1
Important Natural Products

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1.1
Introduction

The development of synthetic methodologies in the last quarter of the twentieth century has been truly impressive, but the stereoselective construction of quaternary centers remains a significant challenge in the total synthesis of natural products. It is quite difficult to invert undesired configurations of quaternary centers to the desired ones, so the stereoselectivities of reactions on quaternary carbons often govern the total efficiency of the syntheses. In this chapter, we highlight recent natural product syntheses, with emphasis on the stereoselective preparation of the quaternary carbons [1, 2].

Unfortunately, the term "quaternary center" is a cause of confusion in terminology, because it is also used to mean "quaternary-substituted carbon", which includes tri-carbon-substituted carbon such as occurs in tertiary alcohols. The term "all-carbon quaternary centers" is also found in the literature. Quaternary-substituted carbons and quaternary carbons in the full sense must be distinguished carefully. Thus, in this chapter we use the term "quaternary carbon" to designate those carbon centers that are substituted with four carbon substituents.

Quaternary-substituted carbons can be prepared routinely by the face selective addition of carbon nucleophiles to carbon–heteroatom double bonds such as asymmetrical ketones or imines [3]. Stereochemical induction may be achieved based either on neighboring functional groups in the substrate or on chiral catalysts.

On the contrary, the stereoselective synthesis of quaternary carbon (all-carbon quaternary centers) is still challenging and only limited options are available. The most popular and powerful concept at present is the chirality transfer of configurations at neighboring heteroatom-substituted asymmetric centers to the quaternary carbons. As described above, enantioselective preparation of heteroatom-substituted centers has become much easier. Asymmetric oxidations of tri- or tetrasubstituted alkenes to diols, epoxides, or amino alcohols also give quaternary-substituted centers, which are now regarded as conventional

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approaches. A variety of asymmetric reagents and catalysts is now available for these purposes [4].

Total syntheses of natural products are usually achieved through multi-step transformations from simple starting materials. Needless to say, the efficiency of a total synthesis depends not only on the yield or selectivity of each synthetic operation (strategy) but also on the overall synthetic plan. In the case of target compounds with a small number of asymmetric centers, each quaternary carbon center could be built directly by asymmetric catalysis (such as an asymmetric Heck reaction or an asymmetric Diels–Alder reaction, *vide infra*). Although wide varieties of chiral starting materials are available either from natural sources (e.g. sugars, amino acids) or from asymmetric reactions [5], chiral building blocks with a quaternary center are rare.

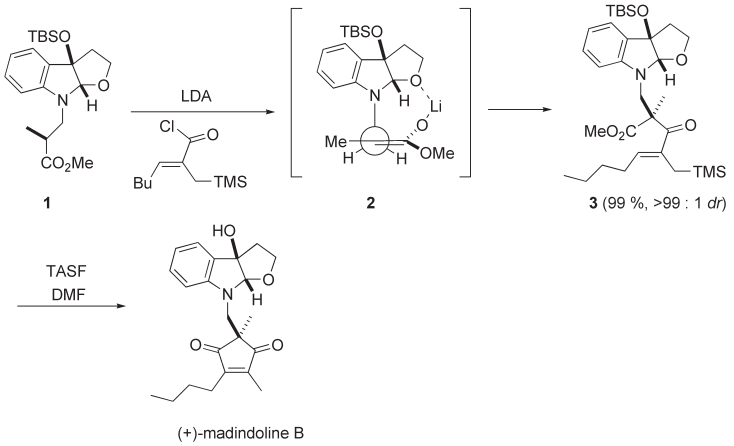
When there are two or more asymmetric centers in the target molecule, the timing of the construction of quaternary centers should be considered in the whole scheme of the synthetic route. Thus, catalytic asymmetric methods are not always the choice in the synthesis of quaternary centers in multi-stereogenic compounds. The introduction of a small number of non-quaternary stereocenters in the early stage, followed by a series of diastereoselective transformations to control quaternary center(s), is a popular approach in the synthesis of complex natural products owing to the overall total efficiency. The central issue in the context of quaternary centers seems to be how to induce quaternary carbons efficiently and stereospecifically, based on the preexisting secondary or tertiary stereocenters. Another challenge exists in the construction of quaternary carbons. This often suffers from hindered chemical environments around reaction centers, and the use of intramolecular reactions is a popular approach to enhance reactivity.

1.2
Alkylation of Tertiary Carbon Centers

Alkylations, or acylations, of enolate equivalents are straightforward approaches to the construction of quaternary carbons. Stereoinductions at newly formed quaternary carbons are often achieved diastereoselectively based on preexisting chiral centers.

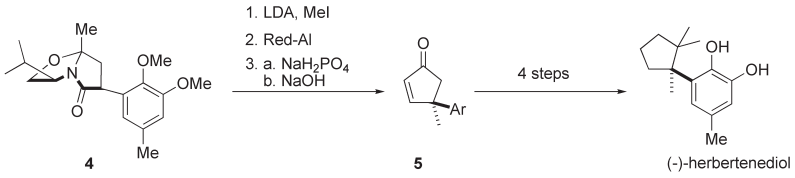
Omura et al. have reported an elegant asymmetric total synthesis of madindolines [6]. An impressive remote diastereomeric induction was observed in the acylation of the lithium enolate of ester **1**. When hexamethylphosphoramide (HMPA) was employed as a co-solvent in the acylation, or potassium diisopropylamide (KDA) was used as base, the selectivity of the acylation dropped considerably. Thus, the authors suggested that oxygen in both enolate and tetrahydrofuran coordinated to a lithium cation, and this chelation directed the electrophile attack on the less hindered face of enolate. The acylation product was converted in one step to the natural product.

Incorporation of a chiral auxiliary into carbonyl compounds is also a popular and reliable method, although it requires additional steps to introduce and



Scheme 1.1 Omura's remote diastereomeric alkylation in the synthesis of (+)-madindoline.

remove the auxiliary. The pioneering contributions of Meyers, for instance, have been employed extensively in natural product synthesis, where amino acid-derived amino alcohols were the chiral sources [7].

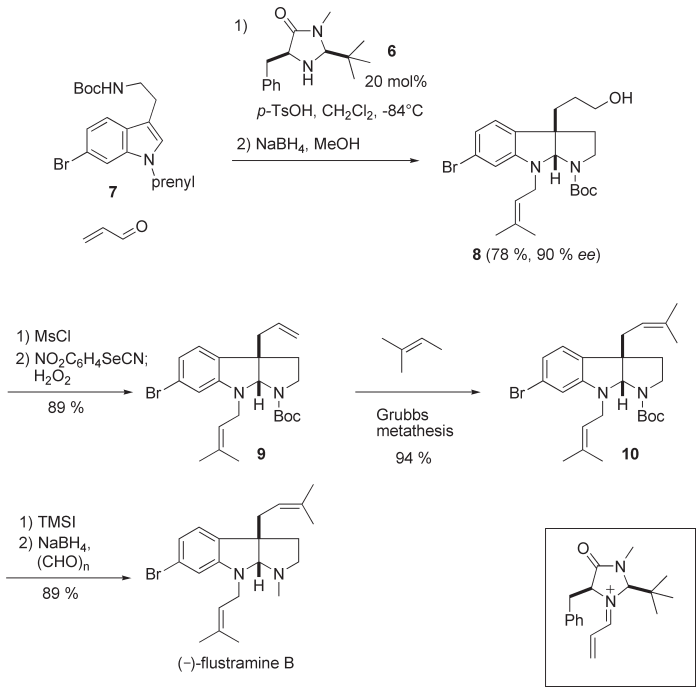


Scheme 1.2 Meyers' asymmetric synthesis of (–)-herbertenediol.

In the synthesis of (–)-herbertenediol [8], a chiral bicyclic lactam was methylated from the *endo* face to construct a quaternary stereogenic center with complete stereocontrol. Reduction and hydrolytic cleavage afforded the cyclopentenone, which was subsequently converted to herbertenediol, containing vicinal quaternary centers.

Catalytic methods of generating a chiral enolate have also been explored in order to construct quaternary centers. Sodeoka et al. have reported asymmetric Michael addition .catalyzed by a palladium aqua complex (see Chapter 4, Scheme 4.19) [9]. Cyclic and acyclic achiral β-ketoesters added to methyl vinyl ketones via chiral palladium enolate with high yields and *ee*s (in most cases *ee* > 90%). Metal-catalyzed asymmetric Michael-type reactions have been investigated, but the enantioselectivity and reactivity were, in general, not sufficient. Sodeoka's landmark results will be applied in natural products synthesis shortly.

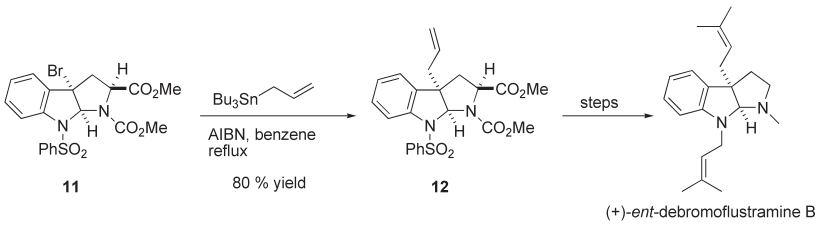
Although less frequently employed, asymmetric alkylation of non-chiral enolate equivalents with chiral electrophiles has also been investigated as a complementary approach. MacMillan employed his chiral organocatalyst for asymmetric Michael-type addition in the total synthesis of (–)-flustramine B [10, 11].



Scheme 1.3 MacMillan's organocatalyzed asymmetric Michael-type addition in the total synthesis of (–)-flustramine B.

The chiral organocatalyst **6** generated *in situ* an iminium salt (in box) with acrolein, and the alkylation occurred to give a quaternary center enantioselectively. The iminium ion was expected to be formed with (*E*)-isomer selectively to avoid the repulsion of the bulky *tert*-butyl group. The benzyl and *tert*-butyl groups shield the upper face (*Si*-face) of the substrate, leaving the down face (*Re*-face) exposed for enantioselective bond formation. However, the cause of enantiofacial selectivity on indole **7** was not clear. The choice of solvent has been shown to be the major controlling factor. The indolium ion thus formed was attacked intramolecularly by a Boc-protected amine to afford pyrroloindoline **8**.

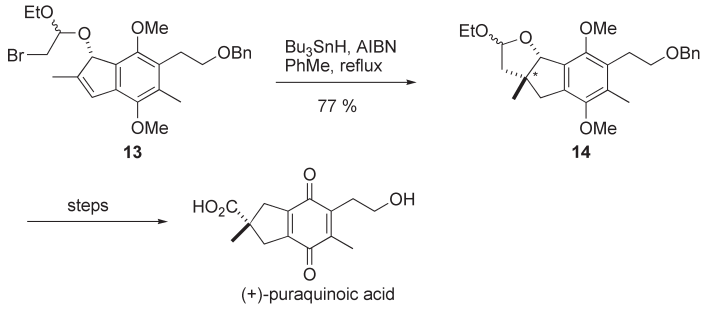
In addition to carbanion-mediated reactions, radical alkylations can also be employed. The high reactivity of radical species is an advantage for the generation



Scheme 1.4 Radical allylation by Crich et al.

of congested quaternary carbons. Thus Crich's synthesis of a marine alkaloid, (+)-*ent*-debromoflustramine B, involved radical allylation of a tertiary bromide with allyltributyltin to **12** [12].

Clive achieved total synthesis of (+)-puraquinoic acid using a route based on radical cyclization of the Stork bromoacetal **13** [13]. The chirality of the quaternary carbon center was controlled by a temporary adjacent tertiary asymmetric center.



Scheme 1.5 Generation of an asymmetric quaternary center based on a temporary adjacent chiral center.

1.3 Cycloaddition to Alkenes

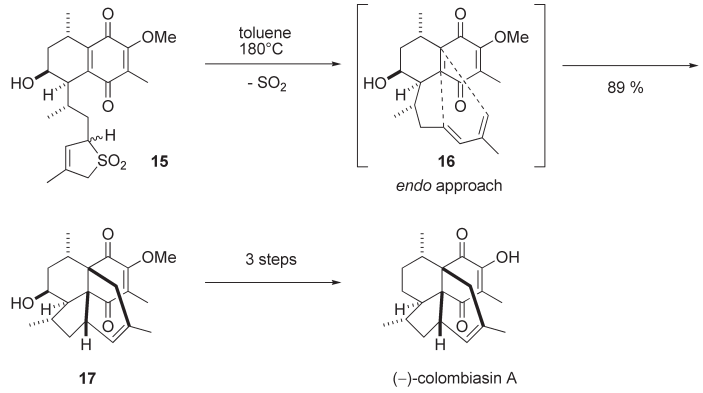
1.3.1 Diels–Alder Reaction

There have been significant numbers of applications of the Diels–Alder reaction for the synthesis of polycyclic natural products, inspired by their biogenesis. The Diels–Alder reaction provides one of the most powerful strategies for forming a quaternary carbon within a cyclohexane system.

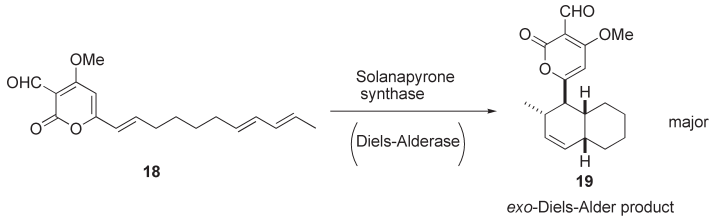
Nicolaou et al. reported the total synthesis of colombiasin A, a marine diterpenoid, using an intramolecular Diels–Alder reaction (IMDA) [14]. Six stereogenic centers, two of which are adjacent quaternary carbons, exist in the compact tetracyclic framework of colombiasin. The construction of contiguous stereogenic quaternary carbons posed a synthetic challenge arising from the steric congestion imposed by the four attached substituents. Stereoselective generation of both quaternary centers was accomplished via an *endo*-specific Diels–Alder cycloaddition with quinone as dienophile (Scheme 1.6).

It has been proposed since the early 1960s that the Diels–Alder reaction is involved in the biosynthetic pathways of natural products. Oikawa proved for the first time that the decaline skeleton of solanapyrone was biosynthesized by a "Diels–Alderase" [15].

Following Oikawa's report, two additional Diels–Alderases, lovastatin nonaketide synthase [16] and macrophomate synthase [17] were purified.



Scheme 1.6 Construction of contiguous quaternary centers in (–)-colombiasin A by an intramolecular Diels–Alder reaction.



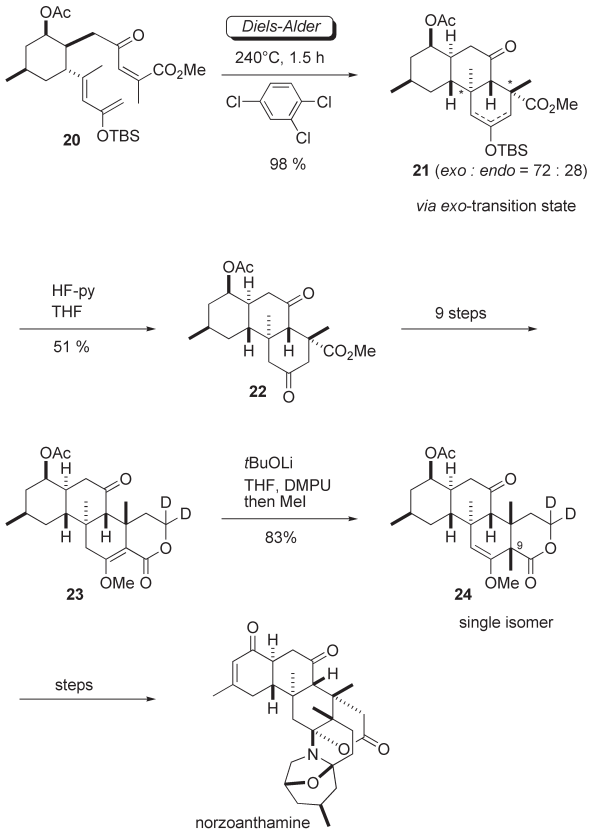
Scheme 1.7 The first identified Diels–Alderase by Oikawa et al.

X-ray crystallographic analysis of a Diels–Alderase complex with its substrate analogue has been reported, which allowed the reaction mechanism to be analyzed at the molecular level [18]. Owing to the limited number of Diels–Alderases identified so far, there has been no confirmed example of an enzyme-catalyzed Diels–Alder reaction forming quaternary centers. However, the advance of investigations into biosynthesis did inspire synthetic chemists to consider biomimetic approaches to quaternary carbon centers in polycyclic natural products.

It is also noteworthy that the Diels–Alderases described above catalyze not only the cycloaddition but also the oxidation of allylic alcohols to enals, the dienophile. It is not certain at this stage if all Diels–Alderases must have oxidase activity. The fact that all Diels–Alderases found have oxidase activity seems suggestive in designing the Diels–Alder precursors for biomimetic synthesis.

Norzoanthamine, a marine polyketide that was isolated by Uemura in 1995 [19], exhibits promising antiosteoporotic activity in ovariectomized mice. Miyashita achieved the first total synthesis of norzoanthamine in 2004 [20]. Among the three quaternary carbons, the C-12 and C-22 stereocenters were constructed through an IMDA reaction, which was designed by taking into account the proposed biogenetic pathway [19b].

As shown in Scheme 1.8, this IMDA reaction of **20** proceeded at 240°C and gave rise to a 72:28 ratio of the *exo* and *endo* adducts. The remaining quaternary



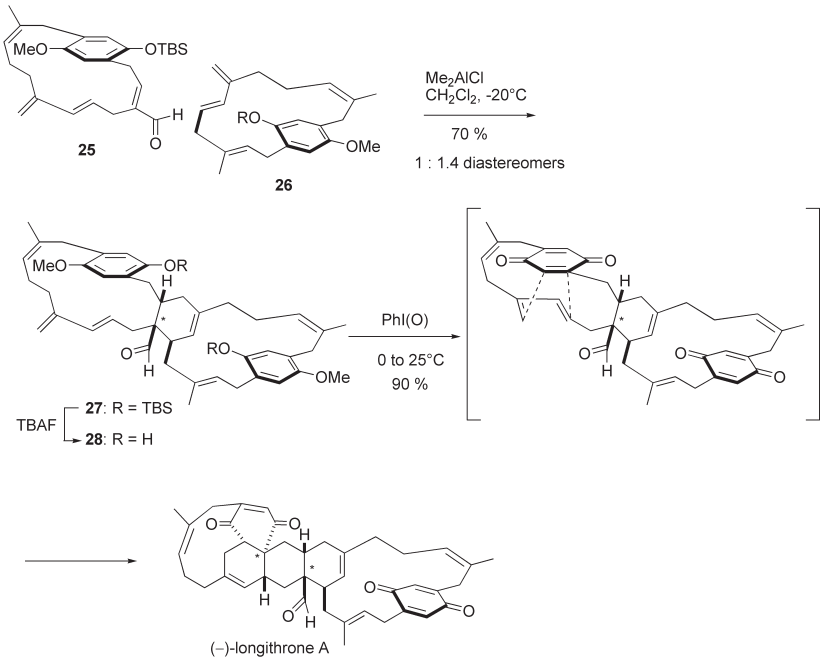
Scheme 1.8 Miyashita's synthesis of norzoanthamine via an IMDA reaction.

center at C-9 was then constructed by a diastereoselective methylation of enolate from the β side. The methylated products were obtained as a single isomer in 83% yield.

The discovery of Diels–Alderases allowed these biomimetic total syntheses to give an insight into whether the natural product is biosynthesized by the enzyme.

In the biomimetic total synthesis of longithrone by Shair, combinations of inter- and intramolecular Diels–Alder reactions were employed to construct two quaternary centers [21].

The first Diels–Alder reaction of Shair's synthesis (from **25** and **26** to **27**) required activation of the dienophile by Lewis acids, and the desired stereoisomer was obtained as the minor isomer. Heating at 80°C without Lewis acid did not give the intermolecular Diels–Alder adducts, but the second intramolecular (transannular) Diels–Alder (TADA) reaction of **28** proceeded at room temperature with higher yield. Low reactivity and lack of substrate-induced stereoselectivity might suggest the involvement of a Diels–Alderase in the former Diels–Alder



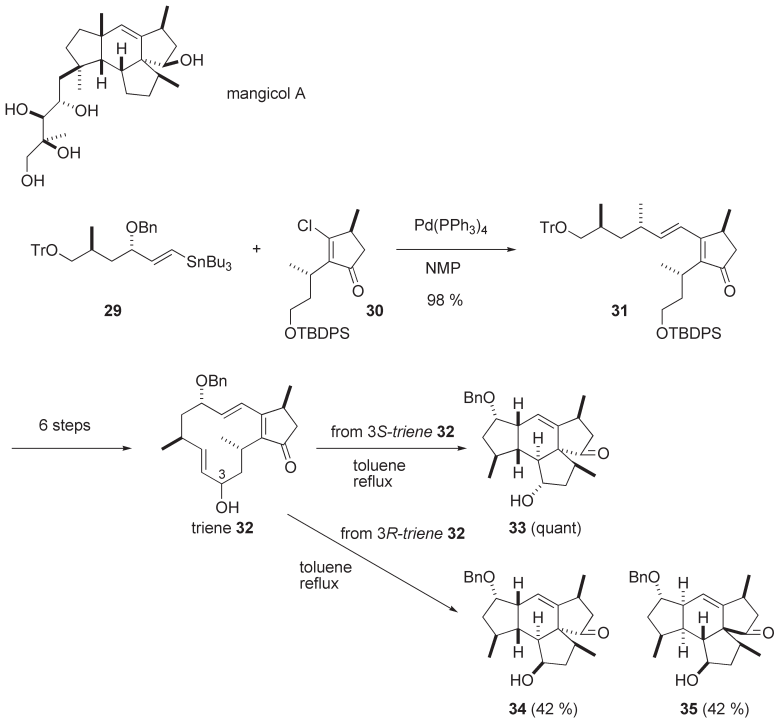
Scheme 1.9 Biomimetic synthesis of (–)-longithrone A by Shair et al.

reaction. Similar observations in the total synthesis of keramaphidine B might also suggest that the biosynthesis is Diels–Alderase catalyzed [22].

As demonstrated in the total synthesis of longithrone described above, a well-designed TADA approach can reduce the entropic requirement $\Delta S^{\ddagger}$ in the transition state; thus it has a potential advantage in reactivity over the IMDA reaction [23]. Another application of a TADA reaction in the stereoselective construction of a quaternary spirocenter was reported in a synthetic study on a marine sesterterpene mangicol [24, 25]. In this case, the design of the synthetic scheme was not based on biogenesis of the natural product.

In Uemura's synthetic study of mangicol, the configuration of the C-3 secondary alcohol in the triene precursor **32** had an unexpectedly significant effect on the stereocontrol of the Diels–Alder reaction. A calculation (B3LYP level, basis set 6-31G*) of the transition states revealed that intramolecular hydrogen bonding of the alcohol with the cyclopentenone carbonyl oxygen stabilizes the transition state to the desired product **33** from the 3*S*-triene precursor **32** [26], whereas with 3*R*-triene the hydrogen bond destabilized the desired transition state. In general, detailed analysis of the relative energies among the possible modes of cycloaddition is the key to the success of the TADA approach.

The use of Diels–Alder reactions for stereoselective construction of quaternary carbons will continue to be popular in the synthesis of polycyclic natural products.



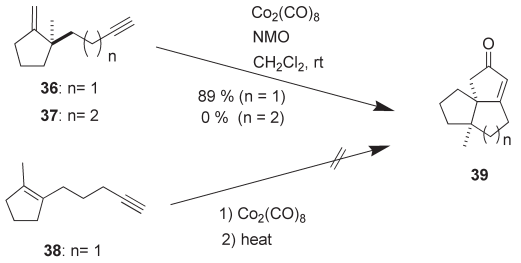
Scheme 1.10 Uemura's TADA approach to mangicol A.

1.3.2
Other Types of Cycloaddition

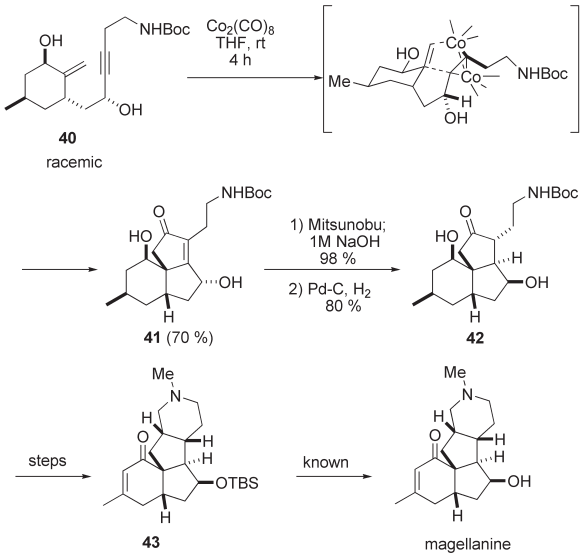
The Pauson–Khand reaction (PKR) is a powerful tool for assembling polycyclic natural products that involve cyclopentane rings [27]. An alkyne–cobalt complex, derived from $Co_2(CO)_8$ and alkyne, reacts with an alkene to generate cyclopentenone. Additives, such as amine N-oxide, are used to lower the reaction temperature to room temperature.

The PKR is known to be sensitive to steric factors in the transition states. For instance, PKR of the ene-yne **36** afforded the desired product **39** with two adjacent quaternary centers in excellent yield [27b]. However, neither a similar substrate with a longer alkyl tether **37** [27b] nor the tetrasubstituted *endo*-cyclic alkene **38** [27c] gave the cyclized product.

A formal total synthesis of magellanine, a lipodium alkaloid, is shown in Scheme 1.12 [28].



Scheme 1.11 Construction of adjacent quaternary carbon centers by a PKR.

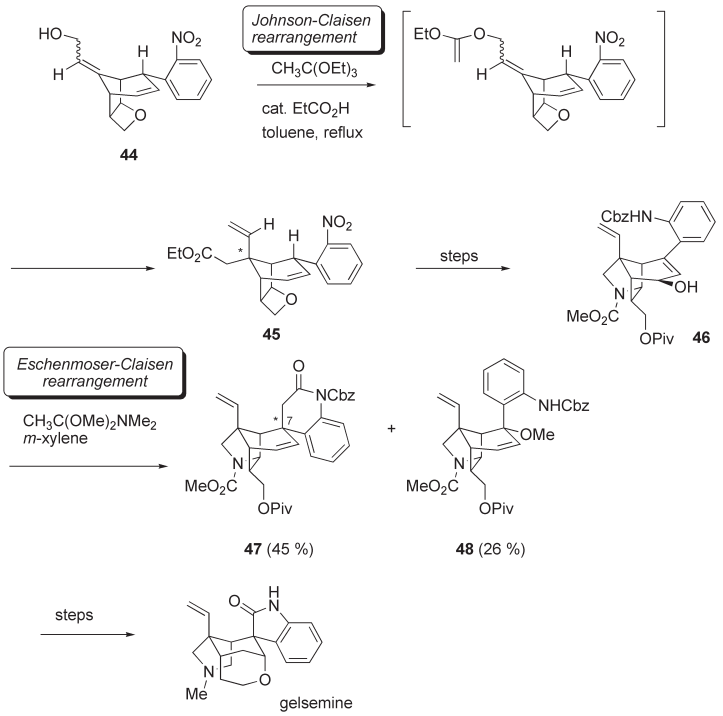


Scheme 1.12 Hoshino's formal total synthesis of magellanine with a PKR as a key step.

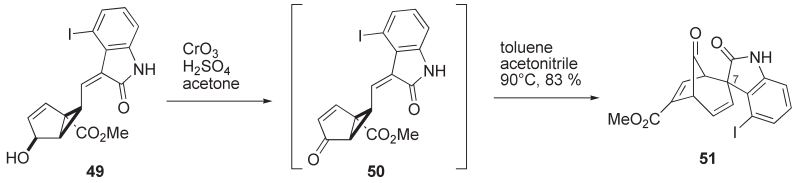
1.4
Rearrangement Reactions

The sterically hindered nature of quaternary centers makes the rearrangement reaction an attractive strategy for their synthesis. Danishefsky employed two [3,3]-sigmatropic rearrangements (a Johnson–Claisen rearrangement, **44** to **45**; an Eschenmoser amide acetal Claisen rearrangement, **46** to **47**) for stereocontrol of the quaternary carbon centers in gelsemine [29].

The quaternary carbon center at C-7 of gelsemine was constructed also by a [3,3]-sigmatropic rearrangement in a more straightforward manner (Fukuyama, Scheme 1.14) [30]. The stereochemical information about a quaternary center in a cyclopropane ring in **49** was transferred to the spiro-quaternary carbon center of **51**.



Scheme 1.13 Danishefsky's total synthesis of gelsemine.

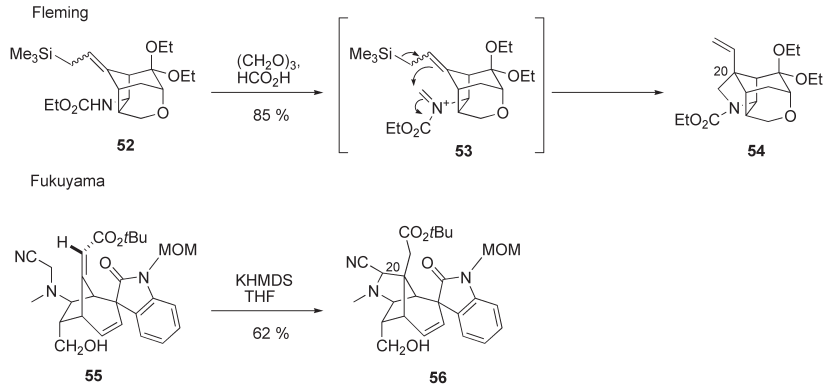


Scheme 1.14 Construction of the C-7 quaternary center of gelsemine in Fukuyama's total synthesis.

Both Fleming [31] and Fukuyama [30] employed intramolecular alkylation in the construction of the C-20 stereocenter in their gelsemine synthesis (Scheme 1.15).

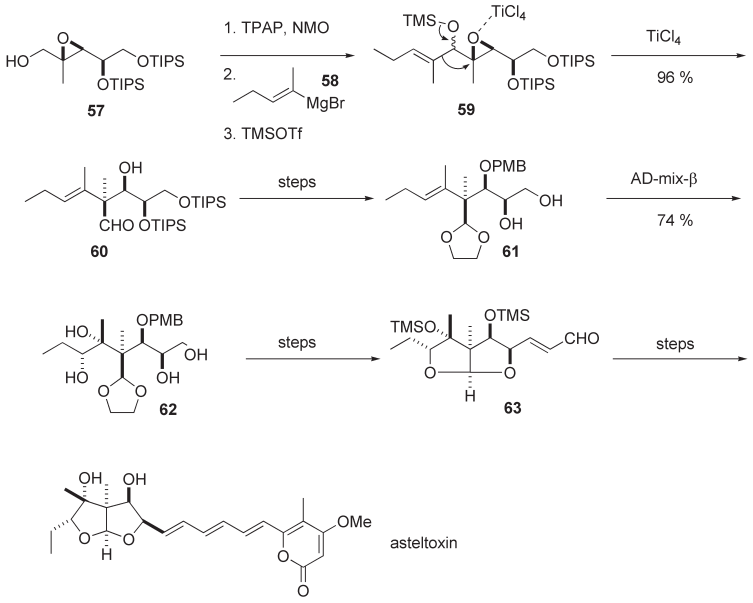
Besides the [3,3]-sigmatropic rearrangements, 1,2-rearrangements are also very important approaches to quaternary carbon centers. It is noteworthy that 1,2-diols or 2,3-epoxy alcohols, which are frequently employed as substrates, can be prepared easily by methods such as those of Sharpless, Katsuki, and Jacobsen [4].

In their asymmetric total synthesis of (+)-asteltoxin Cha et al. used the Suzuki–Tsuchihashi 1,2-rearrangement [32]. Chiral epoxy alcohol **59** was prepared by Sharpless asymmetric epoxidation and was rearranged in the stereospecific manner under Suzuki–Tuchihashi conditions to afford the quaternary carbon center.



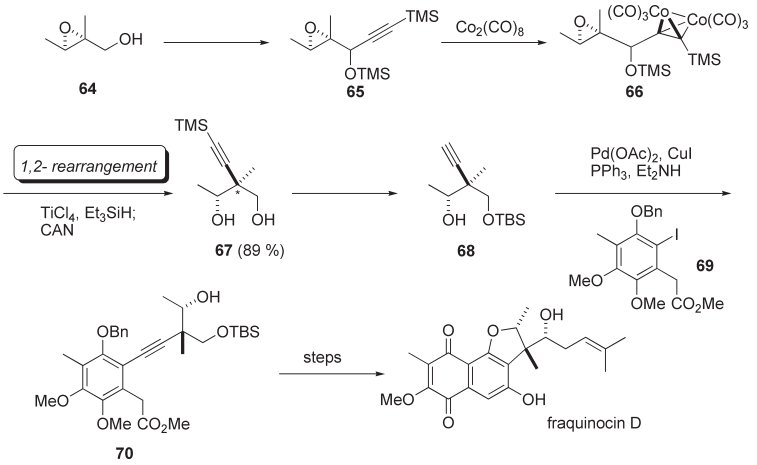
Scheme 1.15 Construction of the C-20 stereocenter of gelsemine by Fleming et al. and Fukuyama et al.

The product aldehyde **60** was further converted to (+)-asteltoxin via the Sharpless asymmetric dihydroxylation of **63**. Cha's total synthesis was inspired by the proposed biogenesis of asteltoxin by Vleggar [34].



Scheme 1.16 Cha's total synthesis of asteltoxin via stereospecific 1,2-rearrangement.

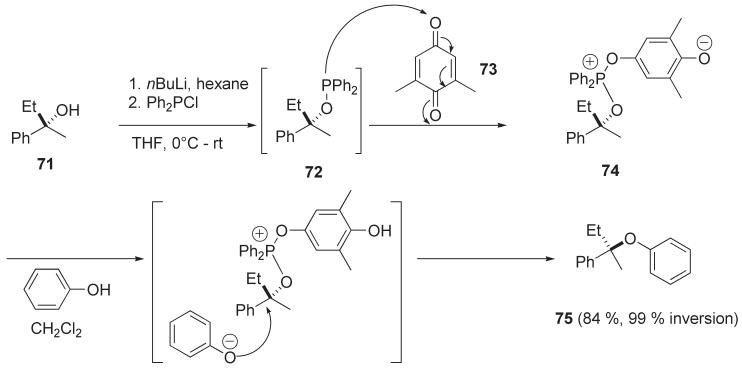
Suzuki also utilizes his 1,2-rearrangement conditions in the total synthesis of furaquinocin Scheme 1.17) [35]. The starting material was again prepared by Sharpless epoxidation. An alkyne, which is not a good migrating group owing to



Scheme 1.17 Suzuki's synthesis of furaquinocin D.

its electron-poor nature, was transformed to its Co-complex, and was successfully employed for the stereospecific rearrangement.

These 1,2-rearrangements might be regarded as special cases of intramolecular S_N2 displacement at tertiary stereocenters by carbon nucleophiles. For a long time S_N2 reactions at tertiary centers have been believed to be quite difficult. Organic chemistry textbooks state that S_N2 reactions cannot occur with nucleophiles at tertiary centers owing to steric hindrance at the backside of leaving groups. However, such descriptions are not always true for oxygen nucleophiles. It seems worth mentioning that Mukaiyama (Scheme 1.18) [37] and Shi [38] recently showed that highly stereospecific S_N2 replacements are possible when tertiary alcohols are activated by phosphonium salts. In both of these examples, the nucleophiles are so far limited to phenols. Considering that carbon nucleophiles



Scheme 1.18 Complete S_N2 inversion of a tertiary alcohol by phenol.

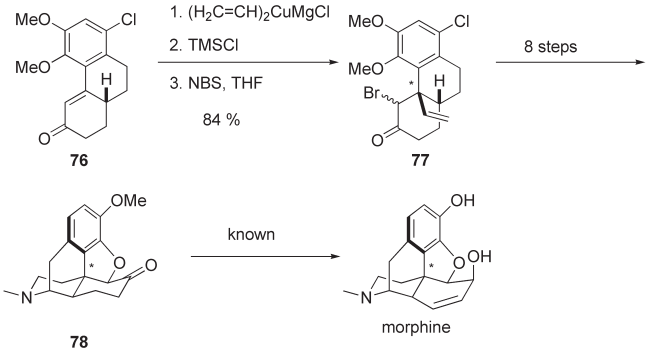
has been employed in the modified Mitsunobu reactions of secondary systems [39], hitherto unexplored approaches to quaternary carbons, i.e. the stereospecific inversion of tertiary alcohols by carbon nucleophiles, might be available in the near future.

1.5
Carbometallation Reactions

1.5.1
Addition of a Carbon Nucleophile to a β,β-Disubstituted α,β-Unsaturated Enone

Tetrasubstituted carbon centers, such as tertiary alcohols or amines, can be prepared by the stereoselective nucleophilic addition of carbon nucleophiles to polar C=X bonds. Conjugate addition of a carbon nucleophile to a β,β-disubstituted α,β-unsaturated enone affords a quaternary carbon center.

Mulzer [40] and Ogasawara [41] independently used the conjugate addition of a vinyl cuprate to α,β-unsaturated enones in their synthesis of morphine, where the neighboring chemical environments controlled the stereochemical outcomes.

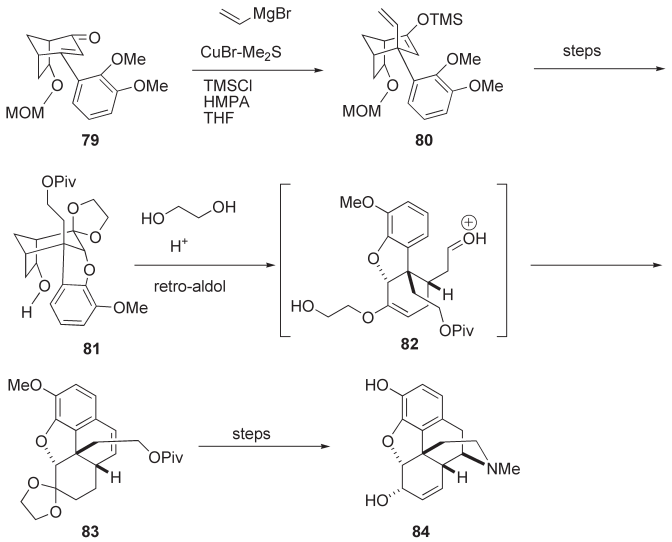


76 77 78

Scheme 1.19 Mulzer's morphine synthesis via conjugate addition of a vinyl cuprate to form a quaternary center.

1.5.2
Asymmetric and Diastereomeric Addition of a Carbon Nucleophile to Unactivated Alkenes Catalyzed by Palladium [42]

The Heck reaction is a palladium-catalyzed coupling of alkenes with organic halides or triflates lacking an sp^3-hybridized β-hydrogen. The intramolecular Heck reaction is a powerful tool not only in the assembly of complex natural-product skeletons but also in diastereomeric stereoinductions. When a trisubstituted alkene is employed as the coupling partner, the products include a new quaternary carbon center with excellent diastereomeric control.



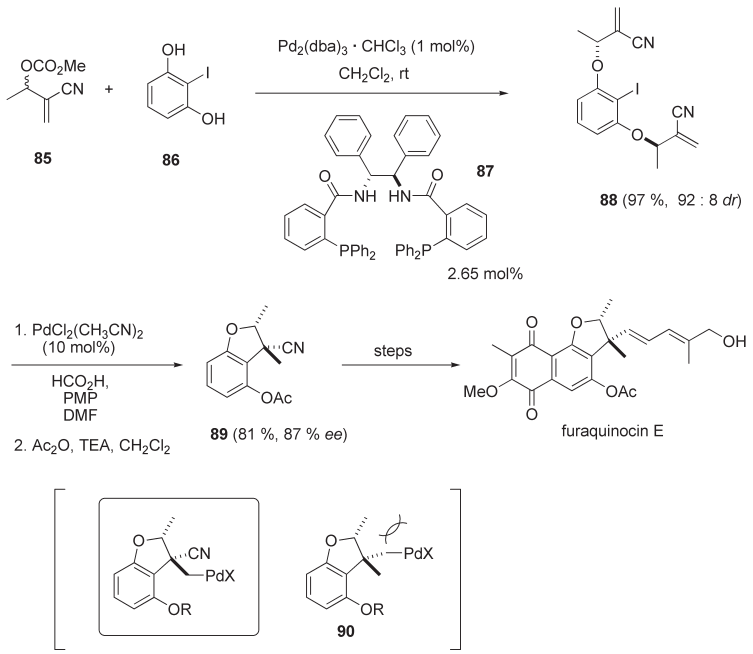
Scheme 1.20 Ogasawara's morphine synthesis.

Configuration information of carbon–heteroatom bonds, which might be constructed by asymmetric catalysts, can be transferred to the new quaternary carbon centers. Scheme 1.21 shows a brief outline of Trost's total synthesis of furaquinocin [36b]. The π-allyl palladium complex intermediate with optically active bisphosphine ligands **87** was generated from an allyl carbonate, and reacted with a bisphenol to gave bisallyl ether **88**. Subsequently, a reductive Heck cyclization of **88** to a furan ring generated a quaternary carbon stereocenter. The authors rationalized the stereochemical outcome by suggesting that steric repulsion between the palladium and the adjacent methyl group in the intermediate **90** played an important role in the diastereoinduction. The enantiomeric purity of the Heck cyclization product **89** was 87% *ee*, which was raised to 99% *ee* by recrystallization.

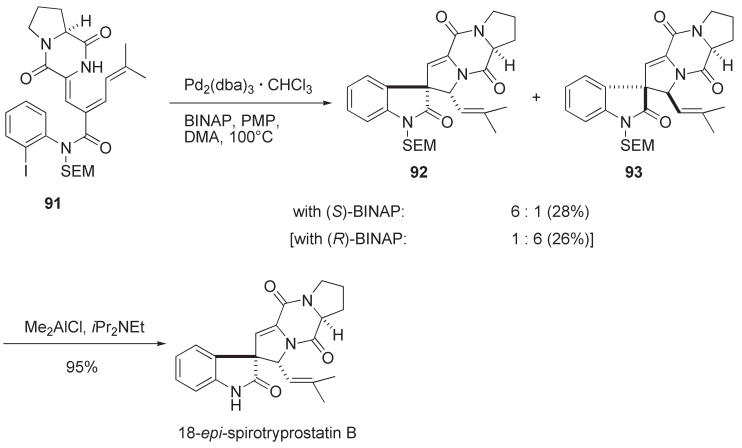
The enantioselective formation of quaternary carbon centers by a Heck reaction was first reported by Overman in 1989 [43]. This asymmetric Heck (AH) reaction was extensively investigated by Overman and Shibasaki [44, 45]. A number of applications of the AH reaction have been reported. A recent example is the total synthesis of (–)-spirotryprostatin B [46].

Among the three stereocenters in the molecule, quaternary spiro and adjacent centers were stereoselectively constructed via Heck insertion of a conjugated triene. The η^3-allylpalladium intermediate was trapped by the nitrogen of a tethered diketopiperazine which proceeds with *anti* stereochemistry (PMP: 1,2,2,6,6-pentamethylpiperidine).

Shibasaki has also reported the synthesis of halenaquinol [47]. Heck cyclization of (*Z*)-trisubstituted alkene **94** in the presence of $Pd(OAc)_2$-(*R*)-BINAP afforded the tetrahydronaphthalene with 99% *ee*. The one-pot Suzuki coupling–asymmetric

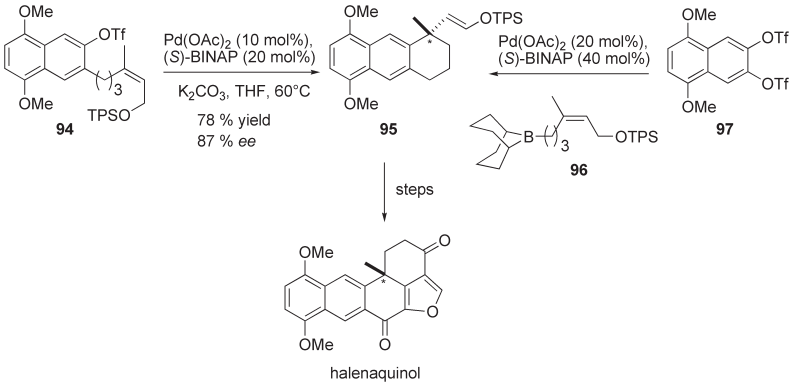


Scheme 1.21 Trost's synthesis of furaquinocin E.



Scheme 1.22 Heck cyclization in the synthesis of 18-*epi*-spirotryprostatin B by chiral palladium catalysts.

Heck cyclization from ditriflate **97** was also achieved in 85% *ee*, albeit the yield was poor (20%).



Scheme 1.23 Application of an asymmetric Heck reaction to the total synthesis of halenaquinol.

1.6
C–H Functionalization Reactions

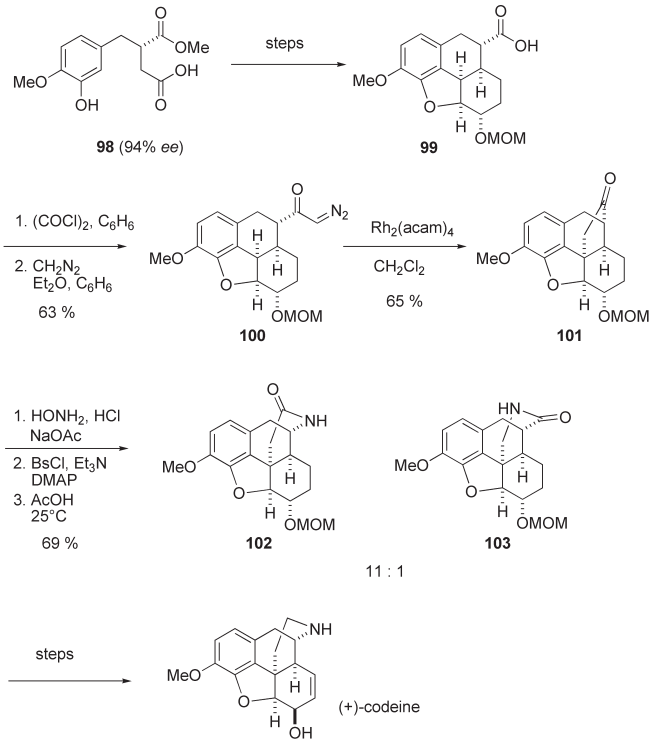
The successful development of practical methods for C–C bond formation via C–H activation would revolutionize natural-product synthesis. However, the use of highly oxidative metal catalysts for oxidative addition to C–H bonds is in essence very difficult. The catalyst needs to be highly reactive and simultaneously selective among the ubiquitous C–H bonds.

On the other hand, C–H insertion reactions mediated by carbenes or by metal–carbenoid complexes are powerful methods to functionalize unactivated C–H bonds [48]. The latter complexes are easily generated from diazo compounds. In general, C–H insertion reactions occur preferentially at tertiary and secondary sites, and often form five-membered rings among other sized rings. An important feature of the reaction is the inherent ability to convert a tertiary stereogenic center into a quaternary center with retention of the absolute configuration.

White utilized a diastereoselective C–H insertion reaction in the total synthesis of (+)-codeine (Scheme 1.24) [49].

The product distribution from decomposition of diazoketone **100** was found to depend markedly on the Rh(II) catalyst employed as well as on small structural variations in the substrate.

Du Bois has reported a beautiful total synthesis of tetrodotoxin, which is the active poison of Japanese *fugu*, with C–H bond functionalization as the key steps [50, 51]. Many functional groups exist densely in the rather small carbon framework. Actually, tetrodotoxin does not contain any quaternary carbon centers but only quaternary-substituted carbons. However, stereoselective construction of the C-6 and C-8a quaternary-substituted carbons was synthetically challenging and Du Bois' elegant synthesis of this difficult target underscores the power of carbene/nitrene insertion reactions.

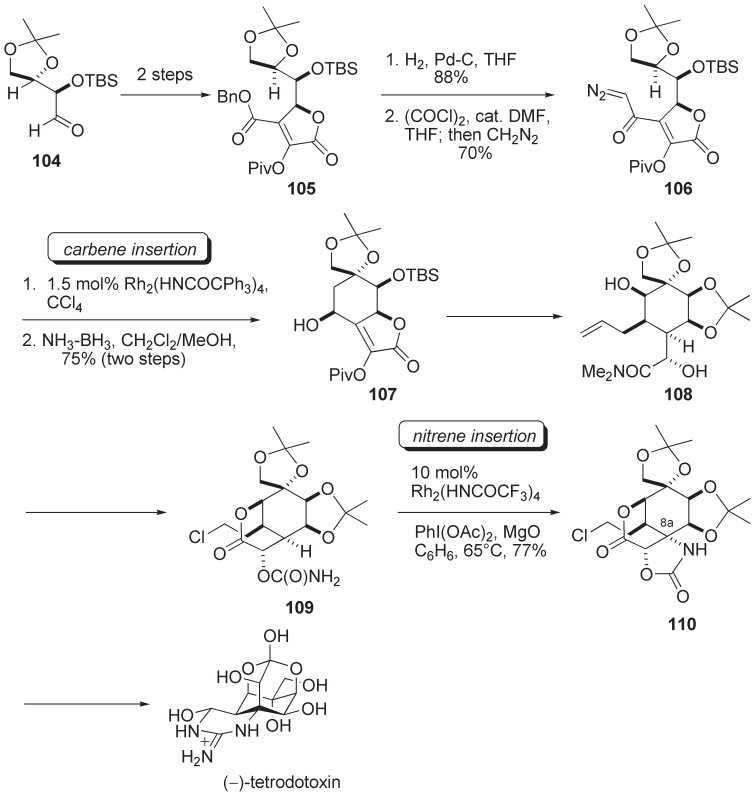


Scheme 1.24 Total synthesis of codeine with C–H insertion as the key step.

Two key C–H functionalizations are incorporated in the scheme. In the first stereospecific Rh-carbene C–H insertion reaction of **106**, the choice of Rh-catalyst was quite important. The first attempts using $Rh_2(OAc)_4$ yielded a complex product mixture, but it was found after screening catalysts that 1.5 mol% $Rh_2(HNCOCPh_3)_4$ gave the cyclic ketone as the sole product. The cyclohexanone was converted to a primary carbamate **109**. Installation of the tetrasubstituted carbinolamine at C-8a was accomplished through stereospecific Rh-catalyzed nitrene insertion using 10 mol% $Rh_2(HNCOCF_3)_4$.

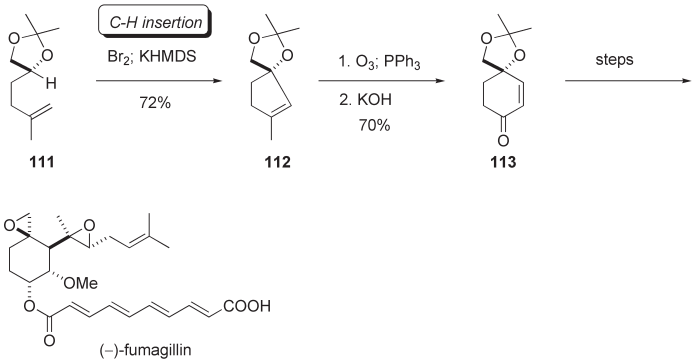
Stereoselective construction of trisubstituted carbons is less difficult, and application of the above C–H functionalization reaction enables them to be converted stereospecifically to tetrasubstituted carbon centers. Steric, electronic, and conformational variations have a great effect on the favored reaction pathway and product distribution. These parameters include catalyst ligands and diazo and substrate substitution patterns. No catalyst has been found to be effective for all substrates. Readers should also be careful to optimize selectivity over C–H insertion, cyclopropanation, Buchner reaction, and ylide generation with the appropriate structural choices.

There are also examples of C–H insertion reactions that do not use diazo-precursors and Rh-catalysts (Scheme 1.26). Taber et al. investigated the use of

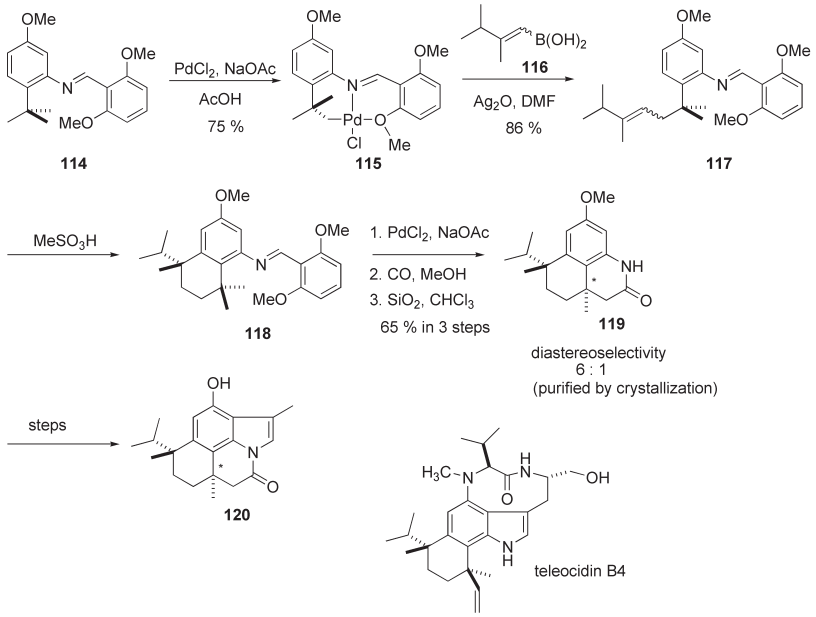


Scheme 1.25 Total synthesis of (–)-tetrodotoxin by Du Bois.

alkylidene carbenes, which can be generated from haloalkenes [52]. Their total synthesis of fumagillin is noteworthy.



Scheme 1.26 The use of a haloalkene as the source of a carbene intermediate and its application to the total synthesis of fumagillin.



Scheme 1.27 Consecutive functionalizations of three methyls of the *tert*-butyl substituent by diastereoselective C–H activations.

1.7
Asymmetric Modification of Enantiotopic/Diastereotopic Substituents of Quaternary Carbon Centers

Asymmetric quaternary centers can also be generated indirectly via selective modification of diastereotopic or enantiotopic substituents on a symmetric quaternary center. Traditionally, desymmetrizations of enantiotopic substituents have frequently been conducted with enzymes [53]. Sames et al. employed C–H bond activation to desymmetrize *gem*-dimethyl groups in their synthesis of the teloocidin B4 core [54].

This was accomplished via sequential cyclometallation and transmetallation. Stoichiometric $PdCl_2$ in the presence of NaOAc afforded palladacycle **115**. Two methoxy groups on the aryl imine were proved to be important as the directing element. The organopalladium **115** was coupled with vinyl boronic acid to accomplish the first functionalization of a *tert*-butyl group. After the acid-catalyzed cyclization of a cyclohexane ring to **118**, the second C–H activation was conducted. The intermediate palladacycle was treated with CO and methanol to give the methyl ester. Hydrolysis of the Schiff base was accompanied by lactam cyclization. The stereoselectivity in the second C–H bond functionalization was 6:1.

1.8 Summary

This chapter has attempted to present an overview of the stereoselective formation of quaternary carbon centers in reported natural product syntheses. We have tried to choose examples from recently published papers, and did not intend to make this chapter comprehensive. Thus, much outstanding work may have been excluded.

There can be little doubt that the stereoselective construction of quaternary centers is one of the most challenging issues in synthetic natural product chemistry. Catalytic asymmetric alkylations or asymmetric Heck reactions have been employed as powerful tools in the total syntheses, especially for those target compounds with one or a small number of asymmetric centers. For the synthesis of polystereogenic targets, these asymmetric reactions are often used in the very early stage so that substrate-dependent stereoinductions are minimized.

Diastereoselective transformations to quaternary centers will continue to be very important, and these are complementary to those involving asymmetric catalysts. Among them all, the alkylation of chiral enolates is the most popular approach. Intramolecular Diels–Alder reactions will continue to be investigated, in part owing to the rapid progress of biosynthetic studies on Diels–Alderase.

The development of methods applicable for the diastereomeric construction of quaternary carbon centers in the very late stage of total synthesis is still in great demand. Recent attention in the synthetic community to unactivated C–H bond functionalization has also led to the revisiting of transformations such as Rh-carbenoid chemistry.

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