The Construction of All-Carbon Quaternary Stereocenters by Use of Pd-Catalyzed Asymmetric Allylic Alkylation Reactions in Total Synthesis

Allen Y. Hong[a] and **Brian M. Stoltz**[a]

Brian M. Stoltz: stoltz@caltech.edu

[a]Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E. California Blvd., MC 101-20, Pasadena, CA 91125, USA, Homepage: http://stoltz.caltech.edu

Abstract

All-carbon quaternary stereocenters have posed significant challenges in the synthesis of complex natural products. These important structural motifs have inspired the development of broadly applicable palladium-catalyzed asymmetric allylic alkylation reactions of unstabilized non-biased enolates for the synthesis of enantioenriched α-quaternary products. This microreview outlines key considerations in the application of palladium-catalyzed asymmetric allylic alkylation reactions and presents recent total syntheses of complex natural products that have employed these powerful transformations for the direct, catalytic, enantioselective construction of all-carbon quaternary stereocenters.

Keywords

Total synthesis; Asymmetric catalysis; Natural products; Palladium; Allylation; All-carbon quaternary stereocenters

1. Introduction and Background

Complex natural products serve a vital role in chemistry as a driving force for the invention of new chemical transformations.[1] The fundamental synthetic challenges posed by all-carbon quaternary stereocenters[2] contained in many natural products have inspired the development of new synthetic methods for the enantioselective construction of these important motifs. In particular, the research area of Pd-catalyzed asymmetric allylic alkylation[3,4] has been advanced significantly in response to synthetic limitations identified during efforts directed towards complex molecules (Figure 1). Modern catalytic enantioselective methods of this type have led to the development of new strategies for the efficient and direct assembly of challenging cyclic core structures in many natural products and have additionally provided powerful and broadly applicable tools for the functionalization of highly substituted ketone-derived enolates. In this short review, the

Correspondence to: Brian M. Stoltz, stoltz@caltech.edu.

direct construction of all-carbon quaternary stereocenters at nucleophilic enolates by means of Pd-catalyzed allylic alkylation reactions is discussed within the broader context of challenges originating from total synthesis.

An all-carbon quaternary stereocenter – that is, one composed of a central carbon atom bound to four carbon substituents (Figure 1) – should be distinguished from a heteroatom-substituted tertiary center (with one heteroatom and three carbon substituents).

In the following discussion, particular attention is given to reported syntheses that have appeared since the most recent reviews.[5] Total syntheses featuring enantioselective tertiary stereocenter formation[6] or catalyst-controlled diastereoselective transformations[7] are not discussed in detail in this microreview.

2. Reaction Design and Mechanistic Considerations

Pd-catalyzed allylic alkylation reactions have found increasingly wide synthetic applications, due to the continued evolution of the methodology. The invention of highly enantioselective transformations for the assembly of all-carbon quaternary stereocenters has facilitated efficient asymmetric syntheses of numerous complex natural products. Although a number of factors have been instrumental in the success of these Pd-catalyzed reactions in complex settings, advances in substrate scope and identification of suitable chiral ligands for these substrate types have had a direct impact on the general utility of these reactions.

2.1. General Aspects of Pd-Catalyzed Asymmetric Allylic Alkylation

In a typical allylic alkylation reaction, a Pd^0 complex undergoes initial olefin coordination and subsequent oxidative addition to an allyl electrophile (Scheme 1). Expulsion of the leaving group leads to a cationic Pd^{II} π-allyl complex. Upon combination with an enolate in the reaction mixture, subsequent C–C bond formation can lead to the α-quaternary ketone product and regenerate the initial Pd^0 complex. The precise reaction mechanism can vary, depending on the choice of ligand, palladium precursor, substrate, allyl source, additive, and solvent.

2.2. Development of Methods for Enolate Generation

Various methods have been employed for the generation of ketone enolates for Pd-catalyzed asymmetric allylic alkylation reactions, but important advances in the past decade have rendered these transformations more practical and useful for the preparation of complex molecules. An unavoidable and general problem in the allylation of differentially substituted ketones with multiple acidic sites is the formation of isomeric enolates, which can proceed to afford different products in the presence of a palladium π-allyl complex (Scheme 2, A).

To circumvent this problem, many groups have employed substrates that contain either α′-blocking groups to shield undesired deprotonation sites (Scheme 2, B) or α-electron withdrawing groups to provide large reductions in pK_a at the desired deprotonation sites (Scheme 2, C). Although both of these strategies have afforded control of regioselective deprotonations in asymmetric alkylation reactions, and enantioselective transformations on substrates of these types have been documented,[8,9,10,11] this approach can introduce

unwanted functional groups into cyclic ketone scaffolds. The modification or removal of these vestigial functionalities from the α-quaternary ketone products can greatly diminish the general application of these compounds in total synthesis.

The general synthesis of chiral α-quaternary ketone building blocks by means of Pd-catalyzed asymmetric allylic alkylation reactions of non-biased unstabilized enolates constituted a major synthetic challenge until the past decade. The lack of established methods for the preparation of relatively simple compounds such as ketone **4** (Figure 1) in high *ee* presented a significant obstacle to the synthesis of complex natural products with all-carbon quaternary stereocenters.

Alternative methods for selective enolate generation can be found in the work of Tsuji and co-workers in the 1980s (Scheme 3). By use of either enol acetate[12] or silyl enol ether[13] substrates in the presence of appropriate additives, it was possible to unmask the latent enolates as single isomers. Subsequent allylic alkylation provided the α-quaternary ketone products without ancillary group incorporation. Additionally, Tsuji's work showed that it was possible to incorporate allyl fragments into substrates by use of allyl enol carbonates[14] or allyl β-keto esters.[15,16] The in situ formation of both an allyl electrophile and an enolate nucleophile could be conveniently initiated by a Pd^0 catalyst with both of these substrate types. With all of these methods explored by Tsuji, the enolates formed under the reaction conditions maintain high regiochemical fidelity and proceed smoothly to afford the corresponding allylation products. Although these methods provided promising strategies for generating enolates in a widely applicable manner, asymmetric variants of these transformations did not surface until over 20 years later.

2.3. Development of Asymmetric Allylic Alkylation Reactions

In the past decade, contributions predominantly from the Stoltz and Trost groups have helped address the difficulty of performing Pd-catalyzed asymmetric allylic alkylations on non-stabilized unbiased enolates to give α-quaternary ketones. In the earliest report by Stoltz in 2004, numerous chiral bidentate ligands were screened for their ability to promote high asymmetric induction in reactions with allyl enol carbonate and silyl enol ether substrates (Scheme 4).[17a] Ultimately, it was found that treatment of these substrates with the combination of (*S*)-*t*Bu-PHOX (**13**, Figure 2) and [Pd$_2$(dba)$_3$] provided the highest degrees of enantioenrichment in the α-quaternary ketone products. Other *P*,*N*- and *P*,*P*-chelating ligands were investigated, but they proved to be less effective under the optimized conditions. Carbocyclic substrates with various ring sizes could undergo transformation to give product in high *ee*s. Examples of benzannulated and non-benzannulated substrates were reported.

Shortly afterward, a study by the Trost group in 2005 involved the development of a different catalyst system for the decarboxylative allylic alkylation of allyl enol carbonates (Scheme 4).[18] A screening of various Trost bis-phosphane ligands with modified diamine backbones and aryl-phosphanes found that ligand (*R*,*R*)-**17** (Figure 2) was most effective for this transformation. Complexation of this ligand with [Pd$_2$(dba)$_3$]·CHCl$_3$ provided an effective catalyst for the synthesis of chiral α-quaternary ketone products with various ring sizes. Although most of the examples consist of benzannulated substrates, two examples of

non-benzannulated ketones were also presented. Notably, several cyclic ketones with incorporated heterocycles could also be prepared. The catalyst system was additionally shown to be applicable for the formation of α-tertiary ketones.

Subsequent work by the Stoltz group extended the asymmetric alkylation methodology with the PHOX ligand system to β-keto ester substrates (Scheme 4).[17b,17c] The starting materials are racemates, so the destruction and reconstruction of stereochemical information through the intermediacy of a prochiral enolate must take place in order for these compounds to form asymmetric alkylation products in what has been termed a stereoablative process.[19] Despite this key mechanistic difference, these substrates demonstrated yields and levels of asymmetric induction similar to those obtained with the silyl enol ethers and enol carbonates. The development of reactions for this class of substrates had practical advantages because various α-substituents could be introduced under relatively mild conditions and because β-keto ester substrates typically have higher thermal and chemical stabilities than silyl enol ether and enol carbonate substrates.

The bis-phosphane and phosphanyloxazoline-type ligands described in the examples above (Figure 2) have enjoyed notable success in the construction of challenging all-carbon quaternary stereocenters to prepare key intermediates for natural product synthesis. Trost ligands[20] possess C_2 symmetry and equivalent donor atoms as well as amide functionality capable of hydrogen bonding. To date, numerous ligands with modified backbone scaffolds and arylphosphane substitution have been reported. Structural modification of these ligands has led to changes in reactivity in cases with multiple possible asymmetric alkylation pathways. PHOX ligands,[21] pioneered by Pfaltz, Helmchen, and Williams, have also proven to be useful ligands for asymmetric allylic alkylation reactions. These ligands possess C_1 symmetry and non-equivalent donor atoms. This lack of symmetry has important ligand design implications, because the oxazoline and arylphosphane regions of the ligand can be tuned somewhat independently. Overall, the ligand classes have unique and complementary steric and electronic features that make them particularly useful and adaptable for Pd-catalyzed asymmetric allylic alkylation reactions in total synthesis.

3. Catalytic Asymmetric Synthesis of Natural Products

The development of Pd-catalyzed asymmetric allylic alkylation reactions of non-biased unstabilized enolates for the synthesis of α-quaternary ketone products has provided a powerful tool for total synthesis. The following case studies not only illustrate important advances in synthetic chemistry, but also provide examples of how broader, longstanding problems in the field have been identified and overcome in the process of constructing complex molecules.

3.1. Total Syntheses of Hamigeran B and Allocyathin B₂

The synthetic potential of Pd-catalyzed allylic alkylation reactions for the assembly of all-carbon quaternary stereo-centers was illustrated by the early enantioselective syntheses of hamigeran B (**27**, Scheme 5)[22] and allocyathin B₂ (**37**, Scheme 6, below)[23] by the Trost group. The common component for both of these syntheses was enantioenriched exocyclic vinylogous ester **19**.

In order to form the requisite quaternary stereocenter, the development of an effective asymmetric allylic alkylation reaction for exocyclic vinylogous ester **18** was needed. The treatment of this compound with allyl acetate as the allyl source, LDA as base, trimethyltin chloride as Lewis acid, and $[(\eta^3-C_3H_5)PdCl]_2$ and chiral ligand (*S*,*S*)-**15** (Figure 2) as catalyst precursors in DME at 0 °C provided α-quaternary ketone (*R*)-**19** (Scheme 6, below) in 93% yield but only 12% *ee*. Extensive reaction optimization revealed that the use of *t*BuOH as an additive greatly improved asymmetric induction and provided optimized reaction conditions leading to the formation of product **19** in 87% yield and 91% *ee*. Additionally, it was found that reduced catalyst loadings could also be employed to obtain similar results. The exocyclic vinylogous ester functionality not only served an important purpose as an α′-blocking group to prevent the formation of isomeric enolates, but also enabled subsequent transformations later in the synthetic sequence.

The convergent synthetic approach to hamigeran B (**27**)[22] sought to unite an aryl fragment with a cyclopentenyl fragment containing an all-carbon quaternary stereo-center (Scheme 5). Subsequent formation of the central six-membered ring would provide the core of the target. In order to proceed toward hamigeran B (**27**), it was necessary to obtain the *S* enantiomer of **19** generated from the optimization studies. By application of Trost ligand (*R*,*R*)-**15** under otherwise identical reaction conditions, vinylogous ester (*S*)-**19** was obtained in 77% yield and 93% *ee*. Subsequent treatment with lithium dimethylcuprate in Et₂O led to the formation of cyclopentanone **20**, containing an all-carbon quaternary stereocenter. Triflate formation and oxidative cleavage of the allyl group provided aldehyde **21**. Nucleophilic addition of the aryllithium of **22**, followed by oxidation of the intermediate alcohol with Dess–Martin periodinane and selective monodemethylation with BCl₃, gave ketone **23**. Enol triflate reduction under palladium catalysis conditions, formation of the aryl triflate **24**, and application of Heck cyclization conditions in the presence of Pd(OAc)₂, dppb, and K₂CO₃ in toluene afforded a mixture of isomeric disubstituted, trisubstituted, and tetrasubstituted olefinic tricycles. After BBr₃-induced demethylation, phenolic trisubstituted olefin **25** could be isolated from the mixture in 51% yield over two steps. The selection of appropriate hydrogenation conditions proved crucial for the formation of the remaining stereocenter. Treatment of alkene **25** with 1500 psi H₂ in the presence of Pd/C in ethanol led to the undesired C(6) epimer, but hydrogenation with Ir black in ethanol directly provided the desired tricycle **26**. Late-stage diketone formation with SeO₂ and acetic acid in *p*-dioxane, followed by regioselective arene bromination, led to hamigeran B (**27**).

By employing the enantiomeric chiral intermediate (*R*)-**19**, the Trost group completed the synthesis of allocyathin B₂ (**37**, Scheme 6) shortly after their investigations of hamigeran B (**27**). The challenging central cyclohexane ring bearing two all-carbon quaternary stereocenters presented an opportunity to test the group's methods for Ru-catalyzed enyne cycloisomerizations. Exocyclic vinylogous ester **19** underwent a double organocuprate addition to give ketone **20** as in the earlier synthesis of hamigeran B (**27**). Triflation and Sonagashira coupling provided alkyne **28**. Oxidative olefin cleavage, aldehyde reduction, and terminal alcohol substitution provided iodide **29**. Lithium/halogen exchange and zincation enabled a Negishi coupling with iodide **30**. Esterification of the alkyne and alcohol deprotection provided enyne **32**. Treatment of this compound under the group's previously

developed conditions for Ru-catalyzed cycloisomerization[24] provided a mixture of *E* and *Z* olefin isomers. An investigation of various ester groups found that the *tert*-butyl ester provided the best ratio of *E*/*Z* olefin isomers. Ultimately, the *E* isomer could be isolated and advanced to unsaturated lactone **35** by a hydroxylative Knoevenagel reaction with phenylsulfinyl acetonitrile.[25] Hydrogenation of the less hindered disubstituted double bond, hydride reduction, and aldol cyclization completed the total synthesis of allocyathin B$_2$ (**37**). The preparation of this compound also constituted a formal synthesis of erinacine A (**38**) based on prior work by Snider.[26] By applying their asymmetric alkylation methodology, the Trost group achieved the divergent total syntheses of hamigeran B (**27**) and allocyathin B$_2$ (**37**) with exocyclic vinylogous ester **19** as the common precursor.

3.2. Total Syntheses of Dichroanone and Liphagal

After the development of a Pd·PHOX catalyst system for the catalytic construction of α-quaternary cyclic ketones,[17a] the Stoltz group sought to prepare the unique and highly substituted carbocyclic structures of dichroanone (**46**, Scheme 7)[27] and liphagal (**56**, Scheme 8, below).[28] Central to their divergent synthetic approach to these natural products was the preparation of bicyclic enone **41** (Scheme 7), which contains two quaternary carbons in close proximity in the cyclohexane ring. The synthetic routes to both of these natural products began with the Pd-catalyzed asymmetric decarboxylative allylic alkylation of cyclic enol carbonate **39**. The addition of this compound to a solution of [Pd$_2$(dba)$_3$] and (*S*)-*t*Bu-PHOX (**13**, Figure 2) in THF (or TBME) led to enantioenriched ketone **40** in 83% yield and 92% *ee*. The presence of the α′-methyl groups in the substrate did not appear to impede catalysis. Through Wacker oxidation and intramolecular aldol cyclization by previously developed protocols,[17a] bicyclic ketone **41** could be obtained in 74% yield over two steps. The key enone possesses a prevalent substitution pattern found not only in dichroanone (**46**) and liphagal (**56**), but also in many other terpenoid natural products.

The *S* enantiomer of bicyclic enone **41** was advanced towards dichroanone (**46**) by the de novo construction of the fully substituted quinone nucleus. A Robinson annulation sequence followed by vinyl triflate formation and Pd-catalyzed Kumada coupling with isopropenylmagnesium bromide led to isopropyl arene **44**. The reaction likely proceeds through coupling product **43**, which can undergo facile aromatization to give the benzannulated ring system. Titanium-mediated formylation of the aromatic ring proceeded smoothly to give an intermediate aldehyde, which was converted into the corresponding phenol **45** by Baeyer–Villiger oxidation. Careful generation of a reactive intermediate *o*-quinone could be achieved by treatment of the tricycle with IBX. Subsequent trapping of the reactive intermediate with pentafluorothiophenol, reoxidation with NaOH/MeOH/O$_2$, and hydrolysis with aqueous HCl completed the synthesis of dichroanone (**46**). Notably, the total synthesis proceeded without the use of protecting groups and provided an asymmetric route to this family of quinone norditerpenoids.

Whereas the route to dichroanone demonstrated the utility of bicyclic enone **41** in α-functionalization reactions, the synthesis of liphagal[28] (**56**, Scheme 8) demonstrated further synthetic applications for this bicyclic scaffold. With enone (*R*)-**41** available by allylic alkylation of substrate **39** with (*R*)-*t*Bu-PHOX (**13**, Figure 2), a photoinduced [2+2]

cycloaddition with TMS-acetylene was performed (Scheme 8). Treatment of the crude cycloadduct with $BF_3 \cdot OEt_2$, followed by TBAF, led to cyclobutene **47**. The strained ketone underwent α-arylation with 4-bromoveratrole (**48**) under microwave irradiation conditions to give highly functionalized tricycle **49**. Arene bromination of this compound proved to be remarkably chemoselective, with the strained cyclobutene remaining intact during the transformation. Subsequent microwave-assisted thermal ring expansion provided conjugated cycloheptadienone **50**. Selective hydrogenation of the less substituted double bond, followed by base-mediated epimerization, led to bicycle **52** after two equilibration cycles. LDA-mediated methylation of the nonconjugated cycloheptenone and DIBAL reduction provided alcohol **53**. Treatment of this compound with LDA led to a reactive aryne intermediate, which could react intramolecularly with the adjacent lithium alkoxide to provide dihydrobenzofuran **55**. Hydrogenation of the remaining olefin provided the necessary stereochemistry at the junction of the six- and seven-membered rings. Dihydrobenzofuran oxidation, followed by arene formylation and phenol demethylation, provided liphagal (**56**). Taken together, the two syntheses demonstrate the unique synthetic utility of bicyclic enone **41**, which is formed from the decarboxylative asymmetric allylic alkylation of enol carbonate **39**.

3.3. Total Syntheses of Elatol, α-Chamigrene, and Laurencenone C

After successfully demonstrating the utility of the allyl enol carbonate approach[17a] for enolate generation in the asymmetric construction of quaternary stereocenters, the Stoltz group sought to extend the scope of the asymmetric decarboxylative allylic alkylation reactions in order to gain access to the chamigrene family of natural products[29] (Scheme 9). These compounds are each distinguished by a central all-carbon quaternary stereocenter connecting two highly substituted six-membered rings, as shown by the structures of laurencenone C (**63**) and α-chamigrene (**64**). The halogenation patterns for members such as elatol (**66**) presented additional synthetic challenges. In order to arrive at these natural products, a flexible synthetic route was needed.

The *gem*-dimethyl group adjacent to the desired alkylation site in substrates **57** and **58** presented a formidable challenge for the decarboxylative allylic alkylation methodology with the Pd·PHOX catalyst system. Investigation of enol carbonate and β-keto ester substrates with (*S*)-*t*Bu-PHOX (**13**, Figure 2) led to the product in 81% *ee*, but levels of conversion were consistently poor in both cases. Faced with these synthetic difficulties, ligand modifications were explored to promote the desired C–C bond-forming step in the catalytic cycle. It was reasoned that through employment of the electron-deficient PHOX derivative **14** (Figure 2), the increased electrophilicity of the derived Pd π-allyl complex should override the steric constraints imposed by the substrate. The combination of electron-deficient PHOX ligand **14** and [Pd(dmdba)$_2$] in toluene or benzene ultimately provided the most effective conditions. Vinylogous ester **59** could be obtained in 87% yield and 87% *ee*, whereas the analogous chlorinated vinylogous ester **60** could be obtained in 82% yield and 87% *ee*. In the presence of catalyst, these substrates could be converted into products below ambient temperature. In addition to these two substrates, the reaction conditions could also be applied to numerous α-substituted analogues.

From enantioenriched vinylogous esters **59** and **60**, it was envisioned that ring-closing metathesis to form a trisubstituted or tetrasubstituted olefin should provide the spirobicylic core of the chamigrene natural products (Scheme 9). Unfortunately, the application of commonly used ruthenium metathesis catalysts **67** and **68** (Figure 3) gave unsatisfactory results. Use of the metathesis catalyst **69**,[30] concurrently developed by the Grubbs laboratory, provided an effective solution. Trisubstituted olefin **61** and chlorinated tetrasubstituted olefin **62** were both formed in excellent yields. Notably, the advances enabled by ruthenium complex **69** provided one of the first examples of effective ring-closing metathesis to form highly substituted halogenated olefins.

With the spirocyclic core of the target natural products secured, short sequences enabled the synthesis of various chamigrene natural products. The addition of methyllithium to spirocycle **61** in the presence of $CeCl_3$ activator, followed by acid workup, provided laurencenone C (**63**). Formation of the corresponding thioketal, followed by dissolving metal reduction, provided α-chamigrene (**64**) in only two additional steps. Application of the same methyllithium addition and acidic workup conditions to vinylogous ester **62** enabled the formation of enone **65**, a chlorinated analogue of **63**. Although this structure had been reported as laurencenone B, the spectra did not match those of the published compound. Nevertheless, the compound was brominated and reduced with DIBAL to afford elatol (**66**). Overall, three spirocyclic natural products in the family were prepared by this unified asymmetric alkylation/ring-closing metathesis strategy.

3.4. Formal Synthesis of Platencin

Maier completed a formal synthesis of platencin (**82**, Scheme 10)[31] by employing a decarboxylative allylic alkylation reaction to establish the substitution around a central quaternary carbon atom joining three different rings. Beginning from vinylogous ester **70**, formylation and allyl enol carbonate construction provided rapid access to allylic alkylation substrate **71** as a mixture of *E* and *Z* isomers. Treatment with catalytic $Pd(OAc)_2$ and PPh_3 provided allylation product (±)-**72**. Subsequent Luche reduction and rearrangement under acidic conditions provided enone **73**, esterification of the primary alcohol and silylation gave silyl dienol ether **74**, and aerobic oxidative cyclization under Toyota's conditions[32] afforded [3.2.1] bicycle **75**. Addition of silyl ketene acetal **76** provided conjugate adduct **77**, subsequent tosylhydrazone formation and skeletal rearrangement led to [2.2.2] bicycle **78**, and Weinreb amide formation and treatment with methyllithium gave hemiacetal **79** as an inconsequential mixture of diastereomers. Reduction and oxidation of this compound provided the ring-opened keto-aldehyde **80**. A straightforward aldol cyclization completed the advanced intermediate **81** employed in numerous syntheses of (±)-platencin (**82**).[33]

To provide an asymmetric entry into this route, Maier returned to the allylic alkylation step with a focus on the development of an enantioselective variant. Treatment of (*Z*)-**71** with catalytic $[Pd_2(dba)_3]\cdot CHCl_3$ and ligand (*S*,*S*)-**17** (Figure 2) in THF at 0 °C provided access to α-quaternary product **72** in 78% *ee*. Further optimization revealed that decreasing the reaction temperature to −20 °C provided improved results, with the desired compound isolable in 95% yield and 87% *ee*. As observed in Trost's initial studies on decarboxylative alkylations of allyl enol carbonates,[18] the chiral diamine scaffold of ligand **17** proved

effective for quaternary stereocenter formation. As a demonstration of the essentially neutral conditions of the decarboxylative alkylation reaction, the potentially sensitive aldehyde functionality underwent minimal side reactions after quaternary stereocenter formation.

3.5. Formal Synthesis of Hamigeran B

A report from the Stoltz group outlined an intramolecular aldol strategy for the construction of the tricyclic framework of hamigeran B (**27**, Scheme 11).[34] The synthetic plan targeted the early construction of an α-quaternary tetralone fragment through a Pd-catalyzed decarboxylative allylic alkylation reaction.[17a] Facile access to enol carbonate **83** enabled rapid evaluation of reaction conditions for the construction of the key quaternary stereocenter. The initial evaluation of (*S*)-*t*Bu-PHOX (**13**, Figure 2) and [Pd$_2$(dba)$_3$] as catalyst precursors in THF provided functionalized tetralone **84** in 71% yield and 88% *ee*. The application of the electron-deficient ligand **14** (Figure 2) provided greater levels of asymmetric induction, with the product isolable in 83% yield and 94% *ee*. Subsequent olefin cross-metathesis with methyl vinyl ketone provided enone **85** for the evaluation of the planned tandem conjugate reduction and aldol cyclization. Treatment of the compound with Stryker's reagent ([Ph$_3$PCuH]$_6$) gave desired β-hydroxyketone **86** along with the uncyclized reduction product. Dehydration of compound **86** led to a tricyclic enone **87**, previously reported by Miesch,[35] and completed an asymmetric formal synthesis of hamigeran B (**27**). The synthesis provides another example of the beneficial effect of electron-deficient PHOX ligand **14** in enantioselective allylic alkylation reactions. When taken together with Trost's earlier total synthesis,[22] the value of asymmetric allylic alkylation reactions can be seen in the different chiral ketone synthons available for the construction of a common natural product target.

3.6. Total Synthesis of Carissone and Cassiol

The dual syntheses of carissone (**99**, Scheme 13, below)[36] and cassiol (**105**, Scheme 14, below)[37] by the Stoltz group were enabled by the unique synthetic potential of vinylogous thioester-derived β-keto ester substrates. Whereas Stoltz developed the first asymmetric allylic alkylation reactions for cycloalkanone-derived β-keto ester substrates[17b] (Scheme 4), Trost succeeded in extending the substrate scope to vinylogous thioester-derived β-keto ester substrates (Scheme 12).[38] In the presence of chiral ligand **17** (Figure 2), α-quaternary vinylogous thioesters such as **89** were prepared in high *ee*s. These products could readily be converted into γ-quaternary enone derivatives through Stork–Danheiser-type transformations. Vinylogous ester-derived β-keto ester substrates were also evaluated, but conversion was typically sluggish, due to the greater orbital overlap of oxygen relative to sulfur.

Concurrent work in the Stoltz group sought to develop a PHOX-based catalyst system for the preparation of these useful compounds and their further application in the total synthesis of natural products. Investigation of β-keto ester and enol carbonate derivatives of α′-substituted isobutyl vinylogous esters provided low levels of conversion and unsatisfactory *ee* values, but the asymmetric allylic alkylation of vinylogous thioester-derived β-keto ester substrate **91** (Scheme 13) with [Pd$_2$(pmdba)$_3$] and (*S*)-*t*Bu-PHOX (**13**, Figure 2) led to enantioenriched product **92** in 85% yield and 92% *ee*.

Further manipulations provided an asymmetric synthetic route to eudesmane sesquiterpenoids such as carissone and α-eudesmol[36] (Scheme 13). The addition of the Grignard reagent of bromide **93**, followed by acid-promoted ketone transposition, led to enone **94**. Ring-closing metathesis with Grubbs second-generation catalyst (**67**) led to fused bicycle **95**. Selective hydrogenation of the less substituted double bond and desilylation provided hydroxy enone **96**. Oxidation of the alcohol, followed by carboxylate methylation, led to enone **97**. Subsequent Luche reduction of the enone and dimethylation of the ester led to diol **98**. Allylic alcohol oxidation provided carissone (**99**). Notably, the assembly of diol **98** also completed a formal synthesis of (−)-α-eudesmol (**100**) by interception of Aoyama's route.[39]

The concise synthesis of cassiol (**105**, Scheme 14)[37] also illustrated the utility of α-quaternary vinylogous thioesters formed through decarboxylative asymmetric allylic alkylation reactions. The key enantioenriched vinylogous thioester **92** was subjected to palladium-catalyzed olefin isomerization, oxidative olefin cleavage, and aldehyde reduction steps to provide alcohol **103**. Treatment of this compound with the vinyllithium derivative of **104**, followed by aqueous acid workup, led to cassiol (**105**) in a concise sequence. Both of the syntheses completed by the Stoltz group illustrate the conversion of α-quaternary vinylogous thioesters into γ-quaternary cyclohexenones in a unified catalytic asymmetric strategy directed towards natural products.

3.7. Total Syntheses of Flustramides A and B and Flustramines A and B

Trost devised a novel and concise strategy for the synthesis of highly substituted pyrroloindoline and pyrroloindolone-type alkaloids such as flustramines A and B and flustramides A and B (**111**–**114**, Scheme 15).[40] His group sought to develop reactions based on chiral Pd π-prenyl complex **108**, which can undergo regioselective asymmetric alkylation by an oxindole enolate to produce either the linear prenylated product or the branched reverse prenylated product. Past work has shown that C–C bond formation predominantly occurs at the less substituted allyl terminus,[41] favoring linear product **109**, but the successful modification of reaction conditions would provide branched isomer **110**, which would be difficult to form by alternative means given the proximity of two quaternary carbons.

With this overall problem in mind, a variety of reaction conditions were evaluated to provide potential access to the linear or branched prenylated products. Carbonate **107** was identified as an excellent prenyl source and masked alkoxide base, generating one equivalent of each after oxidative addition and decarboxylation of the substrate by Pd^0. With carbonate **107**, chiral phenyl bisphosphane ligand **15** (Figure 2), and $[Pd_2(dba)_3]\cdot CHCl_3$ in toluene, a 1:2 ratio of branched/linear products was observed, and the linear product **109** could be isolated in 66% yield and 94% *ee*. Conversely, combination of the naphthyl bis-phosphane ligand **16** (Figure 2), $[Pd_2(dba)_3]\cdot CHCl_3$, and catalytic TBAT (tetrabutylammonium triphenylsilyldifluorosilicate) in CH_2Cl_2 led to a 5.7:1 ratio of branched/linear products with the branched product **110** isolable in 58% yield and greater than 99% *ee*. These results show that the careful choice and modification of the chiral ligand can greatly influence the regioselectivity of the asymmetric alkylation event leading to an all-carbon quaternary

stereocenter. Additionally, the general method could be extended to geranylation reactions,[40] providing impressive access to vicinal all-carbon quaternary stereocenters. Trost's studies show that it is possible to exert control over the regioselectivity, enantio-selectivity, and diastereoselectivity of asymmetric alkylation reactions with these chiral ligand systems.

Adoption of Kawasaki's reductive amide cyclization route[42] provided access to the highly substituted flustramine and flustramide alkaloids. Oxindole reduction of linear alkylation product **109** and branched alkylation product **110** with alane-dimethylethylamine complex at low temperature provided (+)-flustramide A (**111**) and (+)-flustramide B (**113**). Treatment of these compounds with additional reductant at ambient temperature effected lactam reduction to give (+)-flustramine A (**112**) and (+)-flustramine B (**114**). The synthetic route powerfully enables divergent access to C(3)-quaternary prenylated and reverse prenylated oxindole scaffolds through appropriate choice of chiral ligand. In general, examples of the catalytic, asymmetric synthesis of vicinal quaternary stereocenters are quite rare.

3.8. Total Syntheses of Cyanthiwigins B, F, and G

The investigations into Pd-catalyzed allylic alkylations in total synthesis described above sought to establish one quaternary stereocenter at a time. The highly substituted cyclohexane core of the cyathane diterpenoids motivated the Stoltz group to develop new double asymmetric decarboxylative allylic alkylation reactions for efficient construction of multiple all-carbon quaternary stereocenters on a single molecule of substrate. These efforts culminated in efficient total syntheses of cyanthiwigins B, F, and G (**124**, **126**, and **127**, Scheme 17, below).[43]

The Stoltz group investigated reactions of substrate **115** (Scheme 16) in a mixture of catalytic [Pd(dmdba)$_2$] and (S)-*t*Bu-PHOX (**13**, Figure 2) in Et$_2$O.[17b] After two sequential asymmetric alkylation events, diketone **116** could be obtained in 76% yield, 92% *ee*, and 4:1 *dr*. Studies on the related bis-β-keto ester double alkylation substrate **117** provided product **118** in 78% yield, 99% *ee*, and 4.4:1 *dr*.[43] These impressive levels of asymmetric induction can be explained by statistical amplification resulting from multiple asymmetric transformations occurring in sequence.[44,45] The efficiency of these transformations for the assembly of two all-carbon quaternary stereocenters in the same ring system provided an excellent foundation for further synthetic efforts directed towards the cyathane diterpenoids.

With double alkylation product **118** to hand, the synthesis of numerous members of the cyanthiwigin family could be completed (Scheme 17). Desymmetrization of the diketone was achieved by triflation and Negishi coupling to give enone **120**. Subsequent ring-closing metathesis and cross-metathesis with Grubbs–Hoveyda third-generation catalyst (**69**) in the presence of vinylboronate **121** provided aldehyde **122**. Radical cyclization completed the remaining cyclo-pentane ring. Subsequent triflation and Kumada coupling afforded cyanthiwigin F (**124**).

Diketone **123** was further functionalized to related natural products cyanthiwigin B (**126**) and cyanthiwigin G (**127**) in a short, concise sequence (Scheme 17). By means of a Tsuji oxidation[46] and treatment of the intermediate enone with isopropyllithium in the presence

of a CeCl$_3$ activator, adduct **125** could be formed as an inconsequential mixture of diastereomers. Oxidative transposition of the tertiary allylic alcohol enabled the completion of cyanthiwigin B (**126**). Reduction of the ketone and enone moieties with NaBH$_4$, followed by reoxidation of the allylic alcohol, afforded an intermediate alcohol, which could be eliminated by use of Martin's sulfurane to give cyanthiwigin G (**127**). The unified approach to these natural products was enabled by the development of a doubly enantioselective and diastereoselective allylic alkylation of a single substrate compound. The efficient synthetic route provided unique access to the highly substituted cyclohexanoid core of the cyathane diterpenoids.

3.9. Total Synthesis of Presilphiperfolan-1β-ol

Recent work in the Stoltz group has demonstrated the utility of asymmetric allylic alkylation reactions in the construction of functionality-rich γ-quaternary acylcyclopentenes,[47] which proved to be key intermediates for the total synthesis of presilphiperfolan-1β-ol (**134**, Scheme 18).[48] Treatment of β-keto ester substrate **128** with [Pd$_2$(pmdba)$_3$] and (*S*)-*t*Bu-PHOX [(*S*)-**13**, Figure 2] in toluene at 30 °C[17b,47] led to the efficient formation of isoprenyl vinylogous ester **129** in 91% yield and 95% *ee*. An unusual two-carbon ring contraction was achieved through an initial LiAlH$_4$ reduction with acid workup followed by base-promoted rearrangement, to give acylcyclopentene **130** in excellent yield. Although these conditions resemble the Stork–Danheiser-type transformations illustrated in the syntheses of chamigrene natural products (Scheme 9), platencin (Scheme 10), carissone (Scheme 13), and cassiol (Scheme 14), the unusual stability of the intermediate β-hydroxycycloheptanone enabled the formation of acylcyclopentene **130** rather than the more conventional isomeric cycloheptenone elimination product.[47] Subsequent ketalization with neopentyl glycol and 1,4-hydroboration/oxidation with catalytic Ni(cod)$_2$ and PCy$_3$ by Morken's procedure[49] led to allylic alcohol **131**. Activation of the alcohol as an allylic phosphate provided the necessary substrate for a CuCN-catalyzed S$_N$2′ allylic substitution with dimethylzinc. The more functionalized acylcyclopentene **132** underwent silylation, intramolecular Diels–Alder cyclization, and Rubottom oxidation to provide a 90% combined yield of oxidized cycloadducts over three steps, with a 28% yield of the desired diastereomer **133**. Additional Wittig methylenation, silylation, diastereoselective hydrogenation, and desilylation steps completed the total synthesis of presilphiperfolan-1β-ol (**134**).[48]

The diastereoselective preparation of the 9-epimer of pre-silphiperfolan-1β-ol (9α-Me) was also achieved,[48] but the spectrum of this compound did not match that reported for the natural product. After extensive spectroscopic analysis and evaluation of the likely biosynthetic pathway, it was concluded that the epimeric presilphiperfolanol was most likely not a natural product.

The synthetic studies leading to presilphiperfolan-1β-ol (**134**) provided an important opportunity to expand the scope of π-allyl electrophiles for α-quaternary stereocenter construction. The examination of a 2-(vinyl)allyl electrophile in the synthesis complements the Stoltz group's earlier investigation of internal π-allyl substitution in the synthesis of chamigrene natural products[29] (Scheme 9). These studies, together with the Trost group's exploration of terminal π-allyl substitution in the synthesis of flustramine and flustramide

indole alkaloids[40] (Scheme 15), illustrate the wide range of π-allyl electrophiles that can be employed in asymmetric allylic alkylation reactions.

4. Conclusion and Outlook

The pursuit of complex targets has provided inspiration for the development of Pd-catalyzed asymmetric allylic alkylation reactions for the construction of challenging all-carbon quaternary stereocenters. The synthetic methods developed in the past ten years have provided chemists with useful tools for the assembly of densely substituted ring systems, and consequently, the total synthesis of complex natural products. Although major advances have been made, broader examination of reaction scope, development of new catalyst systems, and coupling of palladium enolate chemistry to other powerful bond-forming processes has the potential to reshape the field in future.

Note Added in Proof

Several research groups have recently reported methods for asymmetric allylic alkylation of enolates derived from *N*-heterocyclic frameworks and applied them to the synthesis of polycyclic alkaloid natural products. The Stoltz laboratory employed the PHOX ligands (*S*)-**13** or (*S*)-**14** (Figure 2) with [Pd₂(dba)₂] or [Pd₂(pmdba)₃] to achieve the syntheses of α-quaternary lactams and related heterocycles (Scheme 19).[50] In their report, they also demonstrated the concise formal synthesis of rhazinilam (**138**).[51] The important lactam building blocks can be readily applied to the synthesis of quebrachamine and other related alkaloids (**139**).[52] Recent findings from the same laboratory have generalized the substrate scope to include additional lactam and vinylogous amide-type substrates.[53] Concurrent investigation of the asymmetric alkylation of carbazolone substrates by the Lupton group[54] enabled the successful formal synthesis of kopsihainanine A[55] (Scheme 20). Very recently, the Shao group also documented a similar approach in their total synthesis of (–)-aspidospermidine and (+)-kopsihainanine A.[56]

Acknowledgments

References

1. For a review discussing our strategy of using natural product structures to drive the development of enantioselective catalysis, see: Mohr JT, Krout MR, Stoltz BM. Nature. 2008; 455:323–332. [PubMed: 18800131]

2. For excellent general reviews on the catalytic enantioselective generation of quaternary stereocenters, see: Martin SF. Tetrahedron. 1980; 36:419–460.Fuji K. Chem Rev. 1993; 93:2037–2066.Corey EJ, Guzman-Perez A. Angew Chem. 1998; 110:402–415.Angew Chem Int Ed. 1998; 37:388–401.Christoffers J, Mann A. Angew Chem. 2001; 113:4725–4732.Angew Chem Int Ed. 2001; 40:4591–4597.Denissova I, Barriault L. Tetrahedron. 2003; 59:10105–10146.Douglas CJ, Overman LE. Proc Natl Acad Sci USA. 2004; 101:5363–5367. [PubMed: 14724294] Christoffers J, Baro A. Adv Synth Catal. 2005; 347:1473–1482.Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis. Christoffers J, Baro A. WileyWeinheim, Germany2005Trost BM,

Jiang C. Synthesis. 2006:369–396.Cozzi PG, Hilgraf R, Zimmermann N. Eur J Org Chem. 2007:5969–5994.Das JP, Marek I. Chem Commun. 2011; 47:4593–4623.

3. For general reviews discussing palladium-catalyzed asymmetric allylic alkylation, see: Trost BM. Acc Chem Res. 1996; 29:355–364.Trost BM, Van Vranken DL. Chem Rev. 1996; 96:395–422. [PubMed: 11848758] Helmchen G. J Organomet Chem. 1999; 576:203–214.Pfaltz A, Lautens M. Comprehensive Asymmetric Catalysis. Jacobsen EN, Pfaltz A, Yamamoto H. SpringerNew York1999; 2:833–884.Trost BM, Lee C. Catalytic Asymmetric Synthesis (2). Ojima I. Wiley-VCHNew York2000:593–649.Trost BM. Chem Pharm Bull. 2002; 50:1–14. [PubMed: 11824567] Trost BM. J Org Chem. 2004; 69:5813–5837. [PubMed: 15373468] Lu Z, Ma S. Angew Chem. 2008; 120:264–303.Angew Chem Int Ed. 2008; 47:258–297.Trost BM. Org Process Res Dev. 2012; 16:185–194. [PubMed: 22736934]

4. For reviews discussing Pd-catalyzed decarboxylative allylic alkylation reactions, see: Tunge JA, Burger EC. Eur J Org Chem. 2005:1715–1726.Mohr JT, Stoltz BM. Chem Asian J. 2007; 2:1476–1491. [PubMed: 17935094] Weaver JD, Recio A III, Grenning AJ, Tunge JA. Chem Rev. 2011; 111:1846–1913. [PubMed: 21235271]

5. For an earlier review discussing the application of Pd-catalyzed allylic alkylation reactions in total synthesis, see: Trost BM, Crawley ML. Chem Rev. 2003; 103:2921–2944. [PubMed: 12914486]

6. For some recent examples of Pd-catalyzed enantioselective allylic alkylation reactions of ketone enolates leading to the formation of chiral tertiary centers at the nucleophile in the context of total synthesis, see: nigellamine A$_2$: Bian J, Van Wingerden M, Ready JM. J Am Chem Soc. 2006; 128:7428–7429. [PubMed: 16756282] hyperolactone C and biyouyanagin A: Du C, Li L, Li Y, Xie Z. Angew Chem. 2009; 121:7993–7996.Angew Chem Int Ed. 2009; 48:7853–7856.Tekturna (aliskiren): Hanessian S, Chénard E. Org Lett. 2012; 14:3222–3225. [PubMed: 22668074]

7. For some recent examples of catalyst-controlled Pd-catalyzed diastereoselective allylic alkylation reactions in the context of total synthesis, see: spirotryprostatin B: Trost BM, Stiles DT. Org Lett. 2007; 9:2763–2766. [PubMed: 17592853] epothilone D: Prantz K, Mulzer J. Chem Eur J. 2010; 16:485–506. [PubMed: 19943284] drechslerines A and B: Hagiwara H, Fukushima M, Kinugawa K, Matsui T, Hoshi T, Suzuki T. Tetrahedron. 2011; 67:4061–4068.

8. Hayashi T, Kanehira K, Hagihara T, Kumada M. J Org Chem. 1988; 53:113–120.

9. a) Sawamura M, Nagata H, Sakamoto H, Ito Y. J Am Chem Soc. 1992; 114:2586–2592.b) Sawamura M, Sudoh M, Ito Y. J Am Chem Soc. 1996; 118:3309–3310.c) Kuwano R, Ito Y. J Am Chem Soc. 1999; 121:3236–3237.d) Kuwano R, Uchida K, Ito Y. Org Lett. 2003; 5:2177–2179. [PubMed: 12790558]

10. a) Trost BM, Ariza X. Angew Chem. 1997; 109:2749–2751.Angew Chem Int Ed Engl. 1997; 36:2635–2637.b) Trost BM, Radinov R, Grenzer EM. J Am Chem Soc. 1997; 119:7879–7880.c) Trost BM, Schroeder GM. J Am Chem Soc. 1999; 121:6759–6760.d) Trost BM, Schroeder GM, Kristensen J. Angew Chem. 2002; 114:3642–3645.Angew Chem Int Ed. 2002; 41:3492–3495.e) Trost BM, Schroeder GM. Chem Eur J. 2005; 11:174–184. [PubMed: 15515094]

11. a) You SL, Hou XL, Dai LX, Cao BX, Sun J. Chem Commun. 2000:1933–1934.b) You SL, Hou XL, Dai LX, Zhu XZ. Org Lett. 2001; 3:149–151. [PubMed: 11430021]

12. Tsuji J, Minami I, Shimizu I. Tetrahedron Lett. 1983; 24:4713–4714.

13. Tsuji J, Minami I, Shimizu I. Chem Lett. 1983:1325–1326.

14. Tsuji J, Minami I, Shimizu I. Tetrahedron Lett. 1983; 24:1793–1796.

15. Shimizu I, Yamada T, Tsuji J. Tetrahedron Lett. 1980; 21:3199–3202.

16. Saegusa published very similar work with β-keto esters simultaneously with Tsuji's work, see: Tsuda T, Chujo Y, Nishi S, Tawara K, Saegusa T. J Am Chem Soc. 1980; 102:6381–6384.

17. a) Behenna DC, Stoltz BM. J Am Chem Soc. 2004; 126:15044–15045. [PubMed: 15547998] b) Mohr JT, Behenna DC, Harned AM, Stoltz BM. Angew Chem. 2005; 117:7084–7087.Angew Chem Int Ed. 2005; 44:6924–6927.c) Behenna DC, Mohr JT, Sherden NH, Marinescu SC, Harned AM, Tani K, Seto M, Ma S, Novák Z, Krout MR, McFadden RM, Roizen JL, Enquist JA Jr, White DE, Levine SR, Petrova KV, Iwashita A, Virgil SC, Stoltz BM. Chem Eur J. 2011; 17:14199–14223. [PubMed: 22083969]

18. a) Trost BM, Xu J. J Am Chem Soc. 2005; 127:2846–2847. [PubMed: 15740108] b) Trost BM, Xu J, Schmidt T. J Am Chem Soc. 2009; 131:18343–18357. [PubMed: 19928805]

19. For a review discussing catalytic enantioselective stereoablative processes, see: Mohr JT, Ebner DC, Stoltz BM. Org Biomol Chem. 2007; 5:3571–3576. [PubMed: 17971984]

20. For an early report of Trost ligands in Pd-catalyzed asymmetric alkylation reactions, see: Trost BM, Van Vranken DL, Bingel C. J Am Chem Soc. 1992; 114:9327–9343.

21. For early reports of PHOX ligands, see: von Matt P, Pfaltz A. Angew Chem. 1993; 105:614–615.Angew Chem Int Ed Engl. 1993; 32:566–568.Sprinz J, Helmchen G. Tetrahedron Lett. 1993; 34:1769–1772.Dawson GJ, Frost CG, Williams JMJ, Coote SJ. Tetrahedron Lett. 1993; 34:3149–3150.

22. a) Trost BM, Pissot-Soldermann C, Chen I, Schroeder GM. J Am Chem Soc. 2004; 126:4480–4481. [PubMed: 15070341] b) Trost BM, Pissot-Soldermann C, Chen I. Chem Eur J. 2005; 11:951–959. [PubMed: 15612053]

23. a) Trost BM, Dong L, Schroeder GM. J Am Chem Soc. 2005; 127:2844–2845. [PubMed: 15740107] b) Trost BM, Dong L, Schroeder GM. J Am Chem Soc. 2005; 127:10259–10268. [PubMed: 16028937]

24. a) Trost BM, Toste FD. J Am Chem Soc. 1999; 121:9728–9729.b) Trost BM, Toste FD. J Am Chem Soc. 2000; 122:714–715.c) Trost BM, Toste FD. J Am Chem Soc. 2002; 124:5025–5036. [PubMed: 11982367]

25. a) Nokami J, Mandai T, Imakura Y, Nishiuchi K, Kawada M, Wakabayashi S. Tetrahedron Lett. 1981; 22:4489–4490.b) Ono T, Tamaoka T, Yuasa Y, Matsuda T, Nokami J, Wakabayashi S. J Am Chem Soc. 1984; 106:7890–7893.c) Trost BM, Mallart S. Tetrahedron Lett. 1993; 34:8025–8028.

26. Snider BB, Vo NH, O'Neil SV, Foxman BM. J Am Chem Soc. 1996; 118:7644–7645.

27. McFadden RM, Stoltz BM. J Am Chem Soc. 2006; 128:7738–7739. [PubMed: 16771478]

28. Day JJ, McFadden RM, Virgil SC, Kolding H, Alleva JL, Stoltz BM. Angew Chem. 2011; 123:6946–6950.Angew Chem Int Ed. 2011; 50:6814–6818.

29. a) White DE, Stewart IC, Grubbs RH, Stoltz BM. J Am Chem Soc. 2008; 130:810–811. [PubMed: 18163634] b) White DE, Stewart IC, Seashore-Ludlow BA, Grubbs RH, Stoltz BM. Tetrahedron. 2010; 66:4668–4686. [PubMed: 20798895]

30. Stewart IC, Ung T, Pletnev AA, Berlin JM, Grubbs RH, Schrodi Y. Org Lett. 2007; 9:1589–1592. [PubMed: 17378575]

31. Varseev GN, Maier ME. Angew Chem. 2009; 121:3739–3742.Angew Chem Int Ed. 2009; 48:3685–3688.

32. Toyota M, Wada T, Fukumoto K, Ihara M. J Am Chem Soc. 1998; 120:4916–4925.

33. a) Nicolaou KC, Tria GS, Edmonds DJ. Angew Chem. 2008; 120:1804–1807.Angew Chem Int Ed. 2008; 47:1780–1783.b) Hayashida J, Rawal VH. Angew Chem. 2008; 120:4445–4448.Angew Chem Int Ed. 2008; 47:4373–4376.c) Yun SY, Zheng JC, Lee D. Angew Chem. 2008; 120:6297–6299.Angew Chem Int Ed. 2008; 47:6201–6203.d) Tiefenbacher K, Mulzer J. Angew Chem. 2008; 120:6294–6295.Angew Chem Int Ed. 2008; 47:6199–6200.e) Waalboer DCJ, Schaapman MC, van Delft FL, Rutjes FPJT. Angew Chem. 2008; 120:6678–6680.Angew Chem Int Ed. 2008; 47:6576–6578.f) Nicolaou KC, Toh QY, Chen DYK. J Am Chem Soc. 2008; 130:11292–11293. [PubMed: 18665593] Nicolaou KC, Toh QY, Chen DYK. J Am Chem Soc. 2008; 130:14016.g) Austin KAB, Banwell MG, Willis AC. Org Lett. 2008; 10:4465–4468. [PubMed: 18798641]

34. Mukherjee H, McDougal NT, Virgil SC, Stoltz BM. Org Lett. 2011; 13:825–827. [PubMed: 21271716]

35. Miesch L, Welsch T, Rietsch V, Miesch M. Chem Eur J. 2009; 15:4394–4401. [PubMed: 19283820]

36. Levine SR, Krout MR, Stoltz BM. Org Lett. 2009; 11:289–292. [PubMed: 19093809]

37. Petrova KV, Mohr JT, Stoltz BM. Org Lett. 2009; 11:293–295. [PubMed: 19093836]

38. Trost BM, Bream RN, Xu J. Angew Chem. 2006; 118:3181–3184.Angew Chem Int Ed. 2006; 45:3109–3112.

39. Aoyama Y, Araki Y, Konoike T. Synlett. 2001; 9:1452–1454.

40. Trost BM, Malhotra S, Chan WH. J Am Chem Soc. 2011; 133:7328–7331. [PubMed: 21520958]

41. Kazmaier U, Stolz D, Krämer K, Zumpe FL. Chem Eur J. 2008; 14:1322–1329. [PubMed: 18000997]

42. Kawasaki T, Shinada M, Kamimura D, Ohzono M, Ogawa A. Chem Commun. 2006:420–422.

43. a) Enquist JA Jr, Stoltz BM. Nature. 2008; 453:1228–1231. [PubMed: 18580947] b) Enquist JA Jr, Virgil SC, Stoltz BM. Chem Eur J. 2011; 17:9957–9969. [PubMed: 21769952]

44. Langenbeck W, Triem G. Z Phys Chem Abt A. 1936; 117:401–409.

45. a) Vigneron JP, Dhaenens M, Horeau A. Tetrahedron. 1973; 29:1055–1059.b) Rautentrauch V. Bull Soc Chim Fr. 1994; 131:515–524.c) Baba SE, Sartor K, Poulin J, Kagan H. Bull Soc Chim Fr. 1994; 131:525–533.

46. a) Shimizu I, Tsuji J. J Am Chem Soc. 1982; 104:5844–5846.b) Shimizu I, Minami I, Tsuji J. Tetrahedron Lett. 1983; 24:1797–1800.c) Minami I, Takahashi K, Shimizu I, Kimura T, Tsuji J. Tetrahedron. 1986; 42:2971–2977.

47. a) Hong AY, Krout MR, Jensen T, Bennett NB, Harned AM, Stoltz BM. Angew Chem. 2011; 123:2808–2812.Angew Chem Int Ed. 2011; 50:2756–2760.b) Hong AY, Bennett NB, Krout MR, Jensen T, Harned AM, Stoltz BM. Tetrahedron. 2011; 67:10234–10248. [PubMed: 22347731] c) Bennett NB, Hong AY, Harned AM, Stoltz BM. Org Biomol Chem. 2012; 10:56–59. [PubMed: 22009489]

48. Hong AY, Stoltz BM. Angew Chem. 2012; 124:9812–9816.Angew Chem Int Ed. 2012; 51:9674–9678.this communication is corrected by: Hong AY, Stoltz BM. Angew Chem. 2013; 125:2201.Angew Chem Int Ed. 2013; 52:2147.

49. a) Ely RJ, Morken JP. J Am Chem Soc. 2010; 132:2534–2535. [PubMed: 20136142] b) Ely RJ, Morken JP. Org Synth. 2011; 88:342–352.

50. Behenna DC, Liu Y, Yurino T, Kim J, White DE, Virgil SC, Stoltz BM. Nature Chem. 2012; 4:130–133. [PubMed: 22270628]

51. Magnus P, Rainey T. Tetrahedron. 2001; 57:8647–8651.

52. Amat M, Lozano O, Escolano C, Molins E, Bosch J. J Org Chem. 2007; 72:4431–4439. [PubMed: 17488127]

53. Bennett NB, Duquette DC, Kim J, Liu W-B, Marziale AN, Behenna DC, Virgil SC, Stoltz BM. Chem Eur J. 10.1002/chem.201300030

54. Gartshore CJ, Lupton DW. Angew Chem. 2013; 12510.1002/ange.201209069;Angew Chem Int Ed. 2013; 52 Early View. 10.1002/anie.201209069

55. Jing P, Yang Z, Zhao C, Zheng H, Fang B, Xie X, She X. Chem Eur J. 2012; 18:6729–6732. [PubMed: 22549799]

56. Li Z, Zhang S, Wu S, Shen X, Zou L, Wang F, Li X, Peng F, Zhang H, Shao Z. Angew Chem. 2013; 12510.1002/ange.201209878;Angew Chem Int Ed. 2013; 5210.1002/anie.201209878

Biographies

Allen Y. Hong was born in San Francisco, California in 1984. He began studying chemistry in 2004 at UC Berkeley. In the autumn of 2005 he joined Prof. Richmond Sarpong's laboratory and studied rhodium-catalyzed reactions for the synthesis of highly functionalized furans. Allen graduated from UC Berkeley in 2006 with a B.S. in chemical

biology. After completing his undergraduate education, he moved south to Pasadena, California in 2007 to begin doctoral studies in synthetic organic chemistry at the California Institute of Technology. In January 2008 he joined the research group of Prof. Brian M. Stoltz to study asymmetric catalysis and total synthesis, focusing on the synthesis of presilphiperfolanol natural produc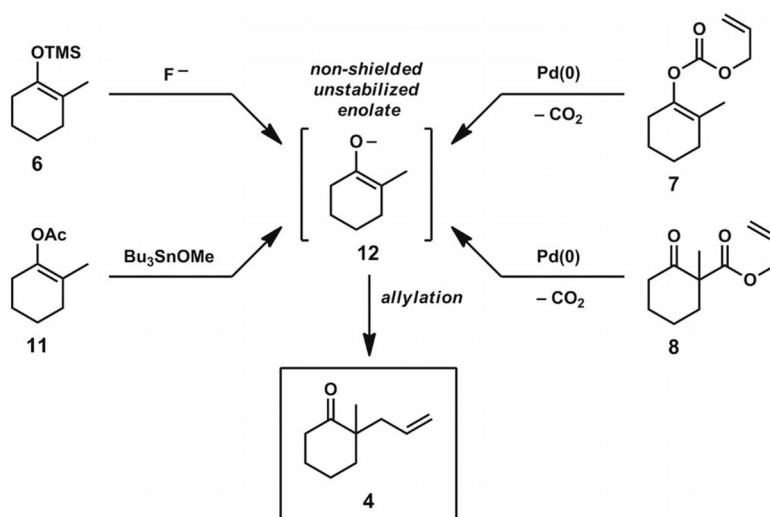ts with the aid of Pd-catalyzed asymmetric allylic alkylation reactions. Allen earned his Ph.D. in chemistry in 2012. In January 2013 he continued the southward trend and began NIH-sponsored postdoctoral research under the guidance of Prof. Chris D. Vanderwal at UC Irvine.

Brian M. Stoltz was born in Philadelphia, PA, in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the laboratories of John L. Wood and an NIH postdoctoral fellowship at Harvard in the Corey laboratories, he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he is currently Professor of Chemistry. His research interests lie in the development of new methodology for general applications in synthetic chemistry.
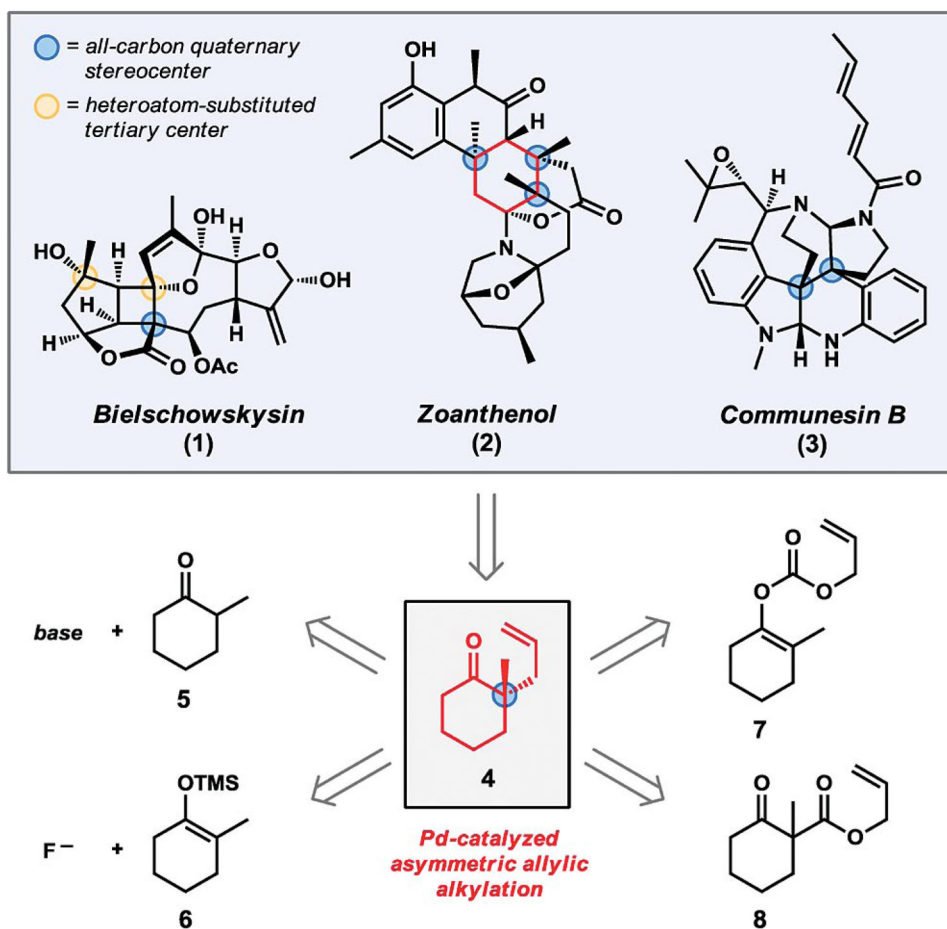
Figure 1.
Natural products as an inspiration for the development of asymmetric catalysis.
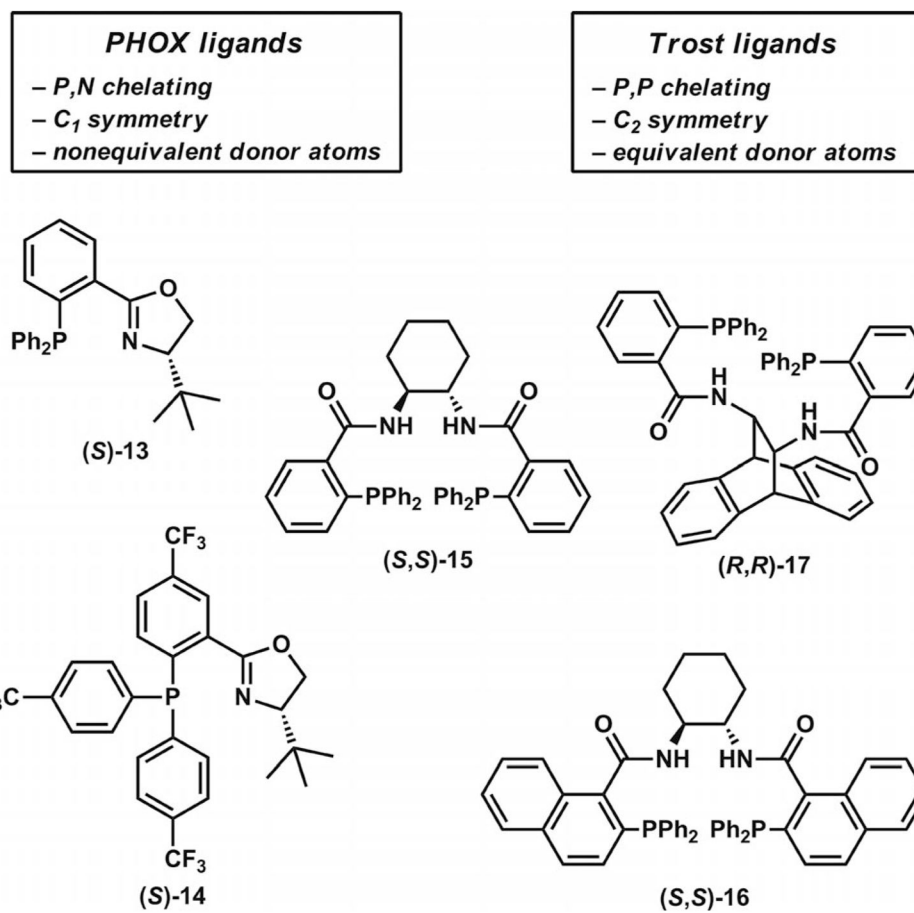
Figure 2.
Selected chiral ligands for Pd-catalyzed asymmetric allylic alkylation reactions.
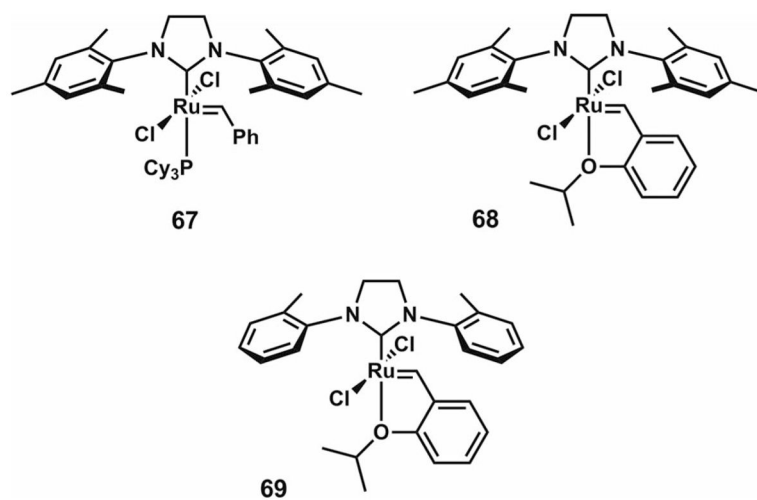
Figure 3.
Ruthenium olefin metathesis catalysts.
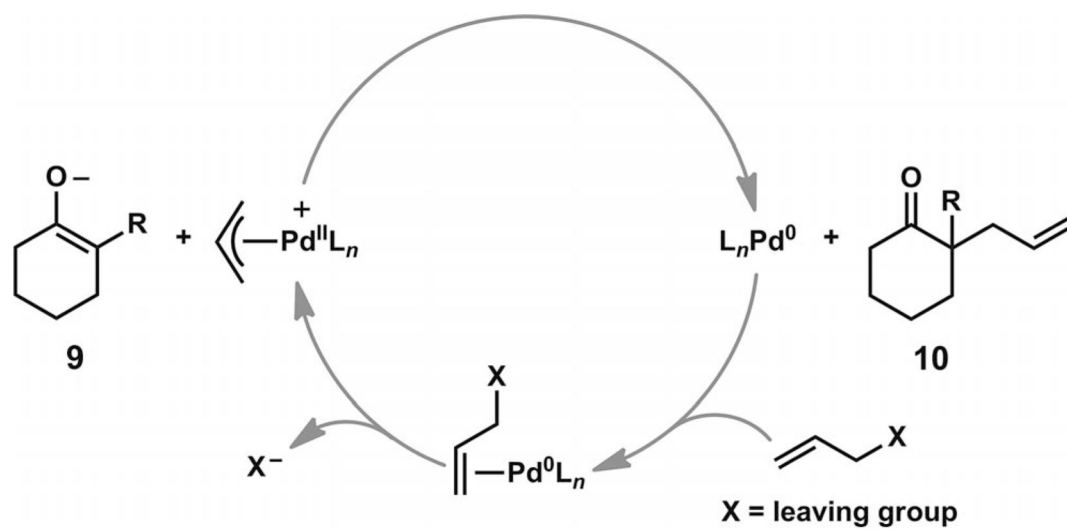
Scheme 1.
General mechanism for Pd-catalyzed allylic alkylation reactions.
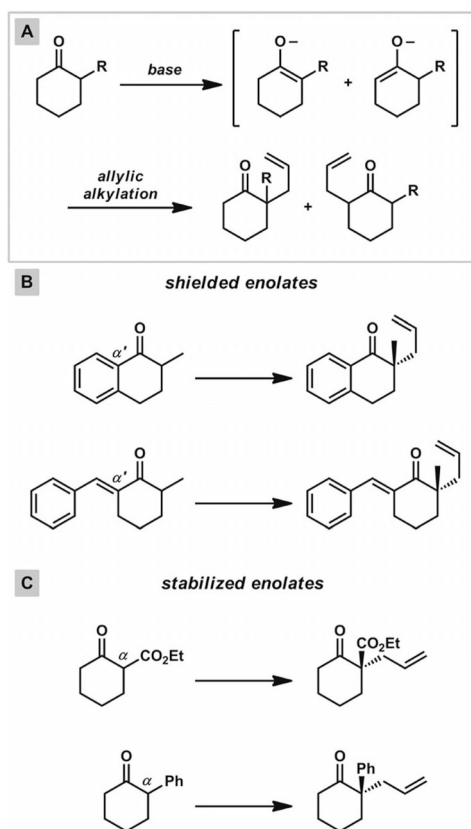
Scheme 2.
The enolate alkylation problem and approaches to selective enolate formation.

Scheme 3.
Tsuji reactions for the allylation of non-shielded, non-stabilized enolates.
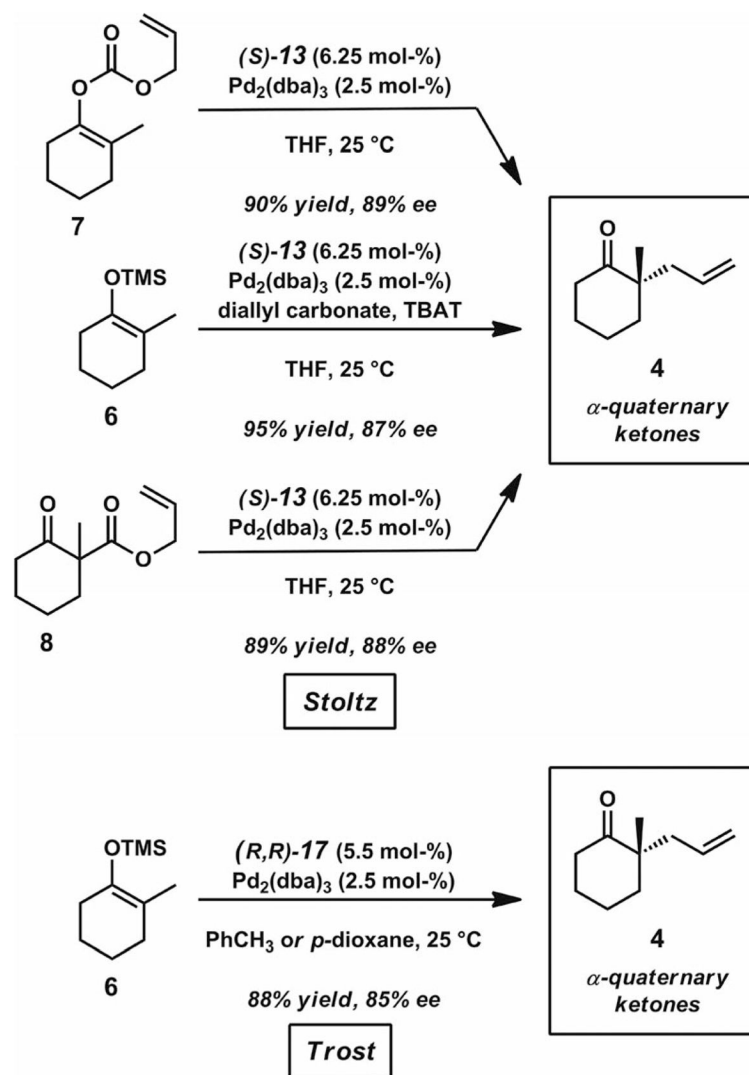
Scheme 4.
Pd-catalyzed asymmetric allylic alkylation reactions with allyl enol carbonate, silyl enol ether, and β-keto ester substrate classes.
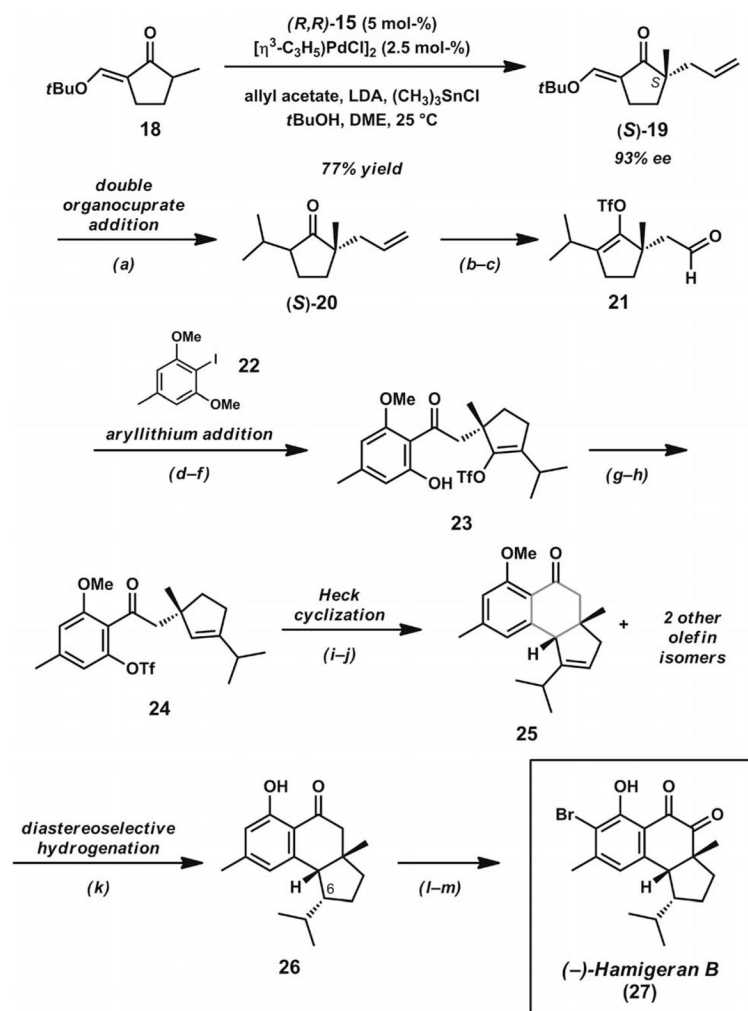
Scheme 5.

Total synthesis of hamigeran B. *Reaction conditions:* a) $(CH_3)_2CuLi$, Et_2O, $-20\ °C$ (89%
yield). b) LDA, THF, $-78 \rightarrow 0\ °C$; then $PhN(Tf)_2$ (87% yield). c) OsO_4 (3.77 mol-%), NMO,
THF, H_2O; then $NaIO_4$. d) Iodoarene **22**, DME, $-55\ °C$; then aldehyde **21**. e) Dess–Martin
periodinane, $NaHCO_3$, CH_2Cl_2, 75% yield (three steps). f) BCl_3, CH_2Cl_2, $-20\ °C$ (85%
yield). g) $Pd(OAc)_2$ (10 mol-%), dppf (20 mol-%), HCO_2H, Et_3N, DMF, $70\ °C$ (94% yield).
h) Tf_2O, CH_2Cl_2, pyridine, $0\ °C$ (94 % yield). i) $Pd(OAc)_2$, dppb, K_2CO_3, $PhCH_3$. j) BBr_3,
CH_2Cl_2, $-78\ °C$ (51% yield, two steps). k) Ir black, H_2 (1500 psi), EtOH (>99% yield). l)
SeO_2, cat. AcOH, *p*-dioxane (90% yield). m) NBS, iPr_2NH (5 mol-%), CH_2Cl_2 (85% yield).
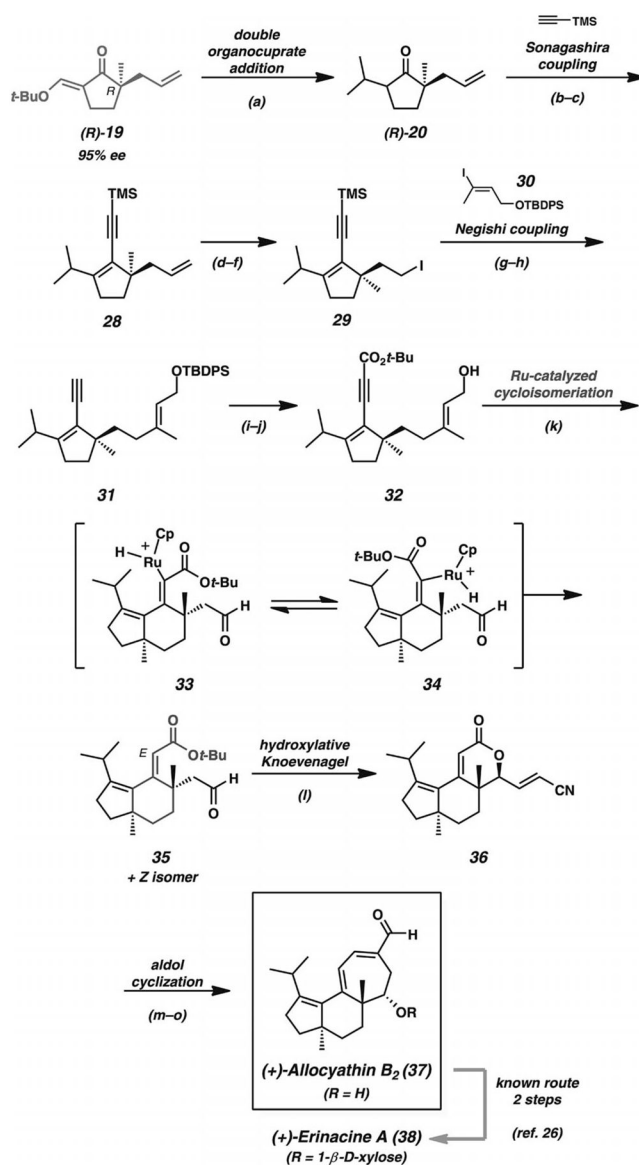
Scheme 6.

Total synthesis of allocyathin B$_2$. *Reaction conditions:* a) (CH$_3$)$_2$CuLi, Et$_2$O, −20 °C (89% yield). b) LDA, THF, −78→0 °C; then PhN(Tf)$_2$ (96% yield). c) [Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5 mol-%), PPh$_3$ (20 mol-%), CuI (5 mol-%), TMS-acetylene, *n*BuNH$_2$, 50 °C (85% yield). d) OsO$_4$ (1 mol-%), NMO; then NaIO$_4$ (87% yield). e) NaBH$_4$, MeOH (94% yield). f) PPh$_3$, I$_2$, imidazole (97% yield). g) *t*BuLi, ZnCl$_2$, THF, −78 °C →r.t.; then [Pd(PPh$_3$)$_4$] (5 mol-%), vinyl iodide **30**. h) K$_2$CO$_3$, MeOH (74% yield, two steps). i) *n*BuLi, THF, −78 °C; then Boc$_2$O, −78 →r.t. (99% yield). j) TBAF, THF (52–55% yield). k) CpRu(CH$_3$CN)$_3$PF$_6$ (20 mol-%), DMF (1 equiv.), butan-2-one, room temp. (48% yield of **35**, or 55% combined yield, 6.7:1 *E/Z* ratio). l) PhS(O)CH$_2$CN, piperidine, PhH (75% yield). m) Pd/C (10%), EtOAc, H$_2$ (1 atm) (83% yield). n) DIBAL, CH$_2$Cl$_2$, −78 °C. o) KOH, MeOH, 60 °C (51% yield, two steps).
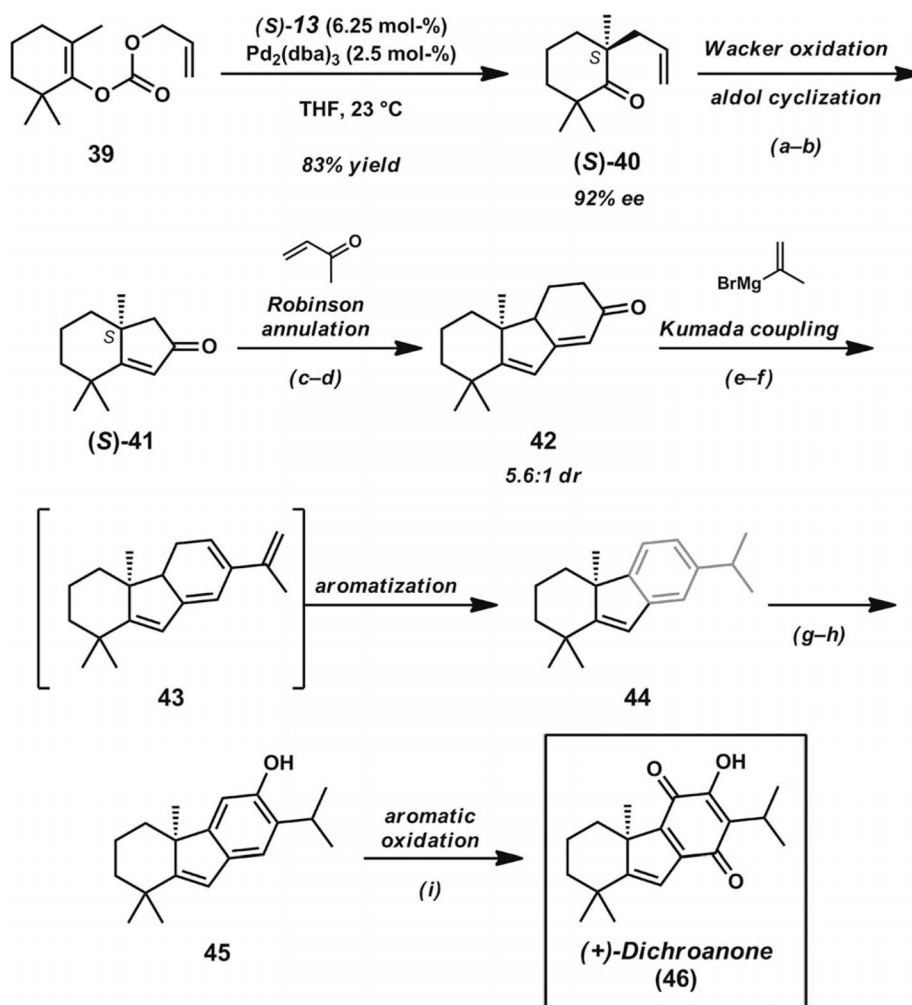
Scheme 7.
Total synthesis of dichroanone. *Reaction conditions:* a) $PdCl_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (25 mol-%), O_2 (1 atm), DMA/H_2O (7:1), 23 °C, Parr shaker (77% yield). b) KOH (0.45 equiv.), xylenes, 110 °C, Dean–Stark (96% yield). c) LiHMDS, THF, 0→23 °C; then methyl vinyl ketone, −78 °C; then aq. NH_4Cl, −78→23 °C (72% yield). d) Powdered KOH (2 equiv.), xylenes, 110 °C, Dean–Stark (80% yield). e) LDA, THF, −78 °C; then $PhN(Tf)_2$, −78→23 °C. f) Isopropenylmagnesium bromide (2 equiv.), [Pd(PPh$_3$)$_4$] (5 mol-%), THF, 23 °C; then 6 M aq. HCl, 23 °C (65% yield, two steps). g) Cl_2HCOCH_3. $TiCl_4$, CH_2Cl_2, −78 → 23 °C (79% yield). h) Aq. H_2O_2, aq. H_2SO_4, THF/MeOH/H_2O (2:5:1), 23 °C (74% yield). i) IBX (1.2 equiv.), $CHCl_3$, 23 °C; then C_6F_5SH (4 equiv.), 23 °C; then O_2 (1 atm), NaOH (10 equiv.), MeOH, 23→75 °C; then 6 M aq. HCl, 23 °C (35% yield).
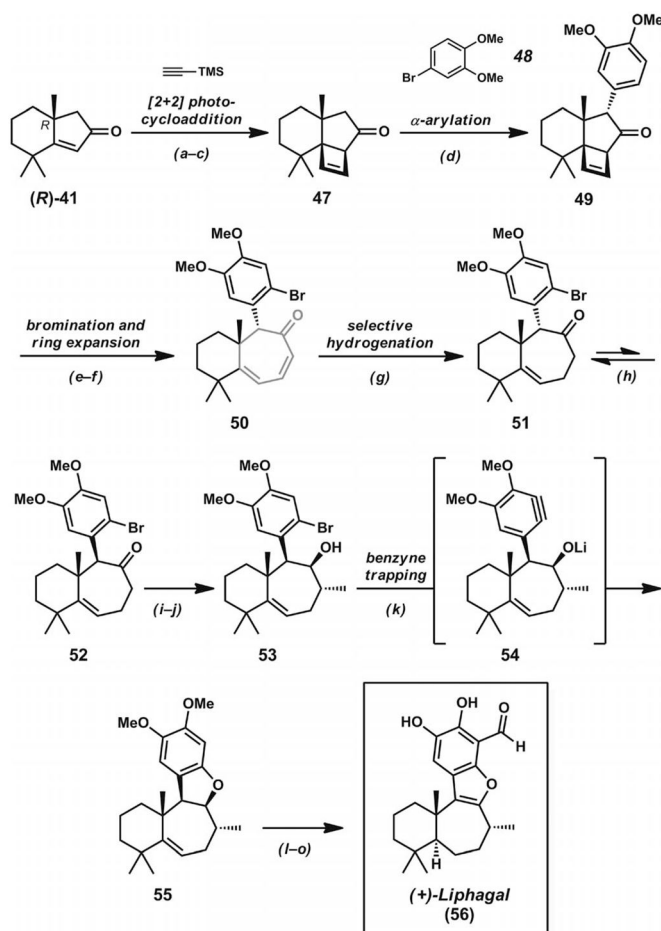
Scheme 8.

Total synthesis of liphagal. *Reaction conditions:* a) TMS-acetylene, UV-B lamps, acetone. b) BF$_3$·OEt$_2$, CH$_2$Cl$_2$. c) TBAF, THF (68% yield, three steps). d) [Pd(P(tBu)$_3$)$_2$] (5 mol-%), 4-bro-moveratrole, NaOtBu, THF, microwave irradiation, 120 °C (67% yield). e) Br$_2$ (1.8 equiv.), CHCl$_3$ (65% yield). f) Microwave irradiation, o-dichlorobenzene, 250 °C (68% yield). g) PtO$_2$ (20 mol-%), H$_2$ (1 atm), EtOAc (69% yield). h) NaOMe, MeOH, 65 °C (78% yield, three cycles). i) LDA, THF, −78→0 °C; then CH$_3$I, −78→0 °C (68% yield). j) DIBAL, PhCH$_3$ (91% yield). k) LDA (3 equiv.), THF, −20 °C (83% yield). l) Pd/C (19 mol-%), H$_2$ (1 atm), EtOH, 21 °C (97% yield). m) NO$^+$BF$_4^-$, CH$_3$CN, 0 °C (70% yield). n) nBuLi, TMEDA, THF, 0 °C; then DMF, 0→21 °C (70% yield). o) BI$_3$, CH$_2$Cl$_2$ (45 % yield).
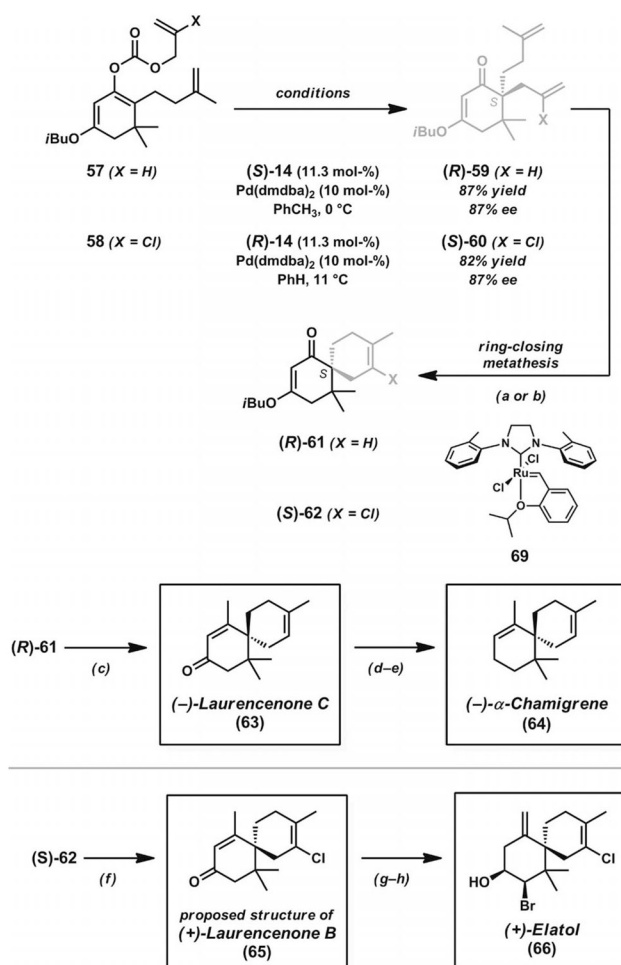
Scheme 9.

Total synthesis of laurencenone C, α-chamigrene, the proposed structure of laurencenone B, and elatol. *Reaction conditions:* a) substrate **59**, Grubbs–Hoveyda third-generation catalyst (**69**, 5 mol-%), PhH, 60 °C (97% yield). b) Substrate **60**, Grubbs–Hoveyda third-generation catalyst (**69**, 5 mol-%), PhH, 60 °C (97% yield). c) MeLi, CeCl$_3$, THF, −78→0 °C; then 10% aq. HCl, 0→23 °C (80% yield). d) BF$_3$·OEt$_2$, HSCH$_2$CH$_2$SH, MeOH, 23 °C (92 % yield). e) Na(0), Et$_2$O/NH$_3$(*l*), −60→reflux (44% yield). f) MeLi, CeCl$_3$, THF, −78→0 °C; then 10% aq. HCl, 0→23 °C (89% yield). g) Br$_2$, 48% aq. HBr, AcOH, 23 °C. h) DIBAL, THF, −78→60 °C (32% yield, two steps).
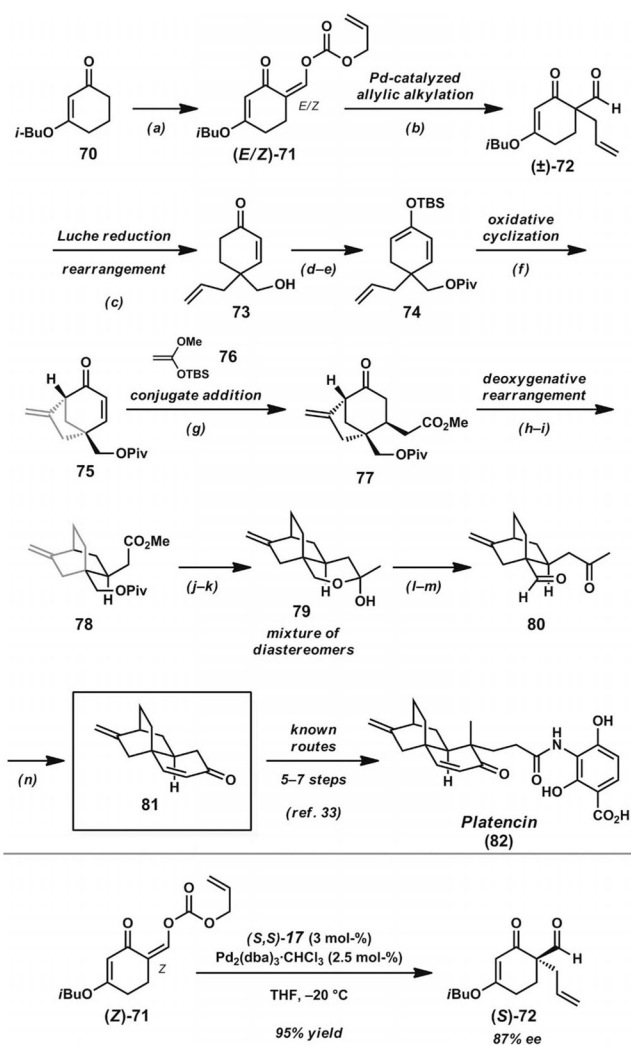
Scheme 10.
Formal synthesis of (±)-platencin. *Reaction conditions:* a) NaH, HCO$_2$*i*Bu, 0 °C; then
ClCO$_2$allyl, cat. KH, THF, 0 °C. b) Pd(OAc)$_2$ (1.3 mol-%), PPh$_3$, THF, 20 °C (92% yield,
two steps). c) NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, 0 °C; then *p*TsOH, H$_2$O/Et$_2$O, room temp. d)
PivCl (2 equiv.), pyridine (4 equiv.), DMAP (0.05 equiv.), CH$_2$Cl$_2$, room temp. (94% yield,
two steps). e) LDA (1.5 equiv.), TBSCl (2 equiv.), HMPA (1 equiv.), THF, −80 °C→r.t.
(88% yield). f) O$_2$, Pd(OAc)$_2$ (5.8 mol-%), DMSO (85 % yield). g) H$_2$C=C(OMe)OTBS
(**76**, 1.5 equiv.), TiCl$_4$ (1.2 equiv.), CH$_2$Cl$_2$, −80 °C (88% yield). h) TsNHNH$_2$ (1.3 equiv.),
MeOH, 60 °C (95% yield). i) NaCNBH$_3$, ZnCl$_2$, MeOH, 60 °C (60% yield). j)
HCl·NH(OMe)Me (6 equiv.), Me$_3$Al (5 equiv.), CH$_2$Cl$_2$, 0 °C. k) MeLi (6 equiv.), Et$_2$O,
−80→−30 °C. l) LiAlH$_4$ (1 equiv.), Et$_2$O, −80→0 °C (85% yield, two steps). m) (COCl)$_2$
(5.8 equiv.), DMSO (9 equiv.), −80 °C, Et$_3$N (73% yield). n) NaOH (6.5 equiv.), EtOH, 20
°C, 20 h (87% yield).
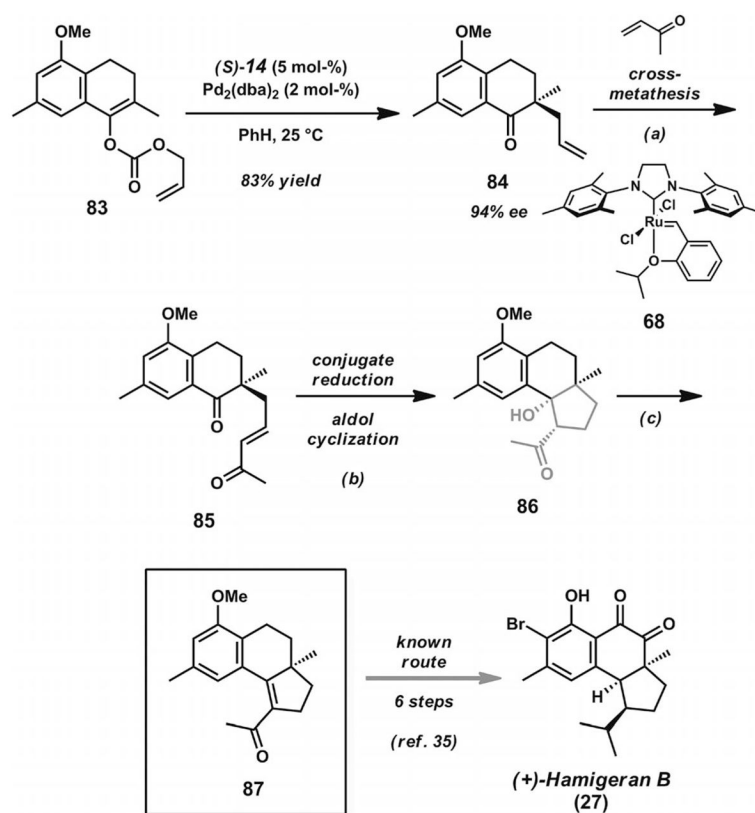
Scheme 11.
Formal synthesis of hamigeran B. *Reaction conditions:* a) methyl vinyl ketone (10 equiv.), Grubbs–Hoveyda second-generation catalyst (**68**, 10 mol-%), PhH, 35 °C (66% yield). b) [Ph$_3$PCuH]$_6$ (0.5 equiv.), PhCH$_3$, −40 °C. c) SOCl$_2$ (15 equiv.), DMAP (30 mol-%), pyridine, 0 °C (62 % yield).
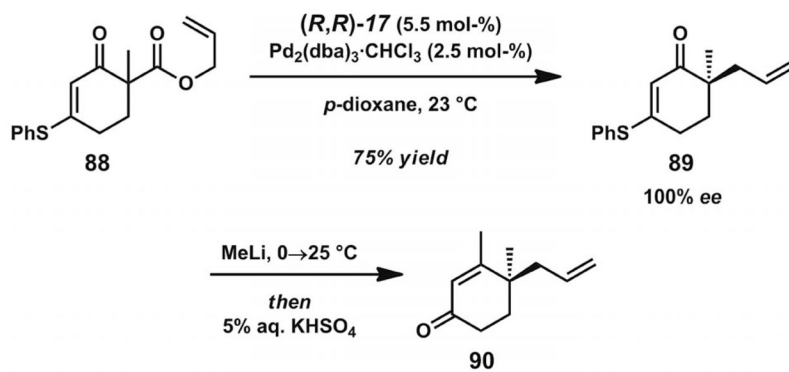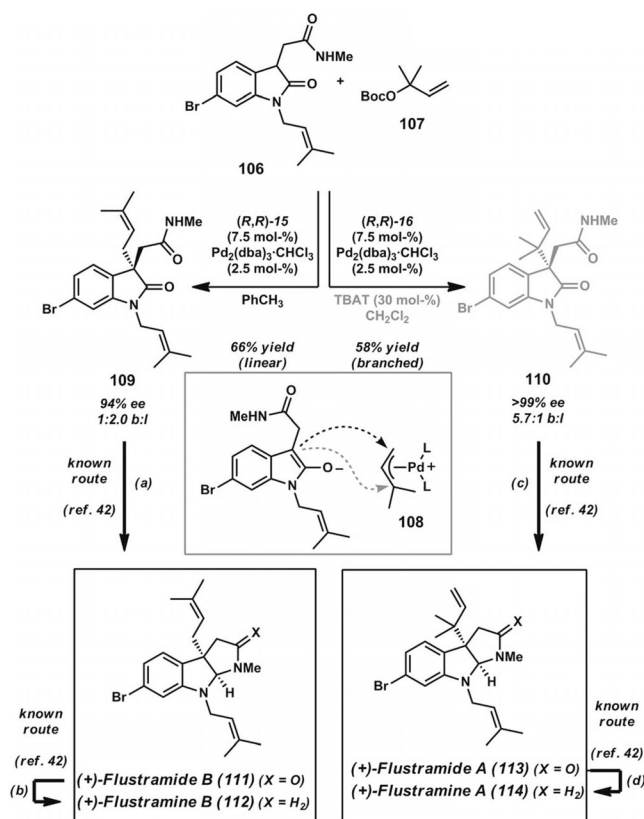
Scheme 12.
Extension of β-keto ester substrate scope to vinylogous ester scaffolds.
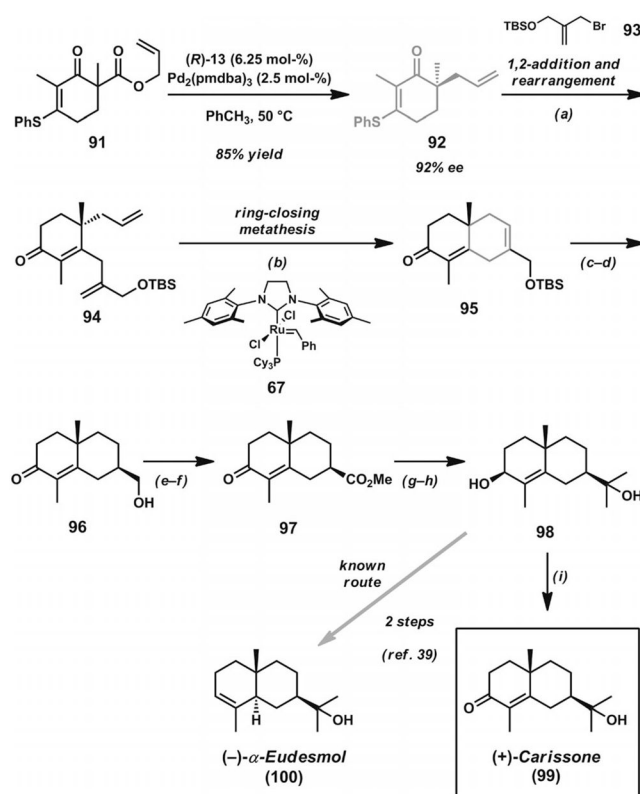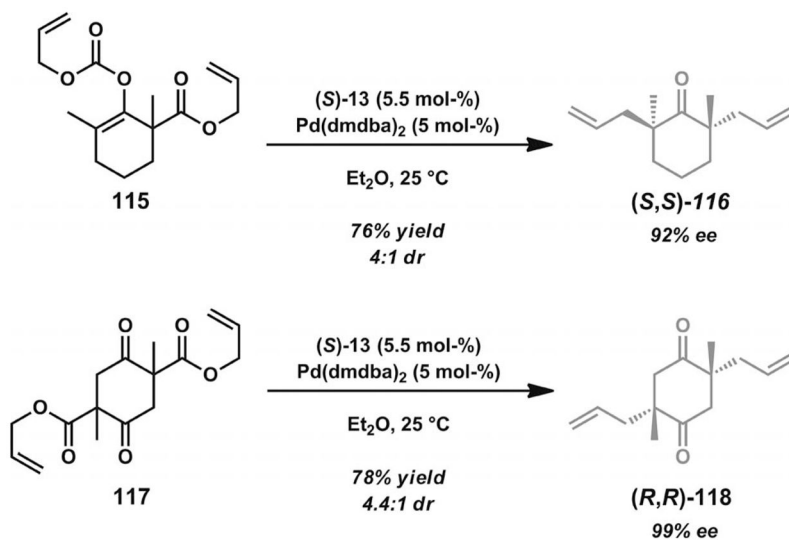
Scheme 13.
Total synthesis of carissone and formal synthesis of α-eudesmol. *Reaction conditions:* a) allylic bromide **93**, Mg(0), I$_2$, 0→23 °C (94% yield). b) Grubbs second-generation catalyst (**67**, 3 mol-%), PhH, 40 °C (99% yield). c) Rh/Al$_2$O$_3$ (5 mol-%), H$_2$ (1 atm), MeOH. d) HCl, THF (56% yield, two steps). e) Dess–Martin periodinane, CH$_2$Cl$_2$, 0→23 °C. f) NaClO$_2$, NaH$_2$PO$_4$, 2-meth-ylbut-2-ene, *t*BuOH/H$_2$O; then CH$_2$N$_2$ (87% yield, two steps). g) CeCl$_3$·7H$_2$O, NaBH$_4$, MeOH, −45 °C. h) MeMgBr, THF, 0→26 °C (73% yield, two steps). i) MnO$_2$, 4 Å MS, CH$_2$Cl$_2$ (100% yield).
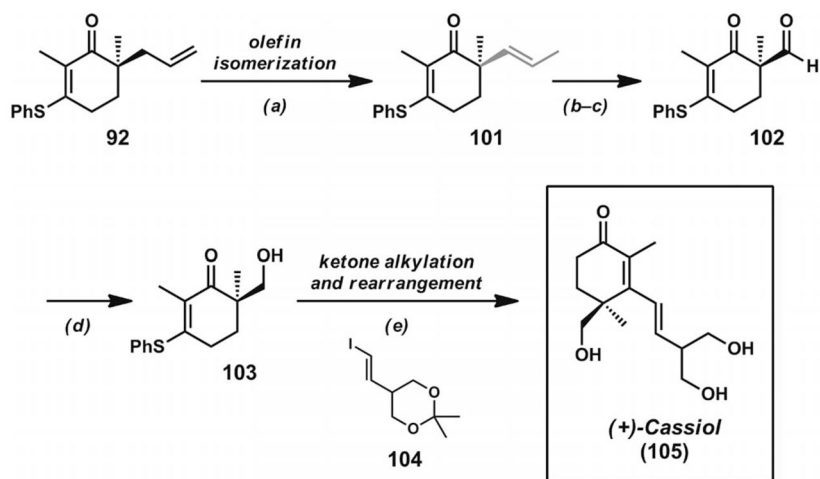
Scheme 14.
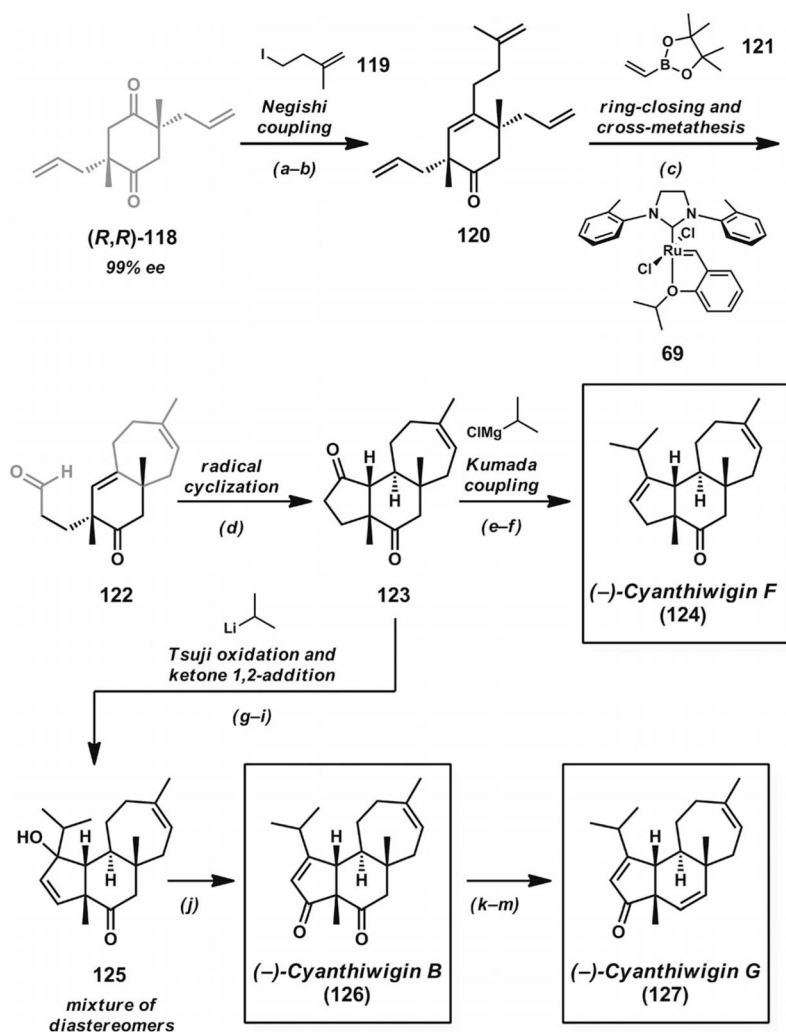Total synthesis of cassiol. *Reaction conditions:* a) [PdCl$_2$(CH$_3$CN)$_2$] (10 mol-%), PhH, 60 °C (99% yield, 13:1 ratio **101/92**). b) OsO$_4$ (10 mol-%), DABCO, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, *t*BuOH/H$_2$O (1:1), 35 °C. c) Pb(OAc)$_4$, PhH, 30 °C (70% yield). d) Li(O*t*Bu)$_3$AlH, THF, 0 °C (85% yield). e) Vinyl iodide **104**, *t*BuLi, Et$_2$O, −78 °C; then vinylogous thioester **103**; then aq. HCl, TBME (36% yield).
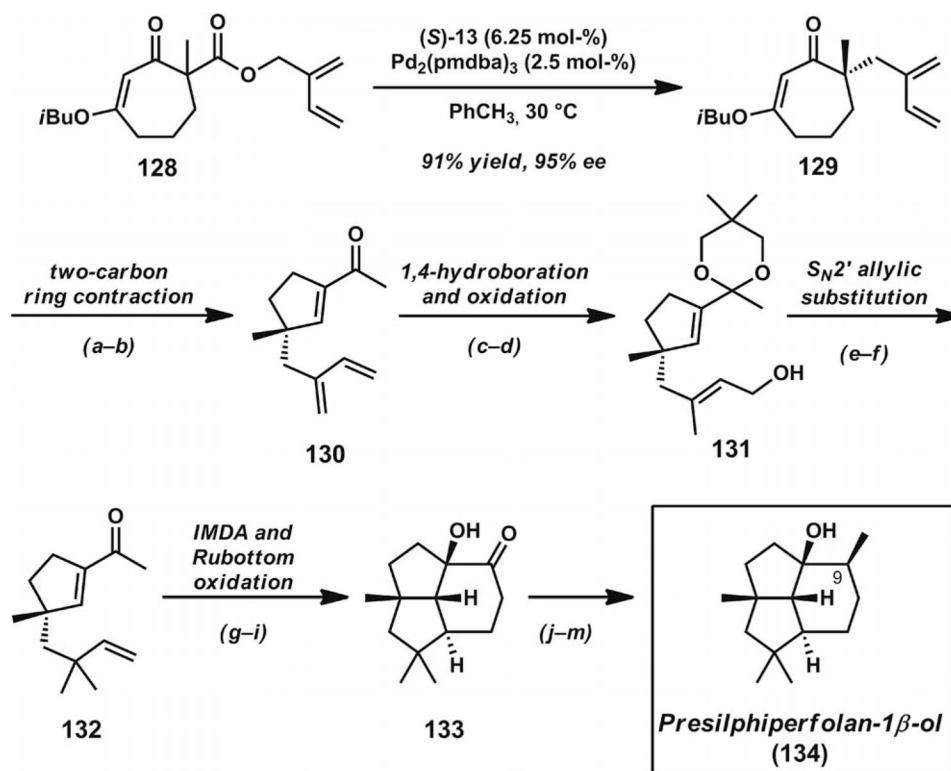
Scheme 15.
Total syntheses of flustramides A and B and flustramines A and B. *Reaction conditions:* a)
AlH$_3$·NMe$_2$Et, THF, −15 °C (95% yield). b) AlH$_3$·NMe$_2$Et, THF, room temp. (97% yield).
c) AlH$_3$·NMe$_2$Et, THF, −15 °C (92% yield). d) AlH$_3$·NMe$_2$Et, THF, room temp. (90%
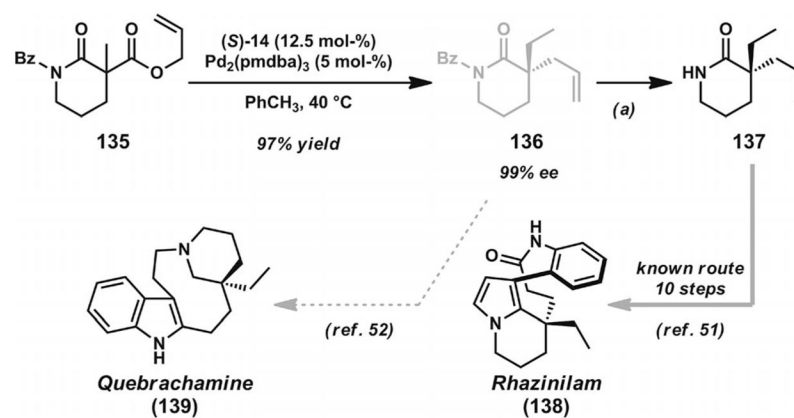yield).

Scheme 16.
Double enantioselective decarboxylative allylic alkylation reactions.
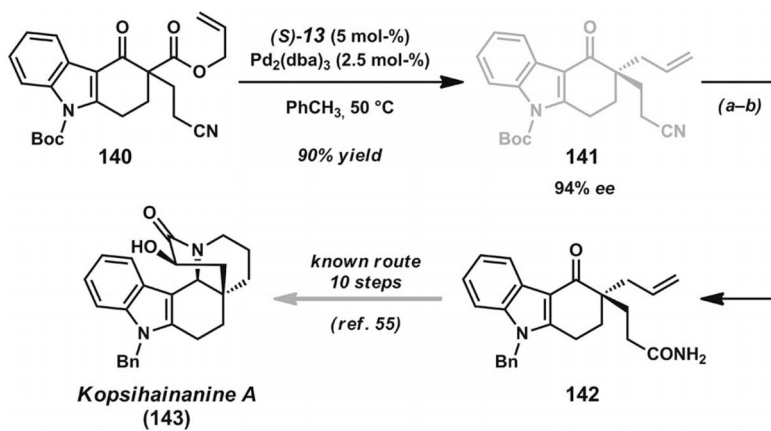
Scheme 17.
Total syntheses of cyanthiwigins B, F, and G. *Reaction conditions:* a) KHMDS, PhN(Tf)$_2$, THF, −78 °C (73 % yield). b) Zn(0), TMSCl, 1,2-dibromoethane, alkyl iodide **119**, THF, 65 °C; then [Pd(PPh$_3$)$_4$] (5 mol-%) (78% yield). c) Vinylboronic ester **121**, Grubbs–Hoveyda third-generation catalyst (**69**, 10 mol-%), PhH, 60 °C; then NaBO$_3$, THF/H$_2$O (51% yield). d) *t*BuSH, AIBN, PhH, 80 °C. e) KHMDS, PhN(Tf)$_2$, THF, −78 °C (60% yield). f) *i*PrMgCl, CuCN, THF; [Pd(dppf)Cl$_2$] (10 mol-%) (41% yield). g) KHMDS, THF −78 °C; then allyl chloroformate. h) [Pd$_2$(pmdba)$_3$] (5 mol-%), CH$_3$CN, 80 °C (57% yield, two steps). i) CeCl$_3$, *i*PrLi, THF, −78 °C (76% yield, mixture of diastereomers). j) PCC, CH$_2$Cl$_2$ (86% yield). k) NaBH$_4$, MeOH/CH$_2$Cl$_2$, 25 °C. l) MnO$_2$, CH$_2$Cl$_2$ (15% yield, two steps). m) Martin's sulfurane, CDCl$_3$ (48% yield).

Scheme 18.
Total synthesis of presilphiperfolan-1β-ol. *Reaction conditions:* a) LiAlH$_4$, Et$_2$O, 0 °C (96% yield). b) LiOH, TFE, THF, 60 °C (96% yield). c) Neopentyl glycol, PPTS (5 mol-%), PhH, reflux (94% yield). d) HBPin, Ni(cod)$_2$ (5 mol-%), PCy$_3$ (5 mol-%), PhCH$_3$, 23 °C; then 3 M aq. NaOH, H$_2$O$_2$, THF, 0→23 °C (81% combined yield, 63% yield of desired linear isomer **131**). e) Diethyl chlorophosphate, Et$_3$N, DMAP (20 mol-%), CH$_2$Cl$_2$, 0→23 °C (84% yield). f) Zn(CH$_3$)$_2$, CuCN (10 mol-%), THF, −78→23 °C; then 10% aq. HCl (94% yield). g) TBSOTf, Et$_3$N, CH$_2$Cl$_2$, 0→23 °C (98% yield). h) *p*-Dioxane, 170 °C, sealed tube. i) DMDO, acetone, −78 °C; then TBAF, −78→23 °C (90 % combined yield, two steps, 1:2 *dr*, 28% yield of desired diastereomer). j) KO*t*Bu, Ph$_3$PCH$_3$Br, THF, 0→23 °C (90% yield). k) HMDS, imidazole, TMSCl, CH$_2$Cl$_2$ (96% yield). l) PtO$_2$ (5 mol-%), EtOAc, H$_2$ (1 atm). m) TBAF, THF, reflux (92% yield, two steps).

Scheme 19.
Formal synthesis of rhazinilam and synthetic approach to quebrachamine. *Reaction conditions:* a) LiOH·H$_2$O, MeOH, 23 °C (96% yield).

Scheme 20.
Formal synthesis of kopsihainanine A. *Reaction conditions:* a) HCO₂H, b) K₂CO₃, BnBr, acetone, 55 °C (94% yield, two steps).