The Use of Domino Reactions for the Synthesis of Chiral Rings

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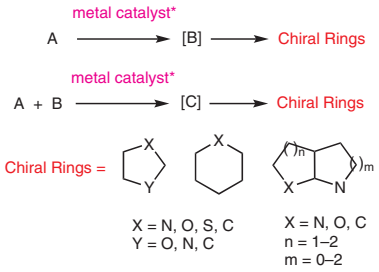


Abstract This short review highlights the recent developments reported in the last four years on the asymmetric construction of chiral rings based on enantioselective domino reactions promoted by chiral metal catalysts.

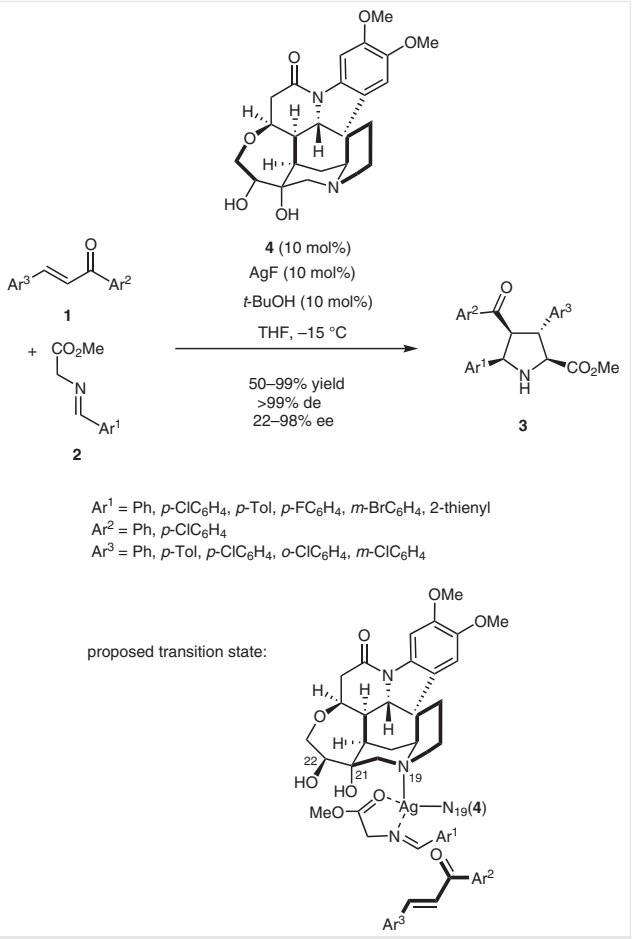
1 Introduction

In the last decades, asymmetric metal catalysis[1] has been intensively combined with various types of domino reactions[2] to give simple and economic access to many highly functionalized and complex chiral molecules.[3] The goal of this short review is to highlight the advances made on the use of domino reactions catalyzed by chiral metals to synthesize chiral rings published in the last four years. It is divided into five parts, outlining successively the formation of one ring containing one nitrogen atom, one ring containing one oxygen/sulfur atom, one ring containing several heterocyclic atoms, one carbon ring, and two rings through enantioselective metal-catalyzed domino reactions.

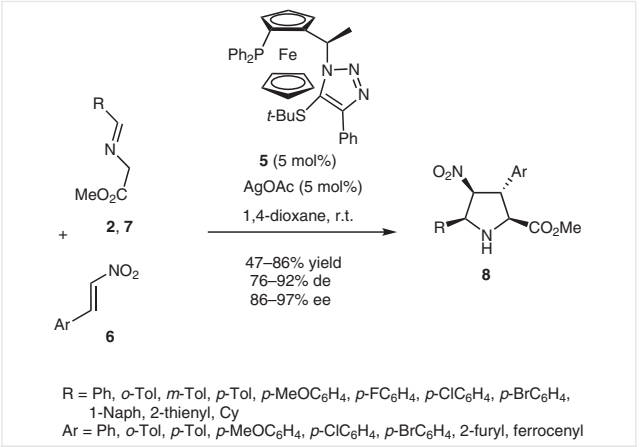
2 Formation of One Ring Containing One Nitrogen Atom

2.1 Five-Membered Rings

Many densely functionalized chiral cyclic molecules have been easily synthesized through a variety of highly efficient enantioselective metal-catalyzed domino reactions. The frameworks of a wide range of natural products contain a five-membered ring.[4] Chiral silver complexes have been shown to efficiently catalyze various types of domino reactions.[5] For example, in 2016, Oh and co-workers described the synthesis of chiral pyrrolidines **3** based on the reaction of α,β-unsaturated ketones **1** with imino esters **2** catalyzed by a catalyst system composed of AgF and chiral 1,2-diol ligand **4**.[6] The chiral five-membered products **3** were obtained from successive Michael and Mannich reactions with complete diastereoselectivity (>99% de), good to quantitative yields (50–99%) and variable enantioselectivities (22–98% ee) (Scheme 1). In the possible transition state depicted in Scheme 1, the silver atom coordinates the two ligands through the N-19 tertiary amine.



Scheme 1 Synthesis of pyrrolidines through an Ag-catalyzed domino reaction



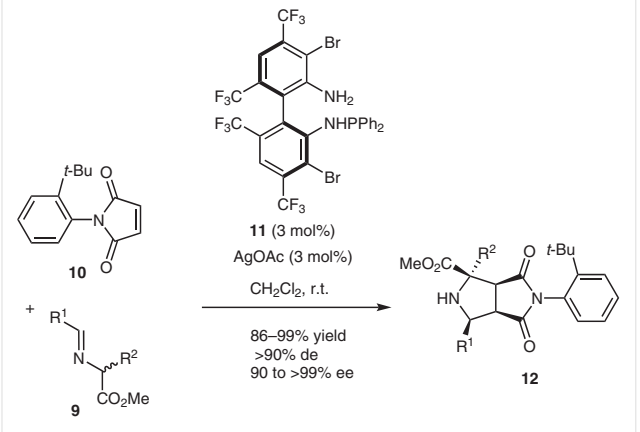
Scheme 2 Synthesis of pyrrolidines through an Ag-catalyzed domino reaction

In 2016, Fukuzawa et al. employed an alternative chiral silver complex derived from AgOAc and ferrocenyl chiral ligand **5** to promote asymmetric domino reactions between imino esters **2**/**7** and nitroalkenes **6**.[7] As illustrated in Scheme 2, chiral pyrrolidines **8** were obtained in good yields (47–86%), diastereoselectivities (76–92% de) and enantioselectivities (86–97% ee) from sequential Michael and aza-Henry reactions.

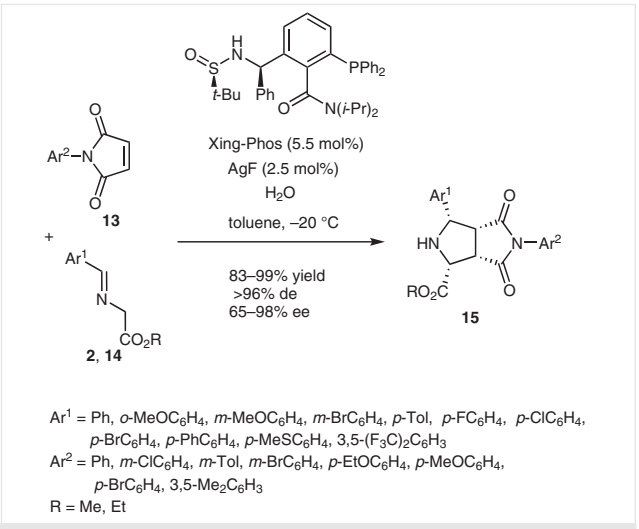
Chiral bicyclic pyrrolidines **12** were synthesized in 2016 by Wang et al. through domino reactions of imino esters **9** with *N*-(2-*t*-butylphenyl)maleimide (**10**) using a combination of AgOAc and chiral phosphine ligand **11** as the catalyst system (Scheme 3).[8] Products **12**, arising from a Michael addition followed by a Mannich reaction, were obtained in homogeneous high yields (86–99%), diastereoselectivities (>90% de) and enantioselectivities (90 to >99% ee).

Similar reactions were also investigated in 2016 by Xia and Xu in the presence of another catalyst system composed of AgF and Xing-Phos ligand.[9] In this case, the reaction of *N*-arylmaleimides **13** with aromatic imino esters **2** or **14** afforded the corresponding bicyclic pyrrolidines **15** as single diastereomers (>96% de) in high yields (83–99%) and enantioselectivities (65–98% ee) (Scheme 4).

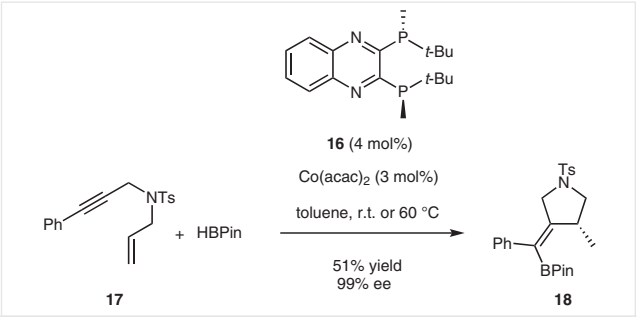
Along with chiral silver catalysts, various chiral cobalt complexes have also been recently investigated as promoters in domino reactions. The use of cobalt catalysts is advantageous because of their low toxicity, their low cost and their ability to adopt various reaction pathways.[10] For example, a chiral cobalt catalyst generated in situ from $Co(acac)_2$ and chiral biphosphine ligand **16** was employed in 2017 by Ge et al. in the synthesis of enantiopure pyrrolidine **18** through the domino reaction of nitrogen-tethered 1,6-enyne **17** with pinacolborane (Scheme 5).[11] The process involved an anti-Markovnikov hydroboration followed by a cyclization.



Scheme 3 Synthesis of bicyclic pyrrolidines through an Ag-catalyzed domino reaction



Scheme 4 Synthesis of other bicyclic pyrrolidines through an Ag-catalyzed domino reaction



Scheme 5 Synthesis of pyrrolidine **18** through a Co-catalyzed domino reaction

While using chiral ligand **16** resulted in an anti-Markovnikov hydroboration of the alkyne moiety of substrate **17** (Scheme 5), the same authors showed that the involvement of chiral ligand **19** combined with the same pre-catalyst led to chiral pyrrolidine **20** with 92% ee and 66% yield, arising from a Markovnikov hydroboration of the alkyne group of the nitrogen-tethered 1,6-enyne **17** with pinacolborane (Scheme 6).[11]

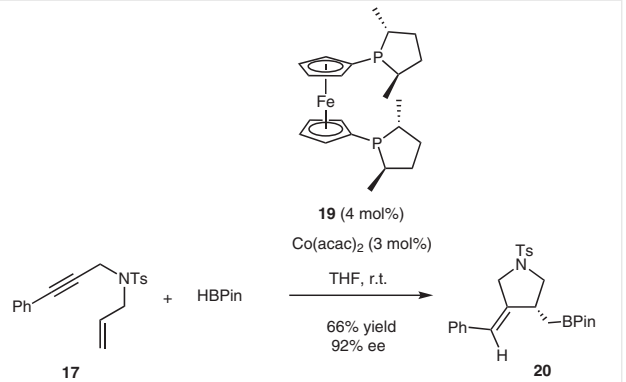
In 2018, Fan et al. developed an unprecedented synthesis of chiral 3,4-dimethylene-pyrrolidines possessing an oxa/azabenzonorbornadiene moiety based on the asymmetric domino reaction of oxa/azabenzonorbornadienes **21** with 1,6-enynes **22**.[12] The process, employing a catalyst system composed of $[Rh(cod)_2]BF_4$ and chiral diphosphine ligand (*R*)-An-SDP, provided enantiopure (97–99% ee) 3,4-dimethylene-pyrrolidines **23** in good yields (44–89%). A possible mechanism for the reaction is depicted in Scheme 7. Complex **24**, arising from the coordination of the rhodium catalyst to 1,6-enyne **22**, underwent a cyclization to afford intermediate **25**. Next, a β-hydride elimination led to intermediate **26** that coordinates to substrate **21** to give intermediate **27**. Subsequent insertion of the alkene into the Rh–C bond led to intermediate **28**, which finally delivered product **23**.

Palladium has been previously applied to promote many enantioselective domino transformations.[13] In 2017, Jia et al. employed asymmetric palladium catalysis to develop a method for the synthesis of chiral 2,3-disubstituted indolines **32**.[14] The process involved the reaction between indoles **29** and terminal alkynes **30** promoted by a chiral palladium catalyst derived from $Pd(dba)_2$ and chiral phosphoramidite ligand **31**. Complex molecules **32** were obtained through consecutive Heck and Sonogashira reactions as almost single diastereomers (>90% de) with high enantioselectivities (79–94% ee) and good yields (50–93%) (Scheme 8).

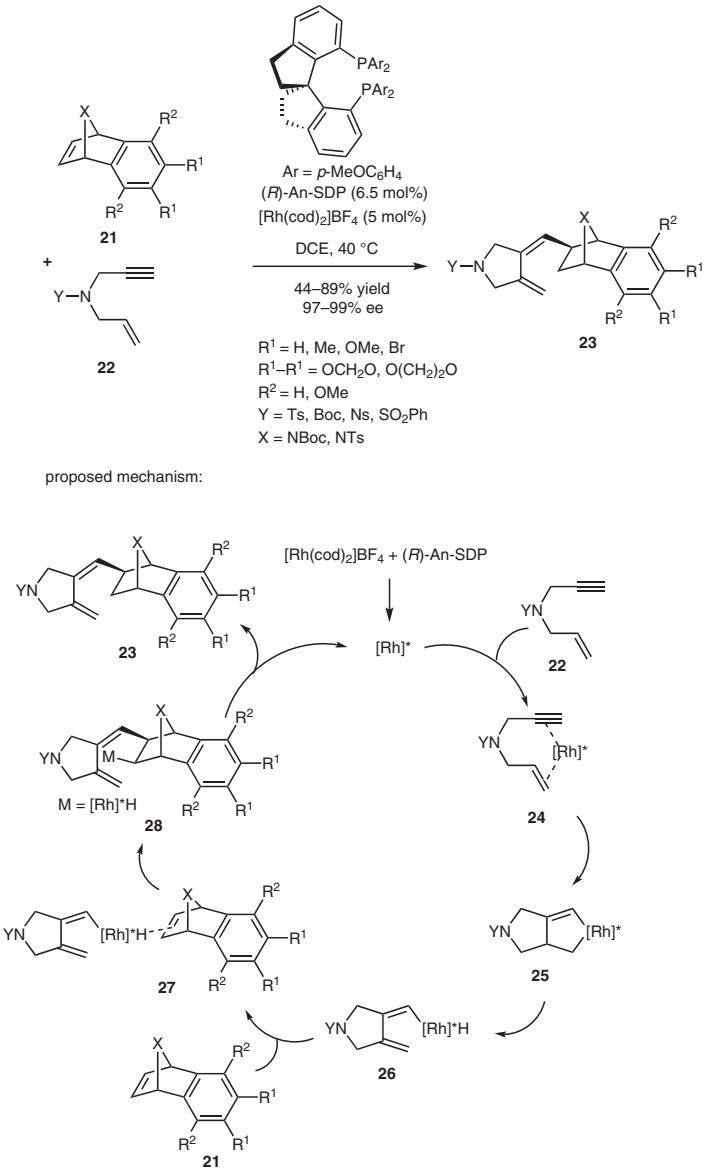
Chiral nickel catalysts[15] have also been successfully applied to promote enantioselective domino processes.[16] For example, the synthesis of chiral bis-heterocycles **35** was developed by Kong et al. in 2018 through enantioselective nickel-catalyzed domino reactions of alkenes **33** with aryl bromides **34**.[17] As presented in Scheme 9, the reactions proceeded with excellent enantioselectivities (94–98% ee), affording the products in good yields (40–81%). The process employed a combination of $Ni(cod)_2$ and chiral ferrocenyl phosphine ligand **36** as the catalyst system leading to a cyclization followed by a cross-coupling reaction.

In 2018, Feng and Liu reported an example of bimetallic relay catalysis applied to the synthesis of chiral 2,2,3-trisubstituted indolines.[18] As shown in Scheme 10, the catalyst system consisted of a combination of $Sc(OTf)_3$, chiral *N*,*N*′-dioxide ligand **37** and $Rh_2(OAc)_4$, which promoted the intramolecular trapping of ammonium ylides generated from α-diazoketones **38** and 2-aminophenyl-substituted α,β-unsaturated ketones **39**. This domino process yielded a range of chiral indolines **40** as single diastereomers (>90% de) in good to excellent yields (66–99%) and enantioselectivities (73–99% ee).

Later, in 2019, the same authors employed related chiral *N*,*N*′-dioxide ligand **41** combined with $Mg(OTf)_2$ to promote



Scheme 6 Synthesis of pyrrolidine **20** through a Co-catalyzed domino reaction



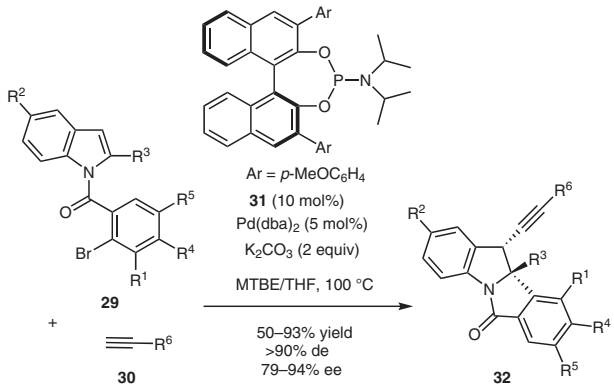
Scheme 7 Synthesis of 3,4-dimethylene-pyrrolidines through a Rh-catalyzed domino reaction

the asymmetric synthesis of spiroindolines **42**.[19] The latter were obtained in good to excellent yields (50–99%), diastereoselectivities (50 to >90% de) as well as enantioselectivities (70–97% ee) via the ring-opening reaction of the corresponding *meso*-aziridines **43** with C2-substituted 2-isocyanoethylindoles **44** followed by intramolecular cyclization (Scheme 11).

2.2 Six-Membered Rings

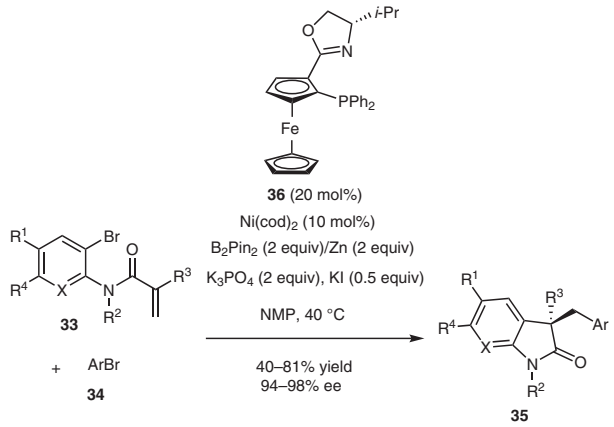
In 2016, chiral tricyclic indolines **48** were synthesized by Reisman et al. through the one-step reaction of amidoacrylate **45** with indoles **46** promoted by a combination of $ZrCl_4$ with chiral BINOL-derived ligand **47**.[20] As illustrated in Scheme 12, the process occurred with high enantioselectivities (81–91% ee), moderate diastereoselectivities (50–66% de) and good yields (66–93%). The domino reaction evolved through successive Michael addition, protonation and aza-Prins reaction.

Asymmetric domino reactions can also be promoted by chiral green copper catalysts.[21] For example, in 2016, chiral 5,6-dihydrocanthin-4-ones **51** were prepared in good yields (57–92%) and enantioselectivities (68 to >99% ee) from a domino reaction promoted by a chiral copper catalyst derived from CuI and chiral proline derivative **50**.[22] The reaction occurred between terminal alkynes **30** and 1-formyl-9*H*-β-carbolines **49** (Scheme 13). The mechanism involved



R^1 = H, Me
R^2 = H, *i*-Pr, Me, Cl, F
R^3 = Me, Ph, *p*-$F_3CC_6H_4$, 2-furyl, Et, CO_2Me
R^4 = H, OMe
R^5 = H, OMe, Me, F
R^6 = Ph, *p*-$MeOC_6H_4$, *p*-Tol, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-(Pent)C_6H_4, *p*-PhC_6H_4, *p*-$F_3CC_6H_4$, *p*-(PentO)C_6H_4, *p*-(*t*-Bu)C_6H_4, *p*-$(MeO_2C)C_6H_4$, *p*-NCC_6H_4, *p*-$NCCH_2C_6H_4$, *p*-$(F_3CO)C_6H_4$, *p*-$(OHC)C_6H_4$, *m*-Tol, *m*-$MeOC_6H_4$, *m*-FC_6H_4, *m*-ClC_6H_4, *o*-Tol, *o*-$F_3CC_6H_4$, *o*-ClC_6H_4, *o*-FC_6H_4, 2-Naph, 2-thienyl, 1-thienyl, 3-pyridyl, 2-ferrocenyl, $CH(OEt)_2$, *t*-Bu, $PhthNCH_2$, $Cl(CH_2)_4$, $HO(CH_2)_4$, $HO(CH_2)_2$, TMS, $(Me)C{=}CH_2$

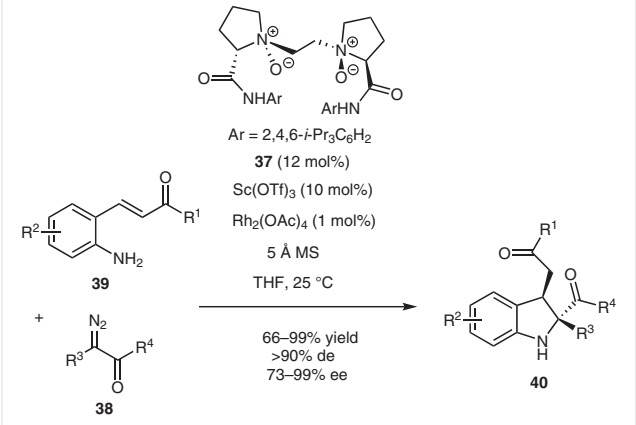
Scheme 8 Synthesis of 2,3-disubstituted indolines through a Pd-catalyzed domino reaction



X = CH, C(Me), N
R^1 = H, Me, F
R^2 = Me, Bn
R^3 = Me, Bn, *n*-Hex, *i*-Pr, $MeOCH_2$
R^4 = H, Cl, Me, Cl, OMe
Ar = Ph, *p*-Tol, 3,4,5-$MeO_3C_6H_2$

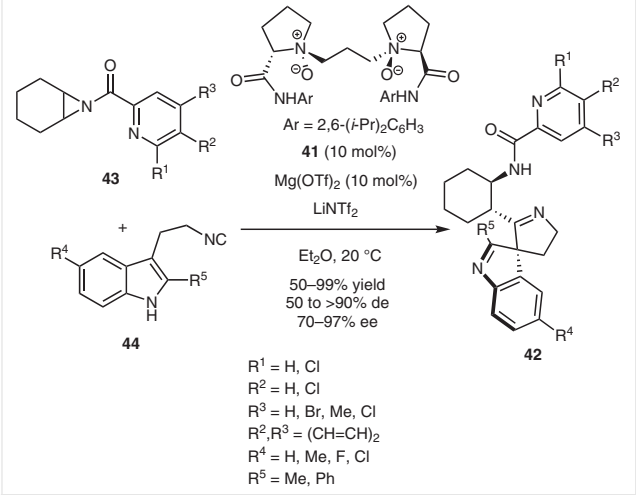
Scheme 9 Synthesis of bicyclic 2-pyrrolidinones through a Ni-catalyzed domino reaction

the formation of iminium species **52** from aldehyde **49** and amine catalyst **50**. Then, iminium ion **52** reacted with copper-coordinated alkyne **53** to give intermediate **54**, which subsequently underwent an intramolecular aza-Michael addition to afford the final product.



R^1 = Ph, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$F_3CC_6H_4$, *p*-Tol, *p*-$MeOC_6H_4$, *p*-PhC_6H_4, 2-furyl, 3-thiophenyl, 1-Naph, 2-Naph, Me, *n*-Bu, Cy,
R^2 = H, 5-F, 4-Cl, 4-Br, 4-F_3C, 4-MeO
R^3 = Ph, *o*-FC_6H_4, *m*-FC_6H_4, *m*-$F_3CC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-Tol
R^4 = Me, Et, *n*-Bu, *i*-Bu, *c*-Pr

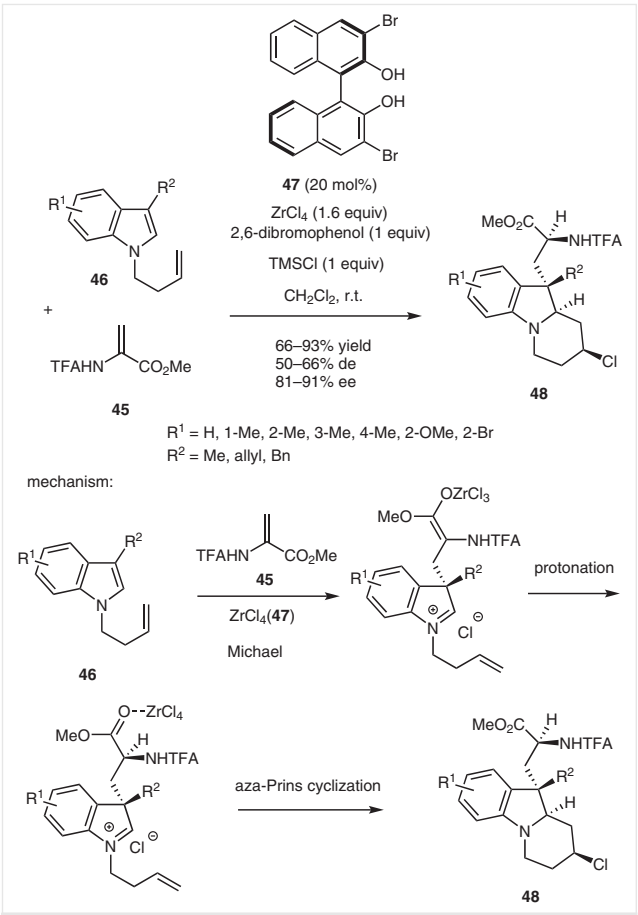
Scheme 10 Synthesis of 2,2,3-trisubstituted indolines through a Rh- and Sc-catalyzed domino reaction



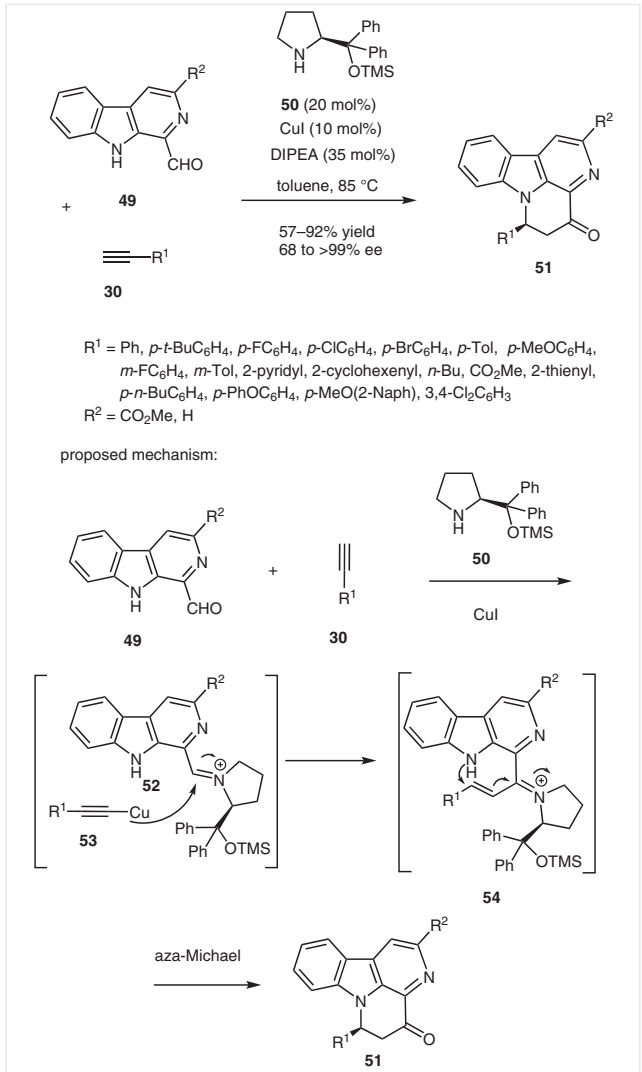
R^1 = H, Cl
R^2 = H, Cl
R^3 = H, Br, Me, Cl
R^2,R^3 = $(CH{=}CH)_2$
R^4 = H, Me, F, Cl
R^5 = Me, Ph

Scheme 11 Synthesis of spiroindolines through a Mg-catalyzed domino reaction

Another green metal, magnesium,[23] has been used by Lin et al. in a recent synthesis of chiral spirooxindole tetrahydroquinolines **57** based on an intramolecular domino reaction of oxindoles **55**.[24] The process occurred through sequential 1,5-hydride transfer and cyclization reactions carried out in the presence of a combination of $MgCl_2$ and chiral phosphoric acid **56** (Scheme 14). The products were formed in high yields (80–95%) and diastereoselectivities (80 to >90% de) combined with good enantioselectivities (50–97% ee).



Scheme 12 Synthesis of tricyclic chiral indolines through a Zr-catalyzed domino reaction



Scheme 13 Synthesis of 5,6-dihydrocanthin-4-ones through a Cu-catalyzed domino reaction

Another chiral magnesium catalyst derived from $MgSO_4$ and a chiral phosphoric acid ligand **60** was applied by Schneider and Hodik in 2018 to develop a synthesis of chiral spirocyclic dihydroquinolones **61** through the reaction of *ortho*-quinone methide imines **58** with cyclic β-oxo esters **59** (Scheme 15).[25] This one-step process evolved through successive addition and lactamization reactions, affording spirocyclic dihydroquinolones **61** with good yields (39–98%) and both moderate to excellent diastereo- (50 to >90% de) and enantioselectivities (66–98% ee).

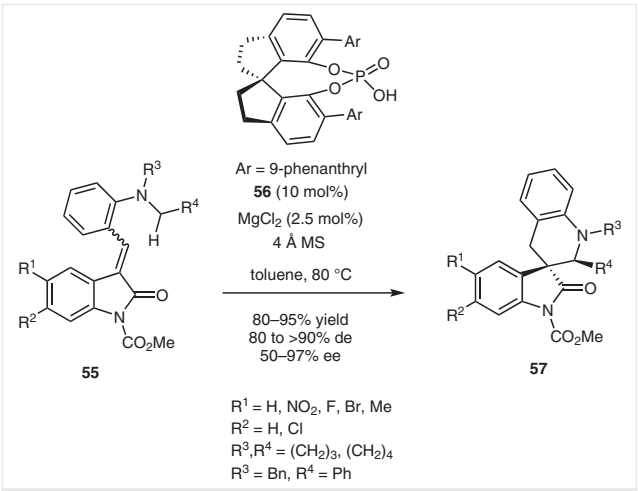
3 Formation of One Ring Containing One Oxygen/Sulfur Atom

3.1 Five-Membered Rings

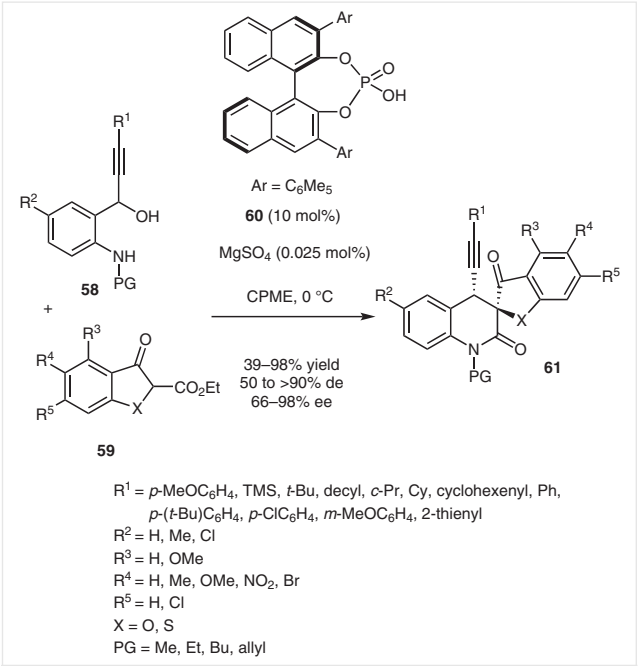
In 2017, Ge et al. disclosed a synthesis of chiral tetrahydrofurans **63** on the basis of a domino reaction of oxygen-tethered 1,6-enynes **62** with pinacolborane (Scheme 16).[11] The process employed a combination of $Co(acac)_2$ with chiral biphosphine ligand **16** as the catalyst system, allowing products **63** to be obtained with homogeneous excellent enantioselectivities (92–99% ee) and good yields (47–87%). The process evolved through an anti-Markovnikov hydroboration followed by a cyclization.

On the other hand, chiral alkyl boronate esters **65**, instead of chiral vinyl-substituted boronate esters **63** (Scheme 16), were generated from the reaction of more sterically hindered oxygen-tethered 1,6-enynes **64** with pinacolborane in the presence of the same catalyst system.[11] Indeed, in this case, a Markovnikov hydroboration occurred, delivering, after subsequent cyclization, tetrahydrofurans **65** in high yields (69–91%) and enantioselectivities (86–92% ee) (Scheme 17).

In 2018, Fan and co-workers reported the synthesis of chiral tetrahydrofuran **68** through a domino reaction between oxygen-tethered 1,6-enyne **66** and azabenzonorbornadiene **67** performed in the presence of a combination of



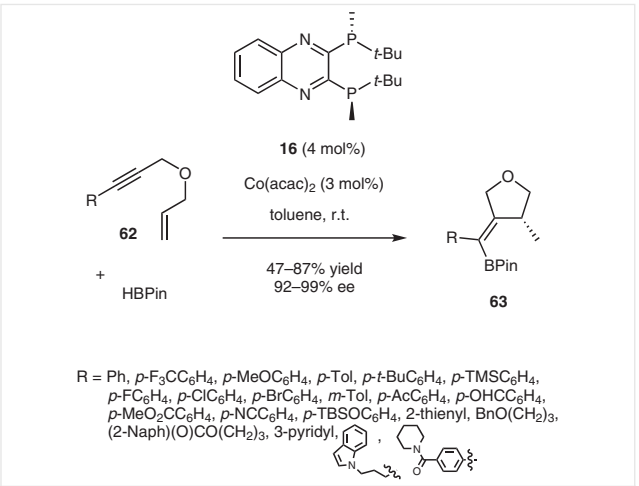
Scheme 14 Synthesis of spirooxindole tetrahydroquinolines through a Mg-catalyzed domino reaction



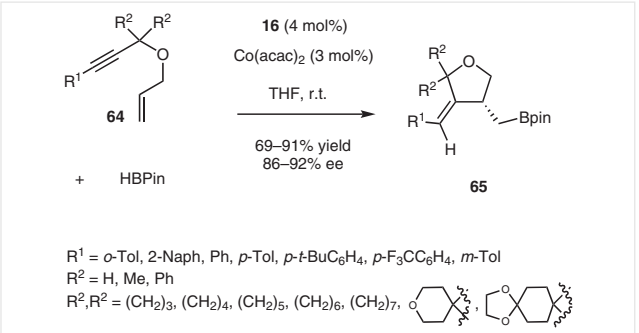
Scheme 15 Synthesis of spirocyclic dihydroquinolones through a Mg-catalyzed domino reaction

$[Rh(cod)_2]BF_4$ and chiral diphosphine ligand (*R*)-An-SDP.[12] The enantiopure product (98% ee) was obtained in 38% yield through cyclization followed by an addition reaction (Scheme 18).

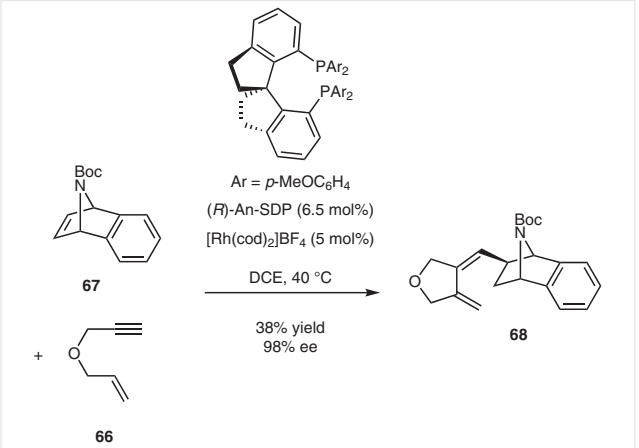
A synthesis of chiral bicyclic furans **72** was disclosed in 2018 by Marinetti and Betzer through a silver-catalyzed domino reaction of 2-(1-alkynyl)-2-cyclohexenone **69** with 5-substituted indoles **70** (Scheme 19).[26] The process was catalyzed by preformed chiral silver phosphate **71** and evolved through successive cycloisomerization and addi-



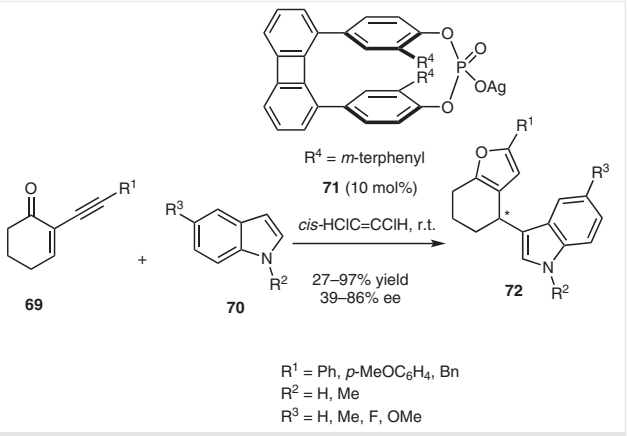
Scheme 16 Synthesis of tetrahydrofurans through a Co-catalyzed domino reaction



Scheme 17 Synthesis of other tetrahydrofurans through a Co-catalyzed domino reaction



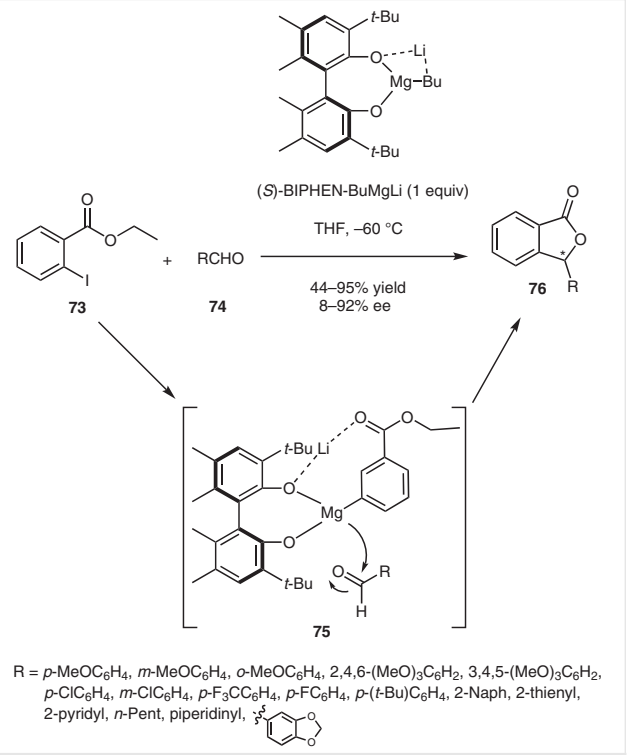
Scheme 18 Synthesis of a tetrahydrofuran through a Rh-catalyzed domino reaction



Scheme 19 Synthesis of bicyclic furans through an Ag-catalyzed domino reaction

tion reactions to deliver the final bicyclic furans **72** in variable yields (27–97%) and moderate to high enantioselectivities (39–86% ee).

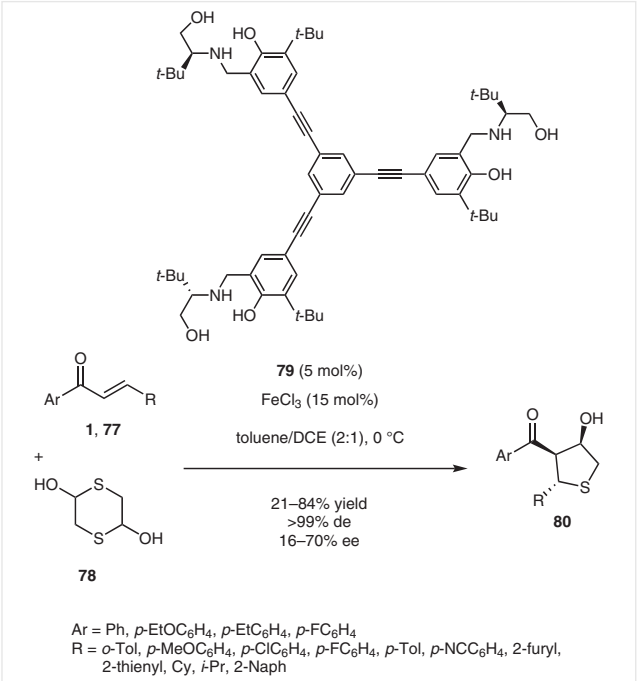
Chiral 3-substituted isobenzofuranones **76** were generated by Gros et al. through a magnesium-catalyzed domino reaction occurring between ethyl 2-iodobenzoate (**73**) and aldehydes **74**.[27] (*S*)-BIPHEN-BuMgLi was used as the catalyst, which formed intermediate **75** on reaction with ethyl 2-iodobenzoate (**73**). Addition of the latter to aldehyde **74** followed by intramolecular cyclization then led to final product **76** in variable enantioselectivities (8–92% ee) and good to excellent yields (44–95%) (Scheme 20).



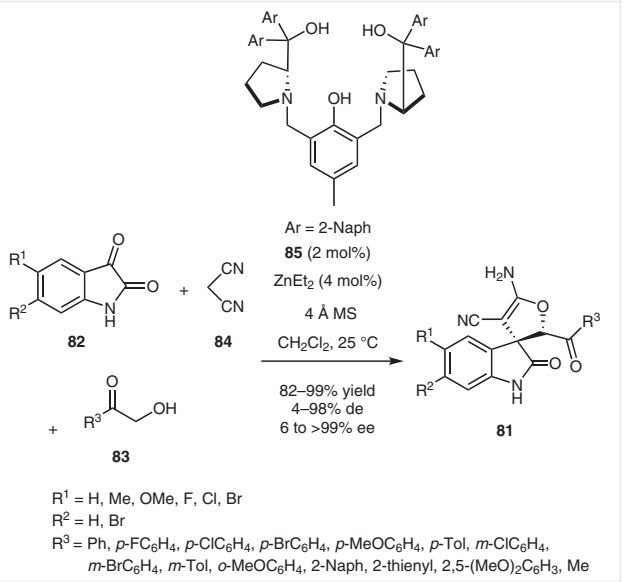
Scheme 20 Synthesis of 3-substituted isobenzofuranones through a Mg-catalyzed domino reaction

Chiral tetrahydrothiophenes **80** were produced by Punniyamurthy et al. through an iron-catalyzed domino reaction of aromatic α,β-unsaturated ketones **1** and **77** with 1,4-dithiane-2,5-diol (**78**).[28] A combination of $FeCl_3$ with novel reusable chiral dendrimer ligand **79** was used as the catalyst system, which triggered successive sulfa-Michael addition and aldol condensation to give chiral tetrahydrothiophenes **80** as single diastereomers (>99% de) in low to high yields (21–84%) and enantioselectivities (16–70% ee) (Scheme 21).

In 2019, Wang et al. reported the synthesis of chiral 3,3′-dihydrofuran spirooxindoles **81** on the basis of an enantioselective zinc-catalyzed three-component reaction of isatins **82**, α-hydroxy ketones **83** and malononitrile **84**.[29] The process involved a bimetallic catalyst generated in situ from $ZnEt_2$ and chiral triol ligand **85**. It evolved through a domino Knoevenagel/Michael/cyclization reaction, affording highly functionalized spirooxindoles **81** in uniformly high yields (82–99%), variable diastereoselectivities (4–98% de) and high enantioselectivities in most cases (6 to >99% ee) (Scheme 22).



Scheme 21 Synthesis of tetrahydrothiophenes through an Fe-catalyzed domino reaction



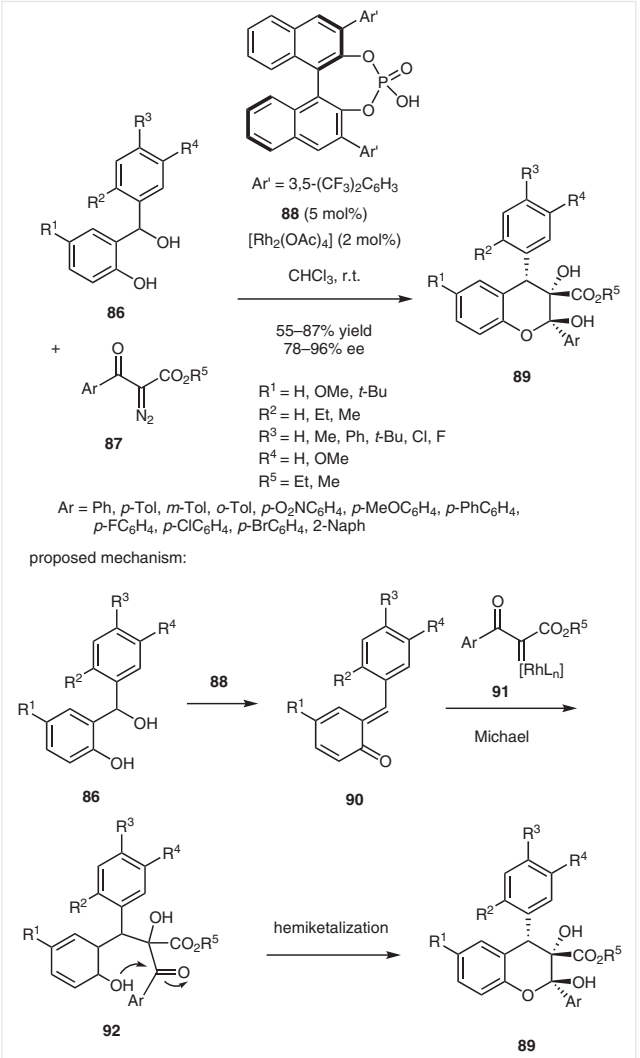
Scheme 22 Synthesis of 3,3′-dihydrofuran spirooxindoles through a Zn-catalyzed domino reaction

3.2 Six-Membered Rings

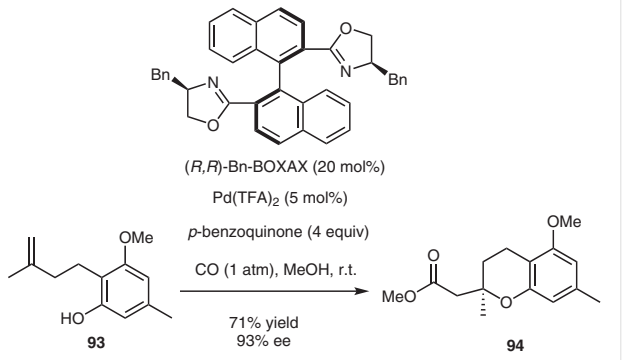
In 2016, densely functionalized chiral chromans **89** were synthesized by Schneider et al. by using $[Rh_2(OAc)_4]$ and chiral phosphoric acid **88** as the catalyst system.[30] As shown in Scheme 23, the reaction of *ortho*-hydroxy benzhydryl alcohols **86** with diazoesters **87** evolved through the Michael addition of rhodium carbene **91** to intermediate *ortho*-quinone methides **90**. This was followed by a hemiketalization reaction of intermediate **92** leading to chiral chromans **89** as single diastereomers in good yields (55–87%) and high enantioselectivities (78–96% ee).

Tietze et al. disclosed the synthesis of another chiral chroman, constituting a key intermediate in a total synthesis of (–)-siccanin, by using a chiral palladium catalyst derived from $Pd(TFA)_2$ and the (*R*,*R*)-Bn-BOXAX ligand.[31] Alkenyl phenol **93** reacted through Wacker oxidation, carbonylation and then methoxylation to afford chiral chroman **94** in 93% ee and 71% yield (Scheme 24).

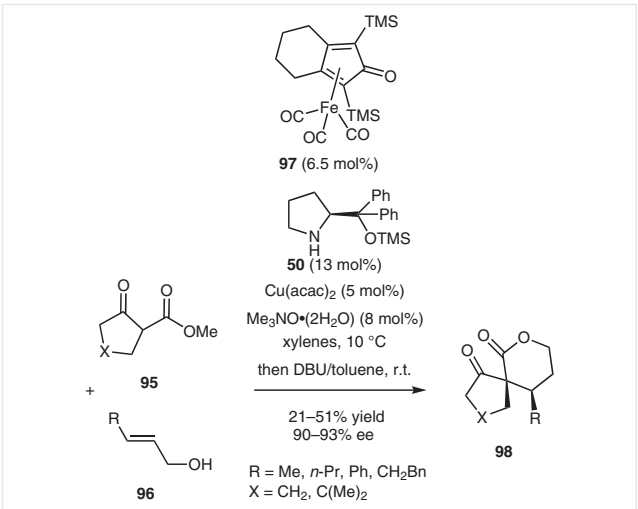
In 2018, Quintard and Rodriguez reported the synthesis of chiral bicyclic δ-lactones **98** through domino reactions of cyclic β-keto esters **95** with allylic alcohols **96**, by employing a combination of achiral iron tricarbonyl complex **97**, $Cu(acac)_2$ and chiral proline derivative **50**.[32] The process evolved through successive oxidation, Michael addition, reduction and lactonization to give bicyclic δ-lactones **98** in high enantioselectivities (90–93% ee) combined with low to moderate yields (21–51%) (Scheme 25).



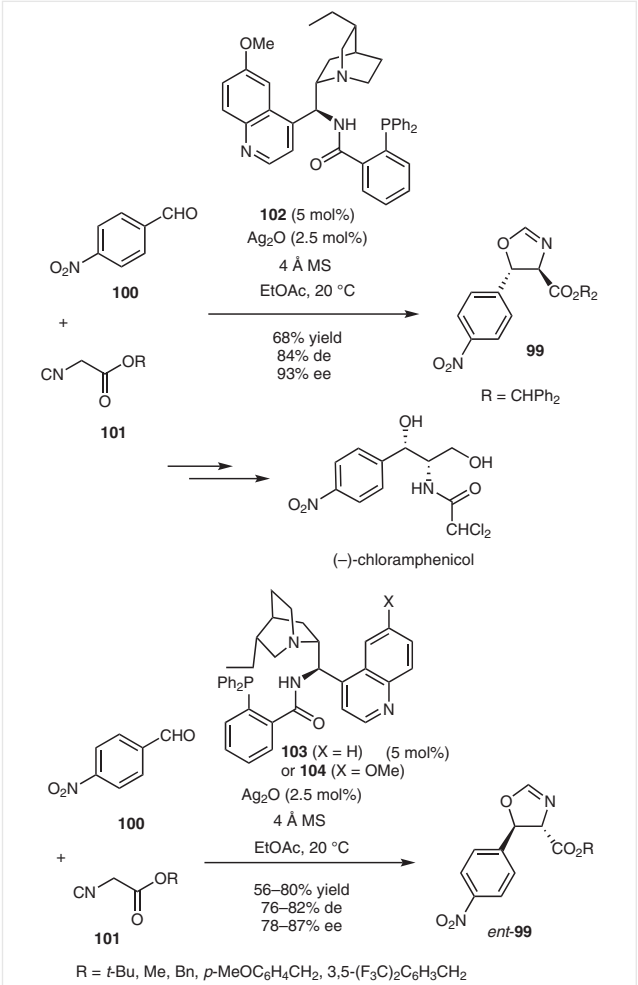
Scheme 23 Synthesis of chromans through a Rh-catalyzed domino reaction



Scheme 24 Synthesis of a chroman through a Pd-catalyzed domino reaction



Scheme 25 Synthesis of bicyclic δ-lactones through a multicatalyzed domino reaction



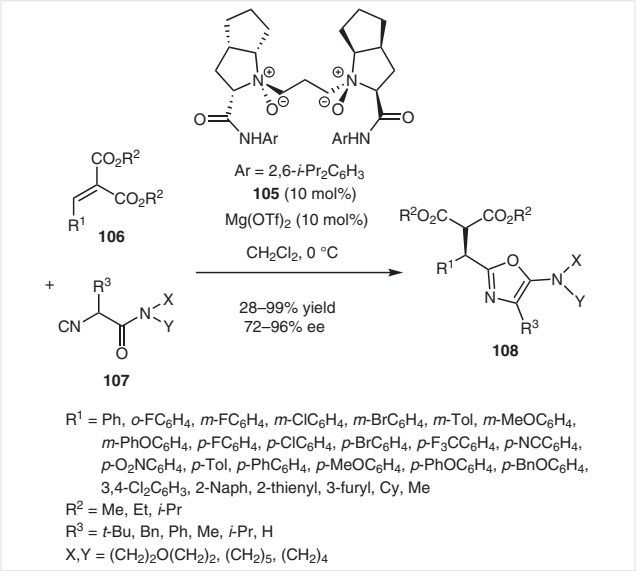
Scheme 26 Synthesis of oxazolines through Ag-catalyzed domino reactions

4 Formation of One Ring Containing Several Heterocyclic Atoms

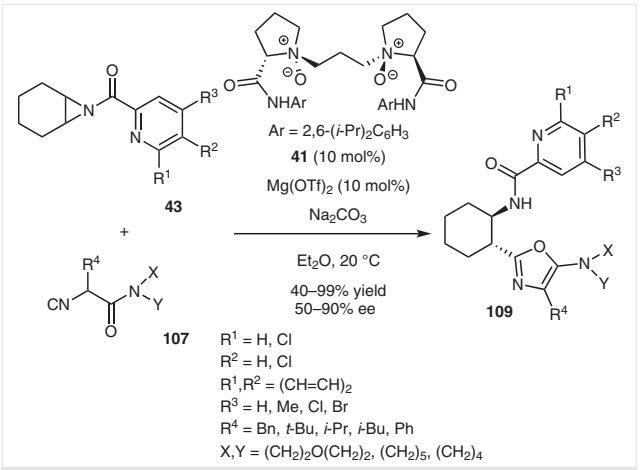
In 2016, Dixon et al. employed a combination of Ag_2O and chiral cinchona alkaloid **102** to develop a novel total synthesis of the antibiotic (–)-chloramphenicol.[33] Actually, the latter was obtained from *trans*-oxazoline **99**, itself prepared from a domino reaction occurring between *p*-nitrobenzaldehyde (**100**) and isocyanoacetate **101** with 93% ee, 84% de and 68% yield. The process evolved through sequential aldol and cyclization reactions. It was found that other alkyl isocyanoacetates **101** were also compatible by using related chiral cinchona alkaloid ligands **103** and **104**, thus leading to chiral oxazolines *ent*-**99** in good yields (56–80%), diastereo- (76–82% de) and enantioselectivities (78–87% ee) (Scheme 26).

In the same year, Feng et al. employed a catalyst system composed of $Mg(OTf)_2$ and chiral *N*,*N*′-dioxide ligand **105** in the synthesis of chiral 2-alkyl-5-aminooxazoles **108**.[34] The process involved the Michael addition of α-isocyanoacetamides **107** to alkylidene malonates **106** followed by an intramolecular cyclization reaction to provide chiral 2-alkyl-5-aminooxazoles **108** in variable yields (28–99%) and good enantioselectivities (72–96% ee) (Scheme 27).

In 2019, the same authors employed related chiral *N*,*N*′-dioxide ligand **41** combined with $Mg(OTf)_2$ to promote the asymmetric synthesis of other 2-alkyl-5-aminooxazoles **109**.[19] The latter were obtained in good to excellent yields (40–99%) and enantioselectivities (50–95% ee) from the ring-opening reaction of the corresponding *meso*-aziridines **43** with α-isocyanoacetamides **107** followed by intramolecular cyclization (Scheme 28).

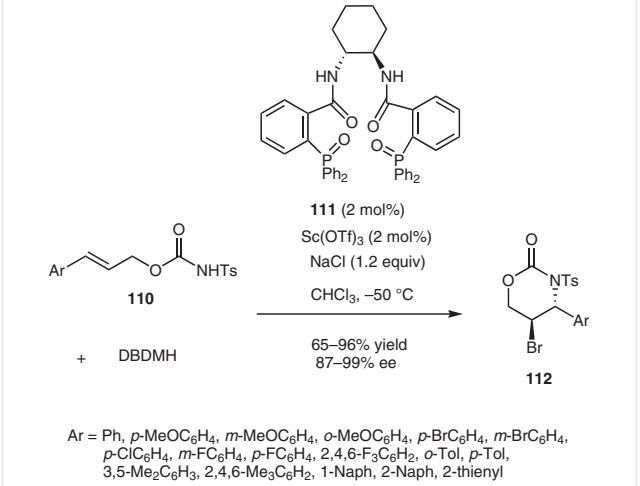


Scheme 27 Synthesis of 2-alkyl-5-aminooxazoles through a Mg-catalyzed domino reaction



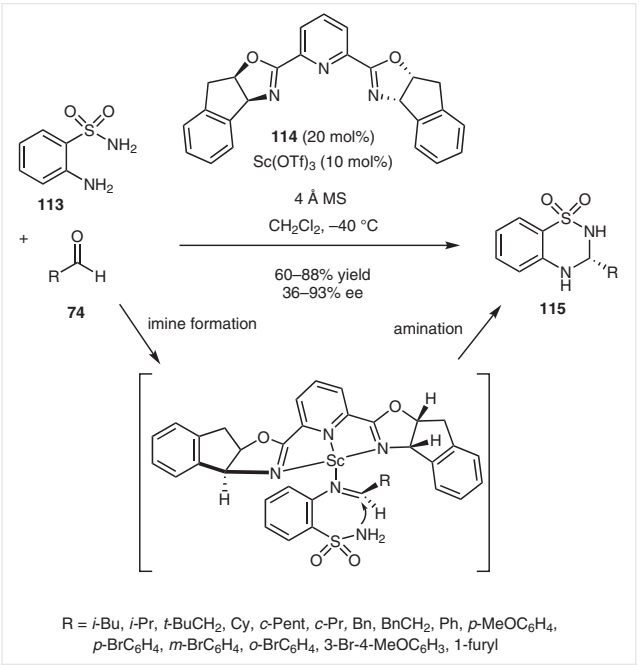
Scheme 28 Synthesis of other 2-alkyl-5-aminooxazoles through a Mg-catalyzed domino reaction

A chiral scandium catalyst derived from $Sc(OTf)_3$ and chiral diphosphine oxide ligand **111** was applied by Shi et al. to promote the synthesis of chiral aryl 5-bromo-1,3-oxazinan-2-ones **112** (Scheme 29).[35] The reaction occurred between (*E*)-cinnamyl tosylcarbamates **110** and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) through successive bromination and amination reactions, delivering the domino products in excellent enantioselectivities (87–99% ee) and good to excellent yields (65–96%).



Scheme 29 Synthesis of aryl 5-bromo-1,3-oxazinan-2-ones through a Sc-catalyzed domino reaction

A novel route to chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides **115** was disclosed in 2016 by Zhou et al. using a catalyst system based on $Sc(OTf)_3$ and chiral Pybox (pyridine-bisoxazoline) ligand **114**.[36] The process involved imine formation using aldehydes **74** and 2-aminobenzenesulfonamide (**113**), followed by an intramolecular amination reaction to provide products **115** in good yields (60–88%) and enantioselectivities (36–93% ee) (Scheme 30).



Scheme 30 Synthesis of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides through a Sc-catalyzed domino reaction

In 2016, Liu and Feng described the first asymmetric synthesis of benzimidazoles based on a metal-catalyzed domino process.[37] The catalyst system was generated from $ScCl_3{\cdot}(H_2O)_6$ and chiral *N*,*N*′-dioxide ligand **121** (Scheme 31). The reaction occurred between cyclopropanes **116** and diamines **117**, which firstly underwent a ring-opening addition reaction to give **118**. The latter intermediate was then submitted to an intramolecular cyclization to provide **119** and a subsequent retro-Mannich reaction afforded the final products **120** in high enantioselectivities (80–97% ee) and good yields (56–99%).

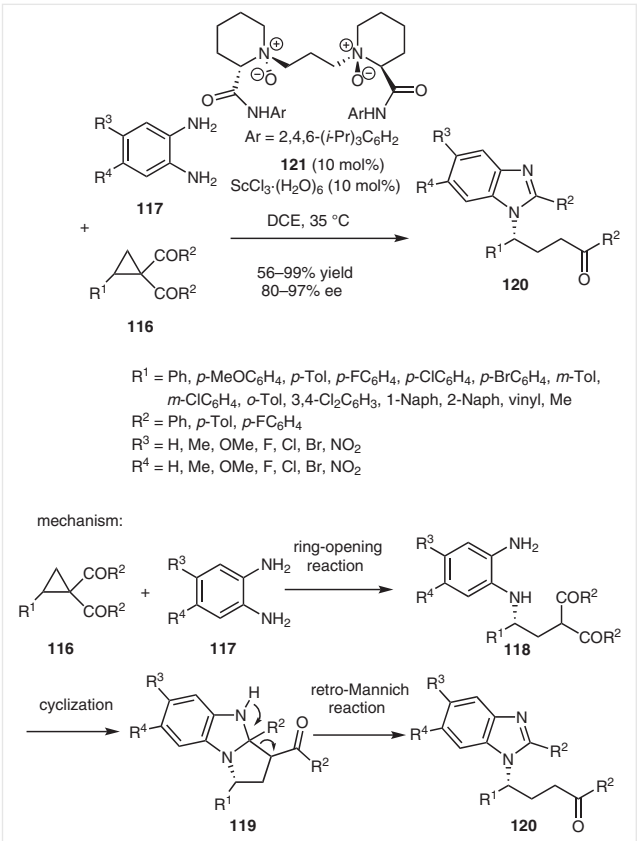
5 Formation of One Carbon Ring

5.1 Five-Membered Rings

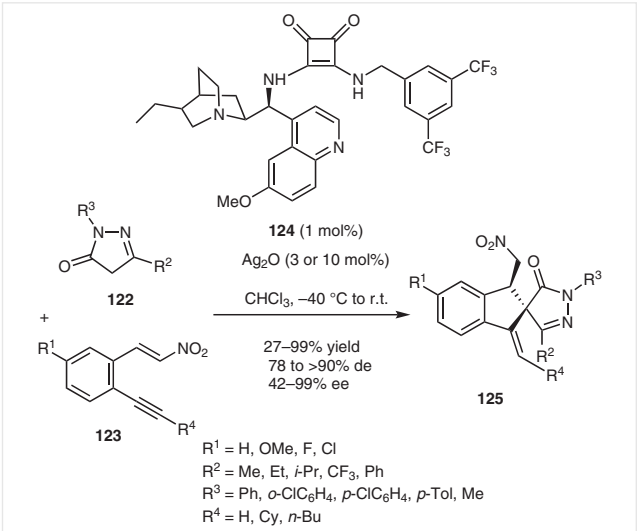
In 2016, Enders et al. reported the synthesis of chiral spiropyrazolones **125** on the basis of a relay multicatalysis with Ag_2O and chiral squaramide **124** as the organocatalyst.[38] The products were formed in variable yields (27–99%) from 5-pyrazolones **122** and alkyne-tethered nitroalkenes **123** through consecutive organocatalyzed Michael addition and Ag-catalyzed Conia-ene reaction. As presented in Scheme 32, high diastereoselectivities (78 to

>90% de) combined with good enantioselectivities (42–99% ee) were obtained.

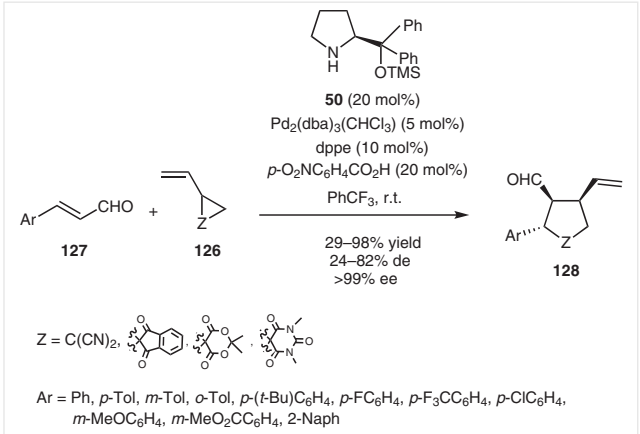
In the same year, Ratovelomanana-Vidal, Michelet and Vitale described a novel diastereo- and enantioselective formal [3+2] cycloaddition of vinyl cyclopropanes **126** with α,β-unsaturated aldehydes **127** catalyzed by a combination of $Pd_2(dba)_3(CHCl_3)$, dppe as the ligand and proline-derived chiral amine **50** as the organocatalyst.[39] The process evolved through a domino Michael/cyclization reaction, affording the corresponding enantiopure trisubstituted cyclopentanes **128** (>99% ee) with good to high yields (54–88%) and diastereoselectivities (72–80% de) when starting from 1,1-dicyano-2-vinyl cyclopropane [Z = $C(CN)_2$] (Scheme 33). The same synergistic catalytic system also promoted the reaction of other vinyl cyclopropanes, such as 1,3-indanedione-derived vinyl cyclopropane, Meldrum's acid derived vinyl cyclopropane and 1,3-dimethylbarbituric vinyl cyclopropane, which led to the corresponding enantiopure cyclopentanes **128** (>99% ee) with low to excellent yields (29–98%) and diastereoselectivities (24–82% de), as shown in Scheme 33.



Scheme 31 Synthesis of benzimidazoles through a Sc-catalyzed domino reaction



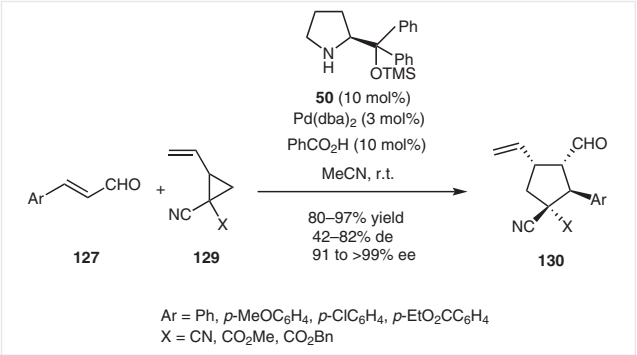
Scheme 32 Synthesis of spiropyrazolones through a multicatalyzed domino reaction



Scheme 33 Synthesis of trisubstituted cyclopentanes through a multicatalyzed domino reaction

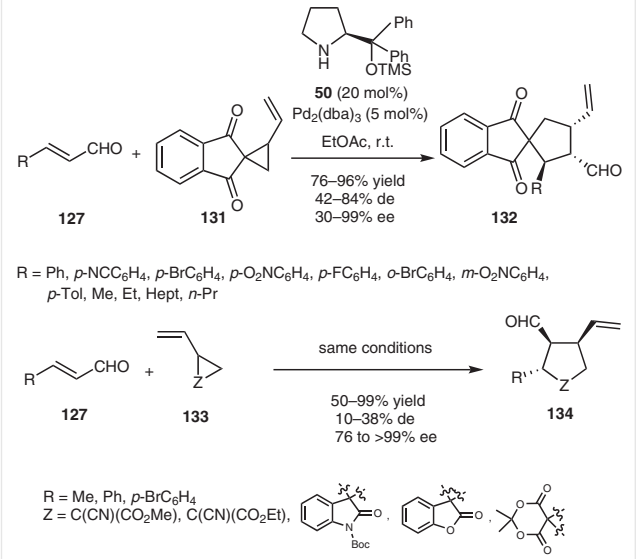
This type of reaction was also investigated at the same time by Jørgensen et al. by using a related catalyst system, albeit employed at lower catalyst loadings.[40] Indeed, performed in the presence of only 10 mol% of organocatalyst **50** and 3 mol% of $Pd_2(dba)_3$, the domino Michael/cyclization reaction of α,β-unsaturated aldehydes **127** with vinylcyclopropanes **129** led to the corresponding chiral pentasubstituted cyclopentanes **130** bearing up to four stereogenic centers, including one quaternary, with both uniformly high yields (80–97%) and enantioselectivities (91 to >99% ee), combined with moderate to high diastereoselectivities (42–82% de) (Scheme 34). In addition to the vinyl cyclopropane **129** bearing two nitrile groups (X = CN), vinyl cyclopropanes possessing a methyl or a benzyl ester were also compatible as were various aromatic α,β-unsaturated aldehydes.

These reactions were also studied by Rios and Meazza almost at the same time.[41] In this case, a combination of 20 mol% of the same organocatalyst **50** with 5 mol% of $Pd_2(dba)_3$ was used. For example, the domino Michael/cy-



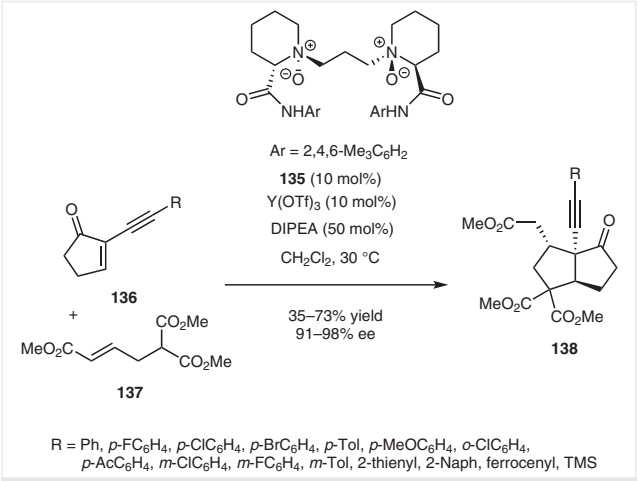
Scheme 34 Synthesis of pentasubstituted cyclopentanes through a multicatalyzed domino reaction

clization reaction of spirocyclic vinyl cyclopropane **131** with a range of either aromatic or aliphatic α,β-unsaturated aldehydes **127** afforded the corresponding chiral spirocyclic products **132** in high yields (76–96%) and both moderate to high diastereo- (42–84% de) and enantioselectivities (30–99% ee) (Scheme 35). The scope of the reaction could be extended to other vinyl cyclopropanes **133**, which through reactions with aromatic α,β-unsaturated aldehydes **127** led to the corresponding chiral cyclopentanes **134** in good to quantitative yields (50–99%) combined with low diastereoselectivities (10–38% de) and good to excellent enantioselectivities (76 to >99% ee) (Scheme 35).



Scheme 35 Synthesis of spirocyclic cyclopentanes through multicatalyzed domino reactions

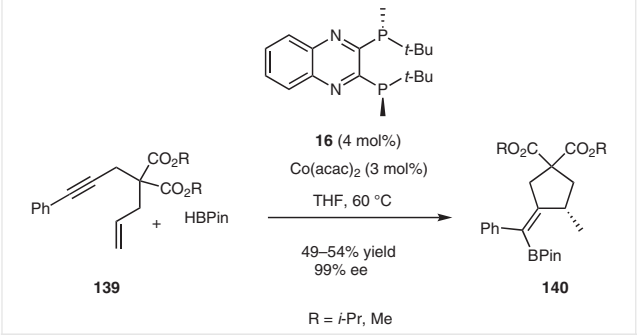
In 2017, Feng et al. employed a chiral yttrium catalyst prepared from $Y(OTf)_3$ and chiral *N*,*N*′-dioxide ligand **135** for the synthesis of chiral tetrasubstituted diquinanes.[42] In this process, electron-deficient enynes **136** reacted with α,β-unsaturated ester **137** through two sequential Michael



Scheme 36 Synthesis of diquinanes through a Y-catalyzed domino reaction

additions to afford almost enantiopure (91–98% ee) diquinanes **138** in variable yields (35–73%) (Scheme 36).

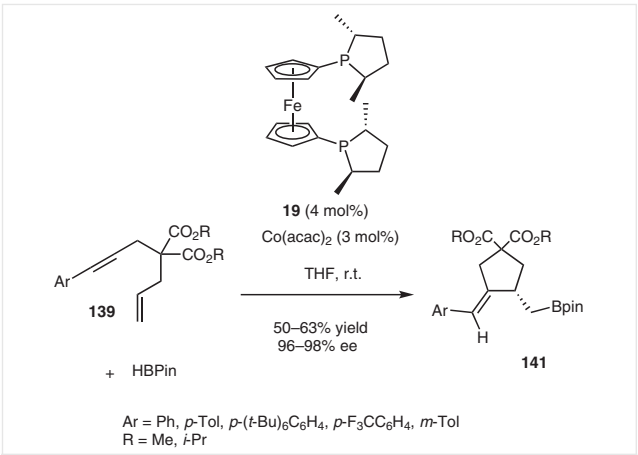
In the same year, Ge et al. described the synthesis of chiral cyclopentanes on the basis of a domino reaction promoted by a combination of $Co(acac)_2$ and chiral biphosphine ligand **16**.[11] As depicted in Scheme 37, 1,6-enynes **139** reacted with pinacolborane through an anti-Markovnikov hydroboration followed by a cyclization to yield the corresponding enantiopure (99% ee) vinyl-substituted boronate esters **140** in good yields (49–54%).



Scheme 37 Synthesis of functionalized cyclopentanes through a Co-catalyzed domino reaction

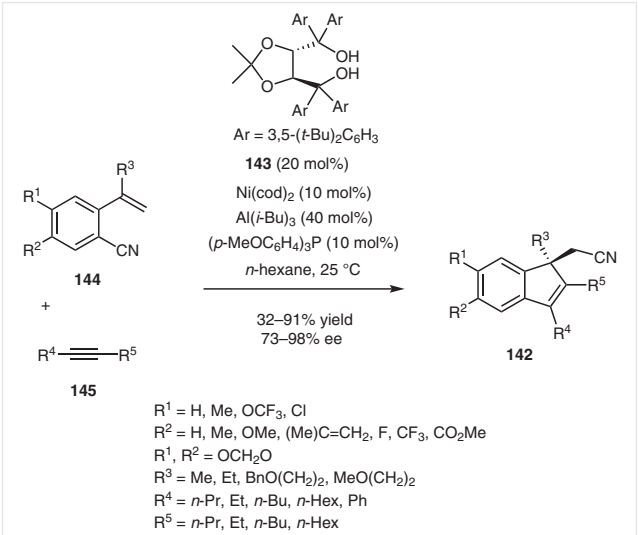
When the same reaction was performed in the presence of related chiral biphosphine ligand **19** instead of ligand **16**, a Markovnikov hydroboration occurred (Scheme 38), which was followed by cyclization to give enantiopure (96–98% ee) alkyl boronate esters **141** in good yields (50–63%).[11]

In 2020, asymmetric nickel catalysis was applied by Ye and Peng to develop a novel synthesis of chiral indenes **142** bearing a quaternary stereocenter.[43] Indeed, in the presence of $Ni(cod)_2$ and α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-di-



Scheme 38 Synthesis of other functionalized cyclopentanes through a Co-catalyzed domino reaction

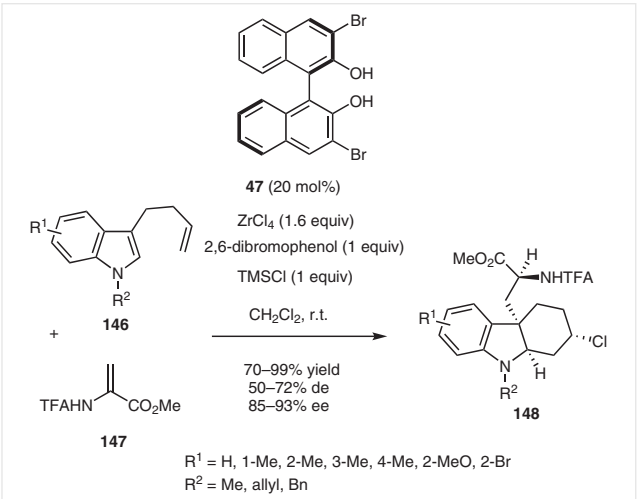
oxolane-4,5-dimethanol (TADDOL)-derived ligand **143**, a range of aryl nitriles **144** reacted with internal alkynes **145** to give the corresponding indenes **142** in moderate to high yields (32–91%) and good to high enantioselectivities (73–98% ee). The process required the use of an achiral phosphine and Al(*i*-Bu)$_3$ as additives (Scheme 39).



Scheme 39 Synthesis of indenes through a Ni-catalyzed domino reaction

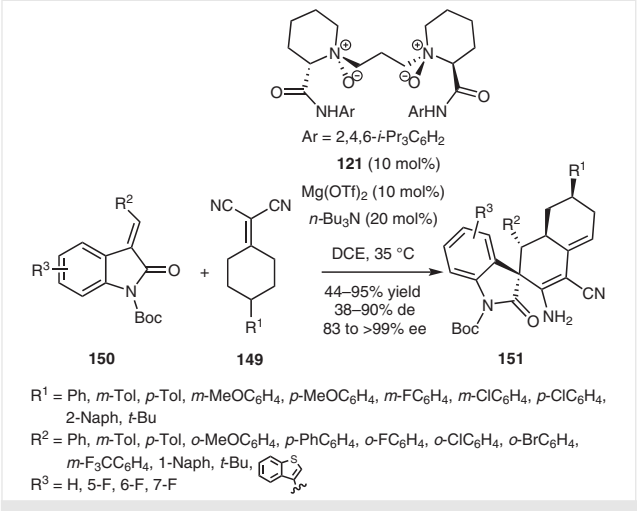
5.2 Six-Membered Rings

In 2016, a catalyst system consisting of $ZrCl_4$ and (*R*)-BINOL-derived ligand **47** was applied by Reisman and coworkers to elaborate an asymmetric synthesis of tricyclic indoles **148** (Scheme 40).[20] These products were generated in good yields (70–99%) from the reaction of indoles **146** with acrylate **147** through sequential Michael addition, protonation and an aza-Prins reaction. High enantioselectivities (85–93% ee) combined with good diastereoselectivities (50–72% de) were obtained.



Scheme 40 Synthesis of tricyclic indoles through a Zr-catalyzed domino reaction

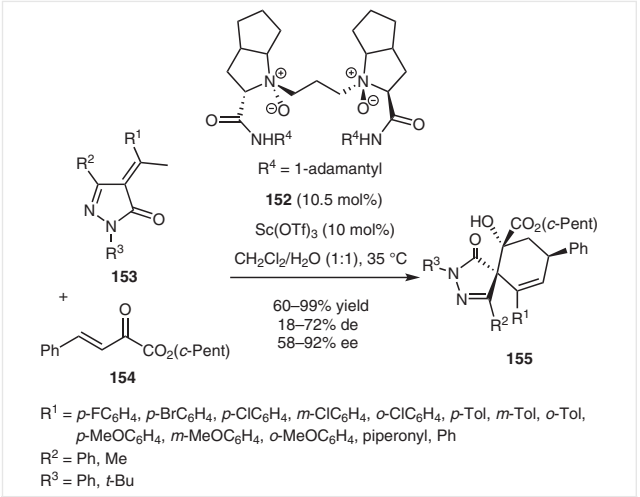
In 2018, chiral spiroindolinones were prepared by Feng and Lin from an enantioselective magnesium-catalyzed one-step reaction between α,α-dicyanoalkenes **149** and 3-arylideneoxindoles **150**.[44] The reaction, evolving through Michael addition followed by cyclization, was performed in the presence of Mg(OTf)$_2$ and chiral *N*,*N*′-dioxide ligand **121** and led to chiral spiroindolinones **151** in high enantioselectivities (83 to >99% ee), good yields (44–95%) and variable diastereoselectivities (38–90% de) (Scheme 41).



Scheme 41 Synthesis of spiroindolinones through a Mg-catalyzed domino reaction

In 2019, another chiral *N*,*N*′-dioxide ligand **152** was combined with Sc(OTf)$_3$ by Feng et al. to promote an asymmetric vinylogous Michael/aldol domino reaction of

α-arylidene pyrazolinones **153** with β,γ-unsaturated-α-ketoester **154** (Scheme 42).[45] The process was performed in aqueous media (CH_2Cl_2/H_2O) and allowed a series of chiral spirocyclohexene pyrazolones **155** to be synthesized in good to high yields (60–99%) and enantioselectivities (58–92% ee), combined with variable diastereoselectivities (18–72% de).

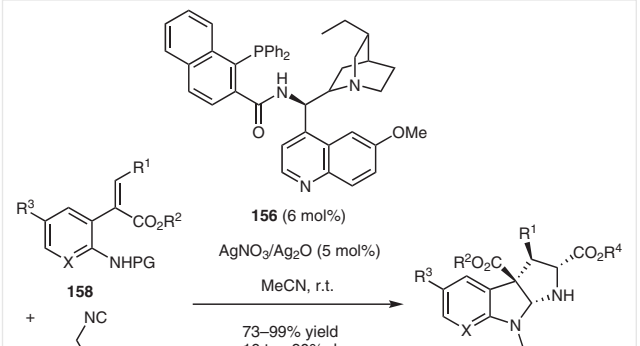


R^1 = *p*-FC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-Tol, *m*-Tol, *o*-Tol, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *o*-$MeOC_6H_4$, piperonyl, Ph
R^2 = Ph, Me
R^3 = Ph, *t*-Bu

Scheme 42 Synthesis of spirocyclohexene pyrazolones through a Sc-catalyzed domino reaction

6 Formation of Two Rings

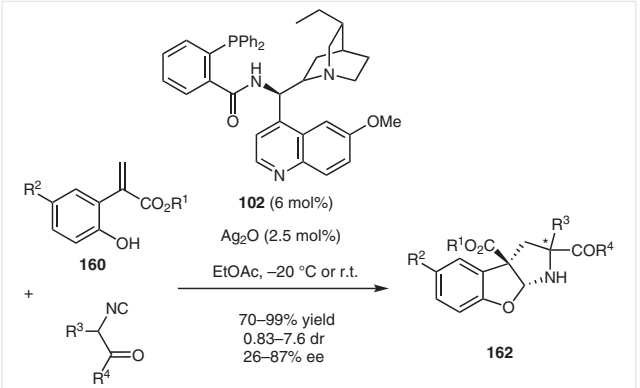
In 2016, a combination of $AgNO_3/Ag_2O$ and cinchona alkaloid ligand **156** was employed by Xie et al. in a novel asymmetric synthesis of *cis*-3a,8a-hexahydropyrrolo[2,3-*b*]indoles **159**.[46] These multifunctionalized products arose from the reaction of isocyanoacetates **157** with acrylates **158** according to sequential Michael addition and cyclization reactions (Scheme 43). Good yields (73–99%) and variable stereoselectivities (16 to >90% de, 0–90% ee) were reported.



R^1 = H, Ph, *n*-Pr
R^2 = Et, Bn, *t*-Bu
R^3= H, Me, Cl
R^4 = Et, Bn, 1-adamantyl, *t*-Bu
PG = Piv, Tos, Ac, Boc
X = CH, N

Scheme 43 Synthesis of *cis*-3a,8a-hexahydropyrrolo[2,3-*b*]indoles through an Ag-catalyzed domino reaction

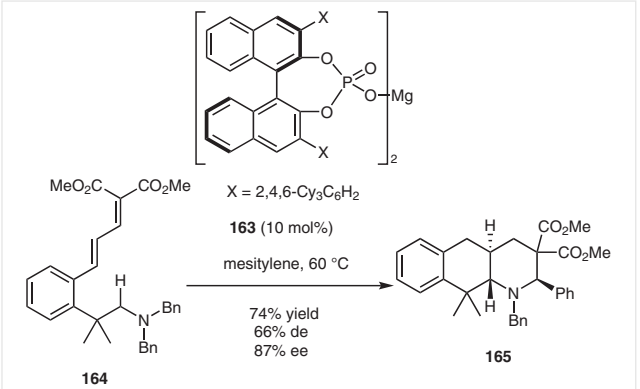
In the same context, these authors also disclosed the reaction of isocyanoacetates **161** with acrylates **160** to give, in the presence of Ag_2O and related cinchona alkaloid ligand **102**, the corresponding chiral tetrahydrobenzofuro[2,3-*b*]pyrroles **162** as mixtures of two diastereomers (0.83–7.6 dr) in high yields (70–99%) and variable enantioselectivities (26–87% ee) (Scheme 44).[47]



R^1 = Et, Me
R^2 = H, Me, F
R^3 = H, Me, Ph
R^4 = OEt, O*t*-Bu, OBn, piperidinyl

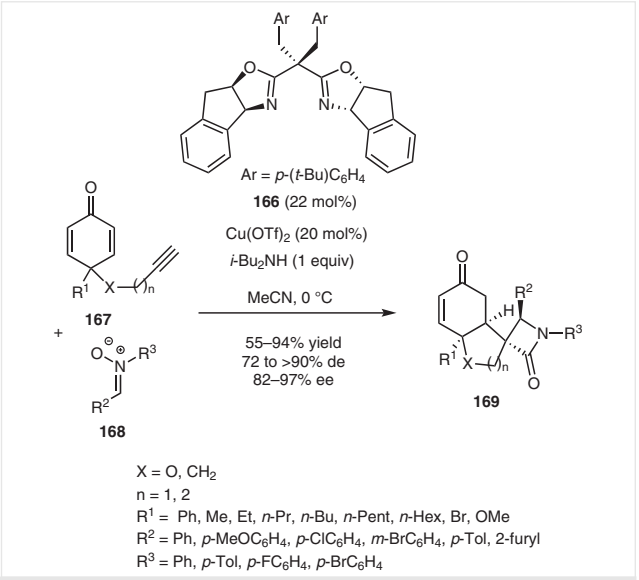
Scheme 44 Synthesis of tetrahydrobenzofuro[2,3-*b*]pyrroles through an Ag-catalyzed domino reaction

In 2018, chiral preformed magnesium catalyst **163** was used by Mori and Akiyama in an asymmetric synthesis of tricyclic piperidine **165** from cinnamylidene malonate **164** (Scheme 45).[48] This substrate underwent an Ag-catalyzed [1,5]-hydride shift followed by a cyclization to provide piperidine **165** in 74% yield, 87% ee and 66% de.



Scheme 45 Synthesis of a tricyclic piperidine through a Mg-catalyzed domino reaction

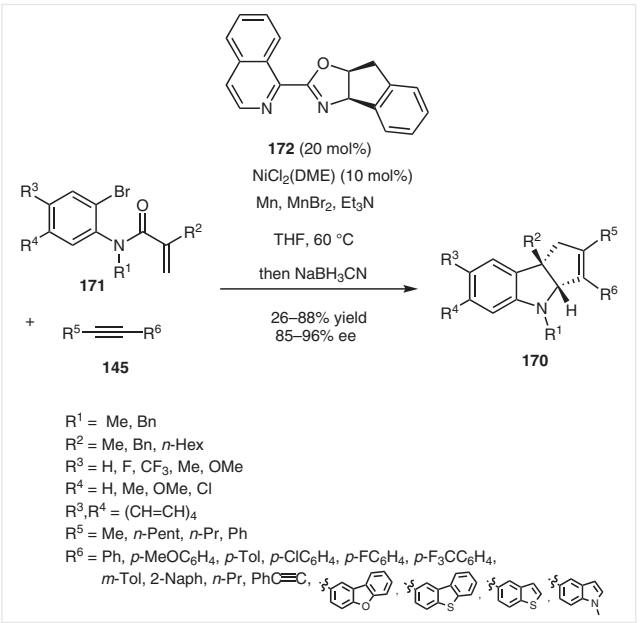
In the same year, an asymmetric synthesis of spirocyclic lactams **169** was reported by Enders and co-workers using copper catalysis.[49] Indeed, cyclohexadienones **167** reacted with nitrones **168** in the presence of $Cu(OTf)_2$ and chiral bisoxazoline ligand **166** as the catalyst system to give domino products **169** in high enantioselectivities (82–97% ee), good diastereoselectivities (72 to >90% de) and moderate to excellent yields (55–94%) through consecutive Kinugasa and Michael reactions (Scheme 46).



Scheme 46 Synthesis of spirocyclic lactams through a Cu-catalyzed domino reaction

Finally, asymmetric nickel catalysis was employed in 2019 by Kong et al. in a novel one-pot synthesis of chiral 2,3-fused cyclopentannulated indolines **170**.[50] As illustrated in Scheme 47, these highly substituted products arose from the domino reaction occurring between internal alkynes **145** and acrylamides **171**, which were performed in the presence of a combination of $NiCl_2$(DME) and chiral Pybox ligand **172** as the catalyst system and Mn as the reducing agent. These biologically interesting products were obtained as single regioisomers in variable yields (26–88%) and uniformly excellent enantioselectivities (85–96% ee).

In 2016, Feng and Liu reported an example of bimetallic asymmetric relay catalysis based on the use of a chiral nickel complex generated in situ from $Ni(ClO_4)_2{\cdot}6H_2O$ and chiral *N*,*N*′-dioxide ligand **173** combined with an achiral gold catalyst, such as $AuCl(PPh_3)$.[51] The process consisted of an enantioselective domino cycloisomerization/hetero-Diels–Alder reaction of α-keto ester **174** with alkynyl alcohols **175**, providing the corresponding chiral bicyclic spiroketals **176** in moderate to quantitative yields (50–99%), low to high diastereoselectivities (34–90% de) and high enantioselectivities (75–98% ee) (Scheme 48). The first cycloisomerization step of the alkynyl alcohol was catalyzed by



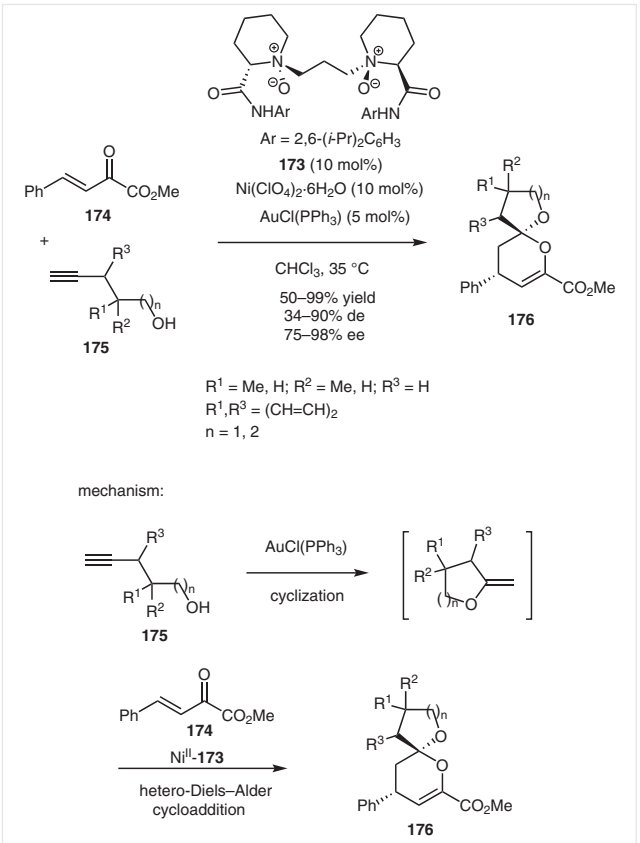
Scheme 47 Synthesis of 2,3-fused cyclopentannulated indolines through a Ni-catalyzed domino reaction

$AuCl(PPh_3)$, leading to a five-membered intermediate, which subsequently underwent an asymmetric hetero-Diels–Alder cycloaddition with α-keto ester **174**, catalyzed by the chiral nickel catalyst, to yield the final domino product **176**.

7 Conclusion

This short review has focused on the asymmetric synthesis of carbo- and heterocycles based on the use of chiral metal catalysts to promote domino reactions, covering the literature since the beginning of 2016. It demonstrates that a wide range of densely functionalized complex chiral rings, including medicinally relevant products, can be generated through simple one-step processes. Very different metal catalysts are today employed in these fascinating reactions, spanning from cobalt, copper, iron, palladium, rhodium, silver and zirconium, to rare earth elements (scandium, yttrium) and alkaline earth metals (magnesium). Generally, excellent enantioselectivities were observed in these processes.

For example, in the field of the formation of five- and six-membered products possessing one nitrogen atom, various densely functionalized pyrrolidines have been prepared with 98–99% ee by using chiral cobalt, nickel, rhodium and silver catalysts. Enantioselectivities of 91–94% ee have been described in the synthesis of chiral indolines through palladium and zirconium catalysis. Chiral magnesium complexes have allowed chiral spirooxindoles and spirodihydroquinolones to be prepared with enantioselec-



Scheme 48 Synthesis of bicyclic spiroketals through a gold- and nickel-catalyzed domino reaction

tivities of up to 97% and 98% ee, respectively. Moreover, chiral copper catalysts were used to prepare enantiopure 5,6-dihydrocanthin-4-ones. In the area of the formation of five- and six-membered products with one oxygen atom, the involvement of chiral cobalt and rhodium complexes has allowed the synthesis of functionalized chiral tetrahydrofurans to be achieved in enantioselectivities of up to 99% ee. Bicyclic furans were obtained with 86% ee by using chiral silver catalysts, while chiral 3-substituted isobenzofuranones were prepared in 92% ee by using magnesium complexes. Oxygenated six-membered products, such as chiral chromans, were synthesized through rhodium or palladium catalysis with enantioselectivities of up to 96% and 93% ee, respectively. Furthermore, chiral bicyclic δ-lactones were prepared with 93% ee on the basis of a multicatalysis approach involving copper and an organocatalyst. Surprisingly, only one method for the synthesis of rings exhibiting a sulfur atom, i.e., tetrahydrothiophenes, was described on the basis of iron catalysis with up to 70% ee.

In the field of five- and six-membered rings bearing several heteroatoms, chiral oxazolines were synthesized through silver catalysis with 87% ee, along with chiral 2-alkyl-5-aminooxazoles through magnesium catalysis with 96% ee, chiral aryl 5-bromo-1,3-oxazinan-2-ones, 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides and chiral benzimidazoles through scandium catalysis with 99%, 93% and 97% ee, respectively. Different types of enantiopure carbon rings have also been generated, such as spiropyrazolones in 99% ee by using chiral silver complexes, diquinanes with 98% ee using yttrium catalysts and functionalized cyclopentanes in 99% ee through cobalt catalysis. Six-membered carbon rings, belonging to chiral indoles and spiroindolinones, were also easily produced on the basis of zirconium and magnesium catalysis in 93% and >99% ee, respectively. Asymmetric metal-catalyzed domino reactions were also applied to simultaneously generate two rings in the same step. For example, silver catalysts allowed chiral *cis*-3a,8a-hexahydropyrrolo[2,3-*b*]indoles and tetrahydrobenzofuro[2,3-*b*]pyrroles to be achieved in 90% and 87% ee, respectively. Moreover, tricyclic piperidines and spirocyclic lactams were synthesized in 87% and 97% ee from magnesium and copper chiral catalysts, respectively.

In the near future, other metal catalysts will undoubtedly be applied to the one-step syntheses of many types of chiral cyclic compounds, with efforts devoted towards the use of 'green' metals.

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