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Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocenters

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Preface

Quaternary carbon stereocenters–carbon atoms to which four distinct carbon substituents are attached–are common features of molecules found in nature. However, prior to recent advances in chemical catalysis, there were few methods available for constructing single stereoisomers of this important structural motif. Here we discuss the many catalytic enantioselective reactions developed during the past decade for synthesizing organic molecules containing such carbon atoms. This progress now makes it possible to selectively incorporate quaternary stereocenters in many high-value organic molecules for use in medicine, agriculture, and other areas.

The properties of organic molecules are intimately tied to their shape. In many structurally complex organic molecules, shape is influenced–or dictated–by the three-dimensional orientation of substituents at stereogenic carbon centers (carbon atoms attached to four different substituents). During the last third of the 20th century, chemists succeeded in developing many powerful methods for directly forming a single three-dimensional orientation (configuration) of carbon centers of this type having one hydrogen substituent. In marked contrast, the construction of a single configuration of stereogenic carbon centers having four different carbon substituents (hereafter referred to as quaternary stereocenters) has until just recently been a daunting challenge for chemical synthesis. Remarkable advances have been recorded during the past decade in the stereocontrolled construction of quaternary stereocenters using chemical catalysis. No longer must the presence of a quaternary stereocenter in a molecule present a major hurdle for chemical synthesis. This exciting prospect prompts us to review the current status of this field of chemical synthesis.

Quaternary stereocenters are found in many biologically active small-molecule natural products, as exemplified by cortisone and morphine (Fig. 1a). One of the difficulties in constructing quaternary carbons is their congested nature, which is illustrated in the space-filling model of morphine wherein this carbon is barely visible at the end of the pointing arrow (Fig. 1b). Besides the challenge of steric hindrance, the stereoselective construction of quaternary stereocenters must involve the use of carbon–carbon bond-forming reactions that provide the desired three-dimensional orientation of the four attached substituents, i.e., the correct absolute configuration of the quaternary stereocenter. The structures of current pharmaceutical agents provide one indication of the substantial challenge in the chemical synthesis of quaternary stereocenters. Molecules containing this structural feature comprised 12% of the top 200 prescription drugs sold in the U.S. in 2011.[1] However, all of these drugs are derived from naturally occurring compounds (steroids, opioids, or taxane diterpenoids),

with a natural product precursor providing the quaternary stereocenters of the marketed drug in virtually every case.[2] The near absence of approved drugs containing chemically synthesized quaternary carbon stereocenters reflects the situation that until recently few reliable methods for preparing such structures existed.[3–5]

In 2004, we surveyed the field of catalytic enantioselective synthesis of quaternary stereocenters and concluded that only four transformations—Diels–Alder reactions, reactions of chiral allylmetal intermediates with carbon nucleophiles, intramolecular Heck reactions, and reactions of chiral carbon nucleophiles with electrophiles—were well documented to be useful.[5] In contrast, today a broad selection of methods is available for this purpose, prompting us to again review the status of this field. Our treatment will be organized by general reaction type in a fashion similar to our previous review.[5] We will highlight methods for which some generality has been demonstrated, and wherever possible catalytic transformations whose utility has been validated by their use in the construction of complex chemical structures, typically natural products.

Cycloaddition reactions

The catalytic enantioselective construction of quaternary stereocenters by cycloaddition reactions has progressed significantly in the past decade. New catalytic paradigms have been introduced, and the type of cycloaddition that can be employed has been expanded beyond Diels–Alder reactions.

An important recent development in this area is the use of small organic molecules to activate the dienophile in Diels–Alder reactions. The MacMillan group has described a number of [4+2]-cycloaddition reactions that proceed via catalytically generated iminium ion intermediates.[6] The utility of these reactions for the enantioselective synthesis of quaternary stereocenters was highlighted in concise total syntheses of various indole alkaloids.[7,8] For example, the rapid construction of intermediate **2** was the central step in total syntheses of (−)-minovincine (**3**), (−)-akuammicine (**4**), and (−)-strychnine (**5**) (Fig. 2a). Tetracyclic product **2** is the result of a cascade sequence, the first step of which is a catalytic enantioselective [4+2]-cycloaddition generating tricyclic intermediate **1**. Notable other recent reports of the construction of quaternary stereocenters using organocatalytic Diels–Alder reactions are the use of secondary amine[9] and hydrogen-bonding thiourea catalysts[10] to synthesize spirocyclic oxindoles and oxindole natural products.

The broad utility of catalytic enantioselective Diels–Alder reactions for constructing quaternary stereocenters is illustrated by several recent natural product total syntheses. For example, the total synthesis of *ent*-hyperforin (**10**) by the Shibasaki group featured a catalytic enantioselective Diels–Alder reaction between dienophile **6** and diene **7** in the presence of an iron complex generated from $FeBr_3$ and the pyridine bisoxazoline (PyBOX) ligand **8** (Fig. 2b).[11] The quaternary stereocenter of cycloadduct **9** subsequently played a decisive role in evolving the two additional quaternary stereocenters of *ent*-hyperforin. Catalytic enantioselective Diels–Alder reactions that form quaternary stereocenters have been orchestrated also in various intramolecular fashions, including macrobicyclization[12] and transannular processes.[13] The former construction is illustrated in the transformation of

polyene aldehyde **11** in the presence of oxazaborolidinium catalyst **12** to form macrobicyclic product **13** in good yield and 90% *ee*. Snyder and Corey elaborated cycloadduct **13** to several natural products, including palominol (**14**) (Fig. 2c).

Catalytic enantioselective cycloaddition reactions of various types have now been used for forming quaternary stereocenters. In particular, constructions to form five-membered rings are widely developed. The Davies group described the reaction of indoles with Rh-carbenoids to produce cyclopentene-fused indolines in excellent yield and enantioselectivity (Fig. 3a).[14] These reactions are believed to proceed in a stepwise fashion via a dipolar intermediate such as **15**. Enantioselective cycloadditions of palladium-trimethylenemethane (Pd-TMM) complexes have been developed extensively over many years by Trost and co-workers.[15] In this way, a variety of functionalized cyclopentene derivatives containing quaternary stereocenters can be accessed directly. For example, the catalytic-enantioselective cycloaddition of propylidene oxindole **16** and TMM donor **17** was the central step in the total synthesis of (−)-marcfortine C (**18**) (Fig. 3b).[16] Several types of ligands were investigated for promoting this transformation, with phosphoramidite ligand **19** found to be optimal. Other notable examples of forming five-membered rings and quaternary stereocenters in cycloaddition reactions that employ organometallic[17] or chiral phosphoric acid catalysts have been reported also.[18,19]

The formation of quaternary stereocenters by catalytic enantioselective cyclopropanation reactions was well established at the time of our previous review.[5] Progress in this area continues at a rapid pace, with the scope of enantioselective Simmons–Smith cyclopropanations and transition-metal catalyzed decomposition of diazoalkanes being continually advanced.[20] Catalytic enantioselective cyclopropanation reactions are also pivotal steps of cascade sequences developed to form larger rings. In their synthesis of (−)-5-*epi*-vibsanin E, the Davies group illustrates one variant: a cyclopropanation/Cope rearrangement sequence.[21] In the example illustrated, cycloaddition of the vinylcarbenoid derived from vinyl diazoester **21** and Rh_2(*R*-PTAD)$_4$ with the terminal double bond of diene **20** delivered *cis*-divinylcyclopropane **22**, which under the reaction conditions underwent Cope rearrangement to furnish cycloheptadiene **23** (Fig. 3c).

Polyene cyclizations

Enantioselective cyclization reactions of acyclic polyenes have been advanced considerably during the past decade. Yamamoto and co-workers described a number of enantioselective polyene cyclizations that proceed in the presence of stoichiometric amounts of protic acids generated upon complexation of $SnCl_4$ with BINOL-derived ligands.[22] Building on these disclosures, Corey and co-workers reported several concise total syntheses in which polyene cyclizations promoted by complexes formed from $SbCl_5$ and (*R*)-*o*,*o*′-dichloro-BINOL were the central steps.[23,24] Generally 1 equivalent of the complex was employed, although with structurally simpler substrates sub-stoichiometric amounts could be employed (Fig. 4a).

The use of transition-metal catalysts has been more successful in achieving good catalytic efficiency in enantioselective polyene cyclizations. Especially promising are iridium-catalyzed polyene cyclizations of allylic alcohol precursors developed by the Carreira

group.[25] A variety of functionalized decalins containing angular substituents can be obtained in this way in useful yields and high enantioselectivity. For example, the transformation of triene allylic alcohol **24** to decalin **25** in 73% yield and 96% *ee* was the central step of a short total synthesis of (+)-asperolide C (**26**) (Fig. 4b).[26] Toste and co-workers have described several gold-catalyzed cyclizations that construct polycyclic products containing quaternary stereocenters, such as the dienyne polycyclization to form tetracyclic product **28** using BIPHEP ligand **29** (Fig. 4c).[27] In addition, this group reported gold- and palladium-catalyzed cyclizations of silyloxyenynes[28] and a palladium-catalyzed variant of the Conia-ene reaction[29] to access functionalized cyclopentenes containing quaternary stereocenters. Rhodium catalysis has also been applied to the cyclization of dienynes to construct bicyclic, spirocyclic, and fused products depending upon the nature of the substrate. For example, the cyclization of acyclic dienyne **30** with a Rh/tol-BINAP catalyst led to the formation of bridged azatricyclic product **32** in 88% yield and 99% *ee*.[30] This reaction presumably takes place via metallacyclic intermediate **31**, which undergoes alkene insertion and reductive elimination to furnish product **32** (Fig. 4d).

The generation of chiral electrophiles to initiate polyene cyclizations using organic catalysts has also been developed in recent years. For example, the Jacobsen group reported the use of hydrogen-bonding thiourea catalysts to generate chiral *N*-acyliminium ion initiators of polyene cyclizations.[31] A novel approach to the catalytic enantioselective cyclization of acyclic polyenes was reported by the MacMillan group in which iminium ion activation and Cu(II)-promoted single-electron oxidation were combined to promote polycyclizations of radical-cation intermediates, as illustrated in the cyclization of polyene **33** (Fig. 4e).[32] Hexacyclic product **35** is produced stereoselectively in 63% yield and 93% *ee* in a remarkable pentacyclization that begins with the generation of radical-cation intermediate **34**. The nitrile substituents were incorporated to favor 6-endo cyclizations of the radical intermediates, a requirement that likely limits the utility of this method for construction of natural terpenoids and steroids.

Transition metal-catalyzed insertions

In our earlier review of catalytic enantioselective synthesis of quaternary stereocenters, intramolecular Heck reactions were suggested to have the broadest demonstrated scope.[5] This method continues to be important. The total synthesis of (+)-minfiensine (**39**) reported by Overman and co-workers provides one recent illustration (Fig. 5a).[33] In the Heck cyclization of dienyl triflate **36**, the use of PHOX ligand **40** was critical in achieving both high stereoinduction and preventing isomerization of the 1,4-diene product **37** to the conjugated 1,3-diene; avoiding double-bond migration was essential in allowing the second azacyclic ring of tetracyclic intermediate **38** to be generated upon exposure of the crude Heck product **37** to excess trifluoroacetic acid (TFA).

A variety of additional transition metal-catalyzed cyclization reactions have been developed recently for constructing polycyclic molecules containing quaternary stereocenters. Enantioselective nickel-catalyzed intramolecular arylcyanation reactions disclosed by the groups of Jacobsen[34] and Nakao[35] are notable examples. The synthesis of indane **41** illustrates this transformation (Fig. 5b). An attractive feature of these isomerization reactions

is the avoidance of the waste that would be generated in more conventional Heck-type cyclizations of related halide or triflate substrates. In another approach, Buchwald and co-workers reported the construction of quaternary stereocenters by palladium-catalyzed cyclization/dearomatization of naphthalene derivatives. For example, tetracyclic amine **43** was obtained in high yield and enantioselectivity from bromodiarylamine precursor **42** using a catalyst generated from $Pd(dba)_2$ and KenPhos (ligand **44**) (Fig. 5c).[36] Guangbin Dong and co-workers recently reported intramolecular carboacylation reactions of alkene-tethered benzocyclobutenones that construct various ring systems containing quaternary stereocenters, such as the formation of oxatricyclic ketone **47** from precursor **45** using a rhodium catalyst containing SEGPHOS ligand **48** (Fig. 5d).[37] This transformation is suggested to proceed by initial formation of metallacyclic intermediate **46**.

Apparent in our discussion to this point is the prevalence of intramolecular reactions that construct quaternary stereocenters during ring formation. In this context, the recent disclosure from the Sigman group of forming aryl-containing quaternary stereocenters in high enantioselectivity by bimolecular Heck-type reactions of arylboronic acids and acyclic trisubstituted alkenes containing alcohol substituents is particularly important.[38] The enantioselective synthesis of ketone **52** from unsaturated alcohol **49** using a catalyst formed from $Pd(CH_3CN)_2(OTs)_2$ and diamine ligand **53** is exemplary (Fig. 5e). This transformation is suggested to proceed by initial enantioselective carbopalladation of the alkene to form intermediate **50**, followed by sequential β-hydride eliminations/migratory insertions along the alkyl chain to eventually yield alkene complex **51** and then ketone product **52**. Considerable variation of the substituents on the alkene is tolerated, and depending upon the starting alcohol, either ketones or aldehydes containing remote quaternary stereocenters can be formed in high enantioselectivity in this way.

Coupling of chiral carbon nucleophiles

The enantioselective formation of quaternary stereocenters by the coupling of chiral carbon nucleophiles with achiral carbon electrophiles has progressed significantly over the past decade. Organocatalytic processes emerged to achieve such transformations, as well as numerous organometallic methods. Of particular note, high enantioselectivies can now be realized in copper-catalyzed additions of various organometallic nucleophiles to prochiral Michael acceptors.

Ten years ago we noted that useful procedures for forming quaternary stereocenters by copper-catalyzed additions of carbon nucleophiles to prochiral β,β-disubstituted enones and related electrophiles were notably absent.[5] This void is rapidly being filled, as many enantioselective copper-catalyzed 1,4-addition reactions have now been reported that proceed with high enantioselectivities. Some of the more important of these methods are illustrated in Fig. 6 for conjugate additions to 3-methyl-2-cyclohexen-1-one (**54**). Copper-catalyzed additions of various alkyl-,[39] alkenyl-,[40] and arylaluminum[41] compounds to cyclic enones in the presence of phosphoramidite ligands such as **58** have been described by Alexakis and co-workers (e.g., **54**→**55**, Fig. 6a). Hoveyda and coworkers reported the use of Cu/Ag–NHC catalyst for the conjugate addition of alkyl- and arylaluminum intermediates to conjugated enones (e.g., the synthesis of **56**, Fig. 6b),[42] as well as the addition of silicon-

containing vinylaluminum intermediates.[43] The addition of arylzinc reagents can also be accomplished using a structurally related Cu/Ag–NHC catalyst generated from silver complex **62**, as exemplified in the formation of *ent*-**55** (Fig. 6c).[44] Catalytic enantioselective conjugate addition reactions of other organometallic intermediates have been disclosed also. Notable examples include enantioselective copper-catalyzed additions of Grignard reagents described by Alexakis and co-workers, as illustrated in the conversion of **54→57** (Fig. 6d),[45] and an alkene hydrozirconation/conjugate addition sequence reported by Fletcher and co-workers to construct cyclohexanone **58** using a copper catalyst containing phosphoramidite ligand **63** (Fig. 6e).[46]

Good success has been realized also in conjugate addition reactions that form quaternary stereocenters using rhodium and palladium catalysts. For example, Hayashi described the use of Rh(I) complexes of chiral dienes to catalyze the addition of arylboronic acids or tetraaryl boronates to maleimides[47] and enones.[48] Exemplary is the synthesis of cyclohexanone **55** in this fashion in 85% yield and 98% *ee*. Rhodium-catalyzed additions of arylaluminum reagents to β-substituted cyclic enones were reported also by the Alexakis group, including the synthesis of **55** in 71% yield and 98% *ee* using an Rh-BINAP catalyst.[49] In addition, Stoltz and co-workers reported palladium-catalyzed variants of the 1,4-addition of boronic acids to enones for the enantioselective formation of chiral 3,3-disubstituted cyclohexanones.[50]

As prochiral β,β-disubstituted α,β-unsaturated carbonyl compounds can be constructed in many ways and are common intermediates in retrosynthetic analysis, the recent development of versatile catalytic methods to transform these intermediates into products containing new quaternary stereocenters is certain to find broad application. The transformations depicted at the bottom of Fig. 6, which were pivotal steps in enantioselective total syntheses of (+)-taxa-4(5),11(12)-dien-2-one[51] and clavirolide C,[52] are two recent examples.

When we discussed this approach for constructing quaternary stereocenters in our earlier review,[5] organic catalysts—typically phase-transfer catalysts—had been employed with considerable success to join enolate intermediates with carbon electrophiles. The notable utility of cinchona alkaloid derivatives in such constructions has been further illustrated by Deng and co-workers in catalytic enantioselective additions of 1,3-dicarbonyl and related compounds to nitroalkenes and α,β-unsaturated ketones,[53] and by Jørgensen in similar additions to allenic esters and ketones and for enantioselective alkynylations of 1,3-dicarbonyl compounds.[54] In addition, the use of enamine catalysis in the enantioselective construction of quaternary stereocenters from α-branched aldehydes—a reaction with broad potential utility for introducing quaternary stereocenters in a diversity of molecules[55]—was reported first by Barbas in 2004.[56] Organocatalysis has been utilized also to construct quaternary stereocenters by enantioselective intramolecular Stetter reactions of aromatic or aliphatic aldehydes (e.g., **64→65**) using triazolium catalysts such as **66** (Fig. 7a).[57] Other promising methods reported recently to exploit catalytically generated nucleophiles in the construction of quaternary stereocenters include the enantioselective insertion of diazoesters into the carbon–carbon bond of aryl aldehydes using an oxazaborolidinium catalyst,[58] and the enantioselective alkylation of acyclic tributyltin enolates in the presence of a Cr(salen) catalyst.[59]

A variety of enantioselective allylic substitution reactions have been reported in recent years that provide many opportunities for incorporating quaternary stereocenters in complex molecules. For example, a procedure developed by the Carreira group utilizes an Ir-cinchona alkaloid derivative dual-catalyst for the allylation of aldehydes. As exemplified in Fig. 7b, 3,3-disubstituted indoline **69** was constructed in this way with excellent enantio- and diastereoselectivity from indoline aldehyde **67** and allylic alcohol **68**.[60] Of most significance, catalytic enantioselective allylic alkylation reactions now allow quaternary stereocenters to be incorporated into many acyclic molecules or acyclic molecular fragments. The Hoveyda group has pioneered in this area by introducing a variety of enantioselective copper-catalyzed allylic substitution reactions.[61–63] In particular, this group has shown that a diverse array of carbon nucleophiles—such as dialkylzinc, vinylboron, vinylaluminum, and alkynylaluminum reagents—can be employed in allylic substitution reactions that form new quaternary stereocenters. The efficient and highly enantioselective alkylation of allylic phosphate **71** with an ester-containing vinylboron nucleophile to form product **72** in the presence of a copper-NHC catalyst is exemplary (Fig. 7c).[61] As a final example, the enantio- and *anti*-diastereoselective allylic coupling of benzyl alcohol **74** with vinyl epoxide **75** to yield 1,3-diol **76** using Ir catalyst **77** disclosed by Krische and co-workers even allows a benzyl alcohol to be employed as the pro-nucleophile in the construction of quaternary stereocenters (Fig. 7d).[64] This reaction, which results in appending a 1-(hydroxymethyl)-1-methylallyl unit to the alcohol fragment, should find use in the synthesis of terpenoid natural products that incorporate this (hydroxy)prenyl motif. A notable feature of redox-triggered couplings of this type pioneered by the Krische group is the absence of stoichiometric byproducts.

Coupling of chiral carbon electrophiles

Reactions of chiral carbon electrophiles with carbon nucleophiles encompass a range of transformations that can be used to form quaternary stereocenters in structurally complex molecules. During the past decade, palladium-catalyzed enantioselective allylic alkylation reactions have been applied widely to achieve this aim, and a number of other promising methods employing transition metal or organic catalysts have been introduced.

The use of enantioselective palladium-catalyzed allylic alkylation reactions to form quaternary stereocenters adjacent to ketone carbonyl groups was initially reported by the Stoltz[65] and Trost groups.[66] Since these initial disclosures, this method has been featured in several natural product total syntheses.[4] For example, a variety of chiral 3,3-disubstituted oxindoles have been prepared in this fashion with good enantioselectivity,[67,68] as exemplified by the enantioselective and regioselective prenylation (**78→79**) utilized in the synthesis of *ent*-flustramines A (**80**) and B (Fig. 8a).[69] In a strategically incisive example, Stoltz and co-workers employed an enantioselective double allylation of racemic bis-β-ketoester **82** to form C_2-symmetric diketone **83** in route to (−)-cyanthiwigin F (**84**) (Fig. 8b).[70] Other significant recent developments in this area include the use of a vinyl epoxide as a coupling partner in the total syntheses of (−)-biyouyanagin A and hyperolactone C,[71] and the application of molybdenum[72] and iridium[73] catalysts in enantioselective allylic alkylation reactions. In addition, the enantioselective C-3 allylation of an indole derivative

using allyl alcohol in combination with a trialkylborane as the alkylating reagent was featured in a synthesis of (−)-esermethole.[74]

Organocatalytic reactions can be employed also to generate chiral electrophiles for constructing quaternary stereocenters. Particularly well developed is the use of catalytic enantioselective Steglich rearrangements. Fu[75] and Vedejs[76] developed chiral-enantiopure variants of 4-(dimethylamino)pyridine (DMAP) to accomplish enantioselective rearrangements of enoxycarbonate derivatives, including those derived from oxindoles and furanones. The Fu group also described related transformations involving the acylation of silyl ketene imines and employed this method as the central step in a synthesis of (*S*)-verapamil.[77] In a concise second-generation total synthesis of (+)-gliocladin C (**87**), Overman and co-workers exploited the planar-chiral DMAP variant **88**[75] to catalyze the enantioselective Steglich rearrangement of enoxycarbonate **85** to yield oxindole **86** (Fig. 9a).[78] In this study, the practicality of Fu's method was highlighted by the formation of **86** in 96% yield and 96% *ee* on multigram scales. In a quite different approach to generating chiral carbon electrophiles, iminium activation developed by the MacMillan group has been used for the enantioselective construction of 3a-substituted pyrrolidinoindolines and featured in the synthesis of (−)-flustramine B.[79]

Although their scope is less well defined at this point than enantioselective palladium-catalyzed allylation reactions or Steglich rearrangements, enantioselective transition metal-catalyzed arylations, vinylations, and alkylations of prochiral nucleophiles have been described recently for the enantioselective construction of quaternary stereocenters. One example is the enantioselective copper-catalyzed indole arylation/cyclization sequence reported by the MacMillan group.[80] In this transformation, tryptophan amides undergo efficient indole arylation in the presence of a diaryliodonium salt, CuOTf, and enantiopure bisoxazoline ligand **91**, followed by intramolecular trapping of the pendant amide to form 3a-arylpyrrolidinoindolines (**89→90**) (Fig. 9b). Other notable examples of copper-catalyzed arylation and vinylation reactions to construct quaternary stereocenters are copper-catalyzed arylations of prochiral β-ketoesters with 2-iodotrifluoroacetanilides described by Ma and co-workers,[81] and palladium-catalyzed enantioselective α-arylations of α-branched aldehydes[82] and the C-3 arylations or vinylations of oxindoles reported by the Buchwald group.[83] Catalytic enantioselective alkylations of prochiral nucleophiles can be achieved as well. A double alkylation of a 3,3′-dioxindole with nitroethylene was reported the Shibasaki group in route to (+)-chimonanthine, (+)-folicanthine, and (−)-calycanthine.[84] In a mechanistically intriguing variant, catalytic enantioselective alkylations of 3-bromooxindoles with 3-substituted indoles were reported by the Wang group for the construction of vicinal quaternary stereocenters using a catalyst formed from $Ni(OAc)_2$ and diamine ligand **92**. This step in the total synthesis of (+)-perophoramidine is illustrated in Fig. 9c.[85] This reaction is suggested to occur by loss of HBr from the 3-bromooxindole to generate an electrophilic indol-2one intermediate, which couples with the indole nucleophile. How the Ni-diamine catalyst organizes this coupling to achieve high enantio- and diastereoselction is unclear at present.

Desymmetrization reactions

In principle, any catalytic enantioselective reaction could be employed to construct a product containing a quaternary stereocenter by desymmetrization of an appropriately constituted prochiral precursor. Since our earlier review,[5] numerous additional examples of using group-selective catalytic enantioselective reactions for this purpose have been described. For instance in their synthesis of (+)-quebrachamine (**95**), Hoveyda and Schrock reported the use of a chiral molybdenum metathesis catalyst to fashion the tetrahydropyridine ring of intermediate **94** from triene precursor **93** in excellent yield and enantioselectivity (Fig. 10a).[86] Enantioselective ring-opening/cross-metathesis has been described also by the Hoveyda group to construct acyclic products bearing quaternary centers.[87] In a quite different approach reported by the Toste group, cyclobutanones containing α-quaternary stereocenters can be prepared by enantioselective gold-catalyzed ring expansion of prochiral allenylcyclopropanols (Fig. 10b).[88] Applications of two recently developed rhodium-catalyzed C–C-bond constructions for enantioselective desymmetrization are exemplified in Figures 10c and 10d. In the first example from the laboratory of Vy Dong, intermolecular hydroacylation of the prochiral cyclopropene **96** with salicylaldehyde delivers the highly substituted cyclopropane product **97** in high yield and enantiomeric purity (Fig. 10c).[89] The second example from the Cramer group, illustrates the use of C–C bond activation in the efficient and enantioselective formation of bridged tricyclic ketone **99** from the prochiral cyclobutanone precursor **98** (Fig. 10d).[90] In an example exploiting enantioselective C–H activation, the Yu group reported palladium(II)-catalyzed group-selective functionalizations of diphenylacetic acid derivatives.[91] Utilizing a palladium catalyst containing protected-amino acid ligands, various diphenylacetic derivatives underwent selective alkenylation with acrylates or styrenes exemplified by the conversion of **100→101** (Fig. 10e). In a final example, a number of prochiral cyclopentene-1,3-diones have been desymmetrized by copper-catalyzed enantioselective additions of dialkylzinc or organoaluminum reagents.[92] The use of a phosphoramidite ligand such as **105** proved optimal in this method, as illustrated in the enantioselective synthesis of cyclopentene-1,3-dione **103**, a key step in the synthesis of (+)-madindoline B (**104**) (Fig. 10f). Organocatalytic methods have also proven useful for constructing quaternary stereocenters by desymmetrization. Protic-acid catalyzed vinylogous α-ketol rearrangements to yield spirocyclic diones,[93] and the preparation of five-membered rings from 1,3-diketone precursors using chiral NHC-catalysts are two important examples.[94]

Looking forward

The research highlighted in this brief survey shows that a variety of chemical transformations are now available to synthetic chemists for incorporating quaternary stereocenters with high enantioselectivity in organic molecules. When the catalytic transformations that are the focus of our analysis are combined with non-catalytic methods, a diversity of chemical transformations are now available for meeting this formidable challenge. Nonetheless, the scope of the majority of the methods discussed in this review is only partially defined, and limitations are certain to be uncovered. One area where the development of methods is still in its early stages is the introduction of quaternary stereocenters in acyclic molecules or acyclic molecular fragments.[95] Even in areas where

substantial progress has been recorded recently in fashioning quaternary stereocenters in cyclic molecules—for example, by conjugate additions to cyclohexenones—enantioselectivities realized in identical reactions with cyclic enones of other ring sizes or acyclic enones can be inferior. It is instructive to note that almost all the methods exemplified in this review involve the functionalization of π-bonds. With the intense attention currently being paid to the direct functionalization of Csp^3–H σ-bonds, one can anticipate that catalytic C–H insertions will play a much larger role in the future in the enantioselective synthesis of quaternary stereocenters. For example, the scope of such transformations for desymmetrizing prochiral quaternary carbons is certain to expand,[96] and new methods exploiting selective C–H functionalizations will likely be developed for transforming chiral tertiary carbons (enantiopure or racemic) and prochiral secondary carbons to new quaternary stereocenters. As nearly half of the transformations we exemplified involve the use of catalysts containing rare and/or expensive metals, the development of alternate catalytic methods based on readily available and less expensive catalysts remains a critical future challenge in this area.

The methods now available for fashioning quaternary stereocenters enantioselectively remove much of the previous barrier to incorporating such functionality in organic molecules for use in medicine, agriculture, and other areas where high-value organic molecules play an important role. One can already see this impact in small-molecules currently undergoing clinical evaluation such as anamorelin.[97] With several recent studies suggesting that drug candidates that contain a larger fraction of sp^3 carbons and chiral centers have lower attrition in the clinic,[98] we anticipate seeing an ever increasing number of drug candidates containing quaternary stereocenters being designed, synthesized, and evaluated. In this context, the unrivaled stability of quaternary stereocenters toward metabolic modification is a unique attraction.

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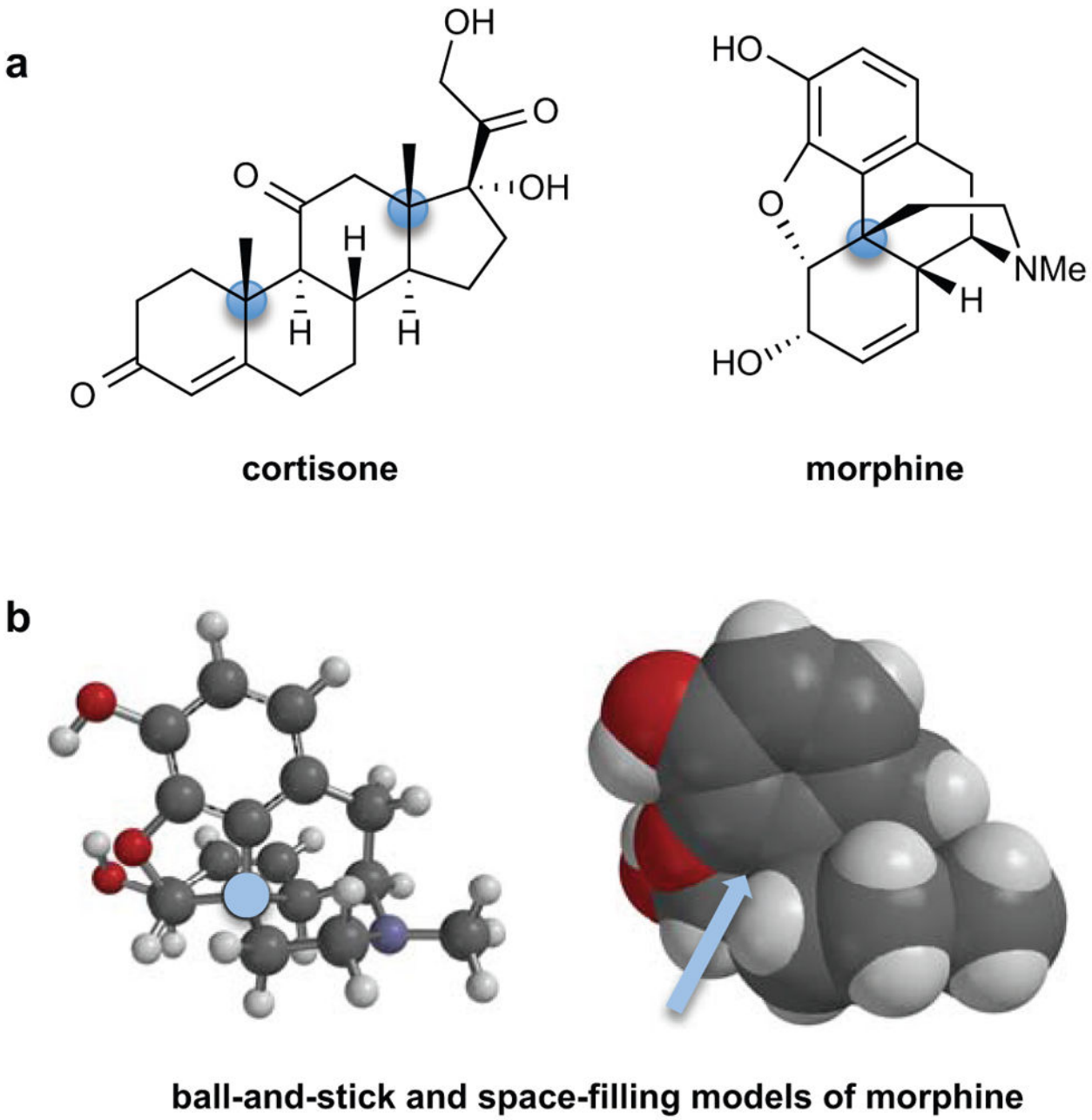

Figure 1. Quaternary stereocenters are important structural features of many biologically active molecules as exemplified by the natural products cortisone and morphine

a, Structures of the steroid cortisone and opioid morphine with their quaternary stereocenters highlighted. Me, methyl. **b**, Steric congestion, which presents a formidable challenge for chemical synthesis of molecules containing quaternary stereocenters, is illustrated in the molecular models of morphine, particularly in the space-filling model on the right in which its sterically congested quaternary center is barely visible at the end of the pointing arrow.

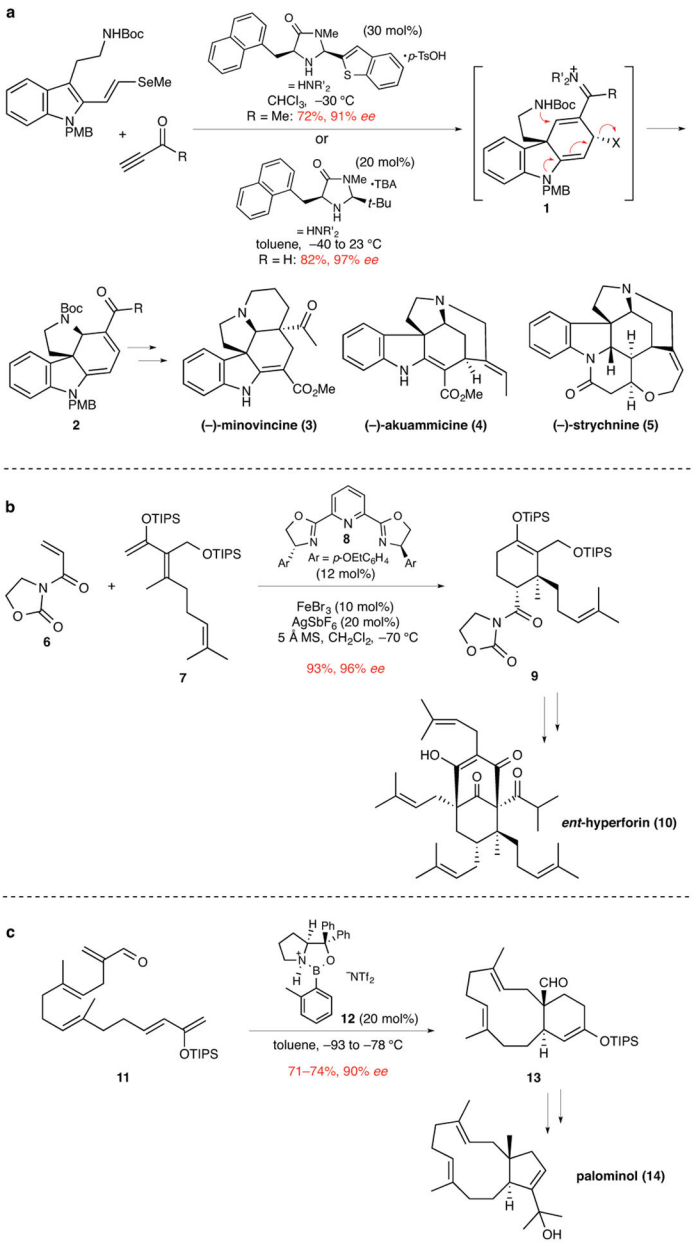

Figure 2. The use of catalytic enantioselective Diels–Alder reactions to synthesize natural products containing quaternary stereocenters

ee, enantiomeric excess. **a**, A bimolecular Diels–Alder reaction promoted by iminium ion activation forms intermediate **1** in the first step of a cascade sequence generating tetracyclic product **2**. This product contains the quaternary stereocenter and four rings common to several groups of indole alkaloids and was employed to complete enantioselective total syntheses of various indole alkaloids, including (−)-minovincine (**3**), (−)-akuammicine (**4**), and (−)-strychnine (**5**).[7] Boc, *tert*-butoxycarbonyl; Me, methyl; PMB, *p*-methoxybenzyl; *p*-TsOH, *p*-toluenesulfonic acid; *t*-Bu, *tert*-butyl; TBA, tribromoacetic acid. **b**, An iron-bisoxazoline catalyzed bimolecular Diels–Alder reaction forms product **9** whose quaternary stereocenter subsequently controlled the elaboration of the two additional quaternary

stereocenters of *ent*-hyperforin (**10**).[11] TIPS, triisopropylsilyl; Et, ethyl; MS, molecular sieves. **c**, Oxazaborolidinium-catalyzed intramolecular Diels–Alder reaction to form the 11-membered ring and quaternary stereocenter of palominol (**14**).[12] Tf, trifluorosulfonyl; TIPS, triisopropylsilyl; Ph, phenyl.

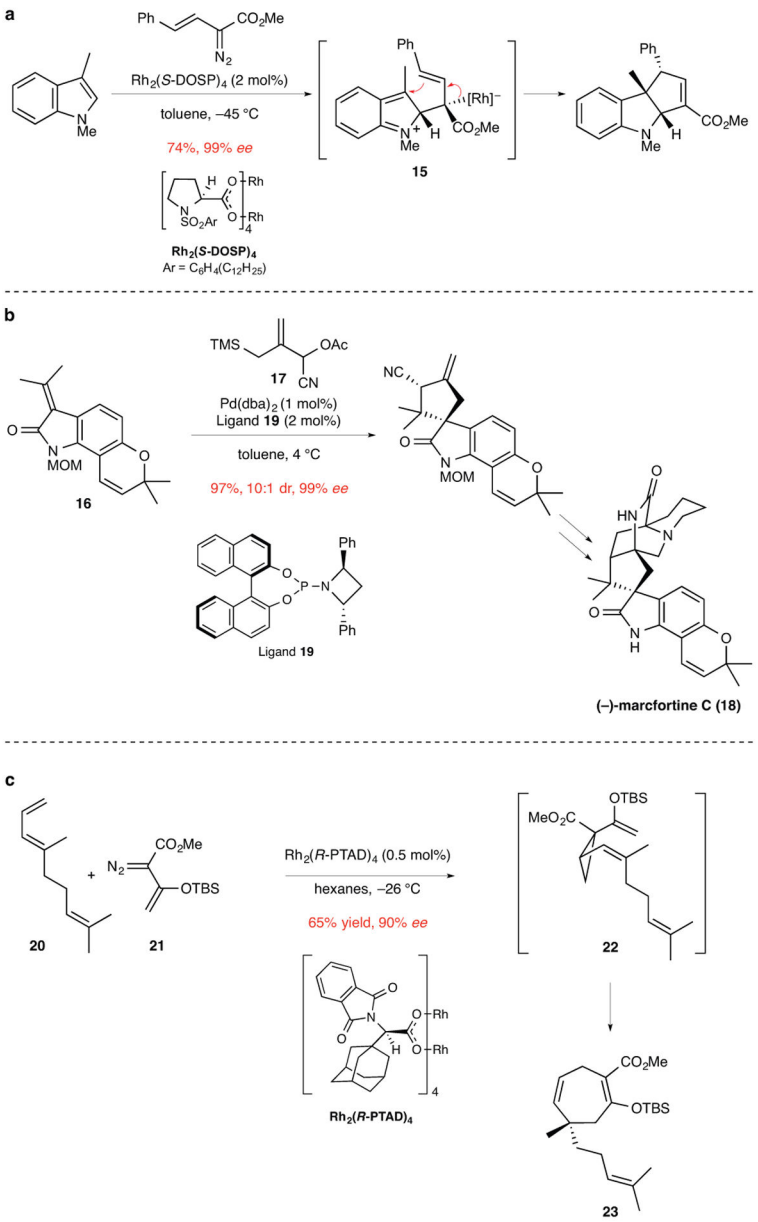

Figure 3. Examples of other catalytic enantioselective cycloaddition reactions used to prepare products containing quaternary stereocenters

ee, enantiomeric excess. **a**, The synthesis of a cyclopentene-fused indoline by a formal [3+2]-cycloaddition of 1,3-dimethylindole and a vinyl diazoester using a rhodium catalyst. This reaction is suggested to take place in a stepwise fashion via dipolar intermediate **15**.[14] Me, methyl; Ph, phenyl. **b**, The [3+2]-cycloaddition of a Pd-trimethylenemethane intermediate generated from allylic acetate **17** to form a tetracyclic intermediate in the total synthesis of (−)-marcfortine C.[16] MOM, methoxymethyl; TMS, trimethylsilyl; Ac, acetate; dba, dibenzylideneacetone; Ph, phenyl. **c**, Enantioselective synthesis of 1,4-cycloheptadiene **23** from triene **20** and vinyl diazoester **21**. The first step in this sequence is Rh-catalyzed cyclopropanation of the terminal double bond of the acyclic triene to form divinyl

cyclopropane **22**, which upon *in situ* Cope rearrangement generates **23** and its quaternary stereocenter. Product **23** was employed in the total synthesis of the diterpenoid (−)-5-*epi*-vibsanin E.[21] Me, methyl; TBS, *tert*-butyldimethylsilyl.

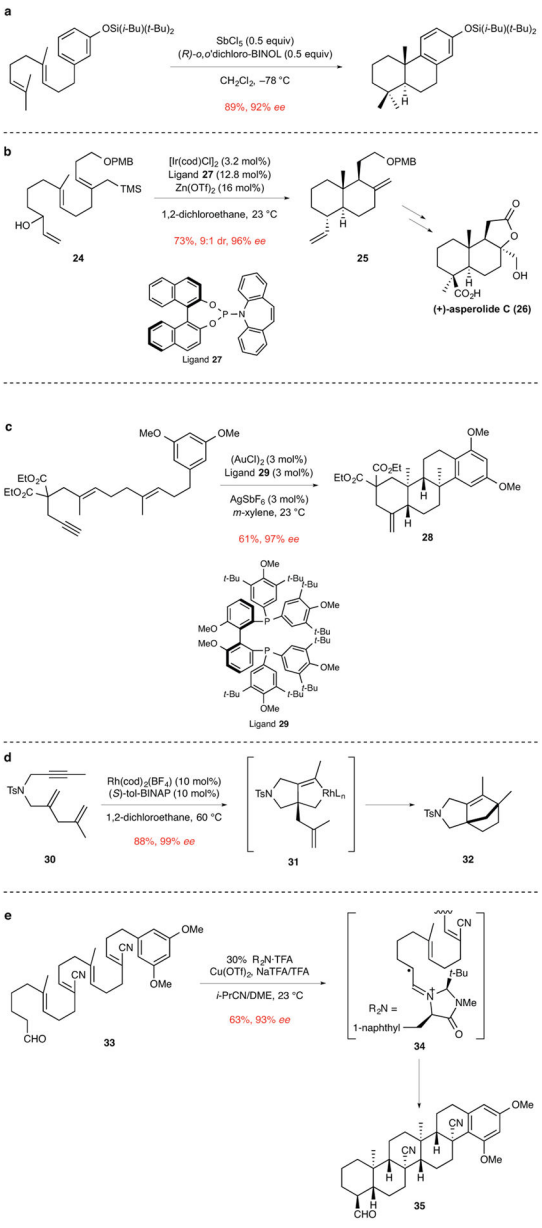

Figure 4. Catalytic enantioselective polyene cyclizations to construct polycyclic products having quaternary stereocenters

ee, enantiomeric excess. **a**, The use of a protic acid catalyst for the cyclization of an aryl diene to form two rings and one quaternary stereocenter.[24] *i*-Bu, isobutyl; *t*-Bu, *tert*-butyl; BINOL, 1,1′-bi-2-naphthol. **b**, The iridium-catalyzed cyclization of a triene alcohol to construct the *trans*-decalin core **25** of the labdane diterpenoid (+)-asperolide C (**26**). The first step in this cascade cyclization is the generation of a η^3-allyliridium cation from the allylic alcohol fragment of **24**.[26] PMB, *p*-methoxybenzyl; TMS, trimethylsilyl; cod, 1,5-cyclooctadiene; Tf, trifluorosulfonyl. **c**, The gold-catalyzed cyclization of an aryl dienyne to form three rings and two quaternary stereocenters of tetracyclic product **28**.[27] Et, ethyl; Me, methyl; *t*-Bu, *tert*-butyl. **d** The rhodium-catalyzed cyclization of dienyne **30** to form bridged

azatricyclic product **32**. This reaction is suggested to take place via metallacyclic intermediate **31**, which undergoes alkene insertion and reductive elimination to furnish product **32**.[30] Ts, *p*-toluenesulfonyl; tol-BINAP, 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthalene; cod, 1,5-cyclooctadiene; L, ligand. **e**, The cyclization of tetraene aldehyde **33** in the presence of an imidazolone catalyst and a Cu(II) oxidant to form five rings and four quaternary stereocenters of hexacyclic product **35**. This novel reaction is suggested to proceed by single-electron oxidation of the initially formed iminium ion intermediate to generate **34**, which undergoes a series of 6-endo radical cyclizations to eventually give product **35**. The nitrile substituents are incorporated to disfavor 5-endo cyclizations in the formation of the second and fourth rings.[32] Me, methyl; Tf, trifluorosulfonyl; TFA, trifluoroacetic acid; NaTFA, sodium trifluoroacetate; *i*-Pr, isopropyl; DME, 1,2-dimethoxyethane.

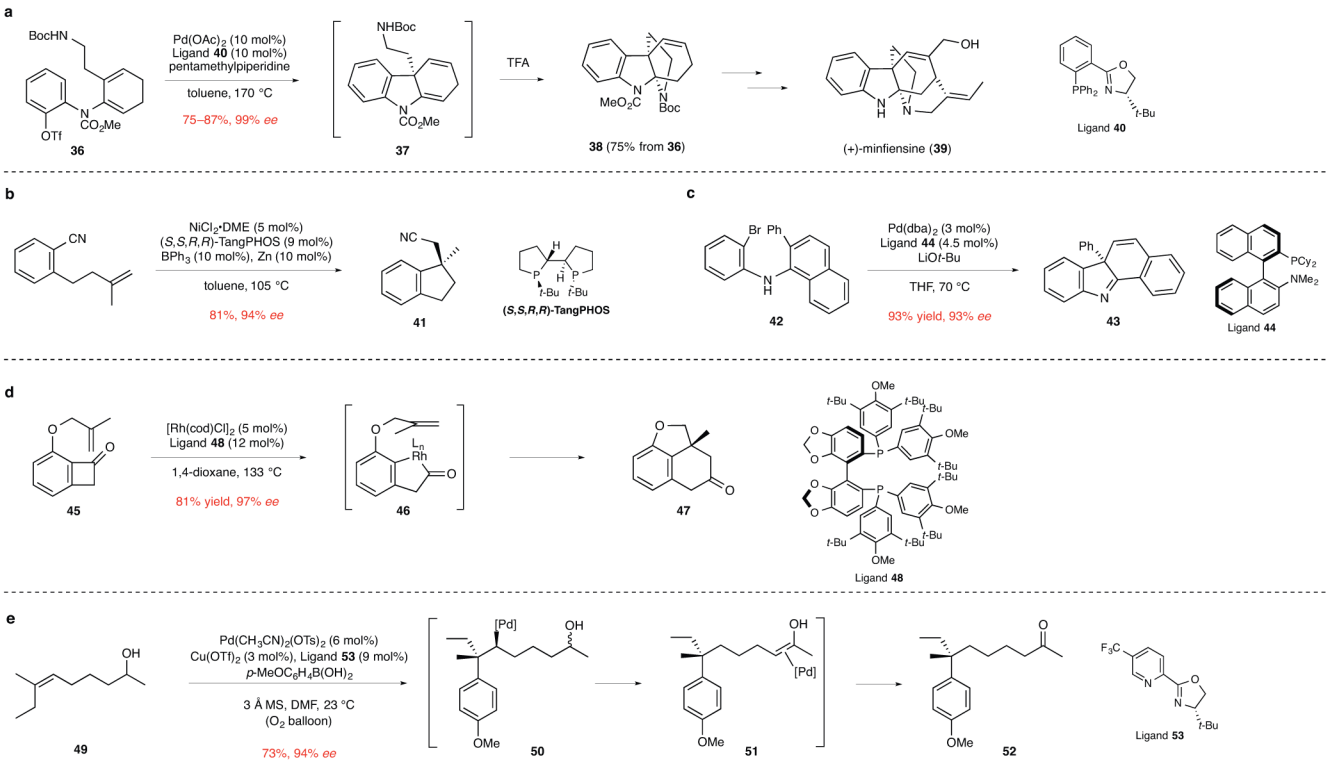

Figure 5. Transition metal-catalyzed insertion reactions that form quaternary stereocenters

ee, enantiomeric excess. **a**, The enantioselective intramolecular Heck cyclization of dienyl triflate **36** to form 1,4-diene intermediate **37**, which upon exposure to excess trifluoroacetic acid provided tetracyclic product **38** in route to the indole alkaloid (+)-minfiensine (**39**). The use of PHOX ligand **40** was critical in achieving both high stereoinduction and preventing isomerization of the initially formed product **37** to the conjugated 1,3-diene regioisomer.[33] Boc, *tert*-butoxycarbonyl; Me, methyl; Tf, trifluorosulfonyl; Ac, acetyl; TFA, trifluoroacetic acid. **b**, The intramolecular nickel-catalyzed arylcyanation of a tethered double bond to form indane **41**.[34] DME, 1,2-dimethoxyethane; Ph, phenyl; *t*-Bu, *tert*-butyl. **c**, The palladium-catalyzed cyclization/dearomatization of aryl(naphthyl)amine **42** to form tetracyclic product **43**. This reaction is suggested to occur via a six-membered palladacyclic intermediate that undergoes reductive elimination to form generate product **43**.[36] Ph, phenyl; dba, dibenzylideneacetone; *t*-Bu, *tert*-butyl; THF, tetrahydrofuran; Me, methyl; Cy, cyclohexyl. **d**, The rhodium-catalyzed conversion of alkenyl benzocyclobutanone **45** to tricyclic ether **47**. This transformation is believed to occur by initial insertion of rhodium into the C–C bond to form acylrhodium intermediate **46**, which in the enantiodetermining step undergoes intramolecular carboacylation of the tethered alkene to form product **47**.[37] cod, 1,5-cyclooctadiene; L, ligand; Me, methyl; *t*-Bu, *tert*-butyl. **e**, The bimolecular Heck-type addition of an arylboronic acid to the trisubstituted double bond of **49** to form ketone product **52**. This rare example of a bimolecular alkene insertion to form a quaternary stereocenter is suggested to occur by initial enantioselective carbopalladation of the alkene to generate intermediate **50**, which undergoes sequential β-hydride eliminations/migratory insertions along the alkyl chain to form alkene complex **51** and then the ketone product.[38]

Ts, *p*-toluenesulfonyl; Tf, trifluorosulfonyl; Me, methyl; MS, molecular sieves; DMF, *N*,*N*-dimethylformamide; *t*-Bu, *tert*-butyl.

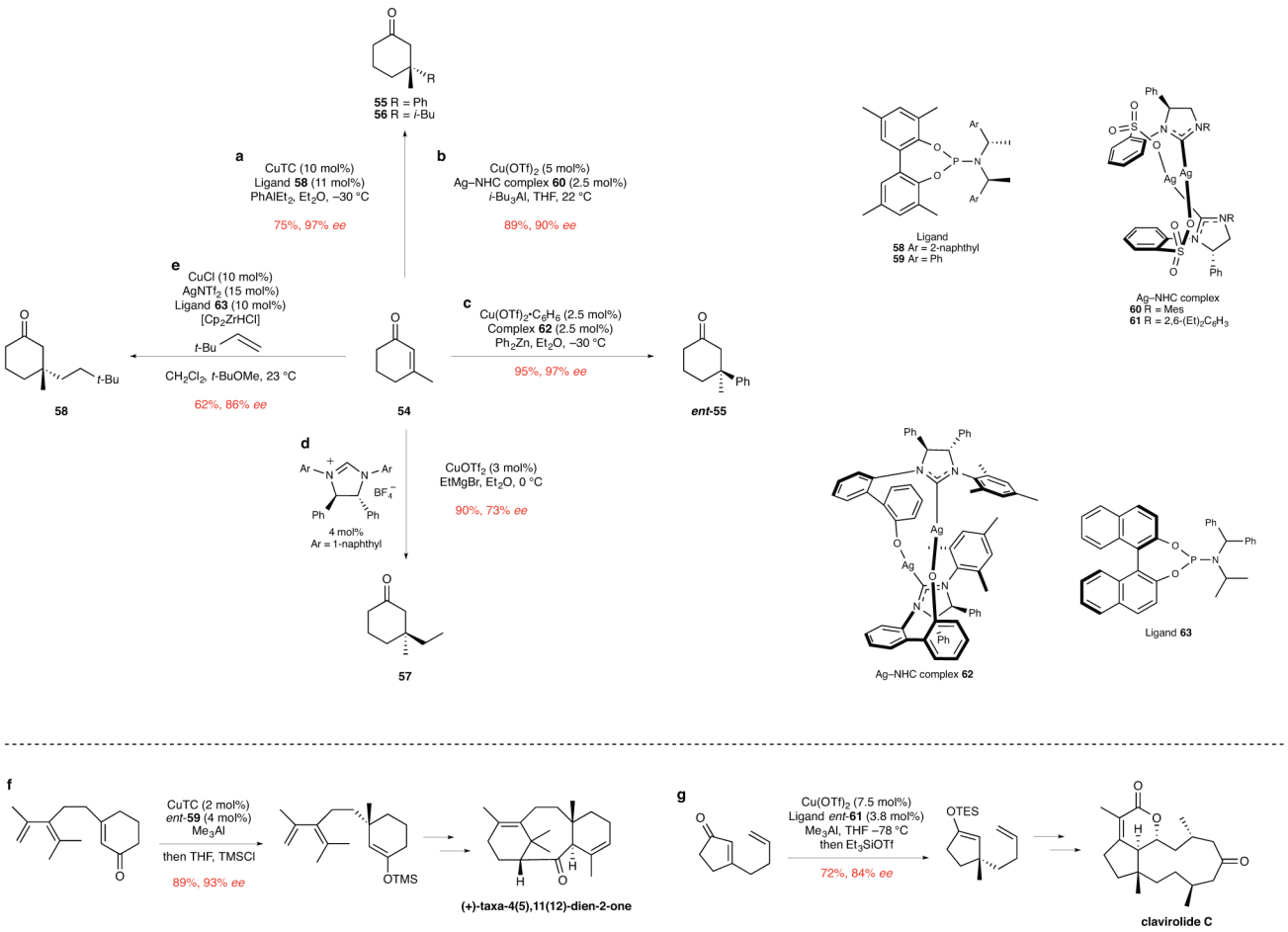

Figure 6. Enantioselective copper-catalyzed conjugate additions to construct quaternary stereocenters

ee, enantiomeric excess. The upper segment of the Figure depicts several Cu-catalyzed conjugate additions to 3-methyl-2-cyclohexen-1-one (**54**) that form new quaternary stereocenters: **a**, The addition of an arylaluminum compound to **54** to form cyclohexanone **55**.[40] CuTC, copper(I) thiophene-2-carboxylate; Ph, phenyl; Et, ethyl. **b**, The addition of a trialkylaluminum compound to **54** to form cyclohexanone **56**.[42] Tf, trifluorosulfonyl; *i*-Bu, isobutyl; THF, tetrahydrofuran; Ph, phenyl; NHC, *N*-heterocyclic carbene. **c**, The addition of an arylzinc compound to **54** to form the enantiomer of cyclohexanone **55**.[44] Tf, trifluorosulfonyl; Ph, phenyl; Et, ethyl. **d**, The addition of an alkyl Grignard reagent to **54** to form 3,3-dialkylcyclohexanone **57**.[45] Tf, trifluorosulfonyl; Ph, phenyl; Et, ethyl. **e**, The addition of an alkylzirconium intermediate generated by hydrozirconation of 3,3-dimethyl-1-butene to **54** to form 3,3-dialkylcyclohexanone **58**.[46] Tf, trifluorosulfonyl; Cp, cyclopentadienyl; *t*-Bu, *tert*-butyl; Me, methyl. The lower segment of the Figure shows the use of two of these methods to form methyl-containing quaternary stereocenters in syntheses of a potential taxane terpenoid precursor and a dolabellane diterpenoid: **f**, The enantioselective copper-catalyzed conjugate addition/enolate trapping to introduce a quaternary methyl group in the construction of a taxadienone.[51] CuTC, copper(I) thiophene-2-carboxylate; Me, methyl; THF, tetrahydrofuran; TMS, trimethylsilyl. **g**, The

enantioselective copper-catalyzed conjugate addition/enolate trapping to introduce a quaternary methyl group in the total synthesis of clavirolide C.[52] Tf, trifluorosulfonyl; Me, methyl; THF, tetrahydrofuran; TES, triethylsilyl.

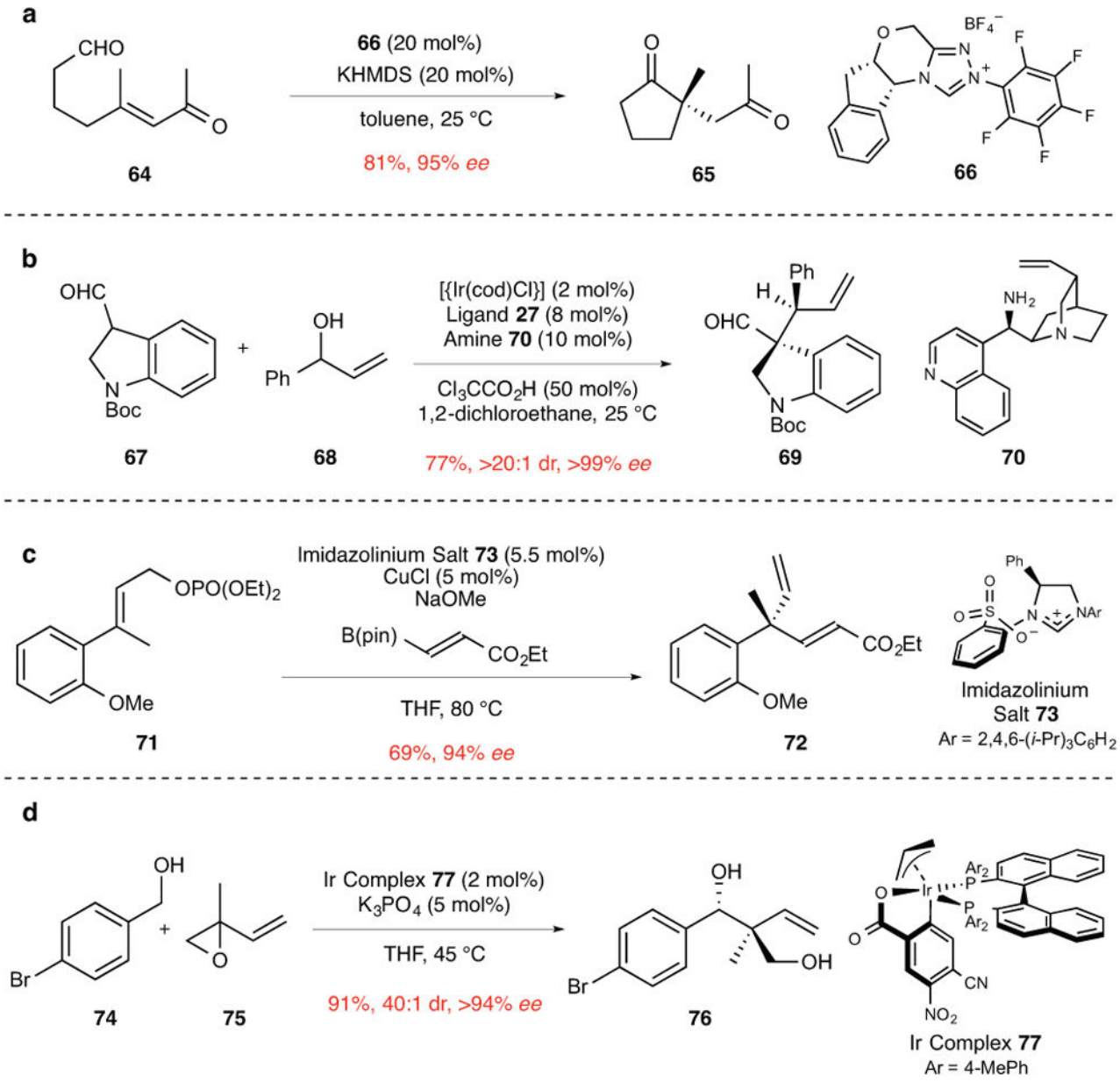

Figure 7. Enantioselective intramolecular Stetter reaction and allylic alkylation reactions to construct quaternary stereocenters

ee, enantiomeric excess. **a**, The intramolecular Stetter reaction of enone aldehyde **64** catalyzed by the carbene generated from triazolium salt **66** to form 2,2-disubstituted cyclopentanone **65**.[57] KHMDS, potassium bis(trimethylsilyl)amide. **b**, The α-allylation of indoline aldehyde **67** with allylic alcohol **68** using the dual activity of iridium and amine catalysts. This reaction constructs the quaternary and adjacent secondary stereocenter of product **69**.[60] Boc, *tert*-butoxycarbonyl; cod, 1,5-cyclooctadiene; Ph, phenyl. **c**, The formation of 4,4-disubstituted 2,5-hexadienoic ester **72** by allylic displacement of phosphate triester **71**. In this reaction, an alkenylcopper carbene complex is generated from a vinylboronate precursor.[61] Me, methyl; pin, pinacolato; THF, tetrahydrofuran; Ph, phenyl.

d, The *anti*-diastereoselective coupling of benzyl alcohol **74** with vinyl epoxide **75** using an iridium catalyst to give the product **76** of carbonyl *tert*-(hydroxy)prenylation. This reaction proceeds by the coupling of aldehyde and (*E*)-σ-allyliridium intermediates respectively generated *in situ* from the alcohol and vinyl epoxide precursors by an iridium-catalyzed redox process.[64] Ph, phenyl.

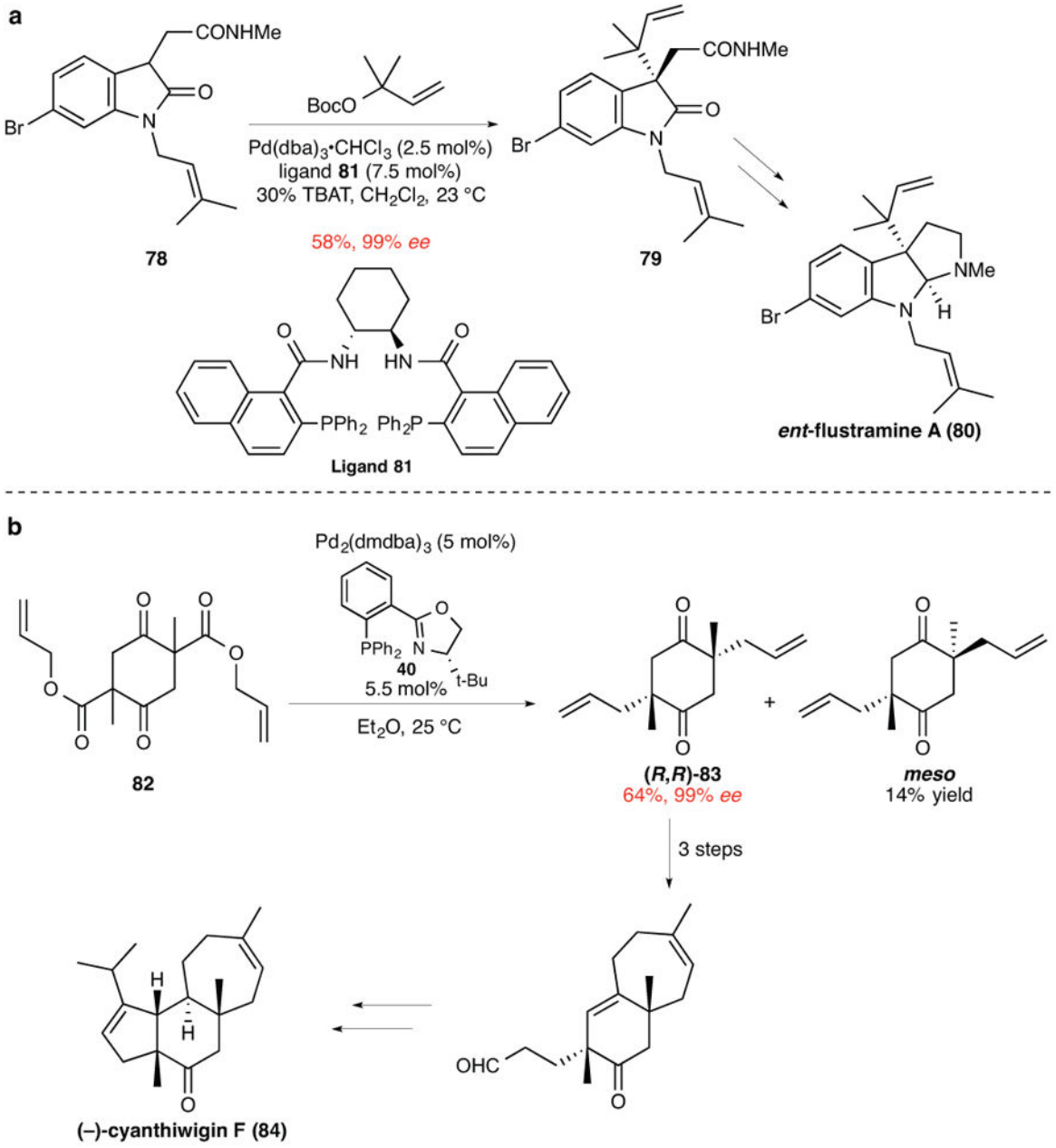

Figure 8. Use of palladium-catalyzed asymmetric allylic alkylation reactions for constructing quaternary centers in alkaloid and terpenoid natural products

a, The regioselective prenylation of oxindole **78** upon base-promoted reaction with the η^3-allylpalladium electrophile generated from a prenyl carbonate to form **79**. This product was a late-stage intermediate in the enantioselective total synthesis of *ent*-flustramine A (**80**).[69] Me, methyl; Boc, *tert*-butoxycarbonyl; dba, dibenzylideneacetone; TBAT, tetrabutylammonium difluorotriphenylsilicate; Ph, phenyl. **b**, The *syn*-diastereoselective diallylation of β-ketoester **82** (a mixture of racemic diastereomers) to give **(*R*,*R*)-83**, a pivotal intermediate in the enantioselective total synthesis of (−)-cyanthiwigin F.[70] dmdba, bis(3,5-dimethoxybenzylidene)acetone; Ph, phenyl; *t*-Bu, *tert*-butyl.

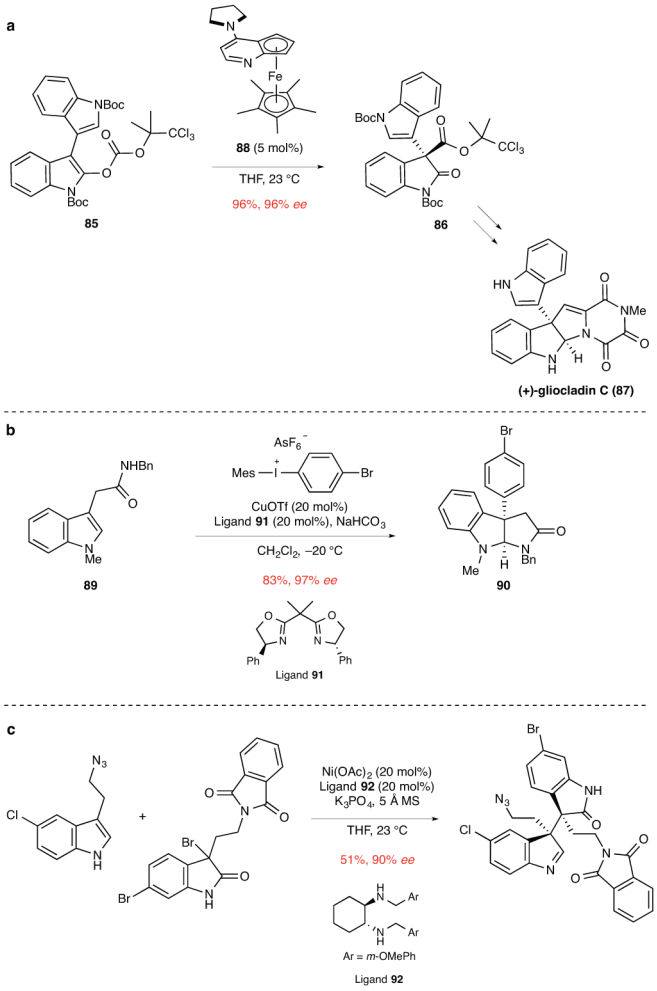

Figure 9. Miscellaneous methods involving the union of a catalytically generated chiral carbon electrophile with a carbon nucleophile

ee, enantiomeric excess. **a**, The Steglich rearrangement of indole carbonate **85** in the presence of Fu's planar-chiral catalyst **88** to give 3,3-disubstituted oxindole **86** in route to (+)-gliocladin C.[78] Boc, *tert*-butoxycarbonyl; Me, methyl; THF, tetrahydrofuran. **b**, The copper-catalyzed β-arylation of indole **89** and concomitant cyclization to form 3a-arylpyrrolidinoindolinone **90**.[80] Me, methyl; Bn, benzyl; Tf, trifluorosulfonyl; Mes, 1,3,5-trimethylbenzene; Ph, phenyl. **c**, The Ni-catalyzed coupling of an indole with a 3-bromooxindole in route to (+)-perophoramidine. This reaction sets the two contiguous quaternary stereocenters of (+)-perophoramidine.[85] OAc, acetoxy; MS, molecular sieves; THF, tetrahydrofuran; Me, methyl; Ph, phenyl.

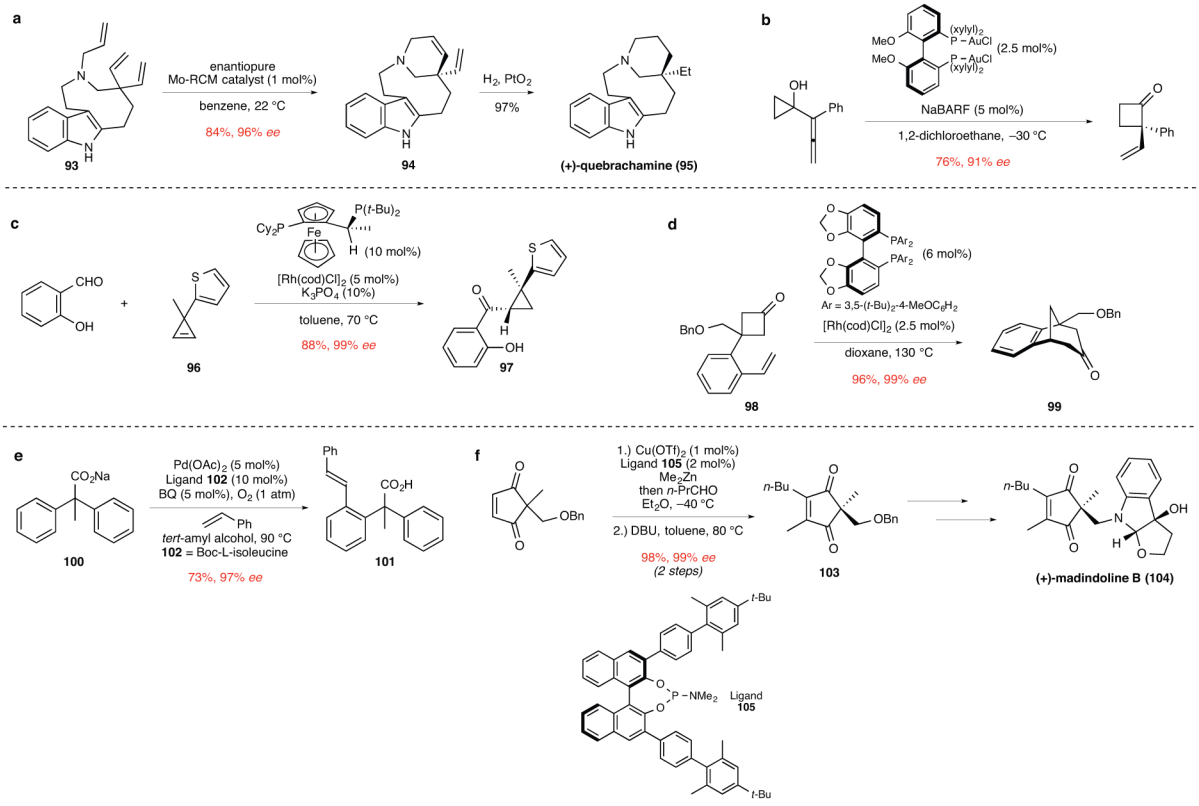

Figure 10. Enantioselective desymmetrization reactions of precursors containing prochiral quaternary carbons

ee, enantiomeric excess. **a**, The ring-closing metathesis of triene **93** to give tetrahydropyridine **94** using a molybdenum catalyst. Catalytic hydrogenation of product **94** then completes a novel construction of (+)-quebrachamine (**95**).[86] RCM, ring-closing metathesis; Et, ethyl. **b**, The gold-catalyzed ring expansion of an allenylcyclopropanol to form (*R*)-2-ethenyl-2-phenylcyclobutanone.[88] Ph, phenyl; Me, methyl, xylyl, 3,5-dimethylphenyl; NaBARF, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. **c**, The rhodium-catalyzed hydroacylation of cyclopropene **96** with salicyaldehyde to form cyclopropane **97**. Coordination of the phenolic oxygen of salicyaldehyde and the ring strain of the cyclopropene promotes this bimolecular hydroacylation reaction. The observed diastereoselectivity is suggested to result from Rh-hydride insertion and subsequent C–C bond reductive elimination taking place preferentially from the cycloproprne face opposite the larger substituent.[89] Me, methyl; Cy, cyclohexyl; *t*-Bu, *tert*-butyl; cod, 1,5-cyclooctadiene. **d**, The enantiotopic rhodium-catalyzed insertion into a C–C bond of cyclobutanone **98**, followed by intramolecular insertion of the rhodium-acyl intermediate to give bridged-tricyclic ketone **99**.[90] Bn, benzyl; Me, methyl; cod, 1,5-cyclooctadiene; *t*-Bu, *tert*-butyl. **e**, The palladium(II)-catalyzed enantiotopic C–H activation of sodium diphenylacetate **100** templated by the carboxylate group, followed by bimolecular Heck coupling with styrene to give product **101**.[91] OAc, acetoxy; BQ, benzoquinone; Ph, phenyl; Boc, *tert*-butoxycarbonyl. **f**, The desymmetrization of a prochiral 1,4-cyclopentenone by copper-catalyzed conjugate addition of a methyl group to give chiral product **103** was the

key step in the total synthesis of (+)-madindoline B.[92] Bn, benzyl; Tf, trifluorosulfonyl; Pr, propyl; Me, methyl; Bu, butyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; *t*-Bu, *tert*-butyl.