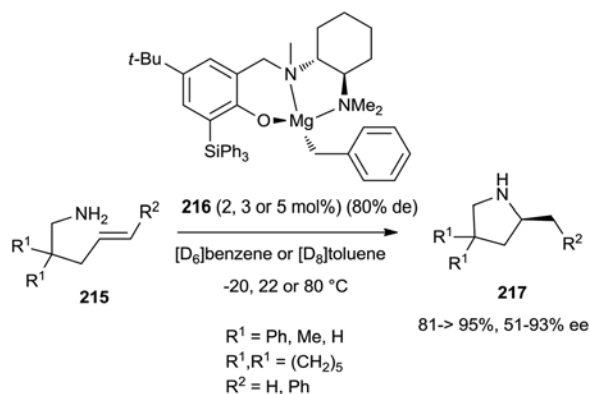


Scheme 56 α -Amination of β -ketoesters with *N*-Boc-hydroxylamine.

high enantioselectivities (85–93% ee). Various electron-donating as well as electron-withdrawing substituents (R^1) were tolerated on the phenyl ring of the tetralone. On the other hand, the reaction of a 1-indanone-derived β -ketoester ($n = 0$) provided a much lower enantioselectivity (26% ee) albeit with good yield (85%). The scope of the methodology was extended to related 1-tetralone-derived β -ketoamides **213** which afforded the corresponding products **214** in moderate to quantitative yields (65–99%) and enantioselectivities (60–95% ee), as shown in Scheme 57. The best enantioselectivities (92–95% ee) were achieved with amides bearing an aliphatic substituent on the nitrogen atom (R^2) while lower enantioselectivities (60–90% ee) were obtained in the reaction of amides bearing aromatic substituents. In both cases, the yields were comparable (71–99% for the former vs. 65–99% for the latter). The synthetic utility of this simple novel methodology was demonstrated in the synthesis of an important precursor of the antibiotic daunomycin.

8. Magnesium-catalyzed hydroamination reactions

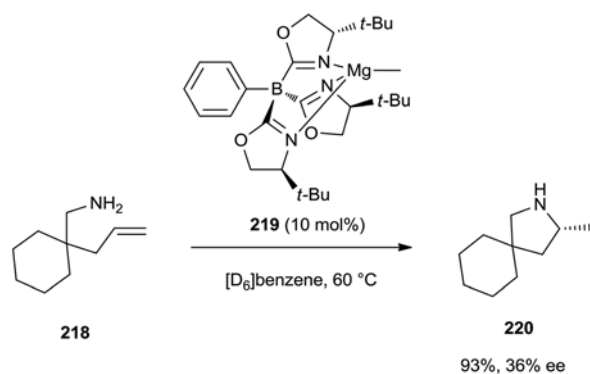
The application of alkaline earth metal complexes as substitutes for transition-metal catalysts in alkene hydrofunctional-



Scheme 58 Hydroamination of aminoalkenes.

zations has drawn increasing attention in recent years.¹⁰³ However, only rare examples dealing with asymmetric versions have been reported. Among them, Hultsch *et al.* have developed enantioselective intramolecular magnesium-catalyzed hydroamination of aminoalkenes **215** performed in the presence of preformed chiral catalyst **216** derived from a chiral phenoxyamine.¹⁰⁴ As illustrated in Scheme 58, the corresponding chiral pyrrolidines **217** were formed in high yields (81–95%) and moderate to high enantioselectivities (51–93% ee). The lowest enantioselectivity of 51% ee was observed in the case of a non-substituted aminoalkene ($\text{R}^1 = \text{R}^2 = \text{H}$) requiring a reaction temperature of 80 °C while enantioselectivities of 74–93% ee were achieved for substituted substrates ($\text{R}^1 \neq \text{H}$) generally reacting below room temperature (–20 °C).

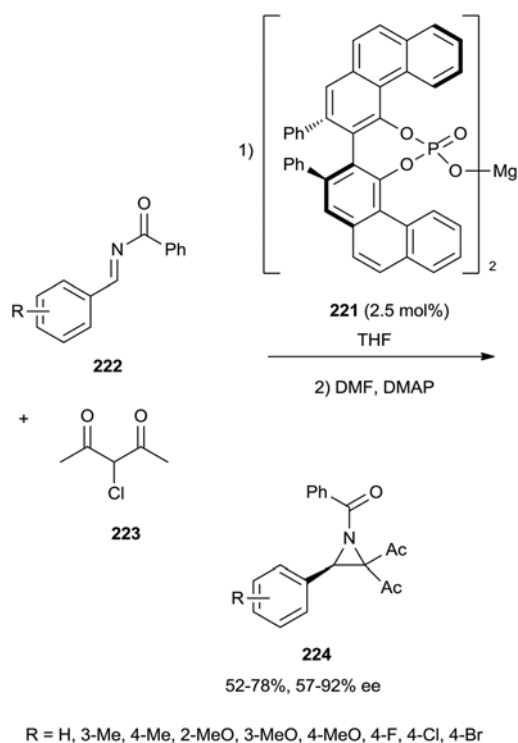
Earlier, enantioselectivities not exceeding 36% ee were reported by using other chiral magnesium complexes. For example, Sadow *et al.* previously developed asymmetric hydroamination of C-(1-allyl-cyclohexyl)-methylamine **218** in the presence of chiral tris(oxazolinyl)borate magnesium complex **219** to give the corresponding bicyclic amine **220** in 93% yield and 36% ee (Scheme 59).¹⁰⁵



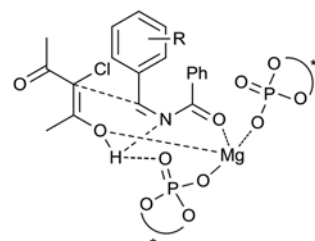
Scheme 59 Hydroamination of an aminoalkene.

9. Magnesium-catalyzed miscellaneous reactions

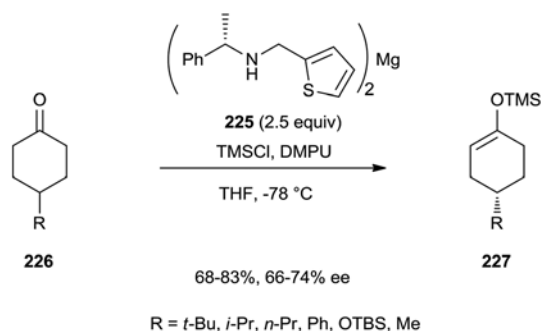
In 2011, Antilla *et al.* demonstrated the utility of (*R*)-VAPOL-derived phosphate magnesium catalyst **221** to promote an enantioselective aza-Darzens aziridination reaction between *N*-benzoyl aldimines **222** and α -chloro-1,3-diketone **223**.¹⁰⁶ The corresponding chiral aziridines **224** were obtained in good yields (52–78%) and moderate to high enantioselectivities (57–92% ee), as shown in Scheme 60. A theoretical study of the active catalytic species was undertaken by the authors to explain the stereoselectivity of the process. It showed coordination of the magnesium to the carbonyl groups of the imine and diketone's enol form, as shown in the transition state depicted in Scheme 60. Additionally, the enol could hydrogen bond to an oxygen atom of the catalyst. Indeed, the latter could simultaneously stabilize the nucleophile and electro-



proposed transition state:



Scheme 60 Aza-Darzens aziridination reaction.

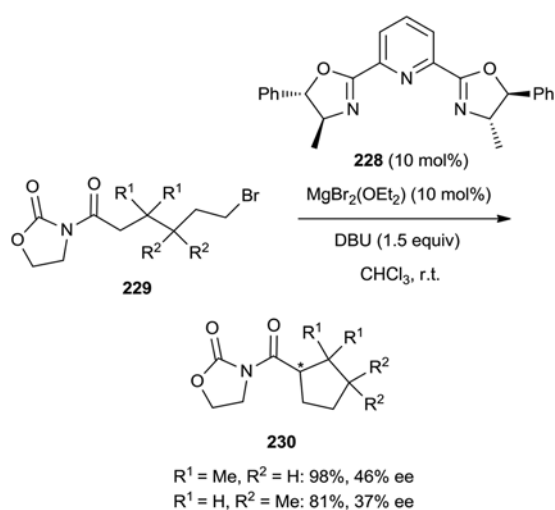


Scheme 61 Deprotonation reaction of 4-substituted cyclohexanones.

phile, while providing the chiral requirement for asymmetric induction.

In 2011, Kerr *et al.* reported the synthesis of novel chiral secondary amines, incorporating a five- or six-membered heterocycle, which were used to prepare new chiral magnesium bisamide complexes.¹⁰⁷ The latter were investigated in the asymmetric deprotonation of prochiral ketones. For example, a superstoichiometric quantity of thiophene-derived magnesium complex **225** was applied to the asymmetric deprotonation of 4-substituted cyclohexanones **226**, which afforded in the presence of TMSCl the corresponding chiral trimethylsilyl ethers **227** in moderate to good yields (68–83%) and enantioselectivities (66–74% ee), as shown in Scheme 61.

While numerous enolate transformations, including Michael, Mannich, aldol and α -functionalization reactions, may be carried out under catalytic enantioselective conditions, the simple alkylation with an unactivated alkyl halide is often performed using stoichiometric amounts of metal enolates. In the past few years, chiral catalysts have been successfully applied to these reactions including magnesium chiral complexes. For example, a catalyst *in situ* generated from chiral pybox **228** and $\text{MgBr}_2(\text{Et}_2\text{O})$ was used in chloroform at room



Scheme 62 Alkylation of oxazolidinone bromoalkanoate imides.

temperature by Gleason *et al.* in the asymmetric intramolecular alkylation of oxazolidinone bromoalkanoate imides **229** performed in the presence of DBU as a base.¹⁰⁸ As shown in Scheme 62, the process afforded the corresponding functionalized cyclopentanes **230** in high yields (81–98%) albeit with moderate enantioselectivities (37–46% ee).

10. Conclusions

Even if transition metal chemistry still constitutes the heart of catalysis, environmentally friendly chemical processes are now strongly preferred from the point of view of green sustainable chemistry. In this context, the use of readily available, cheap, and non-toxic alkaline earth metal catalysts, such as magnesium complexes, is highly promising owing to their milder Lewis acidity in comparison with traditional transition metals. This review illustrates how much enantioselective magnesium catalysis has contributed to the development of a wide variety of enantioselective highly efficient ecological and economical reactions. It updates the major progress in the field of enantioselective transformations promoted by chiral magnesium catalysts, illustrating the power of these mild Lewis acid catalysts to provide many novel reactions. Especially in the last decade, a variety of chiral magnesium complexes derived from bis(oxazoline), N,N' -dioxides, Schiff bases, cinchona alkaloids, BINOL derivatives, and phosphates, among other ligands, have become catalysts of the first choice for many types of asymmetric reactions generally performed under mild reaction conditions. Among them, a number of them have been reported for the first time, including cycloadditions, domino and tandem reactions, ring-opening reactions, Michael reactions, 1,2-nucleophilic additions to carbonyl compounds and imines, α -functionalizations of carbonyl compounds, hydroaminations of alkenes, *etc.*, allowing many chiral cyclic as well as acyclic products to be achieved in generally remarkable enantioselectivities. For example, in the area of cycloadditions Ding has reported the first asymmetric magnesium-catalyzed hetero-Diels–Alder reactions of aldehydes and Danishefsky's diene with 99% ee. Comparable excellent enantioselectivities were also achieved by Feng in the first catalytic asymmetric hetero-Diels–Alder reaction of Brassard's type dienes and isatins. Other than Diels–Alder cycloadditions have encountered success on the basis of asymmetric magnesium catalysis. For example, enantioselectivities of 94% ee were obtained by Wang in the first enantioselective 1,3-dipolar cycloaddition of 3-isothiocyanato oxindoles with alkynyl ketones. Moreover, several asymmetric magnesium-catalyzed carbonyl ene reactions of trifluoropyruvate with alkenes, 1,2-dicarbonyl compounds such as isatins with alkyl enol ethers, or β,γ -unsaturated α -ketoesters with 5-methyleneoxazolines have been reported for the first time by Feng, all providing up to 99% ee. Furthermore, it is only recently that the first enantioselective magnesium-catalyzed domino reactions have been developed, such as Michael-initiated domino reactions reported by Feng with 96% ee. A range of other types of highly

enantioselective domino reactions have also been developed, including domino Mannich/cyclization reactions with 95–99% ee by Willis and Shibasaki, domino aldol/cyclization reactions by Shibasaki with 99% ee, and domino γ -deprotonation/Michael/cyclization reactions with 99% ee by Wang, among others. Several multicatalyzed domino reactions have also been very recently described, such as those by Scheidt and Gong, among others, in which magnesium complexes interact with organocatalysts, such as phosphoric acids or N-heterocyclic carbene catalysts. In addition, highly efficient tandem ring-opening/ring-closing reactions have been described by Wang with >99% ee. Another type of highly enantioselective magnesium-catalyzed tandem reaction was developed by this author, involving 3-isothiocyanato oxindoles and *N*-(2-picolinoyl)aziridines as substrates and constituting the first asymmetric formal [3 + 3] cycloaddition with aziridines. In the last decade, a range of chiral magnesium catalysts derived from different types of ligands, including *N,N'*-dioxides, cinchona alkaloids, amino alcohols, phosphates and BINOL derivatives, have also been successfully applied to ring-opening reactions of *meso*-aziridines with a variety of nucleophiles, yielding many valuable chiral nitrogen-containing products. In the area of Michael additions, many interesting results have been recently reported. Thus, heterogeneous Michael additions of malonates to α,β -unsaturated ketones were achieved with 96% ee by Kantam. Moreover, Michael additions of alkenylboronic acids to indole-appended α,β -unsaturated ketones were developed with 99% ee by May, Michael additions of a α,β -unsaturated γ -butyrolactam to α,β -unsaturated ketones and α,β -unsaturated *N*-acylpyrroles with 98% ee by Wang, and Michael additions of diaryl phosphine oxides to α,β -unsaturated esters with 96% ee by Ishihara, along with a rare example of dearomatization of naphthols described by Wang which was based on a catalytic asymmetric conjugate addition performed with 98% ee. Other types of reactions, such as various 1,2-nucleophilic additions to carbonyl compounds and imines, have been successfully described by using chiral magnesium catalysts. Among them are aldol reactions of ethyl diazoacetate with aldehydes developed with >99% ee by Trost, a novel methodology reported by Antilla to add diphenylphosphine oxide to imines with up to 99% ee, as well as the first enantioselective magnesium-catalyzed Mannich-type reactions of various dialkyl malonates with (hetero)aryl aldimines achieved with 95% ee by Ishihara. Miscellaneous reactions have also been recently developed on the basis of magnesium asymmetric catalysis, such as α -functionalizations of carbonyl compounds. For example, Yamamoto and Maji have reported the first example of a Lewis acid-catalyzed asymmetric hydroamination of β -ketoesters with nitrosocarbonyl compounds generated *in situ*, which provided up to 96% ee. All these excellent results have demonstrated the remarkable efficiency of green magnesium complexes to be substitutes of transition-metal catalysts in asymmetric catalysis, owing to their mild Lewis acidity, opening the way for developing new catalytic systems to perform reactions, such as C–C bond formations, C–heteroatoms bond formations or C–H

functionalizations under more environmentally friendly conditions. Indeed, with the environmentally benign properties of magnesium as an inexpensive, non-toxic, and abundant metal, the asymmetric magnesium catalysis is expected to become an unavoidable tool in the near future.

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