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Enantioselective Palladium-Catalyzed Allylic Alkylation Reactions in the Synthesis of Aspidosperma and Structurally Related Monoterpene Indole Alkaloids

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Abstract

Enantioselective Pd-catalyzed allylic alkylations of prochiral enolates represent a powerful tool for the construction of all-carbon quaternary stereocenters. This review describes the emergence of such reactions as strategic linchpins that enable efficient, stereocontrolled syntheses of *Aspidosperma* and related monoterpene indole alkaloids.

1 Introduction and statement of purpose

The structural intricacies and biological activities of monoterpene indole alkaloids have rendered these compounds attractive targets for total synthesis.[1] In particular, the structurally related *Aspidosperma* and *Kopsia* classes of alkaloids have comprised some of the most frequently targeted structures in chemical synthesis over the course of more than half a century (Figure 1).[2] Consequently, numerous strategically distinct total syntheses have been reported for various *Aspidosperma* and *Kopsia* family members. Without question, there are several strategies toward these targets that made profound contributions to modern organic synthesis.[3] The purpose of this review, however, is to highlight completed enantioselective syntheses of *Aspidosperma* and *Kopsia* alkaloids that implement an enantioselective Pd-catalyzed allylic alkylation as the key stereodefining tactic. In our view, this strategy is distinctive in its widespread adoption by many researchers, and more importantly its prolific assembly of many functionally and topologically unique members of the *Aspidosperma* and *Kopsia* families.

Enantioselective Pd-catalyzed allylic alkylations of prochiral enolates represent one of the most robust methods for the synthesis of α-quaternary carbonyl compounds.[4] Experimental and computational studies have been conducted to elucidate the mechanism of this transformation,[4c–g,5] though the precise reaction pathway varies depending on the ligand, Pd precatalyst, solvent, substrate, allyl electrophile, and additives employed. While enantioselective Pd-catalyzed allylic alkylations of prochiral enolates have been utilized in total synthesis,[6] these reports largely involve the use of *ketone*-derived substrates. Within the

Conflicts of interest

The authors declare no conflicts of interest.

past five years, such enantioselective reactions have been extended to new *heterocylic* substrates to construct the stereogenic all-carbon quaternary center at C20 of *Aspidosperma* and *Kopsia* alkaloids,[7] a unifying feature of these classic targets (see **1**, Figure 1). The C20 quaternary carbon is the stereochemical linchpin of these syntheses, and the remaining chiral centers are built with exceptional stereocontrol. The studies compiled herein, which span several research groups and substrate classes, illustrate the broad applicability of enantioselective allylic alkylation as a highly enabling disconnection for the synthesis of *Aspidosperma* and *Kopsia* alkaloids.

2 Structural overview of *Aspidosperma* and related monoterpene indole alkaloids

The *Aspidosperma* alkaloids are related through a largely conserved pentacyclic core that is most clearly visible in the sparsely functionalized namesake of the family, aspidospermidine (**1**).[8] Two structural outliers are the nine-membered ring-containing quebrachamine (**2**),[9] and the aminal-containing goniomitine (**3**).[10] Vincadifformine (**4**)[11] and tabersonine (**5**)[12] contain additional unsaturation within the pentacyclic core. Common oxygenation patterns include primary alcohols (e.g., **6**),[13] *N,O*-ketals (e.g., **7** and **8**),[14,15] and oxygenation about the benzene fragment (e.g., **9–12**).[16–19] Leuconolam (**13**)[20] is related to *Aspidosperma* alkaloids through indoline oxidative cleavage, and can undergo subsequent ring closure to furnish various aminal-containing structures (e.g., **14–16**)[21–23] or additional rearrangement and fragmentation to give mersicarpine (**17**).[24] The pyrrole ring in rhazinilam (**18**)[25] is expected to originate from a biochemical oxidation pathway similar to that of leuconolam (**13**).[26] *Kopsia* alkaloids (e.g., **19–25**)[27–33] typically contain additional carbon-based rings, often resulting in highly caged structures.

2.1 Biosynthetic hypothesis

The biosynthesis of all monoterpene indole alkaloids is proposed to begin with an enzymatic Pictet–Spengler reaction[34] between secologanin (**26**) and tryptamine (**27**) to yield strictosidine (**28**, Scheme 1).[35] Subsequent deglycosylation and iminium condensation affords 4,21-dihydrogeissoschizine (**29**), which undergoes a series of skeletal rearrangements to arrive at dehydrosecodine (**30**). At this stage, it is envisioned that either a Diels–Alder cycloaddition, or a stepwise enamine-Michael addition/Friedel–Crafts reaction/tautomerization cascade delivers tabersonine (**5**), thereby enabling general entry into alkaloids of the *Aspidosperma* type.[36] This biosynthetic hypothesis, in particular the intermediacy of achiral **30**, accounts for these alkaloids being observed in both enantiomeric series.

2.2 Noteworthy biological activity

In addition to their stereochemically rich polycyclic scaffolds, several *Aspidosperma* and *Kopsia* alkaloids have demonstrated promising biological activity. Vincadifformine (**4**) displays cytotoxicity in KB/VJ300 vincristine-resistant human oral epidermoid carcinoma cells.[37] Tabersonine (**5**) shows cytotoxicity toward HL-60 myeloid leukemia cells at low micromolar concentration.[38] Rhazinilam (**18**) exhibits sub-micromolar toxicities in A549

human lung adenocarcinoma and HT29 human colon adenocarcinoma cell lines,[39a] but is perhaps best known for its remarkable in vitro inhibition of both microtubule assembly and disassembly.[39b,c]

3 Enantioselective Pd-catalyzed allylic alkylations in *Aspidosperma* and *Kopsia* alkaloid syntheses

Among the many synthetic challenges facing chemists in pursuit of *Aspidosperma* and *Kopsia* alkaloids is the ubiquitous all-carbon quaternary stereocenter at C20. Since the mid 2000's, enantioselective Pd-catalyzed allylic alkylation reactions of non-stabilized enolates have enabled access to challenging stereogenic quaternary centers.[4,6] Indeed, our lab has employed this methodology to construct an array of chiral building blocks possessing an all-carbon quaternary center. In one such instance, β-amidoester **31** was exposed to a solution of $Pd_2(pmdba)_3$ (5 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L1**, 12.5 mol %) in toluene to furnish α-quaternary lactam **32** in 97% yield and with 99% ee (Scheme 2). Lactam **32** can be further elaborated to chiral building blocks **33–35**[40] that previously required lengthy synthetic sequences to achieve high levels of enantiopurity. Consequently, the swift preparation of heterocycles **33–35** completed enantioselective formal syntheses of (–)-quebrachamine (**2**),[41] (–)-vincadifformine (**4**),[42] and (+)-rhazinilam (**18**),[43] respectively. While the accessibility of small chiral heterocyclic building blocks (e.g., **33–35**) is valuable in its own right, lengthy synthetic sequences would still be required to reach complex alkaloid targets. Thus, the development of new substrate classes, ideally those possessing an indole fragment, was needed in order to enable expedient total syntheses of *Aspidosperma* and *Kopsia* alkaloids.

Recently, several groups have used Pd-catalyzed allylic alkylations to set the C20 all-carbon quaternary center in de novo enantioselective total syntheses. The stereochemical information at C20 can then be used to set the remaining stereocenters with high levels of selectivity. Most of the studies described herein utilize conditions developed by the Stoltz group for decarboxylative allylic alkylations, namely the combination of a palladium precatalyst (e.g., $Pd_2(dba)_3$) and a phosphinooxazoline (PHOX) ligand.[4a–d] While **L1** is prepared from the readily available (*S*)-*tert*-leucine, the invention of a pseudoenantiomeric PHOX ligand was required to obviate the use of (*R*)-*tert*-leucine, which is prohibitively expensive.[44]

3.1 Lupton's formal synthesis of (+)-Kopsihainanine A

In 2013, the Lupton group reported the enantioselective decarboxylative Pd-catalyzed allylic alkylation of Boc-protected indolone and carbazolone substrates (e.g., **36**, Scheme 3).[45] The authors found that the combination of $Pd_2(dba)_3$ (2.5 mol %) and (*S*)-*t*-BuPHOX (**L2**, 5 mol %) in toluene at 50 °C delivered the α-quaternary products (e.g., **37**) in 69–98% yield and 80–94% ee. Broad functional group tolerance was observed at the α-position, and one example (**37f**) accommodated an electronically differentiated indole fragment.

Noting the clear resemblance between their α-quaternary carbazolone products (e.g., **37d–f**) and monoterpene indole alkaloids, the authors carried out a rapid enantioselective formal synthesis of (+)-kopsihainanine A (**20**). Allylic alkylation product **37d** was treated with

formic acid to effect nitrile hydration with concomitant Boc removal, and subsequent reprotection delivered *N*-benzyl carbazolone **38**. This intermediate was previously carried through six additional steps by She and co-workers in their synthesis of (±)-kopsihainanine A (**20**).[46]

3.2 Ma's total synthesis of methyl *N*-Decarbomethoxychanofruticosinate

Ma and co-workers devised an elegant total synthesis of *Kopsia* alkaloid (+)-methyl *N*-decarbomethoxychanofruticosinate (**24**) featuring an enantioselective Pd-catalyzed allylic alkylation of a carbazolone substrate and a late-stage intramolecular oxidative coupling reaction.[47] Beginning from commercially available carbazolone **39**, a four-step sequence including a Pd-catalyzed allylic alkylation using (*R*)-*t*-BuPHOX (***ent*-L2**) delivered ***ent*-67e** (Scheme 5). Oxidative cleavage of the allyl fragment, reduction of the resulting aldehyde, and alcohol protection using TBSCl gave silyl ether **40**. Reductive cyclization using nickel boride, followed by imine hydrogenation, yield tetracycle **41** with the requisite *trans*-fused octahydroquinoline subunit. Acylation of the secondary amine, followed by alcohol deprotection and subsequent oxidation, gave aldehyde **42**. An intramolecular Reformatsky-type reaction was mediated by SmI_2, and the resulting β-hydroxyamide was subjected to amide reduction and then alcohol oxidation to arrive at ketone **43**. Ketone **43** was deprotonated using LHMDS, and the resulting enolate underwent smooth iodine-promoted oxidative coupling to give imine **44**. Nucleophilic addition of cyanide, followed by hydrolysis and subsequent esterification provided the highly caged target, (+)-methyl *N*-decarbomethoxychanofruticosinate (**24**), in 19 steps and 5% overall yield from commercially available **39**. The Ma group brilliantly combined the stereochemical control afforded by an early enantioselective Pd-catalyzed allylic alkylation, with the bond-forming capabilities of their lab's oxidative coupling chemistry in order to access their highly sterically congested target.

3.3 Mukai's total synthesis of (+)-Kopsihainanine A

Mukai and co-workers exploited the exceptional enantioselectivities achieved through the asymmetric allylic alkylation of piperidin-2-ones[4b] in a highly enantioselective total synthesis of (+)-kopsihainanine A (**20**).[48] The addition of 1,3-dicarbonyl **45**, available in five linear steps from indole, to a solution of $Pd_2(dba)_3$ (5 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L1**, 12.5 mol %) in TBME at 40 °C furnished α-quaternary amide **46** in 82% yield and 98% ee on a one-mmol scale (Scheme 6). Following global deprotection, the key Bischler–Napieralski cyclization was performed to deliver tetracycle **48** in excellent yield as a single diastereomer bearing the desired *trans*-fused octahydroquinoline subunit. A further seven steps were required to advance **48** to (+)-kopsihainanine A (**20**). Despite multiple protecting group and redox manipulations, Mukai and co-workers completed a total synthesis of (+)-kopsihainanine A (**20**) in 15 steps and 3% overall yield from indole. The key primary advantages of their route were the exceptional enantioselectivity (typical of piperidin-2-one substrates), and the highly diastereoselective Bischler–Napieralski cyclization to access the *trans*-fused core of the natural product.

3.4 Qin's total syntheses of multiple *Kopsia* alkaloids

A brilliant unified approach to multiple highly caged *Kopsia* alkaloids was reported by Qin and co-workers in 2017.[49] Racemic carbazolone **51** underwent enantioconvergent Pd-catalyzed allylic alkylation using (*S*)-*t*-BuPHOX (**L2**, 13 mol %) and $Pd_2(dba)_3$ (5 mol %) in refluxing toluene to deliver the α-quaternary product (**52**) in 91% and 94% ee (Scheme 7). Remarkably, the crucial heteroaryl bromide motif withstood this Pd(0)-catalyzed transformation, despite somewhat forcing conditions.

Examples of Pd-catalyzed allylic alkylation substrates bearing a (hetero)aryl bromide moiety are surprisingly uncommon.[50] Even more rare are instances where this motif is strategically leveraged in downstream chemistry, which is peculiar considering the countless modes of reactivity available to (hetero)aryl halides. Mizoroki–Heck,[50b] Suzuki,[50c] and Negishi (*vide infra*) cross-couplings have been achieved using Pd-catalyzed allylic alkylation products, which have enabled convergent syntheses of complex molecules. Qin and co-workers exhibited immense creativity in their use of the bromoisoxazole fragment in **52**, and highlighted the synthetic power available through pairing these highly selective Pd-catalyzed alkylations with other types of reactivity.

To continue their syntheses, the terminal alkene was transformed to a primary azide (**54**), which could undergo an aza-Wittig reaction and ensuing hydride reduction with high diastereoselectivity. Protection of the piperidine nitrogen with TrocCl then delivered tetracycle **55**. The authors masterfully unveiled a β-ketonitrile moiety through reductive N–O cleavage and concomitant bromide elimination. Diazo transfer proceeded smoothly to give α-diazoketone **56**, which enabled the investigation of their key intramolecular cyclopropanation.

After screening various rhodium and copper catalysts, Qin and co-workers found that the use of 20 mol % $Cu(hfacac)_2$ in chlorobenzene at 120 °C resulted in a 52% yield of the desired cyclopropanated indoline **57**. Troc removal and cyclopropane opening was accomplished with zinc dust, and an intramolecular Mannich reaction formed the pyrrolidine subunit to give hexacycle **58**. A three-step sequence of nitrogen deprotection, cyanation, and samarium-mediated acyloin condensation gave highly caged α-hydroxyketone **60**. Nitrile hydration and esterification with 2-mercaptopyridine *N*-oxide delivered **61**, which underwent radical decarboxylation to give a mixture of **62** and **63** (Scheme 7).[51] Critically, intermediates **62** and **63** bear the carbocyclic cores of (–)-isokopsine (**22**) and (–)-kopsine (**21**), respectively. Heptacycle **62** was globally carbomethoxylated, and chemoselective carbonate cleavage occurred to give (–)-isokopsine (**22**).

Oxidative C–C scission was achieved using $Pb(OAc)_4$ to furnish (+)-methyl chanofruticosinate (**23**, Scheme 8A, Left). Furthermore, (–)-isokopsine (**22**) could be swiftly converted to (–)-fruticosine (**25**) using a three-step hydride reduction/diol-cleavage/intramolecular aldol condensation sequence (Scheme 8A, Right).

Lastly, the authors advanced heptacycle **63** to complete the syntheses of (–)-kopsanone (**19**) and (–)-kopsine (**21**). The tertiary alcohol in **63** was converted to a xanthate ester, and ensuing radical deoxygenation gave (–)-kopsanone (**19**, Scheme 8B, Left). Conversely,

treatment of **63** with triphosgene followed by methanolysis gave (–)-kopsine (**21**, Scheme 8B, Right).[52]

In summary, Qin and co-workers have designed and executed an impressive unified strategy toward several structurally daunting targets. Instrumental to their successes was the incorporation of a robust bromoisoxazole fragment, which remained intact during their enantioselective Pd-catalyzed allylic alkylation and underwent subsequent fragmentation to furnish an important β-ketonitrile motif. Following diazo transfer to the β-ketonitrile, a copper-catalyzed intramolecular cyclopropanation forged the indoline quaternary center. Several late-stage skeletal rearrangements were then conducted to complete syntheses of multiple highly caged *Kopsia* alkaloids.

3.5 Qiu's total synthesis of (–)-Aspidophytine

Qiu and co-workers employed a Pd-catalyzed allylic alkylation as a key step in their total synthesis of (–)-aspidophytine (**8**).[53] The authors found that upon treatment to a solution of $[Pd_2(dba)_3]$•$CHCl_3$ and (*S,S*)-ANDEN-Phenyl Trost ligand (**L3**), β-ketoester **64** is converted to known vinylogous thioester **65** in 70% yield and with 85% ee (Scheme 9).[54] Hydrolysis gave cyclohexane-1,3-dione **66**, which was enriched to 97% ee through recrystallization. The dimethoxyindole fragment in (–)-aspidophytine (**8**) was assembled by Pd-catalyzed oxidative cyclization through the intermediacy of a vinylogous amide. Subsequent *N*-tosylation under phase-transfer conditions gave α-quaternary carbazolone **69**. The allyl fragment in **69** was then converted to a primary azide to arrive at carbazolone **70**.

The authors effectively used the single stereocenter in **70** to build the three remaining rings and complete their synthesis of (–)-aspidophytine (**8**) in a stereoselective fashion. A four-step sequence effected ketone and azide reduction, along with amine protection and cyclization to deliver *cis*-fused tetracycle **71**. Deprotection of the Ts and Cbz groups, followed by regioselective alkylation using 2-bromoethanol furnished aminoalcohol **72**. Pyrrolidine annulation and selenoxide elimination gave α,β-unsaturated imine **73**, which underwent hydride reduction and reductive amination in the same pot to yield penultimate *N*-methyl indoline **74**. This intermediate was converted to (–)-aspidophytine (**8**) by adapting a two-step protocol reported by Corey.[55a] While Qiu and co-workers successfully assembled one of the most functionally elaborate members of the *Aspidosperma* family, their synthesis required 21 steps and proceeded in 0.6% overall yield from known α-quaternary vinylogous thioester **65**. Lessons learned in other studies described in this review would likely help cut down the step count of this route. Namely, carbazolone **68** might be available in more rapid fashion and in higher enantiomeric excess starting from carbazolone **36f**, tuning the protecting group on nitrogen, and using the electron-deficient PHOX ligand **L1** (cf. Scheme 3). Alternatively, the use of a dihydropyrido[1,2-*a*]indolone (DHPI) substrate could potentially simplify the beginning of the synthesis, as well as eliminate intermediate nitrogen protecting group manipulations (*vide infra*). Such improvements would elevate the efficiency of this synthesis to that of previous, more convergent reports.[55]

3.6 Shao's total syntheses enabled by enantioenriched α-quaternary carbazolones

In 2013, the Shao group began a fruitful research program in the application of Pd-catalyzed allylic alkylation reactions of carbazolone substrates in the context of monoterpene alkaloid total synthesis. Their initial disclosure was published back-to-back with that of Lupton,[45] and detailed the asymmetric allylic alkylation of *N*-benzyl carbazolone substrates (Scheme 10A).[56,57] Using similar reaction conditions, a series of enantioenriched, functionalized α-quaternary carbazolone products (**76**) were obtained in 70–93% yield and 84–97% ee.

Shao's first application of this chemistry was in the total syntheses of (–)-aspidospermidine (**1**) and (+)-kopsihainanine A (**20**). Beginning from α-quaternary carbazolone **76a**, hydration of the pendant nitrile followed by ketone reduction and acid-promoted cyclization gave lactam **77** (Scheme 10B). A three-step dehomologation protocol was used to convert **77** into tetracycle **79**, which bears the desired C20 ethyl substituent. Lactam reduction and debenzylation under dissolving metal conditions furnished **80**, which was subjected to a three-step sequence adapted from Heathcock and co-workers to arrive at (–)-aspidospermidine (**1**) in 14 steps and 10% overall yield from commercially available carbazolone **39**.[58] The authors found that lactam **77** could also serve as an intermediate toward (+)-kopsihainanine A (**20**, Scheme 10C). Hydroboration/oxidation and base-promoted cyclization of the corresponding mesylate gave pentacycle **81**, which underwent α-hydroxylation and debenzylation to complete the first catalytic enantioselective synthesis of (+)-kopsihainanine (**20**) in short order (10 total steps), albeit in only 3.5% overall yield.

Later that same year, Shao and co-workers published an enantioselective total synthesis of (–)-limaspermidine (**6**, Scheme 11).[59] Utilizing the same α-quaternary carbazolone (**76a**), a six-step sequence gave rise to silyl ether **82** in 65% overall yield. Site-selective acylation delivered α-chloroamide **83**. Finkelstein displacement and subsequent silver-mediated halide abstraction occurred with concomitant annulation to furnish pentacycle **84**. Global hydride reduction and desilylation completed their total synthesis of (–)-limaspermidine (**6**) in 14 steps and 8.9% yield from **39**. The Banwell group showed that (–)-Acetylaspidoalbidine (**7**) can be made in two further steps.[60]

In a subsequent report, the Shao group expanded their investigations to access alkaloids bearing oxygenation on the arene fragment (Scheme 12).[61] Allylic alkylation precursor **85** was synthesized in five steps and 41% overall yield from commercially available materials. Using their previously optimized conditions, α-quaternary carbazolone **86** was obtained in 90% yield and 91% ee. The authors then employed a familiar seven-step sequence to arrive at pentacyclic imine **87**, which served as a common intermediate in their divergent total syntheses of (+)-aspidospermine (**9**), (–)-*N*-acetylcylindrocarpinol (**10**), (+)-cylindrocarpidine (**11**), and (+)-10-oxocylindrocarpidine (**12**). These arene-oxidized alkaloids (**9–12**) were synthesized in 17–18 steps and 2.2–4.6% overall yield. Through their many completed syntheses, the Shao group plainly demonstrated enantioselective Pd-catalyzed allylic alkylation as a key stereodefining feature toward *Aspidosperma* alkaloids, however the consistent drawback to their synthetic plans was the requirement for multi-step derivatizations of the allyl fragment to form the various C20 exocyclic substituents.

3.7 Stoltz's regiocontrolled indole-iminium cyclizations: total synthesis of (–)-Goniomitine

In 2016 the Stoltz lab disclosed the expansion of asymmetric Pd-catalyzed allylic alkylation to a novel substrate class, namely dihydropyrido[1,2-*a*]indolones (DHPIs, Scheme 13A).[62] The α-quaternary DHPI allylic alkylation products can be isolated in consistently high yields and enantioselectivities across a variety of substituents at R^1 and R^2. Further, it was found that hydroamination and reduction of **89** could give rise to a critical indole intermediate bearing a C2-tethered iminium moiety (i.e., **90**, Scheme 13B). By controlling the substitution at the 3-position of the indole moiety, chemoselective cyclization events occur to access isomeric tetracycles **91** and **92** (Scheme 13B). In this way, the allyl fragment in **89** is readily transformed to the propylamine fragment in monoterpene indole alkaloids **1–3** (Scheme 13C). Consequently, the C20 ethyl substituent in **1–3** could be introduced directly at the α-position (i.e., **89**, R^2 = Et), thereby circumventing the dehomologation required by the carbazolone substrate class (cf. Scheme 10B).

Stoltz's total synthesis of (–)-goniomitine (**3**) began from *N*-acylindole **93**, which is available in multi-gram quantities in four steps and 47% overall yield from indole. Regioselective bromination, C-acylation, and C-alkylation proceeded in 71% yield over the three steps to afford β-amidoester **88a** (Scheme 14). While C3-alkyl substrates (i.e., **88**, R^1 = alkyl) performed poorly in the allylic alkylation chemistry, it was found that the C3-brominated substrate **88a** reacted chemoselectively when employing $Pd_2(pmdba)_3$ (5 mol %) and **L1** (12.5 mol %) in TMBE at 60 °C to give α-quaternary DHPI **89a** in 83% yield and with 96% ee. Ensuing Negishi arylation between **89a** and organozinc chloride **94** generated cross-coupled product **95** in 98% yield, and formal anti-Markovnikov hydroamination using conditions reported by Hartwig[63] yielded primary amine **96**. Reduction with $LiAlH_4$, and subsequent acetic acid quench effected the desired aminal-forming indole-iminium cyclization to complete the first catalytic enantioselective synthesis of (–)-goniomitine (**3**) in 11 steps and 8% overall yield from indole. To date, no other catalytic enantioselective syntheses have been reported.

Using the same Pd-catalyzed conditions, C3-unsubstituted α-quaternary DHPI **89b** was synthesized in 71% and with 94% ee (Scheme 15). Bach and co-workers advanced **89b** through six steps, including a chemoselective indole-iminium cyclization (e.g., **90** → **92**, Scheme 13B), to (±)-aspidospermidine (**1**).[64] Furthermore, hydroamination and translactamization of **89b** cleanly delivered δ-lactam **98** in 66% yield over the two steps, thus intercepting Pagenkopf's synthesis of (±)-quebrachamine (**2**).[65] The rapid total synthesis of (–)-goniomitine (**3**), along with formal syntheses of (+)-aspidospermidine (**1**) and (–)-quebrachamine (**2**), demonstrated the ability of the DHPI substrate class to provide access to skeletally diverse indole alkaloids by controlling substitution at the 3-position of the indole moiety.

3.8 Stoltz's stereocontrolled indole-iminium cyclizations: total synthesis of (+)-Limaspermidine and formal synthesis of (+)-Kopsihainanine A

Stoltz and co-workers further highlighted the synthetic versatility of the DHPI substrate class by combining enantioselective Pd-catalyzed allylic alkylations with *stereo*-selective indole-iminium cyclizations (Scheme 16).[66] Following hydroamination of the allyl fragment

in **89**, a Pictet–Spengler reaction effects stereoselective C–C bond formation to furnish *cis*-fused octahydroquinoline **99**, which is present in *Aspidosperma* alkaloids such as (+)-limaspermidine (**6**). Conversely, a Bischler–Napieralski cyclization affords access to *trans*-fused octahydroquinoline **100** via stereodefining C–H bond formation. This orthogonal cylization event enables synthetic entry to the *trans*-fused alkaloids of the *Kopsia* family, including (+)-kopsihainanine A (**20**).

Readily available β-amidoester **88c** was converted to α-quaternary DHPI **89c** in 82% yield and 94% ee (Scheme 17). The authors found that hydroamination, reduction, and acid-promoted Pictet–Spengler cyclization could be achieved in one-pot, and resulted in the stereoselective formation of *cis*-fused tetracycle **102**. Chemoselective piperidine alkylation furnished ethanolamine **103** in 62% yield over two steps. Pyrrolidine annulation and subsequent indolenine reduction gave *O*-benzyl limaspermidine (**105**), which was then debenzylated using excess BF_3•Et_2O to produce (+)-limaspermidine (**6**) in 12 steps and 14.4% overall yield from indole.

Having selectively constructing the *cis*-fused azadecalin motif present in *Aspidosperma* alkaloids (e.g., **6**), the authors turned their attention to a stereodivergent process toward the *Kopsia* alkaloids (e.g., **20**), which instead bear a *trans*-fused azadecalin substructure. Gratifyingly, pendant methyl ester **88d** performed well in the Pd-catalyzed allylic alkylation chemistry, delivering α-quaternary DHPI **89d** in 90% yield and with 92% ee (Scheme 18). Unfortunately, hydroamination of **89d** using Schwartz's reagent was unfruitful due to reduction of the methyl ester. A four-step sequence involving a Staudinger reduction with concomitant lactam exchange provided δ-lactam **106** in 62% overall yield. A Bischler–Napieralski reaction using conditions developed by Movassaghi and co-workers[3b,67] occurred with stereoselective hydride addition to furnish *trans*-fused tetracycle **107** in 84% yield. The guanidine base TBD facilitated lactam formation to provide strained pentacycle **108**, which intercepts Zhu's synthesis of (±)-kopsihainanine A (**20**),[68] thereby completing an enantioselective formal synthesis of (+)-**20** in 14 steps and 12% overall yield from indole.[69]

The DHPI substrate class developed by the Stoltz group affords synthetic access to multiple monoterpene indole alkaloids bearing diverse connectivities and three-dimensional topographies. This work differs from the use of carbazolone substrates in several ways: 1) both *cis*- (*Aspidosperma*) and *trans*- (*Kopsia*) ring fusion geometries can be accessed in a highly predictable fashion, 2) the allyl group of the α-quaternary DHPI Pd-catalyzed allylic alkylation product is transformed into part of the piperidine ring found in these alkaloids, which enables 3) the installation of the C20 exocyclic substituent at an early stage obviates the need for tedious FGIs, and finally 4) the *N*-acyl moiety acts as a traceless protecting group for the indole nitrogen, further reducing unproductive transformations.

3.9 Zhu's oxidation/reduction/polycyclization cascades

The Zhu group has combined Pd-catalyzed allylic alkylation with their oxidation/reduction/polycyclization cascades to complete enantioselective syntheses of a structurally unique subset of *Aspidosperma* alkaloids (e.g., **13–18**).[70] The known enantioselective Pd-catalyzed allylic alkylation of β-ketoester **109** proceeded smoothly to give α-quaternary ketone **110** in

90% yield and 92% ee (Scheme 19). The authors carried out a five-step sequence to introduce the azide and *o*-nitrophenyl substituents present in enone **111**. Ozonolysis of **111**, followed by treatment of the intermediate hydroperoxide with Ac_2O and Et_3N provided methyl ester **112**. Hydrogenation of **112** reveals the nascent aniline and primary amine in **113**, which cyclize regioselectively under the reaction conditions to give tricycle **114**. The addition of KOH prompted lactamization, and sparging with oxygen provided the presumed hydroperoxide (**116**), which was reduced by dimethyl sulfide to deliver (–)-mersicarpine (**17**) in a remarkable 75% one-pot yield from azide **112**. Their synthesis of (–)-**17**, beginning from commercially available diallyl pimelate, was completed in 10 steps and 13.5% overall yield.

Impressively, the authors found that hydrogenation of azide **112** in the presence of acetic anhydride resulted in acetylation of the primary amine to give acetamide **117** (Scheme 20). Aerobic oxidation of the 3-oxindole moiety followed by the addition of KOH produced lactam **118**, which underwent acid-promoted cyclization to afford aminal **119**. An intramolecular aldol reaction completed a total synthesis of (–)-scholarisine G (**16**) in 12 steps and 6.6% overall yield from diallyl pimelate. The tertiary benzylic alcohol in (–)-scholarisine G (**16**) was smoothly dehydrated to give (+)-melodinine E (**14**), which could be further elaborated to (–)-leuconolam (**13**) and (–)-leuconoxine (**15**).[71–73]

Following their successful elaboration of α-quaternary cyclohexanone **110** toward multiple alkaloids, Zhu and co-workers devised a clever synthesis of (–)-rhazinilam (**18**) beginning from five-membered β-ketoester **120** (Scheme 20).[74] The known synthesis of α-quaternary cyclopentanone **121** proceeded in 87% yield and 86% ee under typical reaction conditions.[75] The authors conducted a three-step sequence to access cyclopentenyl triflate **122**, which was advanced through an additional three steps to give cyclopentene **123**. A familiar ozonolysis with an Ac_2O/Et_3N workup in the presence of methanol yielded methyl ester **124**, which could undergo smooth aza-Wittig cyclization to deliver imine **125**. While imine **125** could be isolated, the authors were pleased to find that pyrrole formation could occur in the same pot to afford tetrahydroindolizine **126**. A well-precedented reduction/hydrolysis/macrolactamization sequence completed the synthesis of (–)-rhazinilam (**18**) in 15 steps and 12.2% overall yield from adipic acid.

The Zhu group has elegantly leveraged the high enantioselectivities available in Pd-catalyzed allylic alkylations of cycloalkanones to prepare precursors for their reduction/oxidation/cyclization cascades. Importantly, they have demonstrated the ability to tune participating functional groups for the controlled, divergent construction of multiple *Aspidosperma* alkaloid scaffolds.

4 Conclusion and outlook

Monoterpene indole alkaloids of the *Aspidosperma* type have long inspired innovation in chemical synthesis. Over the past five years, several research groups have utilized enantioselective Pd-catalyzed allylic alkylations of prochiral enolates to synthesize a wide variety of structurally unique *Aspidosperma* and *Kopsia* alkaloids, further highlighting the widespread utility of these reactions.

Perhaps the most notable drawbacks to this strategy are the decrease in convergence, and inefficient redox manipulation of the allyl fragment (e.g., Sections 3.3 and 3.6). These issues can be mitigated by thoughtful selection of the α-substituent, and elaboration of the allyl group as a propylamine synthon (e.g., 3.4 and 3.8). Critically, in all of the aforementioned synthetic endeavors, multiple stereocenters in the respective targets were constructed with high diastereoselectivity by leveraging the all-carbon quaternary center formed in the Pd-catalyzed allylic alkylation event.

Future studies to reduce the loadings of precious-metal catalysts, develop non-precious-metal-catalyzed allylic alkylation reactions, and to combine this reactivity with emerging synthetic methods will be of paramount importance not only in future work toward these classic alkaloid targets, but more broadly for the continued advancement of chemical synthesis.

Acknowledgments

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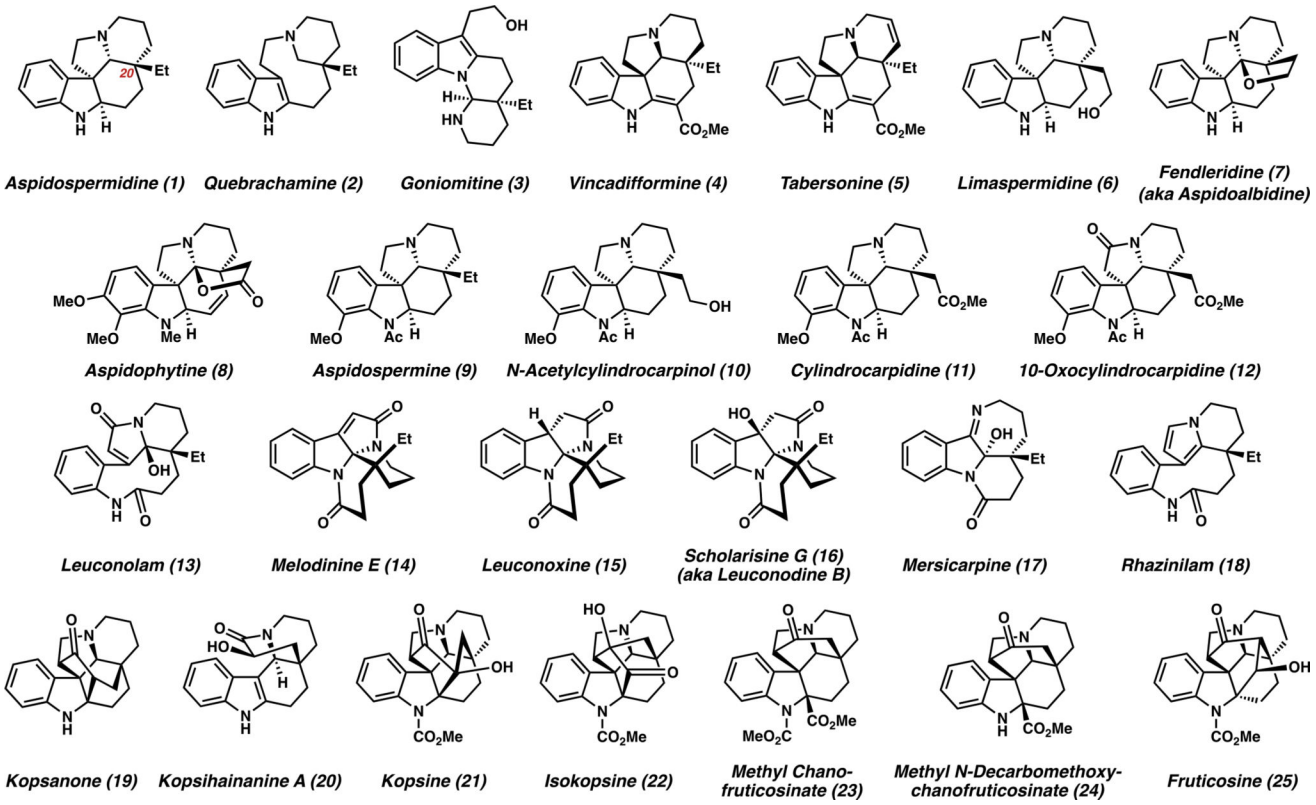
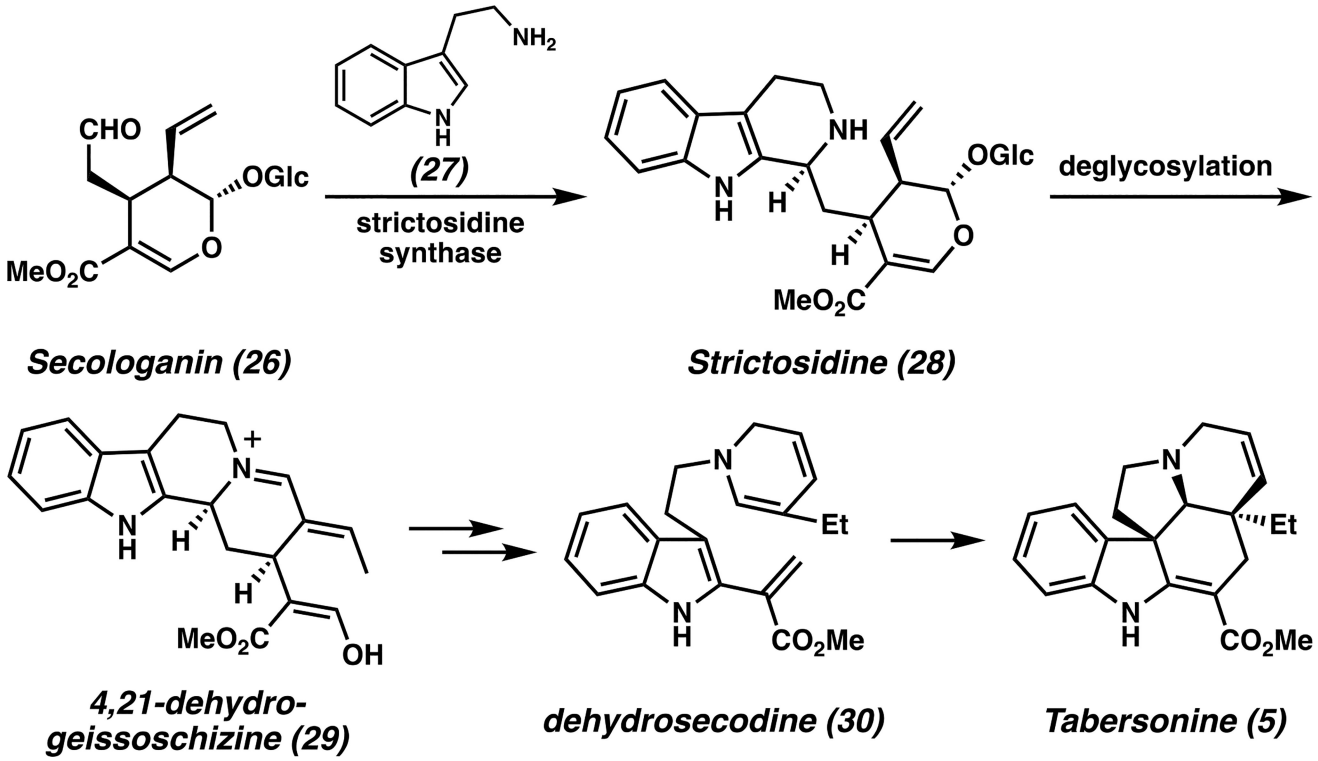
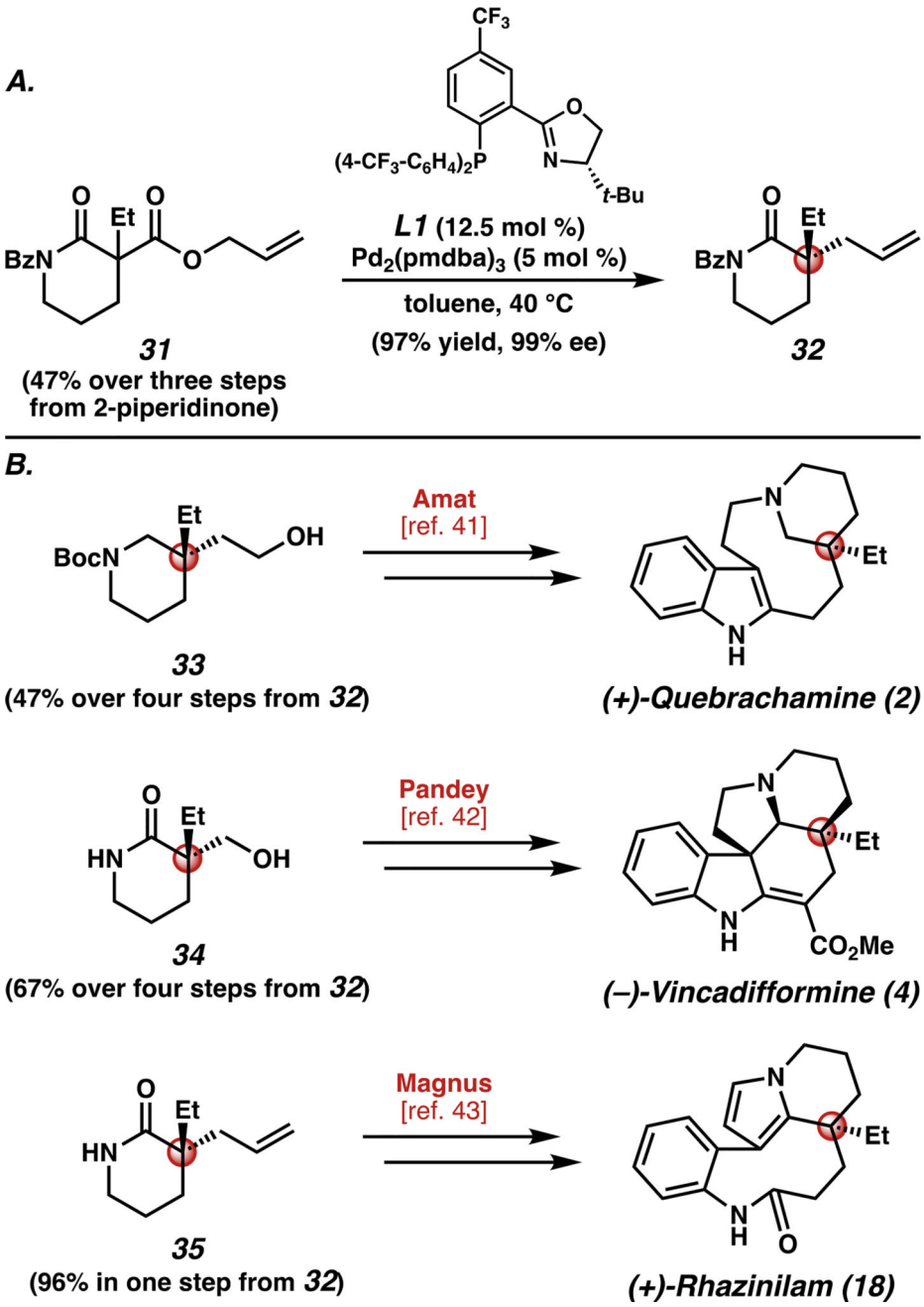


Figure 1.
Representative *Aspidosperma* and related alkaloids.

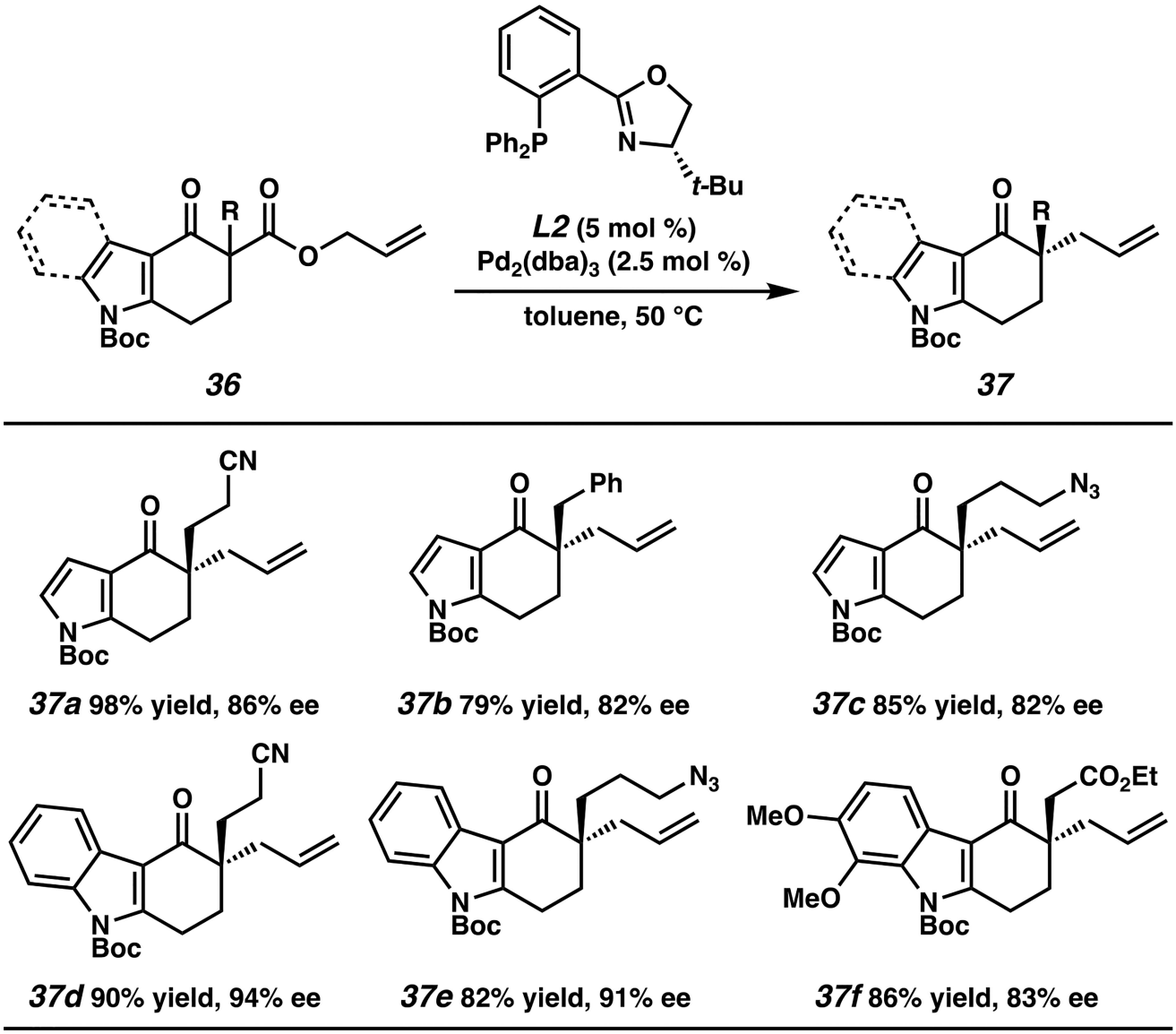


Scheme 1.
Proposed biosynthetic pathway to *Aspidosperma* alkaloids



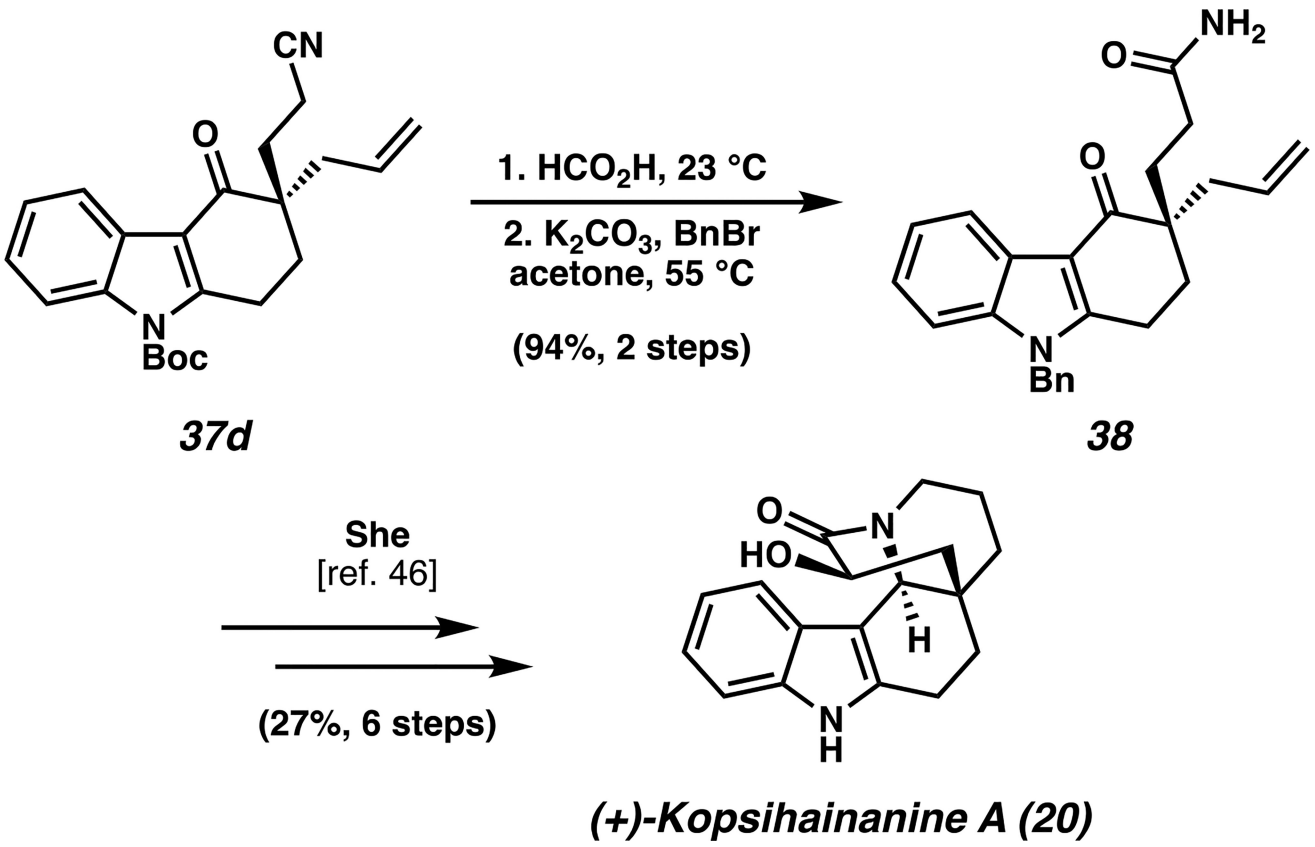
Scheme 2.

A) Pd-catalyzed allylic alkylation; B) Chiral building blocks in the formal synthesis of *Aspidosperma* alkaloids

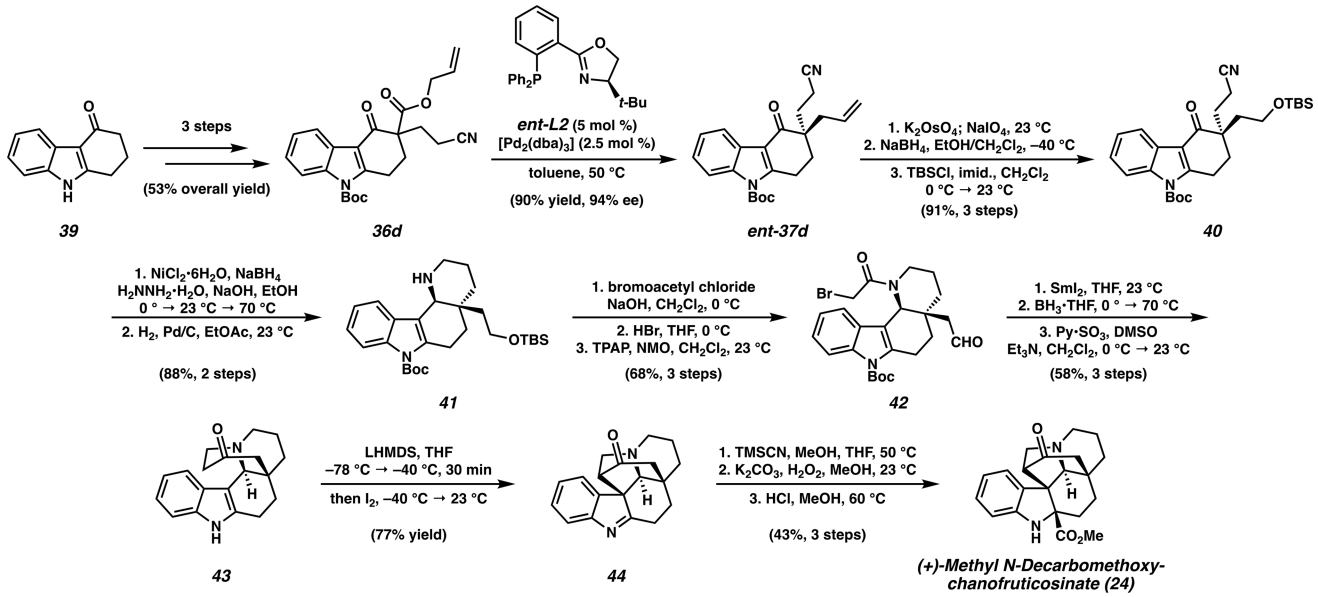


Scheme 3.

Selected examples from Lupton's enantioselective Pd-catalyzed allylic alkylations of indolone and carbazolone

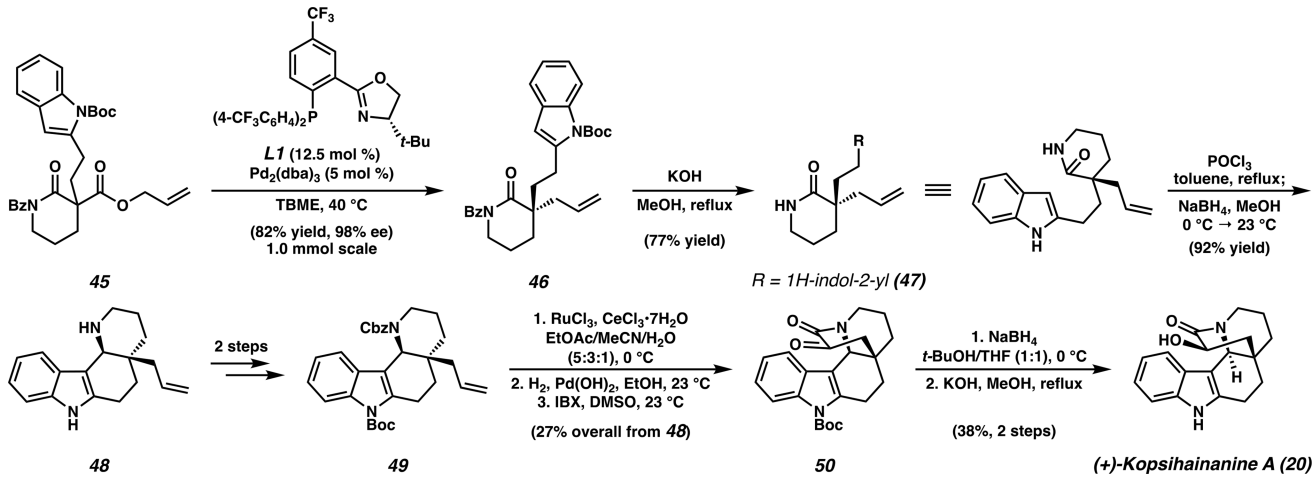


Scheme 4.
Enantioselective formal synthesis of (+)-Kopsihainanine A (**20**)



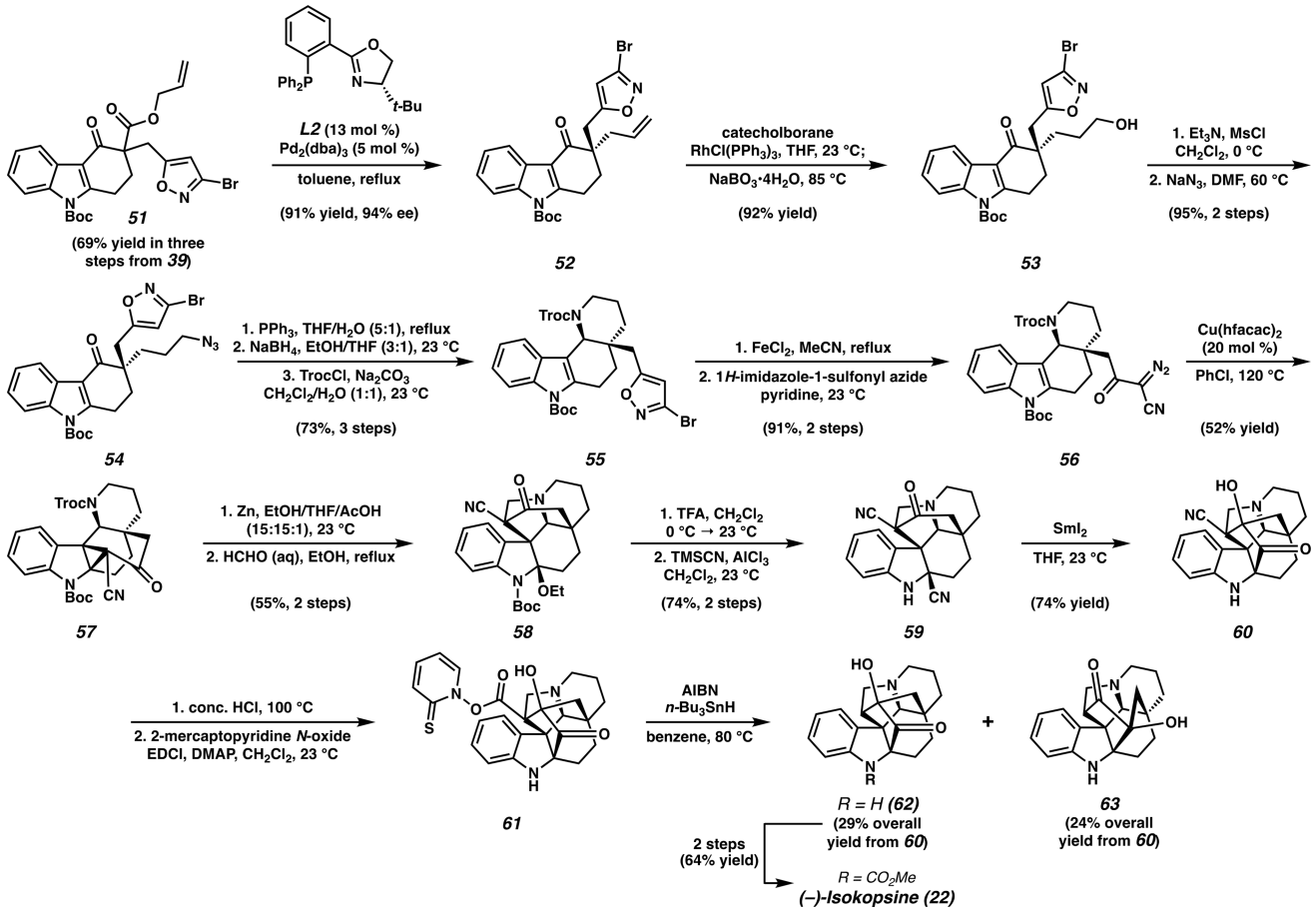
Scheme 5.

Ma's total synthesis of (+)-methyl *N*-Decarbomethoxyfruticosinate (**24**)



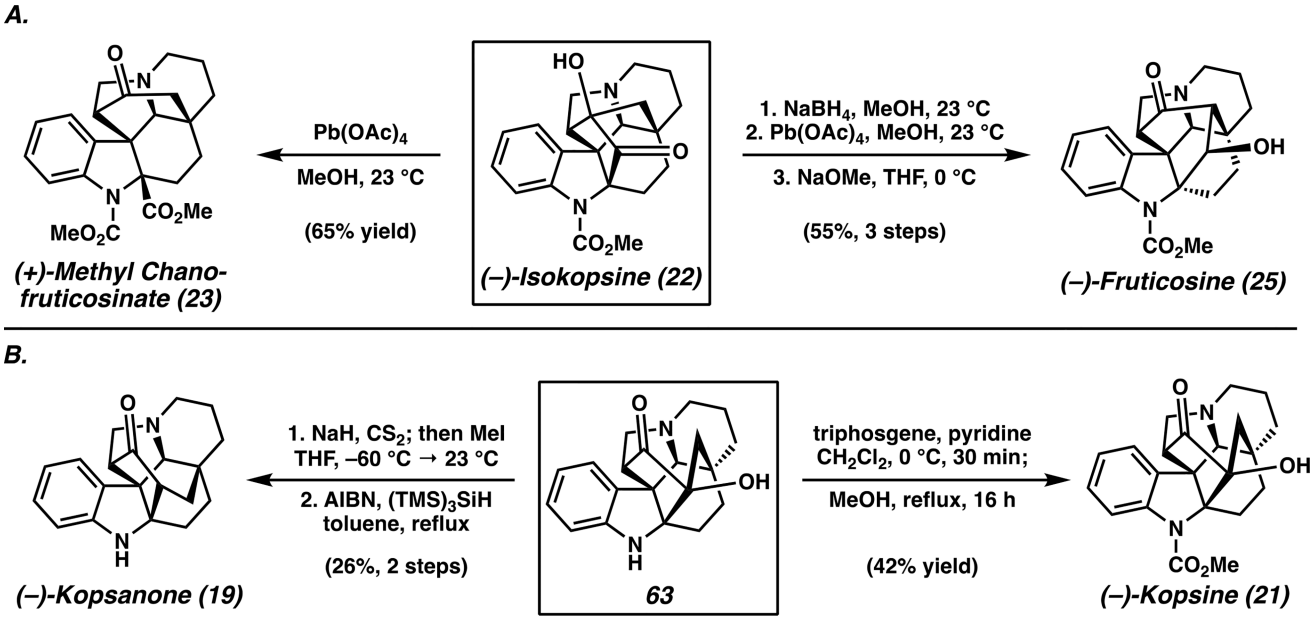
Scheme 6.

Mukai's total synthesis of (+)-Kopsihainanine A (**20**)



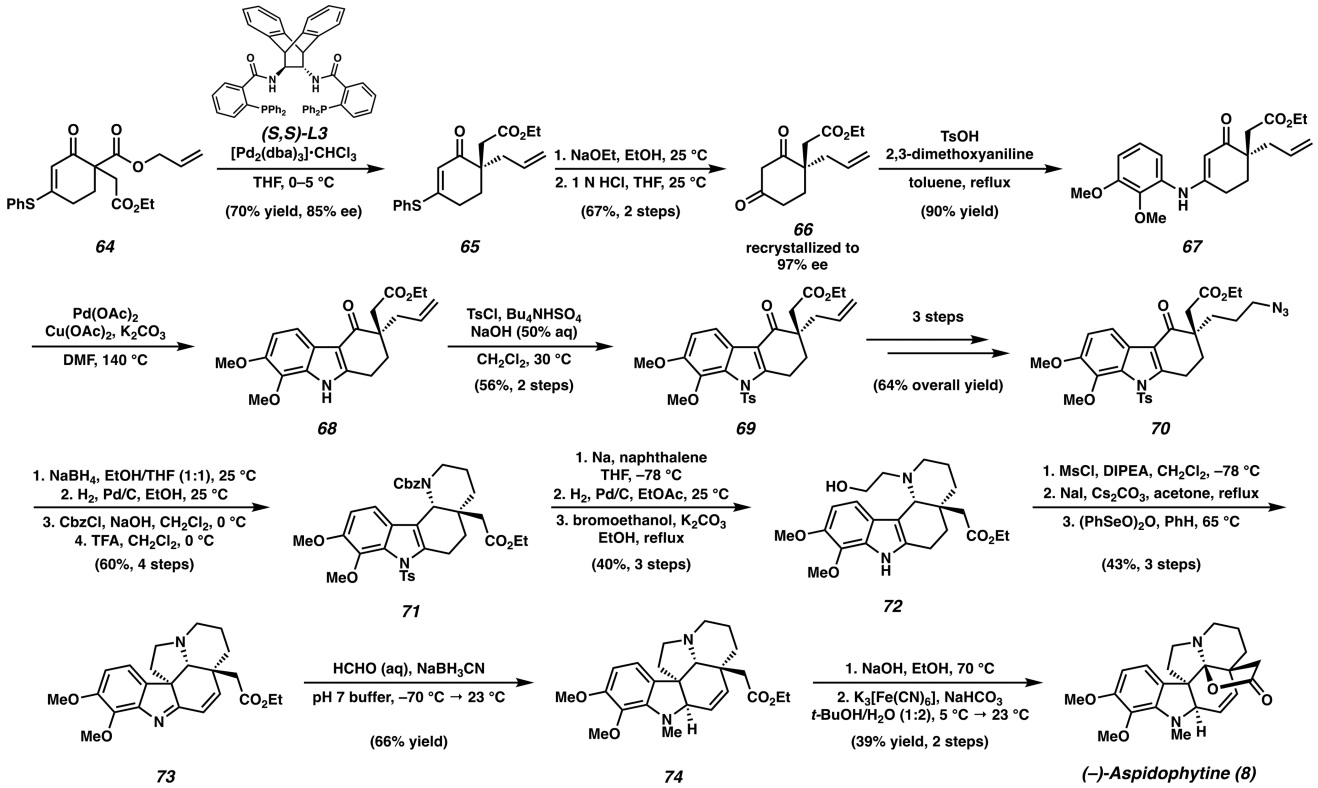
Scheme 7.

Qin's highly stereoselective core construction enabled by early enantioselective Pd-catalyzed allylic alkylation



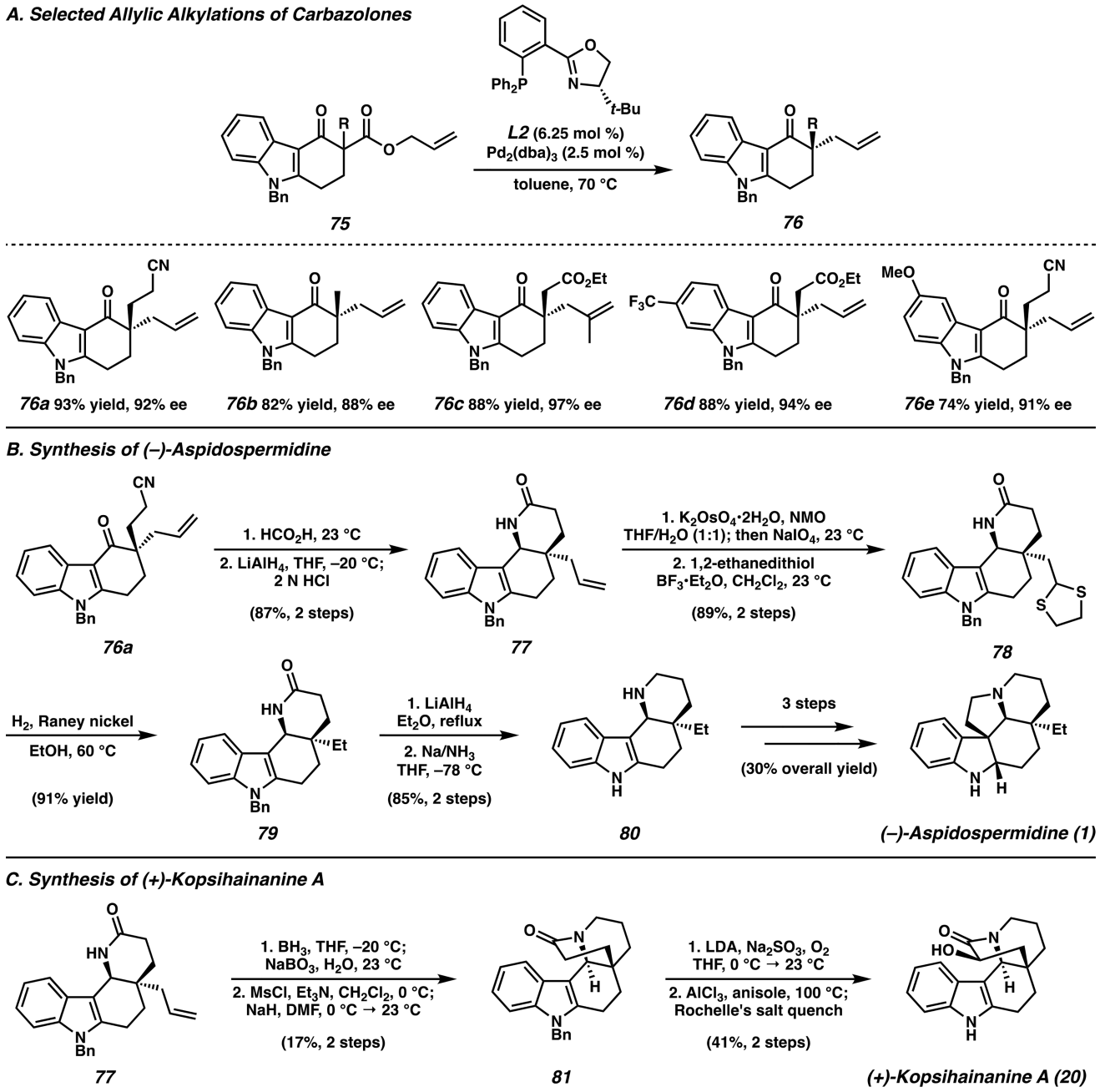
Scheme 8.

Qin's divergent syntheses of multiple *Kopsia* alkaloids



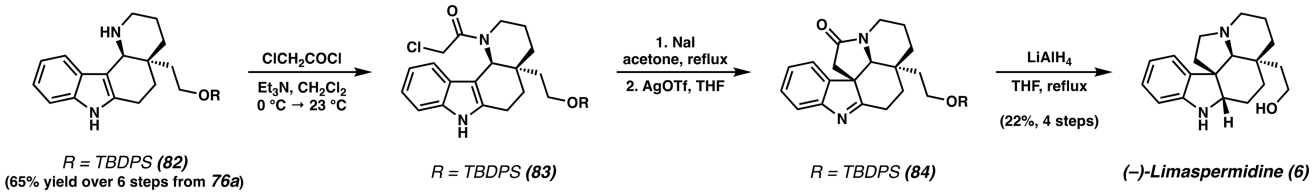
Scheme 9.

Qiu's total synthesis of (–)-Aspidophytine (**8**)



Scheme 10.

Shao's initial report on the Pd-catalyzed allylic alkylation of carbazolone substrates



R = TBDPS ***(82)***
(65% yield over 6 steps from *76a*)

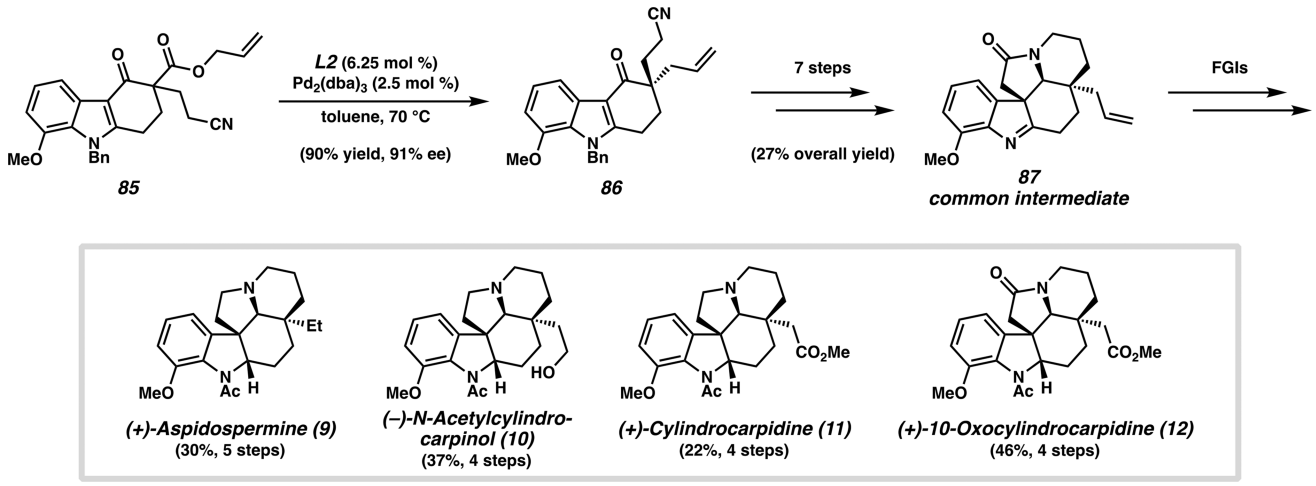
R = TBDPS ***(83)***

R = TBDPS ***(84)***

(–)-Limaspermidine (6)

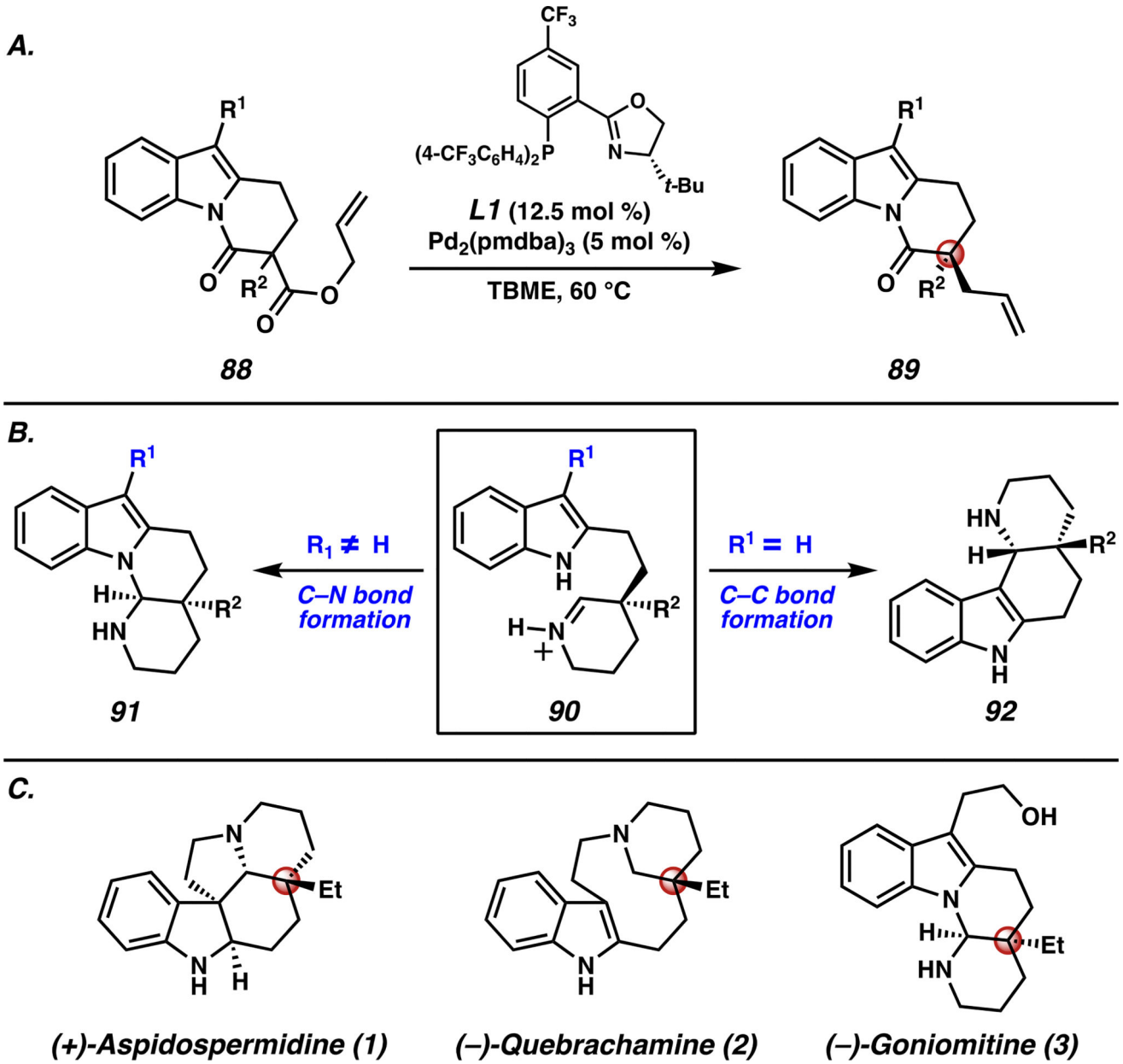
Scheme 11.

Shao's total synthesis of (–)Limaspermidine (**6**)



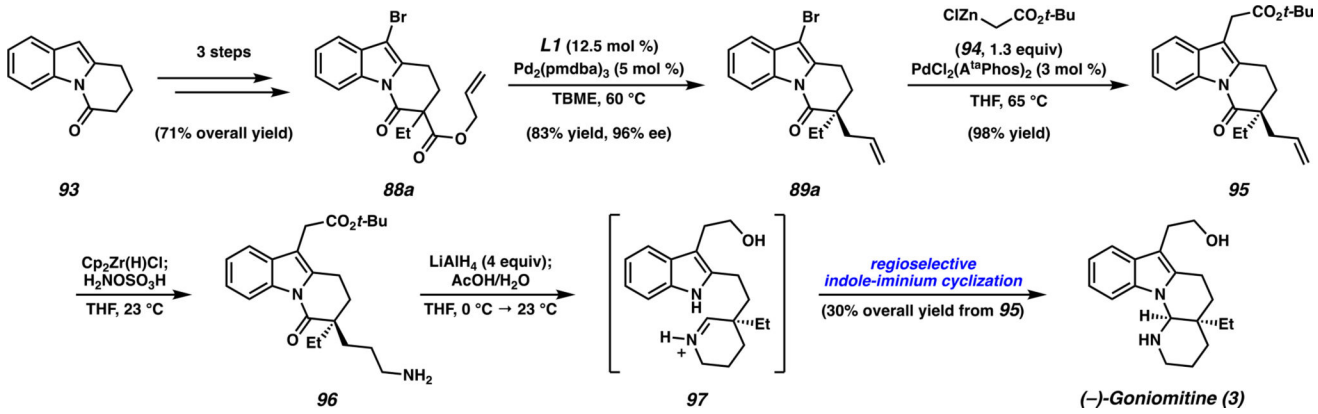
Scheme 12.

Shao's total syntheses of C12-methoxy alkaloids **9–12**



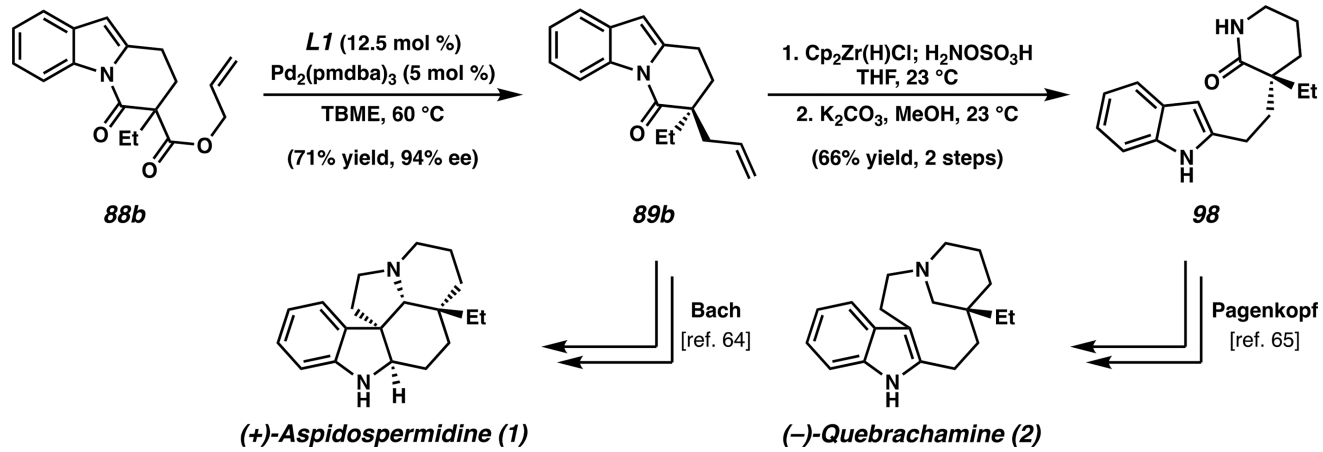
Scheme 13.

Stoltz's Pd-catalyzed allylic alkylation of DHPIs combined with chemodivergent indole-iminium cyclizations



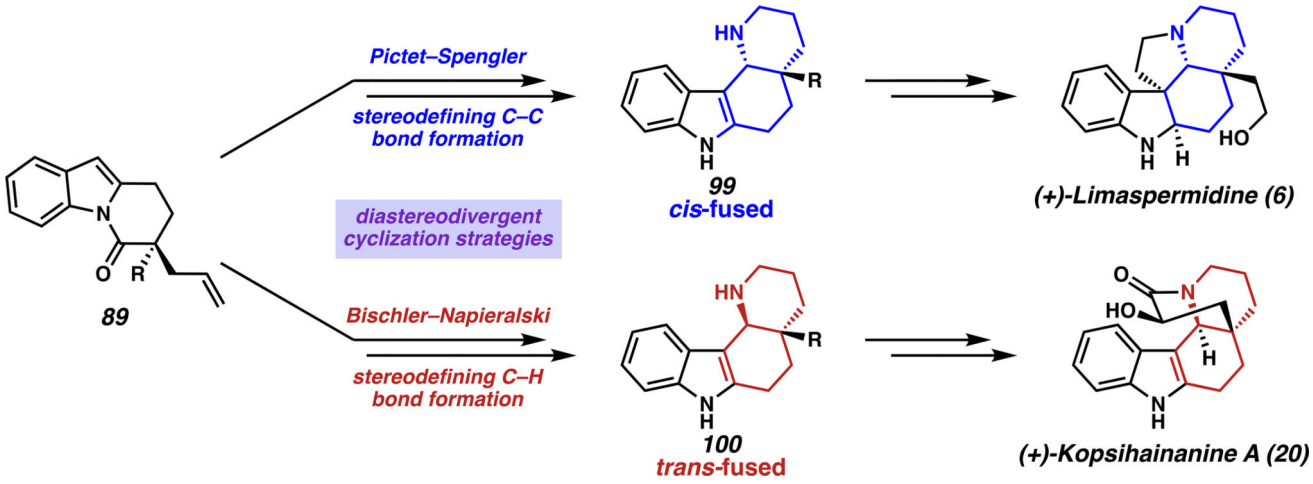
Scheme 14.

Stoltz's catalytic enantioselective synthesis of (–)-Goniomitine (**3**)



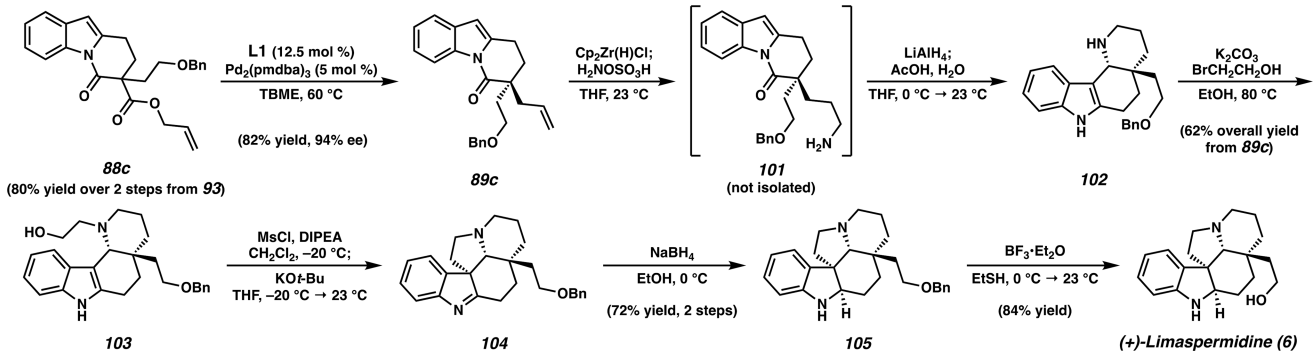
Scheme 15.

Asymmetric formal syntheses of (+)-Aspidospermidine (**1**) and (–)-Quebrachamine (**2**)

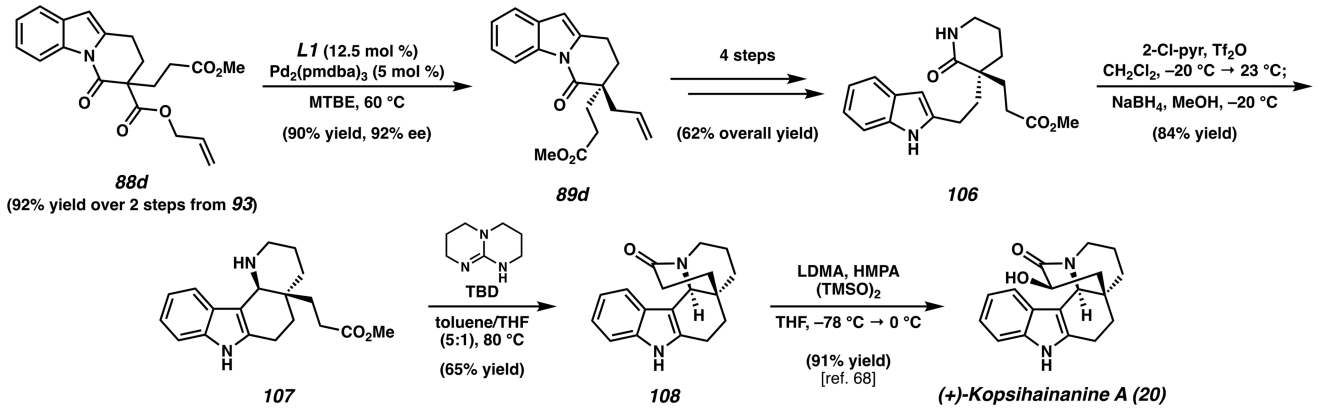


Scheme 16.

Stereodivergent cyclization strategies from a common DHPI precursor

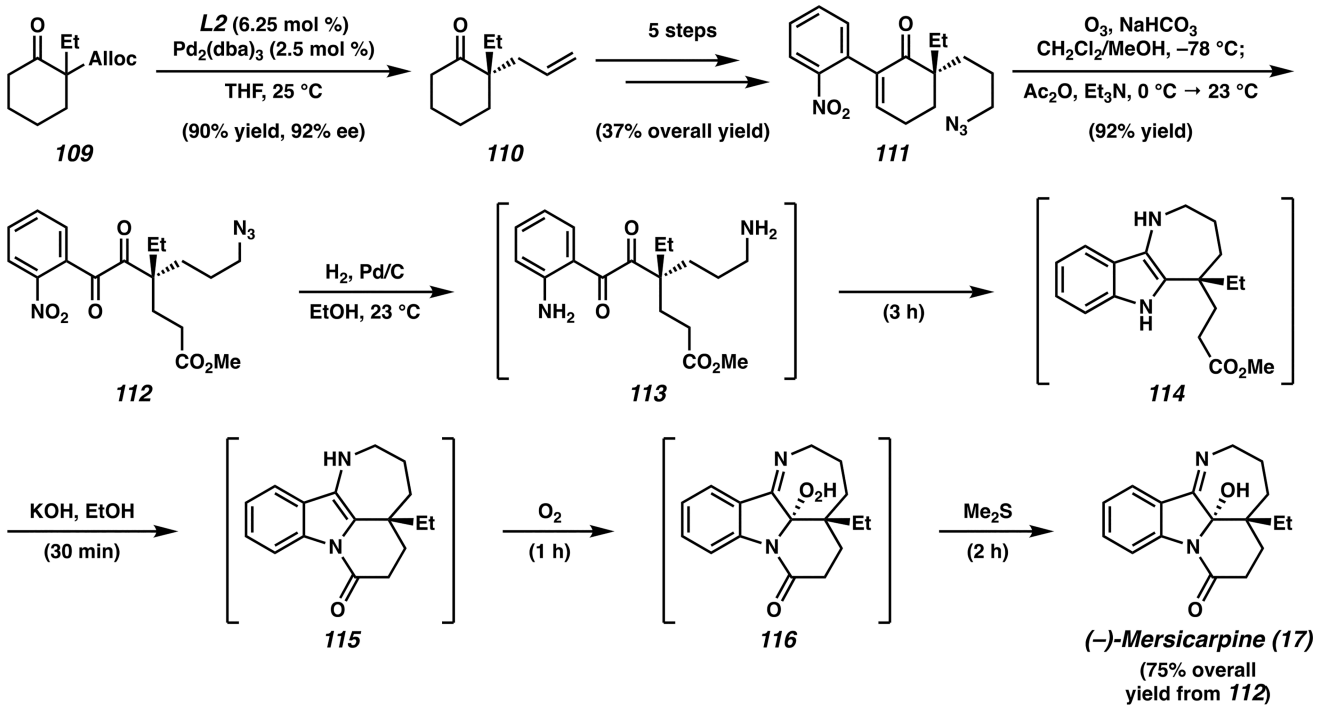


Scheme 17.
Stoltz's total synthesis of (+)-limaspermidine (**6**)



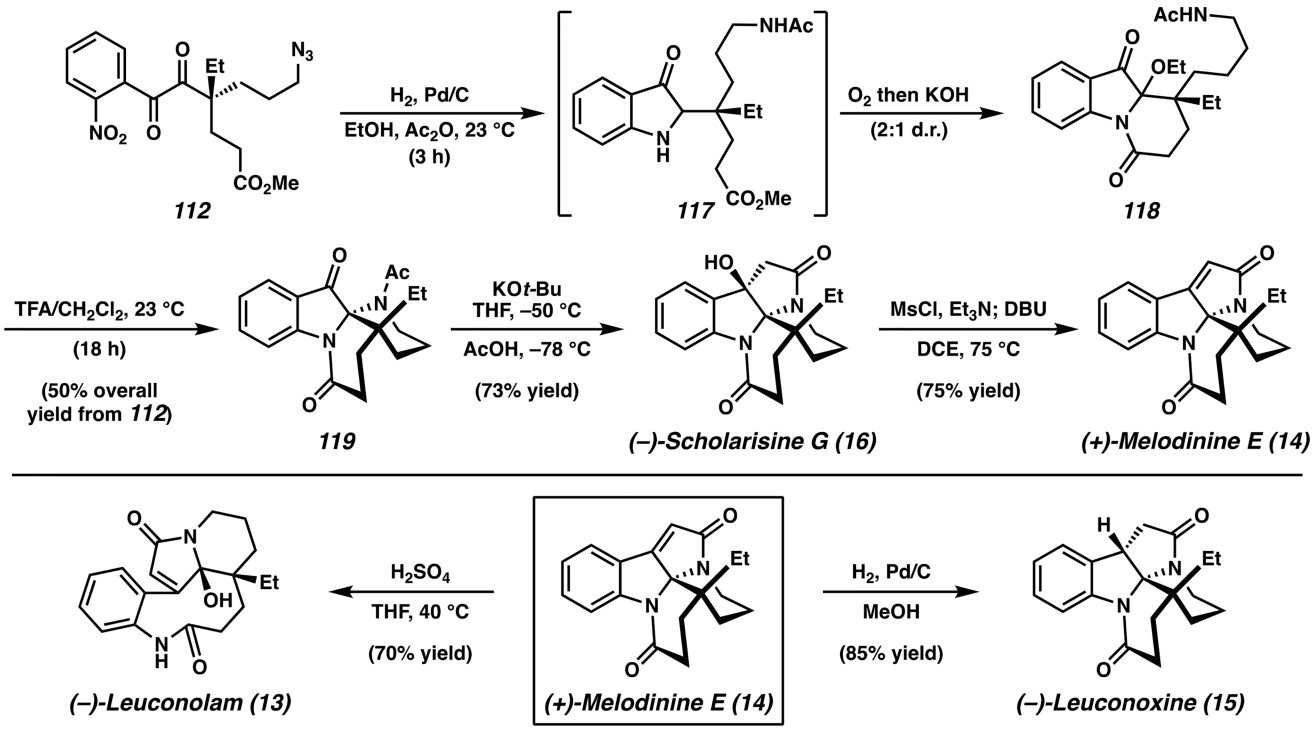
Scheme 18.

Stoltz's formal synthesis of (+)-Kopsihainanine A (**20**)



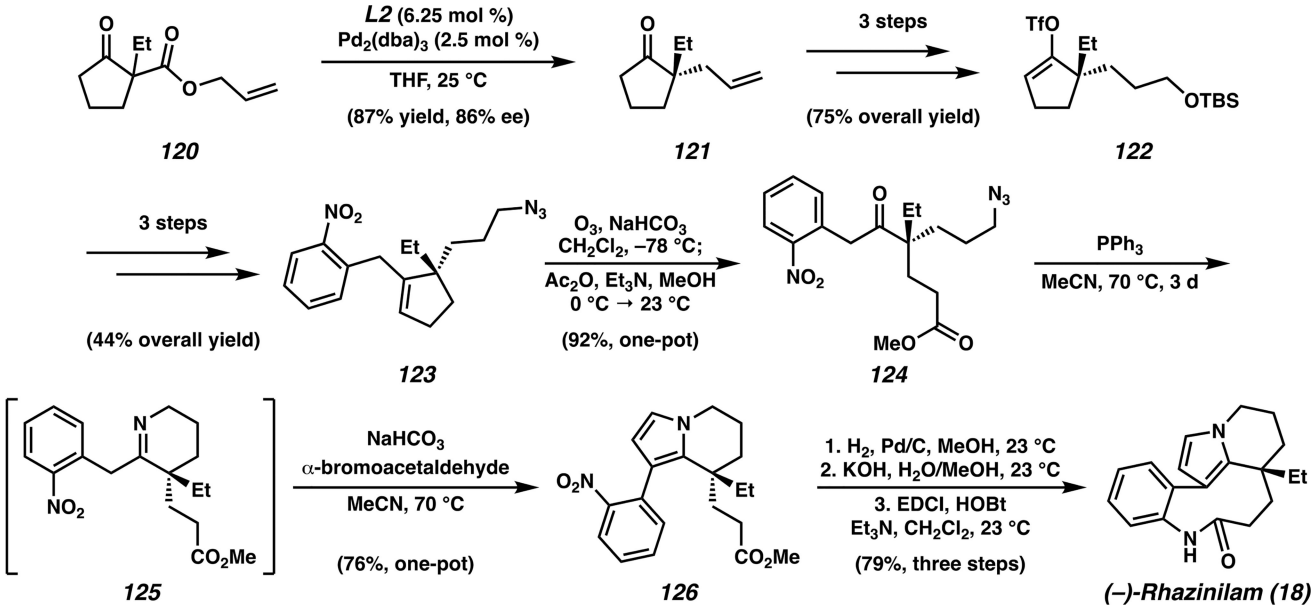
Scheme 19.

Zhu's total synthesis of (–)-Mersicarpine (**17**)



Scheme 20.

Zhu's unified approach to alkaloids **13–16**



Scheme 21.

Zhu's total synthesis of (–)-Rhazinilam (**18**)