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Recent developments in enantioselective nickel-catalysed cycloadditions

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Contents

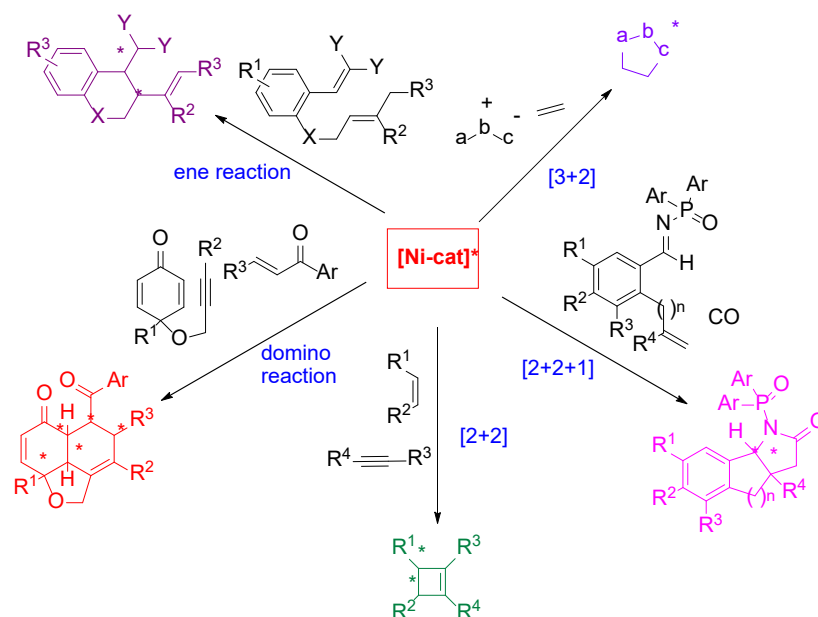
1. Introduction
 2. Enantioselective nickel-catalysed [3+2] cycloadditions
 - 2.1. Cycloadditions of epoxides and aziridines
 - 2.2. Cycloadditions of nitrones
 - 2.3. Cycloadditions of functionalised cyclopropanes
 - 2.4. Cycloadditions of other types of dipoles
 3. Enantioselective nickel-catalysed [2+2] cycloadditions
 4. Enantioselective nickel-catalysed [4+2] cycloadditions
 5. Enantioselective nickel-catalysed [2+2+2] cycloadditions
 6. Other enantioselective nickel-catalysed cycloadditions
 7. Enantioselective nickel-catalysed tandem and domino reactions based on cycloadditions
 8. Conclusions
- References and notes

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Graphical Abstract

This review collects the recent developments in enantioselective nickel-catalysed cycloadditions published since the beginning of 2015. It illustrates the power of these inexpensive and highly abundant catalysts to provide remarkably diverse chemical reactivity. The usefulness of nickel is especially highlighted in the area of enantioselective cycloadditions, allowing the formation of many types of chiral carbo- and heterocycles. The review includes enantioselective nickel-catalysed [3+2] cycloadditions, [2+2] cycloadditions,

[4+2] cycloadditions, [2+2+2] cycloadditions, other cycloadditions, and tandem and domino reactions based on cycloadditions.



Keywords:

Asymmetric metal catalysis; Asymmetric synthesis; Chirality; Enantioselective cycloadditions; Enantioselectivity; Nickel

1. Introduction

In spite of the rapid expansion of organocatalysis, the catalysis of organic reactions by metals is still commonly used to perform highly enantioselectively many types of reactions including cycloadditions [1]. Compared with many transition metals, nickel catalysts present the advantage to be cheaper and abundant [2,3,4]. This usefulness has been particularly demonstrated in the development of enantioselective nickel-catalysed cycloadditions [5]. In the last eight years, a range of chiral nickel complexes predominantly based on various nitrogen-containing chelating ligands, such as chiral *N,N'*-dioxides, bisoxazolines, cyclic 1,2-diamines, binaphthyldiimines, *N*-heterocyclic carbenes and phosphoramidates, have been successfully applied as highly efficient catalysts in various enantioselective cycloadditions,

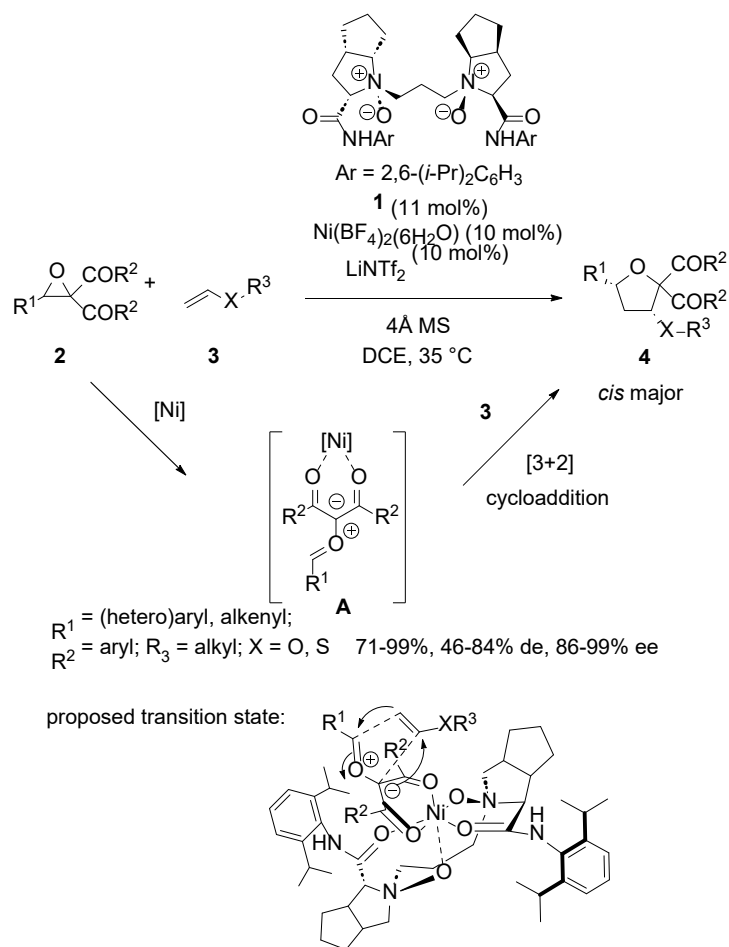
including predominantly [3+2] and [2+2] cycloadditions along with a variety of other cycloadditions, such as [2+2+2], [2+2+1] and [4+2] cycloadditions among others. In addition, several types of tandem and domino processes based on cycloadditions have been successfully developed mostly through dual nickel/organocatalysis. The goal of this review is to update the recent developments in enantioselective nickel-catalysed cycloadditions published in the last nine years since this field was previously reviewed in 2015 [6]. It must be noted that a report covering the year 2015 on general racemic nickel-catalysed cycloadditions and focusing on mechanisms was published by Dennis in 2019 [7]. In addition, Wei and Shi published in 2023 an highlight focusing on nickel-catalyzed asymmetric cyclisations and cycloadditions of special substrates, such as carbonyl-alkynes, cyano-alkynes, and enynes, but it included only five references ≥ 2015 of enantioselective nickel-catalysed cycloadditions along with mostly other cyclisations [8]. The present review is divided into six parts, dealing successively with enantioselective nickel-catalysed [3+2] cycloadditions, [2+2] cycloadditions, [4+2] cycloadditions, [2+2+2] cycloadditions, other cycloadditions, and tandem and domino reactions based on cycloadditions.

2. Enantioselective nickel-catalysed [3+2] cycloadditions

2.1. Cycloadditions of epoxides and aziridines

Asymmetric [3+2] cycloadditions represent privileged direct routes to chiral five-membered heterocycles [9]. Among them, chiral furans constitute key skeletons of many biologically active products [10]. In 2014, the first asymmetric [3+2] cycloaddition between alkynes and epoxides delivering chiral 2,5-dihydrofurans was developed by Feng et al. [11]. This reaction employed a nickel catalyst derived from a chiral N,N' -dioxide ligand that allowed enantioselectivities of up to 95% ee to be achieved. Later in 2016, the same authors involved a closely related chiral ligand **1** to promote the enantioselective nickel-catalysed [3+2] cycloaddition of epoxides **2** with heterosubstituted alkenes **3** [12]. In this reaction, epoxides generated carbonyl ylides **A** through selective C–C bond cleavage in the presence of the nickel catalyst, which further underwent asymmetric [3+2] cycloaddition with heterosubstituted alkenes (Scheme 1). The process was catalysed at 35 °C by a mixture of 10 mol% of $\text{Ni}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and 11 mol% of ligand **1** in the presence of 10 mol% of LiNTf_2 in DCE as solvent. Through selective C–C bond cleavage of epoxides **2**, the reaction afforded a series of chiral highly substituted tetrahydrofurans **4** in good to quantitative yields (66-99%), moderate to high *cis*-diastereoselectivities (46-84% de), and uniformly high enantioselectivities

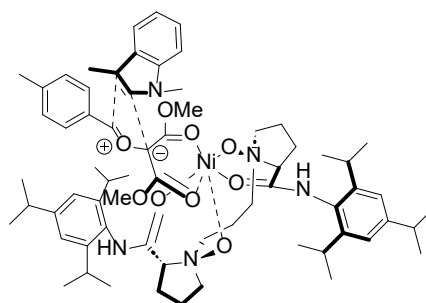
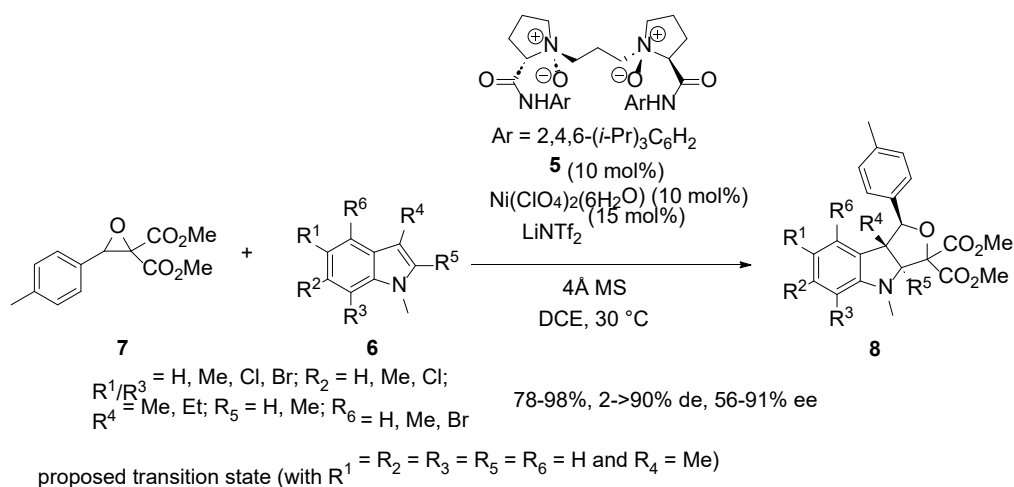
(86-99% ee). Along with phenyl-substituted epoxides ($R^1 = \text{Ph}$), aromatic epoxides exhibiting substituents at the *para*-position of the phenyl ring, afforded the corresponding products in high yields (85-98%), good diastereoselectivity (>80% de), and excellent enantioselectivities (91-93% ee) regardless the electronic nature of these substituents. Excellent results (93-99% yield, 78-80% de, 88-90% ee) were also achieved when an electron-donating group was present at the *meta*- or *ortho*-position. On the other hand, aromatic epoxides bearing an electron-withdrawing group at the *meta*- or *ortho*-position reacted more sluggishly (66-71% yield with $R^1 = m\text{-FC}_6\text{H}_4, o\text{-FC}_6\text{H}_4$). Moreover, heteroaromatic epoxides ($R^1 = 3\text{-furyl}, 3\text{-thienyl}$) as well as ring-fused epoxides ($R^1 = 1\text{-Naph}, 2\text{-Naph}$) were also compatible, delivering the corresponding chiral tetrahydrofurans in high yields (87-99%), moderate to good diastereoselectivities (66-82% de), and high enantioselectivities (88-91% ee). Even good results (98% yield, 84% de, 90% ee) were obtained in the reaction of an unsaturated epoxide ($R^1 = (E)\text{-PhCH=CH}$). In addition, the authors showed that different R^2 substituents on the acyl group of the epoxide were tolerated, giving quantitative yields, good diastereoselectivity (80% de), and excellent enantioselectivities (88-92% ee). The reaction of sterically hindered heterosubstituted alkenes provided higher enantioselectivities combined with lower diastereoselectivities. For example, from $R^3 = \text{Et}$ to $R^3 = t\text{-Bu}$, the enantioselectivity increased from 89 to 99% ee while the diastereoselectivity decreased from 72 to 46% de. On the other hand, the reaction of a cyclohexyl vinyl ether ($X = \text{O}, R^3 = \text{Cy}$) proceeded smoothly, providing the corresponding product in 97% yield, 80% de, and 96% ee as well as an allyl vinyl ether ($X = \text{O}, R^3 = \text{allyl}$) and a vinyl sulfide ($X = \text{S}, R^3 = \text{Et}$) which afforded the corresponding tetrahydrofurans in excellent yields (97-99%), moderate to good diastereoselectivities (60-72% de), and high enantioselectivities (86-89% ee). To explain the stereoselectivity of the reaction, a possible transition state is depicted in Scheme 1 in which the chiral catalyst coordinates with the two carbonyl groups exhibited by the epoxide through a bidentate fashion, which results in the formation of the carbonyl ylide, forming a rigid octahedral complex. The 2,6-diisopropyl-aniline group underneath the ligand shields the *Si* face of the carbonyl ylide. Consequently, the heterosubstituted alkene attacks the *Re* face of the carbonyl ylide, leading to the (3*R*,5*S*)-configured product.



Scheme 1. [3+2] Cycloaddition of epoxides with heterosubstituted alkenes.

In the same area, Feng et al. disclosed in 2015 the use of related chiral N,N' -dioxide ligand **5** in enantioselective [3+2] cycloaddition of N -methyl indoles **6** with epoxides **7** [13]. As shown in Scheme 2, the process was performed at 30 °C in DCE as solvent in the presence of 10 mol% of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, the same quantity of chiral ligand **5**, and 15 mol% of LiNTf_2 . It led to a range of chiral furo[3,4-*b*]indoles **8** through asymmetric C–C cleavage of the epoxides. These tricyclic cycloadducts exhibiting three contiguous stereocentres were obtained in homogeneously high yields (78-98%), variable diastereoselectivities (2->90% de), and generally high enantioselectivities (56-91% ee). The presence of various substituents on the phenyl ring of indoles was tolerated. For example, C4-substituted indoles (R^6) underwent the reaction efficiently, providing both high yields (80-91%) and enantioselectivities (88-90% ee), while combined with variable diastereoselectivities (32->90% de). The lowest de value (32% de) was observed in the case of sterically hindered bromine-substituted substrate ($\text{R}^6 = \text{Br}$). Moreover, C5-, C6- and C7-substituted indoles were well tolerated, affording the products in excellent yields (86-96%), enantioselectivities (86-91% ee), and

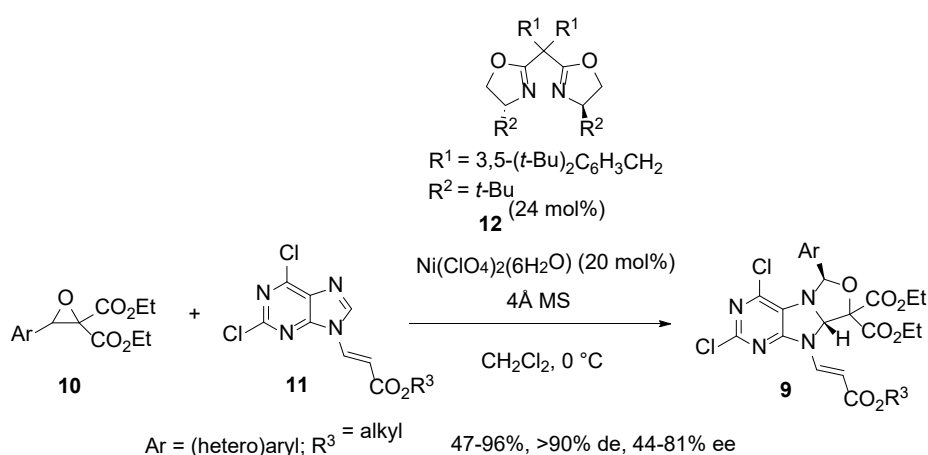
diastereoselectivities generally >90% de with the exception of an indole bearing a bromine atom at C5 position ($R^1 = \text{Br}$) which reacted with only 2% de. The lowest enantioselectivity (56% ee) was obtained in the reaction of 1,2,3-trimethylindole ($R^4 = R^5 = \text{Me}$). The authors proposed the transition state depicted in Scheme 2 in which the four oxygen atoms of the chiral ligand chelated the Ni centre. The latter was also coordinated to the carbonyl group of the epoxide, thus forming the active carbonyl ylide. Then, the indole substrate attacked the epoxide from the upper right corner to the *Re* face to afford the final product.



Scheme 2. [3+2] Cycloaddition of epoxides with *N*-methyl indoles.

Purines and their derivatives constitute one of the most naturally occurring nitrogen-containing heterocyclic products. Among them, many exhibit biological activities, spanning from antitumor, antimicrobial, antiviral to antifungal ones. Especially, tricyclic purines constitute the structural cores of a range of natural products and drugs and, consequently, these molecules have attracted a great attention in drug discovery [14]. In 2022, Guo and Wang reported a novel methodology to synthesise chiral tricyclic purino[3,2-*c*]oxazole derivatives **9** based on an enantioselective nickel-catalysed dearomative [3+2] cycloaddition of epoxides **10** with purines **11** (Scheme 3) [15]. This chemo-, diastereo-, and enantioselective

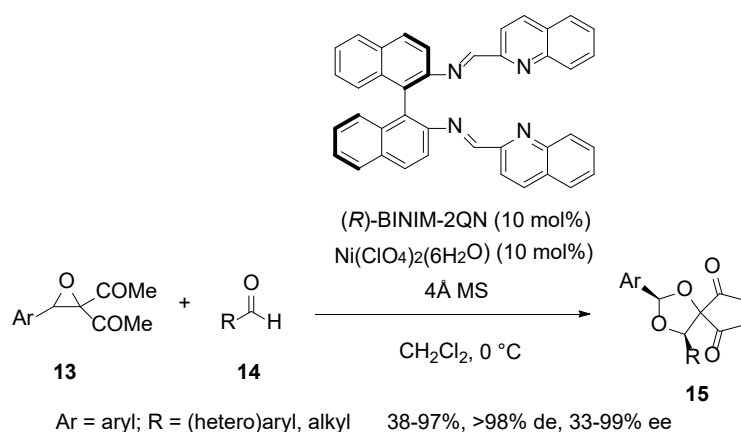
reaction was carried out at 0 °C in dichloromethane as solvent in the presence of a combination of 20 mol% of Ni(ClO₄)₂·6H₂O and 24 mol% of chiral bisoxazoline ligand **12**, resulting in the formation of chiral purino[3,2-*c*]oxazole derivatives **9** as almost single diastereomers (>90% de) in both moderate to high yields (47-96%) and enantioselectivities (44-81% ee). Various substituents were tolerated on different positions of the phenyl ring of the epoxide with the best ee value (81% ee) achieved in the reaction of the 2-methyl substrate (Ar = *o*-Tol) obtained with 90% yield. Moreover, 1- and 2-naphthyl-, as well as 2-thienyl-substituted ethylene oxides provided the corresponding products in both moderate yields (47-65%) and enantioselectivities (44-60% ee).



Scheme 3. [3+2] Cycloaddition of epoxides with purines.

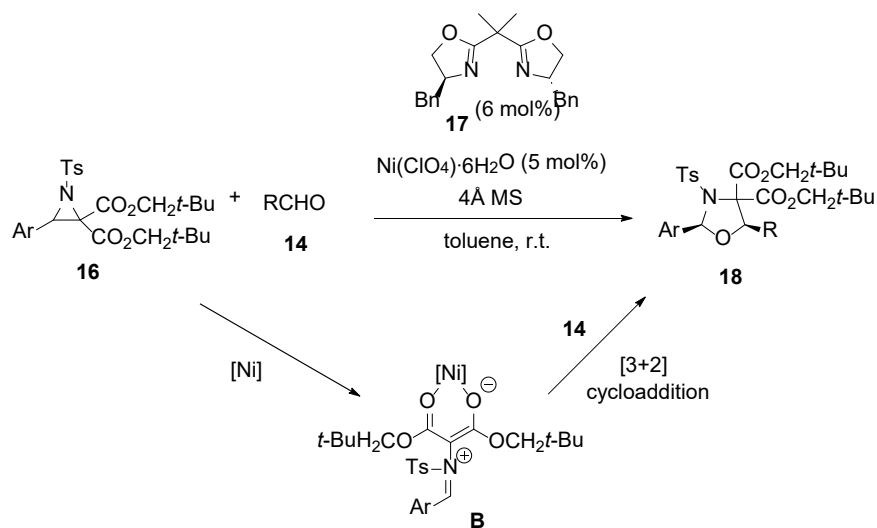
In 2022, Suga et al. employed another type of chiral ligands, namely (*R*)-BINIM-2QN, to promote diastereo- and enantioselective [3+2] cycloadditions between acyclic carbonyl ylides in situ generated from epoxides **13** and aldehydes **14** [16]. This ligand was employed at 10 mol% of catalyst loading in combination with the same quantity of Ni(ClO₄)₂·6H₂O as precatalyst in dichloromethane as solvent (Scheme 4). Performed at 0 °C, the cycloaddition afforded the corresponding chiral 1,3-dioxolanes **15** as single *cis*-diastereomers with both moderate to excellent yields (38-97%) and enantioselectivities (33-99% ee). Both aromatic and aliphatic aldehydes could be used as dipolarophiles. Actually, the ee values were all ≥79% ee excepted in the reaction of a sterically hindered aldehyde (R = *o*-MeOC₆H₄) which led to the corresponding product with only 33% ee. Benzaldehydes exhibiting either electron-withdrawing or electron-donating groups afforded the desired *cis*-1,3-dioxolanes with both high yields (79-89%) and enantioselectivities (87-92% ee). An heterocyclic aldehyde (R = 2-furyl) was also compatible (97% yield, 93% ee). Even more interesting, aliphatic aldehydes

bearing primary or secondary alkyl substituents were also tolerated, leading to the corresponding cycloadducts with uniformly high ee values (84-97% ee). Concerning the scope of epoxides, chloro- or methyl-substituted phenyl derivatives reacted smoothly with benzaldehyde and several *para*-substituted benzaldehydes to give the desired products with both good to high yields (77-93%) and enantioselectivities (79-99% ee).



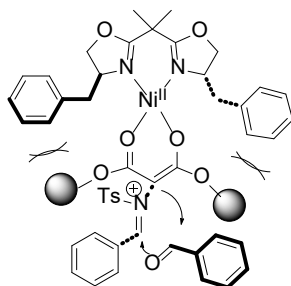
Scheme 4. [3+2] Cycloaddition of epoxides with aldehydes.

Earlier in 2017, an enantioselective [3+2] cycloaddition between *N*-tosylaziridines **16** and aldehydes **14** was disclosed by Zhang et al. based on the use of a nickel catalyst derived from 6 mol% of chiral oxazoline ligand **17** and 5 mol% of $\text{Ni}(\text{ClO}_4) \cdot 6\text{H}_2\text{O}$ (Scheme 5) [17]. The reaction, involving the in situ generation of azomethine ylides **B** from the aziridines, occurred at room temperature in toluene as solvent and resulted in the formation of chiral 1,3-oxazolidines **18** as single diastereomers with both good to high yields (68-96%) and enantioselectivities (69-96% ee). Aziridines with either electron-donating or electron-withdrawing substituents at different positions of the phenyl ring reacted with uniformly high ee values (89-92% ee). Furthermore, aromatic aldehydes bearing different types of substituents on the phenyl ring all provided excellent enantioselectivities (89-96% ee). Good results were also obtained in the reaction of an heterocyclic aldehyde (R = 2-furyl, 88% ee) and several α,β -unsaturated aldehydes (85-92% ee) including cyclic ones (R = 2-cyclohexenyl, 85% ee). The lowest ee value (69% ee) was observed by using crotonaldehyde as substrate. To explain their results, the authors proposed the transition state depicted in Scheme 5, showing that the chirality arose from the presence of bulky ester groups on the aziridine partner.



Ar = aryl; R = (hetero)aryl, alkenyl 68-96%, 69-96% ee

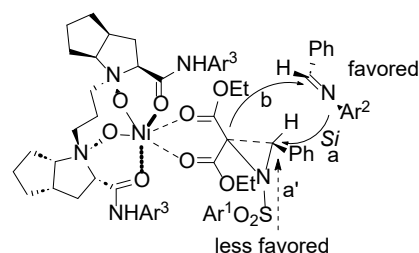
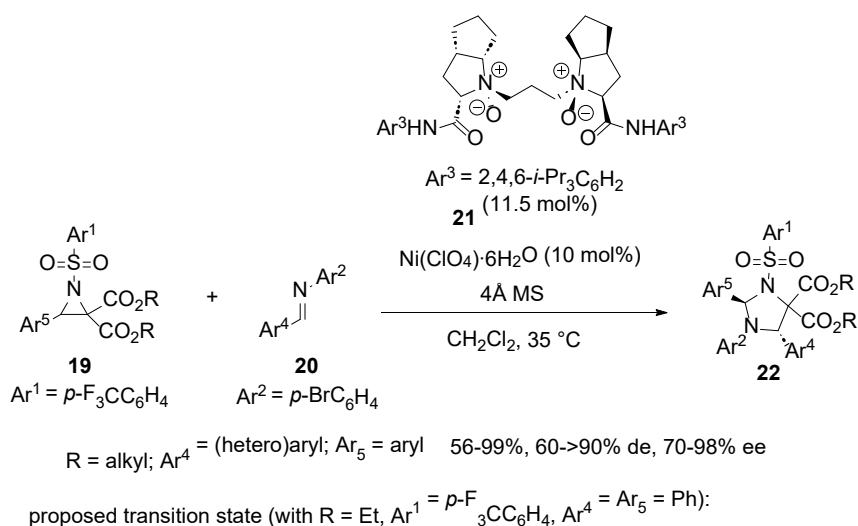
proposed transition state (with R = Ar = Ph and CH₂CO₂t-Bu =):



Scheme 5. [3+2] Cycloaddition of *N*-tosylaziridines with aldehydes.

More recently in 2023, Feng and Liu developed *trans*-diastereo- and enantioselective [3+2] cycloaddition of donor-acceptor aziridines **19** with *N*-aryl protected imines **20** [18]. As illustrated in Scheme 6, the optimal catalyst was derived from 10 mol% of Ni(ClO₄)·6H₂O and 11.5 mol% of chiral *N,N'*-dioxide ligand **21**, providing at 35 °C in dichloromethane as solvent a broad range of chiral densely substituted imidazolidines **22** with moderate to quantitative yields (56-99%) as single *trans*-diastereomers in almost all cases (60->90% de) and generally excellent ee values (70-98% ee). Studying the substrate scope, the authors found that either electron-withdrawing or electron-donating groups could be present at the *para*-position of the phenyl ring (Ar⁵) of aziridines, affording the imidazolidines with uniformly high enantioselectivities (91-93% ee) and good yields (65-99%), whereas the reactivity and ee value slightly dropped when halo-substitutions were installed at the *ortho*- or *meta*-positions (Ar⁵ = *o*-FC₆H₄: 77% yield, 82% de, 84% ee). Concerning the imine partner, the electronic nature and the steric hindrance of substituents situated at the *meta*- or *para*-position of the phenyl group (Ar⁴) had a negligible impact on the enantiocontrol and reactivity (78-97% yield, 91-98% ee) of the process. On the other hand, an *ortho*-substituted substrate

(Ar⁴ = *o*-BrC₆H₄) reacted with a decreased yield (56%) and enantioselectivity (78% ee). The stereoselectivity of the reaction can be explained by the transition state depicted in Scheme 6 in which the C–C bond of the aziridine was broken to form the 1,3-dipolar intermediate through the activation of the chiral nickel complex via bidentate coordination of the diesters. The ligand coordinated to the nickel centre to form an octahedral complex with two solvent molecules at the equatorial positions. Then, the imine attacked the ylide from its *Si* face (path a) rather than the more sterically hindered *Re* face (path a') with the bulky *N*-arylsulfonyl unit. Subsequently, ring-closure occurred through path b in order to minimize the steric repulsion between the two aryl groups. Moreover, the phenyl group of the imine was situated away from the upper amide unit of the catalyst. This resulted in the preferred formation of the (2*R*,5*S*)-configured product.

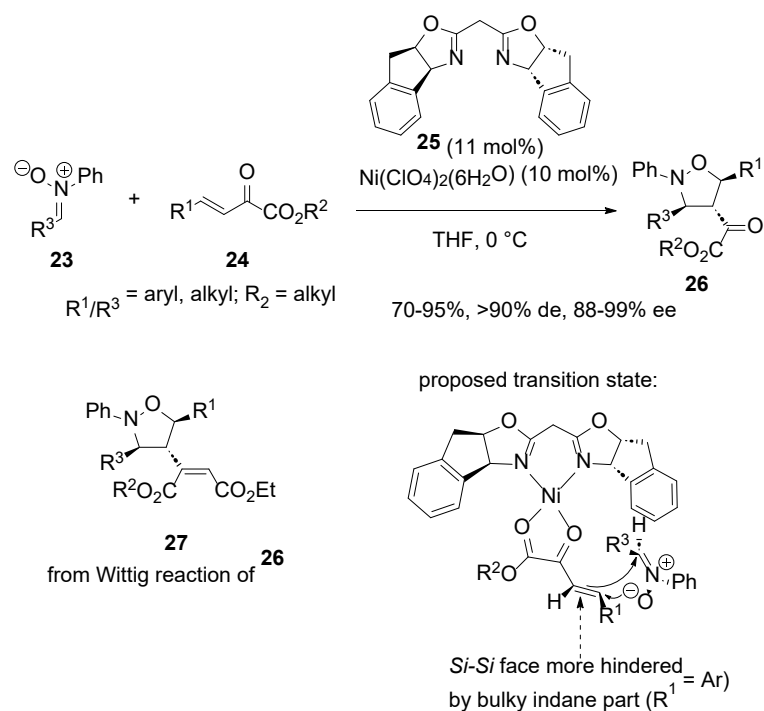


Scheme 6. [3+2] Cycloaddition of donor-acceptor aziridines with *N*-aryl protected imines.

2.2. Cycloadditions of nitrones

The use of nitrones as stable and easily prepared 1,3-dipole partners in asymmetric [3+2] cycloadditions with alkenes has been widely investigated [9a-b,19]. These reactions allow the synthesis of isoxazolidines which are potent precursors of many biologically important heterocycles. While numerous asymmetric [3+2] cycloadditions are based on the use of either

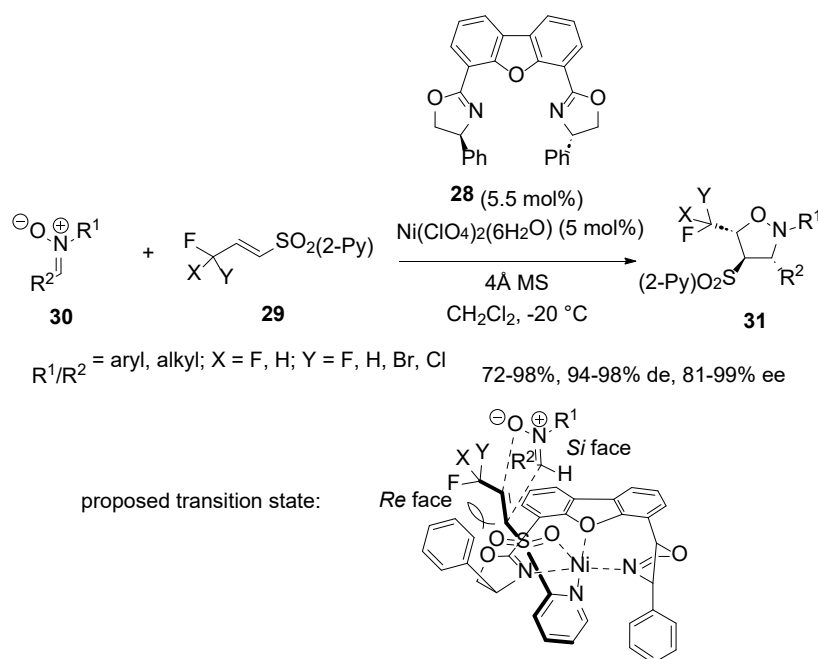
chiral alkenes or nitrones, enantioselective [3+2] cycloadditions of nitrones based on the use of chiral catalysts have been developed more recently [9c-d,20]. As an example, Fu et al. reported in 2017 the first highly enantioselective [3+2] cycloaddition of nitrones **23** with α,β -unsaturated acylcarboxylates **24** using a chiral bis(indano-oxazoline)-based nickel complex (Scheme 7) [21]. The catalyst was in situ prepared from 10 mol% of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and 11 mol% of chiral bisoxazoline ligand **25** in THF at 0 °C. Under these mild conditions, nitrones **23** reacted smoothly with α,β -unsaturated acylcarboxylates **24** to afford the corresponding chiral isoxazolidines **25** bearing three contiguous stereocentres as almost single diastereomers (>90% de) in good to excellent yields (70-95%) and homogeneous high enantioselectivities (88-98% ee). In some cases, the enantioselectivity of the reaction was determined through the conversion of isoxazolidines **26** into the corresponding chiral isoxazolidinylalkenes **27** through a Wittig reaction. The conditions were compatible with a wide variety of β -phenyl-substituted acylcarboxylates bearing either electron-withdrawing or electron-donating substituents at different positions of the phenyl group (75-95% yield, >90% de, 94-99% ee). Moreover, an excellent enantioselectivity (95% ee) was achieved in the reaction of a β -(2-naphthyl) unsaturated acylcarboxylate ($\text{R}^1 = 2\text{-Naph}$). β -Alkyl-substituted acylcarboxylates ($\text{R}^1 = \text{Cy}, t\text{-Bu}, n\text{-Hex}$) were also tolerated, leading to the corresponding chiral cycloadducts in high yields (75-95%) and enantioselectivities (95-99% ee). Concerning the substrate scope of nitrones, a range of *N*-phenyl-substituted nitrones gave the corresponding products in high yields (70-93%) and enantioselectivities (88-98% ee) regardless the position and electronic nature of the substituent on the phenyl ring (R^3) of nitrones. Furthermore, 2-naphthyl- and cyclohexyl-substituted nitrones ($\text{R}^3 = 2\text{-Naph}, \text{Cy}$) were also compatible substrates, providing the corresponding cycloadducts in excellent enantioselectivities (96-98% ee) and high yields (86-93%). On the other hand, the authors found that the catalyst system was not compatible with *N*-alkyl nitrones, thus demonstrating that the *N*-phenyl substitution in the nitrone partner played an important role. To explain the stereoselectivity of the reaction, the authors proposed the transition state depicted in Scheme 7 in which the α,β -unsaturated acylcarboxylate was activated through coordination of its two carbonyl groups to the nickel centre. Then, the nitrone preferentially approached the dipolarophile from the *Re-Re* face of the double bond, due to steric hindrance of the *Si-Si* face by the bulky indane moiety of the ligand, which resulted in the formation of the final product.



Scheme 7. [3+2] Cycloaddition of nitrones with α,β -unsaturated acylcarboxylates.

The asymmetric synthesis of α -fluoroalkylated γ -amino alcohol skeletons is challenging since these products are found in many biologically active products [22]. In 2017, Huang et al. reported a rare example of enantioselective route to chiral α -fluoroalkylated γ -amino alcohols based on asymmetric nickel-catalysed [3+2] cycloaddition of β -fluoroalkylated α,β -unsaturated 2-pyridylsulfones with nitrones [23]. As depicted in Scheme 8, the process was catalysed at $-20\text{ }^\circ\text{C}$ by a chiral nickel complex in situ generated from 5 mol% of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and 5.5 mol% of chiral bisoxazoline ligand **28** in dichloromethane as solvent in the presence of 4 \AA MS as additives. Under these conditions, β -trifluoromethylated α,β -unsaturated 2-pyridylsulfone **29** ($\text{X} = \text{Y} = \text{F}$) reacted with a variety of aromatic and aliphatic nitrones **30** to give the corresponding chiral β -trifluoromethylated isoxazolidines **31** in high yields (81-97%), diastereo- (94-98% de), and enantioselectivities (81-99% ee). Generally, nitrones bearing an aromatic group in R^2 provided better enantioselectivities (87-99% ee) than nitrones exhibiting an alkyl R^2 substituent (83-86% ee) probably because the latter generally required a higher reaction temperature (-10 or $0\text{ }^\circ\text{C}$ vs $-20\text{ }^\circ\text{C}$). In addition to β -trifluoromethylated α,β -unsaturated 2-pyridylsulfone, difluoromethylated and chlorodifluoromethylated α,β -unsaturated 2-pyridylsulfones ($\text{X} = \text{F}, \text{Y} = \text{H}$ and $\text{X} = \text{F}, \text{Y} = \text{Cl}$) reacted smoothly to give the corresponding cycloadducts with high yields (90-92%), diastereo- (94-96% de), and enantioselectivities (91-92% ee). Slightly lower

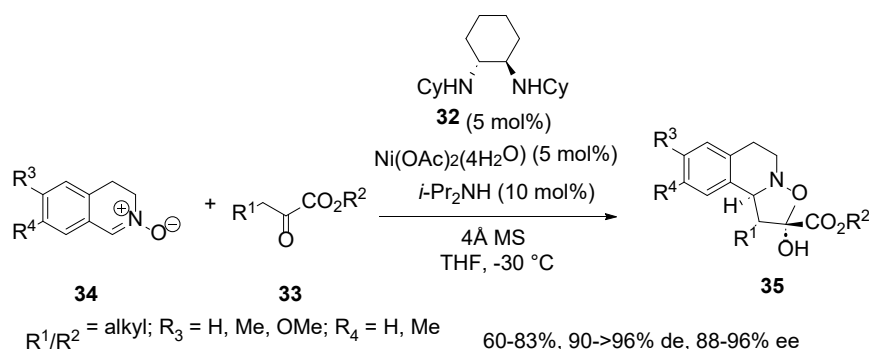
enantioselectivities (81-83% ee) were obtained in the reaction of bromodifluoromethylated ($X = F, Y = Br$) and monofluoromethylated ($X = Y = H$) α,β -unsaturated 2-pyridylsulfones albeit combined with high diastereoselectivities (96-94% de) and good yields (72-89%). It was shown that the presence of fluoroalkylated groups and 2-pyridylsulfone moieties in the dipolarophile partner was essential to obtain good results. To demonstrate the utility of the novel methodology, the authors converted one chiral cycloadduct ($X = Y = F, R^1 = Ph, R^2 = o\text{-FC}_6\text{H}_4$) with 92% yield through reductive ring-opening into the corresponding enantiopure trifluoromethylated 1,3-oxazinan-2-one which is a potent anti-HIV agent. To explain the stereoselectivity of the reaction, the authors proposed the transition state depicted in Scheme 8 in which the tridentate chiral ligand and the olefin substrate coordinated to the nickel(II) ion to form a trigonal bipyramid structure. Due to the face shielding from the top phenyl ring of the ligand, the N-oxide of the nitron could only approach the activated olefin from the *Si* face, thus forming the *endo*-product.



Scheme 8. [3+2] Cycloaddition of nitrones with β -fluoroalkylated α,β -unsaturated 2-pyridylsulfones.

Another type of chiral ligand, such as chiral diamine **32**, was combined in 2017 by Sodeoka et al. at 5 mol% of catalyst loading to the same quantity of $\text{Ni}(\text{OAc})_2\cdot 4\text{H}_2\text{O}$ as precatalyst to promote the first asymmetric [3+2] cycloaddition of α -ketoesters **33** with cyclic nitrones **34** [24]. The process was performed at $-30\text{ }^\circ\text{C}$ in the presence of 10 mol% of

diisopropylamine as an additive in THF as solvent. It afforded the corresponding chiral isoxazolidines **35** bearing three contiguous stereocentres and an *anti,anti*-configuration in good yields (60-83%) and both uniformly high diastereo- (90->96% de), and enantioselectivities (88-96% ee), as presented in Scheme 9. The catalyst system was compatible with a series of α -ketoesters bearing various substituents on the aromatic moiety, that allowed the synthesis of the cycloadducts as almost single diastereomers (>96% de) in good to excellent yields (60->96%) and homogeneous high enantioselectivities (91-96% ee). Substrates with long alkyl chains ($R^1 = \text{BnCH}_2$, allyl, *n*-Pr) also provided good results as well as sterically hindered 1-adamantyl-substituted substrate ($R^1 = (1\text{-adamantyl})\text{CH}_2$) which led to the corresponding isoxazolidine in 74% yield, 92% de and 94% ee. Moreover, an α -ketoester bearing a terminal olefin ($R^1 = \text{allyl}$) reacted smoothly, affording the product in 77% yield, 94% de and 88% ee. Comparable reactivity (73-78% yield) and selectivities (>96% de, 89-95% ee) were also found in the reaction of substituted nitrones ($R^3 = \text{Me}$, OMe, $R^4 = \text{Me}$).

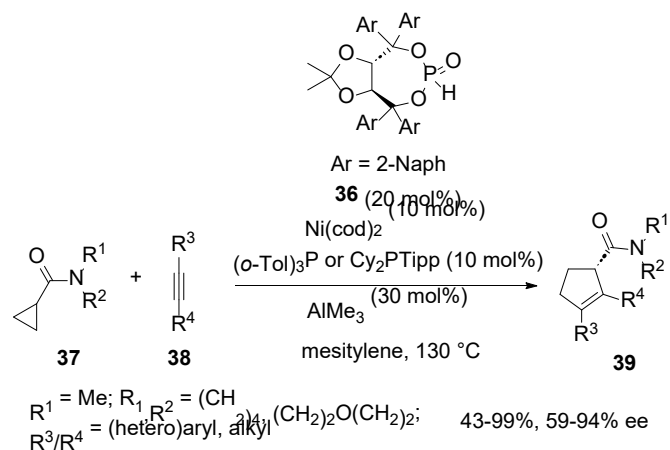


Scheme 9. [3+2] Cycloaddition of cyclic nitrones with α -ketoesters.

2.3. Cycloadditions of functionalised cyclopropanes

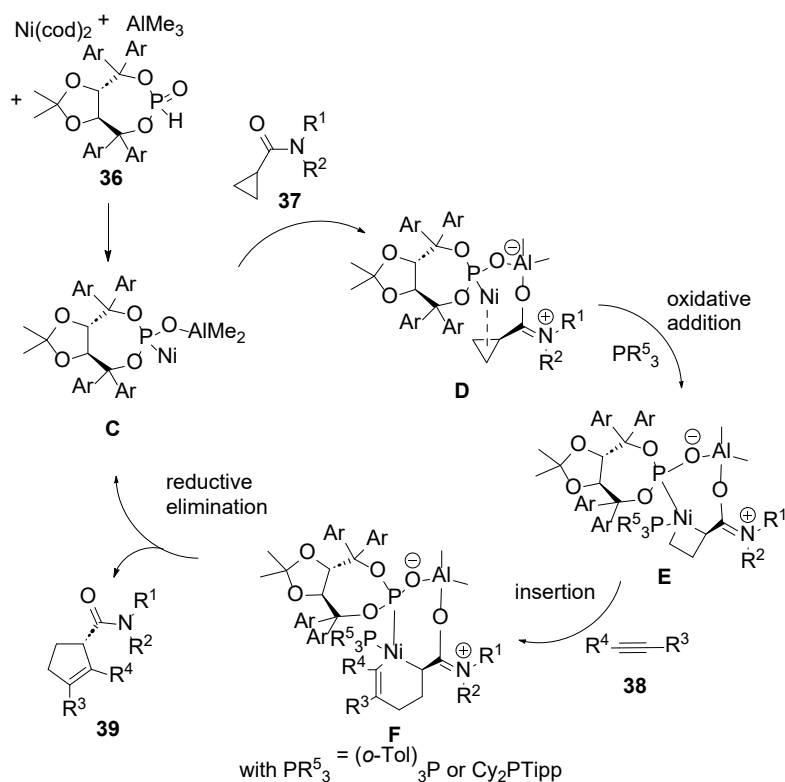
Functionalised cyclopropanes are rarely implicated in cycloaddition reactions in spite of their usefulness. In 2017, Ye et al. reported the first [3+2] cycloaddition of cyclopropyl carboxamides with alkynes based on nickel/aluminum bimetallic catalysis [25]. The catalyst system consisted in a mixture of 10 mol% of $\text{Ni}(\text{cod})_2$, 30 mol% of AlMe_3 , and 20 mol% of TADDOL-derived chiral phosphine oxide ligand **36**. In the presence of 10 mol% of an additional tertiary phosphine, such as $\text{P}(o\text{-Tol})_3$ or Cy_2PTipp , in mesitylene as solvent, cyclopropyl carboxamides **37** reacted at 130 °C with alkynes **38** to give the corresponding chiral cyclopentenyl carboxamides **39** in good to quantitative yields (63->99%) and enantioselectivities (59-94% ee), as depicted in Scheme 10. Generally, better

enantioselectivities (86-94% ee) were achieved in the reaction of symmetrical or unsymmetrical diaryl alkynes while a lower enantioselectivity (59% ee) was observed in the reaction of a dialkyl alkyne ($R^3 = R^4 = n\text{-Bu}$). Moreover, a bulkier amide ($R^1, R^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ and $R^1 = \text{Me}, R^2 = \text{Ph}$) than pyrrolidinylated ones ($R^1, R^2 = (\text{CH}_2)_4$) led to the corresponding cycloadduct with a lower enantioselectivity (65% ee), albeit quantitatively (>99% yield).



Scheme 10. [3+2] Cycloaddition of alkynes with cyclopropyl carboxamides.

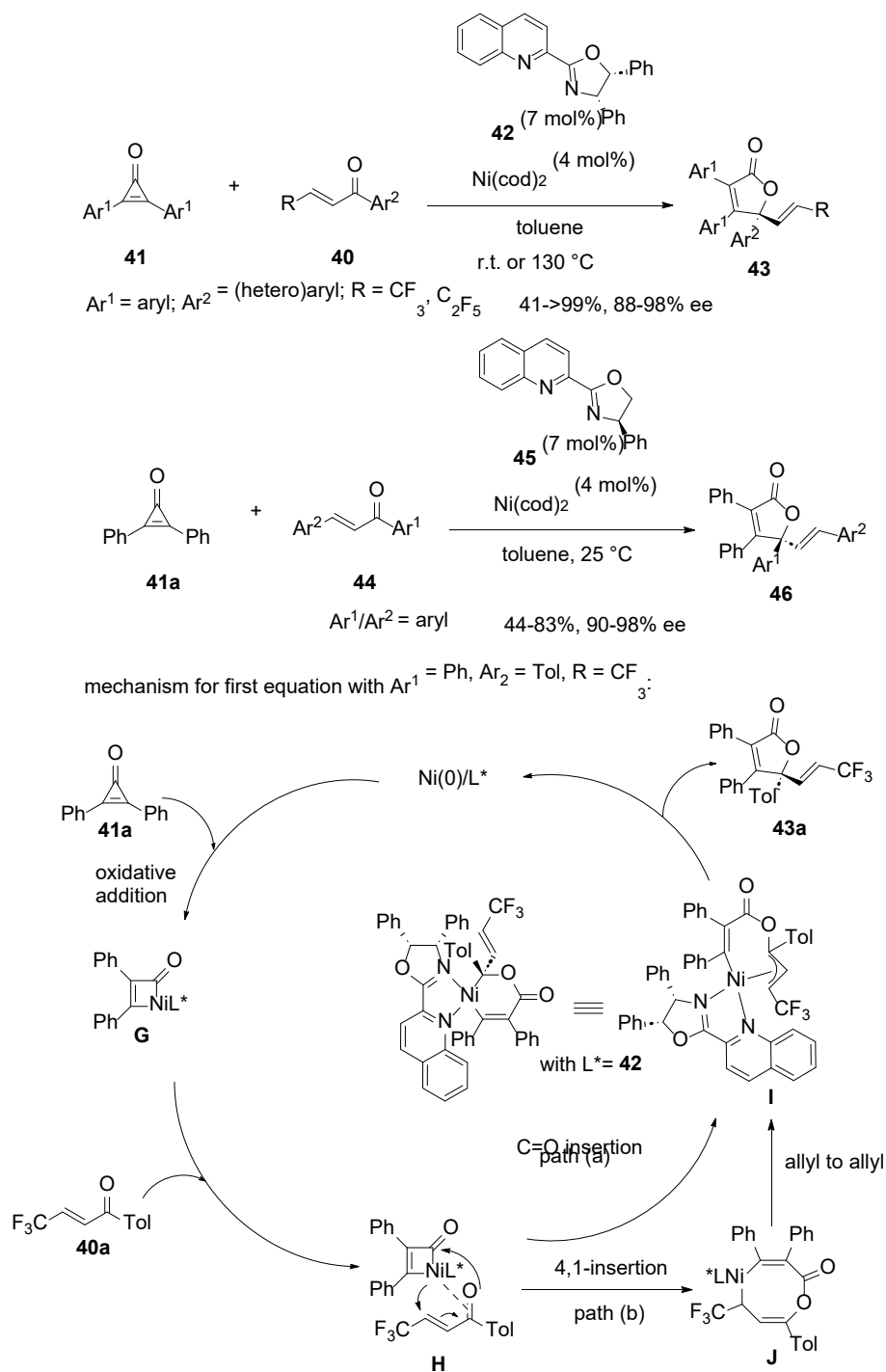
The authors proposed a mechanism for the precedent cycloaddition which is detailed in Scheme 11 [25]. It began with the formation of bimetallic intermediate **C** from the two metals and the chiral ligand which then coordinated the cyclopropyl carboxamide to give intermediate **D**. A subsequent phosphine-assisted oxidative addition of nickel to C–C bond of the cyclopropane led to novel four-membered nickel intermediate **E**, which further inserted the alkyne partner to afford six-membered nickel complex **F**. Then, a reductive elimination provided the final product and released the catalyst.



Scheme 11. Mechanism for [3+2] cycloaddition of alkynes with cyclopropyl carboxamide

In 2020, Bai and Li disclosed an enantioselective formal [3+2] cycloaddition of cyclopropenones with α,β -unsaturated ketones through intermolecular C–C bond activation to afford chiral γ -alkenyl butenolides, constituting the skeleton of many bioactive natural products [26]. As shown in Scheme 12, a range of β -trifluoromethylated α,β -unsaturated ketones **40** reacted at room temperature or 130 °C with symmetrical diarylcyclopropenones **41** in toluene in the presence of 4 mol% of $\text{Ni}(\text{cod})_2$ as precatalyst and 7 mol% of chiral oxazoline ligand **42**, delivering the corresponding chiral γ -alkenyl butenolides **43** in moderate to quantitative yields (41->99%) and uniformly excellent enantioselectivities (88-98% ee). The catalyst system tolerated the presence of diverse electron-donating and electron-withdrawing groups at the *para*-, *ortho*-, and *meta*-position of the phenyl ring (R^2) of the enone. Moreover, (hetero)aryl-substituted enones ($\text{R}^2 = 2\text{-furyl}$, 2-thienyl , 3-thienyl , ferrocenyl, 1-naphthyl , 2-naphthyl) were also compatible, providing excellent enantioselectivities (93-97% ee) combined with moderate to high yields (64-99%). In addition to β -trifluoromethylated α,β -unsaturated ketones, β -pentafluoroethylated enones ($\text{R}^3 = \text{C}_2\text{F}_5$) also reacted smoothly, giving the desired products in good yields (54-99%) and high ee values (88-96% ee). Studying the scope of the symmetrical diarylcyclopropenones, the authors found that both electron-donating and electron-withdrawing groups could be present at the *meta*-

and *para*-position of the phenyl ring (R^1), providing comparable excellent results (41-96% yield, 90-98% ee). With the aim of even more extending the scope of this reaction, less reactive α,β -unsaturated ketones **44** were investigated, however, under the same reaction conditions, only a poor reactivity was observed. On the other hand, using related chiral ligand **45** instead of **42** allowed the corresponding enantiomeric γ -alkenyl butenolides **46** to be synthesised from the reaction with diphenylcyclopropanone **41a** with comparable yields (44-83%) and enantioselectivities (90-98% ee). To explain the results (first equation), the authors proposed the mechanism depicted in Scheme 12. An oxidative addition of diphenylcyclopropanone **41a** to nickel(0) afforded intermediate **G**. The latter then underwent enantioselective Ni–C(acyl) insertion into the C=O bond of β -trifluoromethylated α,β -unsaturated ketone **36a** via intermediate **H** (path a). The resulting Ni(II)-allyl intermediate **I** subsequently led to final product **43a** and regenerated catalyst. Alternatively, intermediate **G** could also undergo a 4,1-insertion of the Ni–acyl into the enone to give a eight-membered nickel intermediate **J**, constituting a precursor of intermediate **I** (path b).

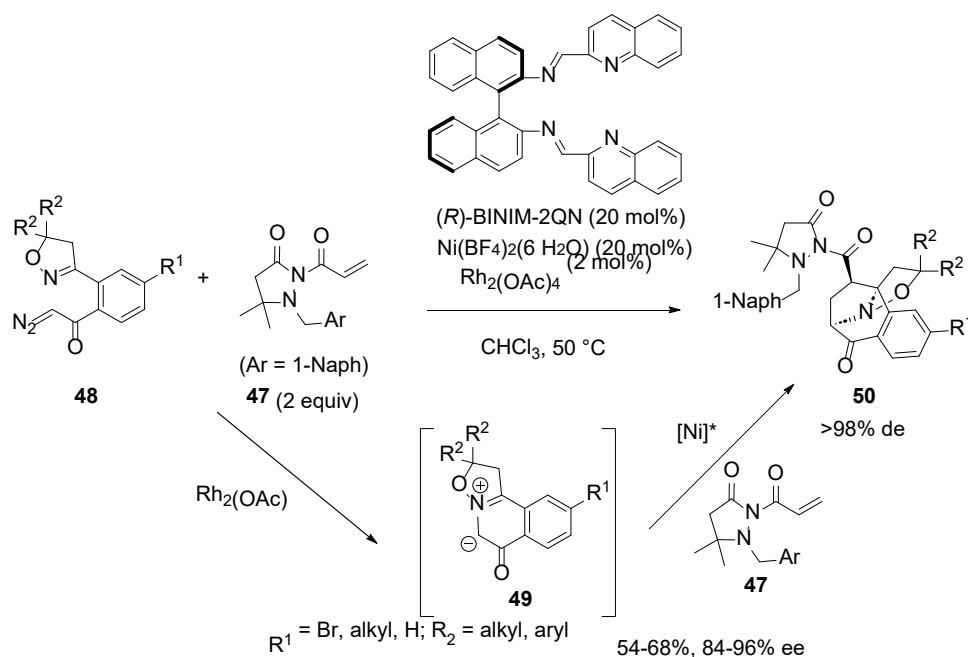


Scheme 12. [3+2] Cycloadditions of cyclopropenones with α,β -unsaturated ketones.

2.4. Cycloadditions of other types of dipoles

In 2019, Suga et al. reported the first asymmetric [3+2] cycloaddition of diazo imine-derived isoxazolines **47** with acryloylpyrazolidinone **48** based on bimetallic nickel/rhodium catalysis [27]. The cycloaddition was performed in chloroform at 50 °C in the presence of 20

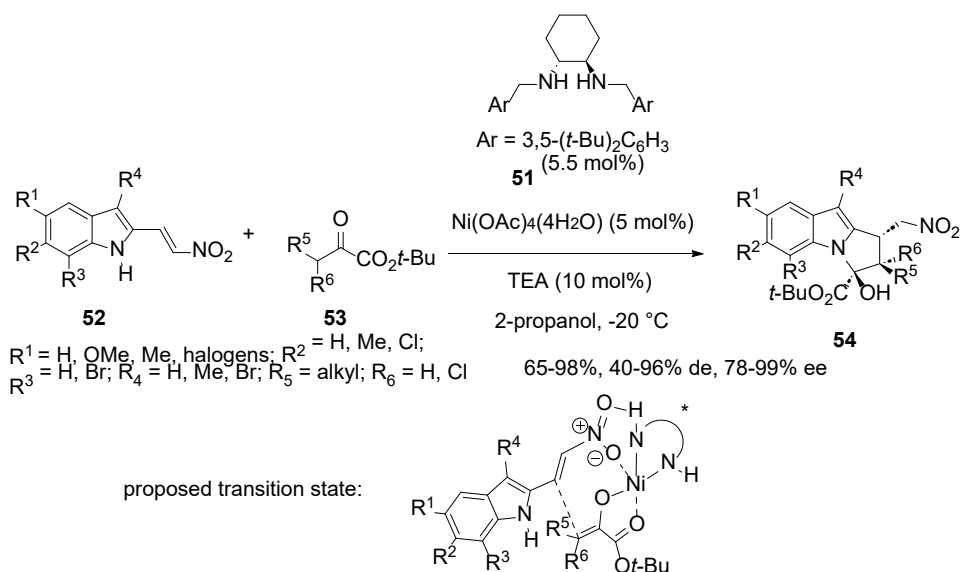
mol% of $\text{Ni}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ associated to the same quantity of chiral binaphthylidene ligand (*R*)-BINIM-2QN and 2 mol% of $\text{Rh}_2(\text{OAc})_4$. As presented in Scheme 13, cyclic azomethine ylides **49** in situ generated from the corresponding diazo imine-derived isoxazolines **47** and rhodium catalyst reacted with acryloylpyrazolidinone **48** to give chiral 8-oxabicyclo[3.2.1]octanes **50** as single diastereomers (>98% de) in moderate to good yields (54-68%) and uniformly high enantioselectivities (84-96% ee).



Scheme 13. [3+2] Cycloaddition of diazo imine-derived isoxazolines with an acryloylpyrazolidinone.

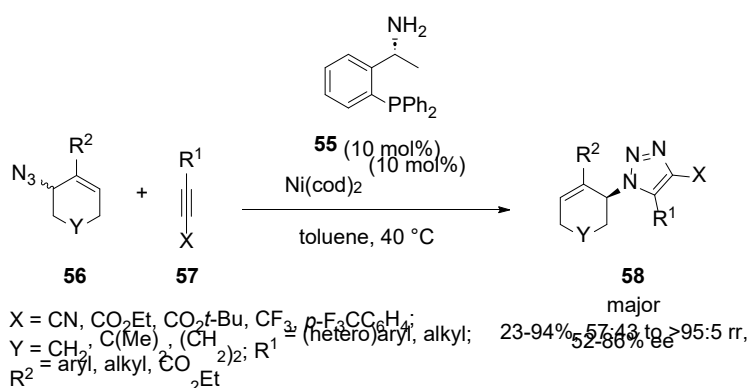
In the same year, Deng et al. reported the synthesis of chiral pyrrolo[1,2-*a*]indoles based on an asymmetric nickel-catalysed [3+2] cycloaddition of α -ketoesters with 2-nitrovinylindoles as NCC 1,3-dipole surrogates (Scheme 14) [28]. The catalyst was in situ generated from 5 mol% of $\text{Ni}(\text{OAc})_4 \cdot 4\text{H}_2\text{O}$ and 5.5 mol% of chiral diamine ligand **51** in 2-propanol as solvent. Performed at $-20\text{ }^\circ\text{C}$ in the presence of 10 mol% of TEA, the reaction of variously substituted 2-nitrovinylindoles **52** with *t*-butyl α -ketoesters **53** afforded the corresponding chiral pyrrolo[1,2-*a*]indoles **54** exhibiting three contiguous stereocentres including one quaternary in good to quantitative yields (63-98%), low to excellent diastereoselectivities (8-96% de) combined with good to excellent enantioselectivities (73->99% ee), as presented in Scheme 13. In most cases, the cycloadducts were achieved in uniformly excellent enantioselectivities (90->99% ee) regardless the nature of substituents

born by the two substrates. In contrast, the reaction between two unsubstituted substrates ($R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$) led to the corresponding product in lower enantioselectivities (73-78% ee) combined with a low diastereoselectivity (8% de). The synthetic utility of this methodology was demonstrated by converting one cycloadduct ($R^1 = R^2 = R^3 = R^4 = R^6 = H$, $R^5 = Bn$) obtained almost diastereo- and enantiopure (90% de, 97% ee) into a tetracyclic psychotropic drug analogue.



Scheme 14. [3+2] Cycloaddition of 2-nitrovinylindoles with α -ketoesters.

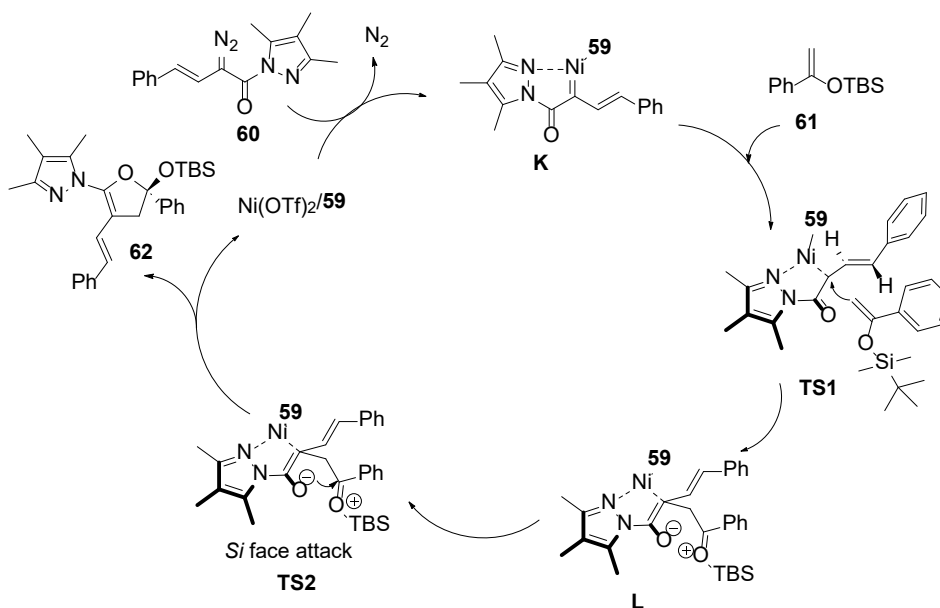
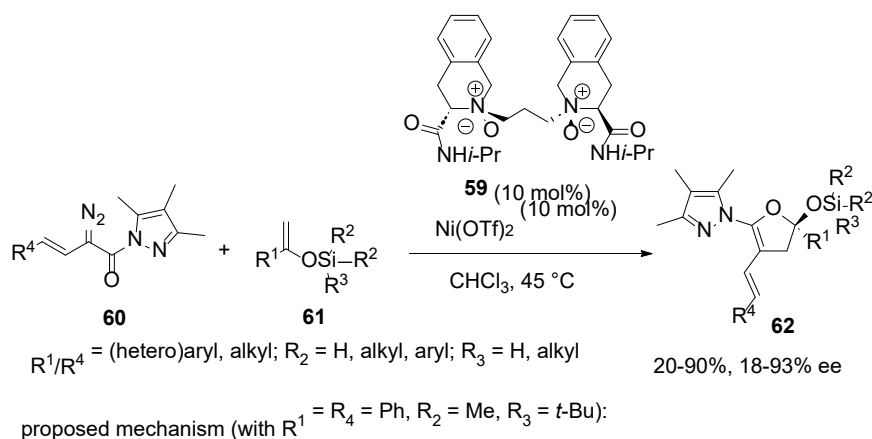
Later in 2021, Liu and Topczewski described the first enantioselective nickel-catalysed [3+2] cycloaddition of azides with internal alkynes [29]. The catalyst system consisted in 10 mol% of $Ni(cod)_2$ combined with the same quantity of chiral primary amine ligand **55** in toluene at 40 °C (Scheme 15). Under these conditions, the reaction of a range of allylic azides **56** with diverse internal alkynes **57** resulted in the synthesis of the corresponding chiral 1,4,5-trisubstituted triazoles **58** with generally very high regioselectivity (57:43 to >95:5), low to excellent yields (23-94%) and moderate to high enantioselectivities (52-86% ee). It was found that the enantioselectivity arose from the involvement of a dynamic kinetic resolution enabled by a spontaneous [3,3]-sigmatropic rearrangement of the starting allylic azide. A range of alkynonitriles ($X = CN$) were found compatible but also alkynoesters ($X = CO_2Et, CO_2t\text{-Bu}$), a trifluoromethyl alkyne ($X = CF_3$), and a thioalkyne ($X = SBn$). Moreover, allylic azides bearing either electron-rich or electron-deficient substituents on the pendent aryl group were tolerated. The cyclohexyl core could also be modified ($Y = C(Me)_2, (CH_2)_2$).



Scheme 15. [3+2] Cycloaddition of azides with internal alkynes.

In 2023, 10 mol% of a chiral nickel catalyst in situ produced from chiral *N,N'*-dioxide **59** and $\text{Ni}(\text{OTf})_2$ was applied by Feng and Liu to promote a highly efficient enantioselective [3+2] cycloaddition between α -diazo pyrazoleamides **60** and 2-siloxy-1-alkenes **61** (Scheme 16) [30]. The reaction performed at 45 °C in chloroform afforded chiral dihydrofuran *O,O*-acetal derivatives **62** with variable yields (20-90%) and enantioselectivities (18-93% ee). Different protected silyl enol ethers were tolerated, affording dihydrofuran acetal derivatives with comparable high ee values. Moreover, various aryl- and alkyl-substituted vinyl α -diazo pyrazoleamides were compatible. In the case of aryl-substituted substrates, it was found that the electronic properties and steric hindrance of the substituents on the phenyl ring had a small impact on the enantioselectivity. A range of aryl-substituted 2-siloxy-1-alkenes could also bear substituents on the phenyl ring but, in this case, both enantioselectivity and reactivity were dependent of the electronic properties of these substituents. For example, the presence of a strong electron-donating substituent at the *para*-position of the phenyl ring ($R^4 = p\text{-MeOC}_6\text{H}_4, p\text{-BnOC}_6\text{H}_4$) resulted in decreasing enantioselectivity (69-71% ee), while that of a strong electron-withdrawing group ($R^4 = p\text{-CF}_3\text{C}_6\text{H}_4$) led to a much lower yield (45% yield, 92% ee). Silyl enol ethers exhibiting heteroaromatic substituents also afforded the desired products with good yields (78-89%) albeit combined with only 44% ee in the case of 2-thienyl-substituted substrate ($R^4 = 2\text{-thienyl}$). Furthermore, the reaction of alkyl-substituted silyl enol ethers ($R^4 = c\text{-Pr}, \text{Cy}$) delivered the related products in either low ee value (66% yield, 18% ee with $R^4 = c\text{-Pr}$) or low yield (20% yield, 86% ee with $R^4 = \text{Cy}$). The mechanism shown in Scheme 16 involves the formation of nickel carbenoid intermediate **K** from the reaction between the α -diazo pyrazoleamide and the catalyst after release of N_2 . Then, the alkene attacks intermediate **K** at the carbene site to form enolate intermediate **L** through

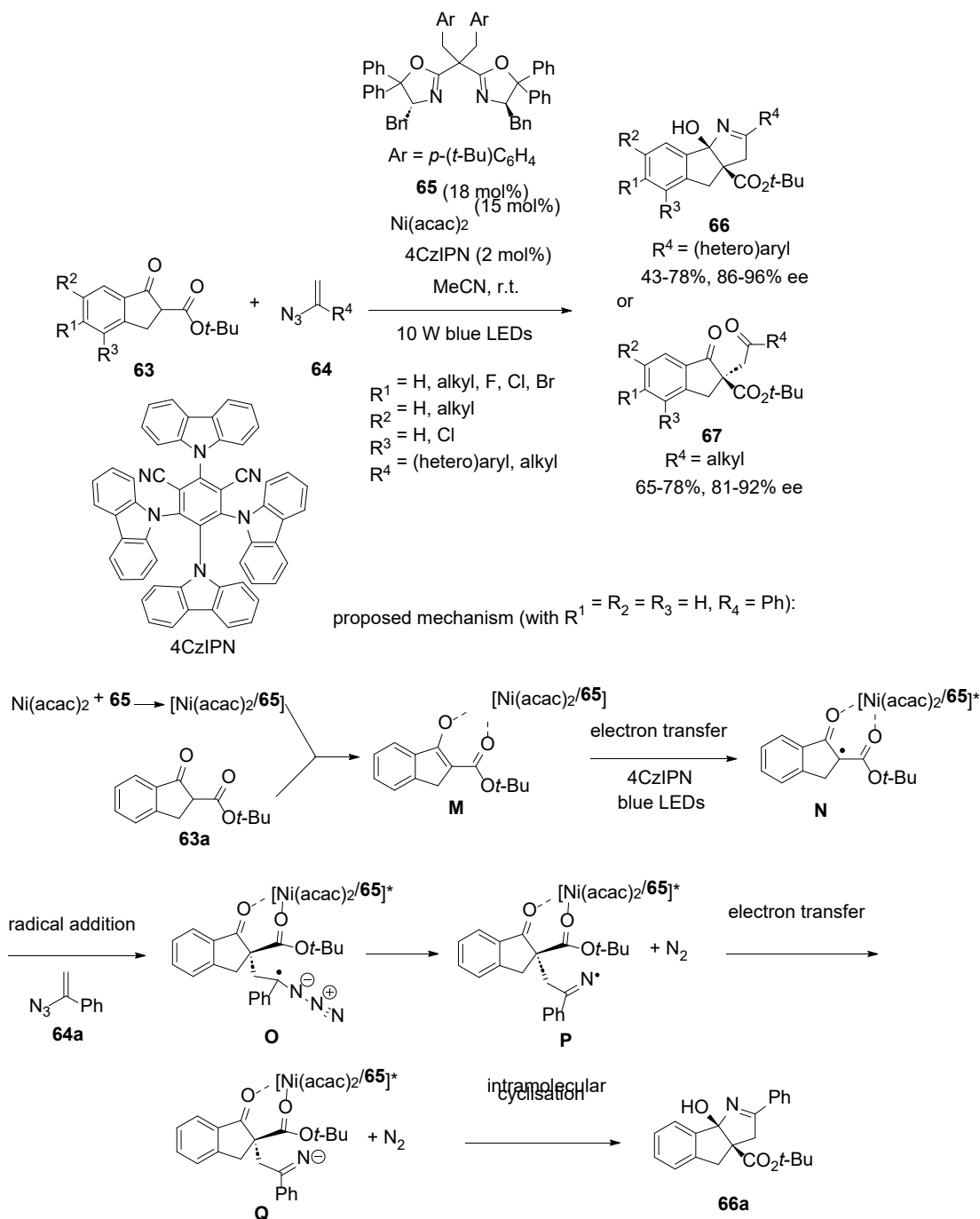
transition state **TS1**. Intermediate **L** subsequently underwent intramolecular nucleophilic attacks to the less sterically hindered *Si* face of the oxonium via transition state **TS2**, which resulted in the formation of the final (*R*)-configured product. The reaction of silyl enol ethers bearing electron-donating substituents provided lower enantioselectivities related to a slower reactivity allowing rotation of the oxonium unit.



Scheme 16. [3+2] Cycloaddition of α -diazo pyrazoleamides with 2-siloxy-1-alkenes.

Visible-light-induced asymmetric [3+2] cycloadditions, allowing the synthesis of medicinally significant chiral five-membered heterocycles, still remain rare. To fill this gap, Chen, Xiao and Jiang recently developed a novel cooperative catalytic system constituted by an organic photocatalyst, namely 4CzIPN, and a chiral nickel catalyst, to promote at room temperature under irradiation with blue LEDs an unprecedented enantioselective [3+2] photocycloaddition of β -keto esters **63** with vinyl azides **64** under redox-neutral conditions

(Scheme 17) [31]. The chiral catalyst was in situ produced from 15 mol% of Ni(acac)₂ and 18 mol% of chiral bisoxazoline ligand **65**. In the presence of the latter combined with 2 mol% of photocatalyst 4CzIPN, a range of (hetero)aryl vinyl azides **64** (R⁴ = (hetero)aryl) reacted with β -keto esters **63** to give the corresponding densely substituted chiral polycyclic 3,4-dihydro-2*H*-pyrroles **66** exhibiting two contiguous quaternary stereocentres. These highly functionalized products were obtained with moderate to high yields (43-78%) and uniformly high enantioselectivities (86-98% ee). The scope of the methodology was extended to alkyl vinyl azides **64** (R⁴ = alkyl) which afforded in this case 1,4-dicarbonyl compounds **67** with both high yields (65-78%) and ee values (81-92% ee) arisen from hydrolysis upon chromatography of the corresponding more labile alkyl-substituted *N,O*-ketals. To explain the results, the authors proposed that the nickel catalyst first activated the redox-inert β -keto ester into redox-active nickel enolate species **M** (Scheme 17). Subsequently, the photoredox-catalysed SET oxidation of this chiral nickel enolate generated the corresponding α -carbonyl carbon radical **N**, which further underwent [3+2] photocycloaddition with the vinyl azide to give iminyl radical **P** with elimination of N₂. Then, the photocatalyst transferred a single electron to iminyl radical **P** to form iminyl anion **Q**, which finally underwent an intramolecular cyclisation to afford the product. The stereoselectivity of the reaction was explained by DFT calculations.

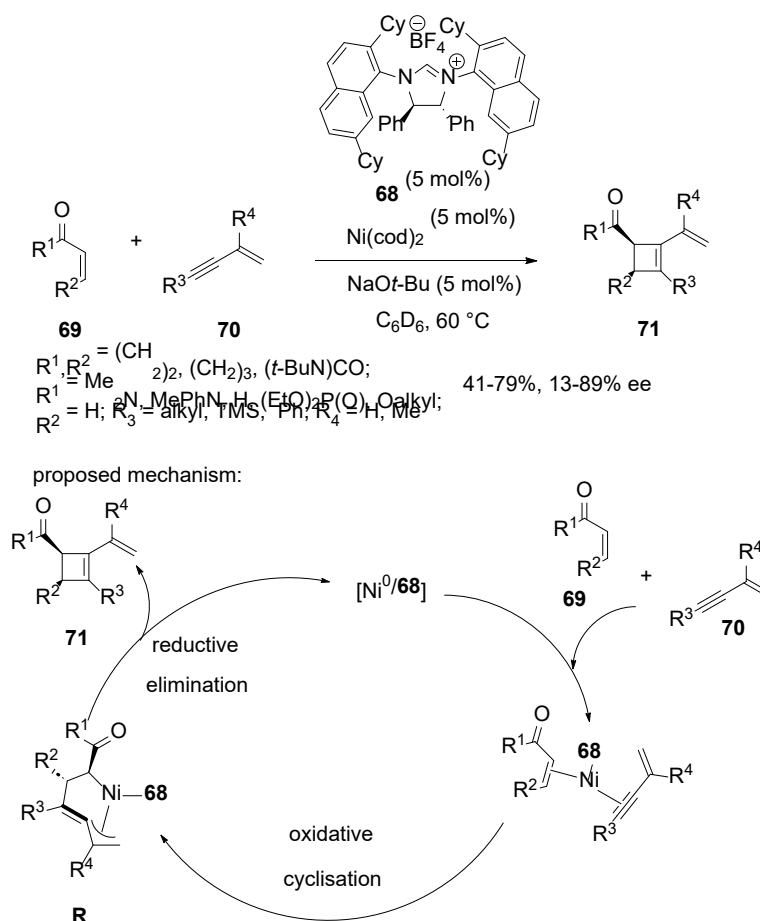


Scheme 17. [3+2] Cycloaddition of β -ketoesters with vinyl azides.

3. Enantioselective nickel-catalysed [2+2] cycloadditions

A number of biologically active products are based on a cyclobutene skeleton. These highly strained reactive structures have been widely synthesised through [2+2] cycloadditions between alkynes and alkenes [32]. However, few asymmetric metal-catalysed versions have been developed so far. The first example involving a chiral nickel catalyst was reported by Ogoshi et al., in 2016 [33]. The methodology involved a catalyst in situ generated from 5

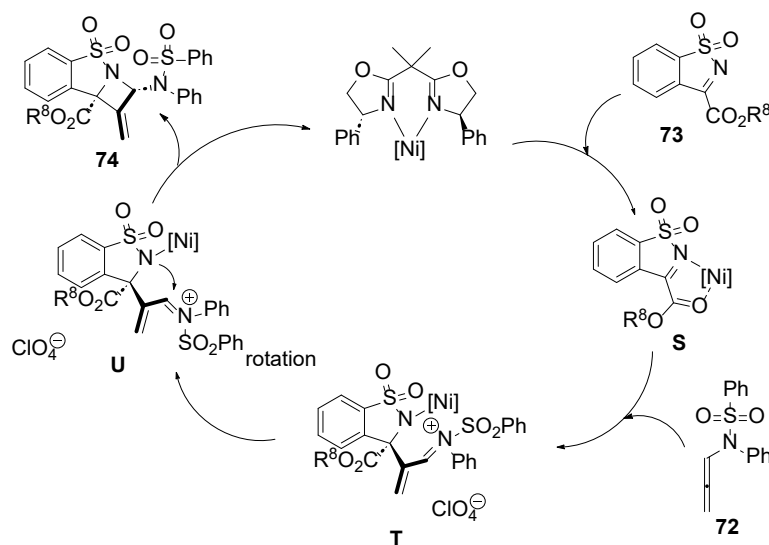
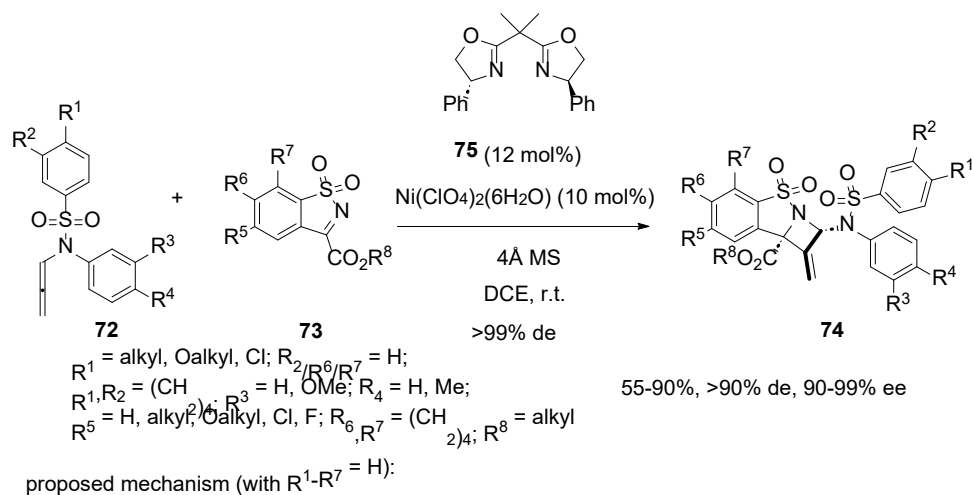
mol% of Ni(cod)₂ and the same quantity of chiral N-heterocyclic carbene ligand **68** in C₆D₆ as solvent. In the presence of 5 mol% of NaO*t*-Bu, a series of α,β -unsaturated carbonyl derivatives **69** reacted with 1,3-enynes **70** to give desired chiral cyclobutenes **71** in moderate to good yields (41-79%) and low to high enantioselectivities (13-89% ee), as illustrated in Scheme 18. The best enantioselectivities (78-89% ee) were achieved in the reaction of a *N*-*tert*-butylmaleimide (R¹,R² = (*t*-BuN)CO) and a *N,N*-dimethylacrylamide (R¹,R² = Me₂N). The authors proposed the mechanism depicted in Scheme 18, beginning with the simultaneous regioselective coordination of the α,β -unsaturated carbonyl derivative and the 1,3-enyne to the nickel catalyst followed by oxidative cyclisation which provided chiral η^3 -butadienyl intermediate **R**. Subsequently, the latter intermediate underwent reductive elimination to deliver the final product.



Scheme 18. [2+2] Cycloaddition of α,β -unsaturated carbonyl derivatives with 1,3-enynes.

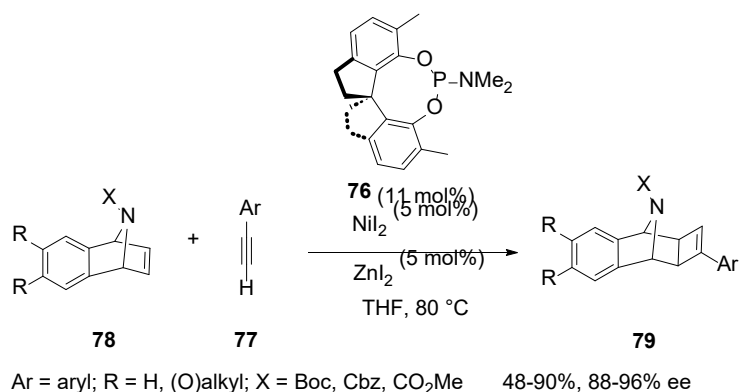
In 2017, Jia et al. developed an enantioselective nickel-catalysed [2+2] cycloaddition of *N*-allenamides **72** with cyclic *N*-sulfonylketimines **73**, affording chiral fused polysubstituted

azetidines **74** bearing two stereogenic centres including a quaternary one (Scheme 19) [34]. The process was found regioselective since it only occurred at the proximal C–C bond of the *N*-allenamides. It required at room temperature 10 mol% of Ni(ClO₄)₂·6H₂O as precatalyst and 12 mol% of chiral bisoxazoline ligand **75** in DCE as solvent. The catalyst system was compatible with a wide range of substrates differently substituted which all provided excellent enantioselectivities (90-99% ee), complete diastereoselectivity, and moderate to high yields (52-90%). The importance of this novel simple methodology is highlighted by the fact that many natural and bioactive products include an azetidine moiety [35]. To explain their results, the authors proposed the mechanism depicted in Scheme 19, showing that the *N*-sulfonylketimine was firstly activated by the nickel catalyst to form five-membered intermediate **S**. Then, asymmetric nucleophilic addition of the *N*-allenamide to this intermediate produced intermediate **T**. The final cycloadduct was then regioselectively formed through intramolecular cyclisation of the amide with iminium along with regeneration of the catalyst.



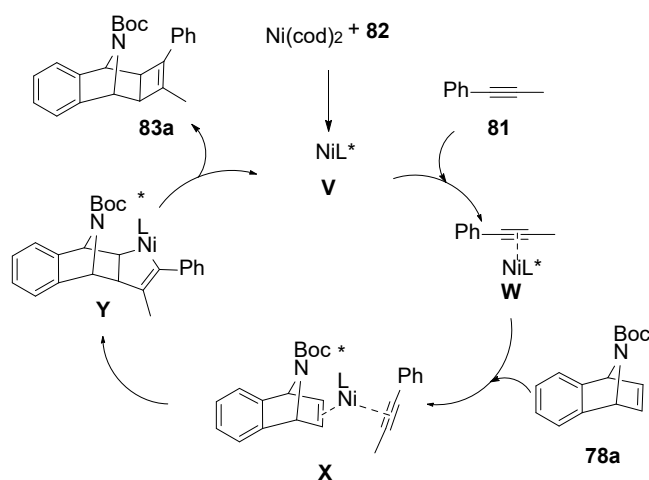
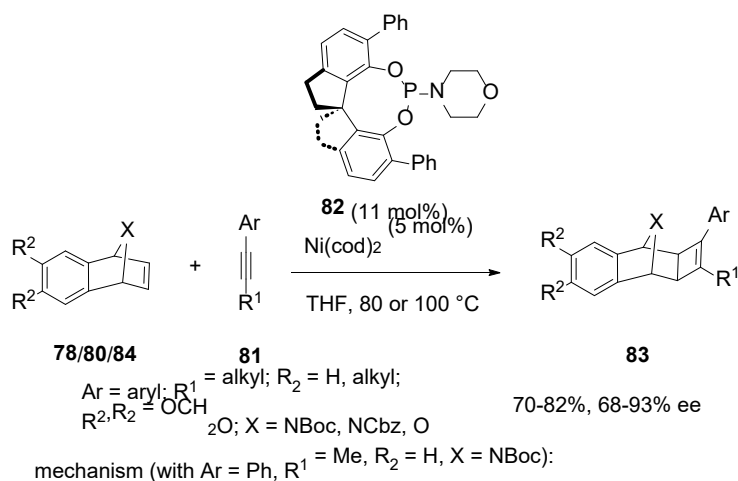
Scheme 19. [2+2] Cycloaddition of cyclic *N*-sulfonylketimines with *N*-allenamides.

In another context, Xu and Fan reported in 2018 the use of a combination of 11 mol% of chiral spiro monophosphoramidate ligand **76**, 5 mol% of NiI_2 , and the same quantity of ZnI_2 to promote the asymmetric [2+2] cycloaddition of terminal aromatic alkynes **77** with azabenzonorbornadienes **78** (Scheme 20) [36]. This process performed at 80 °C in THF led to chiral cycloadducts **79** including a strained cyclobutene in moderate to high yields (48-90%) and uniformly high enantioselectivities (88-96% ee). The dual catalyst system tolerated a wide variety of phenylacetylenes with electron-donating or electron-withdrawing substituents on the phenyl ring, providing homogeneous excellent enantioselectivities. In contrast, aliphatic terminal alkynes as well as internal alkynes were found unreactive under the same conditions.



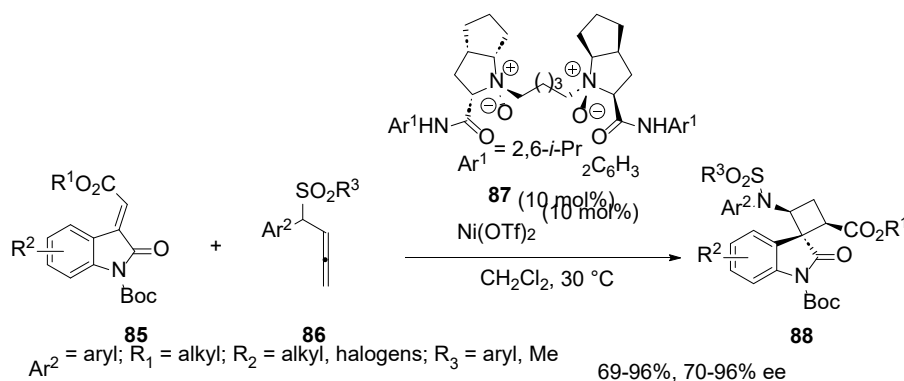
Scheme 20. [2+2] Cycloaddition of azabenzonorbornadienes with terminal aromatic alkynes.

In the same year, these authors disclosed the first asymmetric [2+2] cycloaddition of azabenzonorbornadienes **78,80** (X = NBoc, NCbz) with internal aryl alkyl alkynes **81** (Scheme 21) [37]. In this case, a simple catalyst in situ formed from 5 mol% of Ni(cod)₂ and 11 mol% of related chiral spiro monophosphoramidate ligand **82** was used in THF at 80 °C to promote the cycloaddition, thus leading to chiral nitrogenated *exo*-cycloadducts **89** (X = NBoc, NCbz) with generally both good to high yields (70-92%) and enantioselectivities (74-93% ee). The catalyst system tolerated a series of internal aryl alkyl alkynes with various substituents on the phenyl ring. Even an alkyne exhibiting a free hydroxy group (R¹ = CH₂OH), such as 3-phenyl-2-propynol, was compatible although requiring a higher reaction temperature (100 °C instead of 80 °C). Along with azabenzonorbornadienes, oxabenzonorbornadienes **84** (X = O) also underwent the cycloaddition with 1-phenyl-1-butyne (Ar = Ph, R¹ = Et), yielding the corresponding oxygenated chiral cycloadducts **83** in good yields (70-71%) and enantioselectivities (68-69% ee), as presented in Scheme 21. A mechanism is proposed in Scheme 21 in which the catalytic cycle is initiated by the coordination of the ligand to the precatalyst to generate chiral nickel catalyst **V**. Then, the latter coordinates the alkyne to afford intermediate **W** which further chelates the azabenzonorbornadiene to give intermediate **X**. The following oxidative cyclometallation of **X** affords nickel-cyclopentene intermediate **Y**, which produced the final product through reductive elimination.



Scheme 21. [2+2] Cycloaddition of hetero-bicyclic alkenes with internal alkynes.

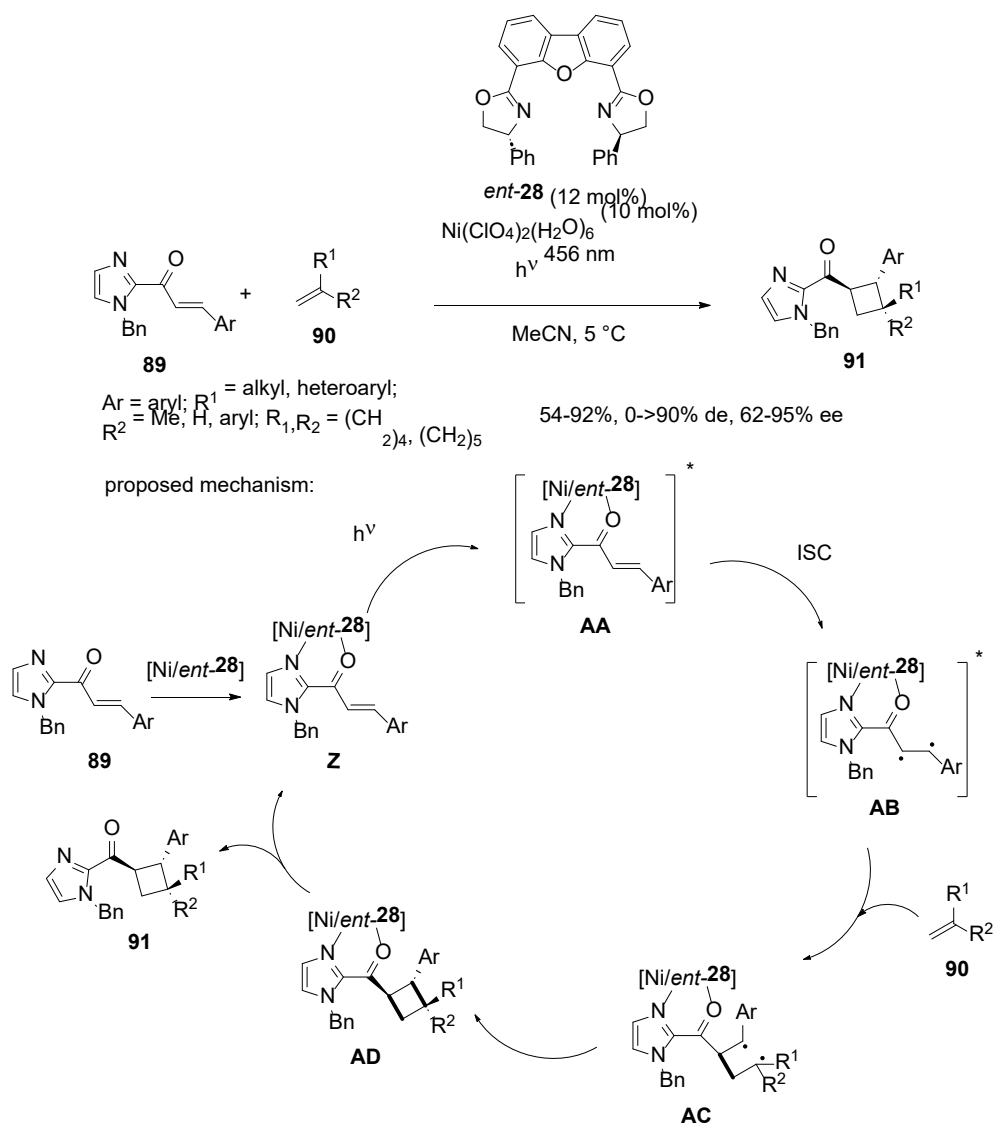
In 2021, Feng and Dong disclosed enantioselective [2+2] cycloaddition of (*E*)-alkenyloxindoles **85** with *N*-allenamides **86** catalysed by a chiral nickel complex in situ produced from 10 mol% of Ni(OTf)₂ and the same quantity of *N,N'*-dioxide chiral ligand **87** [38]. Performed at 30 °C in dichloromethane, the cycloaddition afforded chiral spirocyclobutyl oxindoles **88** in both good to excellent yields (69-96%) and enantioselectivities (70-96% ee), as presented in Scheme 22. Along with variously substituted *N*-allenamides, different substituents (R^2) at C5, C6, and C7 positions on the phenyl ring of the (*E*)-alkenyloxindoles were tolerated, providing the desired products with 88-96% ee. The nature of the ester group (R^1) was found important since the enantioselectivity of the reaction increased gradually with the increase of the steric hindrance of the ester group (R^1 = Me: 70% ee, R^1 = *t*-Bu: 95% ee).



Scheme 22. [2+2] Cycloaddition of (*E*)-alkenyloxindoles with *N*-allenamides.

In 2022, Gong et al. developed enantioselective photochemical [2+2] cycloadditions between α,β -unsaturated 2-acyl imidazoles **89** and alkenes **90** catalysed by a chiral nickel complex (Scheme 23) [39]. The latter arose from the reaction between 10 mol% of Ni(ClO₄)₂·6H₂O and 12 mol% of chiral bisoxazoline ligand *ent*-**28** in acetonitrile as solvent. The process did not require the addition of photosensitizers, since the nickel intermediate complexes upon exposure to visible light served as the active components. Under irradiation with blue light-emitting diodes (LEDs) lamp ($\lambda_{\text{max}} = 456 \text{ nm}$), the reaction of a series of α,β -unsaturated 2-acyl imidazoles **89** with various alkenes **90** performed at 5 °C afforded the corresponding chiral spirocyclic cycloadducts **91** with moderate to high yields (54-92%), variable diastereoselectivities (0->90% de) and moderate to excellent enantioselectivities (62-95% ee). Various α,β -unsaturated 2-acyl imidazoles bearing different substituents at the β -position were compatible. Amongst the alkene partners, an enyne ($\text{R}^1 = \text{TMSC}\equiv\text{C}$) was tolerated but provided the corresponding cyclobutene with the lowest ee value (62% ee). Among styrene derivatives, 1,1-diphenylethylene ($\text{R}^1 = \text{R}^2 = \text{Ph}$) provided the best result (90% yield, >90% de, 95% ee) by reaction with phenyl-substituted α,β -unsaturated 2-acyl imidazole ($\text{Ar} = \text{Ph}$). Another good result (61% yield, >90% de, 94% ee) was obtained in the reaction of a 1,1-dialkyl substituted alkene ($\text{R}^1 = \text{R}^2 = \text{Et}$). Moreover, chiral spirocyclic moieties ($\text{R}^1, \text{R}^2 = (\text{CH}_2)_4, (\text{CH}_2)_5$), often encountered as scaffold products in bioactive molecules, could be synthesised through this methodology with good yields (63-71%) and both high diastereo- (>90% de) and enantioselectivities (90-91% ee). The authors proposed the mechanism depicted in Scheme 23, beginning with a fast ligand exchange between the chiral nickel catalyst and the α,β -unsaturated 2-acyl imidazole which delivered nickel intermediate **Z**. Upon irradiation with blue LEDs, the latter species became excited to its singlet state **AA**. The subsequent intersystem crossing (ISC) of intermediate **AA** resulted in

the formation of intermediate **AB**. Then, the latter species reacted with the alkene substrate to give intermediate **AC**, which subsequently underwent cyclisation to afford a nickel coordinated product **AD**. The final ligand exchange of **AD** with the α,β -unsaturated 2-acyl imidazole resulted in the formation of the product along with regeneration of nickel intermediate **Z**.

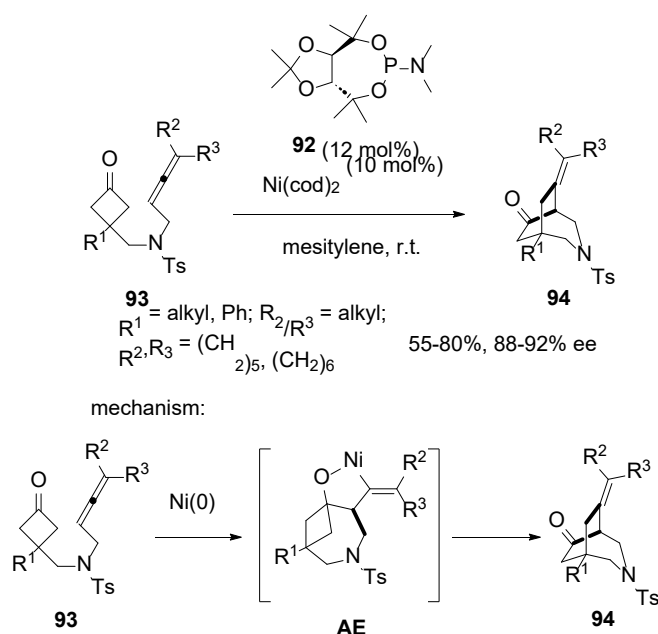


Scheme 23. Photochemical [2+2] cycloaddition of α,β -unsaturated 2-acyl imidazoles with alkenes.

4. Enantioselective nickel-catalysed [4+2] cycloadditions

In 2016, Dong and Zhou reported the use of a chiral nickel catalyst to promote an asymmetric intramolecular [4+2] cycloaddition of cyclobutanones with allenes (Scheme 24)

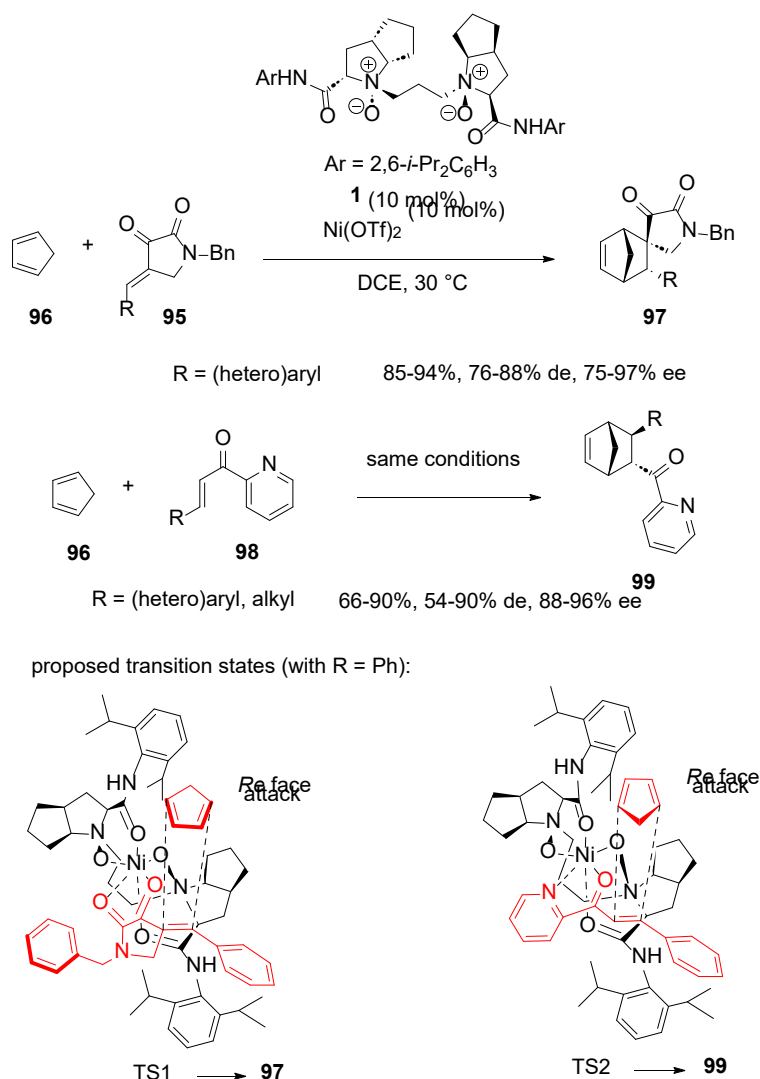
[40]. The catalyst was in situ generated from 10 mol% of Ni(cod)₂ and the same quantity of chiral TADDOL-derived phosphoramidate ligand **92** in mesitylene as solvent. Performed at room temperature, the formal [4+2] cycloaddition of various allenes **93** afforded the corresponding chiral [3.2.2] bicyclic products **94** as single diastereomers in moderate to good yields (55-80%) and uniformly high enantioselectivities (88-92% ee). Dialkyl- as well as cycloalkyl-substituted allenes provided comparable excellent results. The authors proposed a mechanism beginning with a cyclometallation to generate a five-membered metallacycle **AE** between the carbonyl group of cyclobutanone and the unsaturated moiety of allene. Then, this intermediate underwent a β-carbon atom elimination followed by a reductive elimination to give the final cycloadduct (Scheme 24). More recently, computational studies were investigated by Qu et al. [41].



Scheme 24. Intramolecular [4+2] cycloaddition of cyclobutanones with allenes.

Chiral *N,N'*-dioxides [42] were employed as chiral nickel ligands by Feng and Lin in 2016 to promote enantioselective [4+2] cycloadditions of α,β -unsaturated carbonyl compounds with cyclopentadiene (Scheme 25) [43]. For example, the bidentate coordination of 2,3-variably substituted dioxopyrrolidines **95** with 10 mol% of a nickel catalyst in situ generated from Ni(OTf)₂ and chiral *N,N'*-dioxide ligand **1** resulted in the formation of five-membered catalyst/substrate complexes, which allowed controlling the stereoselectivity of the [4+2] cycloaddition with cyclopentadiene **96**. This cycloaddition performed at 30 °C in DCE as

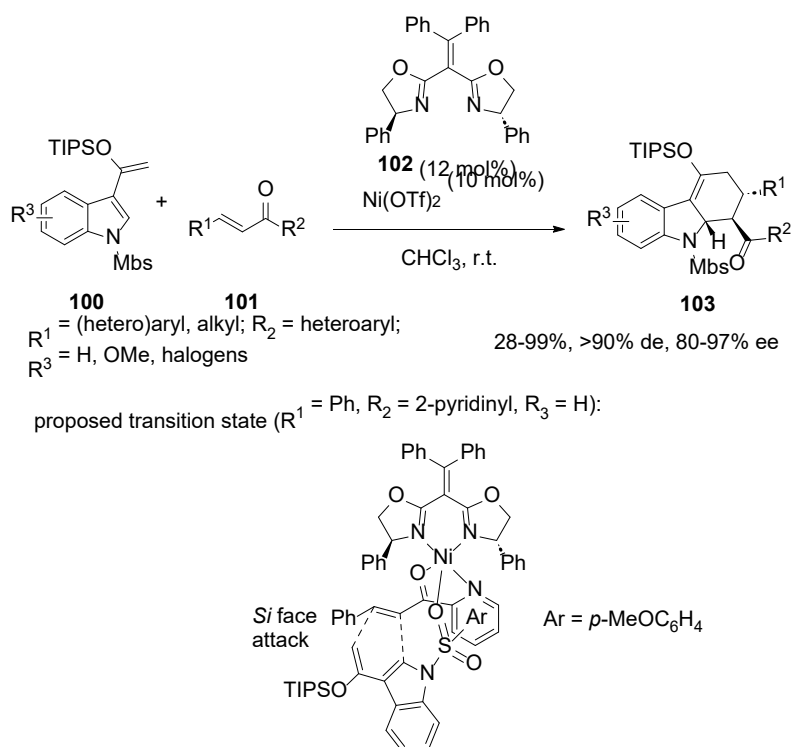
solvent led to chiral bridged products **97** exhibiting three stereocentres in high yields (85-94%), and both good to high diastereo- (76-88% de) and enantioselectivities (75-97% ee). The same conditions were applied to other α,β -unsaturated carbonyl compounds, such as 2-alkenoylpyridines **98**, which afforded by reaction with cyclopentadiene **96** the desired chiral products **99** bearing four adjacent stereocentres with good to high yields (66-90%), moderate to high levels of diastereoselectivity (54-90% de) and uniformly excellent enantioselectivities (88-96% ee). Actually, the diastereoselectivities were $\geq 80\%$ de excepted in the reaction of an alkyl-substituted ($R = c\text{-Hex}$) substrate which provided the corresponding product with only 54% de. The stereoselectivity of the reactions producing products **97** and **99** is explained by transition states TS1 and TS2, respectively (Scheme 25). In a first time, the *N*-oxides and amide oxygens of the chiral ligand coordinated to Ni(II) to form a six-membered chelating ring. Then, 2,3-dioxopyrrolidine **95** coordinated through a bidentate fashion to the chiral catalyst with its two carbonyl groups, while 2-alkenoylpyridine **98** coordinated with its carbonyl group and nitrogen atom of the pyridine moiety, forming rigid octahedral complexes. Then, cyclopentadiene attacked the dienophiles from the *Re-Re* face since the *Si-Si* face was sterically hindered by the amide moiety of the ligand, which resulted in the formation of product **97** exhibiting the (1*R*,2*R*,3*S*,4*S*)-configuration through transition state TS1, and product **99** with the (1*S*,2*R*,3*R*,4*R*)-configuration through transition state TS2.



Scheme 25. [4+2] Cycloadditions of dioxopyrrolidines and 2-alkenoylpyridines with cyclopentadiene.

In 2021, Fu et al. reported the first enantioselective nickel-catalysed [4+2] cycloaddition between silyloxyvinylindoles **100** and 2-enoyl pyridines **101** ($R^2 = 2$ -pyridinyl) [44]. This reaction was achieved at room temperature in chloroform by using a chiral nickel catalyst derived from 10 mol% of Ni(OTf)₂ and 12 mol% of chiral diphenylmethyldene-tethered bisoxazoline ligand **102**. It allowed the synthesis of a range of chiral hydrocarbazoles **103** exhibiting three contiguous stereocentres as almost single diastereomers (>90% de) in variable yields (28-99%) and homogeneously high enantioselectivities (80-97% ee), as shown in Scheme 26. The 2-enoyl pyridines ($R^2 = 2$ -pyridinyl) could be variously substituted (R^1) with (hetero)aryl, styrenyl, as well as alkyl groups. Moreover, the scope of the methodology could be extended to enoyl substrates substituted by other 2-azaarene rings, such as 2-

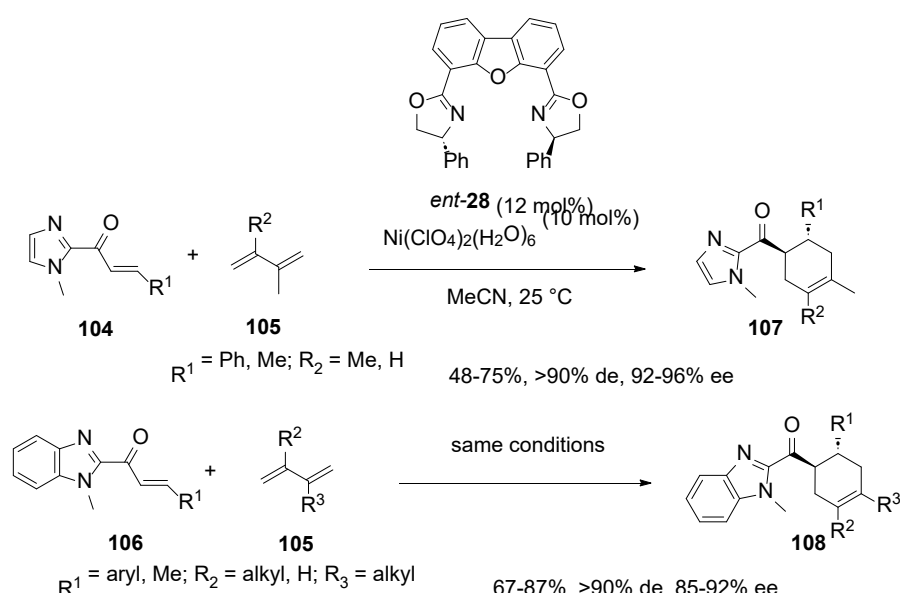
pyrazinyl, 2-quinolinyl, 2-quinoxalanyl, 2-thiazolyl and N-Me-2-imidazolyl groups in place of 2-pyridinyl group. The reactions resulted in the formation of the corresponding products with comparable very high enantioselectivities (88-94% ee). In addition, silyloxyvinylindoles exhibiting either electron-donating or electron-withdrawing groups (R^3) at different positions of their phenyl ring were well tolerated (90-96% ee). The authors proposed the transition state depicted in Scheme 26 in which 2-enoyl pyridine **101a** ($R^1 = \text{Ph}$, $R^2 = 2\text{-pyridinyl}$) coordinated to the nickel catalyst through its O and N atoms, resulting in the activation of the dienophile. Then, the N-sulfonyl group of silyloxyvinylindole substrate **100a** ($R^3 = \text{H}$) chelated to the nickel centre through the O atom of its ArSO_2 group. Then, the silyloxyvinylindole attacked preferentially from the *Si-Si* face (away from oxazoline phenyl) of the 2-enoyl pyridine to afford the final product.



Scheme 26. [4+2] Cycloaddition of silyloxyvinylindoles with 2-enoyl pyridines.

In the absence of irradiation, α,β -unsaturated 2-acyl imidazoles **104** underwent at 25 °C [4+2] cycloaddition with dienes **105** in the presence of the same chiral nickel complex as that employed to induce photochemical [2+2] cycloaddition described in Scheme 23 [39]. Indeed, a variety of dienophiles, such as α,β -unsaturated 2-acyl imidazoles **104** and 2-acyl

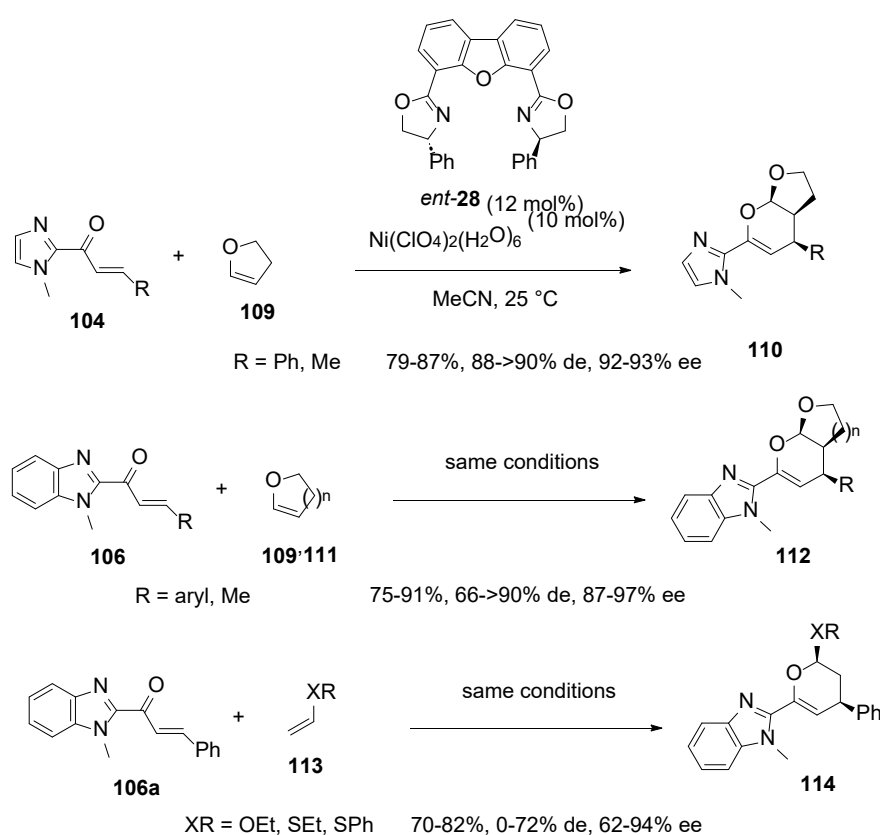
benzimidazoles **106**, reacted with various dienes **105** through a Diels–Alder reaction promoted by 10 mol% of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ combined in acetonitrile with 12 mol% of chiral bisoxazoline ligand *ent*-**28** (Scheme 27). The reaction of α,β -unsaturated 2-acyl imidazoles **104** with dienes **105** delivered the corresponding chiral cyclohexenes **107** bearing contiguous tertiary stereocentres as almost single diastereomers (>90% de) in moderate to good yields (48-75%) and uniformly high enantioselectivities (92-96% ee). In addition, the Diels–Alder reaction of 2-acyl benzimidazoles **106** with dienes **105** afforded chiral cycloadducts **108** as single diastereomers (>90% de) in moderate to high yields (67-87%) and high ee values (82-92% ee). Generally, the reactions of α,β -unsaturated 2-acyl benzimidazoles **106** proceeded more rapidly than those of the α,β -unsaturated 2-acyl imidazoles **104**, thus demonstrating the influence of the auxiliary moiety on the reaction rate.



Scheme 27. [4+2] Cycloadditions of α,β -unsaturated 2-acyl (benz)imidazoles with dienes.

In addition, the same authors applied this catalyst system to develop asymmetric inverse-electron-demand oxa-Diels–Alder cycloadditions between α,β -unsaturated 2-acyl imidazoles and electron-rich alkenes as dienophiles [39]. As presented in Scheme 28, 2,3-dihydrofuran **109** underwent oxa-Diels–Alder reaction with α,β -unsaturated 2-acyl imidazoles **104** to give chiral bicyclic products **110** with high yields (79-87%), diastereo- (88->90% de), and enantioselectivities (92-93% ee). The same reaction conditions were also applied to the oxa-Diels–Alder reactions of α,β -unsaturated 2-acyl benzimidazoles **106** with dihydrofuran **109** (n

= 1) and dihydropyran **111** ($n = 2$), which resulted in the formation of chiral cycloadducts **112** with high yields (75-91%), moderate to excellent diastereoselectivities (66->90% de), and high enantioselectivities (87-97% ee). Interestingly, either imidazoles or benzimidazoles exhibiting a β -methyl substituent provided the products as almost single diastereomers (>90% de). Furthermore, other electron-rich alkenes **113** bearing substituents, such as alkoxy and thioether groups, could be used as dienophiles in the reaction with α,β -unsaturated 2-acyl benzimidazole **106a** to give the corresponding dihydropyranes **114** with good yields (70-82%), variable diastereoselectivities (0-72% de), and moderate to high ee values (62-94% ee).

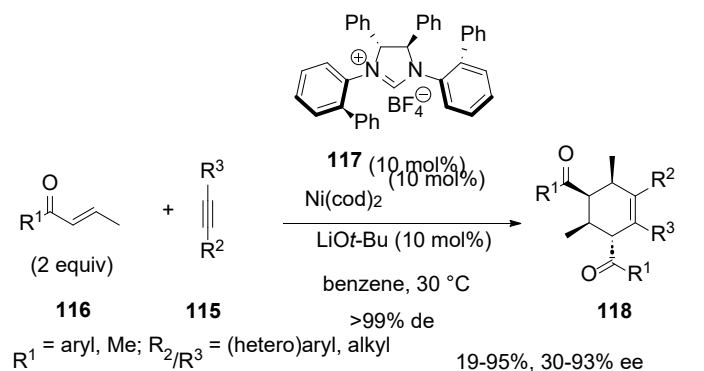


Scheme 28. Oxa-Diels–Alder cycloadditions of α,β -unsaturated 2-acyl (benz)imidazoles with electron-rich alkenes.

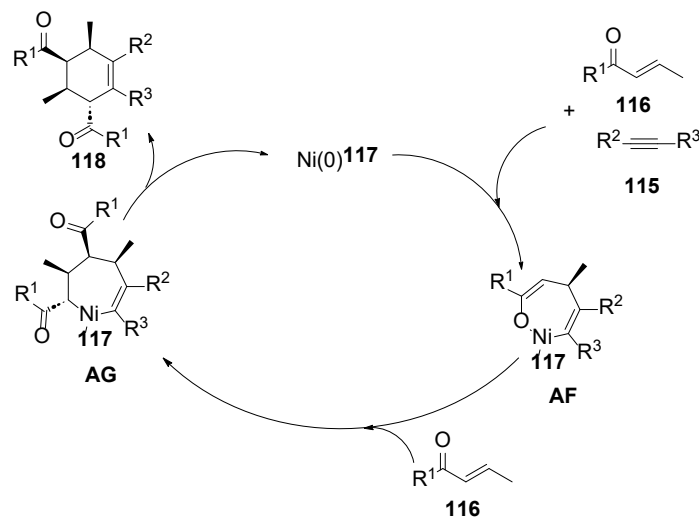
5. Enantioselective nickel-catalysed [2+2+2] cycloadditions

Considerable advances have been made in the last decade in the development of [2+2+2] cycloadditions, allowing a direct access to many functionalised six-membered derivatives. Especially, a variety of metal catalysts have been applied to catalyse a range of [2+2+2]

cycloadditions of alkenes as well as alkynes [45]. Even more interesting, enantioselective catalytic versions of these reactions have been successfully developed to afford chiral cyclic products.⁴⁶ As a recent example, Ogoshi et al. described in 2015 an asymmetric nickel-catalysed [2+2+2] cycloaddition of internal alkynes **115** with two equivalents of α,β -unsaturated ketones **116** (Scheme 29) [47]. The process involved a chiral nickel catalyst in situ generated from 10 mol% of Ni(cod)₂ and the same quantity of chiral *N*-heterocyclic carbene ligand **117** in benzene at 30 °C. Performed in the presence of 10 mol% of LiOt-Bu as base, the [2+2+2] cycloaddition of internal alkynes **115** with two equivalents of α,β -unsaturated ketones **116** provided the corresponding chiral functionalised cyclohexenes **118** exhibiting four contiguous stereocentres as single diastereomers in low to excellent yields (19-95%) and enantioselectivities (30-93% ee). Generally, alkyl-substituted alkynes provided lower enantioselectivities (30-69% ee) than diaryl-substituted ones (44-93% ee). The steric hindrance of the alkyne was found important in the enantioselectivity of the reaction. Indeed, the longer the alkyl chain of the alkyl-substituted alkyne was, the lower was the ee value (69, 50, 30% ee, respectively for R⁴ = Et, *n*-Pr, *n*-Bu). The lowest yield (19%) was observed in the reaction of an α,β -unsaturated ketone exhibiting a *p*-anisyl group (R¹ = *p*-anisyl). The authors proposed the mechanism depicted in Scheme 29, in which the oxidative cyclisation of the enone and alkyne with the chiral nickel catalyst afforded chiral seven-membered nickel enolate intermediate **AF**, which then reacted diastereoselectively with a second equivalent of enone to generate seven-membered nickel intermediate **AG**. The latter species subsequently underwent reductive elimination to give the final cycloadduct.



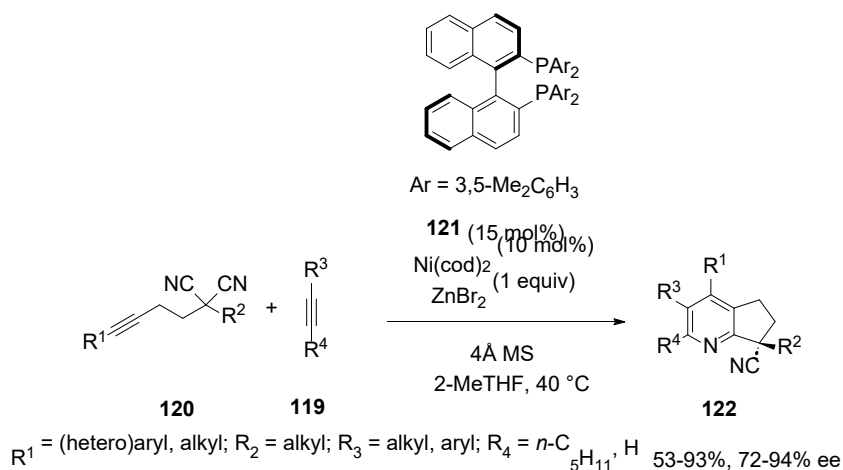
proposed mechanism:



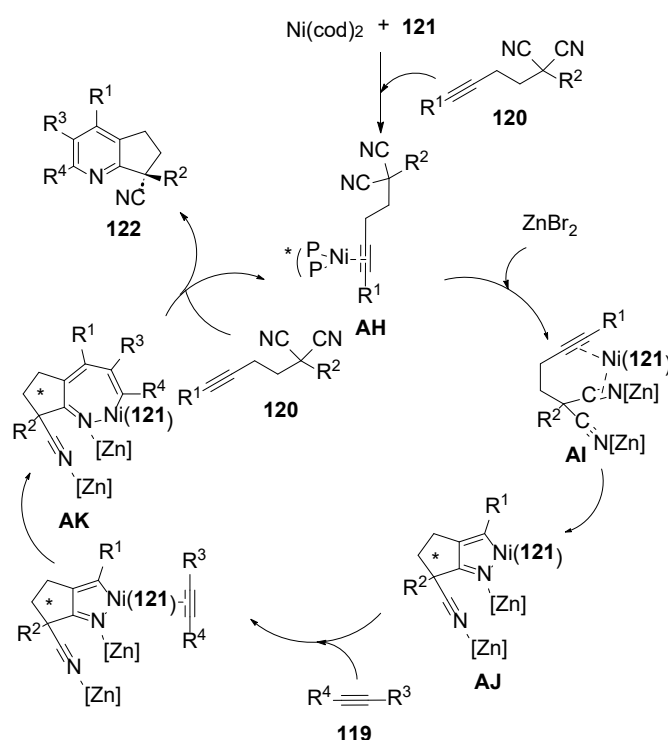
Scheme 29. [2+2+2] Cycloaddition of internal alkynes with two equivalents of α,β -unsaturated ketones.

In 2021, Liu et al. reported a novel methodology to synthesise densely substituted chiral pyridines based on an enantioselective nickel-catalysed [2+2+2] cycloaddition of alkynes **119** with alkyne-tethered malononitriles **120** [48]. The process was promoted at 40 °C by a nickel catalyst in situ generated from 10 mol% of $\text{Ni}(\text{cod})_2$ and 15 mol% of chiral biphosphine ligand **121** in 2-MeTHF as solvent (Scheme 30). One equivalent of ZnBr_2 was required to allow the hetero-cyclometallation step. The reaction led to a wide variety of chiral pyridines **122** exhibiting an all-carbon quaternary centre adjacent to the pyridine moiety. The latter were produced with moderate to excellent yields (53-93%) and good to high enantioselectivities (72-94% ee). Notably, along with internal alkynes, terminal alkynes were tolerated with very high regioselectivity to afford the corresponding tetrasubstituted chiral pyridines. A high functional group compatibility was observed for substituents of either alkynes and malononitriles. In almost all cases of substrates, the ee values were found $\geq 77\%$ ee. For example, a range of substituents (R^2) attached to the α -prochiral centre of the malononitrile

were compatible. It was found that the enantioselectivity decreased with a smaller size of R² substituents. Therefore, the reaction with a cyclohexylmethyl substrate (R² = CyCH₂) resulted in the formation of the corresponding pyridine with 94% ee, while a methyl-substituted substrate (R² = Me) reacted with only 72% ee. A mechanism is proposed in Scheme 30, beginning with the formation of the nickel complex **AH** through the coordination of the alkyne-tethered malononitrile to the chiral nickel catalyst. In the presence of ZnBr₂, intermediate **AI** was formed which then underwent an oxidative heterocyclometallation to give bicyclic nickel intermediate **AJ**. Then, coordination and insertion of the second alkyne into nickel intermediate **AJ** led to seven-membered nickel intermediate **AK**, which finally underwent a reductive elimination to deliver final pyridine **122**.



proposed mechanism:

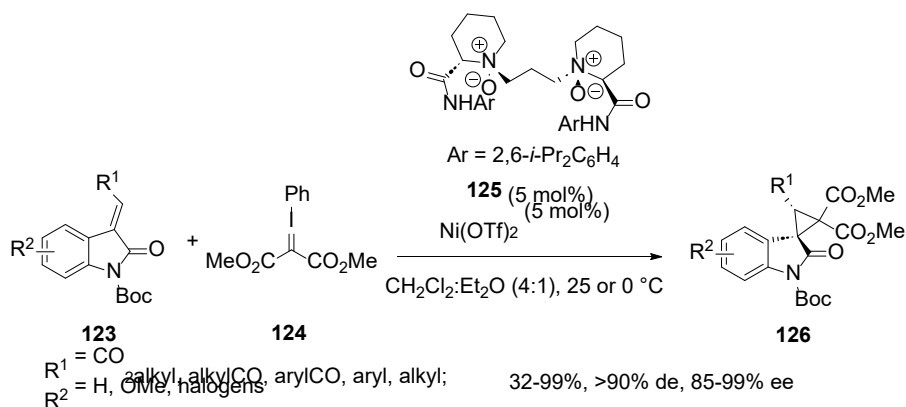


Scheme 30. [2+2+2] Cycloaddition of alkynes with alkyne-tethered malononitriles.

6. Other enantioselective nickel-catalysed cycloadditions

In 2016, Liu and Feng reported an asymmetric nickel-catalysed [2+1] cycloaddition of 3-alkenyl-oxindoles **123** with phenyliodonium ylide **124** as the carbene precursor [49]. The process was performed at 25 °C in a 1:4 mixture of dichloromethane and diethylether as solvent in the presence of 5 mol% of Ni(OTf)₂ and the same quantity of chiral *N,N'*-dioxide ligand **125**. It afforded chiral spirocyclopropane-oxindoles **126** exhibiting two contiguous tertiary and all carbon quaternary centres as single diastereomers (>90% de) in moderate to

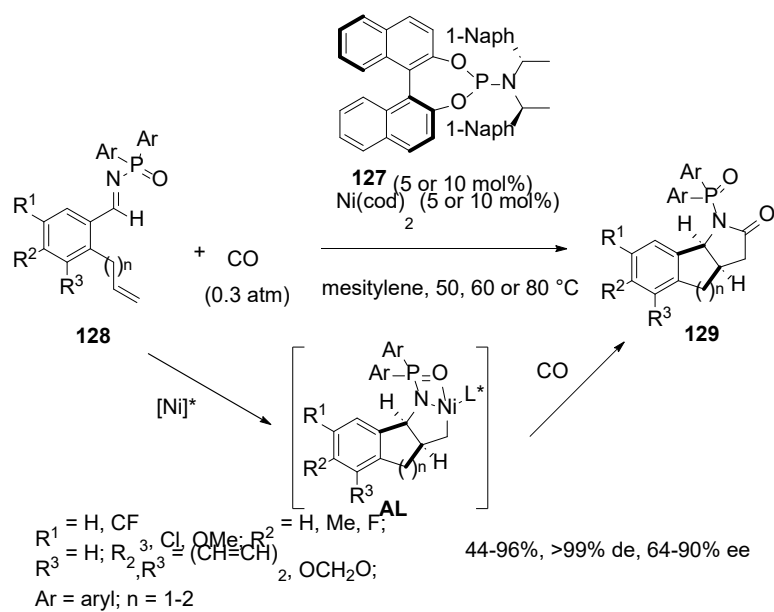
quantitative yields (32-99%) and generally high enantioselectivities (85-99% ee), as illustrated in Scheme 31. A wide variety of (*E*)-3-ester-substituted methyleneindolinone derivatives ($R^1 = \text{ester}$) were compatible, leading to the desired products with 90-99% yields and 91-99% ee. Moreover, different substituents were tolerated at the C5- and C6-positions of the phenyl ring of the oxindole ring. Along with ester groups, 3-acyl substituted methyleneindolinone derivatives produced the corresponding spirocyclopropane products in both excellent yields (80-95%) and ee values (90-98% ee) at lower reaction temperature (0 °C instead of 25 °C). Different alkyl-substituted alkenes ($R^1 = n\text{-Pr, Cy, CN}$) also underwent the reaction to give the desired adducts in low to good yields (32-82%) and high enantioselectivities (85-98% ee). Furthermore, the reaction of variously substituted aryl substituted 3-alkenyl-oxindoles afforded the corresponding chiral products with 60-93% yields and 94-99% ee regardless the electronic nature and position of the substituents on the 3-phenyl group.



Scheme 31. [2+1] Cycloaddition of 3-alkenyl-oxindoles with phenyliodonium ylide.

In 2020, Ogoshi et al. reported the synthesis of chiral polycyclic γ -lactams on the basis of an asymmetric nickel-catalysed [2+2+1] carbonylative cycloaddition of ene-imines with carbon monoxide (Scheme 32) [50]. It was promoted by 5 or 10 mol% of a chiral nickel complex in situ generated from $\text{Ni}(\text{cod})_2$ and chiral phosphoramidate ligand **127** in mesitylene as solvent. A range of variously substituted ene-imines **128** smoothly underwent the cycloaddition at 50, 60 or 80 °C with carbon monoxide (0.3 atm) to afford chiral γ -lactams **129** bearing two contiguous stereocentres as single diastereomers in moderate to excellent yields (44-96%) and enantioselectivities (64-90% ee). The lowest enantioselectivities were obtained in the synthesis of sterically hindered γ -lactams, such as a tetracyclic one ($R^1 = \text{H}$, $R^2, R^3 = (\text{CH}=\text{CH})_2$, 64% ee) or γ -lactams including a tetralin core ($n = 2$, 70% ee). The

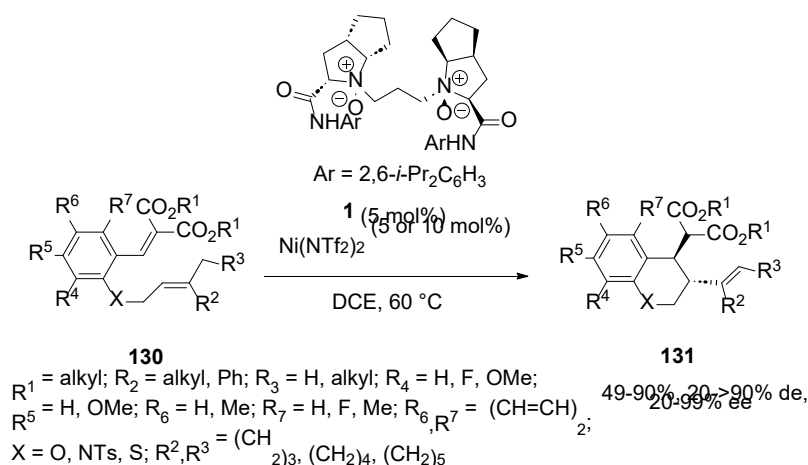
authors demonstrated the formation of chiral intermediate heteronickelacycle **AL** through oxidative cyclisation. CO further inserted this intermediate to afford after reductive elimination the final cycloadduct (Scheme 32). The utility of this simple methodology was shown by conversion of one product ($R^1 = R^2 = R^3 = H$) into physiologically active strigolactam GR-24.



Scheme 32. [2+2+1] Carbonylative cycloaddition of ene-imines with carbon monoxide.

In another context, Feng and Dong described an enantioselective nickel-catalysed intramolecular ene reaction of heteroatom-tethered 1,7-dienes **130**, in 2019 (Scheme 33) [51]. The reaction consisted in connecting an α,β -unsaturated ester and an alkene exhibiting an allylic hydrogen. The process, performed at 60 °C in DCE as solvent, was promoted by a nickel catalyst in situ generated from 5 or 10 mol% of $Ni(Tf_2)_2$ and 5 mol% of chiral N,N' -dioxide ligand **1**. Under these conditions, a range of 1,7-dienes **130** bearing an heteroatom-incorporated tether underwent asymmetric ene reaction to give the corresponding chiral (thio)chromanes ($X = O$ or S) and tetrahydroquinolines ($X = N$) **131** in variable yields (20-90%), diastereo- (0->90% de), and enantioselectivities (20-99% ee). In particular, a range of variously substituted oxygen-tethered 1,7-dienes **130** ($X = O$) underwent the reaction with moderate to high yields (42-90%) combined with both low to excellent diastereo- (20->90% de) and enantioselectivities (20-99% ee). The position of substituents (R^4 - R^7) on the phenyl ring was found crucial on the diastereoselectivity of the reaction. For example, the reaction of sterically hindered 5- and 6-substituted substrates ($R^6 = Cl, Br, R^7 = F$) provided the

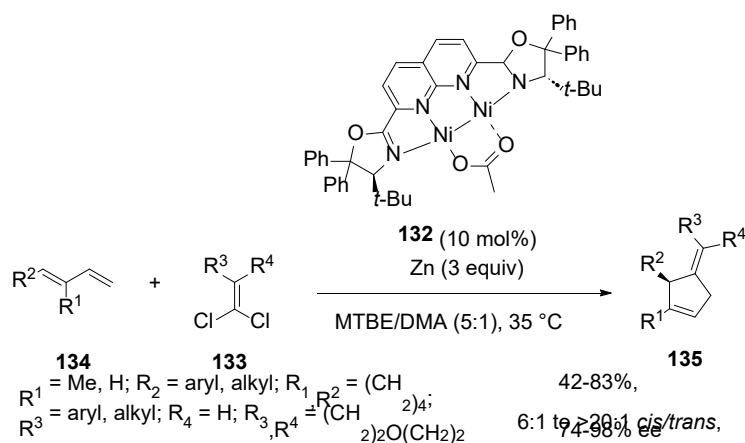
corresponding products in lower diastereoselectivities (20-50% de). The scope of the process was also extended to nitrogen-tethered 1,7-dienes **130** (X = NTs), which afforded the corresponding tetrahydroquinolines **131** with both uniformly high yields (75-89%) and enantioselectivities (78-98% ee) combined with variable diastereoselectivities (0->90% de). Indeed, once again the diastereoselectivity was found highly dependent on the presence of substituents at the 5- and 6-positions of the phenyl ring. For example, the reaction of 5- and 6-unsubstituted substrates ($R^6 = R^7 = H$) all provided an almost complete diastereoselectivity (>90% de) while the presence of a chlorine atom ($R^6 = Cl$) or a methyl group ($R^7 = Me$) at one of these positions made the diastereoselectivity dramatically decrease (0-72% de). Furthermore, a sulfur-tethered 1,7-diene **130** (X = S) was tolerated, leading to the desired thiochromane **131** in 71% yield, 60% de, and 80% ee. It must be noted that these complex heterocyclic moieties belong to many biologically highly interesting products.



Scheme 33. Intramolecular ene reaction of heteroatom-tethered 1,7-dienes.

In 2020, Uyeda and Behten showed that novel preformed chiral dinickel naphthyridine-bisoxazoline catalyst **132** were capable of promoting enantioselective intermolecular [4+1] cycloaddition of vinylidene equivalents, such as 1,1-dichloroalkenes **133**, with 1,3-dienes **134** (Scheme 34) [52]. The products of this transformation, performed at 35 °C in a 5:1 mixture of MTBE and DMA as solvent, were chiral methylenecyclopentenes **135** exhibiting an exocyclic alkene. In most cases, high *cis*-selectivity (up to >20:1 *cis/trans*) was observed by using 10 mol% of catalyst system in the presence of 3 equivalents of zinc. The cycloadducts were produced with moderate to good yields (42-83%) and high enantioselectivities (74-98% ee). Various terminal monosubstituted and 1,2-disubstituted dienes were tolerated as well as the presence of a variety of functional groups, such as

(thio)ethers, esters, nitriles, boronate esters, heterocycles and alkenes, on the 1,1-dichloroalkenes.

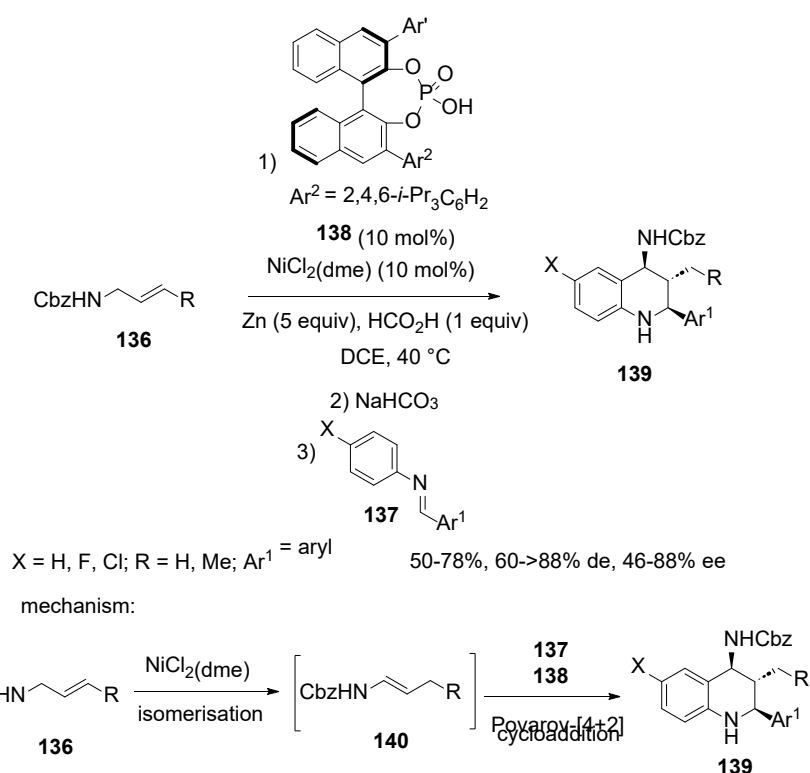


Scheme 34. Intermolecular [4+1] cycloaddition of vinylidene equivalents with 1,3-dienes.

7. Enantioselective nickel-catalysed tandem and domino reactions based on cycloadditions

The synthesis of chiral highly complex molecules through simple one-step processes, such as domino and tandem reactions, constitutes one of the most important area of organic chemistry [53]. These economic and direct reactions have been widely employed in total synthesis [54]. Among them, a range of asymmetric domino and tandem reactions based on cycloadditions have been successfully promoted by chiral nickel catalysts [53ac] often combined with chiral organocatalysts through the concept of multicyclic catalysis [55]. For example, a dual nickel/organocatalysis was applied by Moran et al. in 2016 to promote an enantioselective tandem isomerisation/Povarov-[4+2] cycloaddition reaction of carboxybenzyl-protected *N*-allylcarbamates **136** with aromatic imines **137** (Scheme 35) [56]. The reaction was catalysed at 40 °C in DCE as solvent with a combination of 10 mol% of NiCl₂(dme) and the same quantity of chiral phosphoric acid **138** in the presence of zinc (5 equivalents) and formic acid (5 equivalents) as superstoichiometric additives. After subsequent additions of NaHCO₃ and then aromatic imine partners **137**, the tandem isomerisation/Povarov reaction of *N*-allylcarbamates **136** led to tetrahydroquinolines **139** bearing three contiguous stereocentres in moderate to good yields (50-78%) combined with moderate to high diastereo- (60->88% de) and enantioselectivities (46-88% ee). Better enantioselectivities (74-88% ee) were achieved in the reaction of methyl-substituted *N*-allylcarbamates (R = Me) while an ethyl-substituted *N*-allylcarbamate (R = Et) provided the

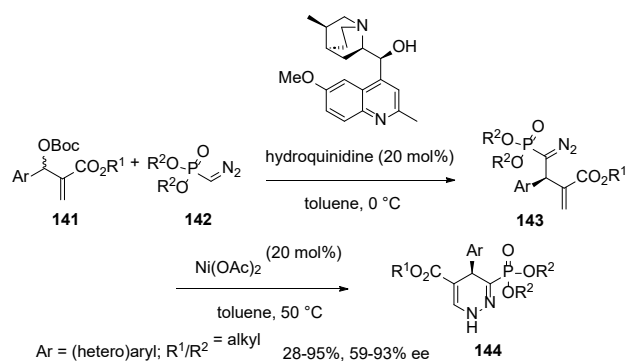
lowest enantioselectivity (46% ee). The first step of the sequence consisted in the nickel-catalysed isomerisation of *N*-allylcarbamate **136** into the corresponding imine intermediate **140**. This imine species subsequently underwent in the presence of chiral organocatalyst **138** a Povarov-[4+2] cycloaddition with additional imine partner **137** to give the final tetrahydroquinoline **139**. Because of the presence of residual formic acid which decreased the enantioselectivity of the process by competing racemic background reaction, it was crucial to add separately NaHCO₃ and then the imine partner at the end of the isomerisation step.



Scheme 35. Multicatalysed tandem isomerisation/Povarov-[4+2] cycloaddition reaction of aromatic imines with *N*-allylcarbamates.

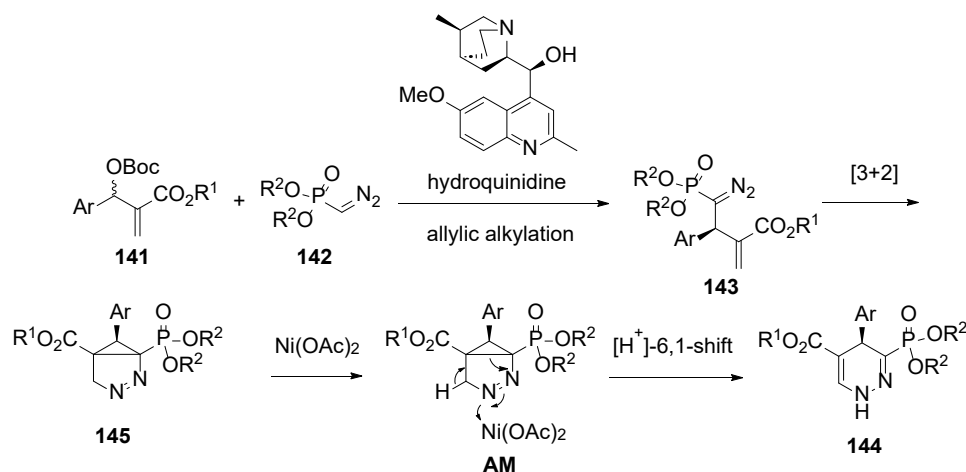
In spite of the fact that 1,4-dihydropyridazines are biologically highly interesting products, few asymmetric methodologies to prepare them enantiopure are available. Among them, an enantioselective tandem allylic alkylation/intramolecular [3+2] cycloaddition/rearrangement reaction of Morita–Baylis–Hillman carbonates **141** with α -diazophosphonates **142** was developed by Peng et al., in 2016 [57]. The first step of the sequence, dealing with the allylic alkylation of carbonates **143** with α -diazophosphonates **142**, was promoted at 0 °C in toluene by 20 mol% of chiral hydroquinidine as organocatalyst, leading to the corresponding chiral α -diazo- γ -methylene-phosphonates **143**. The latter were isolated and subsequently submitted to

a sequential intramolecular [3+2] cycloaddition/rearrangement reaction catalysed by 20 mol% of Ni(OAc)₂ at 50 °C in toluene as solvent to give the corresponding chiral phosphoryl-1,4-dihydropyridazines **144** in low to excellent yields (28-95%) and good to high enantioselectivities (59-93% ee), as shown in Scheme 36.



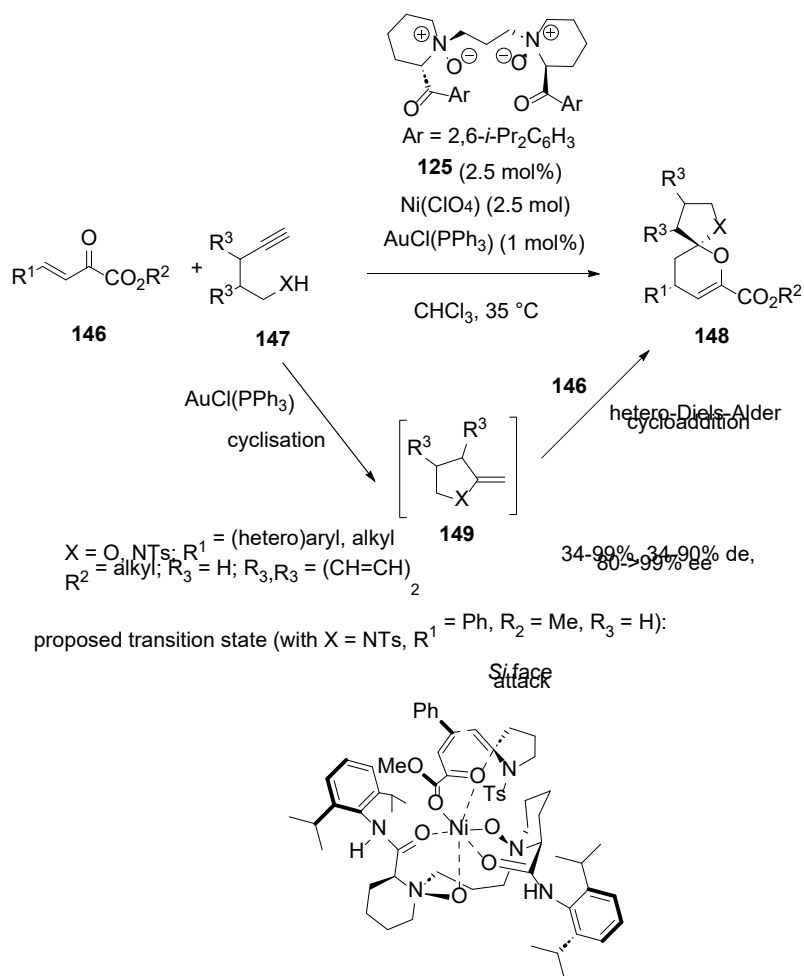
Scheme 36. Multicatalysed tandem allylic alkylation/intramolecular [3+2] cycloaddition/rearrangement reaction of Morita–Baylis–Hillman carbonates with α -diazophosphonates.

The mechanism of this tandem reaction is detailed in Scheme 37. The organocatalysed allylic alkylation reaction of Morita–Baylis–Hillman carbonate **141** with α -diazophosphonate **142** yielded the corresponding chiral α -diazo- γ -methylene-phosphonate **143**. When this product was heated at 50 °C in toluene during the second step of the sequence, it underwent a reversible intramolecular [3+2] cycloaddition to give the six-membered intermediate **145** that, in the presence of Ni(OAc)₂, provided nickel transition state **AM**. The latter was further submitted to a 6,1-shift rearrangement to afford, through three-membered ring opening, the final chiral phosphoryl-1,4-dihydropyridazine **144** without loss of enantioselectivity.



Scheme 37. Multicatalytic mechanism for tandem allylic alkylation/intramolecular [3+2] cycloaddition/rearrangement reaction of Morita–Baylis–Hillman carbonates with α -diazophosphonates.

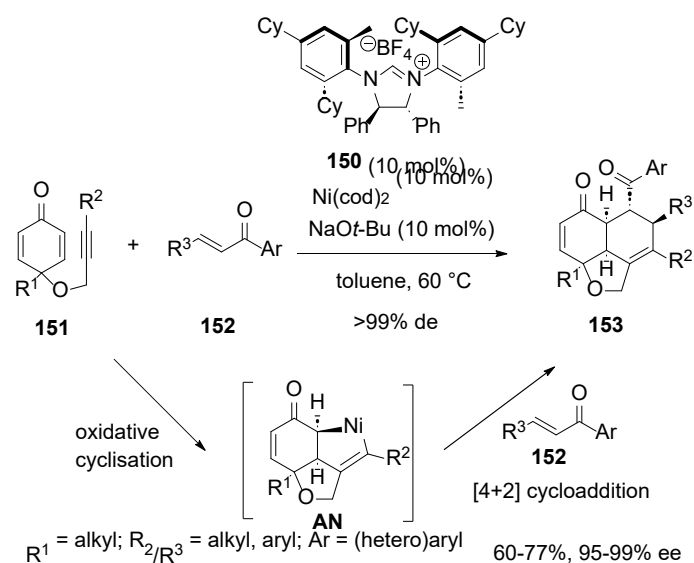
A novel dual-metal relay catalyst system was disclosed by Liu and Feng, in 2016 [58]. It involved a combination of 2.5 mol% of Ni(ClO₄), the same quantity of chiral *N,N'*-dioxide ligand **125**, and 1 mol% of AuCl·PPh₃ employed at 35 °C in chloroform as solvent (Scheme 38). In the presence of this combination of a chiral nickel *N,N'*-dioxide catalyst with an achiral gold(I) catalyst, β,γ -unsaturated α -keto esters **146** reacted with alkynyl-tethered alcohols/amides **147** according to an asymmetric domino intramolecular cyclisation/inverse electron-demand hetero-Diels–Alder cycloaddition reaction to afford chiral spiroketals (X = O)/spiroaminals (X = NTs) **148** with both moderate to quantitative yields (34-99%) and diastereoselectivities (34-90% de) combined with high ee values (80->99% ee). Indeed, alkynyl alcohols/amides **147** underwent in the presence of AuCl·PPh₃ an intramolecular cyclisation to form intermediates **149**. Then, this electron-rich alkene acted as a dienophile with α -keto esters **146** through an enantioselective inverse electron-demand hetero-Diels–Alder cycloaddition promoted by the chiral nickel catalyst to give the final bicyclic products. The authors explained the stereoselectivity of the process by the transition state depicted in Scheme 38 in which the tetradentate *N,N'*-dioxide ligand and the bidentate α -keto ester coordinated to Ni(II) to form an octahedral complex. The *Re* face of the α -keto ester was sterically hindered by the neighboring amide group of the ligand and, consequently, the enamide attack occurred from the *Si* face of the α -keto ester to produce the *endo*-cycloadduct.



Scheme 38. Multicatalysed domino intramolecular cyclisation/inverse electron-demand hetero-Diels–Alder cycloaddition reaction of β,γ -unsaturated α -keto esters with alkynyl-tethered alcohols/amides.

In 2017, a chiral nickel catalyst in situ generated from 10 mol% of Ni(cod)₂ and the same quantity of NHC chiral ligand **150** was employed by Ogoshi et al. to promote a regio-, diastereo-, and highly enantioselective domino oxidative cyclisation/intermolecular [4+2] cycloaddition reaction between alkynyl-cyclohexadienones **151** and α,β -unsaturated ketones **152** (Scheme 39) [59]. The reaction was performed in toluene at 60 °C in the presence of NaO*t*-Bu as an additive. The first step of the sequence involved an asymmetric oxidative cyclisation of alkynyl-cyclohexadienones **151** to give tricyclic fused nickel intermediate **AN**. The latter subsequently underwent a [4+2] cycloaddition in the presence of α,β -unsaturated ketones **152** to afford the almost enantiopure hydronaphtho[1,8-*bc*]furans **153** exhibiting five contiguous stereocentres in homogeneous good yields (60-77%) and uniformly remarkable

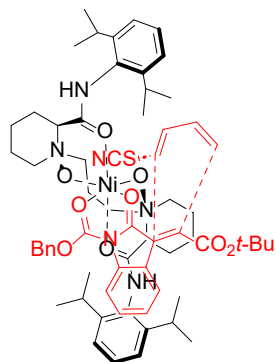
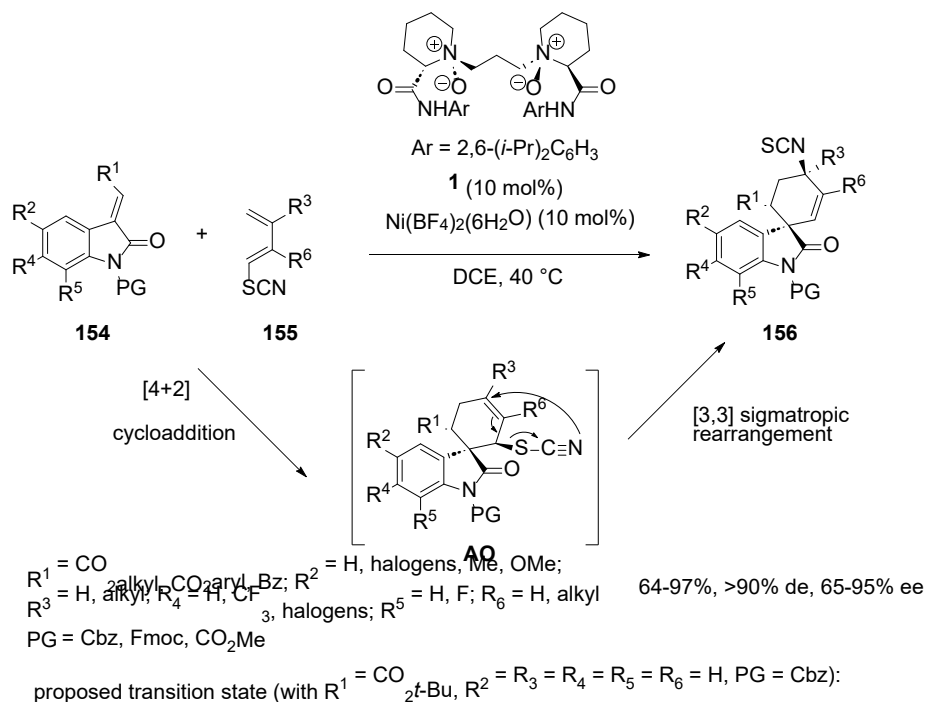
enantioselectivities (94-99% ee) regardless the nature of the substituents born by the two substrates.



Scheme 39. Domino oxidative cyclisation/intermolecular [4+2] cycloaddition reaction of alkyne-cyclohexadienones with α,β -unsaturated ketones.

In 2018, Liu and Feng reported a rare example of enantioselective domino [4+2] cycloaddition/[3,3] sigmatropic rearrangement reaction involving methyleneindolinones **154** and 1-thiocyanatobutadienes **155** as substrates (Scheme 40) [60]. When the reaction was catalysed by a combination of 10 mol% of $\text{Ni}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and the same quantity of chiral N,N' -dioxide ligand **1** in DCE as solvent, it led at 40 °C to the corresponding densely substituted chiral cyclohexenyl isothiocyanates **156** with good to high yields (64-97%), excellent diastereoselectivities (>90% de), and moderate to very high enantioselectivities (65-95% ee). Methyleneindolinones bearing an ester group ($\text{R}^1 = \text{ester}$) reacted with better enantioselectivities than benzoyl-substituted substrates ($\text{R}^1 = \text{Bz}$, 76% ee). The presence of electron-withdrawing or electron-donating groups on the phenyl ring of the methyleneindolinones ($\text{R}^2, \text{R}^4, \text{R}^5$) was well tolerated but generally substrates with electron-donating groups exhibited higher reactivity and enantioselectivity than those with electron-withdrawing groups. Along with Cbz-N-protected methyleneindolinones, Fmoc- and CO_2Me -N-protected substrates were also compatible. Concerning the 1-thiocyanatobutadiene partner, either methyl or ethyl substituted-substrates ($\text{R}^3, \text{R}^6 = \text{Me, Et}$) reacted smoothly with high ee values. A possible transition state is proposed in Scheme 40, showing that the *Si* face of the methyleneindolinone was sterically hindered by the neighboring amide group of the ligand

and, consequently, the 1-thiocyanatobutadiene approached the methyleneindolinone from the *Re* face.



Scheme 40. Domino [4+2] cycloaddition/[3,3] sigmatropic rearrangement reaction of methyleneindolinones with 1-thiocyanatobutadienes.

8. Conclusions

This review contributes to demonstrate that a range of chiral nickel catalysts are today available to promote the formation of many complex chiral carbo- and heterocycles of various types through asymmetric cycloadditions. Almost all the ligands employed in the last nine years in enantioselective nickel-catalysed cycloadditions were nitrogenated ones, including chiral *N,N'*-dioxides, bisoxazolines, cyclic 1,2-diamines, binaphthyldiimines, *N*-heterocyclic carbenes, and phosphoramidates along with rare non-oxygenated phosphine oxide ligands.

Achiral nickel complexes were also employed in combination with chiral organocatalysts, such as phosphoric acids and hydroquinidine, especially in the development of enantioselective domino and tandem reactions. In the last nine years, the most developed cycloadditions were [3+2] and [2+2] cycloadditions along with one-step tandem and domino processes including cycloadditions often based on dual nickel/organocatalysis. These reactions have allowed the synthesis of many types of complex chiral heterocycles, such as chiral tetrahydrofurans through [3+2] cycloaddition of epoxides with heterosubstituted alkenes with up to 99% yield, 84% de and 99% ee; chiral β -trifluoromethylated isoxazolidines with up to 97% yield, 98% de and 99% ee through [3+2] cycloaddition of β -fluoroalkylated α,β -unsaturated 2-pyridylsulfones with nitrones; chiral cyclopentenyl carboxamides through [3+2] cycloaddition of cyclopropyl carboxamides with alkynes with up to quantitative yield and 94% ee; chiral 8-oxabicyclo[3.2.1]octanes as single diastereomers in up to 96% ee and 68% yield through [3+2] cycloaddition of diazo imine-derived isoxazolines with acryloylpyrazolidinone; chiral pyrrolo[1,2-*a*]indoles with up to quantitative yield, 96% de and complete enantioselectivity from [3+2] cycloaddition of 2-nitrovinylindoles with *t*-butyl α -ketoesters; chiral isoxazolidines through either the first highly enantioselective [3+2] cycloaddition of nitrones with α,β -unsaturated acylcarboxylates with up to 98% ee, complete diastereoselectivity and 95% yield, or from the first enantioselective [3+2] cycloaddition of α -ketoesters with cyclic nitrones with up to 83% yield, >96% de and 96% ee. Along with [3+2] cycloadditions, several highly efficient enantioselective nickel-catalysed [2+2] cycloadditions have allowed the synthesis of other chiral heterocycles as well as carbocycles. Among them, are chiral cyclobutenes synthesised from either the first example of nickel-catalysed [2+2] cycloadditions of α,β -unsaturated carbonyl derivatives with 1,3-enynes with up to 79% yield and 89% ee, or [2+2] cycloaddition of terminal alkynes with azabenzonornbornadienes with up to 90% yield and 96% ee; enantiopure complex fused polysubstituted azetidines with up to 90% yield and complete diastereoselectivity from [2+2] cycloaddition of *N*-allenamides with cyclic *N*-sulfonylketimines. Other complex chiral carbo- and heterocycles have been synthesised from miscellaneous cycloadditions, including chiral functionalised cyclohexenes exhibiting four contiguous stereocentres with up to 95% yield and 93% ee from [2+2+2] cycloaddition of internal alkynes with two equivalents of α,β -unsaturated ketones; densely substituted chiral pyridines through [2+2+2] cycloaddition of alkynes with alkyne-tethered malononitriles with up to 93% yield and 94% ee; chiral polycyclic γ -lactams with up to 90% ee and 96% yield from [2+2+1] carbonylative cycloaddition of ene-imines with carbon

monoxide; chiral [3.2.2] bicyclic products with up to 80% yield and 92% ee through intramolecular [4+2] cycloaddition of cyclobutanones with allenes; chiral (thio)chromanes and tetrahydroquinolines with up to 90% yield, >90% de and 99% ee from intramolecular ene reaction of heteroatom-tethered 1,7-dienes. In addition, dual nickel/organocatalysis has been applied to promote various tandem and domino reactions based on cycloadditions, thus affording chiral indoles with up to 90% yield and 96% ee from domino oxidative cyclisation/intermolecular [4+2] cycloaddition reaction of alkynyl-cyclohexadienones with α,β -unsaturated ketones; chiral tetrahydroquinolines with up to >88% de and 88% ee from tandem isomerisation/Povarov-[4+2] cycloaddition reaction of carboxybenzyl-protected *N*-allylcarbamates with aromatic imines; chiral phosphoryl-1,4-dihydropyridazines with up to 95% yield and 93% ee from tandem allylic alkylation/intramolecular [3+2] cycloaddition/rearrangement reaction of Morita–Baylis–Hillman carbonates with α -diazophosphonates. Finally, enantiopure tricyclic hydronaphtho[1,8-*bc*]furans exhibiting five contiguous stereocentres were prepared with up to 77% yield and 99% ee from nickel-catalysed domino oxidative cyclisation/intermolecular [4+2] cycloaddition reaction between alkynyl-cyclohexadienones and α,β -unsaturated ketones. Undoubtedly, novel additional chiral nickel catalysts will be developed in the near future to promote other cycloadditions, allowing the synthesis of various complex chiral carbo- and heterocycles to be used as intermediates in the synthesis of important natural/biologically active products.

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