chemistry

MDPI

Review

Recent Developments in Enantioselective Scandium-Catalyzed Transformations

Hélène Pellissier

Aix Marseille Univ., CNRS, Centrale Marseille, iSm2, 13385 Marseille, France; h.pellissier@univ-amu.fr

Abstract: This review collects the recent developments in the field of enantioselective scandium-catalyzed transformations published since the beginning of 2016, illustrating the power of chiral scandium catalysts to promote all types of reactions.

Keywords: scandium; asymmetric catalysis; transition metals; enantioselectivity; chirality; enantioselective transformations

Citation: Pellissier, H. Recent Developments in Enantioselective Scandium-Catalyzed Transformations. *Chemistry* **2024**, *6*, 98–152. https://doi.org/10.3390/chemistry6010007

Academic Editor: Guoqi Zhang

Received: 20 December 2023
Revised: 5 January 2024
Accepted: 8 January 2024
Published: 11 January 2024

1. Introduction

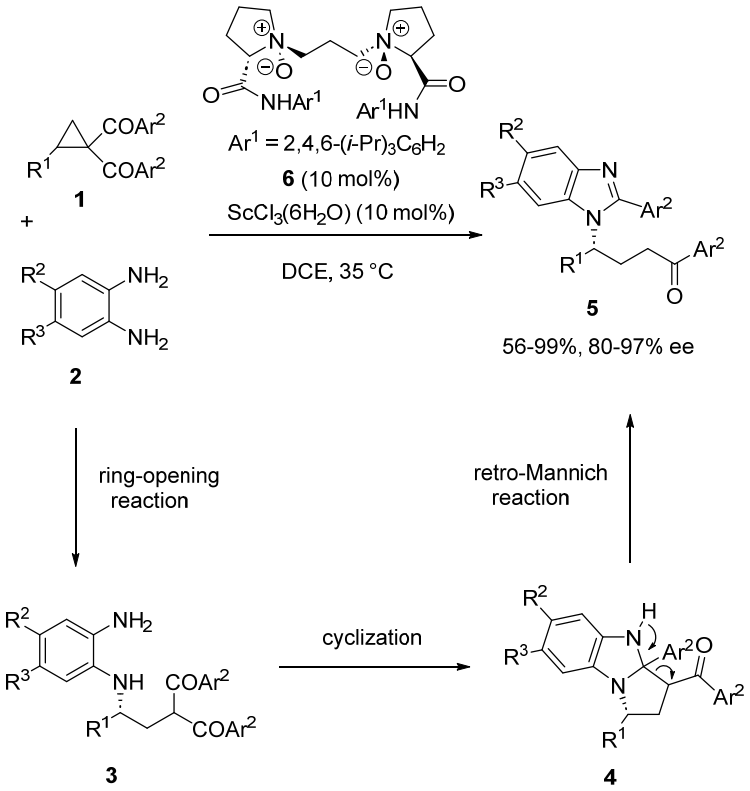
Metal catalysts are still widely employed in asymmetric synthesis in spite of their toxicity and high cost [1–17]. In contrast, inexpensive and non-toxic rare earth metals, such as scandium, have been identified in the last two decades as remarkable environmentally benign Lewis acid catalysts. Especially, chiral complexes derived from $Sc(OTf)_3$ have become unique promotors of many types of asymmetric transformations since the breakthrough early work reported by Kobayashi in 1994, dealing with asymmetric scandium-catalyzed Diels-Alder cycloadditions [18]. This review aims to update the field of enantioselective scandium-catalyzed reactions since the beginning of 2016, as this area was most recently reviewed that year, covering the literature up to 2015 [9]. Other reviews on racemic scandium or other rare earth catalysis have been previously published [19–27]. Moreover, it must be noted that two reviews focusing on C−H activation with 3d transition metals have been recently published by Ackermann but they included none or only one reference ≥2016, respectively, concerning asymmetric reactions [28,29]. The present review is divided into eight parts, dealing successively with enantioselective scandium-catalyzed domino and tandem reactions, cycloadditions, Michael additions, ring-opening reactions, Friedel-Crafts reactions, ring-expansion reactions, rearrangement reactions, and miscellaneous reactions.

2. Enantioselective Scandium-Catalyzed Domino and Tandem Reactions

2.1. Ring-Opening-Initiated Domino Reactions

A wide number of asymmetric domino reactions have been successfully catalyzed by many types of chiral metal complexes, allowing the synthesis of very complex molecules [30–45]. In the last few years, different types of chiral ligands, including *N*,*N*′-dioxides, pyridine-2,6-bisoxazolines, bipyridines, phosphine oxides, and phosphoric acids, have been chelated to scandium to promote a range of unprecedented highly efficient domino reactions. Many bioactive and natural products include benzimidazole moieties in their skeleton. In 2016, the first asymmetric synthesis of benzimidazole derivatives was disclosed by Liu and Feng [45]. The process deals with an enantioselective scandium-catalyzed domino ring-opening/cyclization/retro-Mannich reaction of cyclopropyl ketones **1** with aryl 1,2-diamines **2** catalyzed in DCE at 35 °C by a chiral scandium complex in situ generated from 10 mol% of $ScCl_3 \cdot 6H_2O$ and the same quantity of chiral *N*,*N*′-dioxide ligand **6**. It afforded the corresponding domino products **5** in moderate to quantitative yields (56–99%) and uniformly high enantioselectivities (80–97% ee). The reaction evolved through the ring-opening of the cycloprane substrate **1** by the diamine **2** to give the corresponding ring-opened intermediate **3**. The latter then underwent cyclization to form intermediate **4**, which was subsequently

submitted to a retro-Mannich reaction to afford the final benzimidazole **5** bearing a chiral side chain (Scheme 1).



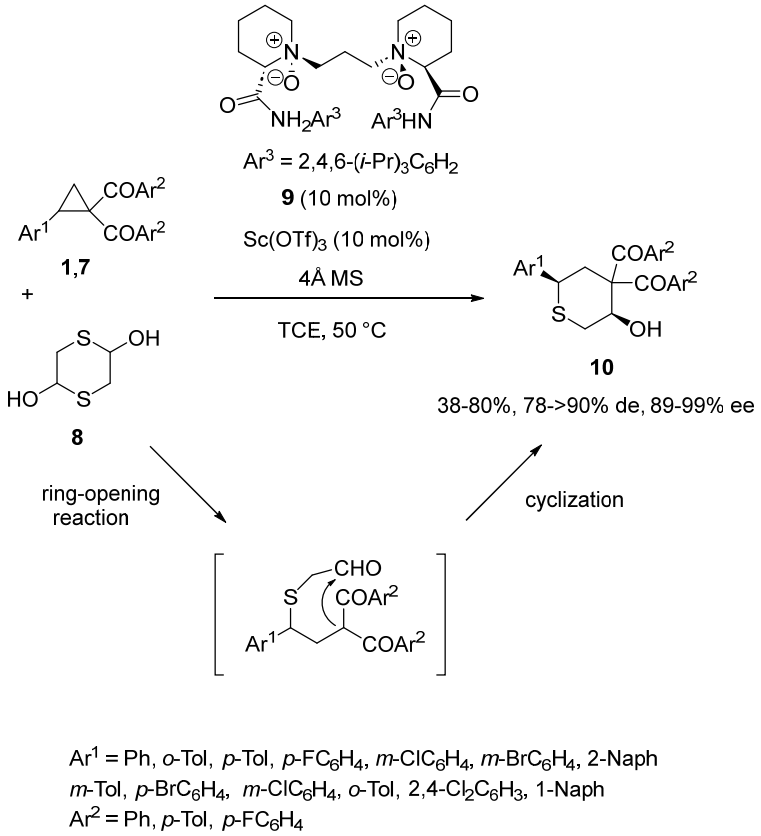
R^1 = Ph, *p*-$MeOC_6H_4$, *p*-Tol, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-Tol, *m*-ClC_6H_4, *o*-Tol, 3,4-$Cl_2C_6H_3$, 1-Naph, 2-Naph, vinyl, Me
Ar^2 = Ph, *p*-Tol, *p*-FC_6H_4
R^2 = H, Me, OMe, F, Cl, Br, NO_2
R^3 = H, Me, OMe, F, Cl, Br, NO_2

Scheme 1. Domino ring-opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with 1,2-diamines [45].

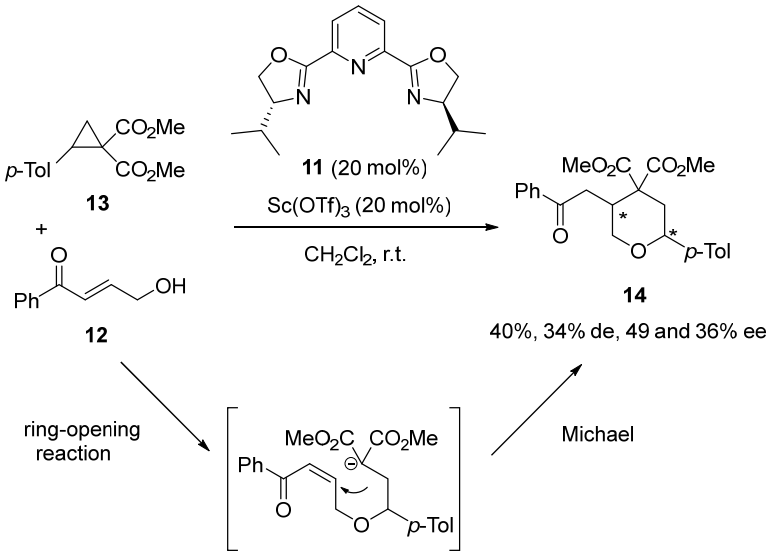
In the same year, Lin and Feng described the first enantioselective [3 + 3] annulation of aryl cyclopropyl ketones **1**,**7** with mercaptoacetaldehyde **8** catalyzed by a combination of 10 mol% of chiral *N*,*N*′-dioxide ligand **9** and the same quantity of $Sc(OTf)_3$ [46]. As illustrated in Scheme 2, the domino reaction evolved through the ring-opening of the cyclopropyl ketones by mercaptoacetaldehyde followed by cyclization to give the corresponding chiral tetrahydrothiopyranols **10** with moderate to high yields (38–80%) and both uniformly high diastereo- (78 $\geq$ 90% de) and enantioselectivities (89–99% ee).

Other ring-opening-initiated domino reactions have been successfully catalyzed by chiral scandium complexes. For example, Pan and Mondal described in 2017 scandium-catalyzed domino ring-opening/Michael reactions of cyclopropane-1,1-esters with γ-hydroxyenones, leading to functionalized tetrahydropyrans [47]. An asymmetric version of this methodology was developed by using chiral Pybox ligand **11** at 20 mol% of catalyst loading combined with the same quantity of $Sc(OTf)_3$ as precatalyst (Scheme 3). Under these catalytic conditions, the reaction of γ-hydroxyenone **12** with cyclopropane-1,1-dimethylester **13** carried out at room temperature in dichloromethane provided functionalized chiral tetrahydropyran **14** as major *cis*-diastereomer in 40% yield, with moderate diastereo- (34% de), and enantioselectivities (36–49% ee). In spite of these modest results, this methodology presented the advantage to allow an easy access to tetrasubstituted

tetrahydropyrans exhibiting two stereogenic centers, constituting the skeleton of many natural and biologically active products.



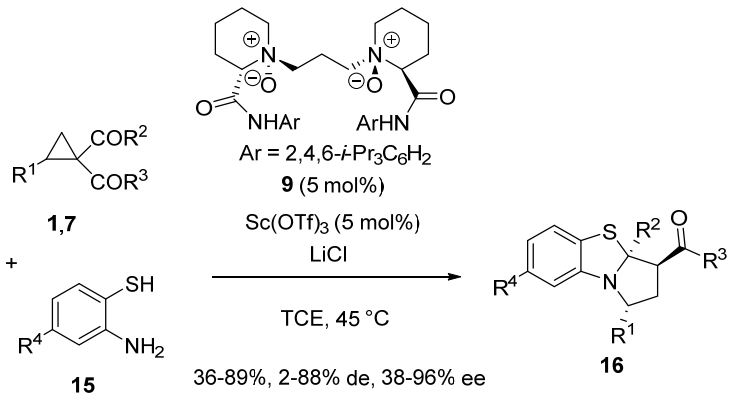
Scheme 2. Domino ring-opening/cyclization reaction of aryl cyclopropyl ketones with mercaptoacetaldehyde [46].



Scheme 3. Domino ring-opening/Michael reaction of cyclopropane-1,1-dimethylesterwith a γ-hydroxyenone [47].

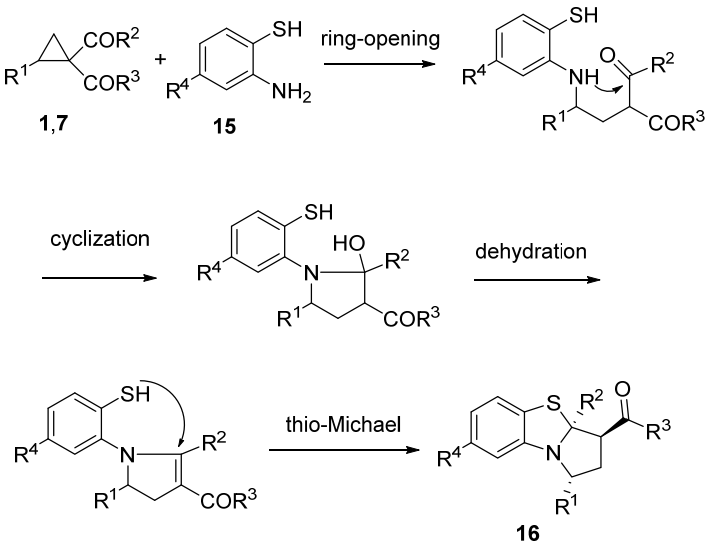
Later in 2020, Feng and Lin employed 5 mol% of a combination of $Sc(OTf)_3$ with chiral *N*,*N*′-dioxide ligand **9** to catalyze an enantioselective domino ring-opening/cyclization/

dehydration/thio-Michael reaction between cyclopropanes **1,7** and 2-aminothiophenols **15** (Scheme 4) [48]. Performed at 45 °C in TCE as solvent, the process resulted in the formation of chiral tricyclic products **16** with moderate to high yields (36–89%), low to high diastereoselectivities (2–88% de), and moderate to excellent enantioselectivities (38–96% ee). The mechanism of the reaction depicted in Scheme 4 begins with the scandium-promoted nucleophilic ring-opening of the three-membered substrate by the 2-aminothiophenol. Then, a cyclization occurred to form a tetrahydropyrrole. The latter was submitted to dehydration to give a dihydropyrrole intermediate, which further underwent a final thio-Michael addition, delivering the product.



R^1 = *p*-Tol, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *m*-Tol, *m*-ClC$_6$H$_4$, *m*-MeOC$_6$H$_4$, *o*-BrC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 1-Naph, 2-Naph, vinyl, Ph
R^2 = Ph, *p*-FC$_6$H$_4$, Me
R^3 = Ph, *p*-FC$_6$H$_4$, Me, OEt, OMe
R^4 = H, Cl

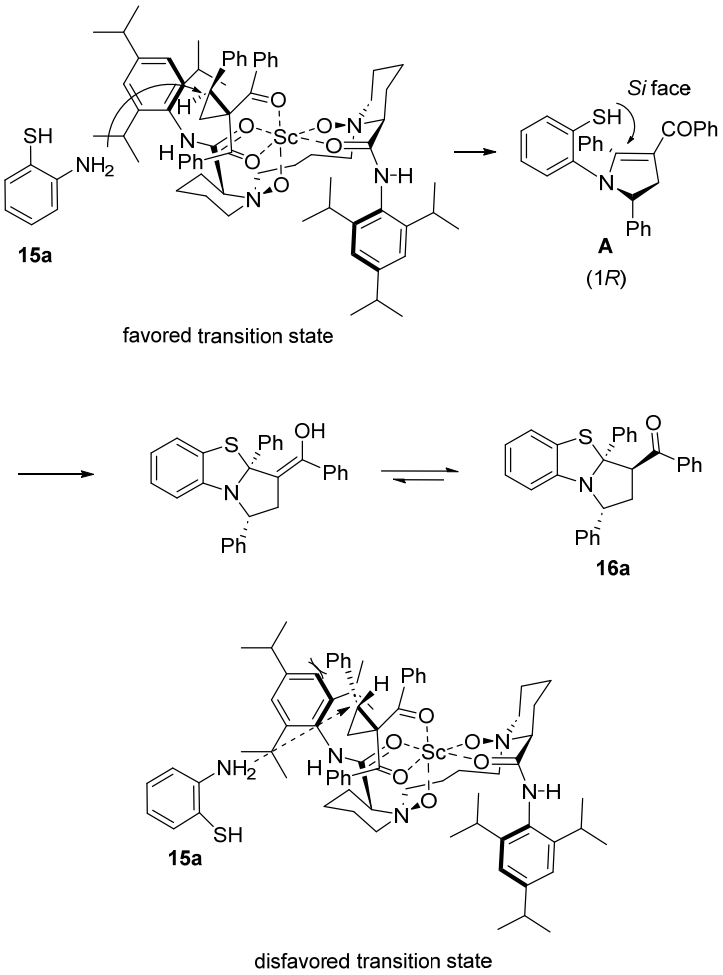
mechanism:



Scheme 4. Domino ring-opening/cyclization/dehydration/thio-Michael reaction of cyclopropane derivatives with 2-aminothiophenols [48].

The authors proposed the favored transition state, depicted in Scheme 5, to explain the stereoselectivity of the reaction in which the four oxygen atoms of the ligand and the two oxygen atoms of the cyclopropane **1a** (R^1 = R^2 = R^3 = Ph) coordinated to the

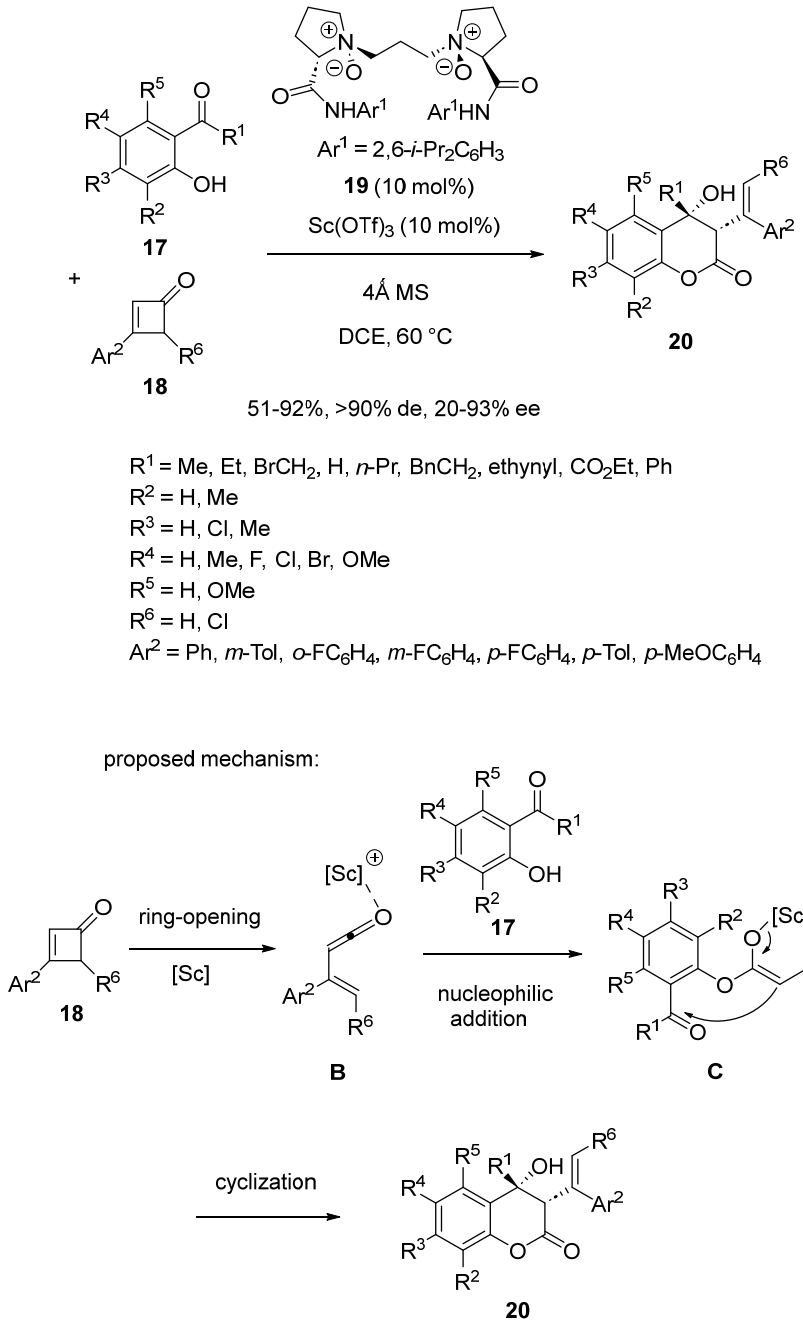
scandium center to form an octahedral complex [48]. The coordination of (*R*)-**1a** with the catalyst resulted in stronger steric repulsion between the 2,4,6-triisopropylphenyl group of the ligand and the phenyl group of the cyclopropyl ketone as shown in the disfavored transition state, making (*R*)-**1a** less reactive. In contrast, 2-aminothiophenol **15a** (R^4 = H) attacked (*S*)-**1a** from less steric hindered face, delivering (*R*)-configured intermediate **A**. Then, the thio-Michael addition occurred from the *Si*-face of the C = C bond in **A** to form a (*R*)-configured quaternary stereogenic center. The chiral center located on the α-position of the carbonyl group could be generated through keto–enol tautomerism, delivering the product with smaller repulsion with the phenyl and benzoyl groups on opposite sides.



Scheme 5. Transition states (with R^1 = R^2 = R^3 = Ph, R^4 = H) for domino ring-opening/cyclization/dehydration/thio-Michael reaction of cyclopropane derivatives with 2-aminothiophenols [48].

So far, only few methodologies have been developed to synthesize enantiopure 4-hydroxy-chroman-2-ones, which are the skeletons of many biologically important products. To fill this gasp, Liu and Feng disclosed in 2019 a novel method based on an asymmetric domino ring-opening/nucleophilic addition/cyclization reaction occurring between 2-hydroxyacetophenones **17** and cyclobutenones **18** [49]. It required to be promoted at 60 °C in DCE as solvent by a chiral catalyst in situ generated from 10 mol% of $Sc(OTf)_3$ and the same quantity of chiral *N*,*N*′-dioxide ligand **19**. As illustrated in Scheme 6, the process began with the ring-opening of the four-membered substrate into the corresponding vinylketene intermediate **B**. Subsequently, a nucleophilic addition of the 2-hydroxyacetophenone to intermediate **B** afforded scandium intermediate **C**, which then underwent cyclization to deliver the final product as a single diastereomer (>90% de). A wide range of these products

was synthesized by this methodology with moderate to high yields (51–92%) and low to excellent enantioselectivities (20–93% ee). In most cases, high enantioselectivities (≥85% ee) were achieved in the reaction of variously substituted 2-hydroxyacetophenones **17**.

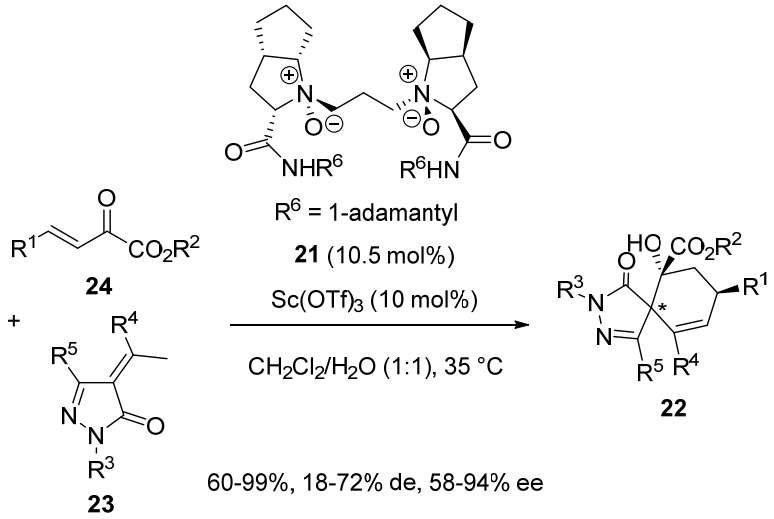


Scheme 6. Domino ring-opening/nucleophilic addition/cyclization reaction of cyclobutenones with 2-hydroxyacetophenones [49].

2.2. Michael-Initiated Domino and Tandem Reactions

In 2019, Feng et al. reported a novel route to chiral spirocyclohexene pyrazolones involving an asymmetric scandium-catalyzed domino Michael/aldol reaction [50]. It evolved in a mixture of dichloromethane and water as solvent in the presence of a combination of 10.5 mol% of chiral *N*,*N*′-dioxide ligand **21** and 10 mol% of $Sc(OTf)_3$ as precatalyst (Scheme 7). In this context, α-arylidene pyrazolinones **23** reacted at 35 °C with β, γ-unsaturated α-ketoesters **24** to afford densely functionalized chiral spiro-bicyclic prod-

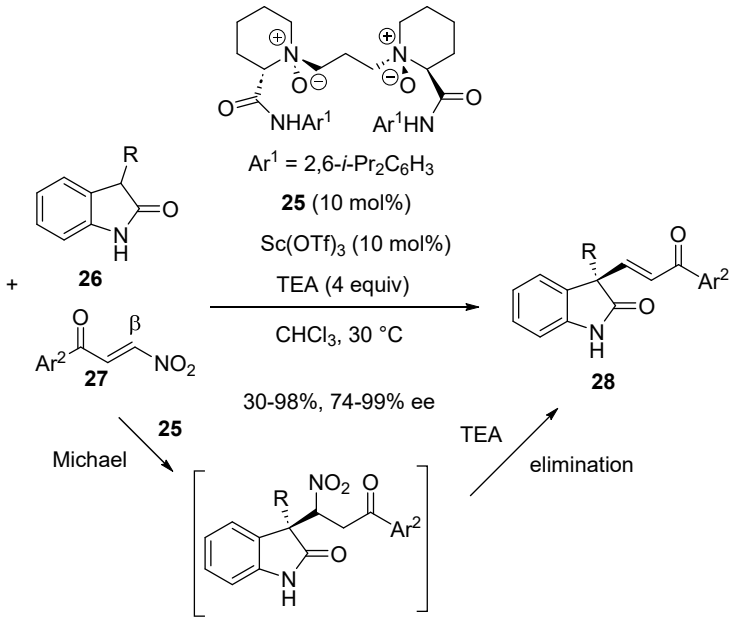
ucts **22** with both moderate to excellent yields (60–99%) and enantioselectivities (58–94% ee) as mixtures of diastereomers with variable diastereoselectivities (18–72% de).



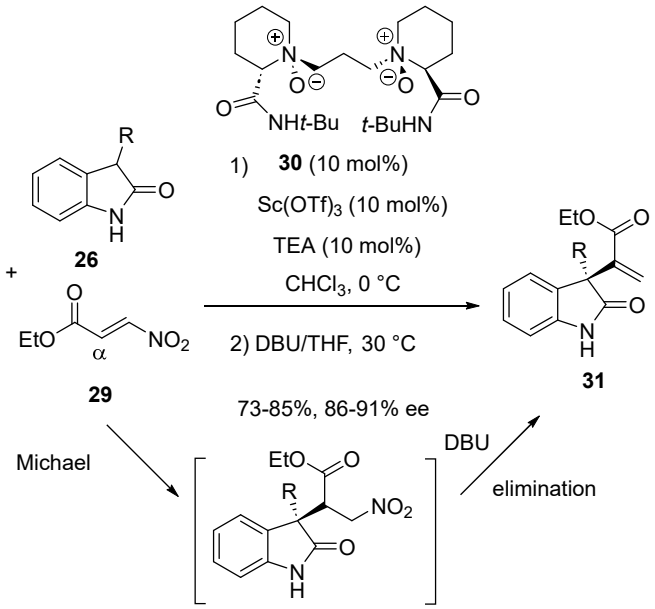
R^1 = Ph, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, Cp, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-Tol, *m*-Tol, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, 2-thienyl, 2-Naph, Cy, Me
R^2 = *i*-Pr, Cp, Me
R^3 = Ph, *t*-Bu
R^4 = Ph, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-Tol, *m*-Tol, *o*-Tol, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *o*-$MeOC_6H_4$, piperonyl
R^5 = Ph, Me

Scheme 7. Domino Michael/aldol reaction of pyrazolinone derivatives with unsaturated α-ketoesters [50].

On the basis of the biological importance of oxindoles, Feng and Liu investigated in 2023 the regio- and enantioselective Michael addition of 3-substituted oxindoles to different types of β-nitro α, β-unsaturated carbonyl compounds in order to synthesize a variety of enantiopure functionalized 3-alkenyl disubstituted oxindoles after subsequent elimination of the nitro group [51]. It was found that in the presence of a chiral catalyst formed from 10 mol% of $Sc(OTf)_3$ and the same quantity of chiral *N*,*N*′-dioxide ligand **25** and TEA as base, the reaction of 3-substituted oxindoles **26** with β-nitroenones **27** occurred through a β-regioselective conjugate addition, in which the benzoyl group of the Michael acceptor acted as a stronger directing group. Consequently, the reaction performed in chloroform at 30 °C afforded, after subsequent nitro-elimination mediated by TEA, the corresponding chiral 3-alkenyl disubstituted oxindoles **28** with moderate to quantitative yields (30–98%) and good to excellent enantioselectivities (74–99% ee), as illustrated in Scheme 8. On the other hand, the reaction of 3-substituted oxindoles **26** with β-nitroacrylates **29** performed in the presence of 10 mol% of $Sc(OTf)_3$ combined with 10 mol% of chiral *N*,*N*′-dioxide ligand **30** occurred through an α-regioselective Michael addition in which the nitro-group acted as the activated group. The non-isolated Michael adducts were directly submitted to elimination by treatment with DBU as base in THF at 30 °C to afford the corresponding chiral *exo*-methylene oxindoles **31** with good yields (73–85%) and high enantioselectivities (86–91% ee).



Ar^2 = Ph, 2-Naph, 1-Naph, 2-thienyl, *o*-Tol,
m-MeOC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-Tol, *p*-MeOC$_6$H$_4$
R = Bn, *p*-ClC$_6$H$_4$CH$_2$, *p*-BrC$_6$H$_4$CH$_2$, *p*-O$_2$NC$_6$H$_4$CH$_2$,
p-NCC$_6$H$_4$CH$_2$, *p*-F$_3$CC$_6$H$_4$CH$_2$, *p*-TolCH$_2$, *p*-MeOC$_6$H$_4$CH$_2$, ,
m-ClC$_6$H$_4$CH$_2$, *m*-BrC$_6$H$_4$CH$_2$, *m*-TolCH$_2$, *m*-MeOC$_6$H$_4$CH$_2$,
o-ClC$_6$H$_4$CH$_2$, *o*-BrC$_6$H$_4$CH$_2$, *o*-TolCH$_2$, 2,4-Cl$_2$C$_6$H$_3$CH$_2$, 2,6-Cl$_2$C$_6$H$_3$CH$_2$,
Me, Ph, 2-NaphCH$_2$, 2-thienylCH$_2$, 1-thienylCH$_2$

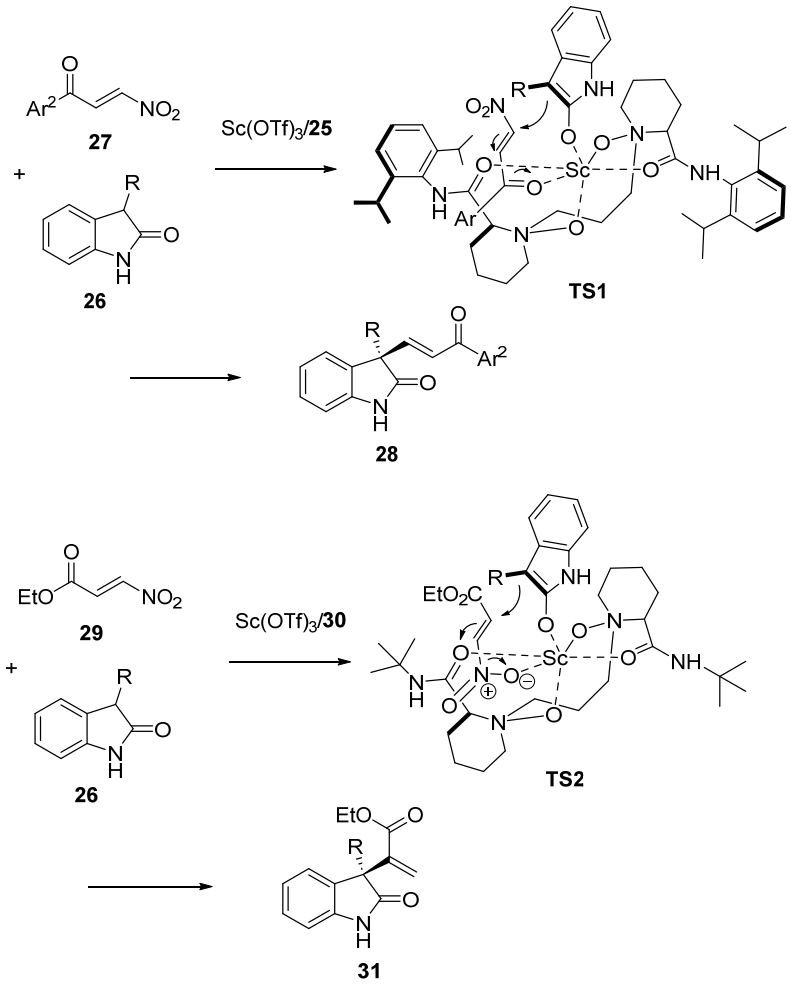


R = Bn, *p*-TolCH$_2$, *m*-TolCH$_2$, *o*-TolCH$_2$, *p*-ClC$_6$H$_4$CH$_2$, ,
p-BrC$_6$H$_4$CH$_2$, *p*-F$_3$CC$_6$H$_4$CH$_2$, *p*-NCC$_6$H$_4$CH$_2$, 2-NaphCH$_2$, 2-thienylCH$_2$

Scheme 8. Domino Michael/elimination reaction of 3-substituted oxindoles with β-nitroenones and tandem Michael/elimination reaction of 3-substituted oxindoles with β-nitroacrylates [51].

To explain the different regioselectivities of the precedent Michael additions of oxindoles **26** to β-nitroenones **27** and β-nitroacrylate **29**, the authors proposed the two respective

transition states **TS1** and **TS2** (Scheme 9). In **TS1**, β-nitroenone **27** is coordinated to the scandium center through its benzoyl group, whereas β-nitroacrylate **29** is chelated to the metal in **TS2** through its nitro group. This decreases the LUMO energy of the Michael acceptors to promote the β-selective Michael addition and α-selective conjugate addition, respectively [52]. The same facial selectivity for the nucleophilic addition of the oxindole to the two types of Michael acceptors was confirmed by X-ray analysis of products **28** and **31**, which were found to exhibit the same configuration.

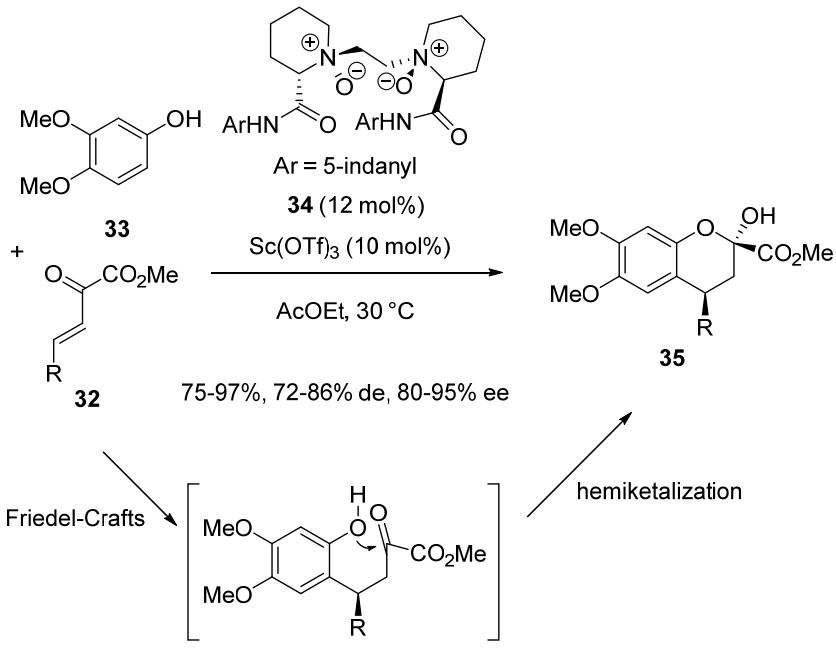


Scheme 9. Proposed transition states for domino Michael/elimination reaction of 3-substituted oxindoles with β-nitroenones and tandem Michael/elimination reaction of 3-substituted oxindoles with β-nitroacrylates [51].

2.3. Friedel-Crafts-Initiated Domino and Tandem Reactions

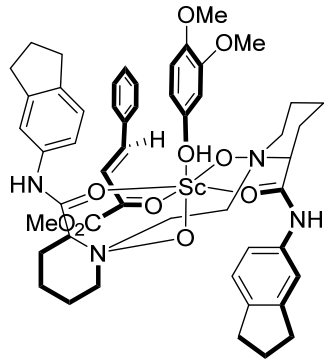
In 2017, Lin and Feng described an enantioselective domino Friedel–Crafts alkylation/hemiketalization reaction between α, β-unsaturated ketoesters **32** and 3,4-dimethoxyphenol **33** (Scheme 10) [52]. Carried out at 30 °C in ethyl acetate as solvent in the presence of 10 mol% of $Sc(OTf)_3$ and 12 mol% of chiral *N*,*N*′-dioxide ligand **34**, the process allowed a direct approach to chiral 2,3-disubstituted chromans **35** to be achieved with high yields (75–97%), good diastereoselectivities (72–86% de) and high enantioselectivities (80–95% ee). In addition to a wide variety of (hetero)aryl-substituted ketoesters, an α, β, γ, δ-unsaturated ketoester (R = (*E*)-PhCH = CH) also afforded the corresponding chiral product with 95% yield and 80% ee. The authors proposed the hexadentate transition state depicted in Scheme 10, in which the four oxygen atoms of the ligand were coordinated to the scandium center. The two adding coordinations arose from the hydroxyl group of the phenol and the carbonyl group of the ketoester. The *Re*-face of C = C bond of the α, β-unsaturated

ketoester was sterically hindered by the amide moiety of the ligand, which resulted in the formation of the (2*R*,3*S*)-chroman.



R = Ph, *o*-FC_6H_4, *m*-ClC_6H_4, *m*-Tol, *m*-$MeOC_6H_4$, *m*-$PhOC_6H_4$, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-PhC_6H_4, 3,4-$Cl_2C_6H_3$, 5-piperonyl, 2-Naph, 2-thiophenyl, 3-thiophenyl, (*E*)-PhCH=CH

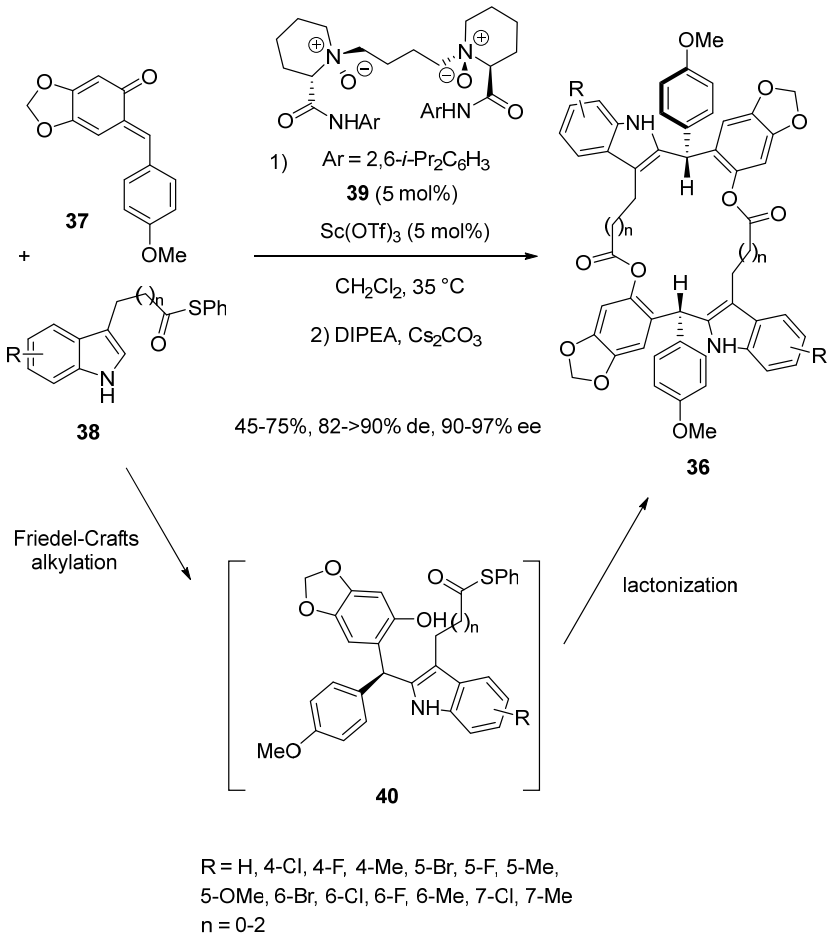
proposed transition state (with R = Ph):



Scheme 10. Domino Friedel–Crafts alkylation/hemiketalization reaction of α, β-unsaturated ketoesters with an 3,4-dimethoxyphenol [52].

Later in 2021, a novel and simple synthesis of C_2-symmetric chiral macrodiolides **36** was developed by Dong and Feng on the basis of an enantioselective scandium-catalyzed tandem reaction occurring between *ortho*-quinone methides **37** and C3-substituted indoles **38** (Scheme 11) [53]. The reaction began with an asymmetric Friedel–Crafts alkylation promoted by 5 mol% of a chiral scandium catalyst in situ generated from $Sc(OTf)_3$ and chiral *N*,*N*′-dioxide ligand **39** performed at 35 °C in dichloromethane as solvent to give intermediate **40**. The latter was subsequently submitted to intermolecular macrolactonization by adding DIPEA as base to the reaction media, which afforded a range of chiral macrodiolides **36** with 16, 18 or 20-membered rings. These complex products were obtained in moderate to good yields (45–75%) with both uniformly excellent enantio- (90–97% ee)

and diastereoselectivities (82 ≥ 90% de). Different substituents on the phenyl ring of the indole moiety were tolerated, regardless of their position and electronic nature.

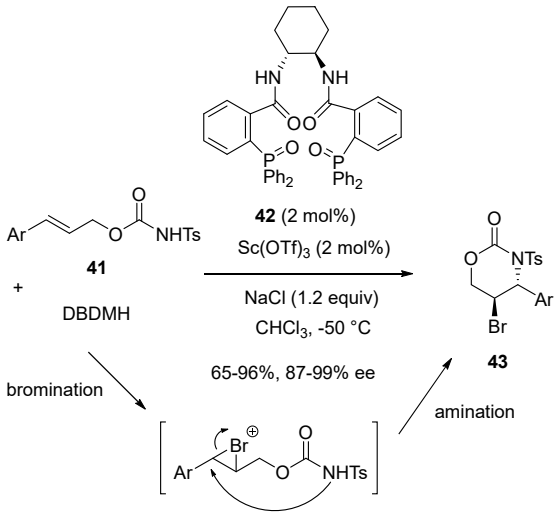


Scheme 11. Tandem Friedel–Crafts alkylation/macrolactonization of *ortho*-quinone methides with C3-substituted indoles [53].

2.4. Bromination-Initiated Domino Reactions

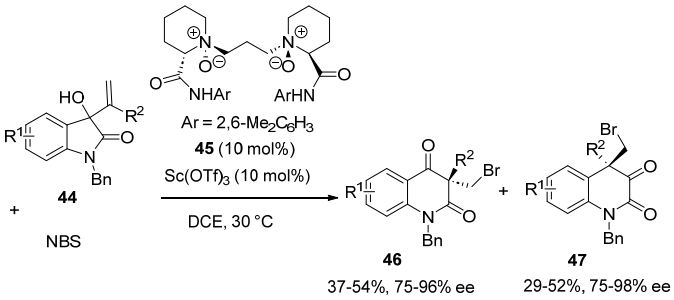
In 2016, Shi et al. disclosed an enantioselective domino bromination/amination reaction of (*E*)-cinnamyl carbamates **41** with DBDMH as the bromination agent (Scheme 12) [54]. The process was catalyzed at −50 °C by only 2 mol% of a mixture of $Sc(OTf)_3$ and chiral phosphine oxide ligand **42**. Performed in chloroform, it provided highly enantioselectively (87–99% ee) chiral aryl 5-bromo-1,3-oxazinan-2-ones **43** in good yields (65–96%).

An asymmetric domino bromination/semipinacol rearrangement reaction was described by Cao and Feng, in 2021 [55]. The reaction occurred between isatin-derived allylic alcohols **44** and NBS at 30 °C in DCE in the presence of a combination of 10 mol% of *N*,*N*′-dioxide ligand **45** and the same quantity of $Sc(OTf)_3$, thus allowing the synthesis of two families of chiral products. The first one deals with brominated dihydroquinoline-2,4-diones **46** arisen from an acyl-migration, while the second one concerns bromo-substituted dihydroquinoline-2,3-diones **47** generated from an aryl-migration (Scheme 13). These two products were generated through kinetic resolution with moderate yields (37–54% and 29–52%, respectively, for **46** and **47**) combined with good enantioselectivities (75–96% ee and 75–98% ee, respectively, for **46** and **47**).



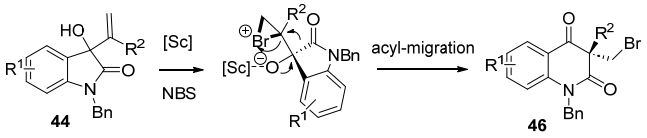
Ar = Ph, *p*-MeOC$_6$H$_4$, *m*-MeOC$_6$H$_4$, *o*-MeOC$_6$H$_4$, *p*-BrC$_6$H$_4$, *m*-BrC$_6$H$_4$, *m*-MeOC$_6$H$_4$, *p*-ClC$_6$H$_4$, *m*-FC$_6$H$_4$, *p*-FC$_6$H$_4$, 2,4,6-F$_3$C$_6$H$_2$, *o*-Tol, *p*-Tol, 3,5-Me$_2$C$_6$H$_3$, 2,4,6-Me$_3$C$_6$H$_2$, 1-Naph, 2-Naph, 2-thienyl

Scheme 12. Domino bromination/amination reaction of (*E*)-cinnamyl tosylcarbamates [54].

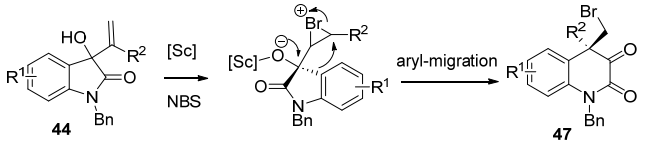


R^1 = H, 7-F, 7-Cl, 7-Br, 7-Me, 7-CF$_3$, 6-F, 6-Cl, 6-Br, 5-F, 5-Cl, 5-Br, 5-Me, 4-Cl, 4,6-F$_2$, 4,7-Cl$_2$, 4,7-Me$_2$
R^2 = Ph, *m*-Tol, *m*-ClC$_6$H$_4$, *m*-FC$_6$H$_4$, *m*-MeOC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-PhC$_6$H$_4$, *p*-*t*-BuC$_6$H$_4$, 2-Naph, Cy

mechanism for the formation of **46**:



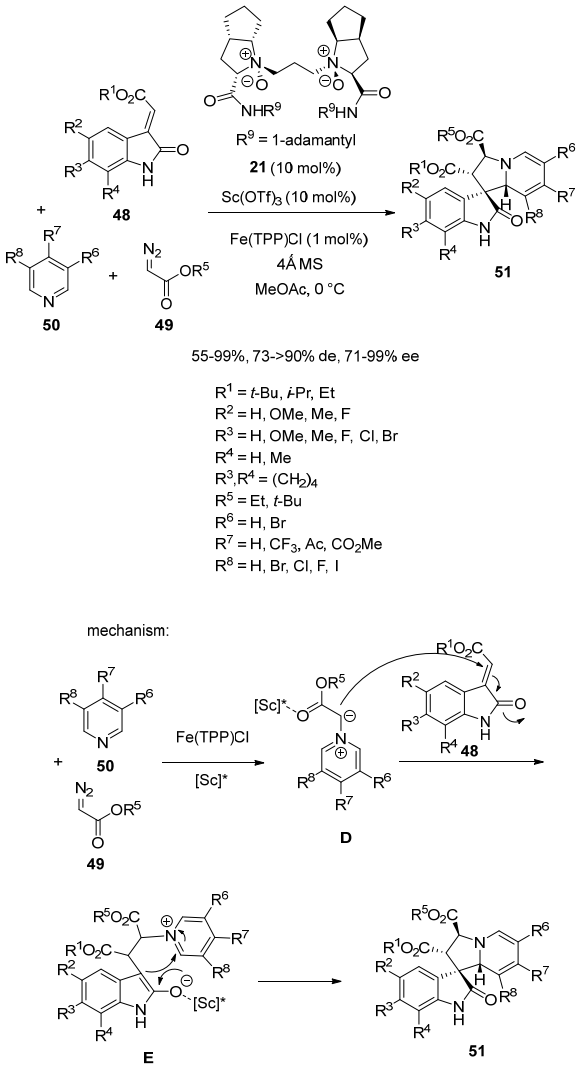
mechanism for the formation of **47**:



Scheme 13. Domino bromination/semipinacol rearrangement of isatin-derived allylic alcohols with NBS [55].

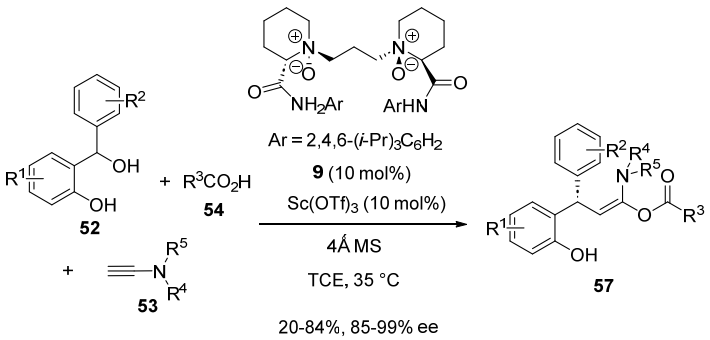
2.5. Three-Component Domino Reactions

In 2018, Feng et al. introduced a novel synthesis of chiral tetrahydroindolizines, exhibiting four contiguous stereocenters by the involvement of an asymmetric multicatalyzed three-component reaction of alkenyloxindoles **48**, diazoacetates **49** and pyridines **50** (Scheme 14) [56]. The process evolved through a relay catalysis involving an achiral iron catalyst, such as Fe(TPP)Cl (TPP = tetraphenylprophyrin), and a chiral scandium catalyst in situ formed from 10 mol% of $Sc(OTf)_3$ and the same quantity of chiral *N*,*N*′-dioxide ligand **21**. Performed at 0 °C in methyl acetate as solvent, the reaction began with the iron-catalyzed formation of an iron carbene species from the corresponding diazoacetate **49**. In the presence of the catalyst, this carbene species was then attacked by pyridine **50** to give pyridinium ylide intermediate **D** which subsequently added to alkenyloxindole **48** to provide zwitterionic intermediate **E**. Then, the latter was submitted to a ring closing to finally afford chiral functionalized tetrahydroindolizine **51,** in most cases, as a single diastereomer (>90% de) in good to high yields (55–99%) and enantioselectivities (71–99% ee). Generally, the best enantioselectivities were obtained in the reaction of alkenyloxindoles bearing electron-donating substituents (R^2–R^4) on their phenyl ring, while lower enantioselectivies (71–73% ee) were obtained in the case of electron-withdrawing substituted substrates. Moreover, lower diastereoselectivities (73–84% de) were observed in the reaction of pyridines exhibiting electron-withdrawing substituents.



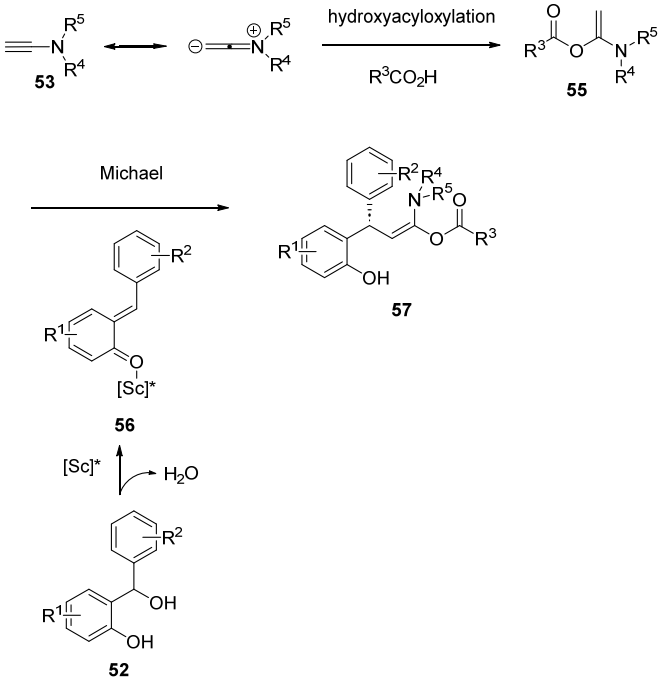
Scheme 14. Three-component reaction of alkenyloxindoles, diazoacetates and pyridines [56].

Later in 2020, a novel asymmetric three-component reaction between *ortho*-hydroxybenzyl alcohols **52**, ynamides **53** and carboxylic acids **54** was catalyzed by Cao and Feng by a combination of 10 mol% of $Sc(OTf)_3$ with 10 mol% of related chiral *N*,*N*′-dioxide ligand **9** [57]. The process dealt with a domino hydroacyloxylation/Michael reaction performed at 35 °C in TCE. As illustrated in Scheme 15, an hydroacyloxylation of ynamide **53** with acid **54** produced acyloxyenamide **55**, which then underwent a Michael addition to *ortho*-quinone methide **56** arisen from dehydration of *ortho*-hydroxybenzyl alcohol **52**. The reaction resulted in the formation of densely functionalized chiral α-acyloxyenamides **57** with high enantioselectivities (85–99% ee) combined with low to high yields (20–84%).



R^1 = H, 5-F, 5-Cl, 5-Br, 4-Cl, 5-Me
R^2 = H, 4-Me, 4-F, 4-Cl, 3-F
R^3 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$O_2NC_6H_4$, *p*-$F_3CC_6H_4$, *p*-Tol, *m*-$O_2NC_6H_4$, *m*-BrC_6H_4, *o*-BrC_6H_4, 2-Naph, 2-thiophenyl, allyl
R^4 = Me, Bn, allyl, $HC{\equiv}CCH_2$, $allylCH_2$
R^5 = Ts, Mes

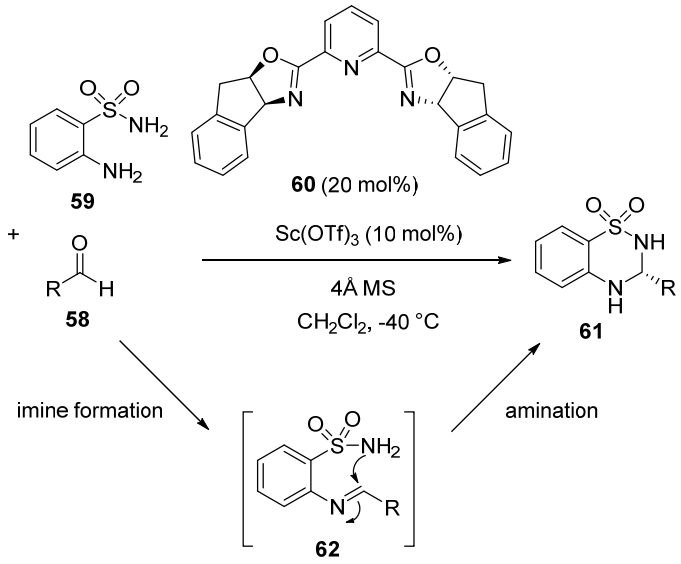
mechanism:



Scheme 15. Three-component reaction of *ortho*-hydroxybenzyl alcohols, carboxylic acids, and ynamides [57].

2.6. Miscellaneous Domino and Tandem Reactions

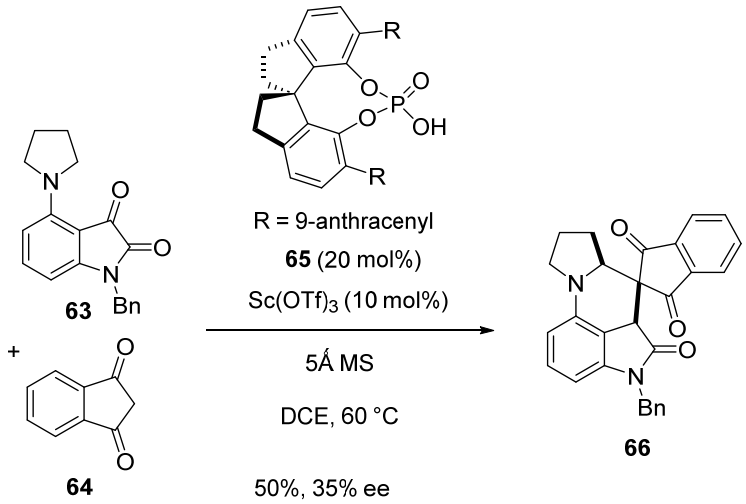
In 2016, Zhou et al. developed an enantioselective domino imine formation/intramolecular amination reaction of aldehydes **58** with 2-aminobenzenesulfonamide **59** (Scheme 16) [58]. The reaction was induced in dichloromethane at −40 °C by a chiral scandium catalyst in situ formed from 10 mol% of $Sc(OTf)_3$ and 20 mol% of chiral Pybox ligand **60**, leading to biologically interesting 3-alkyl- or 3-aryl-substituted chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides **61** in both moderate to high yields (60–88%) and enantioselectivities (36–93% ee). The best enantioselectivities (73–92% ee) were generally obtained in the reaction of aliphatic aldehydes, whereas aromatic aldehydes afforded products with more variable ee values (36–93% ee). In another area, Hannedouche et al. described in 2016 an asymmetric tandem hydroamination/Friedel–Crafts reaction between *N*-tosyl-2-(propylethynyl)aniline and ethyl 3,3,3-trifluoropyruvate, catalyzed by a chiral scandium complex derived from a C_2-symmetric binaphthylamine featuring a pyridylmethylamine moiety, which resulted in the formation of the corresponding indole derivative, albeit with a low enantioselectivity (10–20% ee) [59].

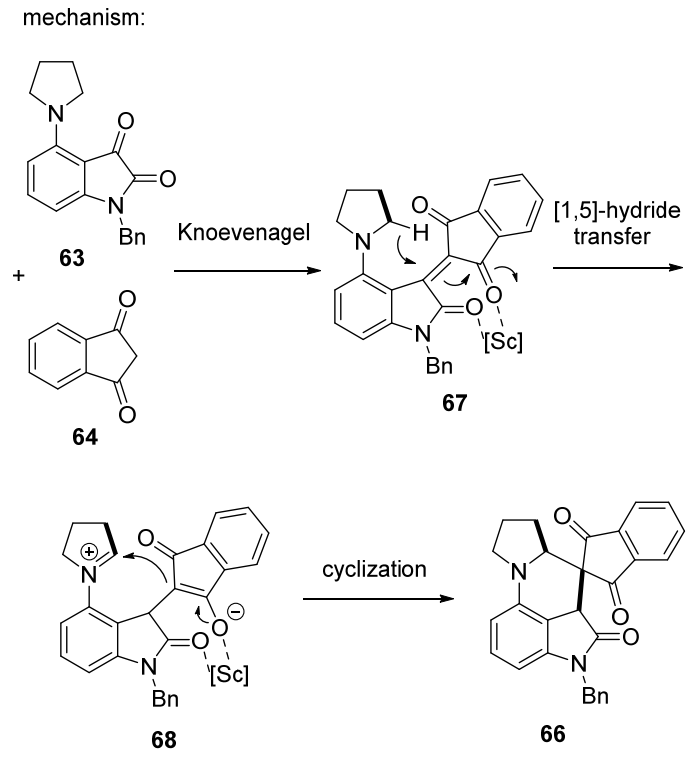


with R = *i*-Bu, *i*-Pr, *t*-$BuCH_2$, Cy, *c*-Pent, *c*-Pr, Bn, $BnCH_2$:
60-75%, 73-92% ee
with R = Ph, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *m*-BrC_6H_4, *o*-BrC_6H_4,
3-Br-4-$MeOC_6H_3$, 1-furyl:
60-88%, 36-93% ee

Scheme 16. Domino imine formation/amination reaction of aldehydes with an aminosulfonamide [58].

An asymmetric domino Knoevenagel/[1,5]-hydride transfer/cyclization reaction between C4-pyrrolidin-substituted isatin **63** and 1,3-indandione **64** was investigated by Li and Xiao, in 2019 (Scheme 17) [60]. Under catalysis with 10 mol% of $Sc(OTf)_3$ and 20 mol% of chiral ligand **65**, the process carried out at 60 °C in DCE afforded complex chiral hexacyclic product **66** in 50% yield and 35% ee. The mechanism shown in Scheme 17 involves a Knoevenagel reaction leading to enone intermediate **67**. A following [1,5]-hydride transfer provides intermediate **68**, which further undergoes cyclization to provide the final product.

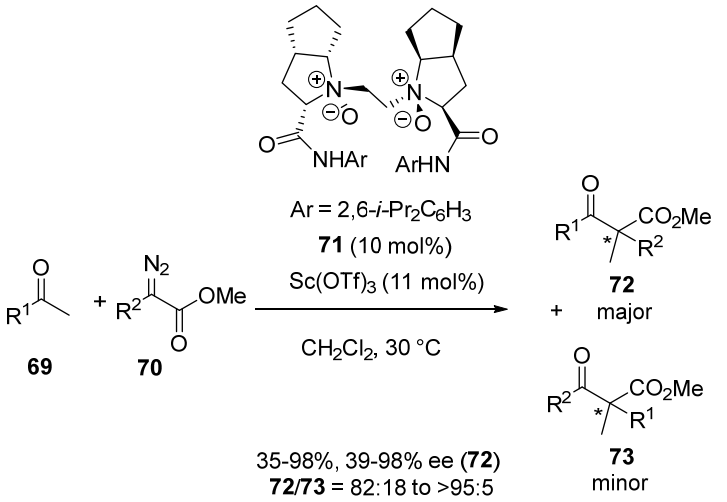




Scheme 17. Domino Knoevenagel/[1,5]-hydride transfer/cyclization reaction of an isatin derivative with 1,3-indandione [60].

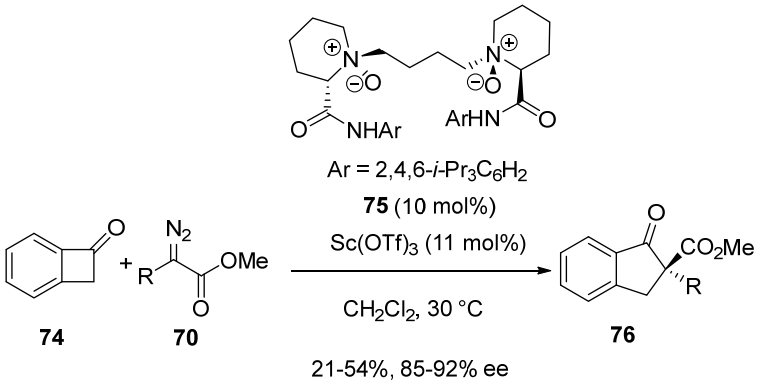
A combination of $Sc(OTf)_3$ (11 mol%) with chiral *N*,*N*′-dioxide ligand **71** (10 mol%) was applied by Wu and Feng in 2021 to promote enantioselective homologation of ketones **69** with α-alkyl α-diazo esters **70** [61,62]. Evolving through a domino addition/rearrangement reaction, the process produced chiral β-keto esters **72** as major products along with minor regioisomers **73** with 35–98% yields and good levels of regioselectivity (**72**/**73** = 82:18 to >95:5). The major products **72** were obtained with 39–98% ee through selective alkyl-group migration of the ketone moieties (Scheme 18). It must be noted that uniformly high enantioselectivities (≥89% ee) were achieved excepted in the reaction of acetone (R^1 = Me) which provided the desired product with only 39% ee. (Hetero)aryl- and alkyl-substituted acyclic ketones were compatible as well as various α-diazo esters. By using a related chiral ligand, such as *N*,*N*′-dioxide ligand **75**, cyclic ketone **74** was capable to undergo the ring

expansion to yield by reaction with various α-diazo esters **70** chiral cyclic β-keto esters **76** with 85–92% ee and 21–54% yields.



R^1 = Ph, *o*-FC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4, *o*-NCC_6H_4, *p*-Tol, *p*-$MeOC_6H_4$, *p*-$MeSC_6H_4$, 2-Naph, 2-furyl, 2-thienyl, (*E*)-PhCH=CH, Me, PhC≡C

R^2 = Bn, *o*-$FC_6H_4CH_2$, *m*-$FC_6H_4CH_2$, *m*-$MeOC_6H_4CH_2$, *p*-$FC_6H_4CH_2$, *p*-$ClC_6H_4CH_2$, *p*-$BrC_6H_4CH_2$, *p*-$F_3CC_6H_4CH_2$, *p*-$TolCH_2$, 2-$NaphCH_2$, allyl, $BnCH_2$, Et, MeO_2CCH_2, F_3CCH_2, $TBSO(CH_2)_3$, $HC{\equiv}CCH_2$

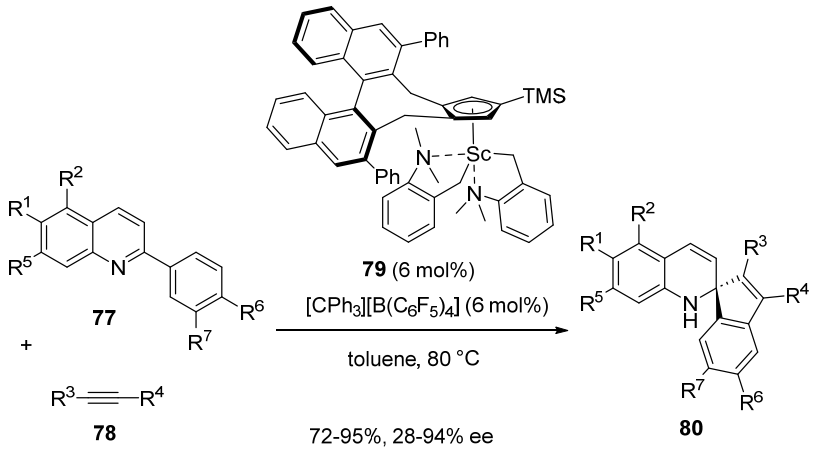


R = Bn, *o*-$FC_6H_4CH_2$, *m*-$FC_6H_4CH_2$, *m*-$TolCH_2$, *m*-$MeOC_6H_4CH_2$, *p*-$FC_6H_4CH_2$, *p*-$ClC_6H_4CH_2$, *p*-$BrC_6H_4CH_2$, *p*-$IC_6H_4CH_2$, *p*-$F_3CC_6H_4CH_2$, *p*-$F_3COC_6H_4CH_2$, *p*-$TolCH_2$, 2-$NaphCH_2$, allyl, $BnCH_2$, *n*-$C_{12}H_{25}$, $HC{\equiv}CCH_2$

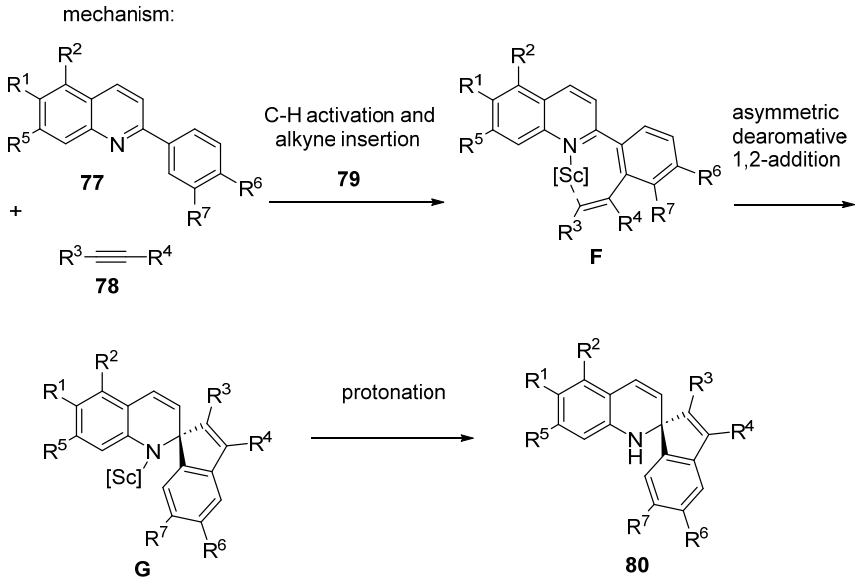
Scheme 18. Domino addition/rearrangement reactions of ketones with α-diazoacetates [61].

In the same year, an asymmetric domino dearomative spiroannulation of quinolines **77** with alkynes **78** was disclosed by Luo and Hou (Scheme 19) [63]. Carried out at 80 °C in toluene in the presence of 6 mol% of chiral half-sandwich scandium catalyst **79**, the reaction resulted in the formation of biologically interesting chiral spiro-dihydroquinolines **80** in good yields (72–95%) and low to excellent ee values (28–94% ee). As shown in Scheme 19, the reaction evolves through the C−H activation of the 2-aryl substituent of **77** promoted by the scandium catalyst to give intermediate **F**. The latter then undergoes nucleophilic

1,2-addition of the resulting scandium alkenyl species to the imine of the quinoline, leading to intermediate **G**, which delivers the final product through protonation.



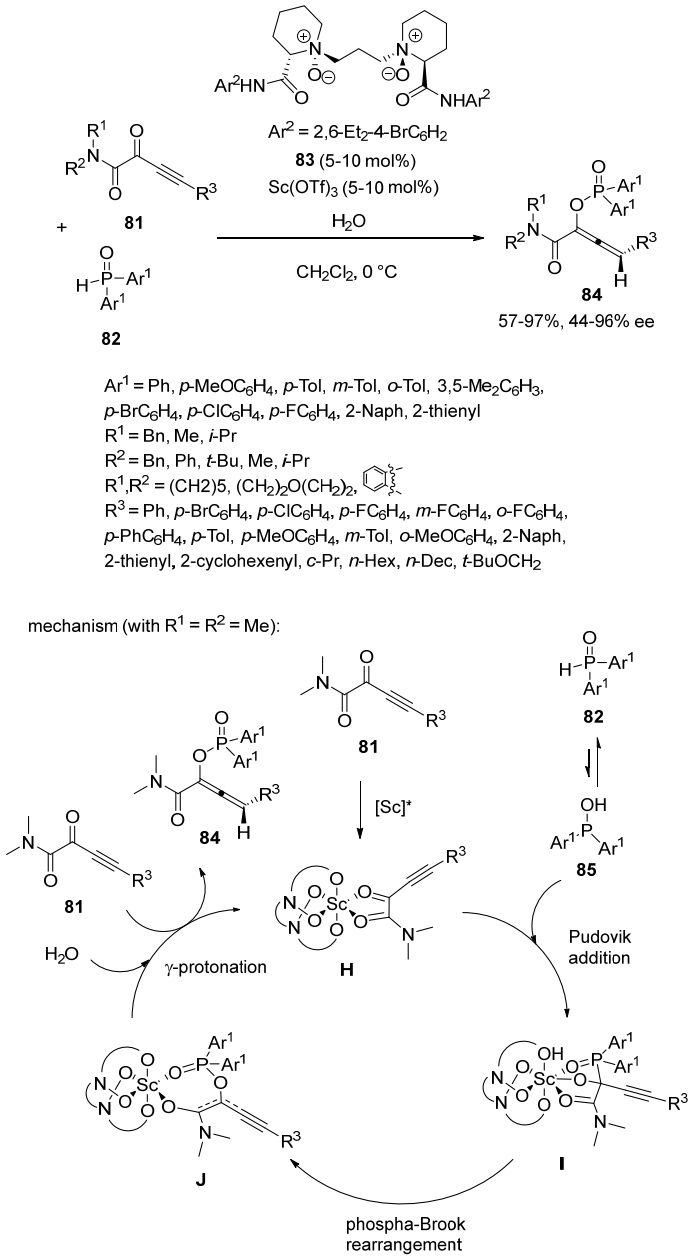
R^1 = H, Br
R^2 = H, Br
R^3 = Ph, *p*-*t*-BuC_6H_4, *p*-PhC_6H_4, *p*-TMSC_6H_4, *p*-BrC_6H_4,  , *p*-PhOC_6H_4, 2-Naph, *p*-ClC_6H_4, Me_2SiPh, Me
R^4 = Me, *c*-Pr, Ph
R^5 = H, Br, Me
R^1,R^5 = $(CH{=}CH)_2$
R^6 = H, Me, *i*-Pr, *i*-Bu, Ph, Br, I, OPh, SMe
R^7 = H, Me



Scheme 19. Domino spiroannulation of 2-arylquinolines with alkynes [63].

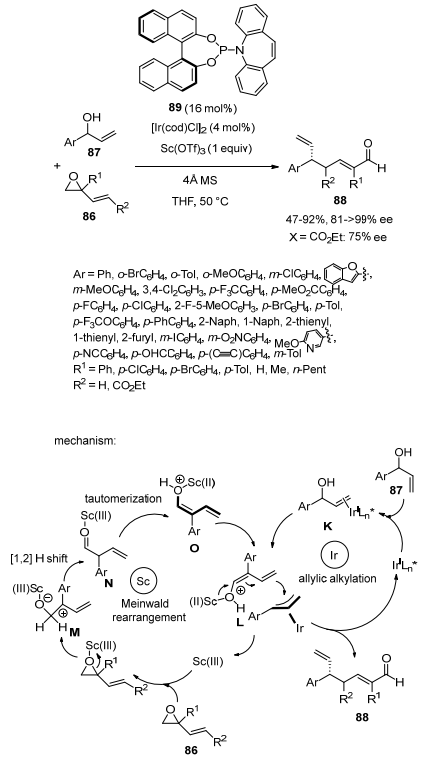
In 2022, Dong, Peng and Feng developed enantioselective catalytic domino Pudovik addition/[1,2]-phospha-Brook rearrangement reaction between α-alkynylketoamides **81** and diarylphosphine oxides **82** (Scheme 20) [64]. The process was promoted at 0 °C in dichloromethane by a chiral scandium catalyst in situ generated from 5–10 mol% of $Sc(OTf)_3$ and the same quantity of chiral *N*,*N*′-dioxide ligand **83**. Using water as an additive, it produced regio- and enantioselectively a range of chiral trisubstituted allenes **84** bearing a diarylphosphinate functionality with good to high yields (57–97%) and gen-

erally excellent ee values (44–96% ee). The substrate scope was found to be wide, since α-alkynylketoamides bearing symmetrical, unsymmetric, acyclic and cyclic *N*-substituents were compatible, thus forming the corresponding products with uniformly high ee values (80–92% ee) excepted substrate exhibiting a *N*,*N*-diisopropyl group ($R^1 = R^2 = i$-Pr), which reacted with a lower enantioselectivity (44% ee). Moreover, different aryl substituents (R^3) on the alkyne terminus were tolerated regardless of the electronic properties and positions of the substituents on the phenyl ring. Heteroaromatic substituents as well as aliphatic ones were also tolerated. To explain their results, the authors proposed the mechanism depicted in Scheme 20 in which the α-alkynylketoamide was activated through bidentate coordination to the catalyst to give intermediate **H**. Then, the latter species underwent nucleophilic Pudovik addition with the isomerized diarylphosphine oxide **85** to generate alkoxide intermediate **I**. Subsequently, 1,2-phospha-Brook rearrangement of **I** occurred, yielding intermediate **J**. In the presence of water, γ-protonation of **J** delivered the final allene.



Scheme 20. Domino Pudovik addition/[1,2]-phospha-Brook rearrangement reaction of phosphine oxides with α-alkynylketoamides [64].

In the same year, a dual scandium/iridium catalysis was applied by Yang and Deng to promote an unprecedented enantioselective γ-allylic alkylation of in situ generated free dienolates, thus allowing the regio- and highly enantioselective synthesis of chiral γ-allylic crotonaldehydes (Scheme 21) [65]. Indeed, the domino reaction began with the in situ generation of dienolates from scandium-mediated Meinwald rearrangement of the corresponding vinyloxiranes **86**. Then, these dienolates subsequently underwent iridium-catalyzed asymmetric γ-allylic alkylation with aromatic allylic alcohols **87** to afford the corresponding chiral γ-allylic crotonaldehydes **88** with moderate to high yields (47–92%) and uniformly high enantioselectivities (81 ≥ 99% ee). The domino Meinwald rearrangement/γ-allylic alkylation reaction was performed at 50 °C in THF and required one equivalent of $Sc(OTf)_3$, 4 mol% of $[Ir(cod)Cl]_2$ and 16 mol% of chiral P,N-ligand **89** as a catalyst system. The substrate scope of the reaction was found remarkably wide, especially for the allylic alcohols, which could bear either electron-donating or electron-withdrawing groups at any position of the phenyl ring but also heteroaromatic substituents. Concerning the vinyloxirane partner, differently substituted phenyl rings were compatible as substituents (R^1), providing the corresponding products with 96–98% ee. Moreover, alkyl-substituted vinyloxiranes (R^1 = Me, *n*-Pent) also reacted smoothly to give the desired products with 95 ≥ 99% ee. Even challenging vinyloxiranes bearing an electron-withdrawing group ($R^2 = CO_2Et$) on the vinyl moiety provided the corresponding trisubstituted crotonaldehyde with 92% yield, 75% de and 81% ee through an exclusive γ-regioselectivity. The authors proposed the mechanism detailed in Scheme 21, beginning with the generation of the active catalyst from $[Ir(cod)Cl]_2$ and ligand **89**. The latter specie further coordinated the allylic alcohol to give intermediate **K**, which then underwent oxidative addition promoted by $Sc(OTf)_3$ to provide π-allyl-iridium intermediate **L**. Concurrently, $Sc(OTf)_3$ triggered the ring opening of the vinyloxirane to give scandium-bound zwitterionic species **M**, which subsequently underwent a 1,2-hydride shift/tautomerization sequence providing the active scandium dienolate **O**. Subsequently, because of the steric hindrance of the *Si*-face in intermediate **L**, the scandium dienolate **O** approached intermediate **L** from the *Re*-face, delivering the product along with regenerated iridium catalyst.

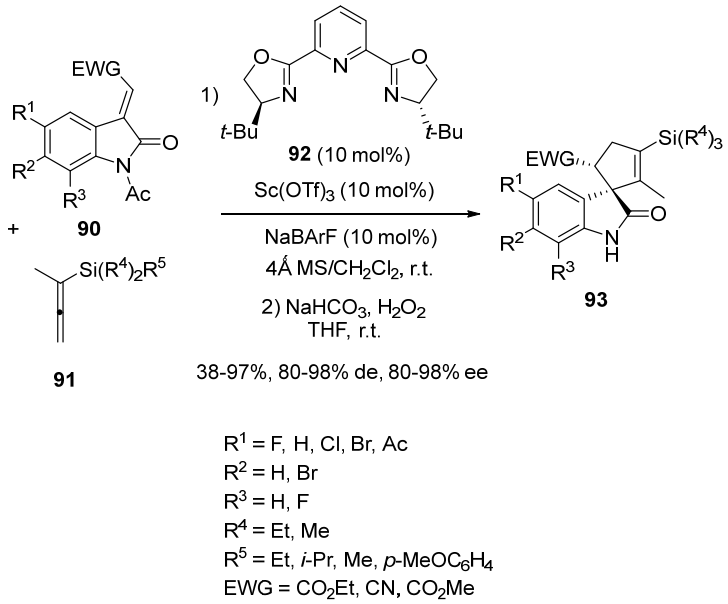


Scheme 21. Domino Meinwald rearrangement/γ-allylic alkylation reaction of vinyloxiranes with aromatic allylic alcohols [65].

3. Enantioselective Scandium-Catalyzed Cycloadditions

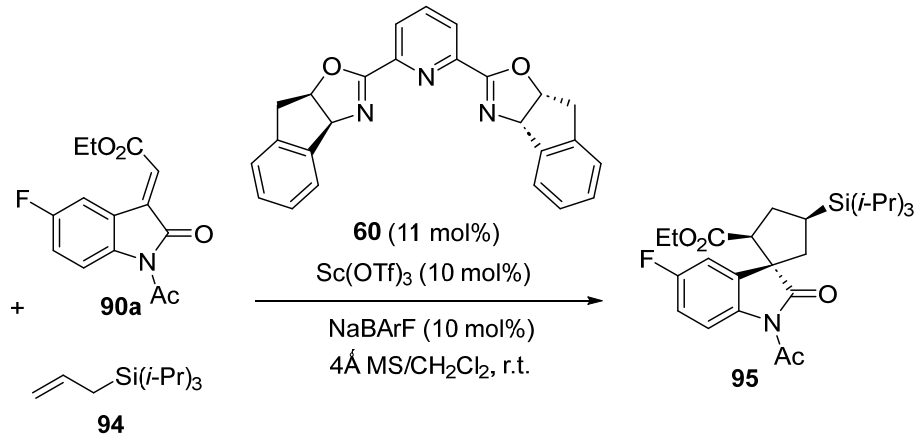
3.1. [3 + 2] Cycloadditions

Spirooxindoles are widely present among natural and pharmaceutical products. In 2019, Franz et al. developed an asymmetric synthesis of cyclopentene-spirooxindoles containing a vinylsilane moiety, which are potentially interesting in medicinal chemistry [66]. It was based on an enantioselective formal [3 + 2] cycloaddition of alkylideneoxindoles **90** with allenylsilanes **91** performed at room temperature in dichloromethane. The cycloaddition was catalyzed in the presence of NaBArF as an additive by a chiral scandium complex in situ, formed from 10 mol% of $Sc(OTf)_3$ and the same quantity of chiral Pybox ligand **92**, as illustrated in Scheme 22. After a subsequent *N*-acyl deprotection of the cycloadduct by treatment with $NaHCO_3/H_2O_2$, the corresponding chiral silylated cyclopentene-spirooxindoles **93** were generated in moderate to quantitative yields (38–97%) as almost single diastereomers (80–98% de) in uniformly high enantioselectivities (80–98% ee). The vinylsilane group provided a versatile functional group to further modify the spirooxindole skeleton to be used in medicinal chemistry. The reaction of alkylideneoxindoles **90** exhibiting an ester group (EWG = ester) at the alkylidene moiety provided both higher yields (64–97% vs. 38%) and enantioselectivities (82–98% ee vs. 80% ee) than that of an alkylidene oxindole bearing a cyano group (EWG = CN). Moreover, a range of electron-donating and electron-withdrawing substituents on the oxindole ring were tolerated.



Scheme 22. Formal [3 + 2] cycloaddition of alkylideneoxindoles with allenylsilanes [66].

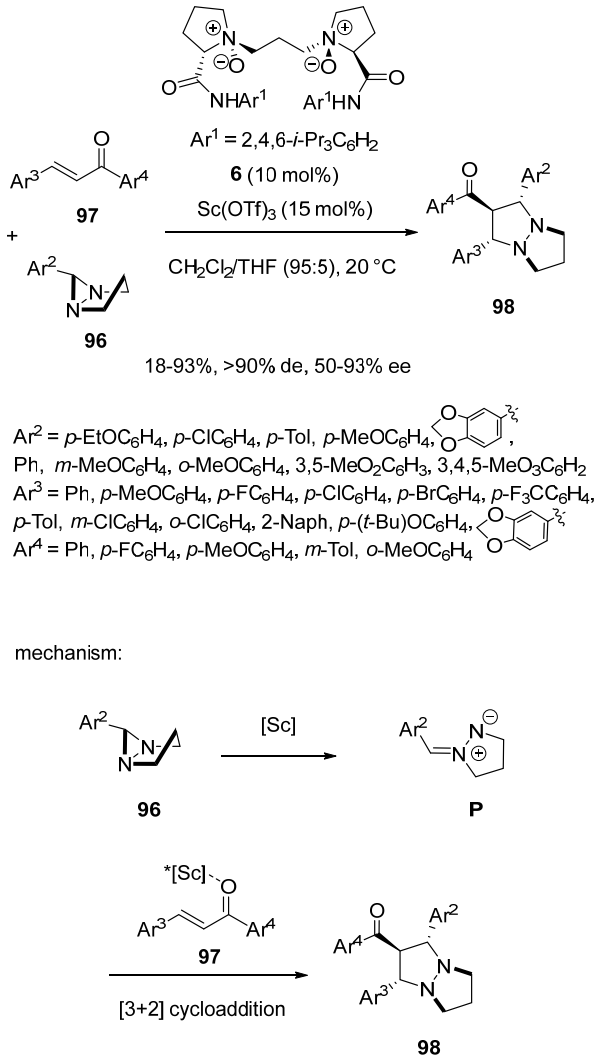
Later in 2022, Franz and Hein employed related chiral ligand **60** in combination with the same precatalyst $Sc(OTf)_3$ to promote the enantioselective formal [3 + 2] cycloaddition between alkylideneoxindole **90a** and allylsilane **94** (Scheme 23) [67]. Employed at respectively 11 and 10 mol% of catalyst loadings in dichloromethane in the presence of NaBArF as an additive, the annulation resulted in the formation of novel tetrahydropyranoindole **95** with complete conversion, excellent diastereoselectivity (90% de) and good enantioselectivity (84% ee).



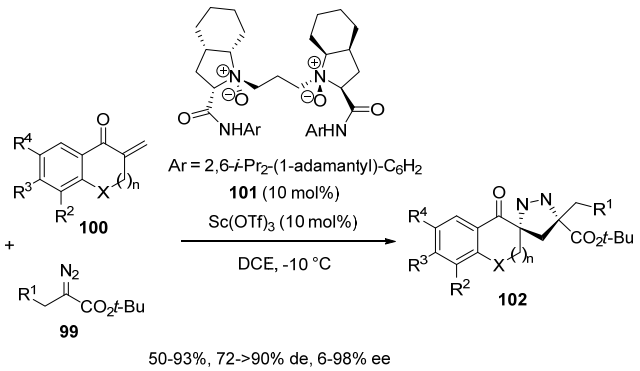
Scheme 23. Formal [3 + 2] cycloaddition of an alkylideneoxindole with an allylsilane [67].

In 2020, Feng and Liu described the first catalytic asymmetric [3 + 2] cycloaddition of diaziridines via C–N bond cleavage [68]. Indeed, in the presence of a chiral scandium catalyst prepared from 15 mol% of $Sc(OTf)_3$ and 10 mol% of chiral *N*,*N*′-dioxide chiral ligand **6** in a 95:5 mixture of dichloromethane/THF as solvent, diaziridines **96** formed the corresponding azomethine imine intermediates **P** through C–N bond cleavage. The latter further reacted with scandium-activated chalcones **97** to give the corresponding chiral 1,5-diazabicyclo [3.3.0]octanes **98**. As presented in Scheme 24, a range of these bicyclic products were synthesized as single diastereomers (>90% de) in variable yields (18–93%) and moderate to high enantioselectivities (50–93% ee). Chalcones bearing an electron-withdrawing substituent on the phenyl ring of R^1 generally provided better yields (76–93%) than those having an electron-donating substituent (70–75%). The position of these substituents was also found crucial, especially to obtain a high enantioselectivity. For example, the enantioselectivity of the reaction decreased from 90% ee for a *para*-chloro-substituted substrate to 84% ee for a *meta*-chloro-substituted substrate and to 50% ee for an *ortho*-chloro-substituted substrate. The electronic nature of the substituents exhibited by the aryl group of the diaziridines was found to play a key influence on the reactivity. For example, *para*-chloro- and *para*-methyl-substituted diaziridines (Ar = *p*-ClC_6H_4, *p*-Tol) led to the corresponding cycloadducts in high enantioselectivities (90% ee) albeit with low yields (20–24%).

In 2021, the same group reported an enantioselective [3 + 2] cycloaddition of α-substituted diazoesters **99** with exocyclic enones **100** under catalysis with a related chiral scandium catalyst in situ formed from 10 mol% of $Sc(OTf)_3$ and the same quantity of chiral *N*,*N*′-dioxide ligand **101** (Scheme 25) [69]. Performed at −10 °C in DCE, the cycloaddition resulted in the formation of a wide range of chiral 1-pyrazolines **102** with good yields (50–93%), generally excellent diastereoselectivities (72 $\geq$ 90% de) and low to excellent enantioselectivities (6–98% ee). A range of *tert*-butyl α-alkyl-α-diazoesters was compatible as well as various exocyclic enones, including chromanones (X = O, n = 1) and other cyclic enones. Indeed, 1-pyrazoline-based spirochromanones **102** (X = O, n = 1) were produced with 35–93% ee, regardless of the electronic nature of the substituents at *meta*- or *para*-position of the benzyl group of the diazoacetates. While the reaction of a 2-naphthyl substituted diazoacetate afforded the corresponding product with 90% ee, that of 1-naphthyl substituted substrate led to the desired product with a drastically lower ee value (56% ee). Concerning the enone partners, the reaction of 5,7-dimethyl enone (X = CH_2, n = 1, R^2 = R^4 = Me) led to the corresponding cycloadduct with a low ee value (27% ee). On the other hand, five-membered 2-methylene-2,3-dihydroindenones (X = CH_2, n = 0) reacted with high enantioselectivities (90–98% ee) while a seven-membered spiropyrazoline (X = CH_2, n = 2) was isolated with the lowest ee value of 6% ee.

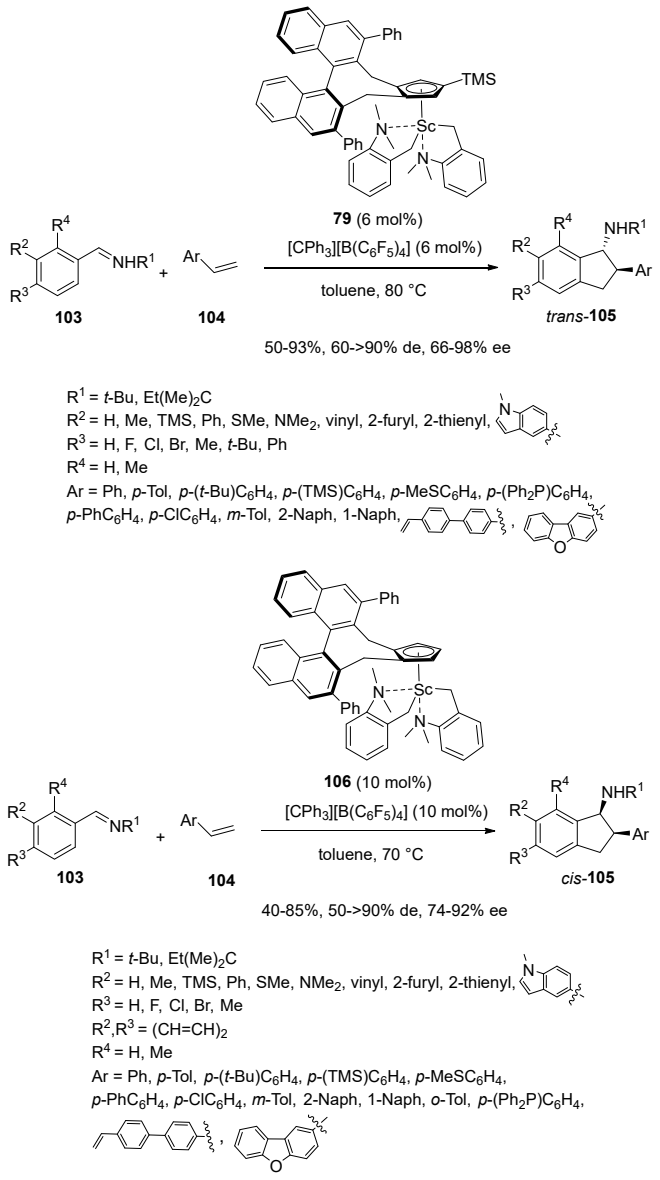


Scheme 24. [3 + 2] Cycloaddition of diaziridines with chalcones [68].



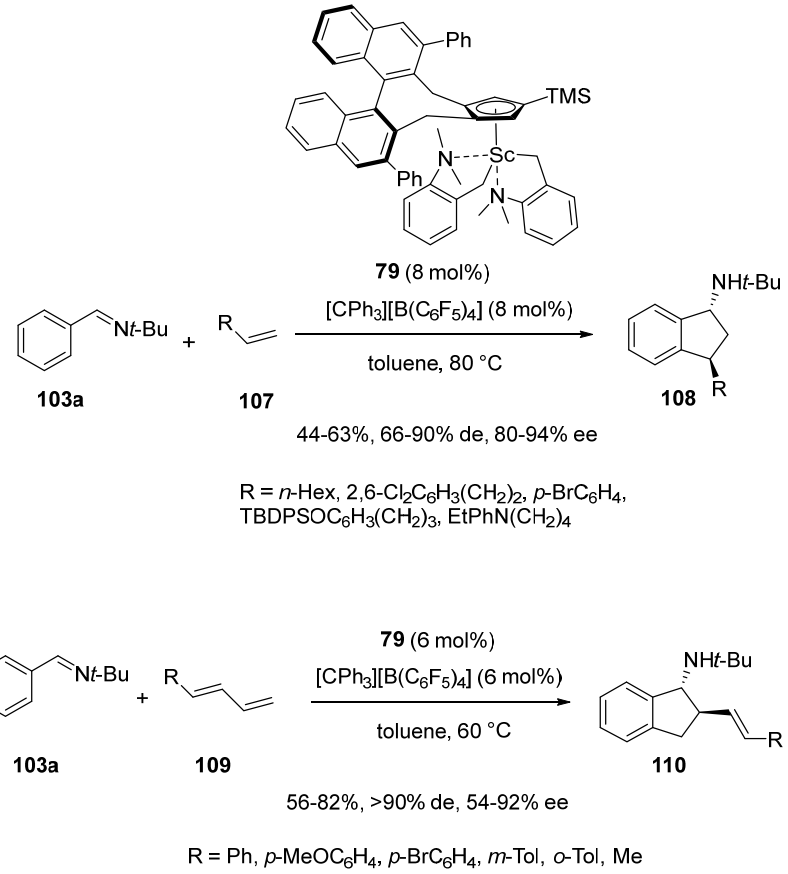
Scheme 25. [3 + 2] Cycloaddition of α-substituted diazoesters with exocyclic enones [69].

Multisubstituted chiral 1-aminoindanes constitute the skeletons of many bioactive molecules. These important products can be directly synthesized via asymmetric [3 + 2] cycloadditions of aldimines with alkenes through C−H activation but these methodologies still remain undeveloped. In 2023, Hou and Cong described the first enantioselective [3 + 2] cycloaddition between aromatic aldimines **103** and styrenes **104** occurring through *ortho*-C(sp^2)−H activation (Scheme 26) [70]. When the reaction was promoted at 80 °C by 6 mol% of chiral half-sandwich scandium catalyst **79** in toluene, it afforded stereoselectively the corresponding chiral *trans*-cycloadducts **105** with moderate to high yields (50–93%), *trans*-diastereo- (60 ≥ 90% de) and enantioselectivities (66–98% ee). The catalyst system tolerated variously substituted aromatic aldimines as well as styrenes bearing diverse functional groups, which allowed the synthesis of a series of multisubstituted chiral 1-aminoindanes. Interestingly, the reaction became *cis*-diastereoselective by using a less-sterically demanding chiral scandium catalyst **106** (Scheme 26). Indeed, in the presence of 10 mol% of this catalyst in toluene at 70 °C, aromatic aldimines **103** reacted with styrenes **104** to give the *cis*-diastereomers of 1-aminoindanes **105** with 40–85% yields, 50 ≥ 90% de, and 74–92% ee.



Scheme 26. [3 + 2] Cycloadditions of aromatic aldimines with styrenes [70].

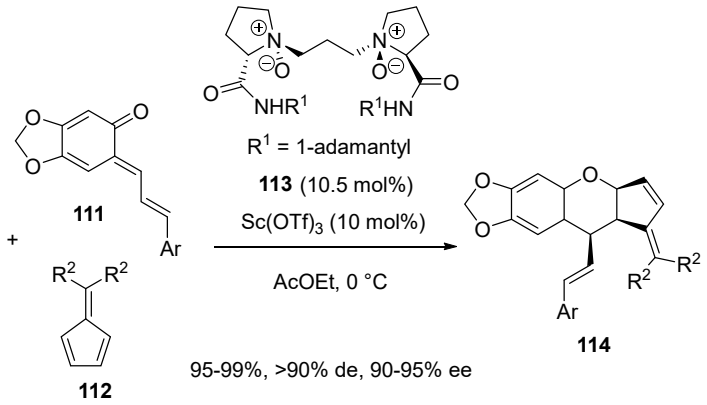
Moreover, these authors also investigated the [3 + 2] cycloaddition of aliphatic alkenes **107** with *N*-*tert*-butylbenzaldimine **103a** by using 8 mol% of chiral catalyst **79** (Scheme 27) [70]. In contrast with the exclusive formation of 2-aryl-1-aminoindanes through 2,1-insertion in the analogous reaction with styrenes, the annulation with aliphatic α-olefins afforded at 80 °C the corresponding chiral 3-alkyl-1-aminoindanes **108** through a 1,2-insertion. These products were generally obtained with moderate yields (44–63%) and moderate to high *trans*-diastereoselectivities (66–90% de) combined with homogeneously high ee values (80–94% ee). The scope of the methodology was also extended to 1,3-dienes **109**, which underwent at 60 °C a *trans*-selective [3 + 2] cycloaddition with *N*-*tert*-butylbenzaldimine **103a** in the presence of 6 mol% of catalyst **79**. The reaction took place exclusively at the terminal C = C bond to afford the corresponding chiral 1-amino-2-alkenyl-substituted indanes **110** as almost single *trans*-diastereomers (>90% de) with moderate to good yields (56–82%) and in most cases with high ee values (54–92% ee).



Scheme 27. [3 + 2] Cycloadditions of aromatic aldimines with aliphatic α-olefins and 1,3-dienes [70].

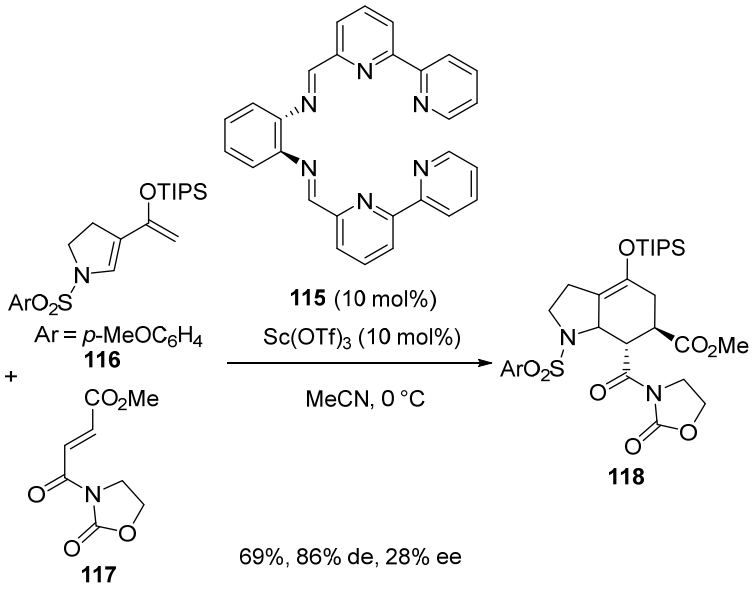
3.2. (Hetero)-Diels–Alder Reactions

In 2018, Feng and Liu developed a highly efficient asymmetric inverse-electron-demand oxa-Diels–Alder reaction of *ortho*-quinone methides **111** with symmetrical fulvenes **112** catalyzed by a chiral scandium complex in situ generated from 10.5 mol% of chiral *N*,*N*′-dioxide ligand **113** and 10 mol% of $Sc(OTf)_3$ (Scheme 28) [71]. Evolving at 0 °C in ethyl acetate, the [4 + 2] cycloaddition allowed the corresponding optically active chromane derivatives **114** to be synthesized as almost single diastereomers (>90% de) with both remarkable yields (95–99%) and enantioselectivities (90–95% ee).



Scheme 28. Oxa-Diels–Alder reaction of *ortho*-quinone methides with fulvenes [71].

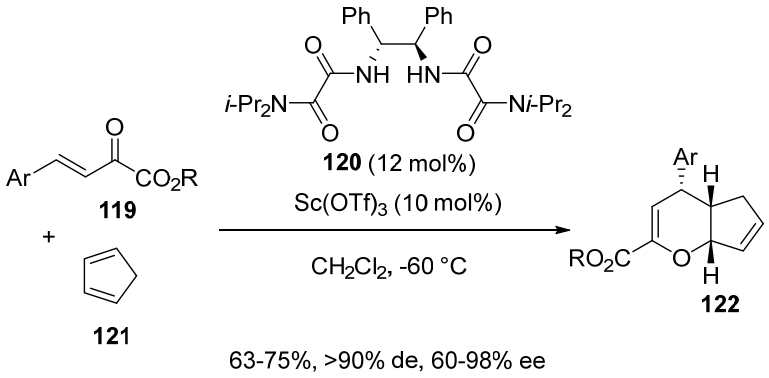
Later in 2020, Harada and Nishida reported the synthesis of novel hexadentate chiral ligands such as **115** [72]. These stable helical catalysts were found efficient to promote the enantioselective Diels–Alder reaction of electron-rich siloxydiene **116** with enamide **117**. For example, when using 10 mol% of $Sc(OTf)_3$ as precatalyst in combination with the same quantity of chiral ligand **115** in acetonitrile at 0 °C, the [4 + 2] cycloaddition of pyrrolidine-incorporated siloxydiene **116** with enamide **117** led to the corresponding cycloadduct **118** in good yield (69%) and *exo*-diastereoselectivity (86% de), albeit associated with a low enantioselectivity (28% ee), as illustrated in Scheme 29.

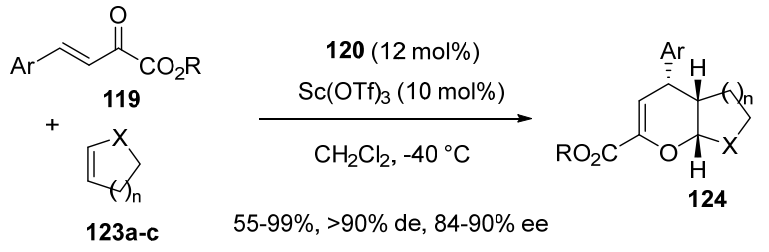


Scheme 29. Diels–Alder reaction of an electron-rich siloxydiene with an enamide [72].

Chiral dihydropyran derivatives are privileged and prevalent structures in many natural and bioactive products. In 2022, Wang, Qi and Wang developed enantioselective scandium-catalyzed inverse-electron-demand oxa-Diels-Alder reactions between β,γ-unsaturated α-ketoesters **119** and various types of electron-enriched dienophiles, such as cyclopentadiene, 2,3-dihydrofuran, 3,4-dihydro-2H-pyran, and tetrahydropyridine (Scheme 30) [73]. To promote these reactions, the authors selected a previously designed chiral bis-oxalamide ligand **120** to be combined at 12 mol% of a catalyst, loading to 10 mol% of $Sc(OTf)_3$ as a precatalyst.

In a first time, cyclopentadiene **121** was employed as an electron-rich dienophile and the hetero-Diels-Alder reactions with various (hetero)aryl-substituted β,γ-unsaturated α-ketoesters **119** performed at −60 °C resulted in the formation of the corresponding chiral 3,4-dihydro-2H-pyran derivatives **122** as almost single diastereomers (>90% de) with good yields (63–75%) and moderate to excellent enantioselectivities (60–98% ee). The scope of the methodology could be extended at −40 °C to other dienophiles, such as 2,3-dihydrofuran **123a** (X = O, n = 1), 3,4-dihydro-2H-pyran **123b** (X = O, n = 2), and 1-tosyl-1,2,3,4-tetrahydropyridine **123c** (X = NTs, n = 2), which smoothly reacted with aryl-substituted β,γ-unsaturated α-ketoesters **119** to give the corresponding chiral cycloadducts **124** with generally high yields (55–99%) and ee values (84–92% ee). Indeed, the products generated from 2,3-dihydrofuran **123a** were obtained with both excellent yields (92–99%) and enantioselectivities (84–90% ee) as well as that derived from 3,4-dihydro-2H-pyran **123b** (Ar = *p*-Tol, R = Me, n = 2: 81%, 92% ee). A slightly lower yield (55%) and ee value (85% ee) were observed for the reaction of 1-tosyl-1,2,3,4-tetrahydropyridine **123c** (Ar = Ph, R = Me, n = 2). This work constituted the first asymmetric hetero-Diels-Alder reactions catalyzed in the presence of a chiral bis-oxalamide ligand.

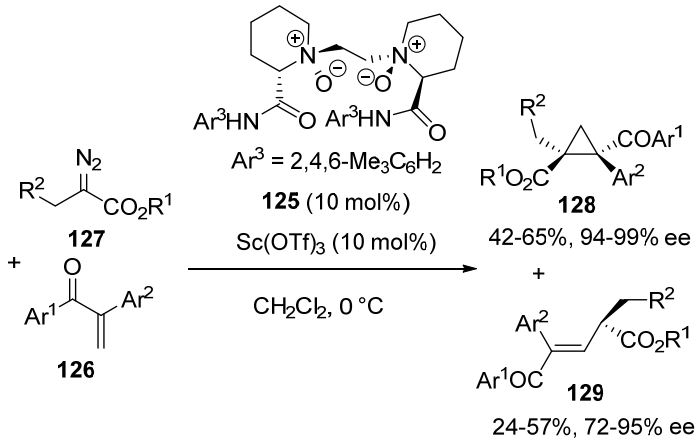




Scheme 30. Oxa-Diels–Alder reactions of β, γ-unsaturated α-ketoesters with cyclopentadiene/2,3-dihydrofuran/3,4-dihydro-2H-pyran/tetrahydropyridine [73].

3.3. [2 + 1] Cycloadditions

In 2018, a chiral scandium complex derived from chiral *N*,*N*′-dioxide ligand **125** was employed by Feng and Liu as promotor in [2 + 1] cycloadditions of α-substituted vinyl ketones **126** with α-substituted α-diazoesters **127** [74]. As shown in Scheme 31, these two substrates underwent at 0 °C in dichloromethane a [2 + 1] cycloaddition to afford the corresponding chiral tetrasubstituted cyclopropanes **128** as single diastereomers in moderate to good yields (42–65%) and uniformly excellent enantioselectivities (94–99% ee). Besides these cycloadducts, chiral products **129** were generated from a competitive C–H insertion reaction. The latter also obtained enantioenriched (72–95% ee) in 24–57% yields.

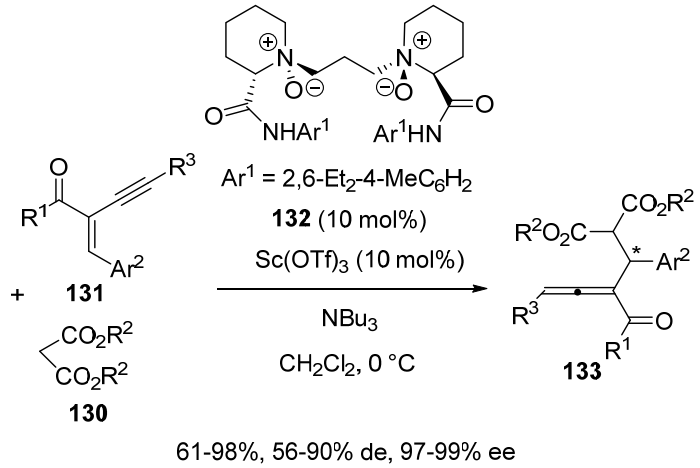


R^1 = Et, *i*-Pr, *t*-Bu, Me
R^2 = Ph, *o*-Tol, *m*-Tol, *m*-$MeOC_6H_4$, *p*-Tol,
p-FC_6H_4, *p*-BrC_6H_4, Et, *n*-Pr
Ar^1 = Ph, *p*-Tol
Ar^2 = Ph, *o*-BrC_6H_4, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$,
p-Tol, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, 2-Naph

Scheme 31. [2 + 1] Cycloaddition of α-substituted vinyl ketones with α-substituted α-diazoesters [74].

4. Enantioselective Scandium-Catalyzed Michael Additions

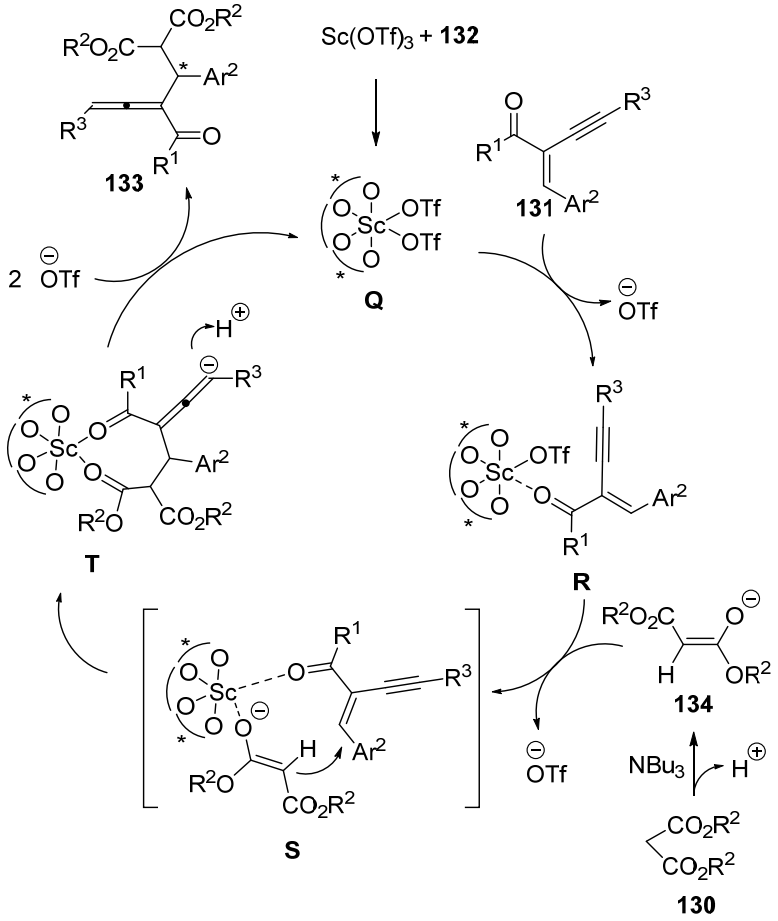
In order to prepare functionalized chiral allenes, which are valuable intermediates in organic synthesis, Liu and Feng developed in 2016 an asymmetric Michael addition of malonates **130** to enynes **131** (Scheme 32) [75]. The catalyst system was composed of 10 mol% of $Sc(OTf)_3$ and the same quantity of chiral *N*,*N*′-dioxide ligand **132**. Performed at 0 °C in dichloromethane as solvent in the presence of NBu_3 as base, the conjugate addition afforded a range of chiral trisubstituted 1,2-allenyl ketones **133** with moderate to quantitative yields (61–98%), moderate to excellent diastereoselectivities (56–90% de), and remarkable enantioselectivities (97–99% ee). To demonstrate the utility of this methodology, some products could be easily converted into chiral furan and 5-hydroxy-pyrazoline derivatives, which are important skeletons of many bioactive compounds. To explain the stereoselectivity of the reaction, the authors proposed the mechanism depicted in Scheme 32 which begins with the coordination of the *N*-oxides and amide oxygen atoms of ligand **132** to scandium to give complex **Q**. Then, the enyne chelated to this complex to give intermediate **R**. Concomitantly, enolate **134** was generated from malonate **130** in the presence of NBu_3. Then, enolate **134** was added to the enyne from the *Si*-face in **S** to give intermediate **T**, which delivered the final product through protonation along with regenerated catalyst.



61-98%, 56-90% de, 97-99% ee

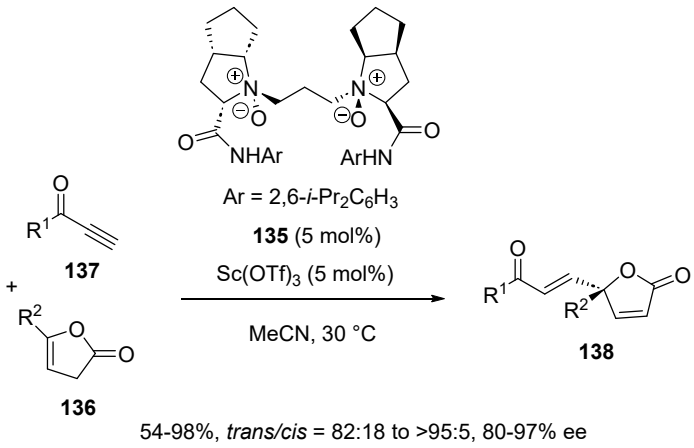
Ar^2 = Ph, *o*-ClC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-Tol, *p*-$MeOC_6H_4$
R^1 = Ph, *m*-Tol, *m*-ClC_6H_4, Me
R^2 = Et, Me, *i*-Pr, *t*-Bu
R^3 = Ph, *o*-FC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4, *o*-ClC_6H_4, *p*-ClC_6H_4, *m*-Tol, *p*-Tol, *p*-$MeOC_6H_4$, 3-thienyl, *n*-Bu

proposed mechanism:



Scheme 32. Michael addition of malonates to enynes [75].

With the aim of opening a novel route to potentially biologically active chiral γ-alkenyl butenolides, the same group investigated in 2017 another chiral *N*,*N*′-dioxide ligand **135** to induce the Michael addition of butenolides **136** to terminal alkynones **137** (Scheme 33) [76]. The process involved 5 mol% of this ligand **135** in combination with the same quantity of $Sc(OTf)_3$ as a precatalyst in acetonitrile as solvent. Carried out at 30 °C, the conjugate addition of variously γ-substituted butenolides **136** to terminal alkynones **137** led to the corresponding chiral γ-alkenyl butenolides **138** as almost single *trans*-diastereomers (*trans*/*cis* = 82:18 to >95:5) in good to quantitative yields (54–98%), and homogeneously high enantioselectivities (80–97% ee). The catalyst system was compatible with a range of aryl-, heteroaryl- and even alkyl-substituted alkynones albeit with lower yields (54–72%) in this last case. On the other hand, while comparable yields and enantioselectivities were obtained in the reaction of alkyl- and aryl-substituted butenolides, the latter generally provided lower *trans*/*cis* ratios.



R^1 = Ph, *o*-Tol, *m*-Tol, *p*-Tol, *p*-MeOC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, 3,4-MeO_2C$_6$H$_3$, 2-Naph, 3-furyl, Me, BnCH$_2$,

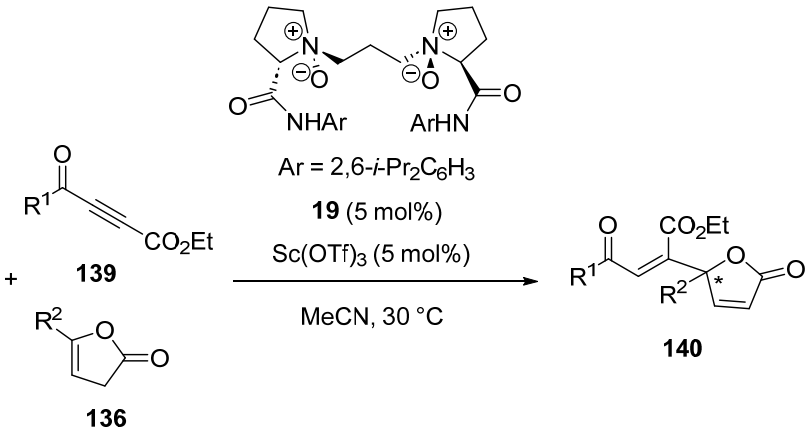
R^2 = Me, Et, *i*-Pr, *n*-C$_{10}$H$_{21}$, Ph, *p*-ClC$_6$H$_4$

Scheme 33. Michael addition of butenolides to terminal alkynones [76].

A closely related catalyst system derived from chiral *N*,*N*′-dioxide ligand **19** and $Sc(OTf)_3$ was also applied to the Michael addition of butenolides **136** to internal alkynones, such as β-ester alkynones **139** (Scheme 34) [76]. Under comparable reaction conditions, the conjugate addition afforded chiral ester-substituted γ-alkenyl butenolides **140** with high *cis*/*trans* ratios (*cis*/*trans* = 81:19 to >95:5), good to quantitative yields (69–99%) and high enantioselectivities (85–95% ee).

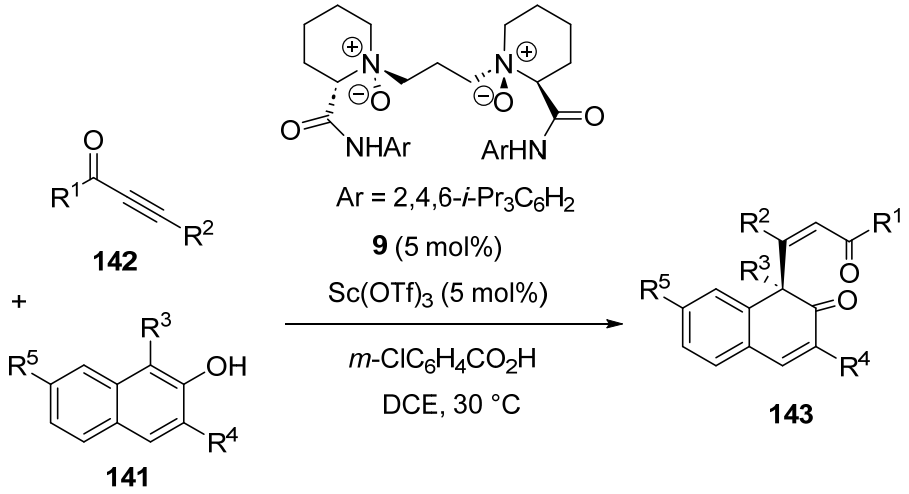
The same year, these authors investigated another type of nucleophiles, such as β-naphthols **141**, in this type of reactions [77]. Indeed, the Michael addition of the latter to either terminal (R^2 = H) or internal alkynones ($R^2 \neq$ H) **142** performed at 30 °C in DCE as solvent led, when catalyzed by a combination of 5 mol% of $Sc(OTf)_3$ with 5 mol% of chiral *N*,*N*′-dioxide ligand **9**, to the corresponding chiral β-naphthalenones **143** (Scheme 35). The process required the presence of *m*-chlorobenzoic acid as an additive. The products were obtained with excellent *cis*/*trans* selectivities (82:18 to >95:5) in all cases of substrates. The products derived from terminal alkynones were obtained in moderate to quantitative yields (33–98%) and generally excellent enantioselectivities (89–98% ee) excepted for C3-H-β-naphthols (R^4 = H), which provided lower enantioselectivities (66–71% ee) than C3-alkyl-substituted-β-naphthols ($R^4 \neq$ H). Internal alkynes (R^2 = CO_2Et) also reacted smoothly to give the corresponding chiral Michael adducts with comparable *cis*/*trans* stereoselectivities (87:13 to >95:5), combined with good yields (72–79%) and excellent enantioselectivities

(98% ee). The authors proposed the transition state depicted in Scheme 35 to explain the stereoselectivity of the reaction. Its formation began with the tetracoordination of the *N*-oxides and amide oxygen atoms of ligand **9** to scandium to form two six-membered chelate rings. Then, the alkynone and the β-naphthol coordinated to scandium. Since the *Si*-face of the β-naphthol was strongly sterically hindered by the nearby phenyl ring of the ligand, the alkynone attacked from the *Re*-face predominantly to afford the final (*R*)-configured product.



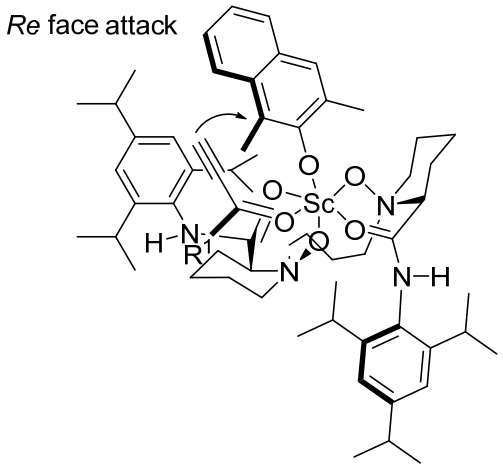
Scheme 34. Michael addition of butenolides to internal alkynones [76].

In another context, another type of chiral 1,5-dicarbonyl compounds, such as products **144**, were synthesized in 2018 by Singh et al. on the basis of an asymmetric scandium-catalyzed Mukaiyama–Michael reaction of α,β-unsaturated 2-acyl imidazoles **145** with trimethylsilyl enol ethers **146** (Scheme 36) [78]. This reaction occurred at room temperature in chloroform in the presence of 10 mol% of Sc(OTf)$_3$ as a precatalyst, 12 mol% of chiral Pybox ligand Pybox ligand **60**, and HFIP as an additive. It afforded chiral 1,5-diketones **144** in both good to high yields (78–93%) and enantioselectivities (70–84% ee). Both the two substrates exhibited aromatic substituents. In the case of the trimethylsilyl enol ether, it could bear either electron-withdrawing or electron-donating substituents on the phenyl ring of Ar^1. Moreover, an heteroaromatic trimethylsilyl enol ether (Ar^1 = 2-thienyl) also reacted smoothly with 84% yield and 81% ee. Concerning the other aromatic substrate partner, a range of electron-withdrawing substituents were tolerated on the phenyl ring of Ar^2. Furthermore, a naphthyl-substituted α,β-unsaturated 2-acyl imidazole (Ar^2 = 2-Naph) led to the corresponding product in 79% yield and 79% ee. Earlier in 2017, the same conditions were applied to develop the first diastereo- and enantioselective vinylogous Mukaiyama–Michael reaction of silyloxyfurans **147** with α,β-unsaturated 2-acyl imidazoles **148**, which allowed chiral γ-substituted- and γ,γ-disubstituted butenolides **149** to be synthesized as almost single diastereomers (>90% de) with excellent enantioselectivities (86–98% ee) and yields (88–93%), as presented in Scheme 36 [79].

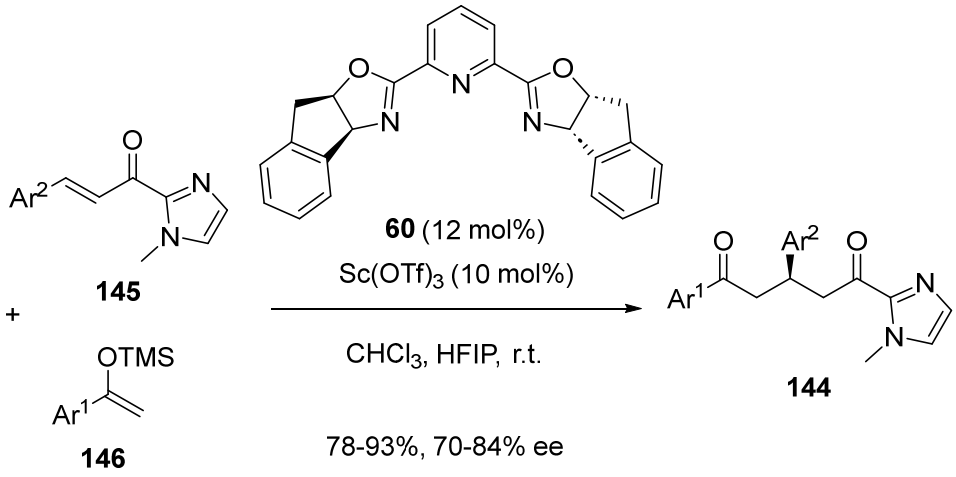


with R^2 = H:
R^1 = Ph, *o*-FC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4, *m*-BrC_6H_4, *p*-BrC_6H_4, *p*-$F_3CC_6H_4$, *p*-$MeOC_6H_4$, *o*-Tol, *p*-PhC_6H_4, *m*-$PhOC_6H_4$, 2-Naph, 2-thienyl, (*E*)-PhCH=CH, Cy
R^3 = Me, *n*-Pr, allyl
R^4 = Me, Et, Bn, allyl, H
R^5 = H, OMe
33-98%, *cis/trans* = 82:18 to >95:5, 66-98% ee
with R^2 = CO_2Et:
R^1 = Ph, *p*-BrC_6H_4, *p*-Tol
R^3 = R^4 = Me
R^5 = H
72-79%, *cis/trans* = 87:13 to >95:5, 98% ee

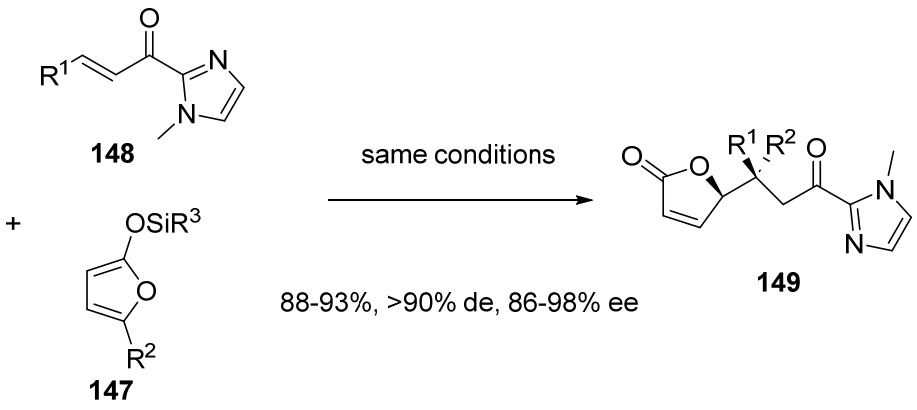
proposed transition state (with R^2 =H):



Scheme 35. Michael addition of β-naphthols to alkynones [77].



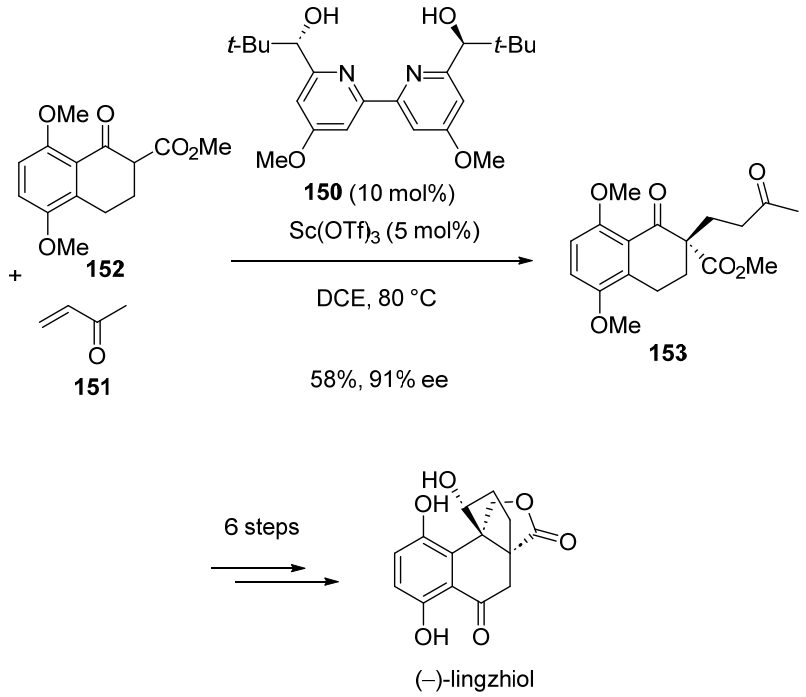
Ar^1 = Ph, *p*-BrC_6H_4, *p*-Tol, 2-thienyl
Ar^2 = Ph, *o*-BrC_6H_4, *o*-ClC_6H_4, *o*-FC_6H_4, *o*-IC_6H_4, *p*-FC_6H_4, 2-Naph, *m*-BrC_6H_4, 2,6-$Br_2C_6H_3$, 2,6-$Cl_2C_6H_3$, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$



R^1 = Ph, *o*-ClC_6H_4, *p*-ClC_6H_4, *o*-BrC_6H_4, *m*-BrC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *m*-$O_2NC_6H_4$, *p*-$O_2NC_6H_4$, *p*-Tol, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, 2-Naph, 2-thienyl, Me
R^2 = H, Me
R^3 = Me, *i*-Pr

Scheme 36. Mukaiyama–Michael additions of trimethylsilyl enol ethers/silyloxyfurans to α,β-unsaturated 2-acyl imidazoles [78,79].

Later in 2020, Schindler et al. described a novel total synthesis of tetracyclic meroterpenoid natural product (−)-lingzhiol, the key step of which dealt with an enantioselective Michael addition catalyzed by a chiral scandium complex in situ produced from $Sc(OTf)_3$ (5 mol%) and chiral bipyridine ligand **150** (10 mol%) [80]. This reaction occurred in DCE as solvent at 80 °C between methyl vinyl ketone **151** and β-ketoester **152** to deliver chiral diketone **153** in 58% yield and 91% ee. The latter was further converted through six additional steps into expected (−)-lingzhiol (Scheme 37).

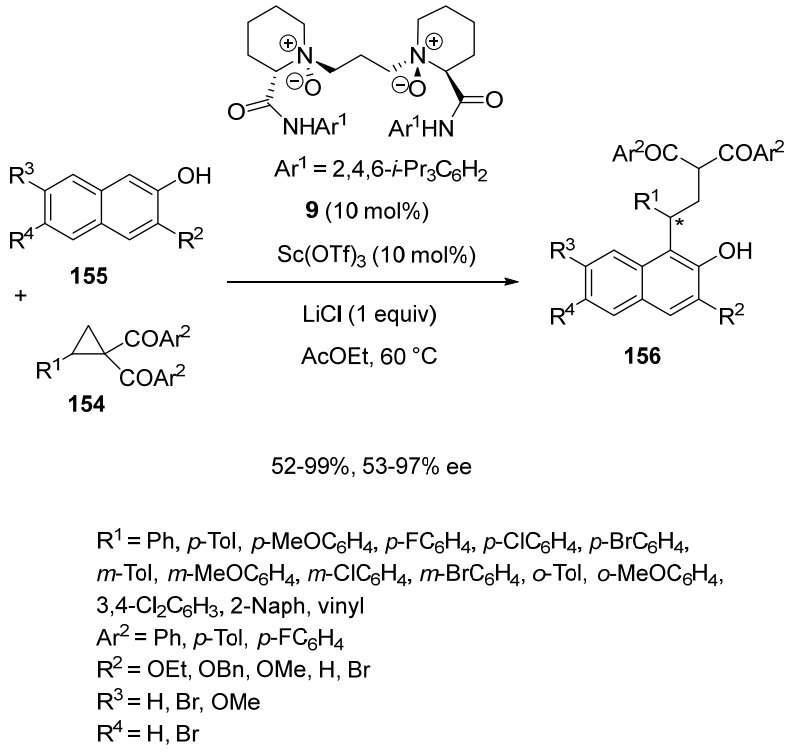


Scheme 37. Michael addition of a β-ketoester to methyl vinyl ketone and synthesis of (−)-lingzhiol [80].

5. Enantioselective Scandium-Catalyzed Ring-Opening Reactions

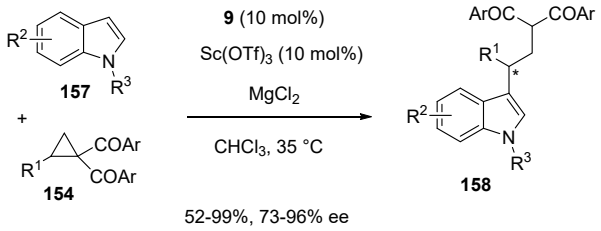
In 2018, another type of chiral scandium catalyst was employed by Feng et al. to develop the first catalytic asymmetric ring-opening reaction of cyclopropyl ketones with β-naphthols (Scheme 38) [81]. Indeed, in the presence of 10 mol% of a chiral complex in situ generated from $Sc(OTf)_3$ and chiral *N*,*N*′-dioxide ligand **9**, the ring-opening reaction of aromatic or vinyl cyclopropyl ketones **154** (R^1 = aryl, vinyl) with β-naphthols **155** performed at 60 °C in ethyl acetate as solvent led to the corresponding chiral β-naphthol derivatives **156** in both moderate to excellent yields (52–99%) and enantioselectivities (53–97% ee). The highest enantioselectivities were generally achieved in the reaction of 3-alkoxy-2-naphthols (R^2 = OMe, OBn, OEt). For example, the reaction of β-naphthols exhibiting an hydrogen atom at R^2 (R^2 = H) provided lower enantioselectivities (53–56% ee vs. 72–97% ee with R^2 = OMe, OBn, OEt). Concerning the cyclopropyl ketones, many aromatic cyclopropyl ketones with either electron-donating or electron-withdrawing substituents on the phenyl ring were tolerated. Surprisingly, the catalyst system was also found compatible with a vinyl cyclopropyl ketone (R^1 = vinyl), providing the corresponding product with 93% ee and 56% yield. Excellent results (99% yield, 95% ee) were also obtained in the reaction of a naphthyl-substituted substrate (R^1 = 2-Naph).

The same group also applied this catalyst system in the presence of $MgCl_2$ as an additive to the enantioselective ring-opening reaction of cyclopropyl ketones **154** with indoles **157** (Scheme 39) [82]. Performed at 35 °C in chloroform, the process delivered chiral 3-alkylated indoles **158** with both moderate to excellent yields (52–99%) and enantioselectivities (73–96% ee). Actually, high enantioselectivities (84–96% ee) were obtained for all (hetero)aryl-substituted cyclopropyl ketones while a vinyl-substituted cyclopropane (R^1 = vinyl) reacted with a lower ee value (73% ee). A transition state is proposed in Scheme 39, in which the four oxygen atoms of the ligand and cyclopropyl ketone **154a** (R^1 = Ar = Ph) coordinated to scandium to form an octahedral complex. Then, indole **157a** (R^2 = H, R^3, =; Me,) attacked the cyclopropyl ketone from the least sterically hindered face to deliver the (*R*)-configured product.



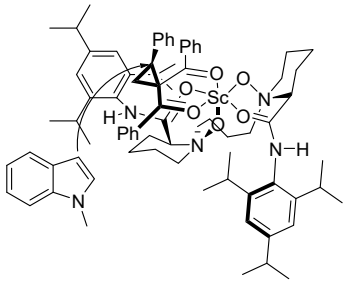
Scheme 38. Ring-opening reaction of cyclopropyl ketones with β-naphthols [81].

In 2021, Kotora et al. developed novel types of chiral bipyridine ligands to be investigated in enantioselective scandium-catalyzed ring-opening reactions of *meso*-epoxides with alcohols (Scheme 40) [83]. When only 2 mol% of optimal ligand **159** was combined with the same quantity of $Sc(OTf)_3$ in dichloromethane at 25 °C, a range of *meso*-epoxides **160** could be submitted to desymmetrization with various alcohols **161** to give the corresponding chiral 1,2-alkoxyalcohols **162** with low to high yields (27–88%) and uniformly high enantioselectivities (85–99% ee). A wide variety of substrates, spanning from alkyl, cycloalkyl, benzyl or allyl to propargyl alcohols, were compatible. The scope of the methodology could be extended to other nucleophiles, such as anilines **163**. However, their reaction with diphenyl epoxide **160a** led to the corresponding chiral 1,2-aminoalcohols **164** with both lower enantioselectivities (68–98% ee) and yields (45–80%). In the same year, Kobayashi and Kitanosono described the synthesis of novel supramolecular chiral scandium catalysts to be used in water [84]. The latter were generated through co-polymerization between a styrene-tagged chiral bipyridine tetraol monomer, divinylbenzene and styrene, providing the corresponding polystyrene-bound chiral 2,2′-bipyridine, which was further submitted to $Sc(OTf)_3$ to give the active supramolecular catalyst. When applied to the same ring-opening reactions of epoxides with either alcohols or amines as nucleophiles, the reaction performed at room temperature in water afforded chiral 1,2-alkoxyalcohols and 1,2-aminoalcohols with both moderate to excellent yields (53–97%) and ee values (70–97% ee). The catalyst could be reused up to ten times without losing its performance.

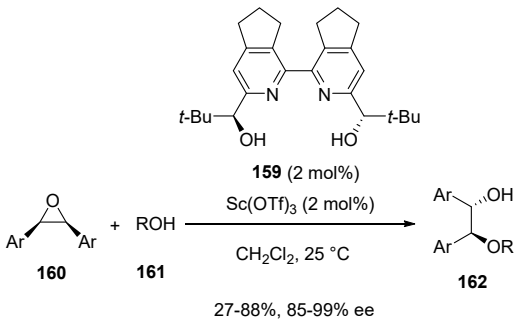


R^1 = Ph, *p*-Tol, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-Tol, vinyl,
m-$MeOC_6H_4$, *m*-ClC_6H_4, *m*-BrC_6H_4, *o*-Tol, 2-Naph, 1-Naph
R^2 = H, 2-Me, 4-Me, 4-Br, 5-Me, 5-OMe, 5-Cl, 5-F, 6-Me, 6-Cl, 7-Me, 7-Cl
R^3 = H, Me, TBS
Ar = Ph, *p*-Tol, *p*-$MeOC_6H_4$, *p*-FC_6H_4

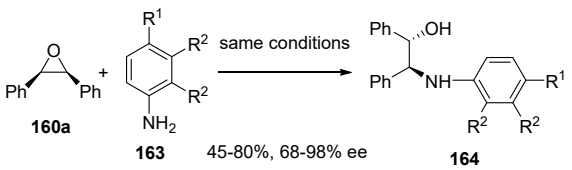
proposed transition state (with R^1 = Ar = Ph, R^2 = H, R^3 = Me):



Scheme 39. Ring-opening reaction of cyclopropyl ketones with indoles [82].



R = Bn, *p*-$MeOC_6H_4CH_2$, *m*-$MeOC_6H_4CH_2$, *o*-$MeOC_6H_4CH_2$,
p-$TolCH_2$, *p*-$BrC_6H_4CH_2$, *p*-$MeO_2CC_6H_4CH_2$, *p*-$O_2NC_6H_4CH_2$,
p-$F_3CC_6H_4CH_2$, 2-$NaphCH_2$, 2-anthracenylCH_2, 2-furylCH_2,
2-thienylCH_2, 2-ferrocenylCH_2, Me, Cy, allyl, HC≡CCH_2
Ar = Ph, *p*-ClC_6H_4

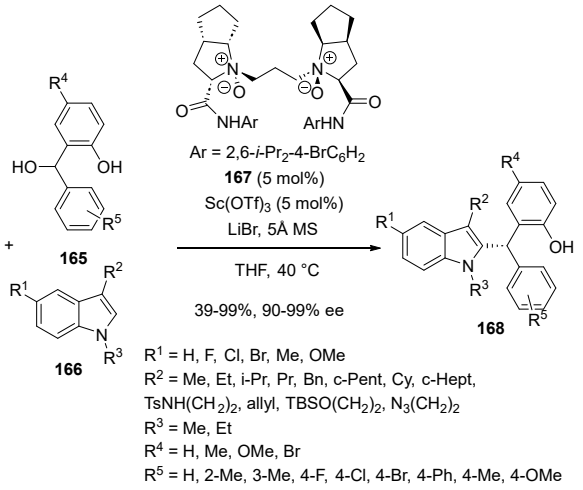


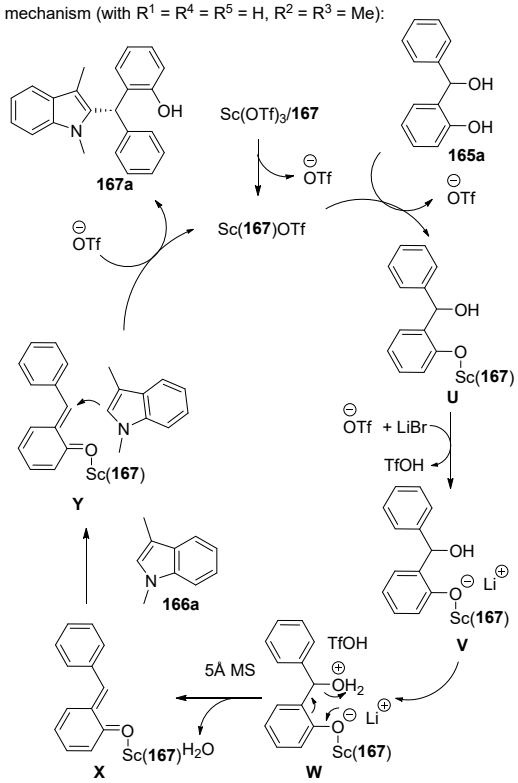
R^1 = OMe, H, Cl
R^2 = H
R^2,R^2 = $(CH=CH)_2$

Scheme 40. Ring-opening reactions of *meso*-epoxides with alcohols/anilines [83].

6. Enantioselective Scandium-Catalyzed Friedel-Crafts Reactions

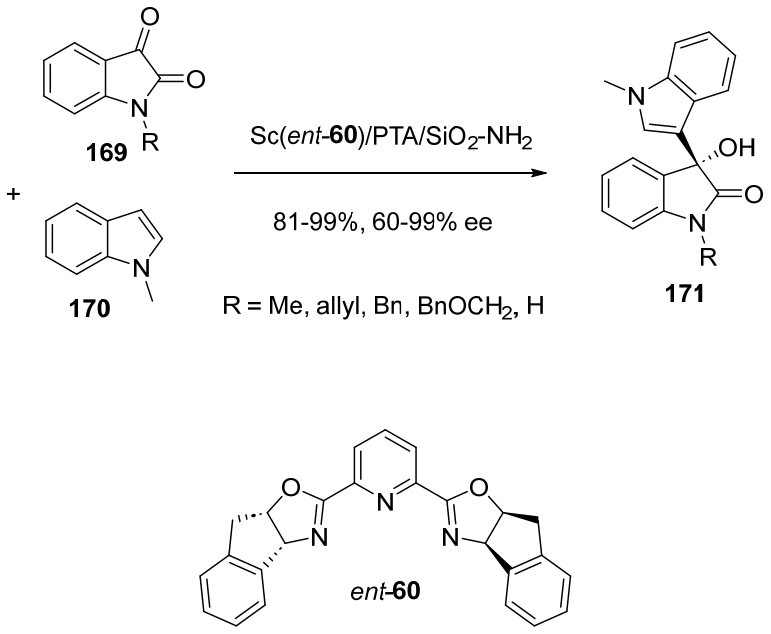
The first asymmetric scandium-catalyzed Friedel–Crafts reaction of *ortho*-hydroxybenzyl alcohols **165** with C3-substituted indoles **166** was developed by Feng and Liu, in 2016 (Scheme 41) [85]. It required the use of 5 mol% of a catalyst system composed of $Sc(OTf)_3$ and chiral *N*,*N*′-dioxide ligand **167**. Under these conditions, chiral diarylindol-2-ylmethanes **168** were produced at 40 °C with 39–99% yields and 90–99% ee. The process evolved through the mechanism detailed in Scheme 41 based on the formation of *ortho*-quinone methides. The scandium center coordinated to one oxygen atom of the *ortho*-hydroxybenzyl alcohol to give intermediate **U**. The latter was further converted into intermediate **V**, resulting from the capture of the proton of the OH group by TfO^-. The reprotonation of the hydroxyl group in the presence of TfOH in **V** generated intermediate **W**. A subsequent dehydration occurred in the presence of 5Å MS to give intermediate **X**. Finally, the indole attacked intermediate **X** from its less-hindered *Si*-face in **Y** to afford the final product.





Scheme 41. Friedel-Crafts reaction of C3-substituted indoles with *ortho*-hydroxybenzyl alcohols [85].

Later in 2021, Kobayashi and Saito developed a novel chiral heterogeneous scandium catalyst to be used under continuous-flow conditions in asymmetric Friedel–Crafts reactions between isatins **169** and indole **170** (Scheme 42) [86]. This catalyst was synthesized by simply mixing a chiral scandium complex in situ generated from $Sc(OTf)_3$ and chiral Pybox ligand *ent*-**60** with heteropoly acid(PTA)-anchored amine-functionalized SiO_2 as a support. Using this heterogeneous catalyst under continuous-flow conditions, differently substituted isatins **169** underwent Friedel–Crafts alkylation with indole **170** to afford the corresponding chiral functionalized products **171** with high yields (81–99%) and moderate to excellent enantioselectivities (60–99% ee). This study constituted the first example of highly efficient continuous-flow heterogeneous chiral scandium catalysis.



Scheme 42. Friedel-Crafts reaction of an indole with isatins [86].

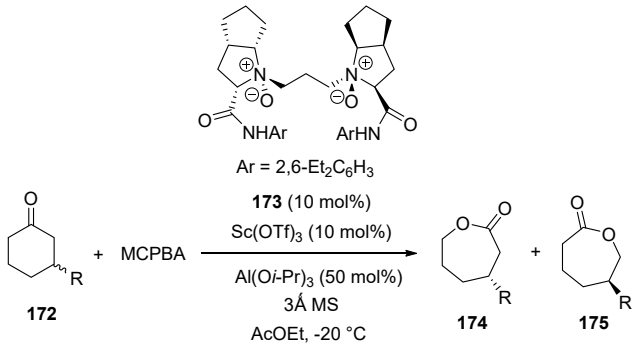
7. Enantioselective Scandium-Catalyzed Ring-Expansion Reactions

In 2019, Liu and Feng investigated the asymmetric Baeyer-Villiger oxidation of 3-substituted cyclohexanones **172** under catalysis with a chiral scandium complex derived from 10 mol% of $Sc(OTf)_3$ and 10 mol% of chiral *N*,*N*′-dioxide ligand **173** (Scheme 43) [87]. The process was performed at −20 °C in ethyl acetate as solvent in the presence of Al(O*i*-Pr)$_3$ as an additive. Evolving through parallel kinetic resolution, 3-substituted cyclohexanones **172** were oxidized with MCPBA to give both the two seven-membered lactones **174** and **175** in high yields (84–98%) and enantioselectivities (80–87% ee for **174**, 91–97% ee for **175**). Aryl-substituted cyclohexanones provided higher enantioselectivities (92–98% ee) than alkyl-substituted ones (84% ee).

Related reaction conditions, albeit based on the use of chiral *N*,*N*′-dioxide ligand **135**, were also applied to the desymmetrization of *meso*-3,5-disubstituted cyclohexanones **176** through Baeyer-Villiger oxidation (Scheme 44) [87]. The oxidation of 3,5-diaryl- and 3,5-dimethylsubstituted cyclohexanones **176** with MCPBA led to the corresponding chiral seven-membered lactones **177** in quantitative yields (97–99%) and excellent enantioselectivities (91–97% ee).

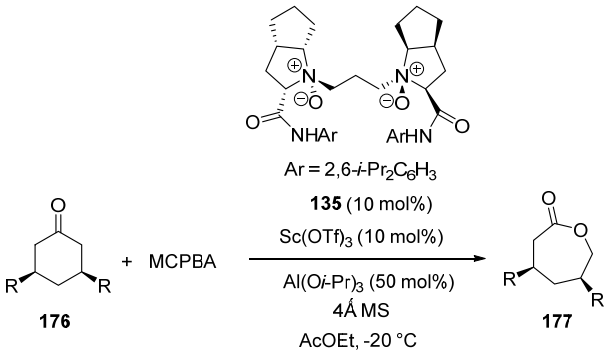
In spite of the fact that fluorinated molecules play a major role in medicinal chemistry, the synthesis of chiral cycloalkanones with a stereocenter bearing a CF_3 group remained undeveloped for a long time. To fill this gasp, Wang et al. disclosed in 2022 an asymmetric homologation reaction of γ-mono-substituted cyclohexanones **178** by reaction with CF_3CHN_2 as the trifluoromethylation agent (Scheme 45) [88]. The process occurred at −20 °C in toluene in the presence of a chiral scandium catalyst in situ generated from 5

or 10 mol% of $Sc(OTf)_3$ and 6 or 12 mol% of chiral bisoxazoline ligand **179**. It allowed desired chiral α-trifluoromethyl cycloheptanones **180** containing a $C(sp^3)$-CF_3 bond to be synthesized with good to high yields (58–88%) and generally excellent enantio- (54–95% ee) and diastereoselectivities (42 ≥ 90% de). Actually, homogeneously high diastereo- (>90% de) and enantioselectivities (83–95% ee) were obtained for a range of variously substituted cyclohexanones excepted in the case of that bearing an OTs substituent on the γ-position which led to the corresponding product with only 42% de and 54% ee. With the aim of extending the scope of this methodology, the authors investigated the use of γ,γ-disubstituted silacyclohexanones **181** as substrates (Scheme 45). The reaction of silacyclohexanones **181** bearing a methyl and aryl group on silicon centers with CF_3CHN_2 afforded the corresponding chiral α-trifluoromethyl silacycloheptanones **182** in moderate to high yields (53–87%), variable diastereoselectivities (0–75% de) and moderate to excellent enantioselectivities (73–94% ee).



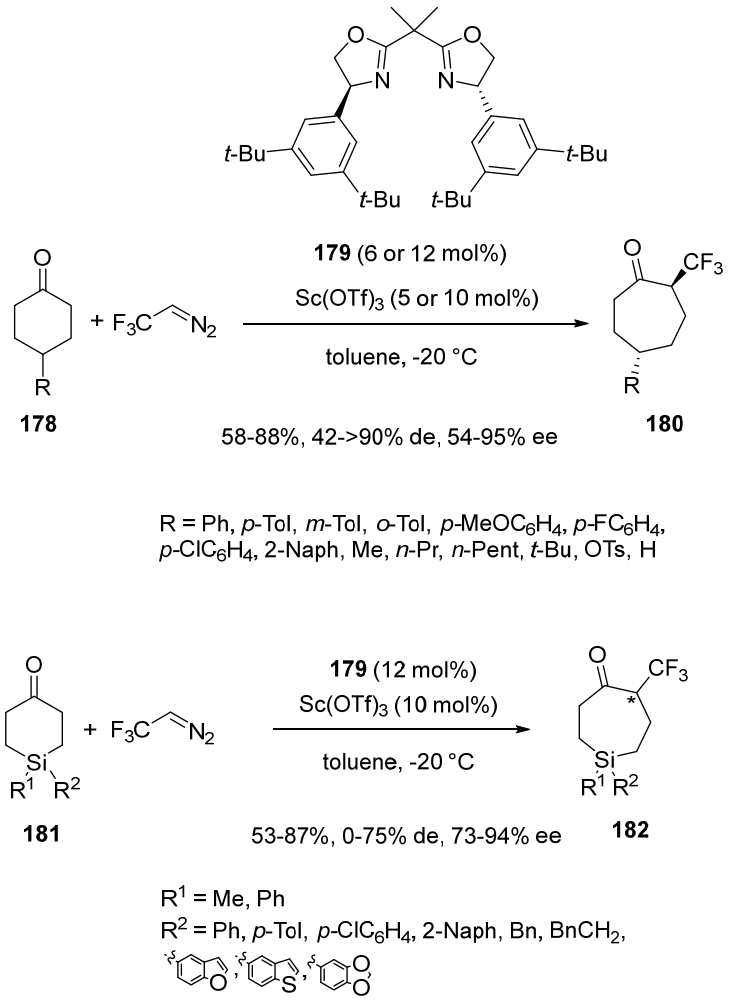
R = Ph: 98%, **174**:**175** = 55:45, ee (**174**) = 81%, ee (**175**) = 97%
R = *o*-Tol: 94%, **174**:**175** = 56:44, ee (**174**) = 80%, ee (**175**) = 93%
R = *m*-Tol: 97%, **174**:**175** = 53:47, ee (**174**) = 82%, ee (**175**) = 91%
R = *p*-Tol: 97%, **174**:**175** = 55:45, ee (**174**) = 80%, ee (**175**) = 96%
R = *p*-*n*-BuC_6H_4: 98%, **174**:**175** = 55:45, ee (**174**) = 83%, ee (**175**) = 95%
R = *p*-$MeOC_6H_4$: 92%, **174**:**175** = 52:48, ee (**174**) = 83%, ee (**175**) = 97%
R = 2-Naph: 94%, **174**:**175** = 55:45, ee (**174**) = 81%, ee (**175**) = 96%
R = *n*-Bu: 84%, **174**:**175** = 62:38, ee (**174**) = 87%, ee (**175**) = 97%

Scheme 43. Baeyer-Villiger reaction of 3-substituted cyclohexanones through parallel kinetic resolution [87].



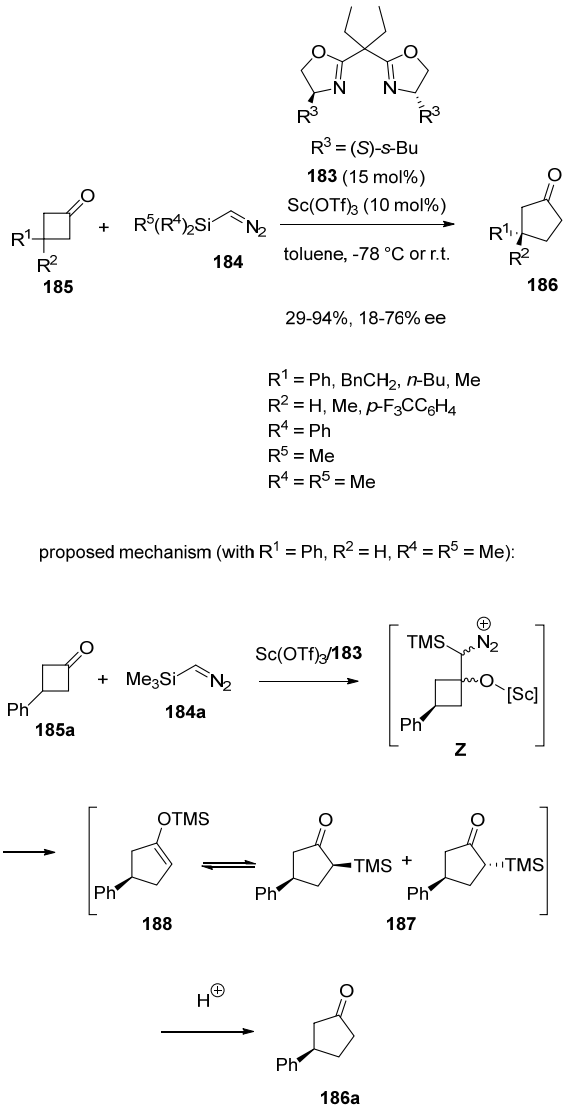
R = Ph: 97%, 96% ee
R = *m*-Tol: 98%, 97% ee
R = *p*-$MeOC_6H_4$: 96%, 93% ee
R = *p*-FC_6H_4: 98%, 94% ee
R = *m*-ClC_6H_4: 99%, 93% ee
R = *p*-ClC_6H_4: 98%, 94% ee
R = *p*-BrC_6H_4: 99%, 94% ee
R = Me: 99%, 91% ee

Scheme 44. Desymmetrization of *meso*-3,5-disubstituted cyclohexanones through Baeyer-Villiger reaction [87].



Scheme 45. Homologation reactions of γ-mono-substituted cyclohexanones/γ,γ-disubstituted silacyclohexanones with CF_3CHN_2 [88].

Cyclopentanones represent important structural motifs in a wide number of natural products, such as prostaglandins and steroids, making their synthesis challenging. In 2023, Wahl and Tenberge described a novel access to chiral β-substituted cyclopentanones based on an enantioselective scandium-catalyzed methylene insertion into the corresponding prochiral cyclobutanones (Scheme 46) [89]. This desymmetrization was catalyzed in toluene by a chiral catalyst in situ, formed from the reaction between 15 mol% of $Sc(OTf)_3$ and 10 mol% of chiral bisoxazoline ligand **183** bearing an CEt_2 moiety. Commercially available trimethylsilyl as well as other silyl diazomethanes **184** acted as one-carbon synthon for insertion into cyclobutanones **185** in the presence of the catalyst to afford the corresponding chiral β-substituted cyclopentanones **186** with moderate to high yields (29–94%) and low to good enantioselectivities (18–76% ee). It was found that alkyl-substituted cyclobutanones (R^1 = $BnCH_2$, *n*-Bu) furnished the corresponding cyclopentanones in slightly lower yields (71–80% vs. 94%) but higher ee values (76% vs. 70% ee) than phenyl-substituted substrate (R^1 = Ph). In the mechanism depicted in Scheme 46, the silyl diazomethane attacks the cyclobutanone activated by the catalyst to give intermediate **Z** as an isomeric mixture. The latter subsequently undergoes rearrangement to provide α-silyl ketones **187**, as a mixture of diastereomers, which rapidly converge to the corresponding silyl enol ether **188** under strongly Lewis acidic conditions. A final hydrolysis delivers the product.

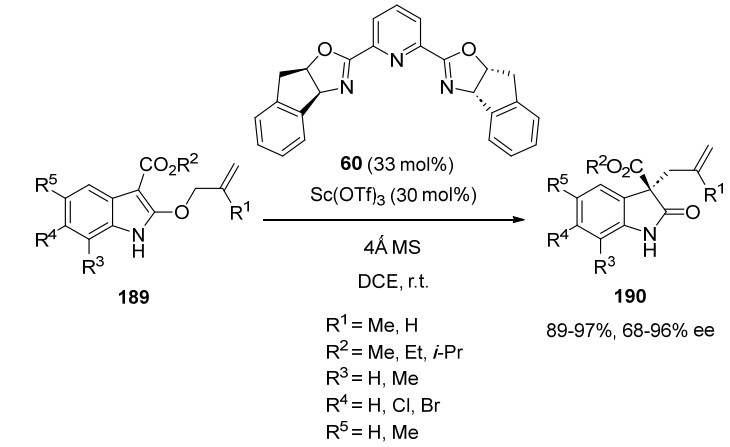


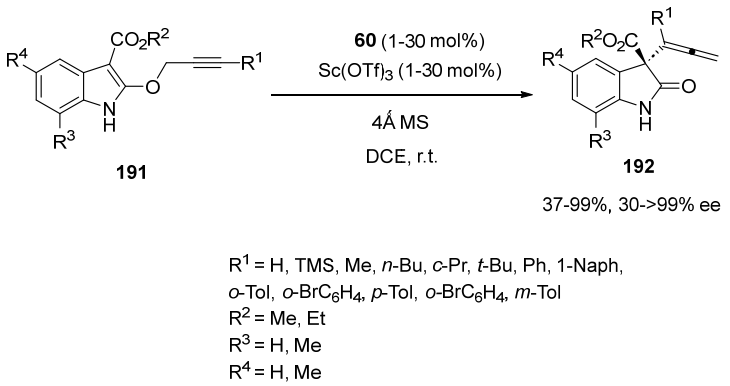
Scheme 46. Ring-expansion of cyclobutanones with silyl diazomethanes [89].

8. Enantioselective Scandium-Catalyzed Rearrangement Reactions

In 2017, You et al. employed a chiral Pybox-derived scandium catalyst to promote enantioselective Claisen rearrangement reactions of 2-allyloxyindoles with 2-propargyloxyindoles [90]. These processes allowed the formation of potentially bioactive chiral oxindoles exhibiting a quaternary stereocenter at the C3-position to be achieved (Scheme 47). When submitted to a chiral scandium catalyst derived from 30 mol% of $Sc(OTf)_3$ and 33 mol % of chiral Pybox ligand **60**, a range of 2-allyloxyindoles **189** underwent at room temperature in DCE as solvent an asymmetric Claisen rearrangement reaction to give the corresponding chiral 3-allyloxindoles **190**. These products were obtained in homogeneous high yields (89–97%) and good to high enantioselectivities (68–96% ee). In all cases of variously substituted 2-allyloxyindoles bearing a methyl group at the allyl C2′ position (R^1 = Me), enantioselectivities of >90% ee were obtained while the presence of an hydrogen atom at this position (R^1 = H) resulted in decreased enantioselectivities (68–74% ee). The same catalyst system was applied to the Claisen rearrangement reaction of 2-propargyloxyindoles **191** (Scheme 47). When using 1–30 mol% of the same scandium complex, the process led to the formation of the corresponding chiral 3-allenyloxindoles **192** in both moderate to excellent yields (37–99%) and enantioselectivities (30 $\geq$ 99% ee). Generally, high enantioselectivities (79 $\geq$ 99% ee) were obtained in the reaction of a range of alkyl- and aryl-substituted alkynes

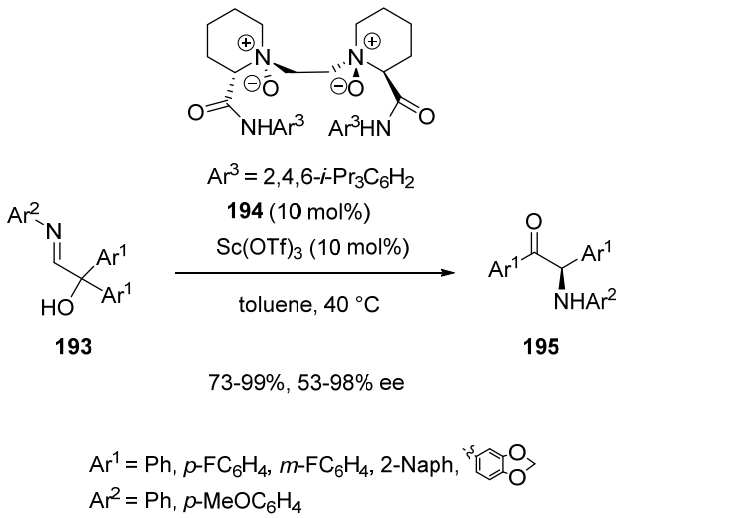
(R^1 = alkyl, aryl) while H- and TMS-substituted alkynes provided lower enantioselectivities (30–72% ee).





Scheme 47. Claisen rearrangement reactions of 2-allyloxyindoles and 2-propargyloxyindoles [90].

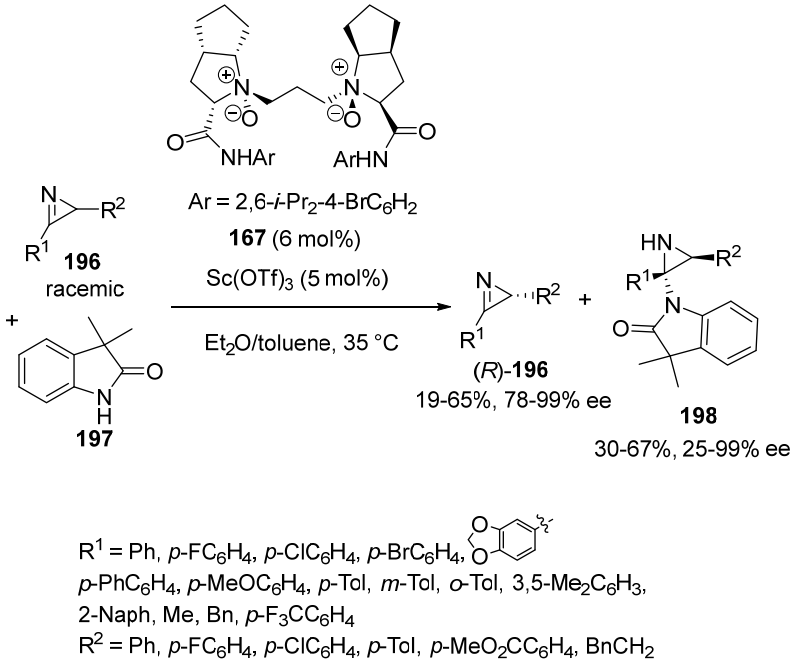
Later in 2020, Zhou and Feng described an asymmetric acyloin rearrangement of acyclic α-hydroxy aldimines **193** promoted by a combination of 10 mol% of $Sc(OTf)_3$ with 10 mol% of chiral *N*,*N*′-dioxide ligand **194** (Scheme 48) [91]. The process performed at 40 °C in toluene resulted in the formation of chiral α-amino ketones **195** in good to quantitative yields (73–99%) and moderate to excellent ee values (53–98% ee).



Scheme 48. Acyloin rearrangement of acyclic α-hydroxy aldimines [91].

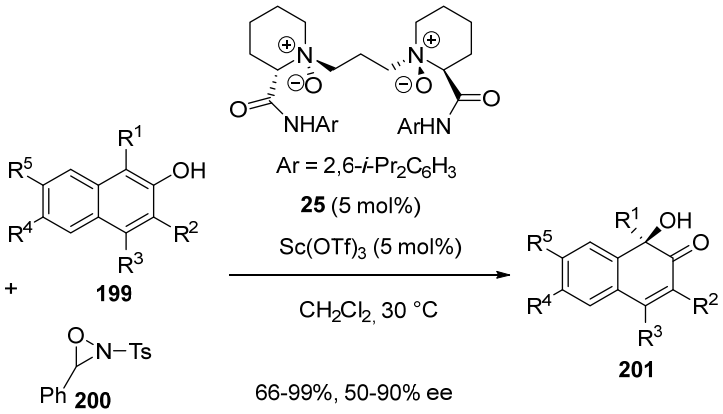
9. Enantioselective Scandium-Catalyzed Miscellaneous Reactions

In 2016, Feng and Liu reported the first kinetic resolution of 2*H*-azirines **196** evolving through asymmetric imine amidation with oxindole **197**, which was catalyzed by a chiral scandium complex [92]. The latter was in situ produced from 5 mol% of $Sc(OTf)_3$ and 6 mol% of chiral *N*,*N*′-dioxide ligand **167** in a mixture of toluene and diethyl ether as solvent (Scheme 49). Performed at 35 °C, the reaction led to unreacted 2*H*-azirines (*R*)-**196** with low to moderate yields (19–65%) and high ee values (78–99% ee) along with protecting-group free aziridines **196** with moderate yields (30–67%) and variable enantioselectivities (25–99% ee). Selectivity factors of up to 790 were achieved in some cases. It must be noted that this is the first example which involved an oxindole reacting with its N1 atom instead of a C3 atom.



Scheme 49. Kinetic resolution of 2*H*-azirines through imine amidation [92].

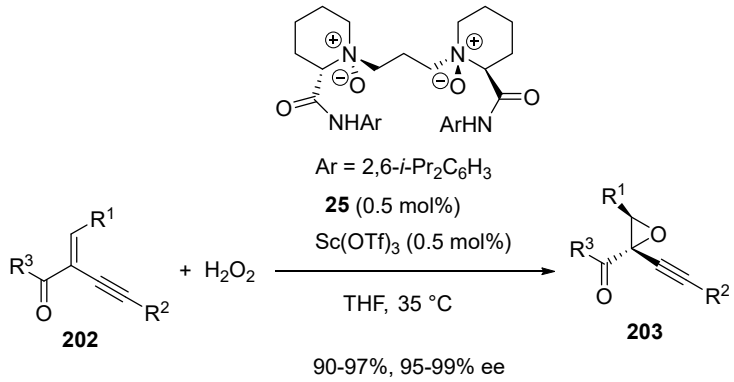
In 2017, the same authors reported the use of a chiral scandium catalyst derived from a *N*,*N*′-dioxide ligand in a novel synthesis of chiral substituted *ortho*-quinols, which are known to be widely present in natural and biologically active product structures [93]. The methodology dealt with an asymmetric hydroxylative dearomatization of variously substituted β-naphthols **199** with oxaziridine **200** as oxidant performed at 30 °C in dichloromethane as solvent (Scheme 50). Only 5 mol% of $Sc(OTf)_3$ and chiral *N*,*N*′-dioxide ligand **25** were sufficient to promote this reaction, which delivered chiral substituted *ortho*-quinols **201** in good to quantitative yields (66–99%) and moderate to high enantioselectivities (50–90% ee). It was found that β-naphthols could be variously substituted, providing the corresponding products with uniformly high enantioselectivities of >84% ee. However, the presence of a substituent at the *ortho*-position of the hydroxyl group (R^2 = Me instead of H) resulted in a decreased enantioselectivity (67% ee). The influence of the steric hindrance of substrates was also shown by changing R^1 from a methyl group to an ethyl group since the enantioselectivity of the reaction decreased to 50% ee in this latter case.



Scheme 50. Hydroxylative dearomatization of β-naphthols with an oxaziridine [93].

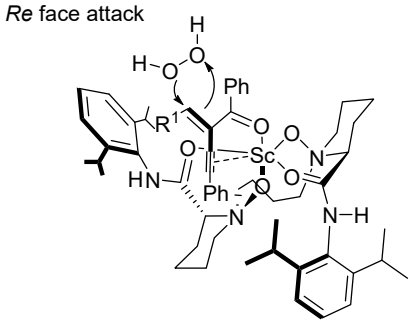
An enantioselective epoxidation of electron-deficient enynes **202** with aqueous hydrogen peroxide as an oxidant was also described the same year by Lin and Feng by using an extremely low catalyst loading (0.5 mol%) of a chiral scandium complex [94]. The latter was in situ prepared from Sc(OTf)$_3$ and chiral *N*,*N*′-dioxide ligand **25** in THF at 35 °C (Scheme 51). Under these conditions, a variety of trisubstituted alkynyl chiral epoxides **203** were synthesized in both excellent yields (90–97%) and enantioselectivities (95–99% ee). The authors proposed the transition state depicted in Scheme 51 in which the enyne coordinated to the scandium center through a bidentate fashion. Since the *Si*-face of enyne **202a** (R^2 = R^3 = Ph) was shielded by the nearby isopropylphenyl group of the ligand, hydrogen peroxide attacked the β-carbon atom of the Michael acceptor enyne preferentially from the *Re*-face.

These authors also employed 10 mol% of chiral *N*,*N*′-dioxide ligand **135** in combination with the same quantity of Sc(NTf$_2$)$_3$ as precatalyst to promote enantioselective bromoamination of α,β-unsaturated ketones **204** with NBS as both bromine and amide source (Scheme 52) [95]. Carrying out the reaction at 35 °C in dichloromethane as solvent, the corresponding chiral bromoamination products **205** were obtained with good yields (64–92%) and variable enantioselectivities (11–97% ee). Actually, uniformly excellent ee values (86–97% ee) were achieved in the reaction of chalcones while alkyl-substituted α,β-unsaturated ketones (R^1 = *n*-Bu, CO$_2$*t*-Bu) led to the corresponding products with much lower enantioselectivities (11–30% ee).

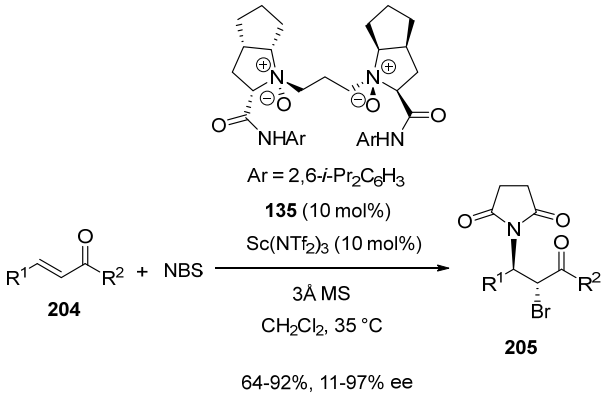


R^1 = Ph, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-Tol, Pr
R^2 = Ph, *o*-FC$_6$H$_4$, *m*-FC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-Tol, *m*-Tol, *p*-*t*-BuC$_6$H$_4$, TMS, *c*-Pr
R^3 = Ph, Me, *n*-Bu, *p*-*t*-BuC$_6$H$_4$, *m*-ClC$_6$H$_4$

proposed transition state (with R^1 = R^3 = Ph):



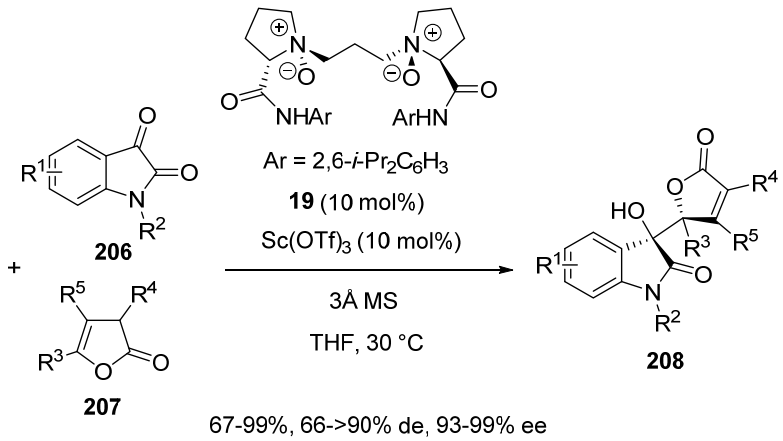
Scheme 51. Epoxidation of electron-deficient enynes with H_2O_2 [94].



R^1 = Ph, *p*-Tol, *m*-Tol, *o*-Tol, *p*-FC$_6$H$_4$, *m*-ClC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-NcC$_6$H$_4$, 2-Naph, 2-thienyl, *n*-Bu, CO$_2$*t*-Bu
R^2 = Ph, *o*-MeOC$_6$H$_4$, *m*-MeOC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *m*-Tol, *p*-Tol, *p*-FC$_6$H$_4$, *m*-ClC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-NCC$_6$H$_4$, *p*-O$_2$NC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 2-Naph, (*E*)-PhCH=CH

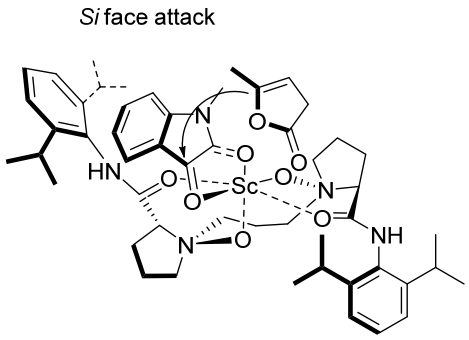
Scheme 52. Bromoamination of α,β-unsaturated ketones with NBS [95].

In order to synthesize biologically interesting γ,γ-disubstituted butenolides, the same group applied in 2017 related chiral ligand **19** at 10 mol% of catalyst loading in combination with 10 mol% of $Sc(OTf)_3$ to promote at 30 °C in THF a direct asymmetric vinylogous aldol reaction of isatins **206** with β,γ-unsaturated butenolides **207** (Scheme 53) [96]. This reaction allowed the synthesis of a wide variety of chiral δ-hydroxybutenolides **208** bearing congested adjacent tetrasubstituted stereocenters to be achieved with both good to excellent yields (67–99%) and diastereoselectivities (66 ≥ 90% de) combined with generally excellent enantioselectivities (93–99% ee). A transition state is proposed in Scheme 53 in which the *N*-oxides and amide oxygens of the ligand are tetracoordinated to scandium to form two six-membered chelate rings. Meanwhile, the two carbonyl groups of isatin **206a** (R^1 = H, R^2 = Me) coordinate to the scandium center so that β,γ-unsaturated butenolide **207a** (R^3 = Me, R^4 = R^5 = H) attacks the *Si*-face of isatin **206a** to afford the final (3S,2′S)-configured product.



R^1 = H, 6-F, 6-Cl, 6-Br, 6-Me, 7-F, 7-Cl, 7-Br, 7-CF_3, 7-Me
R^2 = Me, H, Bn, Et, *i*-Pr, $BnCH_2$
R^3 = Me, Et, *n*-Dec
R^4 = Me, H, Et
R^5 = H
R^3,R^5 = $(CH_2)_4$

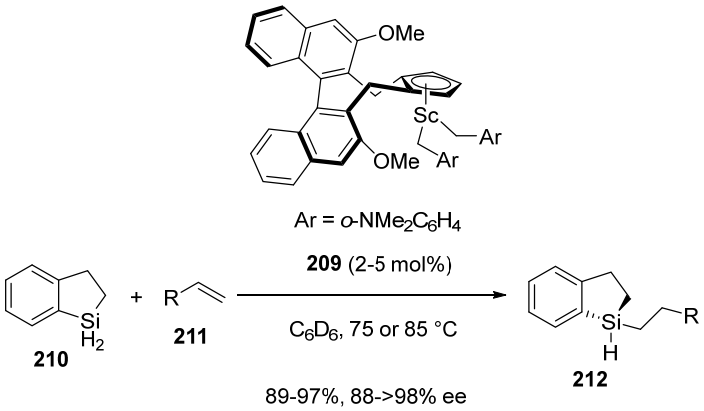
proposed transition state (with R^1 = R^4 = R^5 = H, R^2 = R^3 = Me):



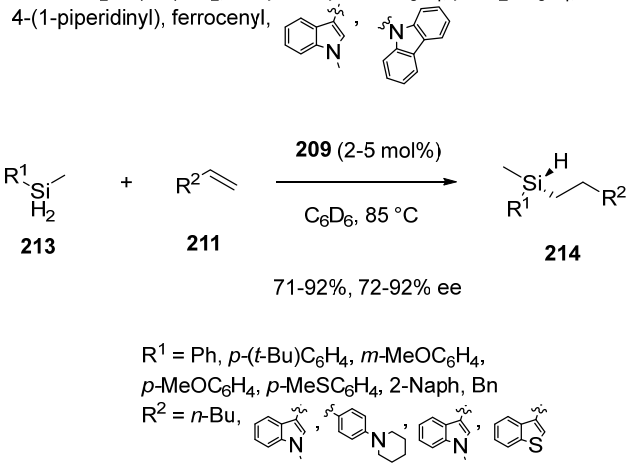
Scheme 53. Vinylogous aldol reaction of isatins with β,γ-unsaturated butenolides [96].

So far, little attention has been paid to the asymmetric synthesis of silicon-stereogenic silanes. In 2018, Hou et al. reported a rare methodology to prepare these products based on the first enantioselective intermolecular hydrosilylation of alkenes with dihydrosilanes catalyzed by chiral preformed half-sandwich scandium complex **209** [97]. Performed in

C_6D_6 at 75 or 85 °C in the presence of only 2–5 mol% of this chiral catalyst **209**, the reaction of cyclic dihydrosilane **210** with monosubstituted alkenes **211** afforded the corresponding chiral tertiary silanes **212** in both uniformly high yields (89–97%) and enantioselectivities (88 ≥ 98% ee). The process tolerated a wide range of differently functionalized alkyl-substituted alkenes as well as (hetero)aryl-substituted ones. The conditions were also applicable to other dihydrosilanes, such as acyclic ones **213**, which underwent the hydrosilylation with alkenes **211** to give the corresponding chiral acyclic silanes **214** in good to high yields (71–92%) and enantioselectivities (72–92% ee), as illustrated in Scheme 54.



R = *n*-Pent, *i*-Pr, *t*-Bu, Ph, *p*-BrC_6H_4, 2,6-$Cl_2C_6H_3$, Cy, $PhOCH_2$, $TBDPSO(CH_2)_2$, $PhSCH_2$, $TMSCH_2$, $BnN(Me)CH_2$, TMS, $CH_2=C(Me)CH_2$, Ph, *p*-Tol, *p*-$MeOC_6H_4$, *p*-$Ph_2PC_6H_4$, 4-(1-piperidinyl), ferrocenyl,

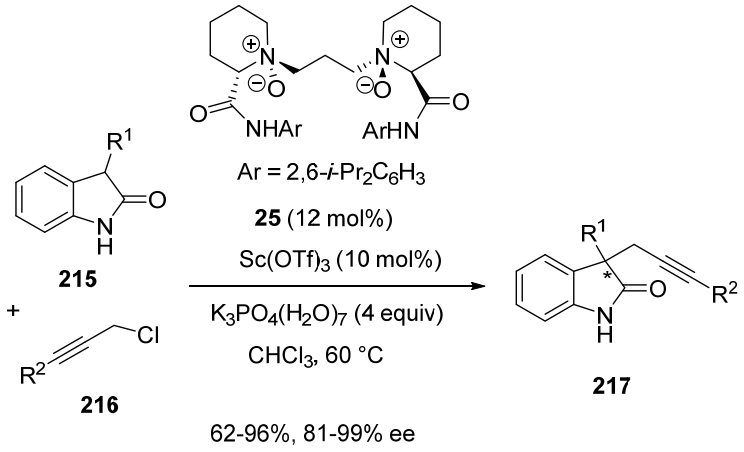


R^1 = Ph, *p*-(*t*-Bu)C_6H_4, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *p*-$MeSC_6H_4$, 2-Naph, Bn
R^2 = *n*-Bu,

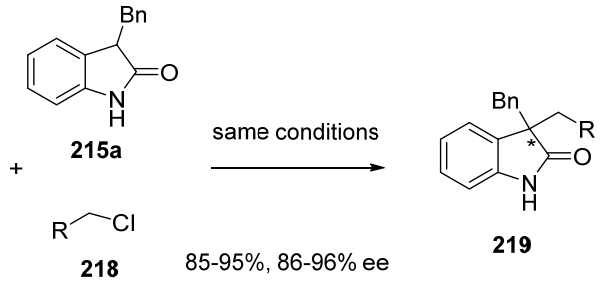
Scheme 54. Hydrosilylations of alkenes [97].

In another area, Cao and Feng reported in 2018 the use of a chiral scandium catalyst derived from a *N*,*N*′-dioxide chiral ligand **25** in asymmetric α-propargylation of *N*-unprotected 3-substituted oxindoles (Scheme 55) [98]. The reaction of a range of *N*-unprotected 3-substituted oxindoles **215** with propargyl chloride derivatives **216** performed at 60 °C in chloroform in the presence of 10 mol% of $Sc(OTf)_3$ and 12 mol% of chiral ligand **25** led to chiral 3,3-dialkylsubstituted oxindoles **217** in good to excellent yields (62–96%) and uniformly high enantioselectivities (81–99% ee). Remarkable enantioselectivities (>95% ee) were achieved for a wide range of variously 3-alkyl substituted oxindoles, while slightly lower enantioselectivities (81–85% ee) were obtained in the reaction of 3-methyl-2-oxindole (R^1 = Me) and 3-(2-furylmethyl)-2-oxindole (R^1 = 2-furylmethyl). Similarly, a broad substrate scope was found for the propargylated chloride partner since enantioselectivities of 91–98% ee were obtained in the reaction of a range of aryl-substituted alkynes (R^2 = aryl) including 1-naphthyl-substituted ones. Furthermore, even a terminal

alkyne (R^2 = H) was compatible, giving the corresponding oxindole in 77% yield and 96% ee. The scope of the process could be extended to other electrophiles, such as allyl and benzoyl chlorides. Indeed, under the same reaction conditions, 3-benzyl-2-oxindole **215a** reacted with many allyl and benzoyl chlorides **218** to afford the corresponding chiral 3,3-dialkylsubstituted oxindoles **219** in both homogeneously high yields (85–95%) and enantioselectivities (86–96% ee).



R^1 = Bn, *p*-$FC_6H_4CH_2$, *p*-$ClC_6H_4CH_2$, *p*-$BrC_6H_4CH_2$, *m*-$BrC_6H_4CH_2$, *o*-$BrC_6H_4CH_2$, *p*-$O_2NC_6H_4CH_2$, *p*-$F_3CC_6H_4CH_2$, *p*-$NCC_6H_4CH_2$, 2,4-$Cl_2C_6H_3CH_2$, *p*-$MeOC_6H_4CH_2$, *p*-TolCH$_2$, *m*-TolCH$_2$, *o*-TolCH$_2$, (1-Naph)CH$_2$, (2-thienyl)CH$_2$, (2-furyl)CH$_2$, Me, *t*-BuCH$_2$
R^2 = *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$F_3CC_6H_4$, 3,4-$Cl_2C_6H_3$, *p*-Tol, *m*-Tol, *o*-Tol, 1-Naph, H

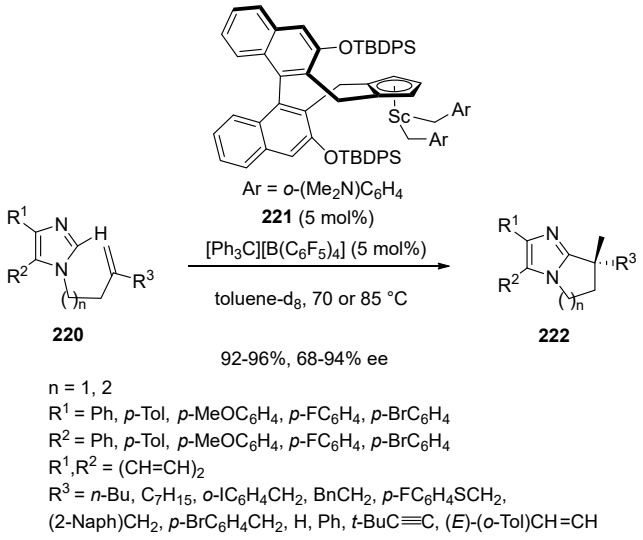


R = (*E*)-PhCH=CH, (*E*)-(*p*-FC_6H_4)CH=CH, (*E*)-(*p*-ClC_6H_4)CH=CH, (*E*)-(*o*-Tol)CH=CH, $(Me)_2C$=CH, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-$O_2NC_6H_4$, *p*-Tol

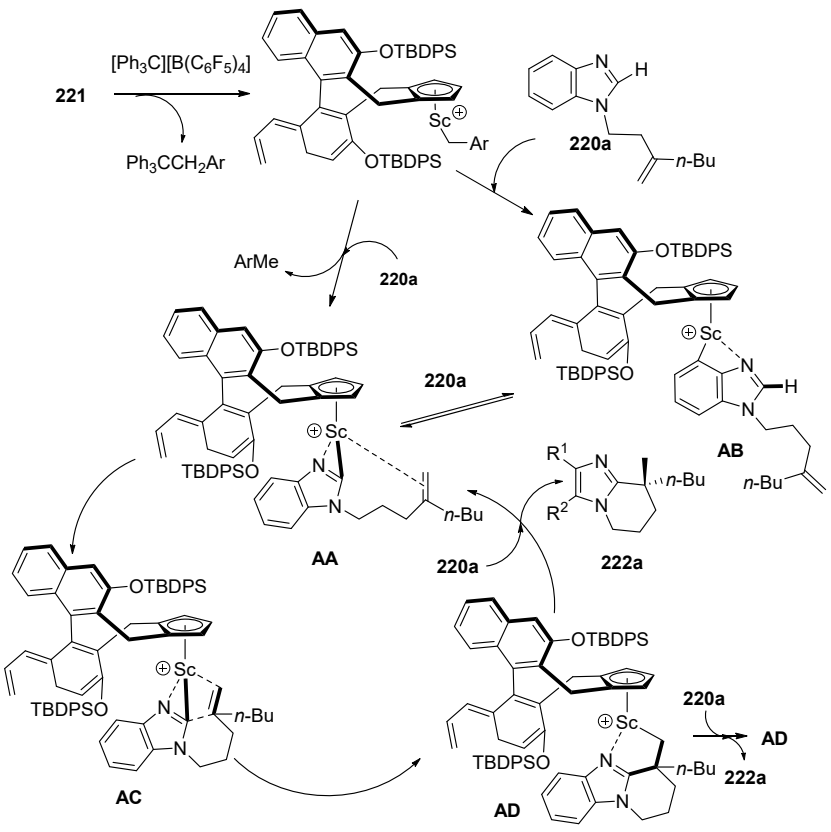
Scheme 55. Alkylations of *N*-unprotected 3-substituted oxindoles with propargyl, allyl and benzyl chlorides [98].

In 2020, Hou et al. disclosed the first *exo*-selective C–H alkylation of imidazoles **220** with 1,1-disubstituted alkenes [99]. This intramolecular reaction was promoted at 70 or 85 °C by only 5 mol% of half-sandwich scandium catalyst **221** in toluene-D_8 as solvent (Scheme 56). It allowed the formation of the corresponding chiral bicyclic imidazole derivatives **222** exhibiting a quaternary stereocenter to be achieved in quantitative yields (92–96%) and good to high enantioselectivities (68–94% ee). The process showed a wide scope since various 1,1-disubstituted (functionalized) aliphatic alkenes, styrenes, enynes and dienes

were all compatible. The authors proposed the mechanism depicted in Scheme 56, which begins with deprotonative C−H activation by the Sc−CH_2Ar species which can occur at either the C2 or C3 position of substrate **220a** (R^1, R^2 = (CH = CH)$_2$, R^3 = *n*-Bu, n = 2), affording intermediates **AA** or **AB**, respectively. The latter can be interconverted by a similar reaction with another molecule of **219a**. The intramolecular insertion (cyclization) of the C = C unit into the Sc−imidazolyl bond in intermediate **AA** via intermediate **AC** leads to intermediate **AD**. The hydrogen abstraction of **220a** by the Sc−C σ-bond in intermediate **AD** resulted in the formation of product **222a** along with regenerated **AA** or **AB**.

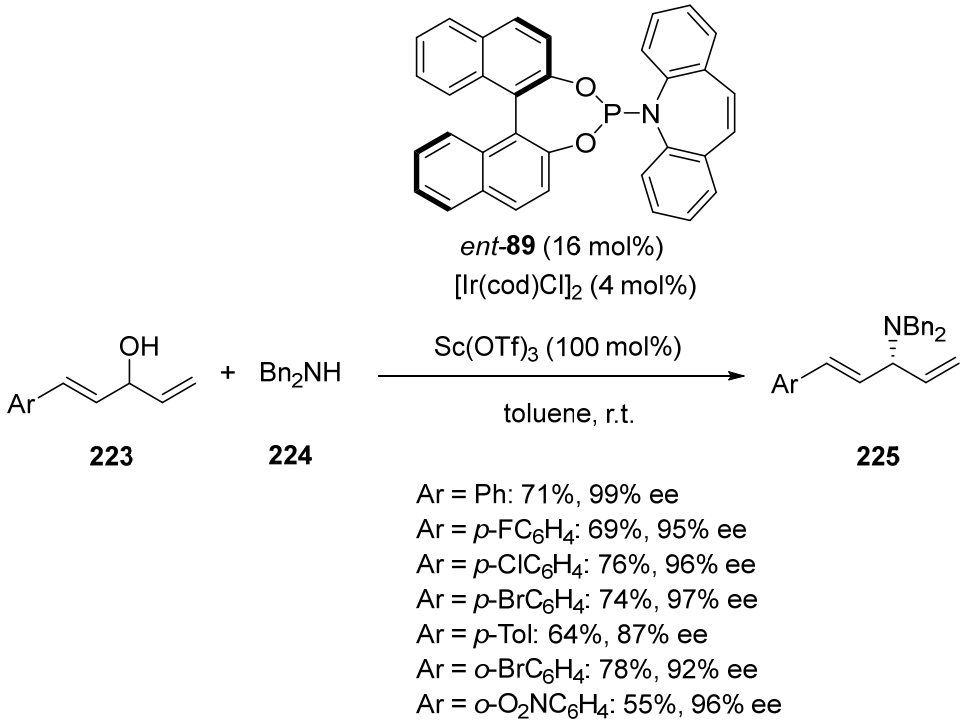


proposed mechanism (with R^1,R^2 = (CH=CH)$_2$, R^3 = *n*-Bu, n = 2):



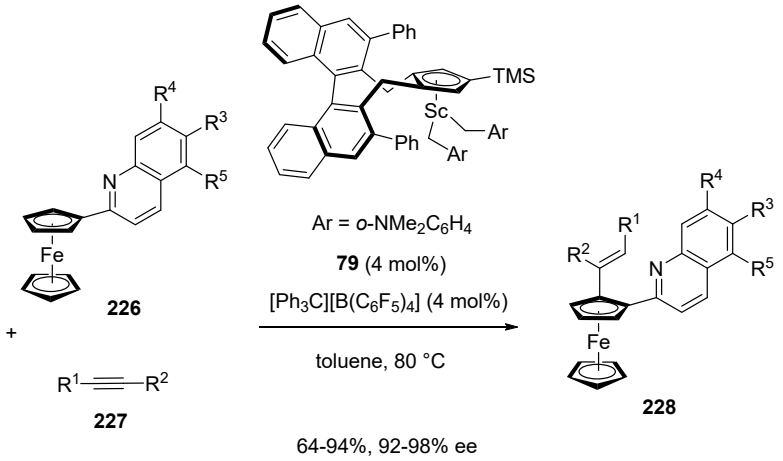
Scheme 56. Intramolecular C–H alkylation of imidazoles with 1,1-disubstituted alkenes [99].

Earlier in 2019, Sun et al. described the first regiocontrolled allylic amination of unactivated dienyl allylic alcohols with secondary amines [100]. The process involved two metal catalysts, such as $Sc(OTf)_3$ and $[Ir(cod)Cl]_2$, at100 and 4 mol%, respectively, of catalyst loadings, in the presence of 16 mol% of chiral phosphoramidite ligand *ent*-**89** (Scheme 57). A series of dienyl allylic alcohols **223** reacted at room temperature in toluene with dibenzylamine **224** to regio- and enantioselectively lead to the corresponding C3-amination products **225** in moderate to good yields (55–78%) and uniformly high enantioselectivities (87–99% ee).



Scheme 57. Allylic amination of dienyl allylic alcohols with dibenzylamine [100].

In 2021, Hou and Luo described the synthesis of novel chiral half-sandwich scandium catalyst **79** which was further applied to promote the first enantioselective alkenylation of quinoline-substituted ferrocenes **226** with alkynes **227** (Scheme 58) [101]. The reaction was performed at 80 °C in the presence of 4 mol% of this novel catalyst in toluene as the solvent, resulting in the formation of a new family of planar-chiral ferrocenes **228** bearing an alkene functionality with remarkable enantioselectivities (92–98% ee) and moderate to high yields (64–94%). The catalyst system tolerated a wide variety of internal alkynes bearing various aryl and alkyl substituents. The carbon−carbon bond formation took place regioselectively at the carbon atom of the alkyne bond unit bearing the alkyl substituent, affording the corresponding alkenylated ferrocene derivatives in both high yields and enantioselectivities. A wide range of alkynes was tolerated, including sterically demanding diphenylacetylene ($R^1 = R^2 =$ Ph), which led to the corresponding almost enantiopure product (96% ee) in 72% yield. Concerning the quinoline-substituted ferrocene partner, it was found that the presence of different substituents (Me, Br, F) at the quinoline moiety had no impact on the enantioselectivity of the reaction. Even a fused polycyclic quinoline unit smoothly underwent the reaction (73% yield, 92% ee).



R^1 = Ph, *p*-*t*-BuC_6H_4, *m*-Tol, *p*-Tol, *p*-PhC_6H_4, 2-Naph, *p*-PhOC_6H_4, *p*-TMSC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, 3,5-$Cl_2C_6H_3$, *p*-MeOC_6H_4, 2-thienyl, *p*-(CH_2=CH)C_6H_4, PhS, *i*-PrS
R^2 = Me, *n*-Bu, *n*-Pr, Ph
R^3 = H, Me, Br
R^4 = H, F, Me
R^3,R^4 = $(CH=CH)_2$
R^5 = H, Me

Scheme 58. Alkenylation of ferrocenes [101].

10. Conclusions

This review updates the progress achieved in the application of asymmetric scandium catalysis to enantioselective organic reactions since the beginning of 2016. In this period, the use of chiral scandium catalysts has allowed many types of transformations to be developed with generally very high enantioselectivities, spanning from modern domino reactions to more simple cycloadditions, Michael additions, and miscellaneous reactions. In most cases, the catalysts employed were derived from *N*,*N*′-dioxide ligands albeit several other types of ligands, including Pybox ligands, phosphoramidites, or phosphine oxides among others, also gave successful results. The review demonstrates that these novel methodologies have allowed the synthesis of a wide diversity of chiral complex and functionalized products, such as benzimidazoles via domino ring-opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with aryl 1,2-diamines with up to 97% ee; 4-hydroxy-dihydrocoumarins via domino ring-opening/nucleophilic addition/cyclization reaction of cyclobutenones with 2-hydroxyacetophenones with up to 93% ee; spirocyclohexene pyrazolones via domino Michael/aldol reaction of α-arylidene pyrazolinones with β,γ-unsaturated α-ketoesters with up to 94% ee; aryl 5-bromo-1,3-oxazinan-2-ones via domino bromination/amination reaction of (*E*)-cinnamyl tosylcarbamates with up to 99% ee; 3-substituted chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides via domino imine formation/intramolecular amination reaction of 2-aminobenzenesulfonamide with aldehydes with up to 93% ee; tetrahydroindolizines via three-component reaction of alkenyloxindoles, diazoacetates and pyridines with up to 99% ee; silylated cyclopentene-spirooxindoles via [3 + 2] cycloaddition of alkylideneoxindoles with allenylsilanes with up to 98% ee; 1,5-diazabicyclo [3.3.0]octanes via [3 + 2] cycloaddition of diaziridines with chalcones with up to 90% ee; tetrasubstituted functionalized cyclopropanes via [2 + 1] cycloaddition of α-substituted vinyl ketones with α-substituted α-diazoesters with up to 99% ee; γ-alkenyl butenolides via Michael addition of butenolides to alkynones with up to 97% ee; β-naphthalenones via Michael addition of β-naphthols to alkynones with up to 98% ee; 2-acyl imidazoles via Mukaiyama–Michael addition of trimethylsilyl enol ethers to α,β-unsaturated 2-acyl imidazoles with up to 84% ee; *ortho*-quinols via hydroxylative dearomatization of β-naphthols with an oxaziridine with up to 90% ee; β-naphthol derivatives via ring-opening reaction of cyclopropyl ketones

with β-naphthols with up to 97% ee; 3-allyloxindoles and 3-allenyloxindoles via Claisen rearrangements of 2-allyloxyindoles and 2-propargyloxyindoles with up to 96 and 99% ee, respectively; cyclic or acyclic tertiary silanes via hydrosilylations of alkenes with up to 98% ee; 3,3-dialkylsubstituted oxindoles via alkylations of *N*-unprotected 3-substituted oxindoles with propargyl, allyl and benzyl chlorides with up to 99% ee; bicyclic imidazoles via intramolecular C–H alkylation of imidazoles with 1,1-disubstituted alkenes with up to 94% ee; dienyl allylic amines via allylic amination of dienyl allylic alcohols with secondary amines with up to 99% ee; seven-membered lactones via Baeyer-Villiger reaction of 3-substituted cyclohexanones with up to 97% ee or Baeyer-Villiger reaction of *meso*-3,5-disubstituted cyclohexanones with up to 97% ee. The uniformly high enantioselectivities described in these simple processes, combined with their diversity, demonstrate that scandium catalysts constitute a great promise for the future of greener catalysis.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Noyori, R. *Asymmetric Catalysts in Organic Synthesis*; Wiley-VCH: New York, NY, USA, 1994.
2. Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1998; Volumes I and II. [CrossRef]
3. Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, NY, USA, 2000. [CrossRef]
4. Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2002; Volume 2, pp. 1689–1705. [CrossRef]
5. Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004. [CrossRef]
6. Tietze, L.F.; Hiriyakkanavar, I.; Bell, H.P. Enantioselective Palladium-Catalyzed Transformations. *Chem. Rev.* **2004**, *104*, 3453–3516. [CrossRef] [PubMed]
7. Ramon, D.J.; Yus, M. In the Arena of Enantioselective Synthesis, Titanium Complexes Wear the Laurel Wreath. *Chem. Rev.* **2006**, *106*, 2126–2208. [CrossRef] [PubMed]
8. Pellissier, H.; Clavier, H. Enantioselective Cobalt-Catalyzed Transformations. *Chem. Rev.* **2014**, *114*, 2775–2823. [CrossRef]
9. Pellissier, H. Recent developments in enantioselective scandium-catalyzed transformations. *Coord. Chem. Rev.* **2016**, *313*, 1–37. [CrossRef]
10. Pellissier, H. Enantioselective Silver-Catalyzed Transformations. *Chem. Rev.* **2016**, *116*, 14868–14917. [CrossRef] [PubMed]
11. Pellissier, H. Recent developments in enantioselective lanthanide-catalyzed transformations. *Coord. Chem. Rev.* **2017**, *336*, 96–151. [CrossRef]
12. Pellissier, H. Enantioselective Magnesium-Catalyzed Transformations. *Org. Biomol. Chem.* **2017**, *15*, 4750–4782. [CrossRef]
13. Pellissier, H. Recent developments in enantioselective cobalt-catalyzed transformations. *Coord. Chem. Rev.* **2018**, *360*, 122–168. [CrossRef]
14. Pellissier, H. Recent Developments in Enantioselective Iron-Catalyzed Transformations. *Coord. Chem. Rev.* **2019**, *386*, 1–31. [CrossRef]
15. Pellissier, H. Recent Developments in Enantioselective Vanadium-Catalyzed Transformations. *Coord. Chem. Rev.* **2020**, *418*, 213395. [CrossRef]
16. Pellissier, H. Recent developments in enantioselective zinc-catalyzed transformations. *Coord. Chem. Rev.* **2021**, *439*, 213926. [CrossRef]
17. Pellissier, H. Recent developments in enantioselective titanium-catalyzed transformations. *Coord. Chem. Rev.* **2022**, *463*, 214537. [CrossRef]
18. Kobayashi, S.; Araki, M.; Hachiya, I. A Chiral Scandium Catalyst for Enantioselective Diels-Alder Reactions. *J. Org. Chem.* **1994**, *59*, 3758–3759. [CrossRef]
19. Yao, Y.; Nie, K. Homogeneous Catalysis. In *The Rare Earth Elements*; Wiley-VCH: Weinheim, Germany, 2012; pp. 459–474.
20. Mori, Y.; Kobayashi, S. Organic Synthesis. In *The Rare Earth Elements*; Wiley-VCH: Weinheim, Germany, 2012; pp. 437–457.
21. Feng, X.; Liu, X. *Scandium: Compounds, Productions, and Applications*; Nova Science Publishers: New York, NY, USA, 2011; pp. 1–47.
22. Roesky, P.W. *Molecular Catalysis of Rare Earth Elements*; Springer: Heidelberg, Germany, 2010.
23. Brennan, J.G.; Sella, A. *Organometallic Chemistry*; Royal Society of Chemistry: Cambridge, UK, 2010; Volume 36, p. 121.
24. Ogawa, C.; Gu, Y.; Boudou, M.; Kobayashi, S. *Acid Catalysis in Modern Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2008; p. 589.
25. Zeimentz, P.M.; Arndt, S.; Elvidge, B.R.; Okuda, J. Cationic Organometallic Complexes of Scandium, Yttrium, and the Lanthanoids. *Chem. Rev.* **2006**, *106*, 2404–2433. [CrossRef] [PubMed]
26. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W.W.-L. Rare-earth metal triflates in organic synthesis. *Chem. Rev.* **2002**, *102*, 2227–2302. [CrossRef] [PubMed]

27. Kobayashi, S. Scandium Triflate in Organic Synthesis. *Eur. J. Org. Chem.* **1999**, *1999*, 15–27. [CrossRef]
28. Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019**, *119*, 2192–2452. [CrossRef]
29. Loup, J.; Dhawa, U.; Pesciaioli, F.; Wencel-Delord, J.; Ackermann, L. Enantioselective C-H Activation with Earth-Abundant 3d Transition Metals. *Angew. Chem. Int. Ed.* **2019**, *58*, 12803–12818. [CrossRef]
30. Tietze, L.F.; Beifuss, U. Sequential Transformations in Organic Chemistry: A Synthetic Strategy with a Future. *Angew. Chem. Int. Ed.* **1993**, *32*, 131–163. [CrossRef]
31. Tietze, L.F. Domino Reactions in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 115–136. [CrossRef]
32. Tietze, L.F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.
33. Pellissier, H. Asymmetric domino reactions. Part B: Reactions based on the use of chiral catalysts and biocatalysts. *Tetrahedron* **2006**, *62*, 2143–2173. [CrossRef]
34. Clavier, H.; Pellissier, H. Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions. *Adv. Synth. Catal.* **2012**, *354*, 3347–3403. [CrossRef]
35. Pellissier, H. Stereocontrolled Domino Reactions. *Chem. Rev.* **2013**, *113*, 442–524. [CrossRef]
36. Tietze, L.F. *Domino Reactions—Concepts for Efficient Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2014.
37. Zhu, J.; Wang, Q.; Wang, M. *Multicomponent Reactions in Organic Synthesis*; Wiley: Weinheim, Germany, 2014.
38. Pellissier, H. Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions. *Adv. Synth. Catal.* **2016**, *358*, 2194–2259. [CrossRef]
39. Snyder, S.A. *Science of Synthesis. Applications of Domino Transformations in Organic Synthesis*; Thieme Verlag: Stuttgart, Germany, 2016; Volumes 1 and 2.
40. Pellissier, H. Recent developments in enantioselective metal-catalyzed domino reactions. *Adv. Synth. Catal.* **2019**, *361*, 1733–1755. [CrossRef]
41. Pellissier, H. The Use of Domino Reactions for the Synthesis of Chiral Rings. *Synthesis* **2020**, *52*, 3837–3854. [CrossRef]
42. Pellissier, H. Asymmetric Zinc Catalysis in Green One-Pot Processes. *Curr. Org. Chem.* **2021**, *25*, 857–875. [CrossRef]
43. Pellissier, H. Recent Developments in Enantioselective Domino Reactions. Part A: Noble Metal Catalysts. *Adv. Synth. Catal.* **2023**, *365*, 620–681. [CrossRef]
44. Pellissier, H. Recent Developments in Enantioselective Domino Reactions. *Part B First Row Metal Catalysts. Adv. Synth. Catal.* **2023**, *365*, 768–819. [CrossRef]
45. Xia, Y.; Lin, L.; Chang, F.; Liao, Y.; Liu, X.; Feng, X. Asymmetric Ring Opening/Cyclization/Retro-Mannich Reaction of Cyclopropyl Ketones with Aryl 1,2-Diamines for the Synthesis of Benzimidazole Derivatives. *Angew. Chem. Int. Ed.* **2016**, *55*, 12228–12232. [CrossRef]
46. Fu, X.; Lin, L.; Xia, Y.; Zhou, P.; Liu, X.; Feng, X. Catalytic asymmetric [3 + 3] annulation of cyclopropanes with mercaptoacetaldehyde. *Org. Biomol. Chem.* **2016**, *14*, 5914–5917. [CrossRef]
47. Mondal, K.; Pan, S.C. Lewis Acid Catalyzed [3+3] Annulation of Donor–Acceptor Cyclopropanes with γ-Hydroxyenones: Access to Highly Functionalized Tetrahydropyrans. *Eur. J. Org. Chem.* **2017**, *2017*, 534–537. [CrossRef]
48. Chang, F.; Shen, B.; Wang, S.; Lin, L.; Feng, X. Lewis acid catalysed asymmetric cascade reaction of cyclopropyl ketones: Concise synthesis of pyrrolobenzothiazoles. *Chem. Commun.* **2020**, *56*, 13429–13432. [CrossRef]
49. Zhang, H.; Luo, Y.; Li, D.; Yao, Q.; Dong, S.; Liu, X.; Feng, X. Enantioselective Synthesis of 4-Hydroxy-dihydrocoumarins via Catalytic Ring Opening/Cycloaddition of Cyclobutenones. *Org. Lett.* **2019**, *21*, 2388–2392. [CrossRef]
50. Xu, J.; Hu, L.; Hu, H.; Ge, S.; Liu, X.; Feng, X. Enantioselective Vinylogous Michael–Aldol Reaction to Synthesize Spirocyclohexene Pyrazolones in Aqueous Media. *Org. Lett.* **2019**, *21*, 1632–1636. [CrossRef] [PubMed]
51. He, C.; Tang, X.; He, X.; Zhou, Y.; Liu, X.; Feng, X. Regio- and enantioselective conjugate addition of *β*-nitro *α*,*β*-unsaturated carbonyls to construct 3-alkenyl disubstituted oxindoles. *Chin. Chem. Lett.* **2023**, *34*, 107487. [CrossRef]
52. Hao, X.; Lin, L.; Tan, F.; Ge, S.; Liu, X.; Feng, X. Asymmetric synthesis of chromans via the Friedel–Crafts alkylation–hemiketalization catalysed by an *N*,*N*′-dioxide scandium(iii) complex. *Org. Chem. Front.* **2017**, *4*, 1647–1650. [CrossRef]
53. Xiao, W.; Mo, Y.; Guo, J.; Su, Z.; Dong, S.; Feng, X. Catalytic enantioselective synthesis of macrodiolides and their application in chiral recognition. *Chem. Sci.* **2021**, *12*, 2940–2947. [CrossRef] [PubMed]
54. Pan, H.; Huang, H.; Liu, W.; Tian, H.; Shi, Y. Phosphine Oxide–Sc(OTf)3 Catalyzed Highly Regio- and Enantioselective Bromoaminocyclization of (*E*)-Cinnamyl Tosylcarbamates. An Approach to a Class of Synthetically Versatile Functionalized Molecules. *Org. Lett.* **2016**, *18*, 896–899. [CrossRef]
55. Dai, L.; Liu, W.; Zhou, Y.; Zeng, Z.; Hu, X.; Cao, W.; Feng, X. Catalytic Asymmetric Halogenation/Semipinacol Rearrangement of 3-Hydroxyl-3-vinyl Oxindoles: A Stereodivergent Kinetic Resolution Process. *Angew. Chem. Int. Ed.* **2021**, *60*, 26599–26603. [CrossRef]
56. Zhang, D.; Lin, L.; Yang, J.; Liu, X.; Feng, X. Asymmetric Synthesis of Tetrahydroindolizines by Bimetallic Relay Catalyzed Cycloaddition of Pyridinium Ylides. *Angew. Chem. Int. Ed.* **2018**, *57*, 12323–12327. [CrossRef] [PubMed]
57. Li, X.; Jiang, M.; Zhan, T.; Cao, W.; Feng, X. Catalytic Asymmetric Three-component Hydroacyloxylation/1,4-Conjugate Addition of Ynamides. *Chem. Asian J.* **2020**, *15*, 1953–1956. [CrossRef] [PubMed]
58. Du, P.; Zhou, H.; Sui, Y.; Liu, Q.; Zou, K. Asymmetric synthesis of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1- dioxides catalyzed by scandium(III)-*inda*-Pybox. *Tetrahedron* **2016**, *72*, 1573–1578. [CrossRef]

59. Aillerie, A.; Rodriguez-Ruiz, V.; Carlino, R.; Bourdreux, F.; Guillot, R.; Bezzenine-Lafollée, S.; Gil, R.; Prim, D.; Hannedouche, J. Asymmetric Assisted Tandem Catalysis: Hydroamination followed by Asymmetric Friedel–Crafts Reaction from a Single Chiral *N,N,N′,N′*-Tetradentate Pyridylmethylamine-Based Ligand. *ChemCatChem* **2016**, *8*, 2455–2460. [CrossRef]
60. Zhu, S.; Chen, C.; Duan, K.; Sun, Y.-M.; Li, S.-S.; Liu, Q.; Xiao, J. Cascade [1,5]-Hydride Transfer/Cyclization for Synthesis of [3,4]-Fused Oxindoles. *J. Org. Chem.* **2019**, *84*, 8440–8448. [CrossRef] [PubMed]
61. Tan, F.; Pu, M.; He, J.; Li, J.; Yang, J.; Dong, S.; Liu, X.; Wu, Y.-D.; Feng, X. Catalytic Asymmetric Homologation of Ketones with α-Alkyl α-Diazo Esters. *J. Am. Chem. Soc.* **2021**, *143*, 2394–2402. [CrossRef]
62. Dong, S.; Liu, X.; Feng, X. Asymmetric Catalytic Rearrangements with α-Diazocarbonyl Compounds. *Acc. Chem. Res.* **2022**, *55*, 415–428. [CrossRef]
63. Lou, S.-J.; Luo, G.; Yamaguchi, S.; An, K.; Nishiura, M.; Hou, Z. Modular Access to Spiro-dihydroquinolines via Scandium-Catalyzed Dearomative Annulation of Quinolines with Alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 20462–20471. [CrossRef]
64. Lin, Q.; Zheng, S.; Chen, L.; Wu, J.; Li, J.; Liu, P.; Dong, S.; Liu, X.; Peng, Q.; Feng, X. Catalytic Regio- and Enantioselective Protonation for the Synthesis of Chiral Allenes: Synergistic Effect of the Counterion and Water. *Angew. Chem. Int. Ed.* **2022**, *61*, e202203650. [CrossRef]
65. Zhang, J.; Yang, W.-L.; Zheng, H.; Wang, Y.; Deng, W.-P. Regio- and Enantioselective γ-Allylic Alkylation of In Situ-Generated Free Dienolates via Scandium/Iridium Dual Catalysis. *Angew. Chem. Int. Ed.* **2021**, *61*, e202117079. [CrossRef]
66. Cobo, A.A.; Armstrong, B.M.; Fettinger, J.C.; Franz, A.K. Catalytic Asymmetric Synthesis of Cyclopentene-spirooxindoles Bearing Vinylsilanes Capable of Further Transformations. *Org. Lett.* **2019**, *21*, 8196–8200. [CrossRef]
67. Ball-Jones, N.R.; Cobo, A.A.; Armstrong, B.M.; Wigman, B.; Fettinger, J.C.; Hein, J.E.; Franz, A.K. Ligand-Accelerated Catalysis in Scandium(III)-Catalyzed Asymmetric Spiroannulation Reactions. *ACS Catal.* **2022**, *12*, 3524–3533. [CrossRef]
68. Hu, H.; Xu, J.; Wang, F.; Dong, S.; Liu, X.; Feng, X. Chiral ScIII–*N,N′*-Dioxide-Catalyzed 1,3-Dipolar Cycloaddition of Diaziridines with Chalcones. *Org. Lett.* **2020**, *22*, 93–97. [CrossRef]
69. Zhao, P.; Li, Z.; He, J.; Liu, X.; Feng, X. Asymmetric catalytic 1,3-dipolar cycloaddition of α-diazoesters for synthesis of 1-pyrazoline-based spirochromanones and beyond. *Sci. China Chem.* **2021**, *64*, 1355–1360. [CrossRef]
70. Mishra, A.; Cong, X.; Nishiura, M.; Hou, Z. Enantioselective Synthesis of 1-Aminoindanes via [3 + 2] Annulation of Aldimines with Alkenes by Scandium-Catalyzed C–H Activation. *J. Am. Chem. Soc.* **2023**, *145*, 17468–17477. [CrossRef] [PubMed]
71. Zhang, J.; Len, L.; He, C.; Xiong, Q.; Liu, X.; Feng, X. Chiral scandium-complex-catalyzed asymmetric inverse-electron-demand oxa-Diels–Alder reaction of o-quinone methides with fulvenes. *Chem. Commun.* **2018**, *54*, 74–77. [CrossRef]
72. Harada, S.; Nakashima, S.; Sekino, S.; Oishi, W.; Nishida, A. Optically Active Helical Lanthanide Complexes: Storable Chiral Lewis Acidic Catalysts for Enantioselective Diels–Alder Reaction of Siloxydienes. *Chem. Asian J.* **2020**, *15*, 483–486. [CrossRef] [PubMed]
73. Yang, H.-D.; Chen, J.-B.; Peng, C.; Liu, W.-K.; Zhou, S.-S.; Song, J.-X.; Qi, Z.-H.; Wang, Y.; Wang, X.-W. Chiral Bis-Oxalamide-Rare Earth Complex Catalyzed Inverse- Electron-Demand Asymmetric *oxa*-Hetero-Diels-Alder Reaction for Optically Active Dihydropyran Core Structures. *Adv. Synth. Catal.* **2022**, *364*, 4347–4362. [CrossRef]
74. Zhao, P.; Wu, S.; Ke, C.; Liu, X.; Feng, X. Chiral Lewis acid-catalyzed enantioselective cyclopropanation and C–H insertion reactions of vinyl ketones with α-diazoesters. *Chem. Commun.* **2018**, *54*, 9837–9840. [CrossRef]
75. Yao, Q.; Liao, Y.; Lin, L.; Lin, X.; Ji, J.; Liu, X.; Feng, X. Efficient Synthesis of Chiral Trisubstituted 1,2-Allenyl Ketones by Catalytic Asymmetric Conjugate Addition of Malonic Esters to Enynes. *Angew. Chem. Int. Ed.* **2016**, *55*, 1859–1863. [CrossRef]
76. Ji, J.; Tang, Q.; Kang, T.; Liu, X.; Feng, X. First-Principles Selection of Solute Elements for Er-Stabilized Bi2O3 Oxide-Ion Conductor with Improved Long-Term Stability at Moderate Temperatures. *ACS Catal.* **2017**, *7*, 3763–3768. [CrossRef]
77. Ge, S.; Kang, T.; Lin, L.; Zhang, X.; Zhao, P.; Liu, X.; Feng, X. Chiral *N,N′*-dioxide/Sc(OTf)3 complex-catalyzed asymmetric dearomatization of β-naphthols. *Chem. Commun.* **2017**, *53*, 11759–11762. [CrossRef]
78. Rout, S.; Das, A.; Singh, V.K. Metal-Controlled Switching of Enantioselectivity in the Mukaiyama–Michael Reaction of α,β-Unsaturated 2-Acyl Imidazoles Catalyzed by Chiral Metal–Pybox Complexes. *J. Org. Chem.* **2018**, *83*, 5058–5071. [CrossRef] [PubMed]
79. Rout, S.; Dasa, A.; Singh, V.K. An asymmetric vinylogous Mukaiyama–Michael reaction of a,b-unsaturated 2-acyl imidazoles catalyzed by chiral Sc(III)– or Er(III)–pybox complexes. *Chem. Commun.* **2017**, *53*, 5143–5146. [CrossRef] [PubMed]
80. Riehl, P.S.; Richardson, A.D.; Sakamoto, T.; Schindler, C.S. Eight-Step Enantiodivergent Synthesis of (+)- and (−)-Lingzhiol. *Org. Lett.* **2020**, *22*, 290–294. [CrossRef] [PubMed]
81. Xia, Y.; Chang, L.; Lin, L.; Xu, Y.; Liu, X.; Feng, X. Asymmetric ring-opening of cyclopropyl ketones with β-naphthols catalyzed by a chiral *N,N′*-dioxide–scandium(iii) complex. *Org. Chem. Front.* **2018**, *5*, 1293–1296. [CrossRef]
82. Chang, F.; Lin, L.; Xia, Y.; Zhang, H.; Dong, S.; Liu, X.; Feng, X. Scandium-Catalyzed Enantioselective Ring-Opening of Cyclopropyl Ketones with Indoles. *Adv. Synth. Catal.* **2018**, *360*, 2608–2612. [CrossRef]
83. Malatinec, S.; Bednařova, E.; Tanaka, H.; Kotora, M. Highly Enantioselective Ring-Opening of *meso*-Epoxides with O- and *N*-Nucleophiles Catalyzed by a Chiral Sc(III)/bipyridine Complex. *Eur. J. Org. Chem.* **2021**, *2021*, 1249–1257. [CrossRef]
84. Kitanosono, T.; Lu, F.; Masuda, K.; Yamashita, Y.; Kobayashi, S. Efficient Recycling of Catalyst-Solvent Couples from Lewis Acid-Catalyzed Asymmetric Reactions in Water. *Angew. Chem. Int. Ed.* **2022**, *61*, e202202335. [CrossRef]

85. Zheng, J.; Lin, L.; Dai, L.; Yuan, X.; Liu, X.; Feng, X. Chiral *N,N′*-Dioxide–Scandium(III) Complex-Catalyzed Asymmetric Friedel–Crafts Alkylation Reaction of *ortho*-Hydroxybenzyl Alcohols with C3-Substituted N-Protected Indoles. *Chem. Eur. J.* **2016**, *22*, 18254–18258. [CrossRef]
86. Saito, Y.; Kobayashi, S. Chiral Heterogeneous Scandium Lewis Acid Catalysts for Continuous-Flow Enantioselective Friedel–Crafts Carbon–Carbon Bond-Forming Reactions. *Angew. Chem. Int. Ed.* **2021**, *60*, 26566–26570. [CrossRef]
87. Wu, W.; Cao, W.; Hu, L.; Su, Z.; Liu, X.; Feng, X. Asymmetric Baeyer–Villiger oxidation: Classical and parallel kinetic resolution of 3-substituted cyclohexanones and desymmetrization of *meso*-disubstituted cycloketones. *Chem. Sci.* **2019**, *10*, 7003–7008. [CrossRef]
88. Li, S.-S.; Sun, S.; Wang, J. Catalytic Asymmetric Homologation of 4-Substituted Cyclohexanones with CF3CHN2: Enantioselective Synthesis of α-Trifluoromethyl Cycloheptanones. *Angew. Chem. Int. Ed.* **2022**, *61*, e202115098. [CrossRef] [PubMed]
89. Tenberge, M.; Wahl, J.M. Lewis Acid Catalysed Asymmetric One-Carbon Ring-Expansion of Prochiral Cyclobutanones. *Synthesis* **2023**, *55*, 892–898. [CrossRef]
90. Lai, Z.-W.; Liu, C.; Sun, H.; You, S.-L. Asymmetric Synthesis of 3-Allyloxindoles and 3-Allenyloxindoles by Scandium(III)-Catalyzed Claisen Rearrangement Reactions. *Chin. J. Chem.* **2017**, *35*, 1512–1516. [CrossRef]
91. Dai, L.; Li, X.; Zeng, Z.; Dong, S.; Zhou, Y.; Liu, X.; Feng, X. Catalytic Asymmetric Acyloin Rearrangements of α-Ketols, α-Hydroxy Aldehydes, and α-Iminols by *N,N′*-Dioxide–Metal Complexes. *Org. Lett.* **2020**, *22*, 5041–5045. [CrossRef] [PubMed]
92. Hu, H.; Liu, Y.; Lin, L.; Zhang, Y.; Liu, X.; Feng, X. Kinetic Resolution of 2*H*-Azirines by Asymmetric Imine Amidation. *Angew. Chem. Int. Ed.* **2016**, *55*, 10098–10101. [CrossRef] [PubMed]
93. Zhang, Y.; Liao, Y.; Liu, X.; Xu, L.; Lin, L.; Feng, X. Catalytic asymmetric hydroxylative dearomatization of 2-naphthols: Synthesis of lacinilene derivatives. *Chem. Sci.* **2017**, *8*, 6645–6649. [CrossRef]
94. Zhang, H.; Yao, Q.; Lin, L.; Xu, C.; Liu, X.; Feng, X. Catalytic Asymmetric Epoxidation of Electron-Deficient Enynes Promoted by Chiral *N,N′*-Dioxide-Scandium(III) Complex. *Adv. Synth. Catal.* **2017**, *359*, 3454–3459. [CrossRef]
95. Wang, Z.; Lin, L.; Zhou, P.; Liua, X.; Feng, X. Chiral *N,N′*-dioxide-Sc(NTf2)3 complex-catalyzed asymmetric bromoamination of chalones with *N*-bromosuccinimide as both bromine and amide source. *Chem. Commun.* **2017**, *56*, 3462–3465. [CrossRef]
96. Tang, Q.; Lin, L.; Ji, J.; Hu, H.; Liu, X.; Feng, X. Catalytic Asymmetric Direct Vinylogous Aldol Reaction of Isatins with β,γ-Unsaturated Butenolides. *Chem. Eur. J.* **2017**, *23*, 16447–16451. [CrossRef]
97. Zhan, G.; Teng, H.-L.; Luo, Y.; Lou, S.-J.; Nishiura, M.; Hou, Z. Enantioselective Construction of Silicon-Stereogenic Silanes by Scandium-Catalyzed Intermolecular Alkene Hydrosilylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 12342–12346. [CrossRef]
98. He, C.; Cao, W.; Zhang, J.; Ge, S.; Feng, X. Chiral *N,N′*-Dioxide/Scandium(III)-Catalyzed Asymmetric Alkylation of *N*-Unprotected 3-Substituted Oxindoles. *Adv. Synth. Catal.* **2018**, *360*, 4301–4305. [CrossRef]
99. Lou, S.-J.; Mo, Z.; Nishiura, M.; Hou, Z. Construction of All-Carbon Quaternary Stereocenters by Scandium-Catalyzed Intramolecular C–H Alkylation of Imidazoles with 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 1200–1204. [CrossRef] [PubMed]
100. Tang, S.; Li, Z.; Shao, Y.; Sun, J. Ir-Catalyzed Regiocontrolled Allylic Amination of Di-/Trienyl Allylic Alcohols with Secondary Amines. Ir-Catalyzed Regiocontrolled Allylic Amination of Di-/Trienyl Allylic Alcohols with Secondary Amines. *Org. Lett.* **2019**, *21*, 7228–7232. [CrossRef] [PubMed]
101. Lou, S.-J.; Zhuo, Q.; Nishihura, M.; Luo, G.; Hou, Z. Enantioselective C–H Alkenylation of Ferrocenes with Alkynes by Half-Sandwich Scandium Catalyst. *J. Am. Chem. Soc.* **2021**, *143*, 2470–2476. [CrossRef]