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Catalytic enantioselective construction of vicinal quaternary carbon stereocenters

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This review summarizes the advances in the catalytic enantioselective construction of vicinal quaternary carbon stereocenters, introduces major synthetic strategies and discusses their advantages and limitations, highlights the application of known protocols in the total synthesis of natural products, and outlines the synthetic opportunities.

1. Introduction

Contiguous carbon stereogenic centers are a common feature of complex natural products and drugs.[1] They represent a large fraction of three-dimensional space, and the orientation of substituents at carbon stereocenters has an impact on the shape of many structurally complex molecules, which are closely related to the properties of organic molecules.[2] Contiguous stereogenic carbon atoms also greatly add complexity and diversity to organic molecules because they encompass a wide range of substructures depending on the types of chiral carbons involved. As shown in Fig. 1, even the simplest subclass, two adjacent stereogenic carbons, can be classified into vicinal tertiary carbon stereocenters (**I**), vicinal stereocenters containing a fully substituted carbon (**II** and **III**), and vicinal fully substituted carbon stereocenters (**IV**, **V**, and **VI**). With both adjacent stereocenters changing from tertiary carbons to tetrasubstituted ones that bear at least one heteroatom substituent, and to quaternary carbon stereocenters, the steric hindrance substantially increases and imposes remarkable difficulties on the synthesis. In particular, sterically congested vicinal quaternary carbon stereocenters (**VI**) constitute a daunting challenge in synthetic chemistry.[3]

However, vicinal quaternary carbon stereocenters often feature in various types of fused-ring, spirocyclic, and bridged-ring skeletons of biologically active complex natural products (Fig. 2).[4–12] Notably, there are even three or up to four contiguous stereogenic quaternary carbon atoms in architecturally complex molecules, as seen in *laurenene*, *salvileucalin B*, *sordarin*, *taiwaniadduct B*, and *musabalbisiane A*.[12a–e]

Vicinal quaternary carbon stereocenters also exist in drugs, as exemplified by the semisynthetic opioid derivative of thebaine, *buprenorphine*, a mixed partial agonist opioid receptor modulator to treat opioid addiction.[12f] Considering that it is a routine strategy in medicinal research to introduce conformational constraints to alleviate the conformational entropy penalty upon binding to the target, the enhanced conformational restriction of vicinal stereogenic quaternary carbons would be helpful to improve the pharmaceutical properties of organic molecules in drug discovery and development.[13] Therefore, development of efficient construction of such structural motifs for the synthesis and modification of bioactive compounds is much sought after.

Despite significant achievements in the diastereoselective synthesis of adjacent quaternary carbon stereocenters using chiral substrates or reagents,[4] the exploitation of catalytic enantioselective methods is urgent, important, and at the forefront of asymmetric catalysis. However, it is extremely difficult to achieve reasonable reactivity, and control both diastereoselectivity and enantioselectivity in the key catalytic C–C bond-forming step because of the challenge of steric hindrance, such as the steric congestion in the transition state and the diminished steric dissimilarity of carbon substituents on both prochiral carbons.[3] In addition, the electronic effect represents another challenge, as it may not only influence the reactivity of reaction reagents but also affect the substrate–catalyst interaction. Therefore, the catalytic enantioselective construction of contiguous stereogenic quaternary carbon atoms constitutes an ideal testing ground for new chiral catalysts and methodologies to exhibit their potency and potential, and reflects some of the latest achievements in asymmetric catalysis.

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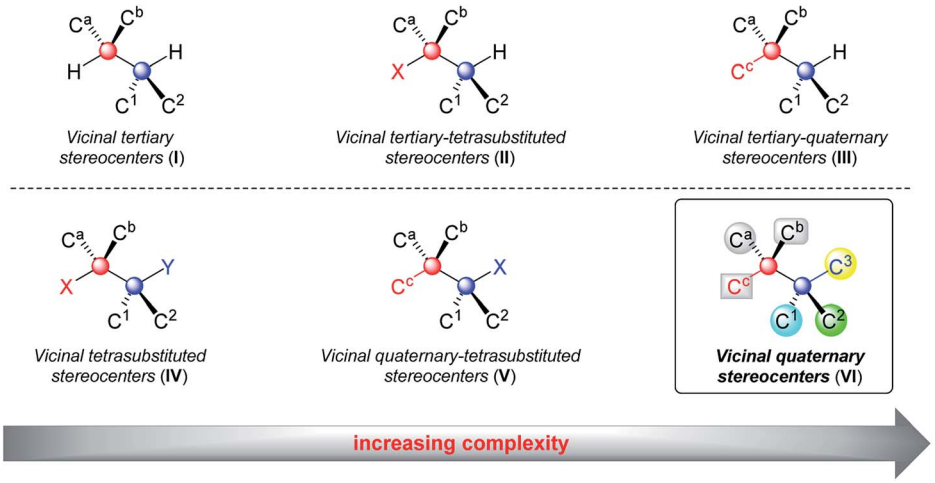


Fig. 1 Two adjacent carbon stereocenters.

In the past decade, much progress has been made in catalytic enantioselective creation of two vicinal quaternary carbon stereocenters. A variety of elegant protocols have been developed on the basis of four basic synthetic strategies shown in Fig. 3: (a) the reaction of trisubstituted carbon nucleophiles and electrophiles, (b) difunctionalization of all-carbon tetrasubstituted alkenes, (c) sequential modification of vicinal-activated methines, and (d) the desymmetrization of *meso* compounds. Despite ongoing progress, a comprehensive review summarizing the latest advances in this important and active research field has not been performed yet, although Overman and coworkers continuously highlighted the importance and challenge of efficient construction of continuous stereogenic quaternary carbon atoms in natural product synthesis.[3,4a,b] Synthetic efforts to construct contiguous quaternary carbon stereocenters of selected natural products are nicely summarized in several reviews contributed by the groups of Overman,[3,4a,b] and Gong & Yang;[4c] however, they are mainly based on diastereoselective methods using chiral starting materials or auxiliaries. Several review articles on catalytic enantioselective construction of quaternary stereocenters have been published by Overman,[2,14] Stoltz[15] and other groups,[16–23] but they only introduced limited methods to construct vicinal quaternary carbon atoms depending on the topic of these reviews. In light of this, we feel it is necessary to present a timely comprehensive review article to summarize the latest advances until now, discuss in depth the advantages and limitations of each strategy, and give the readers some inspiration to develop more useful and excellent methods to construct vicinal quaternary carbon stereocenters.

2. The reaction of trisubstituted carbon nucleophiles and electrophiles

The C–C bond-forming reaction between two trisubstituted prochiral carbons, in most cases a nucleophile and an electrophile, is a straightforward strategy for the simultaneous construction of vicinal quaternary carbon stereocenters in one step. Despite the advantages, such as the flexible and diverse synthesis using many types of substrates for reaction design, there are difficult challenges in the reaction development, the low reactivity caused by the steric repulsion and the difficulty in the control of diastereo- and enantioselectivity due to the lesser steric dissimilarity of the substituents on both prochiral carbons. Apart from steric hindrance, the inherent electronic challenges impose extra difficulty for the reaction development. According to the Lapworth–Evans model,[24] the all-carbon tertiary anion might be highly unstable and reactive in its own right; meanwhile, the tertiary carbocation should be stable but highly prone to side reactions such as rearrangements and eliminations. In this context, the engineering of adjacent functionality to stabilize these reaction centers and to promote substrate–catalyst interactions plays an important role in utilizing this strategy successfully. Nevertheless, substantial achievements have been made by using highly active substrates or by integrating both prochiral partners into an intramolecular reaction. These elegant advances will be introduced according to reaction types in this section, including cyclopropanation, cycloaddition, cyclization, alkylation, rearrangement, and domino reactions. Notably, there are no clearly defined nucleophiles or electrophiles in some reactions, although they involve the C–C bond formation between two trisubstituted prochiral carbons.

2.1 Cyclopropanation reaction

The cyclopropanation is probably the most investigated process for the construction of vicinal quaternary carbon stereocenters. The resulting congested cyclopropanes are interesting targets for medicinal research. In this context, olefin cyclopropanation using diazo reagents, cycloisomerization of enynes and tandem sequences have shown their value.

Although the olefin cyclopropanation is the first metal catalyzed asymmetric reaction, pioneered by Nozaki in 1966,[25] it was applied to construct vicinal quaternary stereocenters 30 years later, when Doyle reported the reaction of phenyldiazoacetate and α-methylstyrene **2a**. The use of catalyst **4** gave

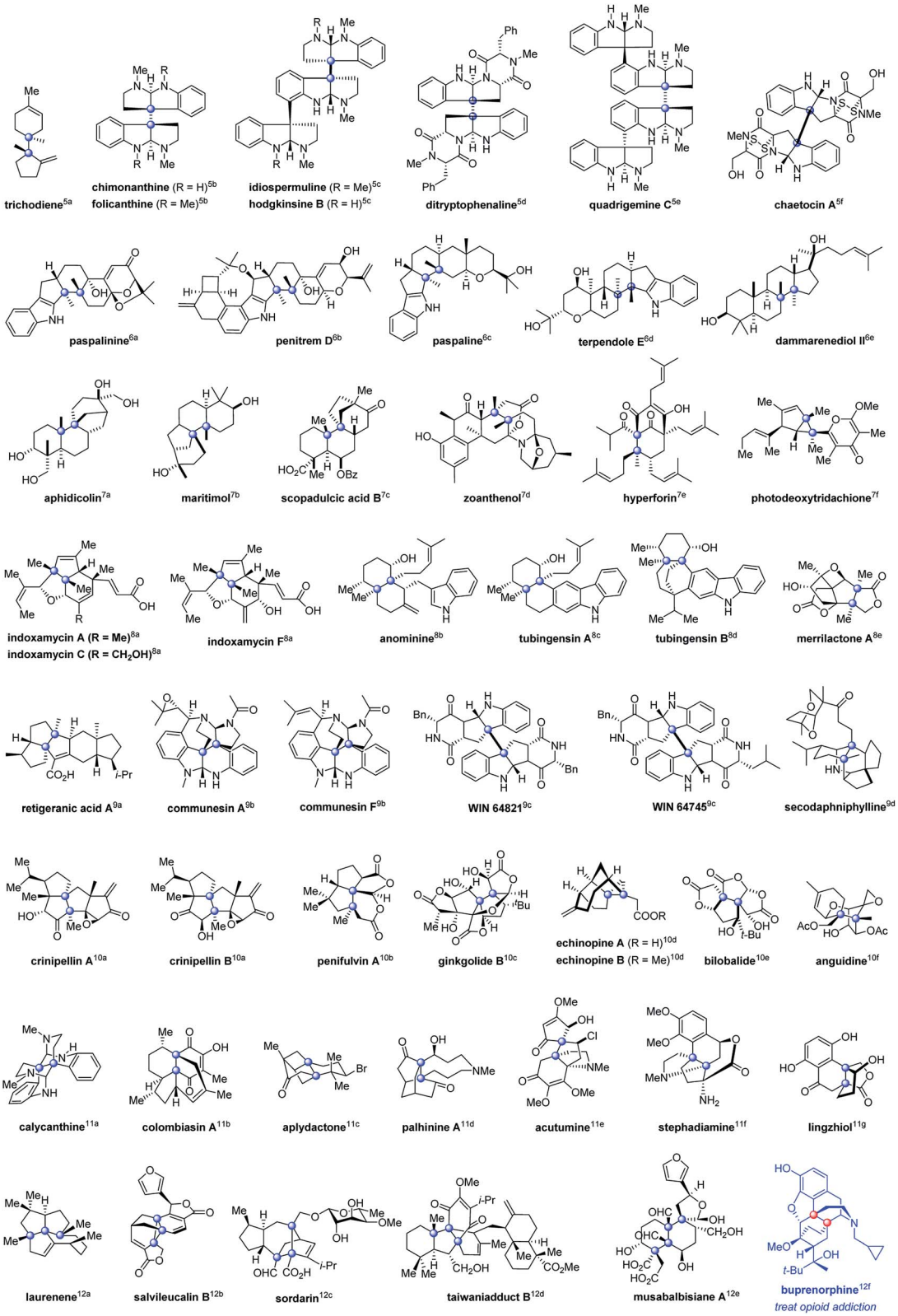


Fig. 2 Typical natural products containing vicinal quaternary carbon stereocenters.

3a in 85% ee.[26] To our knowledge, this is probably the first catalytic asymmetric reaction to construct vicinal all-carbon quaternary stereocenters (Scheme 1).

Thirteen years later, more studies were reported (Scheme 1). Fox reported a Rh_2(S-PTTL)$_4$ mediated highly stereoselective version using α-butyldiazoacetate,[27] without competitive

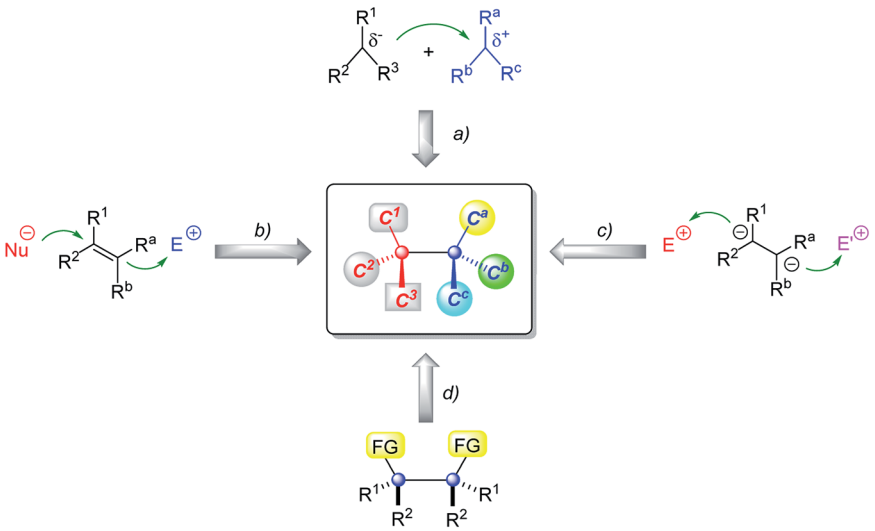
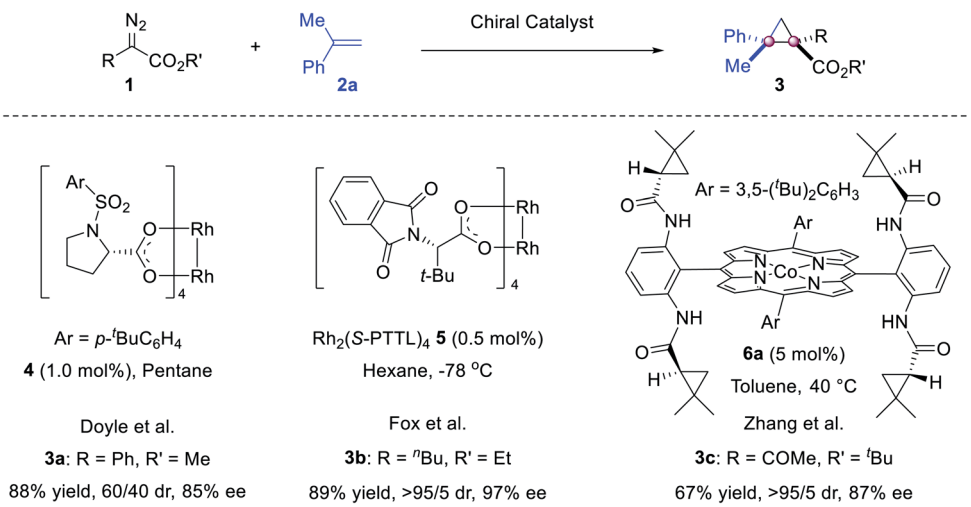


Fig. 3 Synthetic strategies for vicinal quaternary carbon stereocenters.

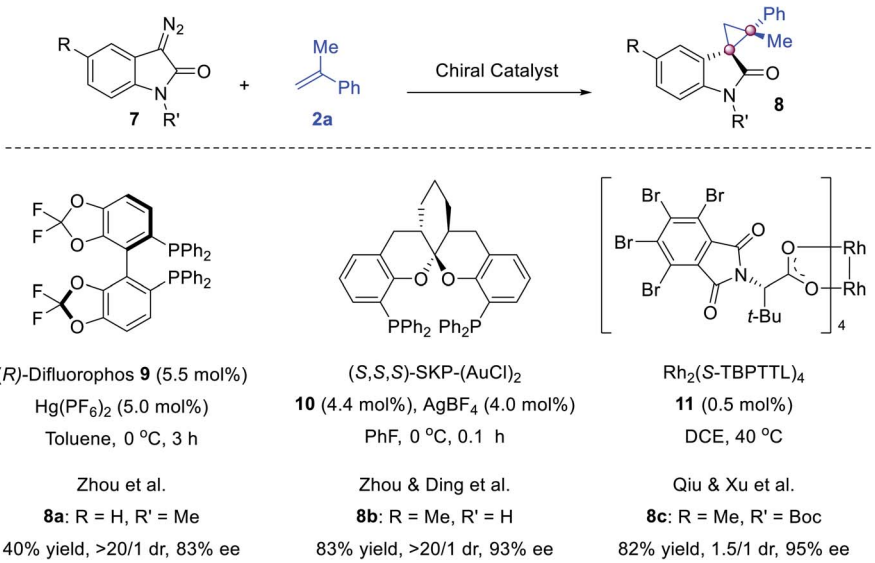
intramolecular C–H insertion[28] and β-hydride elimination[29] by-products. Zhang reported a porphyrin/Co(II) complex **6a** catalyzed reaction of α-ketodiazoacetate,[30] wherein H-bonding interactions between the amide N–H of the catalyst and two carbonyl acceptors on the carbene intermediate are critical for high catalytic activity.[31]

The cyclopropanation of cyclic diazo compounds enables the construction of spirocyclic cyclopropanes (Scheme 2). With our efforts in the syntheses of quaternary oxindoles,[32] we reported the first enantioselective Hg- and Au-catalyzed olefin cyclopropanation using diazo reagents. While (*R*)-difluorophos/$Hg(PF_6)_2$ catalyzed the reaction of diazooxindole and **2a** to give spirocyclopropyloxindole **8a** in 83% ee,[33] Ding's spiroketal bisphosphine[34] (SKP)-derived digold complex **10** was powerful for this reaction, furnishing **8b** in excellent drs and ees.[35] Later, Qiu and Xu reported a Rh_2(*S*-TBPTTL)$_2$ **11** catalyzed version using *N*-Boc diazooxindoles, delivering **8c** in 82% yield and 95% ee albeit with a moderate dr.[36]

The cyclopropanation of electron-deficient olefins and diazo compounds to construct vicinal quaternary carbon stereocenters is also achieved. In 2011, Hwang & Ryu reported that the reaction of α,β-unsaturated aldehydes **12** with diazoacetates **1** catalyzed by chiral (*S*)-oxazaborolidinium **13** gave **14** in high to excellent yield and stereoselectivities (Scheme 3a).[37] It was proposed that the Lewis acid-mediated nucleophilic addition of the diazoester from the *Si* face of the acrolein led to intermediate **I**, and then the loss of nitrogen delivered the desired product. In 2018, Liu and Feng reported the enantioselective cyclopropanation and C–H insertion reactions of α-alkyldiazoesters **16** with α-substituted vinyl ketones **15** in a one-pot manner (Scheme 3b).[38] The chiral *N*,*N*′-dioxide **17a**/Sc(OTf)$_3$ gave cyclopropanes **18** and *E*-enone derivatives **19** simultaneously with good yields and excellent ee values. A monobonding model was proposed to rationalize the generation of chiral cyclopropanes.



Scheme 1 Cyclopropanation of α-methylstyrene with diazoacetates.

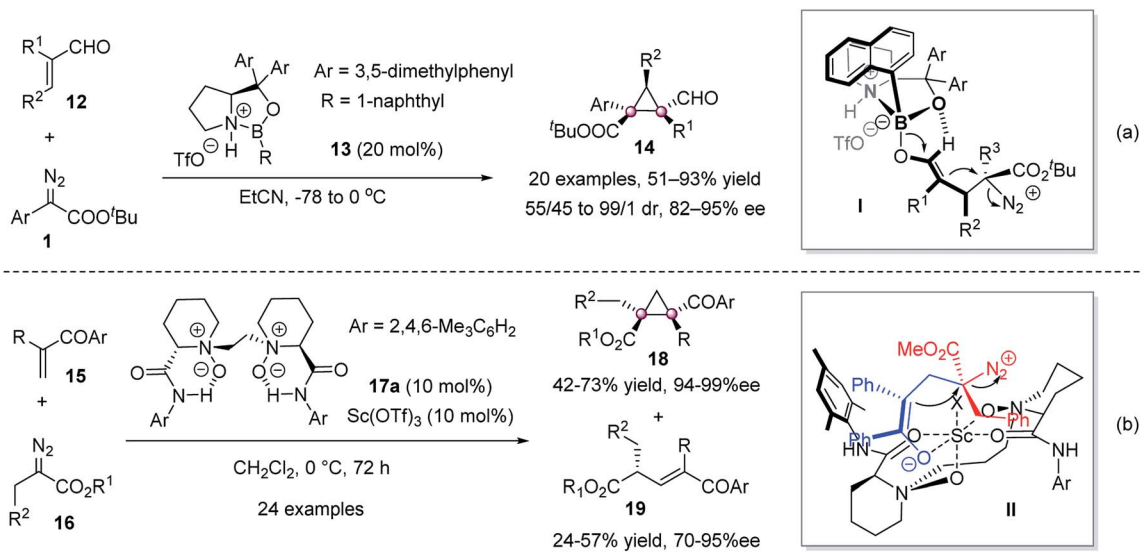


Scheme 2 Enantioselective cyclopropanation to spirocyclopropanes.

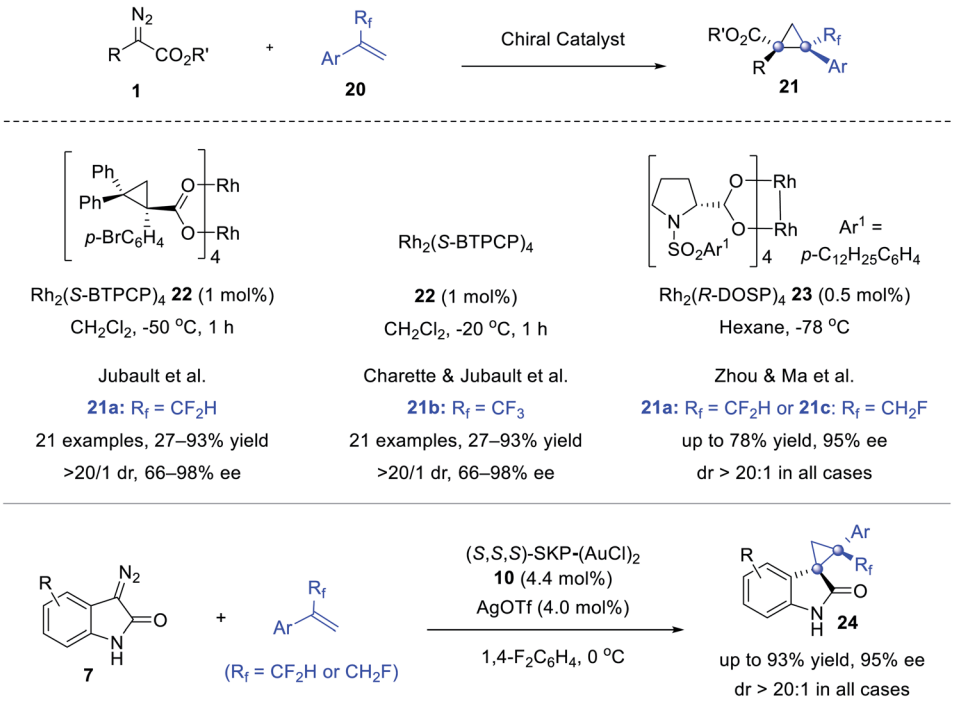
The cyclopropanation of diazo reagents and fluoroalkylated olefins paves the way to fluorinated cyclopropanes that are of interest in drug discovery. In 2017, Jubault reported a highly stereoselective synthesis of CF_2H-cyclopropanes **21a** using difluoromethylated olefins **20a**, catalyzed by Rh_2(*S*-BTPCP)$_4$ **22** (Scheme 4).[39] One year later, Charette and Jubault further extended the reaction to α-trifluoromethyl olefins **20b**.[40] We also developed stereoselective syntheses of congested cyclopropanes **21a** and **21c** and spirocyclopropyl-oxindoles **24** featuring a CF_2H or a CFH_2 group, *via* Rh_2(*R*-DOSP)$_4$ **23** mediated cyclopropanation of α-aryl diazoacetates **1** or digold catalyst **10** catalyzed that of diazooxindoles **7**.[41] A dramatic solvent effect was observed and theoretical calculations suggested that the C–F···H–N interaction between PhF and the N–H bond of the diazooxindole-derived Au(I)-carbenoid intermediate effectively lowered the reaction barrier, and tuned both the reactivity and stereoselectivity.[42]

The intramolecular cyclopropanation to cyclopropanes with bicyclic or polycyclic structures is also accomplished. In 2011, Zhang reported a porphyrin/Co(II) catalyst **6b** for the intramolecular cyclopropanation of acceptor-substituted diazoacetate **25**, giving chiral 3-oxabicyclo[3.1.0]hexan-2-one **26** in 88% yield with 83% ee (Scheme 5a).[43] Zhou and Zhu achieved a spirobisoxazoline **28**/Fe(II) complex catalyzed version using diazoesters **27**, furnishing [3.1.0]bicycloalkanes **29** in high yields with up to 97% ee (Scheme 5b).[44] They further applied this strategy to construct indoline-cyclopropanes efficiently (Scheme 5c).[45]

The cyclopropanation shown above requires using acceptor-substituted diazo reagents to inhibit side reactions and achieve

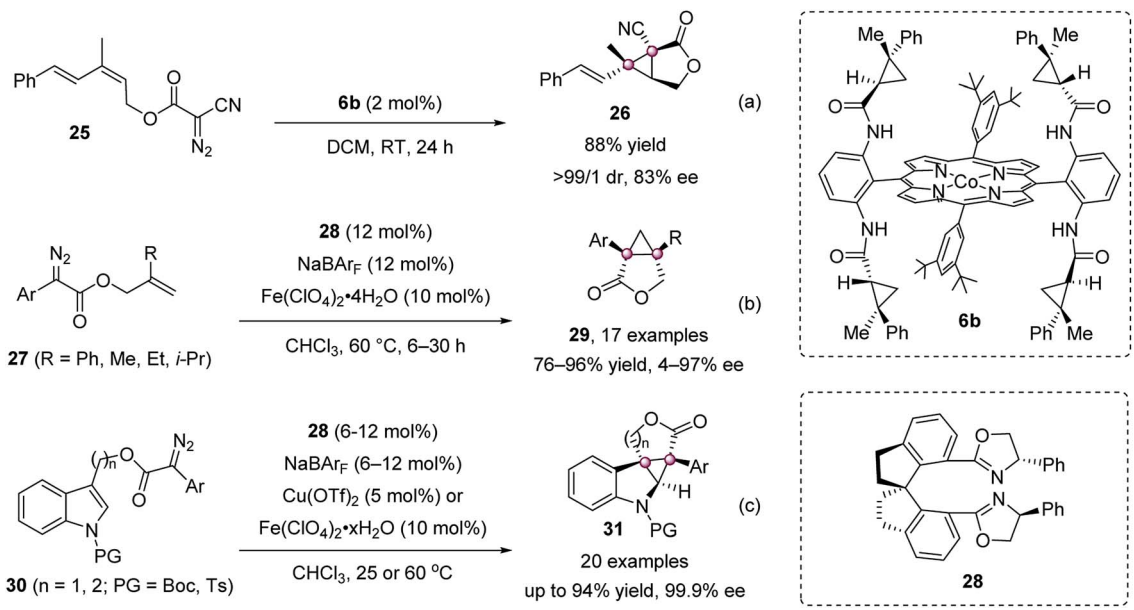


Scheme 3 Lewis acid-catalyzed cyclopropanation of diazo reagents.

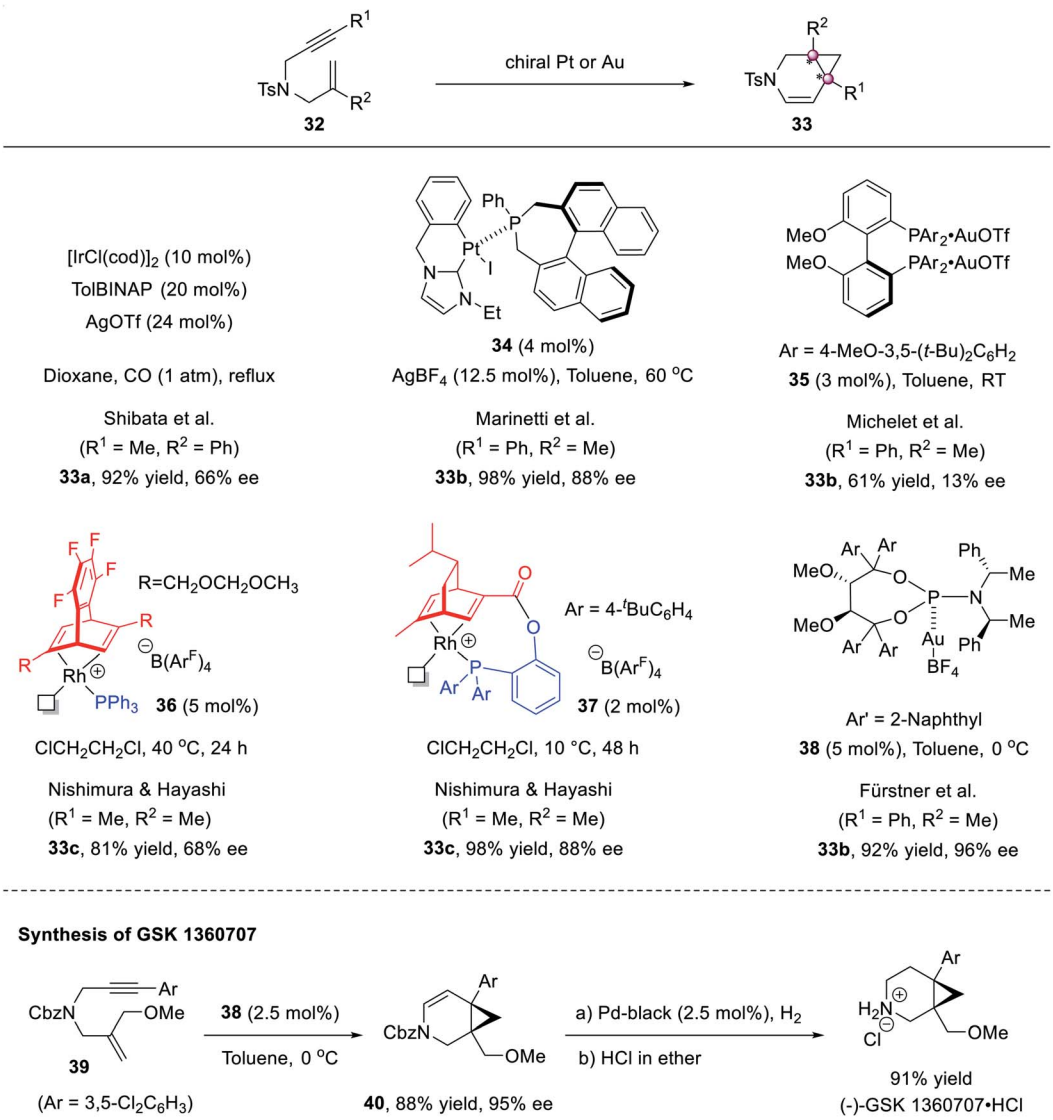


Scheme 4 Cyclopropanation of fluoromethylated olefins.

high stereoselectivity, so it inevitably affords congested cyclopropanes bearing electron-withdrawing substituents. The cycloisomerization of enynes constitutes a complement to access polysubstituted cyclopropanes with aryl or alkyl groups. In 2005, Shibata first conducted catalytic asymmetric studies and found that the TolBINAP/Ir complex mediated the cycloisomerization of 1,6-enyne **32a** well to afford 3-azabicyclo[4.1.0] heptene **33a** in 92% yield and 66% ee.[46] Later, several groups tried improving the stereoselectivities (Scheme 6). NHC–Pt(II) complex **34** (ref. 47) could afford product **33b** in 88% ee, but Au(I) complex **35** (ref. 48) afforded poor enantioselectivity. The use of chiral Ru complex **36** furnished **33c** in 81% yield and 68% ee.[49] To avoid the dissociation of Ph_3P in chiral catalyst **36**, a new tridentate ligand-derived Rh complex **37** was developed and afforded higher 98% yield and 88% ee.[50] Finally, the chiral phosphoramidite–Au(I) complex **38**, developed by Fürstner



Scheme 5 Asymmetric intramolecular cyclopropanation of diazo compounds.



Scheme 6 Transition-metal catalyzed cycloisomerization of 1,6-enyne.

et al., achieved 96% ee.[51] This protocol was applied to the synthesis of anti-depressant agent (−)-GSK 1360707.

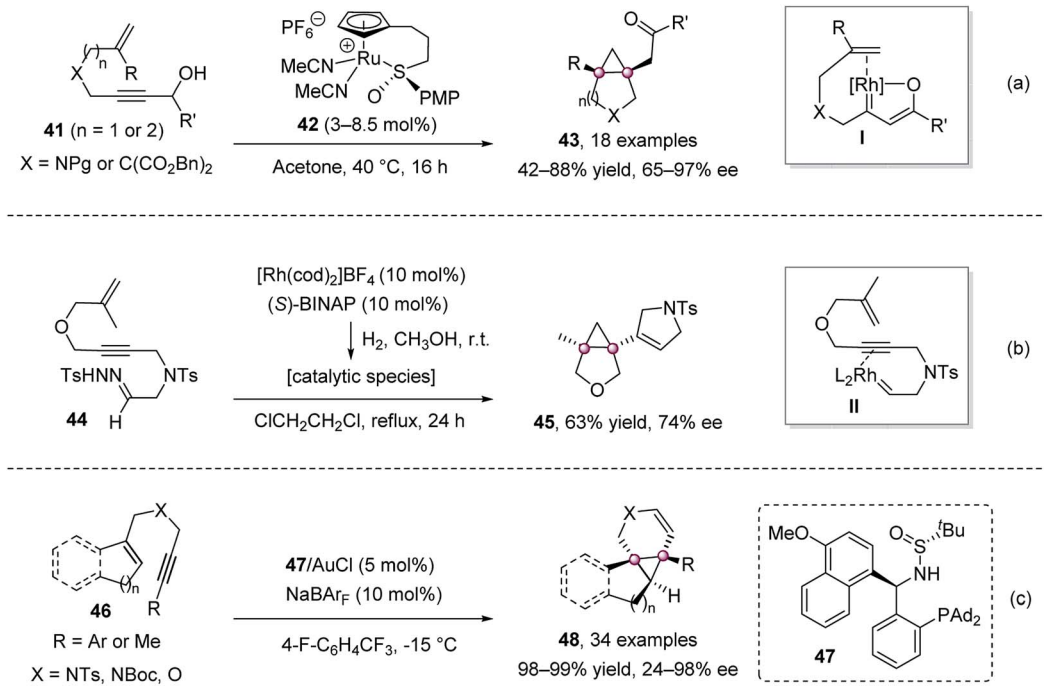
In 2014, Trost *et al.* realized a cycloisomerization of [1,6]- or [1,7]-enynes **41** bearing a propargyl alcohol moiety, affording chiral ketones **43** with a bicyclic backbone in high yield and ee values (Scheme 7a).[52] A β-oxo ruthenium carbenoid **I**, formed *via* 1,2-hydride migration, was proposed to be involved during the reaction. Pla-Quintana *et al.* demonstrated that *N*-tosylhydrazones **44** could deliver metal carbene intermediates **II** by chiral Rh(I)-catalysis, which then underwent carbene–alkyne metathesis/cyclopropanation to give chiral cyclopropane **45** in 63% yield and 74% ee (Scheme 7b).[53] Zhang group reported the gold-catalyzed intramolecular enantioselective cyclopropanation of 1,6-enynes **46** using their chiral sulfonamide–phosphine-type ligand **47** (Scheme 7c).[54]

Tandem sequences are an effective method to build cyclopropanes with vicinal quaternary stereocenters. Malkov used cinchona alkaloid derived bifunctional catalysts to develop two tandem Michael-cyclization reactions for the synthesis of spirocyclic oxindoles from 3-alkylidene oxindoles **49** with α-chloroacetoacetate **50**,[55] or with 3-chlorooxindole **53** (Scheme 8a and b).[56] Feng *et al.* achieved a **17b**/Mg(OTf)$_2$-catalyzed version using cyclic sulfur ylide **56** with 3-alkylidene oxindole **49a**, furnishing chiral **57** in a 57% yield, 95/5 *syn*/*anti*-ratio and 68% ee (Scheme 8c).[57]

An elegant cooperative Cu(I)/secondary amine catalysis directed intramolecular radical cyclopropanation of unactivated alkenes to construct bicyclo[3.1.0]hexanes **61** was invented by Liu *et al.* (Scheme 9).[58] The initial single-electron transfer of the enamine **I** formed *in situ* with external iodine(III) oxidant DF-BI-OH or Cu(II) gave iminium radical cation **II**, followed by a sequential 6-*endo*-trig and 3-*exo*-trig cyclization to give desired products.

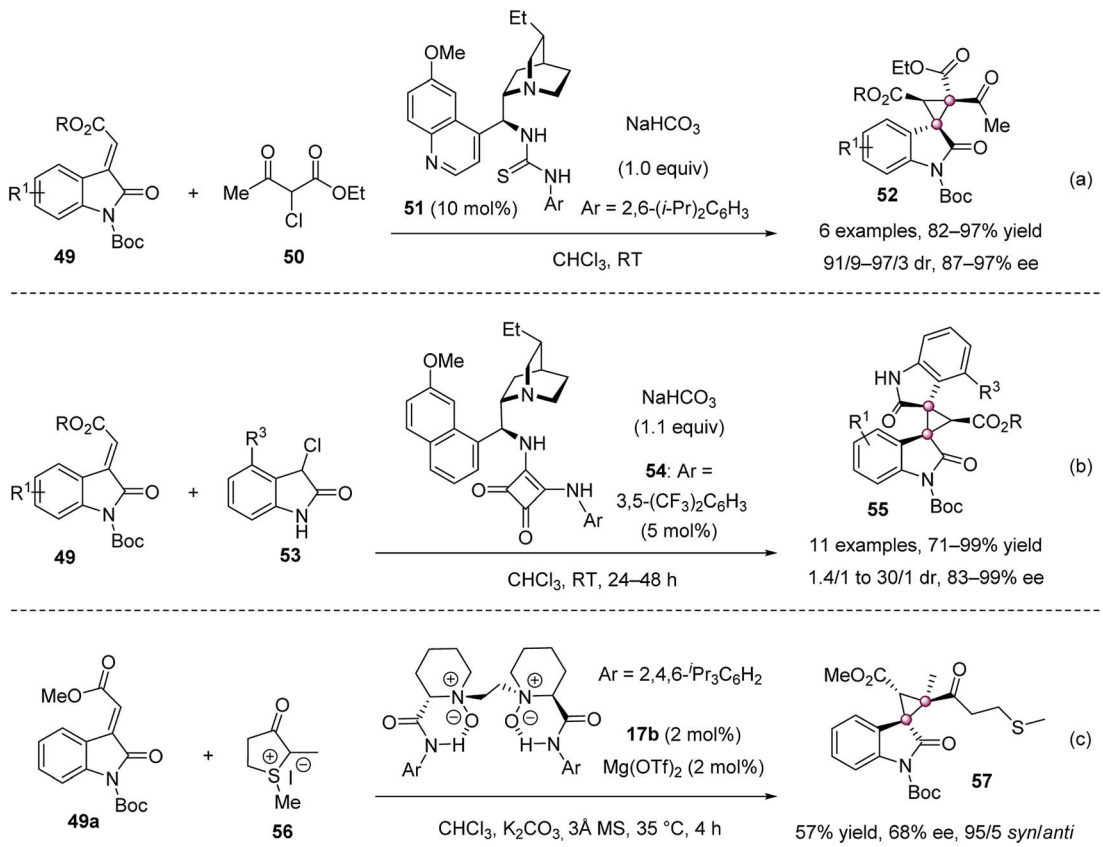
2.2 Cycloaddition reaction

Cycloaddition is a powerful strategy to construct contiguous carbon stereocenters. In 2007, Yamamoto reported a highly

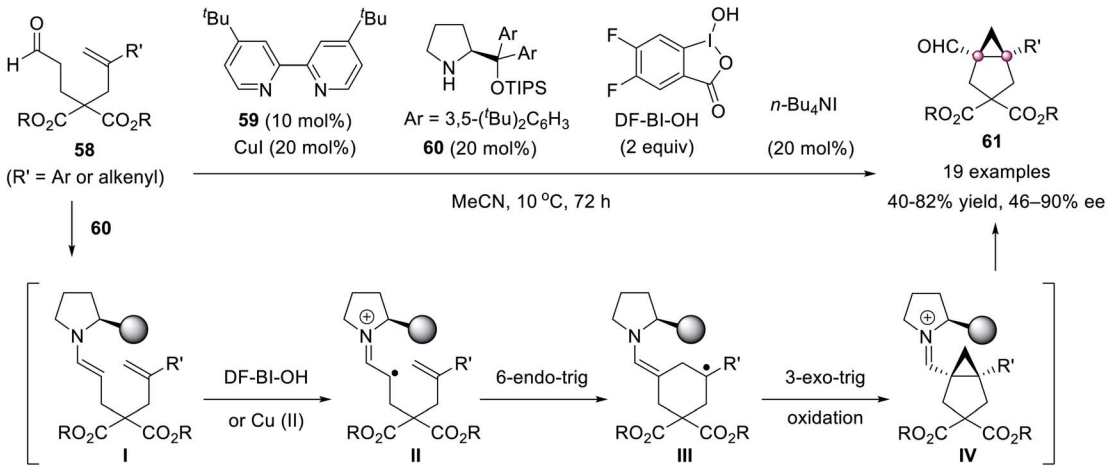


Scheme 7 Enantioselective cycloisomerization of [1,6]- or [1,7]-enyne.

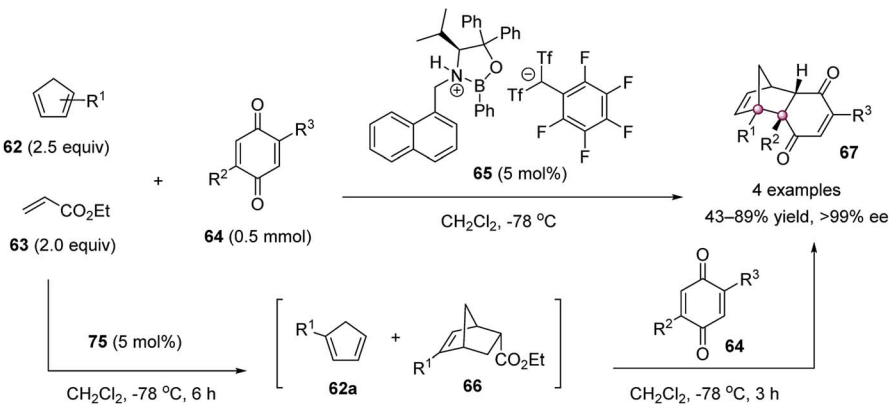
stereoselective Diels–Alder reaction of 1-substituted cyclopentadienes **62** and 2,5-disubstituted benzoquinones **64** catalyzed by oxazaborolidine **65** (Scheme 10).[59] Because cyclopentadienes **62** existed as a mixture of 1- and 2-substituted isomers due to the [1,5]-sigmatropic rearrangement, excess ethyl acrylate **63** was employed to consume the 2-substituted



Scheme 8 Asymmetric Michael-cyclization reaction.



Scheme 9 Radical asymmetric intramolecular α-cyclopropanation.



Scheme 10 Asymmetric Diels–Alder reaction.

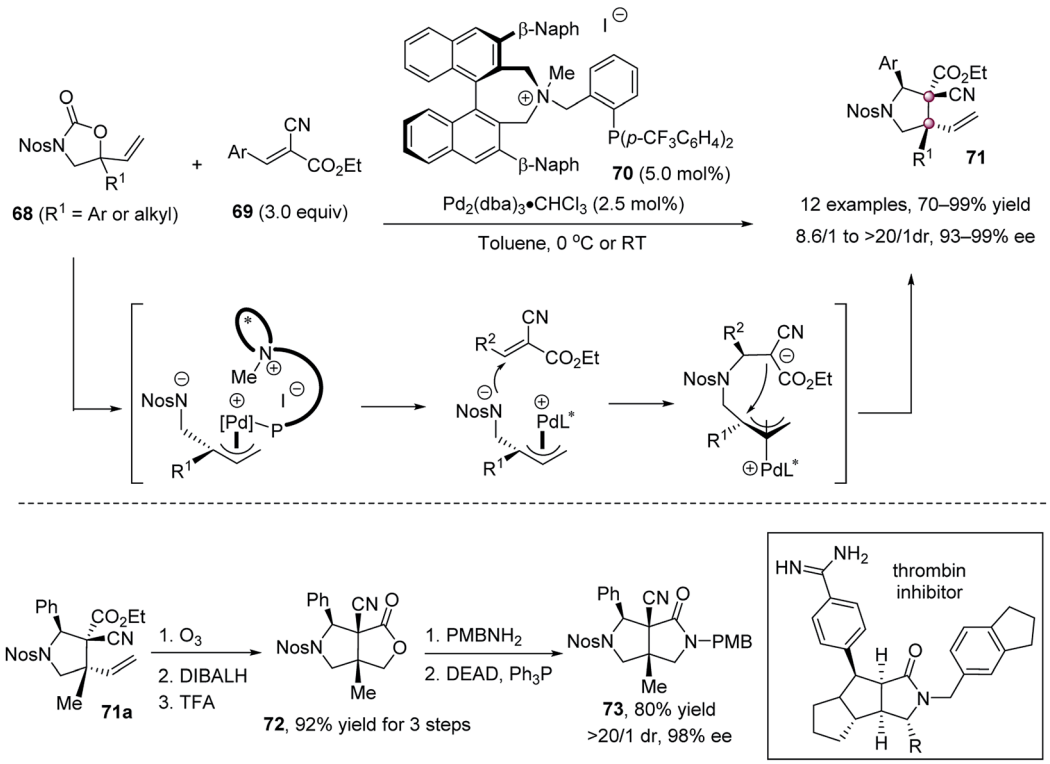
62b *via* the formation of **66**. Then, the remaining 1-substituted **62a** reacted with dienophile **64** to give *endo* adducts **67** as a single regioisomer in high enantiomeric purity. Because of the strong steric interaction between the phenyl group of catalyst **65** and the substituents of cyclopentadiene **62a**, the *endo* approach of **62a** to the double bond of *anti*-coordinated benzoquinone was favored.

In 2013, Ooi and co-workers reported an elegant palladium-catalyzed decarboxylative [3 + 2] cycloaddition of 5-vinyloxazolidinones **68** with activated trisubstituted alkenes **69**, enabling the single-step synthesis of multifunctionalized pyrrolidines **71** bearing contiguous tertiary and vicinal quaternary stereocenters in high yields and excellent stereoselectivities (Scheme 11).[60] The phosphine ligand **70** bearing a chiral ammonium salt component was critical for the reaction development, assisting in the preferable halide–palladium contact and recognizing the anionic site *via* facile pairing with the ammonium ion in the transition state, which in turn provided a precise stereoselective control during the plural bond-forming process. The reaction could be amplified to a 10 mmol scale using only 0.5 mol% catalyst, without the erosion of stereoselectivity. The products **71** are of high synthetic value, as shown by the conversion of **71a** to the core structure of the thrombin inhibitor analogue, a densely substituted bicyclic lactam **73**, as a single stereoisomer.

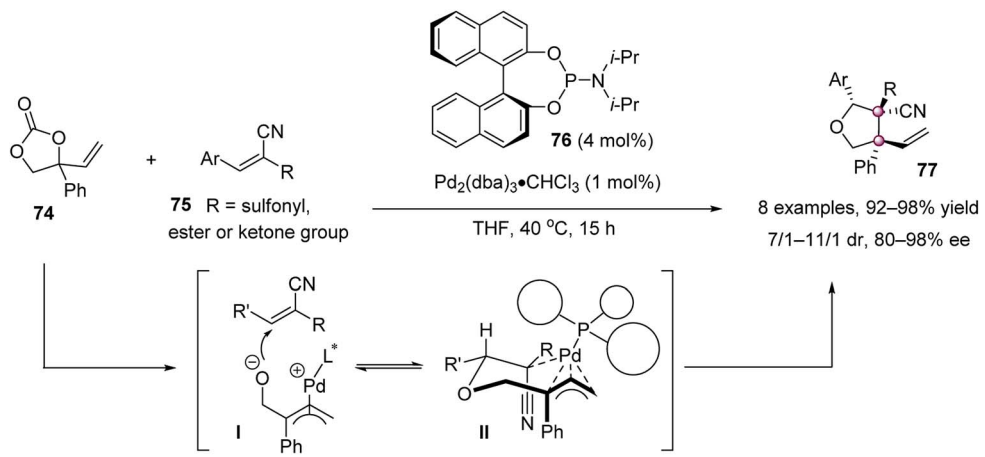
Soon afterward, Zhang *et al.* reported a highly stereoselective palladium-catalyzed decarboxylative cycloaddition of vinylethylene carbonates **74** and trisubstituted electron-deficient alkenes **75**, furnishing densely functionalized tetrahydrofurans **77** in up to 98% yield and 98% ee with a 11/1 dr (Scheme 12).[61] It was proposed that cycloaddition is the stereochemistry-determining step, involving a conformationally favored chair-like transition state **II**.

Most recently, Song and Gong nicely integrated chiral NHC catalysis with copper catalysis to accomplish an elegant [3 + 3] annulation of isatin-derived enals **78** and ethynylethylene carbonates **79**, giving spirooxindole–lactones **81** with excellent stereoselectivities (Scheme 13).[62] It was proposed that $Cu(CH_3CN)_4PF_6$ activated **79** to produce a copper–allenylidene intermediate (**II** or **II′**), which reacted with the chiral NHC–homoenolate **I** to furnish vicinal quaternary stereocenters. The following *O*-acylation cyclization and protonation produced spirocyclic oxindoles **81**.

Meggers and co-workers reported a visible light-activated asymmetric intermolecular [2 + 2] cycloaddition to construct



Scheme 11 Asymmetric [3 + 2] annulation reaction.

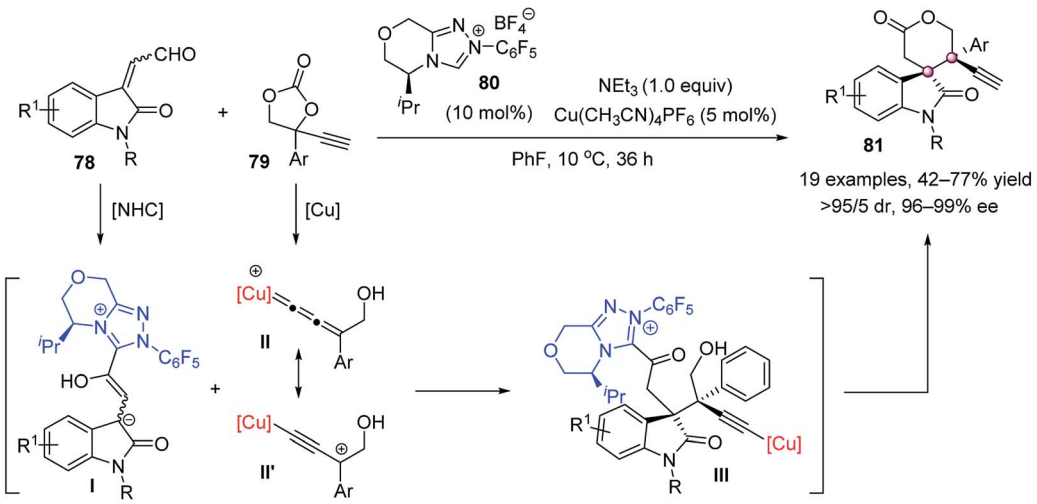


Scheme 12 Asymmetric decarboxylative cycloaddition.

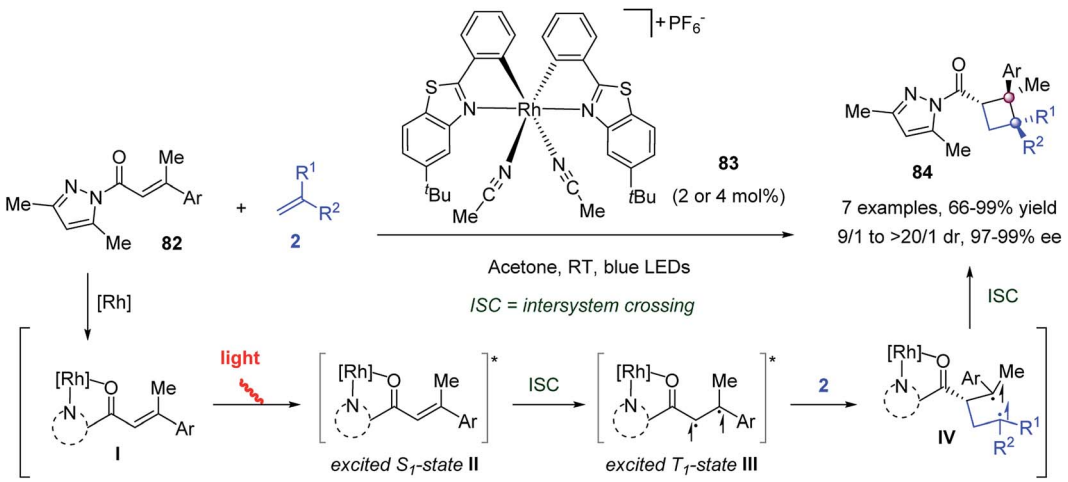
chiral cyclobutenes (Scheme 14).[63] The bis-cyclometalated chiral-at-Rh catalyst **83** played a dual role in both photoredox activation and asymmetric catalysis, allowing the [2 + 2] cycloaddition of α,β-unsaturated 2-acyl imidazole **82** with a wide range of alkenes **2** to work effectively, delivering differently substituted cyclobutanes **84** with up to >99% ee and up to >20 : 1 dr. Mechanism studies suggested the following catalytic cycle. First, the *N*,*O*-chelate coordination of α,β-unsaturated 2-acyl imidazole **82** to catalyst **83** gave intermediate **I**, which was excited by visible light to its lowest singlet state (**II**). After intersystem crossing (ISC), the excited triplet state **III** reacted with alkene **2** to afford Rh-bound 1,4-diradical intermediate **IV**. Then, ISC and cyclization along with the recoordination of another molecule of **82** generated the [2 + 2] cycloaddition product **84** and closed the catalytic cycle.

2.3 Cyclization reaction

Cyclization reactions, such as the Nazarov cyclization, enabled the key diastereo- and enantioselective step of forming two adjacent quaternary carbon atoms to be performed in an intramolecular fashion. In light of this, the cyclization strategy is not only helpful to achieve reasonable reactivity but also beneficial for the control of stereoselectivities.



Scheme 13 NHC-catalyzed [3 + 3] annulation of isatin-derived enals.



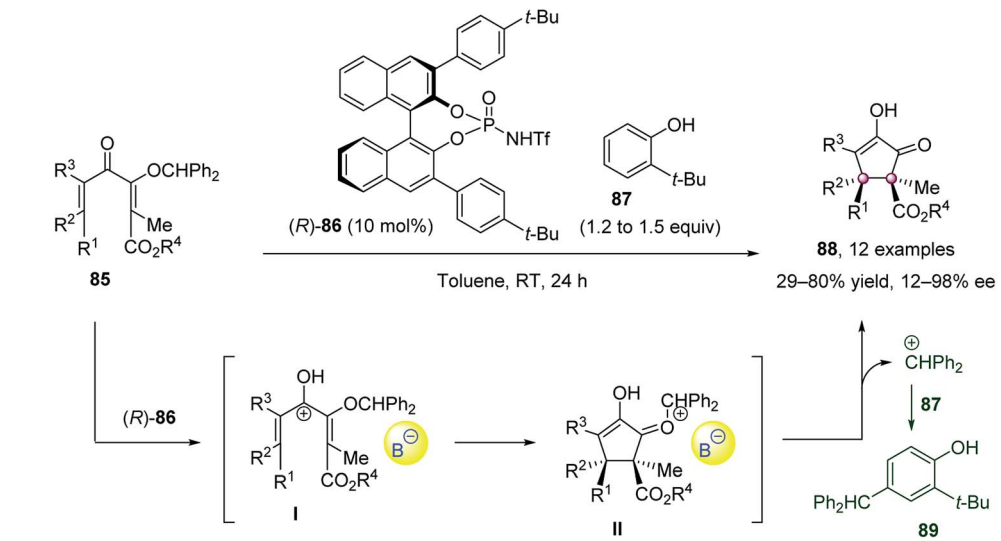
Scheme 14 Visible light-activated asymmetric [2 + 2] cycloaddition.

In 2014, Tius *et al.* accomplished a remarkable Nazarov cyclization to construct chiral cyclopentanone with vicinal quaternary stereocenters (Scheme 15).[64] In the presence of 10 mol% chiral *N*-triflyl phosphoramide **86**, the Nazarov cyclization of fully substituted dienones **85** proceeded smoothly to furnish optically active cyclopentenones **88** as single diastereoisomers in up to 98% ee. 2-*Tert*-butylphenol **87** was employed as a cation scavenger to intercept the diphenylmethyl cation generated.

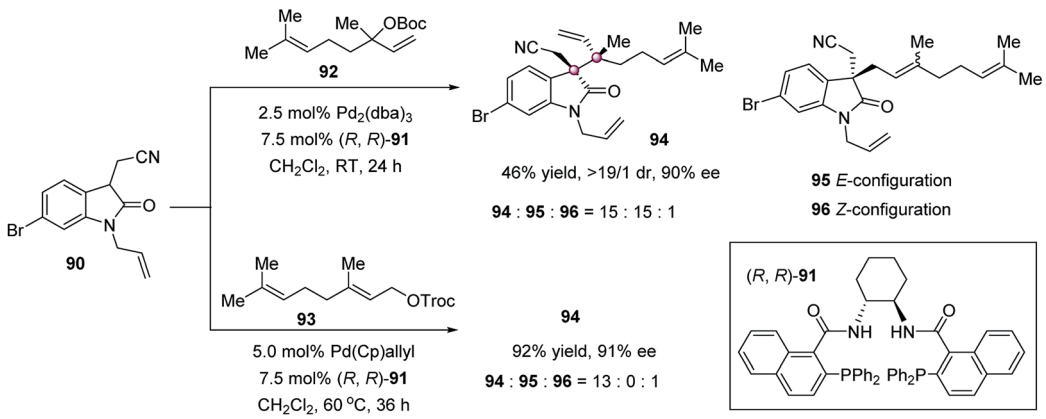
2.4 Alkylation reaction

Asymmetric allylic alkylation is one of the most important reactions for the formation of carbon–carbon and carbon–heteroatom bonds and has been widely applied to the fields of both medicinal chemistry and synthesis of natural products.[65] Despite intensive studies, the employment of this strategy to construct vicinal quaternary stereogenic carbons is underdeveloped. An impressive example was realized by Trost in 2011. Using a ligand **91** derived chiral palladium catalyst, the reaction of 3-alkyloxindole **90** and racemic linalyl carbonate **92** gave the linalylated quaternary oxindole **94** in 46% yield, >19 : 1 dr, and 90% ee, along with the formation of geranylated **95** and nerylated **96** (Scheme 16).[66] The slow interconversion of *syn*- and *anti*-π-allylpalladium complexes leads to the generation of both isomers **94** and **95** in equal amounts. Based on this consideration, the geometrically defined linear carbonate **93** was used, affording the linalylated product **94** in 92% yield with 91% ee and 13 : 1 selectivity to the nerylated **96**.

Since the pioneering work of Stoltz and co-workers,[67] the catalytic enantioselective addition of nucleophiles to indol-2-ones, generated *in situ* from 3-halooxindoles, has emerged as a fruitful strategy to construct enantioenriched 3,3-disubstituted oxindoles, a privileged scaffold widely distributed in bioactive natural products and pharmaceutically active compounds.[68,69] In 2013, Wang and co-workers nicely demonstrated the value of this strategy in constructing oxindoles with vicinal quaternary stereogenic carbons for natural product



Scheme 15 Nazarov cyclization reaction.



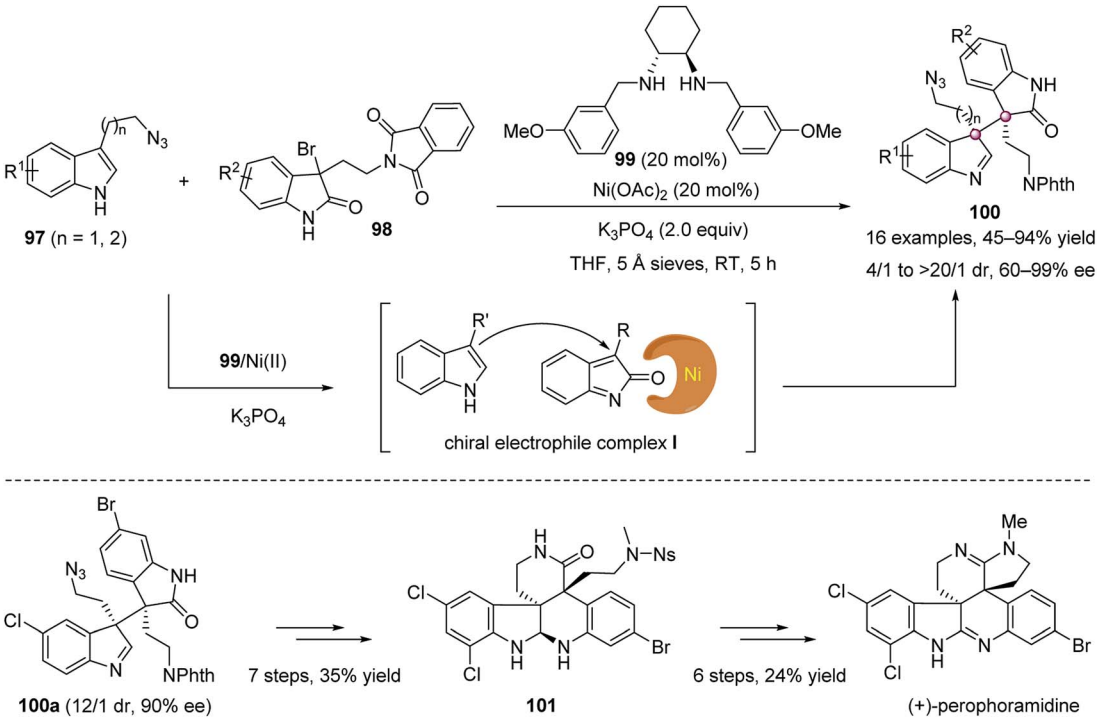
Scheme 16 Asymmetric allylic alkylation.

synthesis. They showed that a chiral diamine **99**-derived Ni complex could catalyze the alkylation of 3-bromooxindoles **98** with 3-substituted indoles **97** smoothly, affording indolenines **100** with excellent diastereo- and enantioselectivity (Scheme 17).[70] Notably, the stereoselectivity was governed by the formation of chiral catalyst–electrophile complex **I**, different from previous reports that used chiral catalyst to control the nucleophiles.[69] Based on this methodology, the first catalytic enantioselective total synthesis of complex natural product (+)-*perophoramidine* was accomplished.

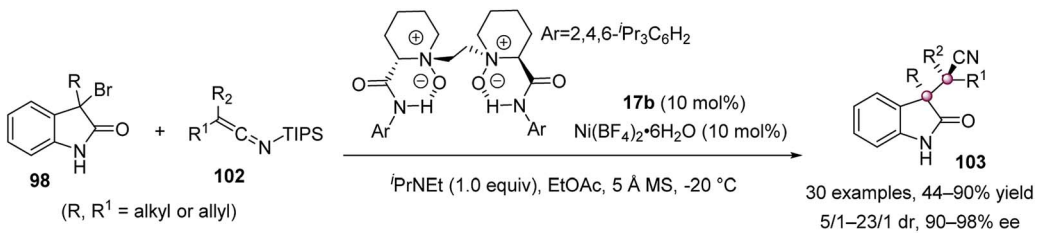
Later, Liu and Feng reported an elegant formal alkylation of 3-bromooxindoles using fully substituted silyl ketene imines **102** (SKI), catalyzed by a chiral *N*,*N*′-dioxide **17b**/Ni(II) complex (Scheme 18).[71] The resulting cyano-substituted quaternary oxindoles **103** were readily accessed in up to 90% yield, 23 : 1 dr, and 98% ee, which could undergo various diversified reactions. It was believed that the *in situ*-generated indol-2-one bound to the chiral Ni(II) catalyst, with its *Si* face blocked by the 2,4,6-triisopropylphenyl group of the ligand, to facilitate the Re-face attack of SKI on the Re face of the electrophile.

In 2013, Ooi *et al.* developed an unusual catalytic enantioselective ring-opening alkylation of racemic 2,2-disubstituted aziridines **105** at the tetrasubstituted terminus (Scheme 19).[72] In the presence of chiral 1,2,3-triazolium salt **106** and K_2CO_3, 3-substituted oxindoles **104** preferentially reacted with (*S*)-**105** to give quaternary oxindoles **107** bearing two adjacent quaternary stereocenters in high to excellent yield and dr values, as well as excellent ee values. Control experiments confirmed this kinetic resolution progress because (*R*)-**105a** could be recovered as the major enantiomer when using 2.0 equiv. of racemic **105a**. On the basis of the absolute configuration of the product with the remaining aziridine, the ring-opening substitution at the tetrasubstituted chiral carbon was believed to proceed in a stereoinvertive manner.

Recently, Jørgensen *et al.* reported a direct diastereo- and enantioselective oxidative homocoupling reaction of α-branched aldehydes (Scheme 20).[73] Using secondary amine catalyst **109** in combination with 4-nitrobenzoic acid, together with Ag_2CO_3 as the oxidant, the succinic 1,4-dialdehydes **110** were obtained in up to 79% yield, 18/1 dr, and 96% ee. It was

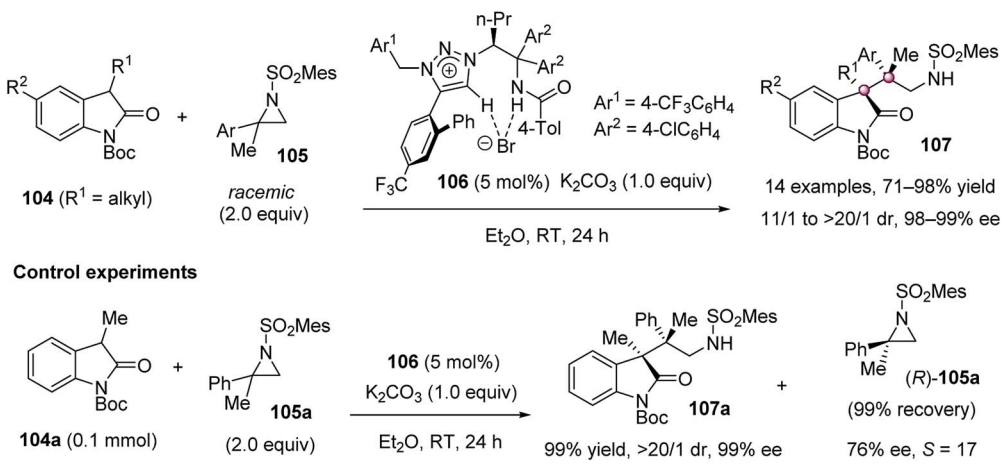


Scheme 17 Alkylation of 3-bromooxindoles and its application.

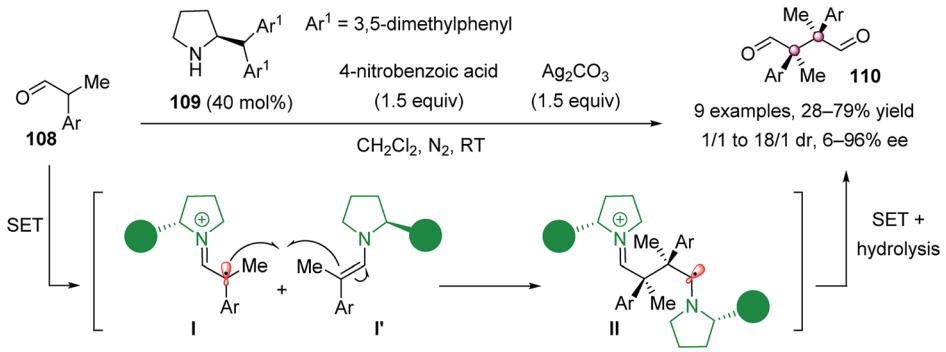


Scheme 18 Asymmetric conjugate addition of SKI.

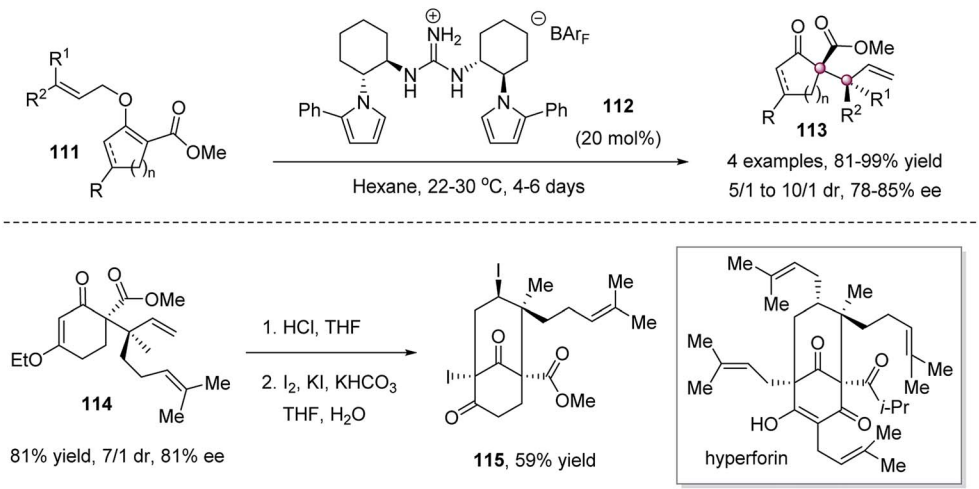
proposed that a radical cation intermediate **I**, formed *via* SET oxidation of enamine by Ag(I), was involved during the reaction process. Mechanistic studies also showed that the reactivity was influenced by radical stability, whereas the stereoselectivity was governed by the cationic character of intermediate **I**.



Scheme 19 Asymmetric ring-opening alkylation.



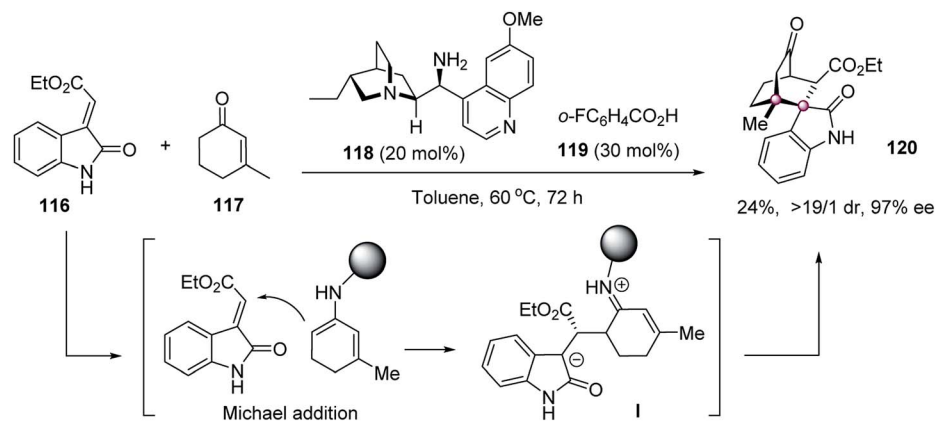
Scheme 20 Direct oxidative homocoupling reaction of α-branched aldehydes.



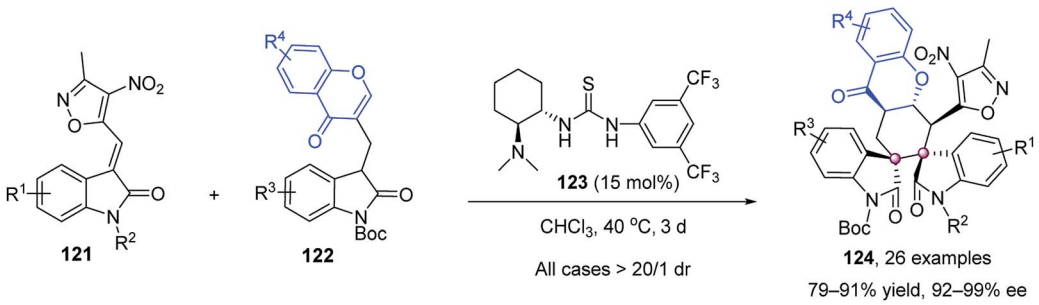
Scheme 21 Guanidinium-catalyzed Claisen rearrangement.

2.5 Rearrangement reaction

The Claisen rearrangement of allyl vinyl ethers[74] is a potentially potent approach to forge vicinal quaternary stereocenters because of the predictable and high diastereoselectivity resulting from the concerted nature of the C–O bond-breaking and C–C bond-forming process *via* a chair-like transition state. The power of this approach was successfully demonstrated by Jacobsen *et al.* in 2010 by a chiral C_2-symmetric guanidinium ion **112**-catalyzed [3,3]-sigmatropic rearrangement of cyclic *O*-allyl β-ketoesters **111** (Scheme 21).[75] The allylation products **113** were obtained in high yield and stereoselectivities. The reaction was successfully applied to the construction of the core structure of natural product *hyperforin*.



Scheme 22 Domino Michael–Michael reaction of alkylidene oxindoles.



Scheme 23 Domino Michael–Michael reaction to hexahydroxanthones.

2.6 Domino reaction

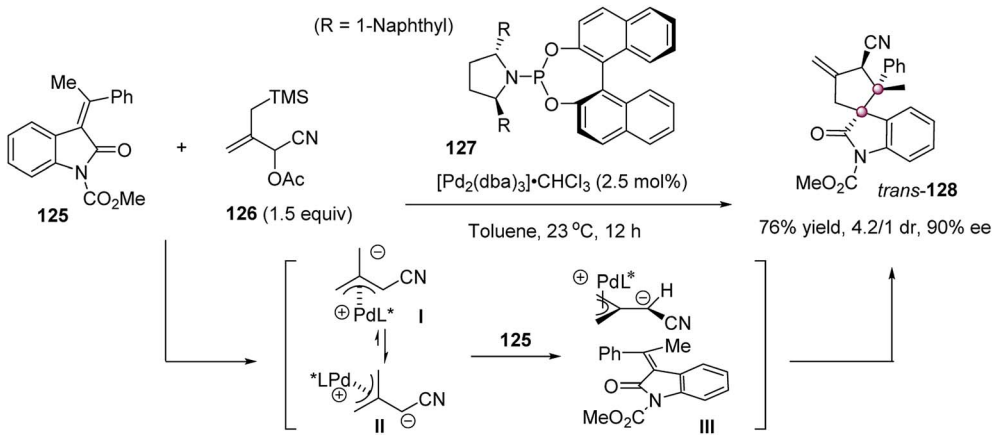
Domino reactions could merge two or more bond-forming transformations in one-step without the isolation of intermediates, thus providing efficient tactics for the construction of vicinal quaternary stereocenters. In 2009, Melchiorre *et al.* reported an elegant organocatalytic Michael–Michael sequence to forge spirocyclic oxindoles with structural and stereochemical complexity (Scheme 22).[76] The merger of chiral primary amine **118** and *ortho*-fluorobenzoic acid mediated the double Michael reaction of 3-alkenyloxindole **116** and enone **117** efficiently. The initial intermolecular Michael reaction was facilitated by enamine activation of enone **117**, affording iminium intermediate **I** that underwent the subsequent Michael addition to give highly congested **120** in 19/1 dr and 97% ee.

Recently, Liu and Zhou designed a novel bifunctional oxindole–chromone 4C synthon **122** as a versatile platform to construct hexahydroxanthones with contiguous stereogenic centers (Scheme 23).[77] Takemoto's tertiary amine–thiourea **123** catalyzed the domino Michael–Michael reaction well to give hexahydroxanthones **124** with five stereocenters, including two adjacent spiro quaternary ones, with excellent dr and ee values.

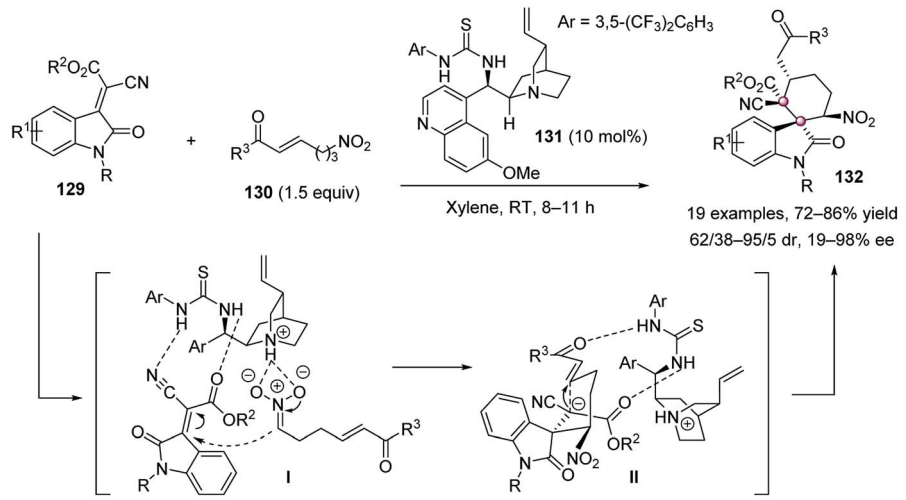
3. Difunctionalization of all-carbon tetrasubstituted alkenes

The concerted or stepwise C–C bond-forming reactions of both prochiral carbon atoms of all-carbon tetrasubstituted alkenes constitute an effective strategy to construct adjacent all-carbon stereocenters. Depending on the electronic or steric nature of such alkenes that are significantly influenced by the substituents, this strategy should incorporate a broad range of reactions to construct the target structures with great diversity. However, because of the challenge of functionalization of all-carbon tetrasubstituted alkenes in terms of reactivity and enantiofacial control, this strategy is much less explored, and known examples are limited to highly active fully substituted alkenes with ring fusion to reduce steric hindrance, such as oxindole-based tetrasubstituted alkenes and cyclobutenones. In addition, the known examples all focused on the use of reagents with both nucleophilic/electrophilic dualistic properties for the difunctionalization of all-carbon tetrasubstituted alkenes, allowing the highly stereoselective construction of polycyclic compounds with multiple contiguous stereogenic centers. This not only exhibits the power of this strategy in constructing complex structures but also suggests great possibilities for further exploration.

In 2007, Trost reported an enantioselective Pd-catalyzed [3 + 2] trimethylenemethane (TMM) cycloaddition of alkylidene oxindole **125** using cyano-substituted allyl acetate **126** as the TMM precursor (Scheme 24).[78] Under the catalysis of **127**/Pd complex, the spirocyclopentane oxindole **128** was obtained in 76% yield, 4.2/1 dr, and 90% ee. It was believed that the initially formed Pd–TMM complex **I** would equilibrate rapidly to the stabilized species **II**, which then underwent cycloaddition to the double bond to give the final product.



Scheme 24 [3 + 2] TMM cycloaddition.



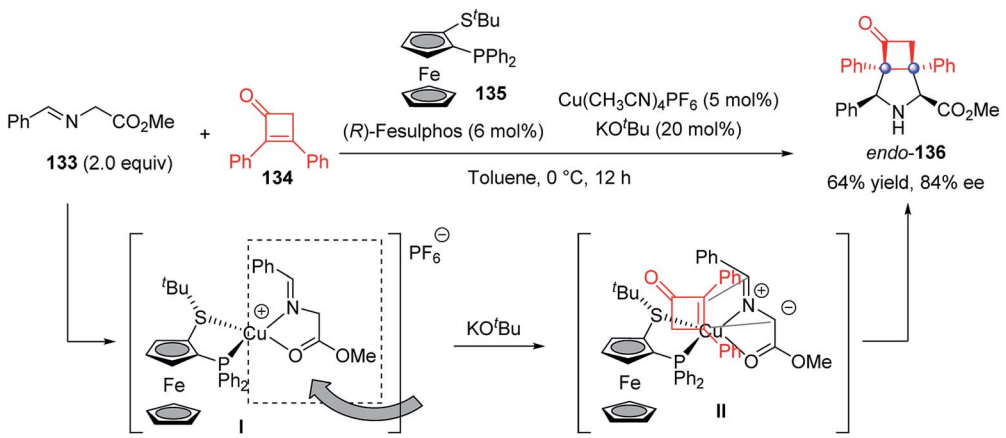
Scheme 25 Tandem Michael–Michael reaction.

In 2015, Zhao reported a tandem Michael–Michael reaction of indolylidene cyanoacetate **129** and nitroalkanes **130** catalyzed by quinidine-derived thiourea **131** to afford spirocyclohexane oxindoles **132** in high yields, up to 95/5 dr and 98% ee (Scheme 25).[79] It was proposed the intermolecular attack of nitroalkane **130** from the back onto the Re face of **129** led to intermediate **II**, which then underwent intramolecular addition to give **132**.

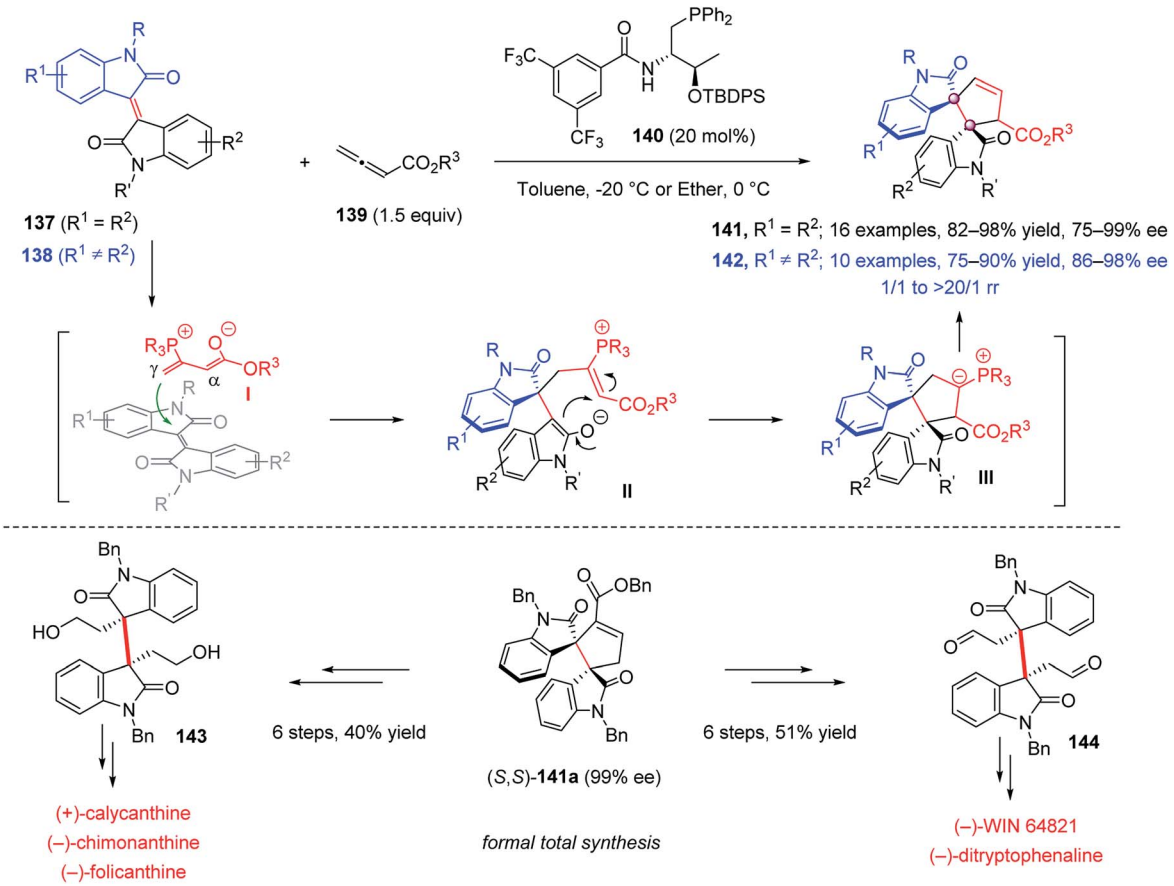
In 2018, an asymmetric [3 + 2] cycloaddition of azomethine ylides **133** and sterically demanding 2,3-diphenyl cyclobutenone **134** was developed by Adrio and Carretero with a chiral Fesulphos **135**/Cu complex as the catalyst, delivering the 3-azabicyclo [3.2.0]heptane **136** in 64% yield and 84% ee (Scheme 26).[80] To avoid the steric interaction with the bulky *t*-Bu group, the cyclobutenone would approach the less hindered face of the tetrahedral chiral Cu complex **I**, thus affording the desired *endo*-product in its current configuration.

In 2019, Mei and Lu reported a chiral phosphine **140**-catalyzed enantioselective [3 + 2] annulation of allenic esters **139** with isoindigos **137**, bearing two identical oxindole moieties, for the synthesis of dimeric spirocyclic bisindolines **141** with high yields and excellent ee (Scheme 27).[81] The reaction of unsymmetric isoindigos **138** was also performed. Using an electronic/steric-differentiation strategy, the structurally distinct spirocyclic molecules **142** were obtained with high yield and excellent ee. It was proposed that the nucleophilic attack of phosphine **140** on allenes **139** produced the zwitterionic intermediate **I**, the less hindered γ-attack of which on the structurally encumbered C=C double bond afforded intermediate **II**. For asymmetric isoindigos, the regioselectivity of this step was governed by the electronic difference between the two oxindole units. The following cyclization and proton transfer gave the final annulation product. The synthetic value of this [3 + 2] annulation was demonstrated by the formal total synthesis of (+)-*calycanthine*, (−)-*chimonanthine*, (−)-*folicanthine*, (−)-*WIN64821* and (−)-*ditryptophenaline*.

Later, Ullah and Lu further utilized Morita–Baylis–Hillman adducts **145** as C3 synthons to realize another chiral phosphine-catalyzed [3 + 2] annulation with pyrazoloneyldiene oxindoles **146**. Under the catalysis of chiral (*S*)-SITCP **147**, bispiro[pyrazolone-3,3′-oxindoles] **148** were obtained in up to 99% yield and 99% ee (Scheme 28).[82]



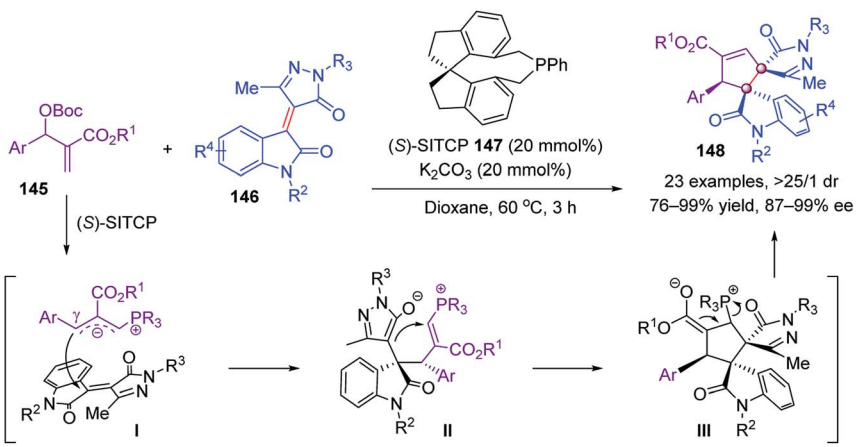
Scheme 26 [3 + 2] cycloaddition of azomethine ylides and cyclobutenones.



Scheme 27 Asymmetric annulation of tetrasubstituted alkenes with allenes.

4. Sequential modification of vicinal-activated methines

Vicinal trisubstituted carbon nucleophiles such as adjacent methines and enolate equivalents contain two masked adjacent trisubstituted carbanions that can be sequentially released to react with the same or different carbon electrophiles, to furnish vicinal quaternary stereogenic carbons. Because the reaction usually occurred in a stepwise manner, the initial step would produce a chiral quaternary carbon, the matching of which with a chiral catalyst may greatly influence the control of diastereoselectivity in the next step. In addition, when the same carbon electrophile was used to react with symmetric substrates capable of forming two vicinal trisubstituted carbanions, it was



Scheme 28 Asymmetric [3 + 2] annulation of pyrazoloneyldiene oxindoles.

possible to generate undesired *meso* products, which presents another difficulty with this strategy.

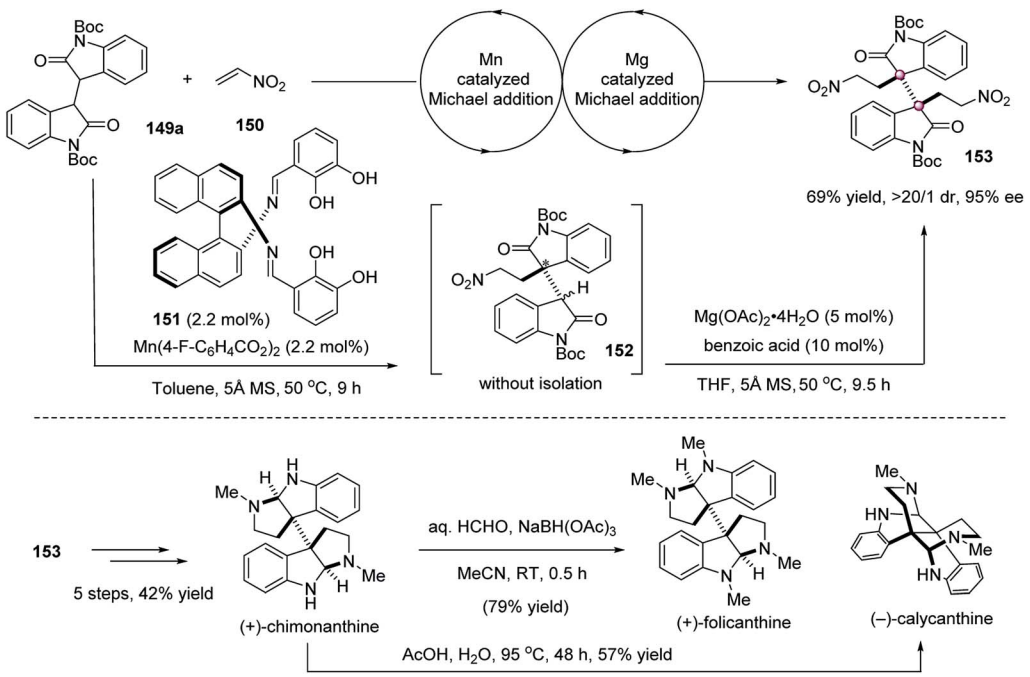
Dimeric cyclotryptamine alkaloids with vicinal quaternary carbon stereocenters at C_{3a} and $C_{3a'}$ are present in many plants and animals, showing an array of biological activities.[83] The catalytic enantioselective construction of such dimeric structures is difficult due to the lability of the C_{3a}–$C_{3a'}$ σ-bond[84] and the undesired steric hindrance in forging vicinal quaternary stereocenters.[85]

In 2012, Kanai and Matsunaga achieved an elegant double Michael reaction of bisoxindole **149a** with nitroethylene to give quaternary bisoxindole **153** (Scheme 29).[86] The chiral **151**/Mn(4-F-BzO)$_2$ complex catalyzed the initial Michael addition well, giving monoalkylated adduct **152** in 96% ee; however, its bulky nature prevented it from mediating the next step well, due to the steric hindrance, and side reactions occurred to a severe degree, including the cleavage of the C_{3a}–$C_{3a'}$ σ-bond. Then, they optimized a sequential procedure that required the removal of the chiral catalyst after the completion of the first step, and a smaller size $Mg(OAc)_2 \cdot 4H_2O$ to realize a highly diastereoselective Michael reaction, giving product **153** in 69% yield, >20 : 1 dr, and 95% ee. Based on chiral synthon **153**, the total synthesis of (+)-*chimonanthine*, (+)-*folicanthine*, and (−)-*calycanthine* was realized successfully.

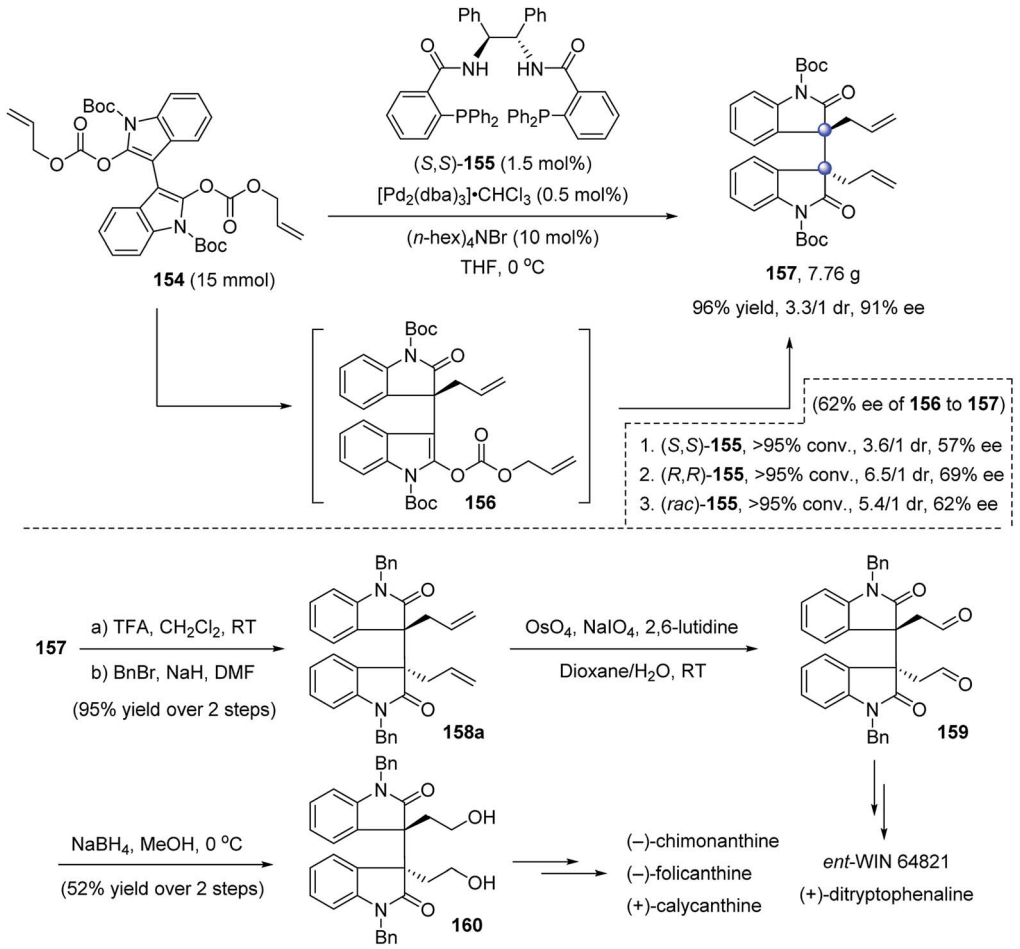
Later, Trost nicely applied decarboxylative asymmetric allylic alkylation (DAAA) to construct such an important bisoxindole structure (Scheme 30).[87] In the presence of 0.5 mol% $Pd_2(dba)_3$ and 1.5 mol% (*S*,*S*)-**155**, dienol dicarbonate **154** readily converted to the C_2-symmetric product **157** on a gram scale in 96% yield, 3.3 : 1 dr, and 91% ee. The first allylation was the enantiodetermining step, whereas the diastereoselectivity of the second step was more controlled by the substrate than by the ligand, and occurred in a mismatched fashion. The bisallylated oxindole **157** was easily converted to known synthons **159** and **160**, enabling the formal total synthesis of cyclotryptamine alkaloids (−)-*chimonanthine*, (−)-*folicanthine*, (+)-*calycanthine*, *ent-WIN 64821* and (+)-*ditryptophenaline*.

Bisai *et al.* further developed a similar enantioselective Pd-catalyzed DAAA of dimeric 2-oxindole esters **161** (Scheme 31).[88] Trost ligand **162** in combination with $Pd_2(dba)_3$ catalyzed the reaction well to afford the *N*-benzyl and *N*-methyl protected products **158a** and **158b** in a high to excellent yield and dr value, with excellent enantioselectivity.

The above protocols allow facile access to the homo-type alkaloids, but were impotent for hetero-type difunctionalization, which requires the matching of the reactivity and stereocontrol of two different electrophiles. To address this challenge, Tu *et al.* developed a novel spirocyclic amide–triazolium salt **165** as a remarkable phase-transfer catalyst accomplishing the enantioselective homo- and heterodialkylation of bisoxindoles **149** (Scheme 32).[89] In the homodialkylation reaction, benzyl bromoacetates, alkyl bromoacetate and allylic bromides were all viable electrophiles which gave the corresponding homodialkylation products **166** in 41–89% yield, 2.1/1 to >20/1 dr, and 46–99% ee. Notably, this protocol could be extended to a one-pot heterodialkylation. The second electrophile **164′** was added after the completion of the initial monoalkylation using electrophile **164**, affording the expected heteroproducts **168** in up to 72% yield, 10.7/1 dr, and 96% ee. The H-bonding between the catalyst amide N–H bond and the enolate intermediate, and the ion-pairing interaction as well as the steric hindrance of the adamantyl group of the chiral catalyst, directed the Re-face nucleophilic attack of the enolate intermediate on electrophiles to afford (*S*, *S*)-**166** or **168**. This elegant protocol paved the way to the formal synthesis of (−)-*folicanthine* and the first catalytic enantioselective total synthesis of (−)-*chimonanthidine*.



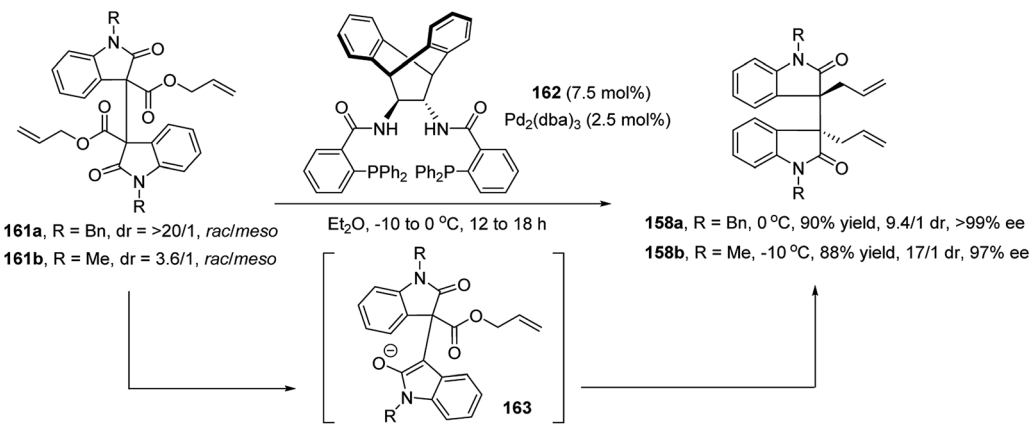
Scheme 29 Sequential Michael reaction.



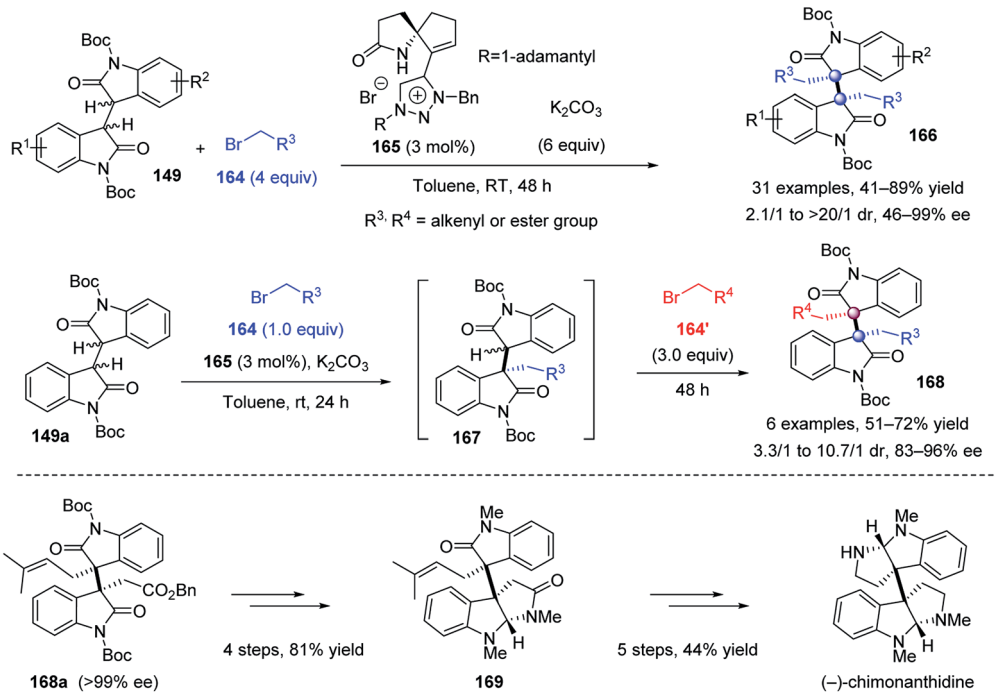
Scheme 30 Asymmetric Pd–DAAA of dienol dicarbonate.

5. The desymmetrization of *meso* compounds

The catalytic enantioselective desymmetrization of *meso* compounds with adjacent quaternary prochiral carbons is a powerful strategy to forge vicinal quaternary carbon stereocenters. This strategy has some unique features. First, an important merit is that it can alleviate steric repulsion because the reaction takes place at the tethered functionality that is at least one covalent bond away from the two existing quaternary carbons. However, this also raises the difficulty in the control of stereoselectivities because the chiral environment of the



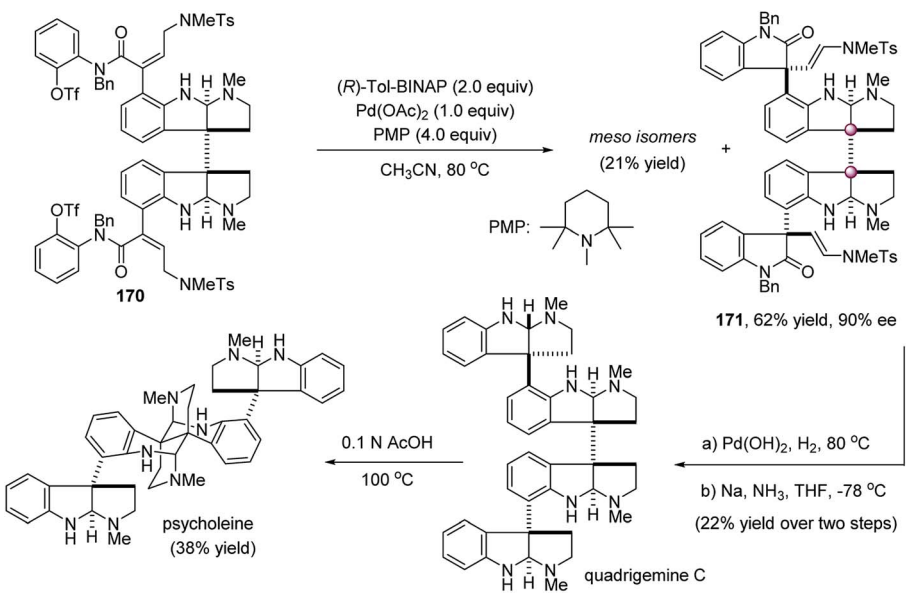
Scheme 31 Asymmetric Pd–DAAA of dimeric 2-oxindole esters.



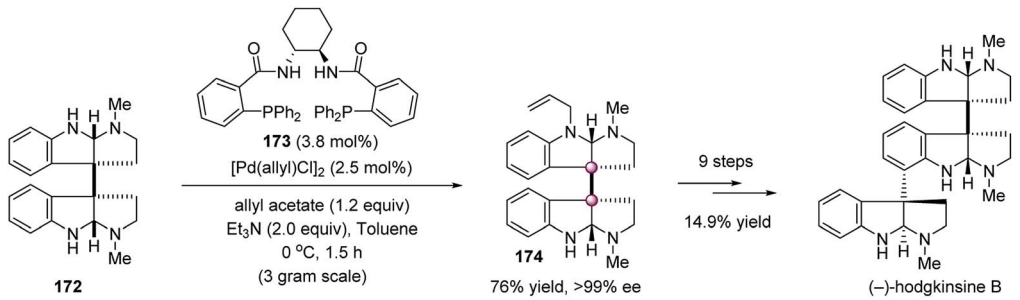
Scheme 32 Asymmetric homo- and heterodialkylation of bisoxindoles.

catalyst is farther away from the reaction site. It takes "remote control" to realize excellent stereoselectivities. Second, in principle, all types of catalytic reactions could be utilized to construct vicinal quaternary carbon stereocenters because no matter what kind of reaction takes place at one of the two identical functional groups attached to the preexisting adjacent quaternary carbons, vicinal quaternary stereocenters formed simultaneously. By this strategy, some elegant protocols have been developed successfully.

Early in 2002, during the total synthesis of *quadrigemine C* and *psycholeine*, Overman *et al.* showed an elegant desymmetrizing double Heck cyclization to forge the contiguous quaternary stereocenters of the C_1-symmetric dioxindole framework (Scheme 33). Under the catalysis of stoichiometric amounts of the chiral (*R*)-Tol-BINAP/Pd(OAc)$_2$ complex, the desymmetric double Heck cyclization of *meso*-dibutenanilide **170** afforded C_1-symmetric dioxindole **171** in 62% yield and 90% ee, along with the formation of 21% *meso*-isomer.[90] The



Scheme 33 Desymmetric double Heck cyclization.



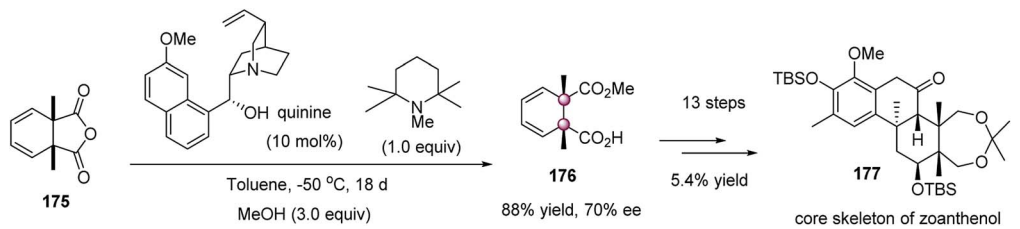
Scheme 34 Desymmetric Trost allylation.

central contiguous quaternary center and the two peripheral quaternary centers were constructed simultaneously, paving way to the alkaloids *quadrigemine* C and *psycholeine*.

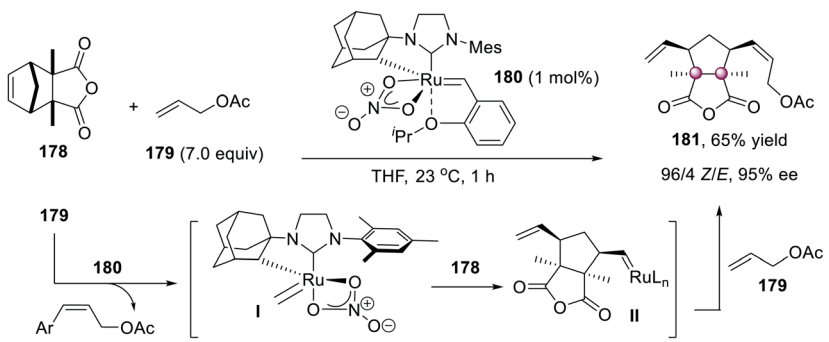
In 2011, Willis *et al.* developed a catalytic asymmetric desymmetrization of *meso*-chimonanthine **172** by means of Trost allylation, enabling the enantioselective total synthesis of *hodgkinsine B* (Scheme 34).[91] The use of a chiral Pd catalyst derived from **173** allowed access to *N*-allylchimonanthine **174** on a gram scale in high yield with >99% ee. The high efficiency of this reaction was very impressive because *meso*-chimonanthine **172** was probably the most complex *N*-nucleophile used in Trost allylation. With dimeric hexahydropyrroloindole **174** as the key intermediate, the total synthesis of *hodgkinsine B* was accomplished in 14.9% yield over nine steps.

In 2009, Stoltz and co-workers first attempted using a catalytic amount of a chiral catalyst to desymmetrize meso compounds to construct vicinal quaternary carbon stereocenters in an effort to construct the challenging carbocyclic core of zoanthenol (Scheme 35).[92] They found that in the presence of 10 mol% quinine and 1.0 equiv. pempidine, *meso*-anhydride **175** reacted with MeOH at −50 °C to afford the half-ester **176** in 88% yield and 70% ee. The key building block half-ester **176** enabled access to the carbocyclic core skeleton of *zoanthenol* **177** in 5.4% yield over 13 steps.

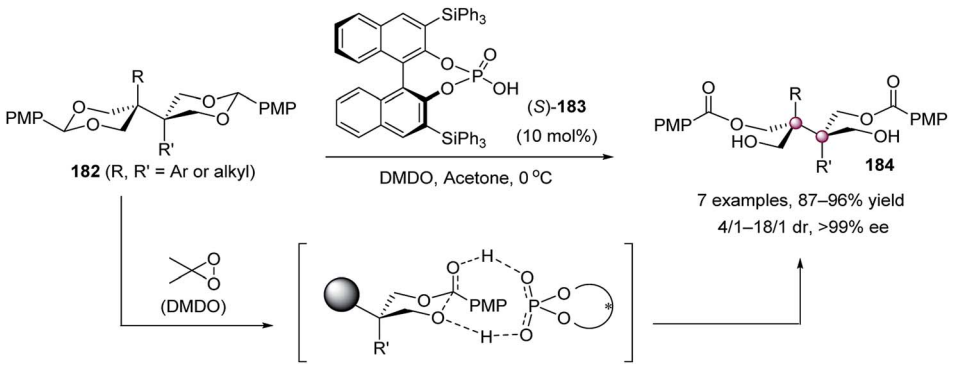
Grubbs *et al.* exploited a novel homochiral stereogenic-at-Ru complex **180** as a powerful catalyst for the *Z*-selective enantioselective ring-opening/cross-metathesis. They also tried using 1 mol% **180** to desymmetrize norbornene anhydride **178** with allyl acetate **179**, affording bicyclic lactone **181** in 65% yield, 96/4 *Z*/*E* ratio, and 95% ee (Scheme 36).[93] The initial cross-metathesis of **180** with allyl acetate **179** gave the ruthenium methylidene **I** that underwent the enantioselective ring-opening reaction with the norbornene **178** to give intermediate **II**. Subsequent cross-metathesis of **II** with allyl acetate **179** gave the final product **181**. It was proposed that the rigidity imparted by the Ru–C chelate was responsible for the high *Z* selectivity and enantioselectivity.



Scheme 35 Desymmetric methanolysis reaction.



Scheme 36 Desymmetric ring-opening/cross-metathesis reaction.



Scheme 37 Desymmetrization of tetrols.

Despite intensive studies on enantioselective desymmetrization of diols or triols, the first desymmetrization of tetrols was published as recently as 2017, when Zheng *et al.* reported a chiral phosphoric acid-mediated oxidative cleavage of benzylidene acetals **182** (Scheme 37).[94] Under the catalysis of phosphoric acid **183**, the desymmetrization of **182** worked well with 3,3-dimethyldioxirane (DMDO) to give products **184** in 87–96% yield, 4/1–18/1 dr, and >99% ee. It was believed that phosphoric acid **183** served as a proton shuttle to mediate the rate- and enantiodetermining DMDO oxidation step. Meanwhile, the interactions between the PMP group of the substrate and the catalyst were essential to obtain high enantioselectivity.

6. Conclusions

Although the catalytic enantioselective construction of two vicinal quaternary carbon stereocenters is a daunting challenge, remarkable achievements have been made in the past two decades. A series of elegant protocols have been exploited based on four major synthetic strategies as introduced. Some methods have demonstrated their value in facilitating the enantioselective total synthesis of natural products. Research in this field also gives an impetus for the development of new chiral catalysts and synthetic strategies.

Despite significant progress, this research is still at its early stage, full of opportunities for future development. First, the discovery of new reactions is the primary task. Although four strategies have been developed for the catalytic enantioselective construction of vicinal quaternary carbon stereocenters, only the strategy using trisubstituted carbon nucleophiles and electrophiles has met with relatively more successful examples, and the other three strategies are less investigated, with only limited examples reported. Second, known protocols have ample room for improvement in terms of stereoselectivities and substrate scope. Many reported reactions are limited in terms of substrate diversity, with only one or several substrates tested. For example, the enantioselective sequential modification of vicinal-activated methines is restricted to active bisoxindole scaffolds, and homo-type reactions dominate, with only one hetero-type reaction known (Scheme 32). In addition, except for the case of the oxidative homocoupling reaction of aldehydes (Scheme 22) and the desymmetrization of tetrols (Scheme 37), the construction of vicinal stereocenters in an acyclic system remains a particularly difficult challenge. Therefore, the development of new reactions using different types of substrates with sufficient structural diversity would be a promising direction. Third, enzyme catalysis has not found its utility in this challenging task, and it is worthwhile to use this powerful tool to realize reactivity and stereoselectivities unattainable by chiral metal catalysis or organocatalysis, which should be a direction that needs to be explored. Nevertheless, as can be expected, with the emergence of new chiral catalysts, more and more efficient enantioselective reactions will be exploited to construct adjacent quaternary carbon stereocenters, and find wide application in natural product and drug synthesis.

Conflicts of interest

The authors declare no competing interests.

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