SYNTHESIS OF CHIRAL HETEROCYCLES THROUGH ENANTIOSELECTIVE METAL-CATALYZED DOMINO REACTIONS

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Hélène Pellissier
Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France
(e-mail: h.pellissier@univ-amu.fr)

Abstract. *This chapter highlights recent developments in the synthesis of chiral heterocycles based on enantioselective domino reactions catalyzed by chiral metal catalysts. It shows that a wide range of densely functionalized chiral complex heterocyclic compounds, including medicinally relevant products, can be easily generated through these highly efficient simple one-step processes.*

Contents

List of abbreviations

acac: acetylacetonate; Ar: aryl; BINOL: 1,1'-bi-2-naphthol; Bn: benzyl; Boc: *tert*-butoxycarbonyl; BOXAX: 2,2’-bis(oxazolyl)-1,1’-binaphthyl; cod: cyclooctadiene; CPME: cyclopentyl methyl ether; Cy: cyclohexyl; dba: (*E,E*)-dibenzylideneacetone; DBDMH: 1,3-dibromo-5,5-dimethylhydantoin; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE: dichloroethane; de: diastereomeric excess; DIPEA: diisopropylethylamine; DME: 1,2-dimethoxyethane; dppe: 1,2-bis(diphenylphosphino)ethane; dr: diastereomeric ratio; ee: enantiomeric excess; Hex: hexyl; MTBE: methyl tert-butyl ether; Naph: naphthyl; M.S.: molecular sieves; NMP: *N*-methyl-2-pyrrolidone; Ns: nosyl; Pent: pentyl; PG: protecting group; PHOX: phosphinooxazoline; Phth: phthaloyl; Pin: pinacolato; Pybox: pyridine-bisoxazoline; r.t.: room temperature; TADDOL: α,α,α’,α’-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TEA: triethylamine; Tf: trifluoromethanesulfonyl; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TMS: trimethylsilyl; Tol: tolyl; Ts: 4-toluenesulfonyl (tosyl).

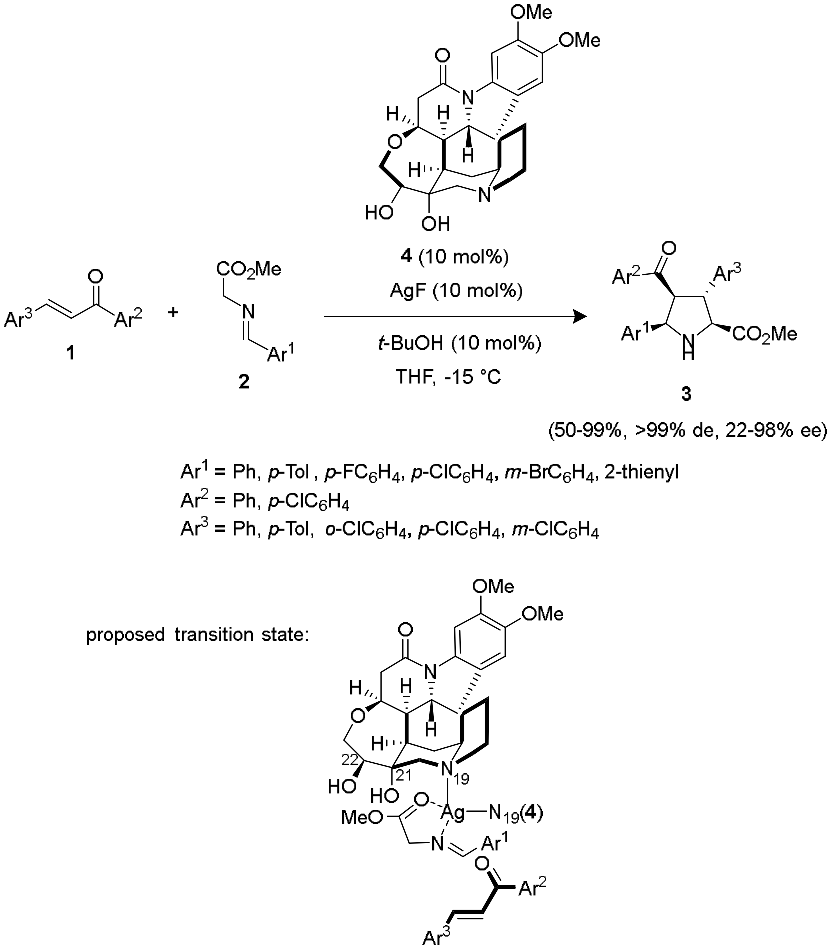
1. Introduction

In the last decades, asymmetric metal catalysis[1-6] has been widely employed to promote many types of enantioselective domino reactions,[7-21] allowing simple and economic access to a very large number of highly functionalized and complex chiral heterocyclic compounds.[22,23] This chapter updates the developments in the use of asymmetric domino reactions catalyzed by chiral metals applied to the synthesis of chiral heterocycles published since 2016. It is divided into four parts, dealing successively with the synthesis of monocyclic, bicyclic, tricyclic and tetracyclic chiral heterocycles through enantioselective metal-catalyzed domino reactions.

2. Synthesis of monocyclic heterocycles

2.1. Pyrrolidines

Among five-membered heterocycles,[24-28] chiral pyrrolidines play an important role both as key structures relevant to biologically active substances as well as chiral building blocks. Since chiral silver complexes have been shown to efficiently catalyze various types of domino reactions,[29-31] a synthesis of chiral pyrrolidines **3** was developed by Oh *et al.* in 2016 on the basis of an asymmetric domino reaction between α,β-unsaturated ketones **1** and imino esters **2** catalyzed by a chiral silver catalyst in situ generated from AgF and chiral 1,2-diol ligand **4** (Scheme 1).[32] The corresponding chiral pyrrolidines **3** were produced as single diastereomers (>99% de) from successive Michael and Mannich reactions with moderate to quantitative yields (50-99%) and low to excellent enantioselectivities (22-98% ee). In the possible transition state depicted in Scheme 1, the silver atom is coordinated by the two ligands through the N-19 tertiary amine.



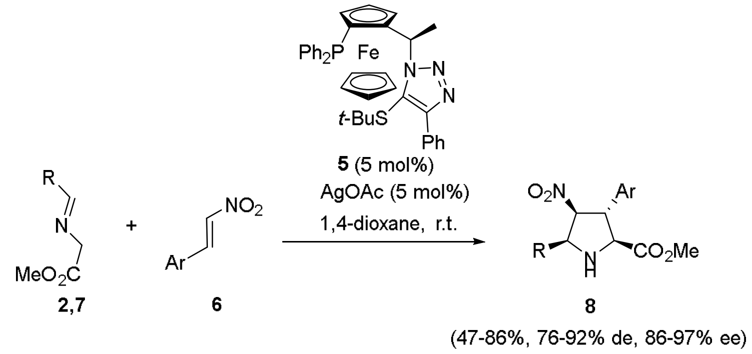
Ar^1 = Ph, p-Tol, p-FC_6H_4, p-ClC_6H_4, m-BrC_6H_4, 2-thienyl
Ar^2 = Ph, p-ClC_6H_4
Ar^3 = Ph, p-Tol, o-ClC_6H_4, p-ClC_6H_4, m-ClC_6H_4

Scheme 1. Synthesis of pyrrolidines through silver-catalyzed domino Michael/Mannich reaction.

The same year, Fukuzawa *et al.* employed another chiral silver complex derived from AgOAc and ferrocenyl chiral ligand **5** to promote enantioselective domino Michael/aza-Henry reactions of nitroalkenes **6** with imino esters **2**,**7**.[33] The process led to the corresponding chiral pyrrolidines **8** in moderate to high yields (47-86%) combined with both high diastereo- (76-92% de) and enantioselectivities (86-97% ee), as presented in Scheme 2.

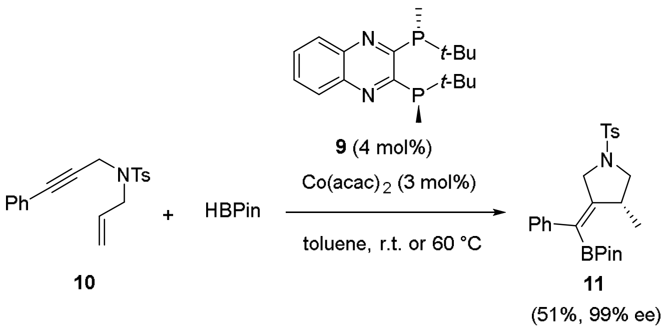
A range of chiral cobalt catalysts have also been recently successfully applied to promote asymmetric domino reactions due to the advantages of cobalt complexes, such as low toxicity and cost.[34-37] For example, a chiral cobalt catalyst in situ generated from Co(acac)$_2$ and chiral biphosphine ligand **9** was employed in

2017 by Ge *et al.* in an asymmetric domino *anti*-Markovnikov-hydroboration/cyclization reaction of nitrogen-tethered 1,6-enyne **10** with pinacolborane (Scheme 3).[38] The process afforded enantiopure pyrrolidine **11** in 51% yield.



R = Ph, *o*-Tol, *m*-Tol, *p*-Tol, *p*-MeOC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, 1-Naph, 2-thienyl, Cy
Ar = Ph, *o*-Tol, *p*-Tol, *p*-MeOC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, 2-furyl, ferrocenyl

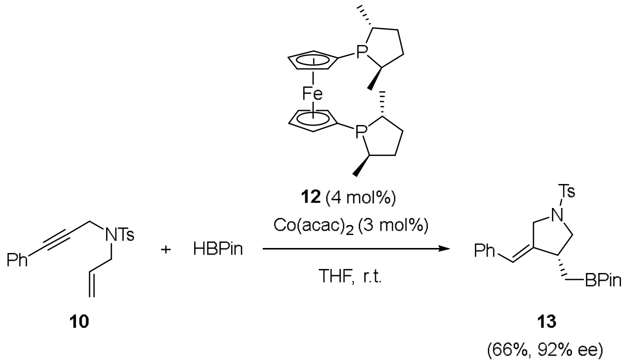
Scheme 2. Synthesis of other pyrrolidines through silver-catalyzed domino Michael/aza-Henry reaction.



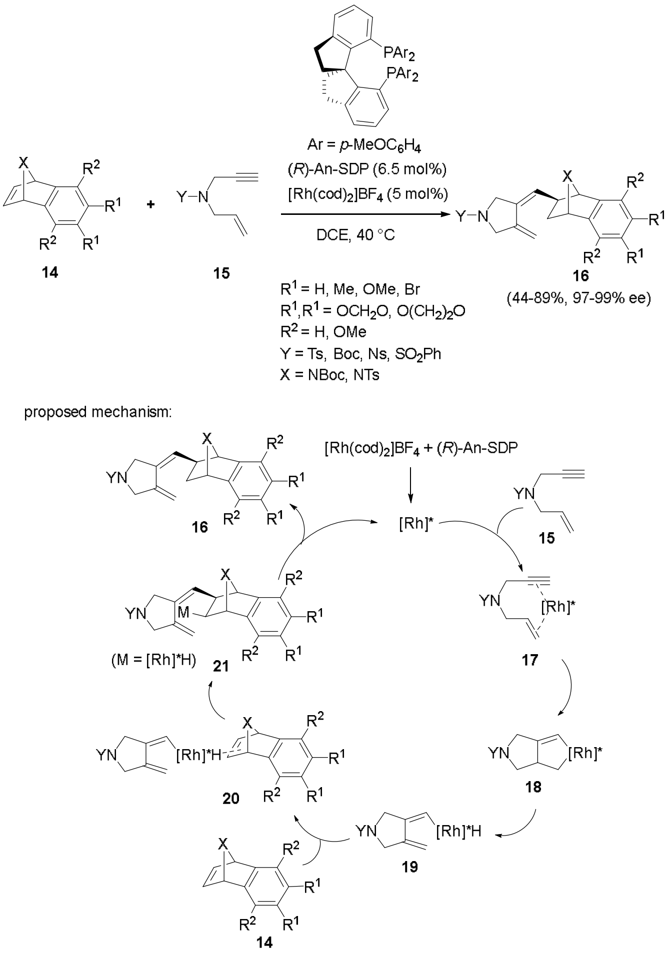
Scheme 3. Synthesis of a pyrrolidine through cobalt-catalyzed domino *anti*-Markovnikov-hydroboration/cyclization reaction.

While using chiral ligand **9** resulted in an *anti*-Markovnikov hydroboration of the alkene moiety of substrate **10** (Scheme 3), the authors showed that the involvement of another chiral ligand **12** combined with the same precatalyst resulted in the formation of chiral pyrrolidine **13** with 66% yield and 92% ee, arising from a Markovnikov hydroboration of the alkene group of nitrogen-tethered 1,6-enyne **10** with pinacolborane (Scheme 4).[38]

A novel synthesis of chiral 3,4-dimethylene-pyrrolidines bearing an oxa/azabenzonorbornadiene moiety was developed in 2018 by Fan *et al.* on the basis of an asymmetric domino reaction of oxa/azabenzonorbornadienes **14** with 1,6-enynes **15**.[39] It was promoted by a catalyst system composed of $[Rh(cod)_2]BF_4$ and chiral diphosphine ligand (*R*)-An-SDP, thus leading to enantiopure (97-99% ee) 3,4-dimethylene-pyrrolidines **16** in moderate to good yields (44-89%). A possible mechanism is proposed in Scheme 5, in which complex **17**, arisen from the coordination of rhodium catalyst to 1,6-enyne **15**, underwent a cyclization to afford intermediate **18**. Then, a β-hydride elimination gave intermediate **19** which coordinated to substrate **14** to provide intermediate **20**. A subsequent insertion of the alkene into the Rh–C bond led to intermediate **21** that afforded the final product **16**.



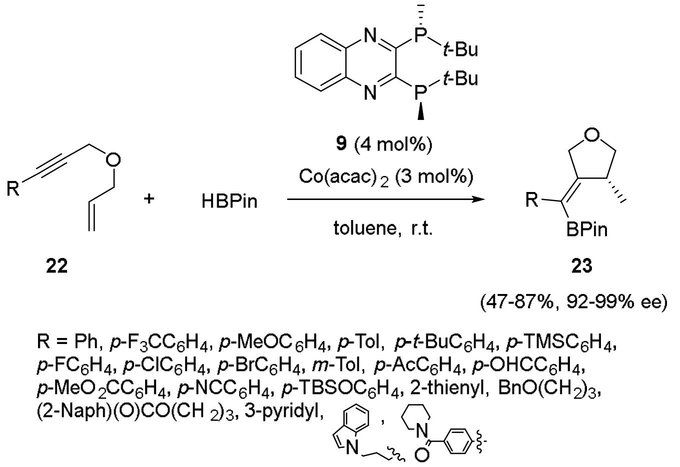
Scheme 4. Synthesis of a pyrrolidine through cobalt-catalyzed domino Markovnikov-hydroboration/cyclization reaction.



Scheme 5. Synthesis of 3,4-dimethylene-pyrrolidines through rhodium-catalyzed domino cyclization/β-hydride elimination/insertion reaction.

2.2. Other monocyclic heterocycles

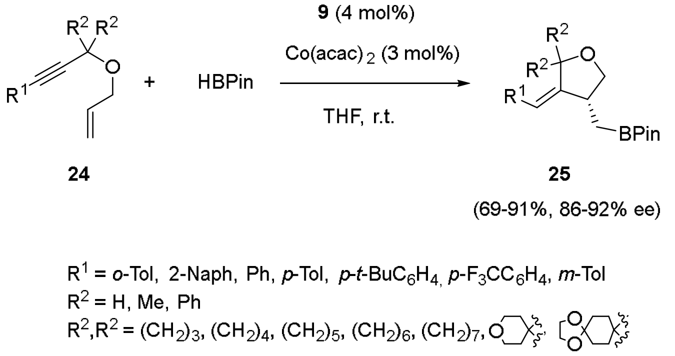
In 2017, Ge *et al.* described the synthesis of chiral tetrahydrofurans **23** on the basis of a domino *anti*-Markovnikov-hydroboration/cyclization reaction of oxygen-tethered 1,6-enynes **22** with pinacolborane (Scheme 6).[38] The reaction was promoted by a chiral cobalt catalyst in situ generated from $Co(acac)_2$ and chiral biphosphine ligand **9**, resulting in the formation of chiral tetrahydrofurans **23** in excellent enantioselectivities (92-99% ee) and moderate to high yields (47-87%).



R = Ph, p-$F_3CC_6H_4$, p-$MeOC_6H_4$, p-Tol, p-t-BuC_6H_4, p-$TMSC_6H_4$, p-FC_6H_4, p-ClC_6H_4, p-BrC_6H_4, m-Tol, p-AcC_6H_4, p-$OHCC_6H_4$, p-$MeO_2CC_6H_4$, p-NCC_6H_4, p-$TBSOC_6H_4$, 2-thienyl, $BnO(CH_2)_3$, (2-Naph)(O)CO$(CH_2)_3$, 3-pyridyl,

Scheme 6. Synthesis of tetrahydrofurans through cobalt-catalyzed domino *anti*-Markovnikov-hydroboration/cyclization reaction.

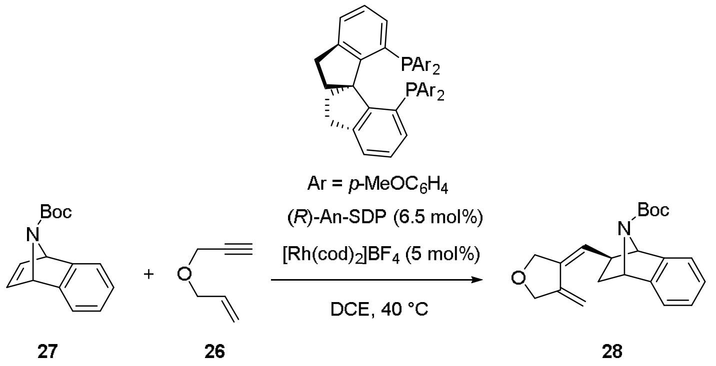
The authors found that chiral alkyl boronate esters **25**, instead of chiral vinyl-substituted boronate esters **23** (Scheme 6), were generated from the reaction of more sterically hindered oxygen-tethered 1,6-enynes **24** with pinacolborane in the presence of the same catalyst system.[38] As illustrated in Scheme 7, in this case a Markovnikov hydroboration occurred, delivering after subsequent cyclization of tetrahydrofurans **25** in both good to high yields (69-91%) and enantioselectivities (86-92% ee).



R^1 = o-Tol, 2-Naph, Ph, p-Tol, p-t-BuC_6H_4, p-$F_3CC_6H_4$, m-Tol
R^2 = H, Me, Ph
R^2,R^2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$, $(CH_2)_7$,

Scheme 7. Synthesis of tetrahydrofurans through cobalt-catalyzed domino Markovnikov-hydroboration/cyclization reaction.

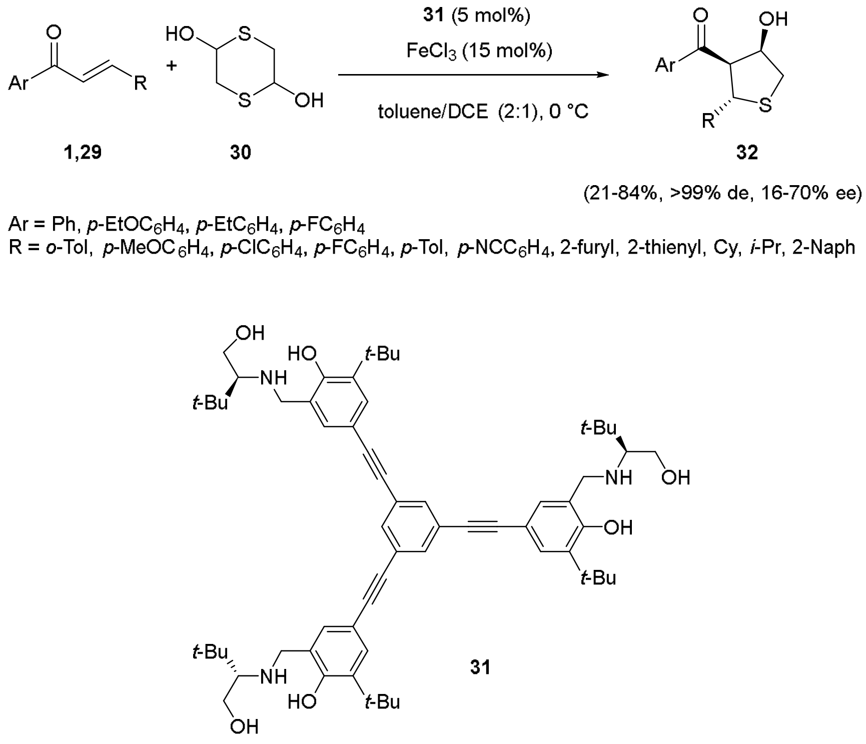
Chiral tetrahydrofuran **28** was synthesized in 2018 by Fan *et al.* through domino cyclization/addition reaction between oxygen-tethered 1,6-enyne **26** and azabenzonorbornadiene **27** (Scheme 8).[39]Errore. Il segnalibro non è definito. The process involved a combination of $[Rh(cod)_2]BF_4$ and chiral diphosphine ligand (R)-An-SDP as catalyst system, delivering enantiopure tetrahydrofuran **28** (98% ee) in 38% yield.



(38%, 98% ee)

Scheme 8. Synthesis of a tetrahydrofuran through rhodium-catalyzed domino cyclization/addition reaction.

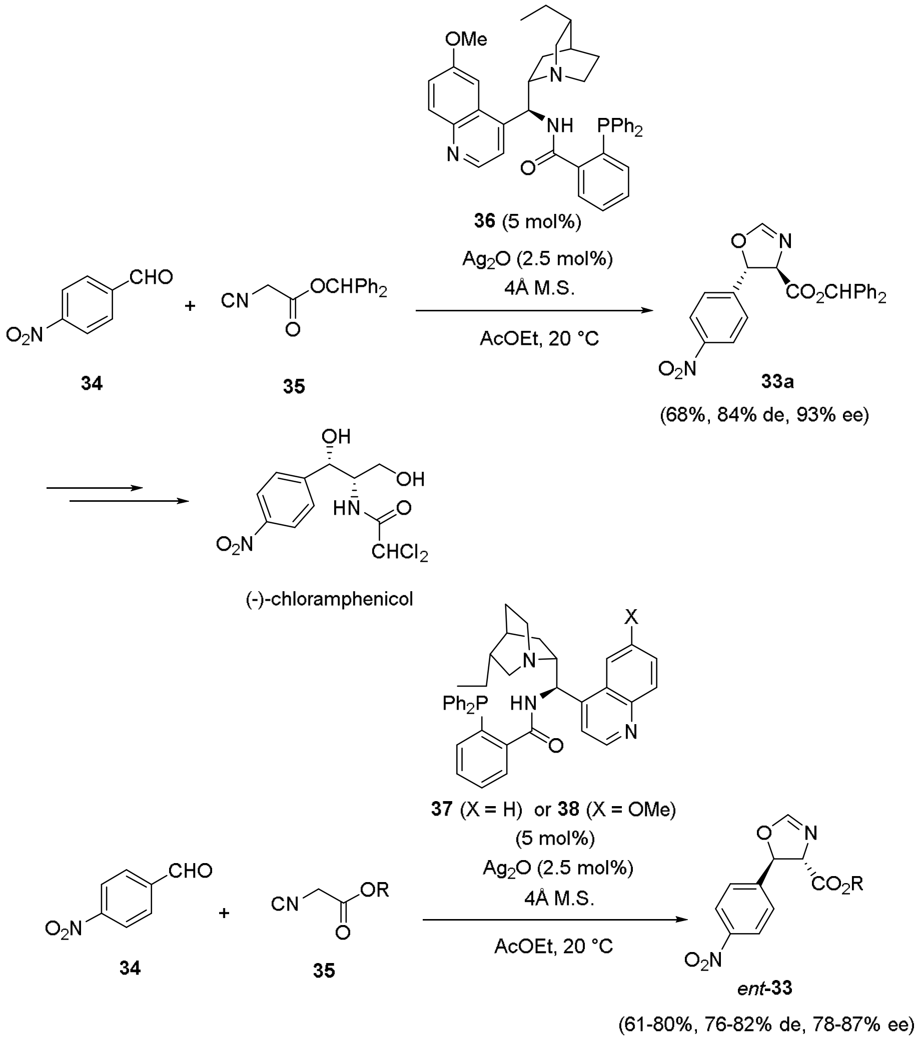
A synthesis of chiral tetrahydrothiophenes **32** was developed by Punniyamurthy *et al.* on the basis of an iron-catalyzed domino reaction of aromatic α,β-unsaturated ketones **1**/**29** with 1,4-dithiane-2,5-diol **30** (Scheme 9).[40] A combination of $FeCl_3$ with novel reusable chiral dendrimer ligand **31** was used as catalyst system, which triggered successive sulfa-Michael addition and aldol condensation to give chiral tetrahydrothiophenes **32** as single diastereomers (>99% de) in both low to high yields (21-84%) and enantioselectivities (16-70% ee).



Ar = Ph, p-$EtOC_6H_4$, p-EtC_6H_4, p-FC_6H_4
R = o-Tol, p-$MeOC_6H_4$, p-ClC_6H_4, p-FC_6H_4, p-Tol, p-NCC_6H_4, 2-furyl, 2-thienyl, Cy, i-Pr, 2-Naph

Scheme 9. Synthesis of tetrahydrothiophenes through iron-catalyzed domino sulfa-Michael/aldol reaction.

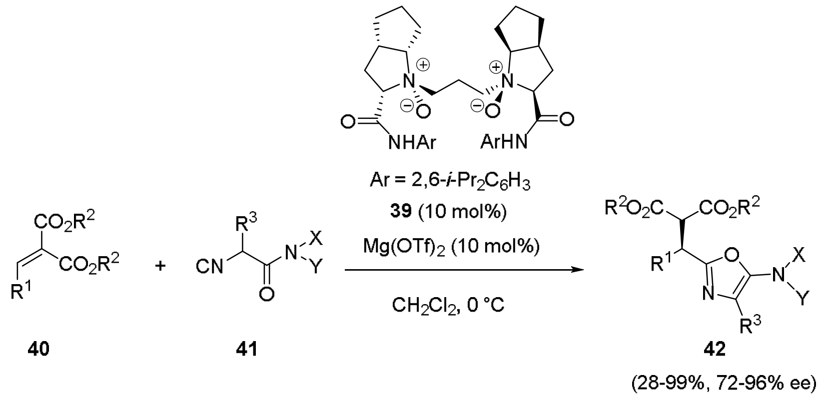
In 2016, Dixon *et al.* employed a combination of Ag_2O and chiral cinchona alkaloid **36** to develop a novel total synthesis of antibiotic (–)-chloramphenicol.[41] Actually, the latter was obtained from *trans*-oxazoline **33a** deriving from a domino reaction occurring between *p*-nitrobenzaldehyde **34** and isocyanoacetate **35** with 68% yield, 84% de and 93% ee. The process evolved through sequential aldol and cyclization reactions. It was found that other alkyl isocyanoacetates **35** were also compatible by using related chiral cinchona alkaloid ligands **37** and **38**, thus leading to chiral oxazolines *ent*-**33** in good yields (61-80%), diastereo- (76-82% de) and enantioselectivities (78-87% ee), as shown in Scheme 10.



R = *t*-Bu, Me, Bn, *p*-$MeOC_6H_4CH_2$, 3,5-$(F_3C)_2C_6H_3CH_2$,Ph_2CH

Scheme 10. Synthesis of oxazolines through silver-catalyzed domino aldol/cyclization reactions.

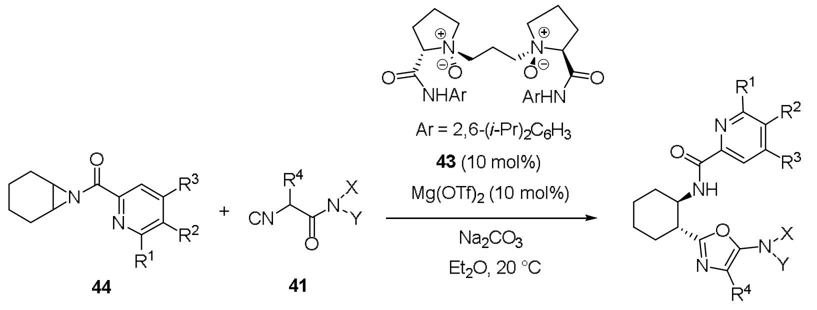
The same year, Feng *et al.* described the synthesis of chiral 2-alkyl-5-aminooxazoles **42** catalyzed by a chiral magnesium complex in situ generated from $Mg(OTf)_2$ and chiral *N,N'*-dioxide ligand **39**.[42] The process involved the Michael addition of α-isocyanoacetamides **41** to alkylidene malonates **40** followed by an intramolecular cyclization reaction, providing chiral 2-alkyl-5-aminooxazoles **42** in low to excellent yields (28-99%) and good enantioselectivities (72-96% ee), as shown in Scheme 11.



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

Scheme 11. Synthesis of 2-alkyl-5-aminooxazoles through magnesium-catalyzed domino Michael/cyclization reaction.

In 2019, the same authors employed related chiral *N,N'*-dioxide ligand **43** combined with Mg(OTf)$_2$ to promote the synthesis of other chiral 2-alkyl-5-aminooxazoles **45**.[43] The latter were obtained in both moderate to excellent yields (40-99%) and enantioselectivities (50-90% ee) from the ring-opening reaction of the corresponding *meso*-aziridines **44** with α-isocyanoacetamides **41** followed by intramolecular cyclization (Scheme 12).



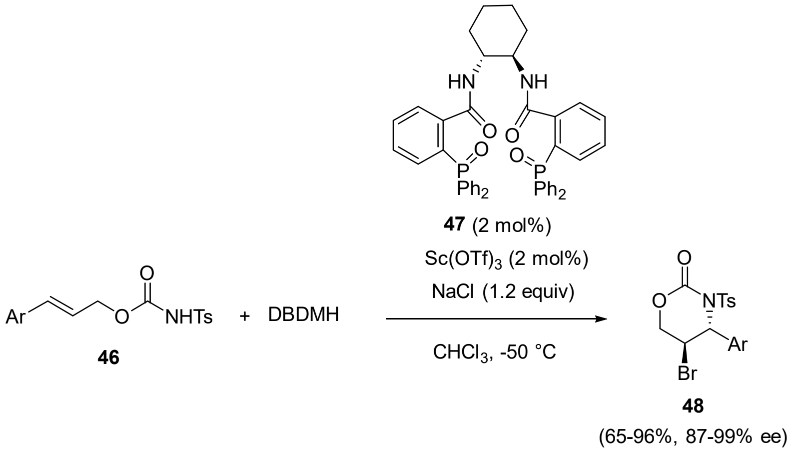
45

(40-99%, 50-90% ee)

R^1 = H, Cl
R^2 = H, Cl
R^1,R^2 = (CH=CH)$_2$
R^3 = H, Me, Cl, Br
R^4 = Bn, *t*-Bu, *i*-Pr, *i*-Bu, Ph
X,Y = (CH$_2$)$_2$O(CH$_2$)$_2$, (CH$_2$)$_5$, (CH$_2$)$_4$

Scheme 12. Synthesis of other 2-alkyl-5-aminooxazoles through magnesium-catalyzed domino ring-opening/cyclization reaction.

Earlier in 2016, a chiral scandium catalyst in situ generated from $Sc(OTf)_3$ and chiral diphosphine oxide ligand **47** was applied by Shi *et al.* to promote the synthesis of chiral aryl 5-bromo-1,3-oxazinan-2-ones **48** (Scheme 13).[44] The reaction occurred between (*E*)-cinnamyl tosylcarbamates **46** and DBDMH through successive bromination and amination reactions, delivering the domino products **48** in excellent enantioselectivities (87-99% ee) and good yields (65-96%).



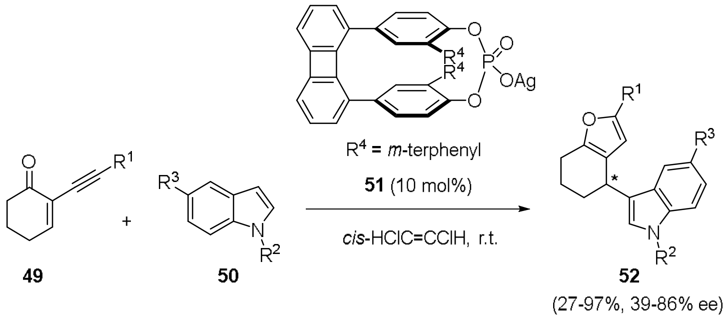
Ar = Ph, p-MeOC$_6$H$_4$, m-MeOC$_6$H$_4$, o-MeOC$_6$H$_4$, p-BrC$_6$H$_4$, m-BrC$_6$H$_4$, p-ClC$_6$H$_4$, m-FC$_6$H$_4$, p-FC$_6$H$_4$, 2,4,6-F$_3$C$_6$H$_2$, o-Tol, p-Tol, 3,5-Me$_2$C$_6$H$_3$, 2,4,6-Me$_3$C$_6$H$_2$, 1-Naph, 2-Naph, 2-thienyl

Scheme 13. Synthesis of aryl 5-bromo-1,3-oxazinan-2-ones through scandium-catalyzed domino bromination/amination reaction.

3. Synthesis of bicyclic heterocycles

3.1. Oxygenated heterocycles

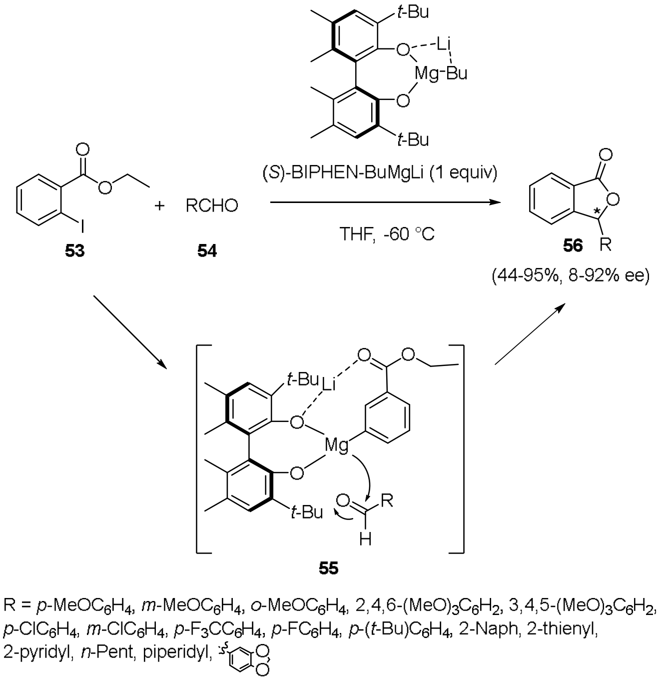
In 2018, Marinetti and Betzer reported the synthesis of chiral bicyclic furans **52** on the basis of an enantioselective silver-catalyzed domino reaction of 2-(1-alkynyl)-2-cyclohexenone **49** with 5-substituted indoles **50** (Scheme 14).[45] The reaction was catalyzed by preformed chiral silver phosphate **51**, evolving through successive cycloisomerization and addition reactions to deliver the final bicyclic furans **52** in low to excellent yields (27-97%) and moderate to high enantioselectivities (39-86% ee).



R^1 = Ph, p-MeOC$_6$H$_4$, Bn
R^2 = H, Me
R^3 = H, Me, F, OMe

Scheme 14. Synthesis of bicyclic furans through silver-catalyzed domino cycloisomerization/addition reaction.

The same year, a synthesis of chiral 3-substituted isobenzofuranones **56** was disclosed by Gros *et al.* through an enantioselective magnesium-catalyzed domino reaction occurring between 2-ethyliodobenzoate **53** and aldehydes **54**.[46] (*S*)-BIPHEN-BuMgLi was used as catalyst which formed intermediate **55** by reaction with 2-ethyliodobenzoate **53**. Then, the addition of the latter to aldehyde **54** followed by intramolecular cyclization led to final product **56** in low to high enantioselectivities (8-92% ee) and moderate to high yields (44-95%), as shown in Scheme 15.



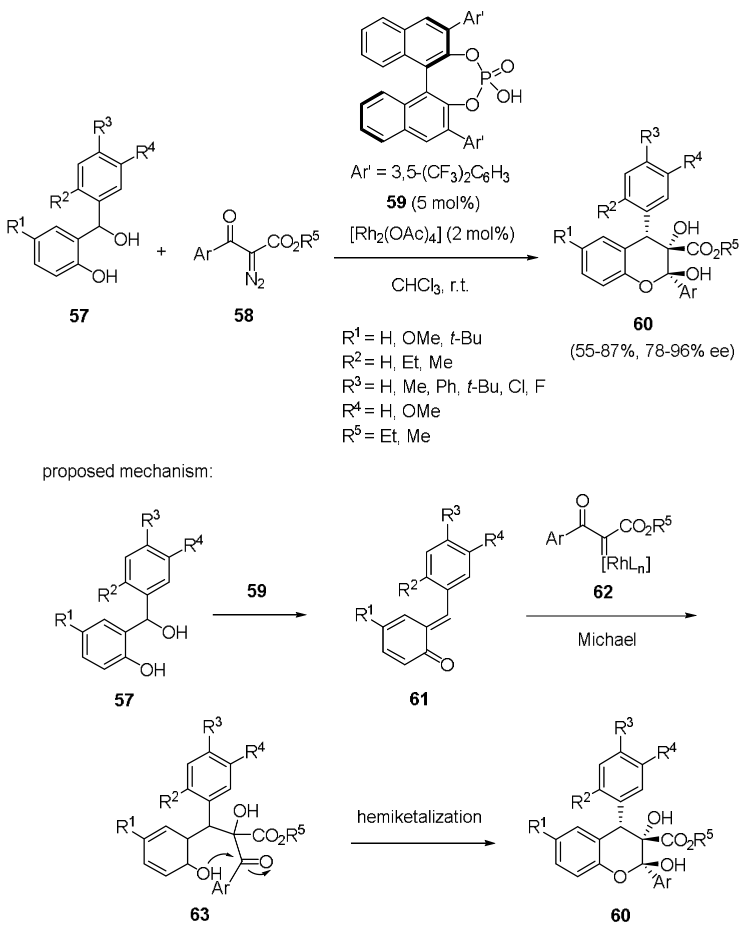
R = *p*-MeOC$_6$H$_4$, *m*-MeOC$_6$H$_4$, *o*-MeOC$_6$H$_4$, 2,4,6-(MeO)$_3$C$_6$H$_2$, 3,4,5-(MeO)$_3$C$_6$H$_2$, *p*-ClC$_6$H$_4$, *m*-ClC$_6$H$_4$, *p*-F$_3$CC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-(*t*-Bu)C$_6$H$_4$, 2-Naph, 2-thienyl, 2-pyridyl, *n*-Pent, piperidyl,

Scheme 15. Synthesis of 3-substituted isobenzofuranones through magnesium-catalyzed domino addition/cyclization reaction.

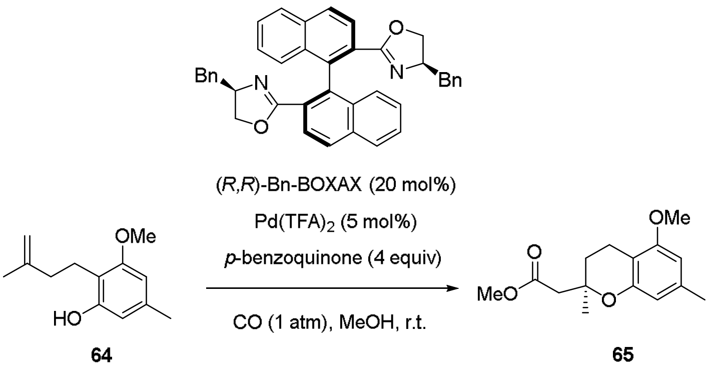
Earlier in 2016, densely functionalized chiral chromans **60** were synthesized by Schneider *et al.* by using [Rh$_2$(OAc)$_4$] and chiral phosphoric acid **59** as catalyst system.[47] As shown in Scheme 16, the reaction of *ortho*-hydroxy benzhydryl alcohols **57** with diazoesters **58** evolved through the Michael addition of rhodium carbene **62** to intermediate *ortho*-quinone methides **61** followed by hemiketalization reaction of intermediate **63**, leading to chiral chromans **60** as single diastereomers in good yields (55-87%) and high enantioselectivities (78-96% ee).

Palladium has been early applied to promote many enantioselective domino transformations.[48,49] For example in 2016, Tietze *et al.* reported 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 (*R,R*)-Bn-BOXAX ligand.[50] As illustrated in Scheme 17, alkenyl phenol **64** reacted through Wacker, carbonylation and then methoxylation to afford chiral chroman **65** in 71% yield and 93% ee.

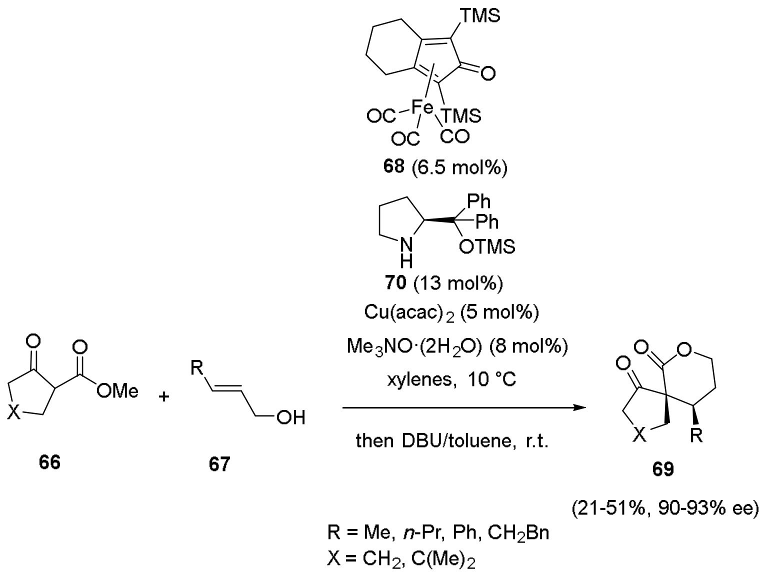
In 2018, Quintard and Rodriguez reported the synthesis of chiral bicyclic δ-lactones **69** through enantioselective domino reactions of cyclic β-keto esters **66** with allylic alcohols **67**, employing a combination of achiral iron tricarbonyl complex **68**, Cu(acac)$_2$ and chiral proline derivative **70** (Scheme 18).[51] The process evolved through successive oxidation, Michael addition, reduction and lactonization to give bicyclic δ-lactones **69** in high enantioselectivities (90-93% ee) combined with low to moderate yields (21-51%).



Scheme 16. Synthesis of chromans through rhodium-catalyzed domino Michael/hemiketalization reaction.



Scheme 17. Synthesis of a chroman through palladium-catalyzed domino Wacker/carbonylation/methoxylation reaction.



Scheme 18. Synthesis of bicyclic δ-lactones through multicatalyzed domino oxidation/Michael/reduction/lactonization reaction.

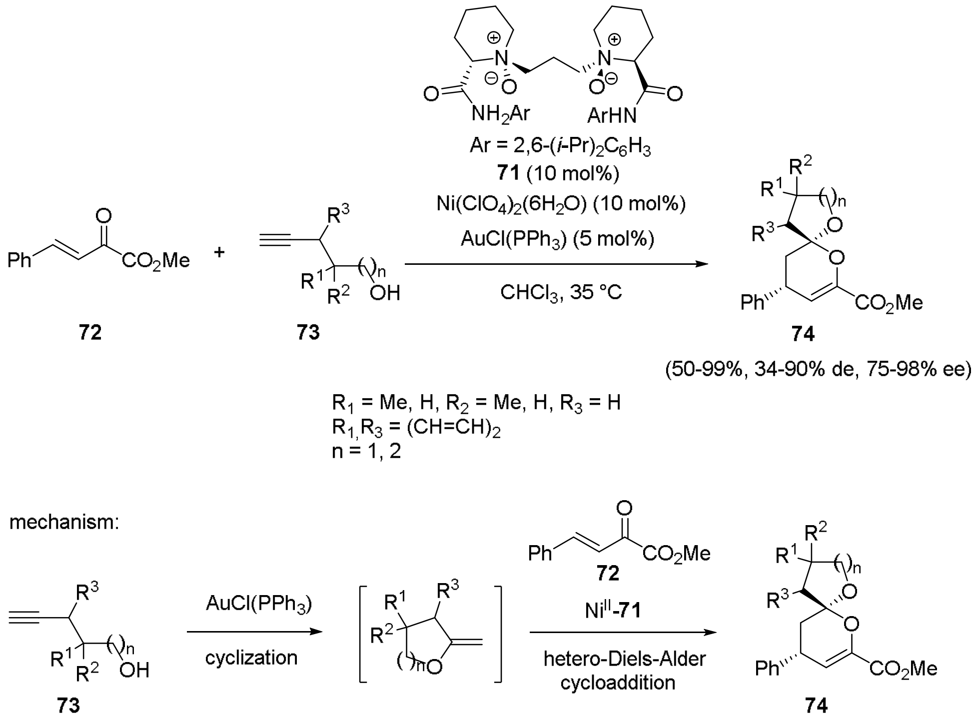
Chiral nickel catalysts[52-55] have also been successfully applied to promote enantioselective domino processes.[56] For example in 2016, Feng and Liu reported an example of bimetallic asymmetric relay catalysis based on the use of a chiral nickel complex *in situ* generated from $Ni(ClO_4)_2{\cdot}6H_2O$ and chiral *N,N'*-dioxide ligand **71** combined with an achiral gold catalyst, such as $AuCl(PPh_3)$.[57] It underwent an enantioselective domino cycloisomerization/hetero-Diels-Alder reaction of α-keto ester **72** with alkynyl alcohols **73**, providing the corresponding chiral bicyclic spiro-ketals **74** in moderate to quantitative yields (50-99%), low to high diastereoselectivities (34-90% de) and high enantioselectivities (75-98% ee), as shown in Scheme 19. The first cycloisomerization step of the alkynyl alcohol was catalyzed by $AuCl(PPh_3)$, leading to a five-membered intermediate, which subsequently underwent an asymmetric hetero-Diels-Alder cycloaddition with α-keto ester **72** catalyzed by the chiral nickel catalyst to yield the final domino product **74**.

3.2. Nitrogenated heterocycles

In 2016, chiral bicyclic pyrrolidines **78** were synthesized by Wang *et al.* through enantioselective domino reactions of imino esters **75** with *N*-(2-*t*-butylphenyl)maleimide **76** using a chiral silver catalyst in situ generated from AgOAc and chiral phosphine ligand **77** (Scheme 20).[58] Chiral bicyclic pyrrolidines **78** ensuing from successive Michael addition and Mannich reaction were obtained in high yields (86-99%), diastereo- (>90% de) and enantioselectivities (90->99% ee).

Similar reactions were also investigated by Xia and Xu in the presence of another catalyst system composed of AgF and Xing-Phos ligand.[59] In this case, the reaction of *N*-arylmaleimides **79** with aromatic imino esters **2**,**80** afforded the corresponding bicyclic pyrrolidines **81** as single diastereomers (>96% de) in high yields (83-99%) and enantioselectivities (65-98% ee), as depicted in Scheme 21.

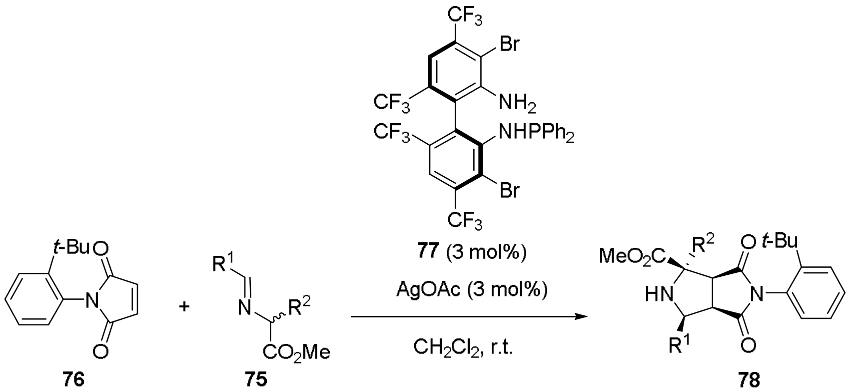
In 2018, Kong *et al.* reported the synthesis of chiral bis-heterocycles **84** based on an enantioselective nickel-catalyzed domino reaction of alkenes **82** with aryl bromides **83** (Scheme 22).[60] The reaction was performed with excellent enantioselectivities (94-98% ee), affording products **84** in moderate to good yields (40-81%). It employed a combination of $Ni(cod)_2$ and chiral ferrocenyl phosphine ligand **85** as catalyst system to undergo a cyclization followed by a cross-coupling reaction.



(50-99%, 34-90% de, 75-98% ee)

R_1 = Me, H, R_2 = Me, H, R_3 = H
R_1,R_3 = $(CH=CH)_2$
n = 1, 2

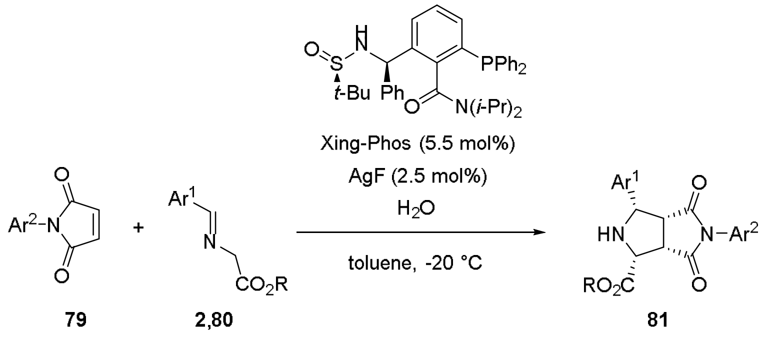
Scheme 19. Synthesis of bicyclic spiro-ketals through gold- and nickel-catalyzed domino cycloisomerization/hetero-Diels-Alder cycloaddition reaction.



(86-99%, >90% de, 90->99% ee)

R^1 = Ph, p-ClC$_6$H$_4$, p-Tol, m-ClC$_6$H$_4$, p-BrC$_6$H$_4$, m-BrC$_6$H$_4$, o-FC$_6$H$_4$,
2-Naph, p-MeOC$_6$H$_4$, m-MeOC$_6$H$_4$, 2-thienyl, (E)-PhCH=CH, n-Bu
R^2 = H, Me, Et, n-Bu, i-Bu, Bn

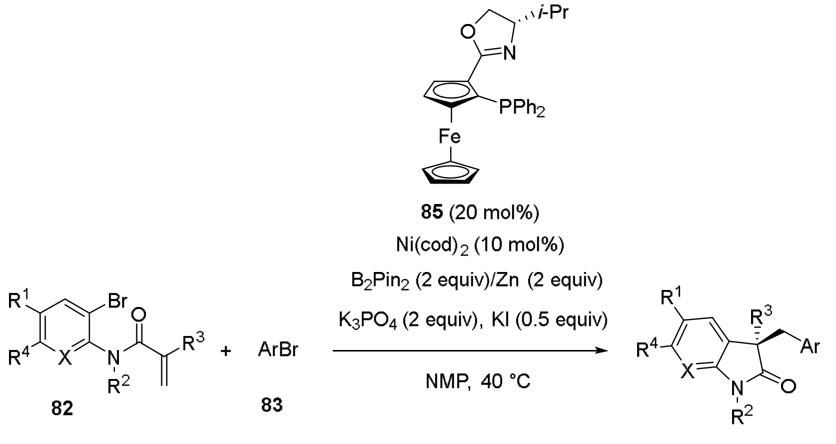
Scheme 20. Synthesis of bicyclic pyrrolidines through silver-catalyzed domino Michael/Mannich reaction.



(83-99%, >96% de, 65-98% ee)

Ar^1 = Ph, o-$MeOC_6H_4$, m-$MeOC_6H_4$, m-BrC_6H_4, p-Tol, p-FC_6H_4, p-ClC_6H_4, p-BrC_6H_4, p-PhC_6H_4, p-$MeSC_6H_4$, 3,5-$(F_3C)_2C_6H_3$
Ar^2 = Ph, m-ClC_6H_4, m-Tol, m-BrC_6H_4, p-$EtOC_6H_4$, p-$MeOC_6H_4$, p-BrC_6H_4, 3,5-$Me_2C_6H_3$
R = Me, Et

Scheme 21. Synthesis of other bicyclic pyrrolidines through silver-catalyzed domino Michael/Mannich reaction.

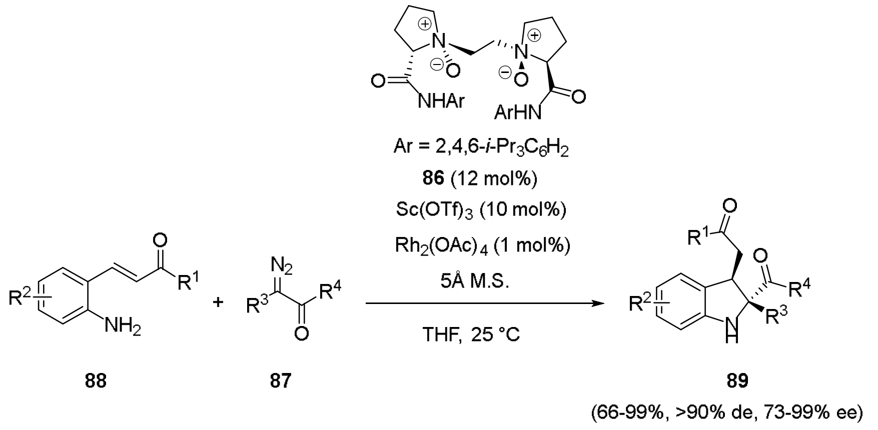


X = CH, C(Me), N
R^1 = H, Me, F
R^2 = Me, Bn
R^3 = Me, Bn, n-Hex, i-Pr, $MeOCH_2$
R^4 = H, Cl, Me, Cl, OMe
Ar = Ph, p-Tol, 3,4,5-$MeO_3C_6H_2$

(40-81%, 94-98% ee)

Scheme 22. Synthesis of bicyclic 2-pyrrolidinones through nickel-catalyzed domino cyclization/cross-coupling reaction.

In the same year, Feng and Liu described an example of bimetallic relay catalysis applied to the synthesis of chiral 2,2,3-trisubstituted indolines.[61] As presented in Scheme 23, the catalyst system consisted in a combination of $Sc(OTf)_3$, chiral *N,N'*-dioxide ligand **86** and $Rh_2(OAc)_4$, which promoted the intramolecular trapping of ammonium ylides generated from α-diazoketones **87** with 2-aminophenyl-substituted α,β-unsaturated ketones **88**. This domino Michael/cyclization process yielded a range of chiral indolines **89** as single diastereomers (>90% de) in good to excellent yields (66-99%) and enantioselectivities (73-99% ee).



R^1 = Ph, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-F$_3$CC$_6$H$_4$, *p*-Tol, *p*-MeOC$_6$H$_4$, *p*-PhC$_6$H$_4$, 2-furyl, 3-thiophenyl, 1-Naph, 2-Naph, Me, *n*-Bu, Cy,
R^2 = H, 5-F, 4-Cl, 4-Br, 4-F$_3$C, 4-MeO
R^3 = Ph, *o*-FC$_6$H$_4$, *m*-FC$_6$H$_4$, *m*-F$_3$CC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-Tol
R^4 = Me, Et, *n*-Bu, *i*-Bu, *c*-Pr

Scheme 23. Synthesis of 2,2,3-trisubstituted indolines through rhodium- and scandium-catalyzed domino Michael/cyclization reaction.

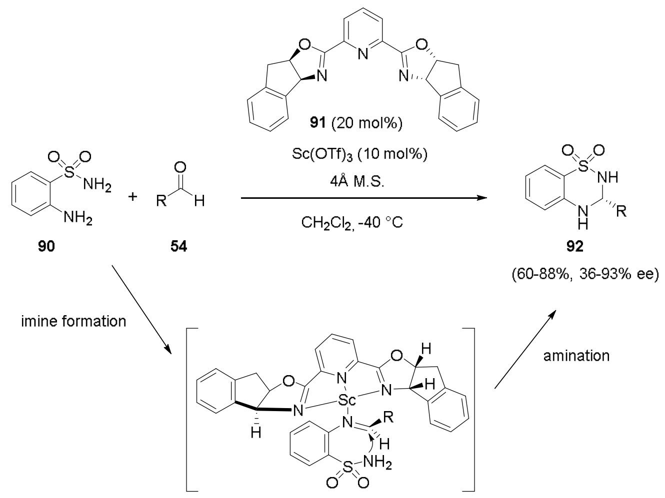
Earlier in 2016, Zhou *et al.* developed a novel access to chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides **92**, which employed a chiral scandium catalyst derived from Sc(OTf)$_3$ and chiral Pybox ligand **91** (Scheme 24).[62] The domino process involved an imine formation from aldehydes **54** and 2-aminobenzenesulfonamide **90** followed by an intramolecular amination reaction to provide products **92** in moderate to high yields (60-88%) and enantioselectivities (36-93% ee).

The first asymmetric synthesis of benzimidazoles based on a metal-catalyzed domino process was reported in 2016 by Liu and Feng.[63] The catalytic system consisted of ScCl$_3$·(H$_2$O)$_6$ and chiral *N,N'*-dioxide ligand **98** (Scheme 25). The reaction occurred between cyclopranes **93** and diamines **94**, which firstly underwent a ring-opening reaction to give **95**. The latter intermediate was then submitted to an intramolecular cyclization to provide **96**, which subsequently underwent a retro-Mannich reaction to afford final products **97** in high enantioselectivities (80-97% ee) and moderate to quantitative yields (56-99%).

4. Synthesis of tricyclic heterocycles

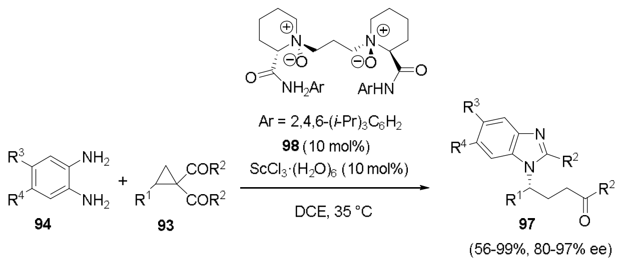
In 2019, Feng *et al.* employed chiral *N,N'*-dioxide ligand **43** combined with Mg(OTf)$_2$ to promote the asymmetric synthesis of spiroindolines **99**.[43] The latter were obtained in moderate to excellent yields (50-99%), diastereoselectivities (50->90% de) as well as enantioselectivities (70-97% ee) from the ring-opening reaction of the corresponding *meso*-aziridines **44** with C2-substituted 2-isocyanoethylindoles **100** followed by intramolecular cyclization (Scheme 26).

Earlier in 2016, chiral tricyclic indolines **104** were synthesized by Reisman *et al.* through the one-step reaction of amidoacrylate **101** with indoles **102** promoted by a combination of ZrCl$_4$ with chiral BINOL-derived ligand **103** (Scheme 27).[64] The process occurred with high enantioselectivities (81-91% ee), moderate diastereoselectivities (50-66% de) and good yields (56-93%). The domino reaction evolved through successive Michael addition, protonation and aza-Prins reaction.



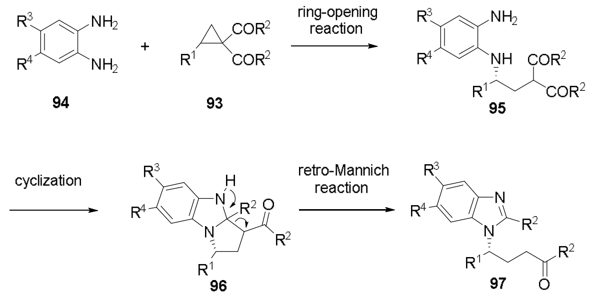
R = *i*-Bu, *i*-Pr, *t*-BuCH$_2$, Cy, *c*-Pent, *c*-Pr, Bn, BnCH$_2$, Ph, *p*-MeOC$_6$H$_4$, *p*-BrC$_6$H$_4$, *m*-BrC$_6$H$_4$, *o*-BrC$_6$H$_4$, 3-Br-4-MeOC$_6$H$_3$, 1-furyl

Scheme 24. Synthesis of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides through scandium-catalyzed domino imine formation/amination reaction.

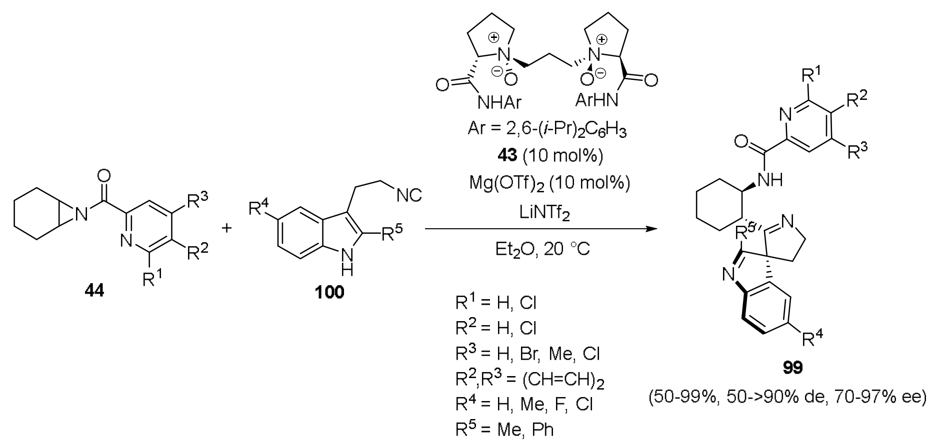


R^1 = Ph, *p*-MeOC$_6$H$_4$, *p*-Tol, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *m*-Tol, *m*-ClC$_6$H$_4$, *o*-Tol, 3,4-Cl$_2$C$_6$H$_3$, 1-Naph, 2-Naph, vinyl, Me
R^2 = Ph, *p*-Tol, *p*-FC$_6$H$_4$
R^3 = H, Me, OMe, F, Cl, Br, NO$_2$
R^4 = H, Me, OMe, F, Cl, Br, NO$_2$

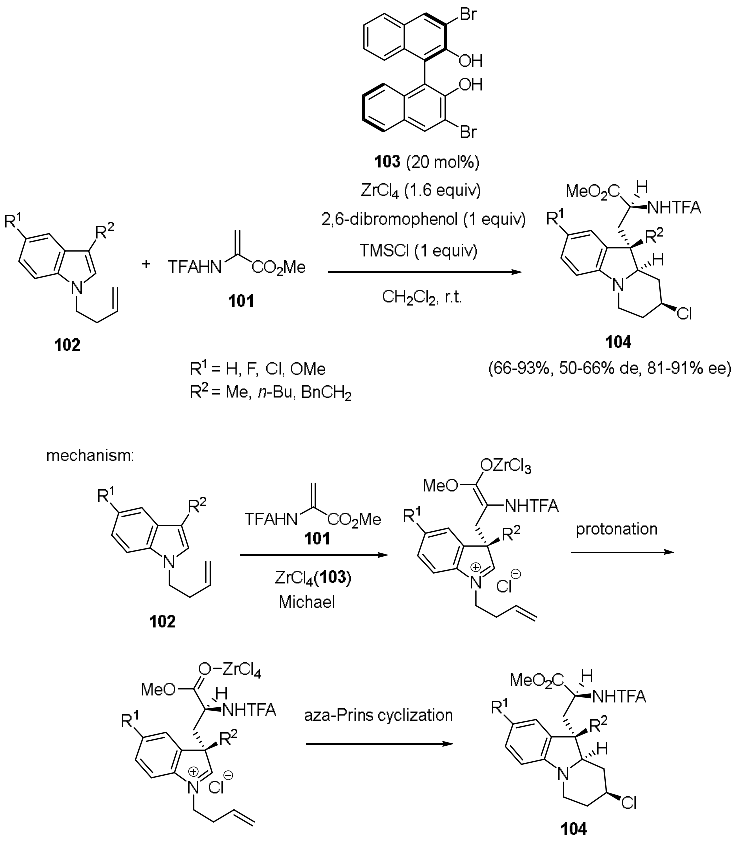
mechanism:



Scheme 25. Synthesis of benzimidazoles through scandium-catalyzed domino ring-opening/cyclization/retro-Mannich reaction.

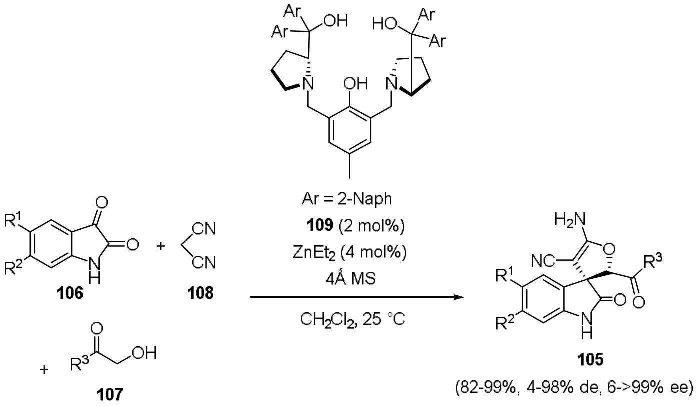


Scheme 26. Synthesis of spiroindolines through magnesium-catalyzed domino ring-opening/cyclization reaction.



Scheme 27. Synthesis of tricyclic chiral indolines through zirconium-catalyzed domino Michael/protonation/aza-Prins reaction.

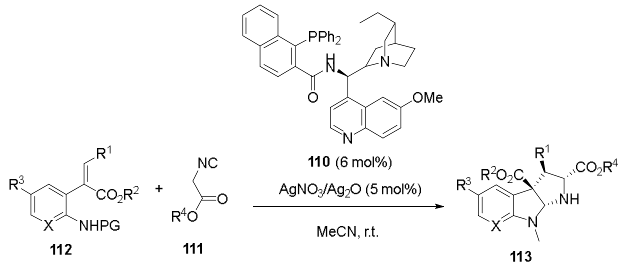
In 2019, Wang *et al.* reported the synthesis of chiral 3,3′-dihydrofuran spirooxindoles **105** on the basis of an enantioselective zinc-catalyzed three-component reaction of isatins **106**, α-hydroxy ketones **107** and malononitrile **108** (Scheme 28).[65] The process involved a chiral bimetallic catalyst in situ generated from $ZnEt_2$ and chiral triol ligand **109**. It evolved through a domino Knoevenagel/Michael/cyclization reaction, affording highly functionalized spirooxindoles **105** in high yields (82-99%), low to excellent diastereoselectivities (4-98% de) and high enantioselectivities in most cases (6->99% ee).



R^1 = H, Me, OMe, F, Cl, Br
R^2 = H, Br
R^3 = Ph, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, *p*-Tol, *m*-ClC_6H_4, *m*-BrC_6H_4, *m*-Tol, *o*-$MeOC_6H_4$, 2-Naph, 2-thienyl, 2,5-$(MeO)_2C_6H_3$, Me

Scheme 28. Synthesis of 3,3'-dihydrofuran spirooxindoles through zinc-catalyzed domino Knoevenagel/Michael/cyclization reaction.

In 2016, a combination of $AgNO_3/Ag_2O$ and cinchona alkaloid ligand **110** was employed by Xie *et al.* in a novel asymmetric synthesis of *cis*-3a,8a-hexahydropyrrolo[2,3-*b*]indoles **113**.[66] These multifunctionalized products arose from the reaction of isocyanoacetates **111** with acrylates **112** according to sequential Michael addition and cyclization reactions (Scheme 29). Good yields (73-99%) and variable stereoselectivities (16->90% de, 0-90% ee) were reported.

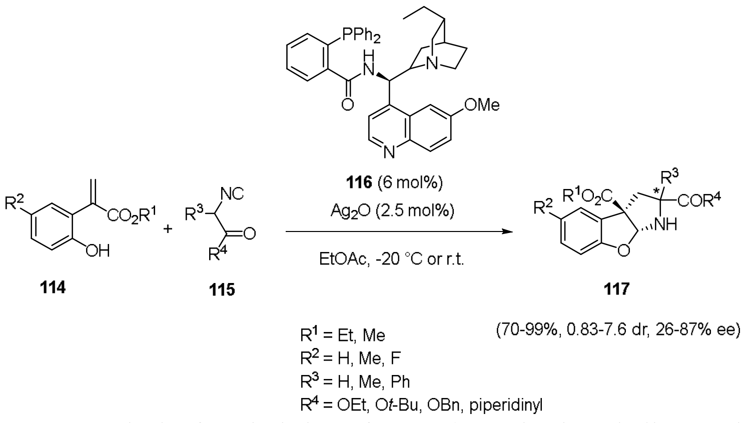


(73-99%, 16->90% de, 0-90% ee)

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

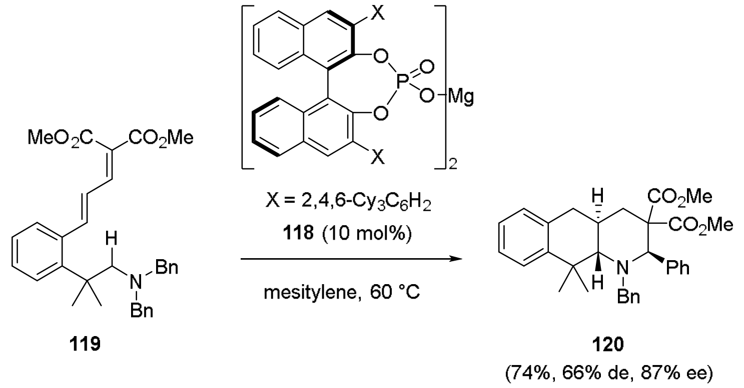
Scheme 29. Synthesis of *cis*-3a,8a-hexahydropyrrolo[2,3-*b*]indoles through silver-catalyzed domino Michael/cyclization reaction.

In the same context, these authors also disclosed in 2018 the reaction of isocyanoacetates **115** with acrylates **114** to give, in the presence of Ag_2O and related cinchona alkaloid ligand **116**, the corresponding chiral tetrahydrobenzofuro[2,3-*b*]pyrroles **117** as mixtures of two diastereomers (0.83-7.6 dr) in high yields (70-99%) and low to high enantioselectivities (26-87% ee), as shown in Scheme 30.[67]



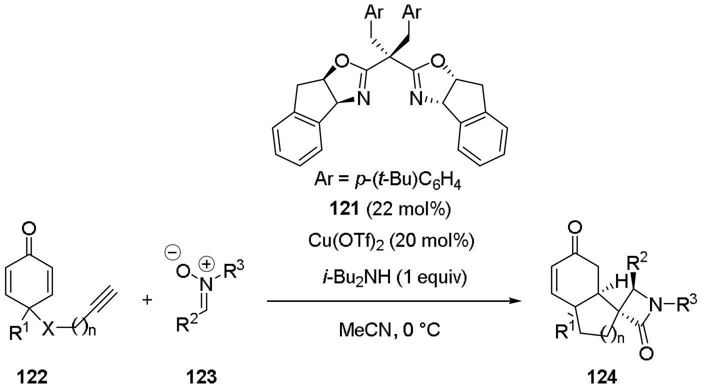
Scheme 30. Synthesis of tetrahydrobenzofuro[2,3-*b*]pyrroles through silver-catalyzed domino Michael/cyclization reaction.

In 2018, chiral preformed magnesium catalyst **118** was employed by Mori and Akiyama to promote an asymmetric synthesis of tricyclic piperidine **120** from cinnamylidene malonate **119** (Scheme 31).[68] This substrate underwent a silver-catalyzed [1,5]-hydride shift followed by a cyclization to provide piperidine **120** in 74% yield, 66% de and 87% ee.



Scheme 31. Synthesis of a tricyclic piperidine through magnesium-catalyzed domino [1,5]-hydride shift/cyclization reaction.

Asymmetric domino reactions can also be promoted by chiral greener copper catalysts.[69,70] For example in 2018, an asymmetric synthesis of spirocyclic lactams **124** was reported by Enders *et al.* using copper catalysis.[71] Indeed, cyclohexadienones **122** reacted with nitrones **123** in the presence of $Cu(OTf)_2$ and chiral bisoxazoline ligand **121** as the catalytic system to give domino products **124** in high enantioselectivities (82-97% ee), good diastereoselectivities (72->90% de) and yields (55-94%) through consecutive Kinugasa and Michael reactions (Scheme 32).

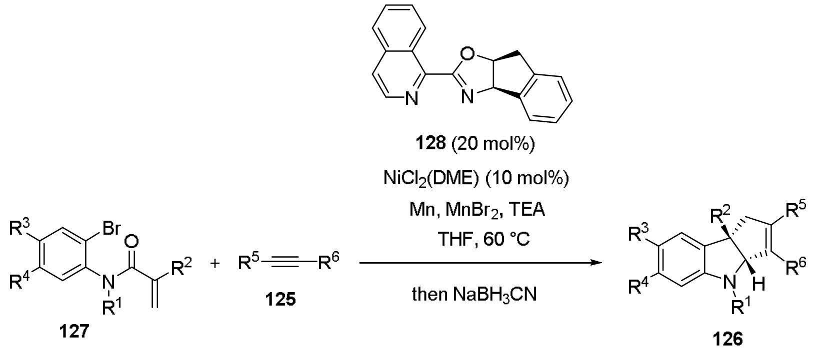


(55-94%, 72->90% de, 82-97% ee)

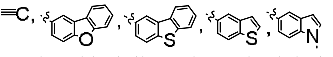
X = O, CH_2
n = 1-2
R^1 = Ph, Me, Et, *n*-Pr, *n*-Bu, *n*-Pent, *n*-Hex, Br, OMe
R^2 = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *m*-BrC_6H_4, *p*-Tol, 2-furyl
R^3 = Ph, *p*-Tol, *p*-FC_6H_4, *p*-BrC_6H_4

Scheme 32. Synthesis of spirocyclic lactams through copper-catalyzed domino Kinugasa/Michael reaction.

In 2019, asymmetric nickel catalysis was applied by Kong *et al.* in a novel one-pot synthesis of chiral 2,3-fused cyclopentannulated indolines **126** (Scheme 33).[72] These highly substituted products arose from the domino reductive cyclization reaction occurring between internal alkynes **125** and acrylamides **127** performed in the presence of a combination of $NiCl_2$(DME) and chiral Pybox ligand **128** as the catalyst and Mn as reducing agent. These biologically interesting products were obtained as single regioisomers in low to high yields (26-88%) and excellent enantioselectivities (85-96% ee).



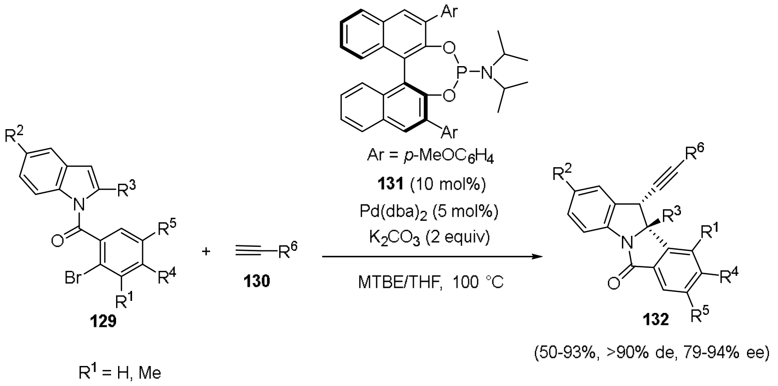
(26-88%, 85-96% ee)

R^1 = Me, Bn
R^2 = Me, Bn, *n*-Hex
R^3 = H, F, CF_3, Me, OMe
R^4 = H, Me, OMe, Cl
R^3,R^4 = $(CH{=}CH)_4$
R^5 = Me, *n*-Pent, *n*-Pr, Ph
R^6 = Ph, *p*-$MeOC_6H_4$, *p*-Tol, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-$F_3CC_6H_4$,
m-Tol, 2-Naph, *n*-Pr, PhC≡C, 

Scheme 33. Synthesis of 2,3-fused cyclopentannulated indolines through nickel-catalyzed domino reductive cyclization reaction.

5. Synthesis of tetracyclic heterocycles

In 2017, Jia *et al.* employed asymmetric palladium catalysis to develop a synthesis of chiral 2,3-disubstituted indolines **132** (Scheme 34).[73] It was based on the reaction of indoles **129** with terminal alkynes **130** promoted by a chiral palladium catalyst in situ generated from Pd(dba)$_2$ and chiral phosphoramidite ligand **131**. The formed complex products **132** were obtained through consecutive Heck and Sonogashira reactions as almost single diastereomers (>90% de) with high enantioselectivities (79-94% ee) and moderate to high yields (50-93%).



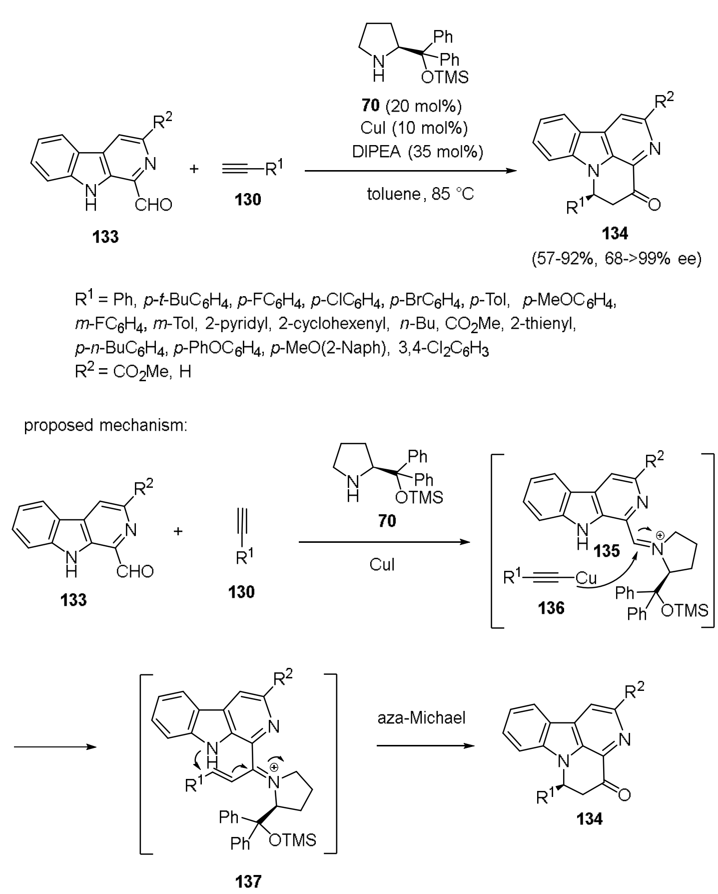
R^1 = H, Me
R^2 = H, *i*-Pr, Me, Cl, F
R^3 = Me, Ph, *p*-$F_3CC_6H_4$, 2-furyl, Et, CO_2Me
R^4 = H, OMe
R^5 = H, OMe, Me, F
R^6 = Ph, *p*-$MeOC_6H_4$, *p*-Tol, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-(Pent)C_6H_4, *p*-PhC_6H_4, *p*-$F_3CC_6H_4$, *p*-(OPent)C_6H_4, *p*-(*t*-Bu)C_6H_4, *p*-(MeO_2C)C_6H_4, *p*-NCC_6H_4, *p*-$NCCH_2C_6H_4$, *p*-(F_3CO)C_6H_4, *p*-(OCH)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 34. Synthesis of 2,3-disubstituted indolines through palladium-catalyzed domino Heck/Sonogashira reaction.

Earlier in 2016, chiral 5,6-dihydrocanthin-4-ones **134** were prepared in moderate to high yields (57-92%) and enantioselectivities (68->99% ee) from a domino reaction promoted by a chiral copper catalyst derived from CuI and chiral proline derivative **70**.[74] The reaction occurred between terminal alkynes **130** and 1-formyl-9*H*-β-carbolines **133** (Scheme 35). The mechanism involved the formation of iminium species **135** from aldehyde **133** and amine catalyst **70**. Then, iminium **135** reacted with copper-coordinated alkyne **136** to give intermediate **134**, which further underwent an intramolecular aza-Michael addition to afford the final product.

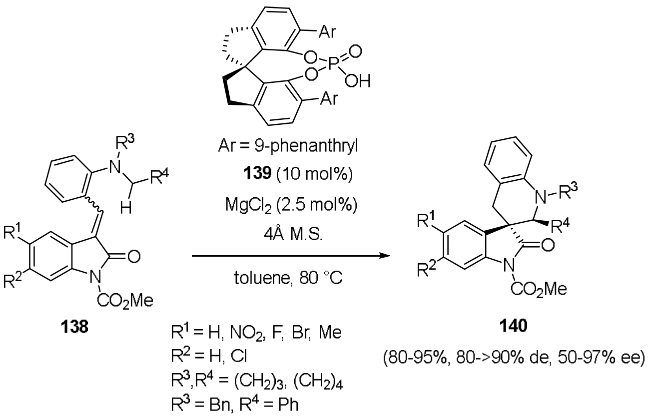
A chiral magnesium catalyst was used by Lin *et al.* in a synthesis of chiral spirooxindole tetrahydroquinolines **140** based on an intramolecular domino reaction of oxindoles **138** (Scheme 36).[75] The process occurred through sequential 1,5-hydride transfer and cyclization reactions performed in the presence of a combination of $MgCl_2$ and chiral phosphoric acid **139**. Chiral spirooxindole tetrahydroquinolines **140** were obtained in high yields (80-95%) and diastereoselectivities (80->90% de) combined with moderate to excellent enantioselectivities (50-97% ee).

In 2018, another chiral magnesium catalyst in situ generated from $MgSO_4$ and chiral phosphoric acid ligand **143** was applied by Schneider and Hodik to develop a synthesis of chiral spirocyclic dihydroquinolones **144** through the reaction of *ortho*-quinone methide imines **141** with cyclic β-oxo esters **142** (Scheme 37).[76] The domino process evolved through successive addition and lactamization reactions, affording spirocyclic dihydroquinolones **144** with moderate to quantitative yields (39-98%) and both moderate to excellent diastereo- (50->90% de) and enantioselectivities (66-98% ee).



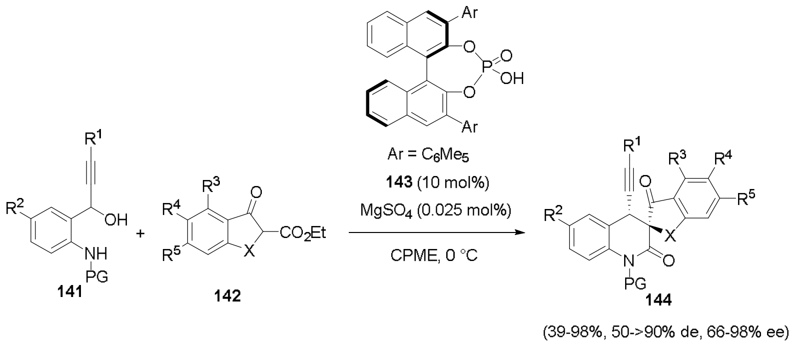
R^1 = Ph, *p*-*t*-BuC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-Tol, *p*-MeOC_6H_4, *m*-FC_6H_4, *m*-Tol, 2-pyridyl, 2-cyclohexenyl, *n*-Bu, CO_2Me, 2-thienyl, *p*-*n*-BuC_6H_4, *p*-PhOC_6H_4, *p*-MeO(2-Naph), 3,4-$Cl_2C_6H_3$
R^2 = CO_2Me, H

Scheme 35. Synthesis of 5,6-dihydrocanthin-4-ones through copper-catalyzed domino iminium ion formation/alkynylation/aza-Michael reaction.



R^1 = H, NO_2, F, Br, Me
R^2 = H, Cl
R^3,R^4 = $(CH_2)_3$, $(CH_2)_4$
R^3 = Bn, R^4 = Ph

Scheme 36. Synthesis of spirooxindole tetrahydroquinolines through magnesium-catalyzed domino 1,5-hydride transfer/cyclization reaction.



R^1 = p-MeOC$_6$H$_4$, TMS, t-Bu, decyl, c-Pr, Cy, cyclohexenyl, Ph,
p-(t-Bu)C$_6$H$_4$, p-ClC$_6$H$_4$, m-MeOC$_6$H$_4$, 2-thienyl
R^2 = H, Me, Cl
R^3 = H, OMe
R^4 = H, Me, OMe, NO$_2$, Br
R^5 = H, Cl
X = O, S
PG = Me, Et, Bu, allyl

Scheme 37. Synthesis of spirocyclic dihydroquinolones through magnesium-catalyzed domino addition/lactamization reaction.

6. Conclusion

This chapter has demonstrated that a broad range of densely functionalized chiral complex heterocyclic compounds, including biologically interesting products, can be easily generated through enantioselective domino processes catalyzed by chiral metal complexes. Very different metal catalysts have already been successfully applied to promote these fascinating one-pot economic reactions, spanning from cobalt, copper, gold, iron, nickel, palladium, rhodium, silver, zinc and zirconium, to rare earth-elements (scandium) and alkaline earth metals (magnesium). In most cases, these transformations occurred with remarkable enantioselectivities, resulting in the formation of monocyclic as well as very complex polycyclic highly functionalized molecules. Indeed, the collection of formed chiral molecules includes monocyclic ones, such as pyrrolidines, tetrahydrofurans, tetrahydrothiophenes, oxazolines, 1,3-oxazinan-2-ones; bicyclic compounds, such as indolines, indoles, isobenzofuranones, chromans, 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides, benzimidazoles; tricyclic products, such as *cis*-3a,8a-hexahydropyrrolo[2,3-*b*]indoles, tetrahydrobenzofuro[2,3-*b*]pyrroles, tricyclic piperidines and spirocyclic lactams; and even more complex tetracyclic molecules, such as spirocyclic dihydroquinolones, 2,3-disubstituted indolines, 5,6-dihydrocanthin-4-ones, spirooxindoles, and spirocyclic dihydroquinolones. In the near future, other metal catalysts will be incontestably applied to the one-step synthesis of other types of chiral heterocycles with an effort towards green metals.

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