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ARTICLE

Palladium-catalyzed cascade cyclizations involving C–C and C–X bond formation: Strategic applications in natural product synthesis

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Palladium-catalyzed cascade cyclizations (PCCs) are powerful synthetic tools that enable rapid assembly of polycyclic scaffolds. Palladium complexes can promote a variety of carbon–carbon and carbon–heteroatom bond-forming reactions with high chemo-, enantio-, and diastereoselectivity. The combination of multiple ring-forming elementary steps into a single cascade sequence can allow complex structures to be accessed with high step economy. This strategy has been employed to access natural products in several distinct classes, including the mitomycins, dragmacidins, isoryanodane diterpenes, and ergot alkaloids. In this tutorial review, we demonstrate how PCCs have expedited natural product synthesis by enabling the formation of both C–C and C–X (X = O, N) bonds in a single synthetic operation.

Key learning points

1. A cascade (or domino) reaction is a process in which multiple bond-forming and/or bond-breaking transformations occur sequentially under a constant set of conditions.
2. Palladium-catalyzed cascade cyclizations (PCCs) can expedite natural product synthesis by enabling the formation of multiple rings, as well as both C–C and C–X bonds (X = O, N), in a single synthetic operation.
3. PCCs can be used early in a synthesis to rapidly access polycyclic natural product frameworks.
4. PCCs can be used in tandem with convergent fragment coupling as a "scaffold-tailoring" step.
5. PCCs can be used at the end of a synthesis to selectively introduce functionality in a complex system.

Introduction

Strategically applied cascade reactions can enable the rapid construction of natural product core structures from simpler starting materials, dramatically shortening and simplifying synthetic plans.[1] As the breadth of palladium-catalyzed C–X (X = O,N) and C–C bond-forming reactions has expanded over the past 30 years, palladium-catalyzed cascade cyclizations (PCCs) have emerged as a powerful strategy to forge multiple rings in a single synthetic operation.[2]

In a cascade (or domino) reaction, multiple bond-forming and/or bond-breaking transformations occur sequentially under a constant set of conditions. In order for a process to be classified as a cascade, the functionality required for the second transformation must be generated as a result of the first.[2] These processes are occasionally referred to as tandem reactions, but there is some controversy to this nomenclature. The term "tandem reaction" has previously been used to describe sequential transformations occurring under a *changing* set of conditions, so we will abstain from using this term to describe the cascade reactions covered herein.[3] It has also become customary to name PCCs after known cross-coupling reactions, such as the Heck reaction, with which they share some mechanistic steps. However, we find this nomenclature to be problematic, given that the mechanisms of most cascades are not identical to those of their parent cross-couplings. Therefore, with the exception of named cascade reactions, such as the Larock heteroannulation, we refer to PCCs by their key bond-forming mechanistic steps.

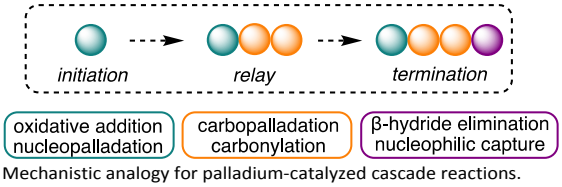

Chart 1 Mechanistic analogy for palladium-catalyzed cascade reactions.

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Palladium-catalyzed cascade reactions have been defined mechanistically as consisting of three parts: initiation, relay, and termination (Chart 1).[4] An initiation step, for example, nucleopalladation or oxidative addition, generates a carbon- or heteroatom-bound Pd species. This intermediate then undergoes one or more bond-forming relay steps, such as olefin carbopalladation or carbonylation. A termination step, such as β-hydride elimination or nucleophilic capture, releases the cascade product and regenerates the Pd catalyst.

In this review, we demonstrate how the strategic application of PCCs can expedite the total synthesis of complex natural products, enabling the formation of multiple rings and both C–C and C–X bonds in a single synthetic operation. We begin by discussing how carbonylative cascades can be employed to build carbocyclic frameworks with fused and spirocyclic lactones, enabling the synthesis of multiple natural products including (±)-schindilactone A (**3**) and (+)-perseanol (**2**, Chart 2). Next, we describe how the Larock heteroannulation cascade can forge both C–C and either C–O or C–N bonds to construct indole or benzofuran-containing natural products. Finally, we focus on cascades that are used to form both C–C and C–N bonds, facilitating the total synthesis of complex alkaloids such as (+)-mitomycin K (**1**).

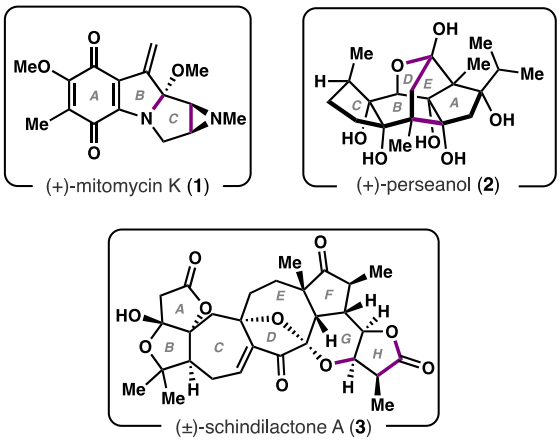
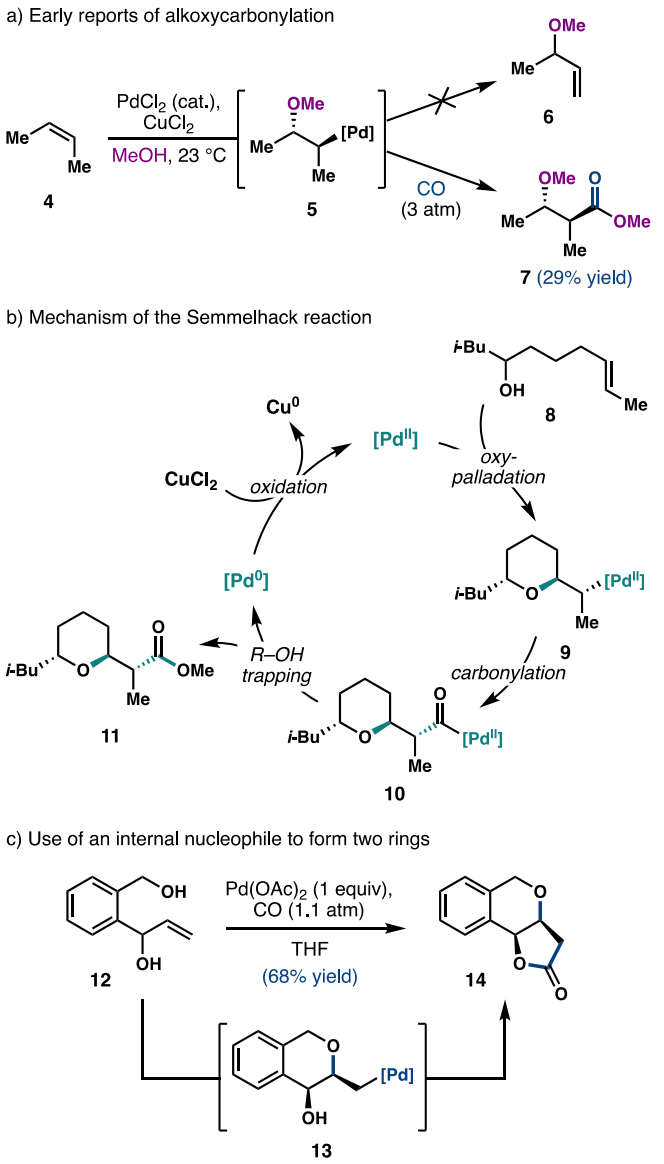


Chart 2 Representative natural products synthesized via PCC.

1. C–C and C–O bond formation: carbonylative cascades

A. The Semmelhack reaction

The Semmelhack reaction was initially developed as a means to investigate the stereoselectivity of olefin oxypalladation, a key mechanistic step in the Wacker process (Scheme 1a). Following oxypalladation of *cis*-2-butene (**4**), Stille and coworkers sought to trap the resultant alkylpalladium intermediate (**5**) before it could undergo β-hydride elimination to form **6**.[5] As carbonylation of alkylpalladium species had previously been shown to occur at a faster rate than β-hydride elimination, **4** was subjected to typical Wacker conditions in the presence of carbon monoxide. *Trans*-oxypalladation was followed by carbonylation and methanol trapping to afford β-methoxyester **7**.



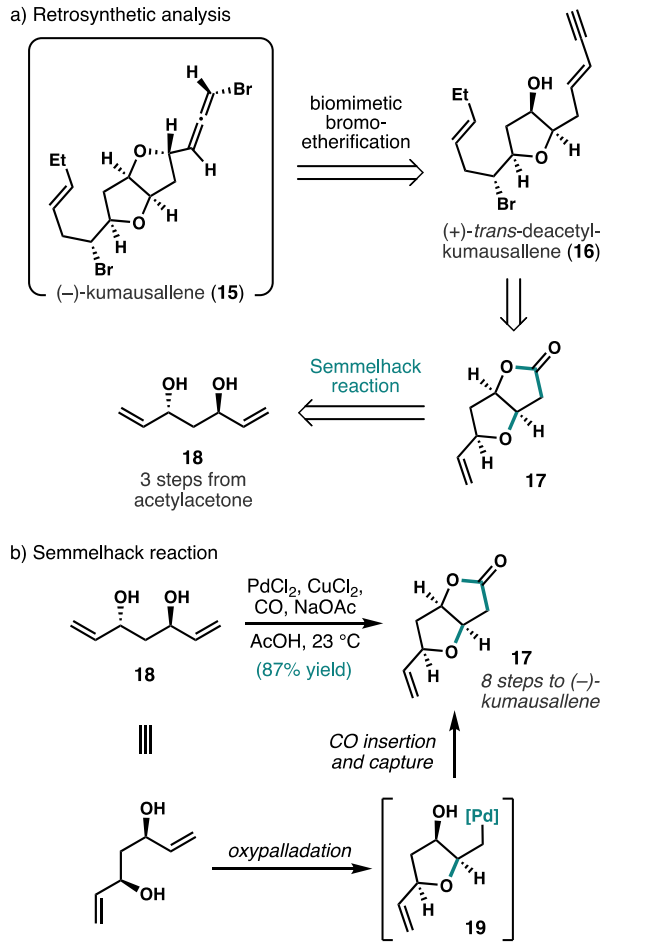
Scheme 1 Development of the Semmelhack reaction.

In 1984, Semmelhack and Bodurow applied this cascade to the synthesis of tetrahydrofuran (THF) and tetrahydropyran (THP) rings from alcohols bearing pendant olefins.[6] Here, the catalytic cycle is thought to be initiated by intramolecular oxypalladation of olefin **8** to form alkylpalladium **9** (Scheme 1b). Carbonylation and methanol trapping then afford **11**, and the liberated Pd^0 complex is oxidized by $CuCl_2$ to regenerate Pd^{II}. In another report, intramolecular trapping of the acyl-Pd^{II} complex was found to give rise to two rings in a single transformation. In this case, stoichiometric $Pd(OAc)_2$ was used instead of $PdCl_2/CuCl_2$ (Scheme 1c).[7] The Semmelhack reaction has since been widely used in the synthesis of complex natural products due to its mild reaction conditions, functional group tolerance, and generally high yields.[8]

Total synthesis of (–)-kumausallene

One notable application of the Semmelhack PCC in natural product synthesis is Tang and Werness' synthesis of (–)-kumausallene (**15**), a bromoallene-containing nonisoprenoid

sesquiterpene (Scheme 2a).[9] Given that previous synthetic approaches by Overman and Evans were challenged by stereoselective bromoallene formation, Tang and Werness envisioned a biomimetic approach. Late-stage biomimetic bromoetherification could selectively afford **15** from (+)-*trans*-deacetylkumausyne (**16**), the putative biosynthetic precursor to (–)-kumausallene. Enyne **16** could arise from pseudosymmetric lactone **17**, which could in turn be formed via Semmelhack reaction of known diol **18**. The use of a PCC early in the synthesis of **15** would allow rapid entry to the polycyclic framework by exploiting the symmetry present in the natural product.



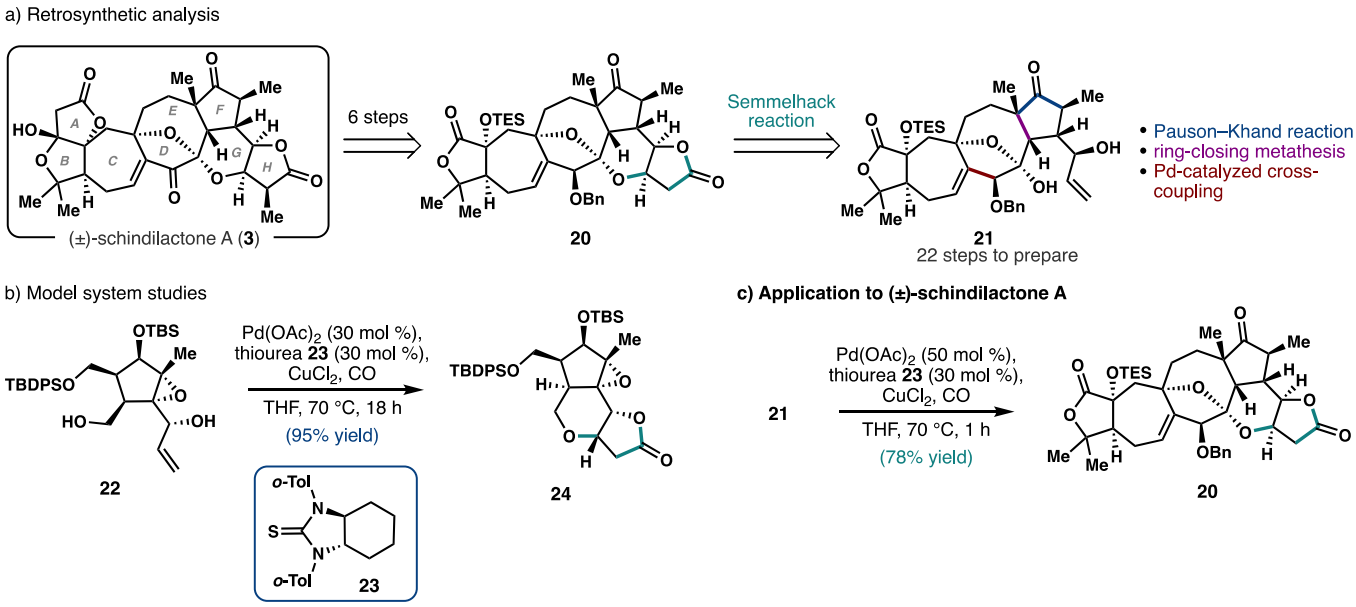
Scheme 2 Total synthesis of (–)-kumausallene.

Key to the success of this strategy was the robust nature of the Semmelhack reaction on scale. Indeed, subjection of C_2-symmetric diol **18**, accessed in three steps from acetylacetone, to typical Semmelhack reaction conditions afforded **17** in 87% yield on gram scale (Scheme 2b). With ready access to lactone **17**, it was then elaborated to enyne **16** in seven steps. Finally, upon treatment with *N*-bromosuccinimide, **16** readily underwent bromoetherification to afford (–)-kumausallene as a single diastereomer.

Total synthesis of (±)-schindilactone A

Tang, Chen, and Yang's synthesis of (±)-schindilactone A (**3**) further demonstrated the utility of the Semmelhack reaction in natural product synthesis (Scheme 3a).[10] Schindilactone A was isolated in 1982 from the *Schisandraceae* family of flowering plants, many species of which have been used in traditional Chinese medicine. With twelve stereogenic centers decorating a highly oxygenated octacyclic framework, **3** is a formidable synthetic target. In contrast to Tang and Werness' synthesis of (–)-kumausallene, wherein the cascade was performed early in the synthesis to rapidly build complexity, here a Semmelhack reaction was used on an advanced substrate.

Retrosynthetically, **3** was first disconnected at the A ring, which was envisioned to arise from aldol addition of an acetyl-protected alcohol to the B ring lactone. Next, a Semmelhack reaction was proposed to form the G and H rings. This disconnection simplified the natural product to pentacyclic



Scheme 3 Total synthesis of (±)-schindilactone A.

compound **21**. The F ring could be installed via a Pauson–Khand reaction, and the central E ring could arise from cross-coupling followed by ring-closing metathesis. The proposed late-stage Semmelhack reaction would be key in constructing two of the final rings of the natural product. However, this strategy would require an especially robust cascade to be able to perform well on highly functionalized **21**.

In prior studies, Chen and Yang found that the Semmelhack reaction could be used to construct the GH ring system of a related natural product. Model substrate **22** underwent Semmelhack reaction to afford **24** in 95% yield (Scheme 3b). Encouraged by these studies, advanced intermediate **21** (prepared in 22 steps) was subjected to similar reaction conditions (Scheme 3c). By increasing the catalyst loading relative to the model studies (from 30 to 50 mol %), **20** could be obtained in 78% isolated yield. Lactone **20** was then elaborated to **3** in a six-step sequence to achieve the first total synthesis of (±)-schindilactone A in 29 steps.

The Semmelhack PCC has been employed in the synthesis of a number of other natural products: (–)-plakortone D (**25**),[11] (±)-crisamicin A (**26**),[12] (±)-pallambins C and D (**27**),[13] and (±)-pallambins A and B (**28**, Chart 3).[14] Together, these syntheses illustrate the utility of the Semmelhack reaction to construct the

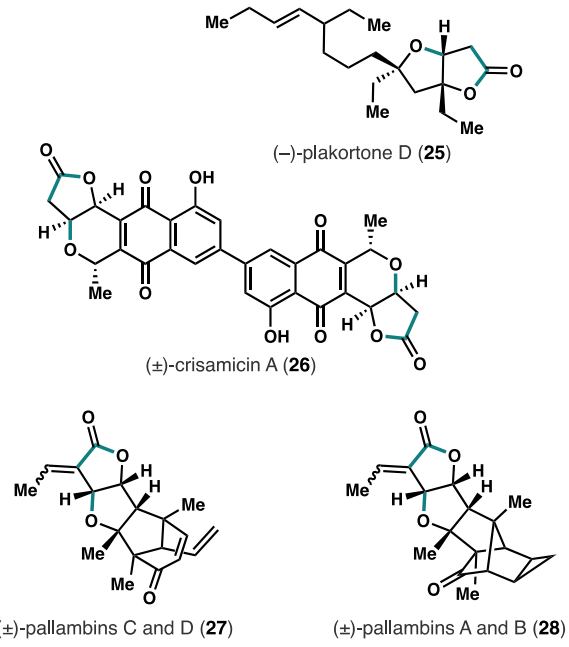
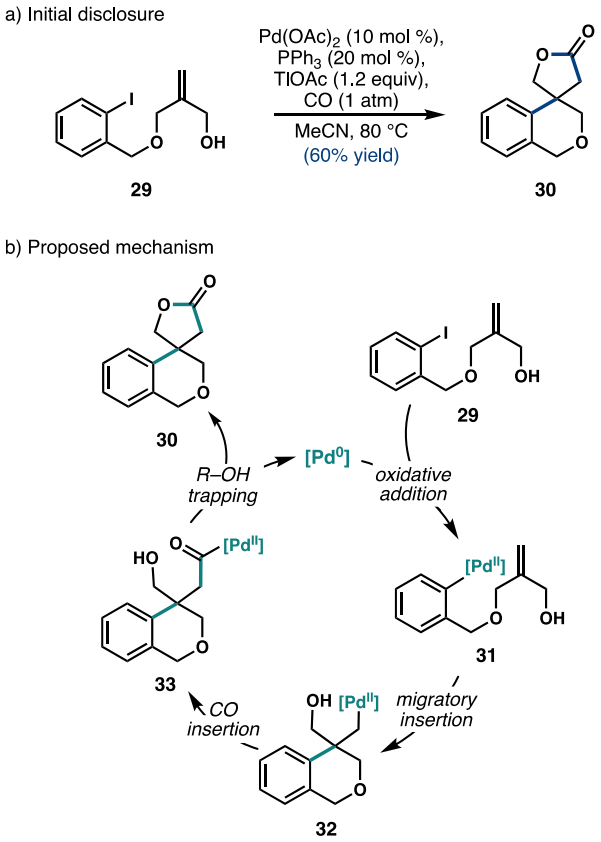


Chart 3 Other natural products synthesized via Semmelhack reaction.

bicyclic lactone motif found in a variety of natural product classes. Although application of this PCC is limited to lactone formation, the compatibility of the Semmelhack reaction with both early and late stages of a synthesis makes it an attractive strategy to synthesize complex, polycyclic systems.

B. Carbopalladation/carbonylative lactonization

Recently, PCCs involving carbopalladation followed by carbonylative lactonization have been used in natural product synthesis. This reaction, initially reported by Grigg and coworkers in 1993, shares some common features with the



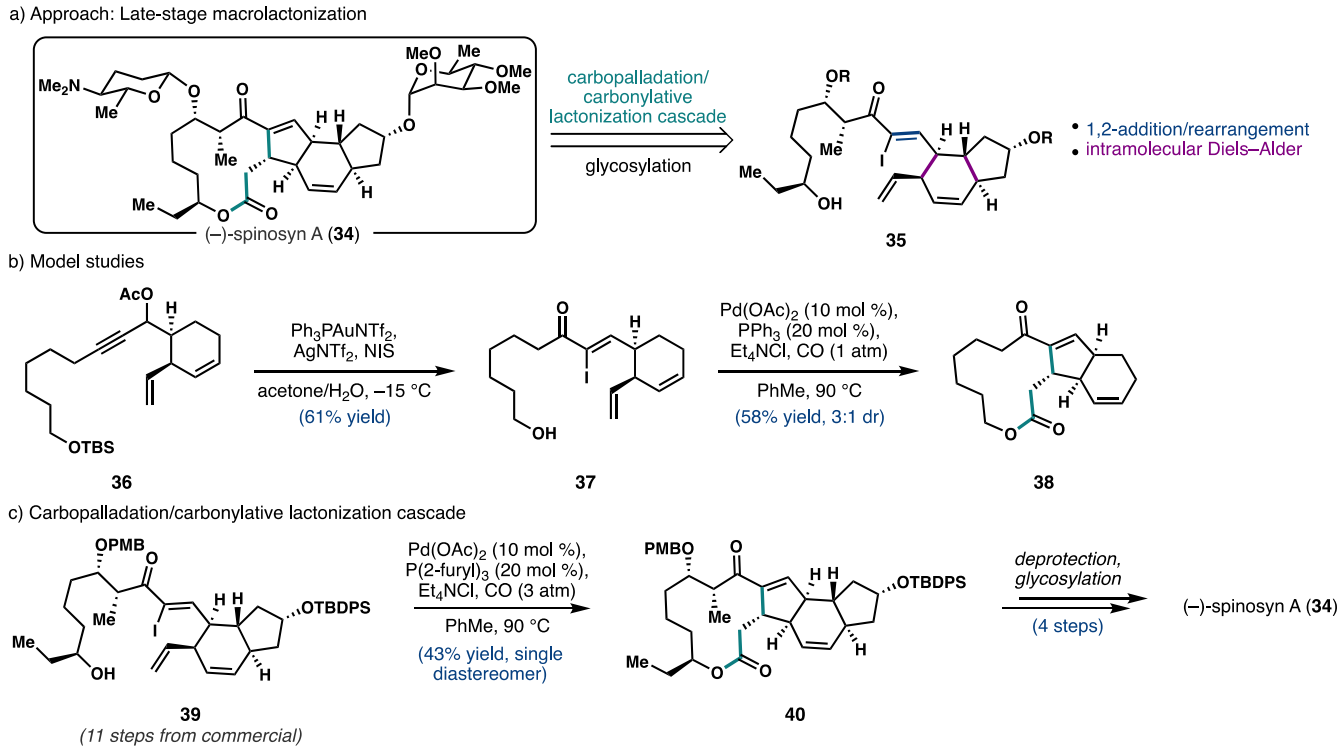
Scheme 4 The carbopalladation/carbonylative lactonization cascade.

Semmelhack reaction (Scheme 4a).[15] Rather than olefin oxypalladation, the initiating step of this cascade is oxidative addition of an aryl or alkenyl halide (**29**) to a Pd^0 species (Scheme 4b). Subsequent migratory insertion (i.e., carbopalladation) of a pendant olefin forms the first ring, resulting in alkyl Pd^{II} species **32**. Carbon monoxide insertion affords acyl Pd^{II} species **33**, then capture by an internal alcohol nucleophile forges the second ring and releases Pd^0. Overall, one C–O and two C–C bonds are formed in a single transformation. This reaction is often referred to in the literature as the "Heck/carbonylative lactonization cascade". However, as we have previously described, this nomenclature is not accurate; the cascade does not involve all of the same mechanistic steps as the Heck reaction. Thus, we refer to this reaction as the carbopalladation/carbonylative lactonization cascade.

Despite their mechanistic similarities, this cascade provides access to structurally distinct scaffolds from the Semmelhack reaction: multiple C–C bonds are formed, enabling construction of a broader variety of ring systems. Additionally, an exogenous stoichiometric oxidant is not required. However, premature carbonylation can be a challenge. In order for this cascade to proceed in high yield, alkene insertion of species **31** must outcompete CO insertion.

Total synthesis of (–)-spinosyn A

The carbopalladation/carbonylative lactonization cascade was first applied to natural product synthesis in Dai and coworkers' synthesis of (–)-spinosyn A (**34**, Scheme 5a).[16] (–)-



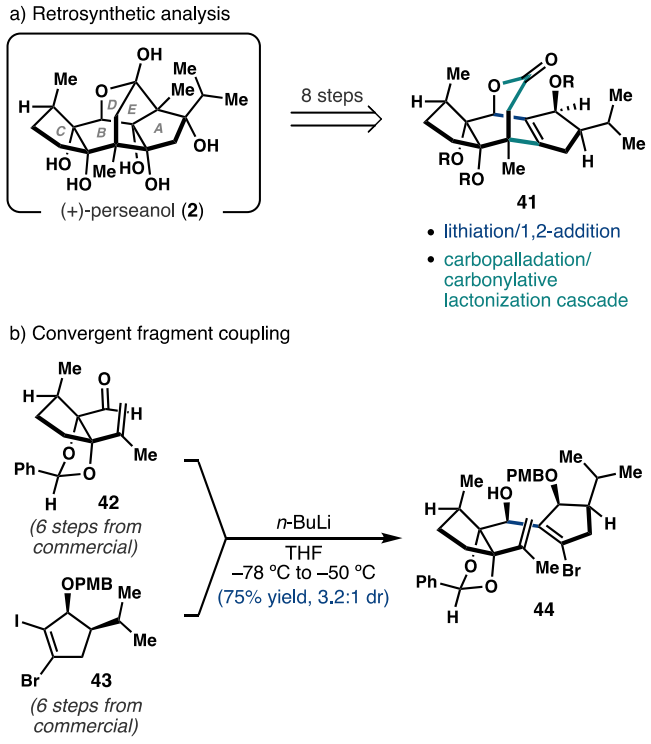
Scheme 5 Total synthesis of (–)-spinosyn A.

Spinosyn A is the primary component of spinosad, a broadly used insecticide with an excellent environmental profile and low mammalian toxicity. Cross-resistance to spinosad has recently emerged, necessitating an efficient synthetic route to **34** for access to structural analogs. Prior to Dai and coworkers' report, the shortest synthesis of **34** required 31 total steps (23 in the longest linear sequence).

Dai and coworkers envisioned disconnecting **34** through a late-stage palladium-catalyzed carbopalladation/carbonylative macrolactonization cascade. The proposed macrolactonization cascade presented several potential challenges: 5-*exo*-*trig* cyclization of the alkenyl- or acyl-Pd intermediates onto the cyclohexene olefin could interfere with desired reactivity, the diastereoselectivity of the olefin carbopalladation was unknown, and macrocycle formation via the carbopalladation/carbonylative lactonization cascade was unprecedented.

The key strategic steps were initially validated in a simpler model system (Scheme 5b). Propargylic acetate **36**, formed via a convergent 1,2-addition, smoothly rearranged under gold catalysis to give **37**. Excitingly, carbopalladation/carbonylative macrolactonization of **37** afforded **38** in 58% yield and 3:1 dr. The 6-membered ring was thought to promote the desired carbopalladation via the Thorpe–Ingold effect, placing the alkenyl iodide and pendant olefin in close proximity.

In light of these promising results, fully elaborated substrate **39** was prepared and subjected to the reaction conditions (Scheme 5c). After some reoptimization, including a change in ligand and increased CO pressure, the desired cyclization proceeded in 43% yield to afford 12-membered lactone **40** as a single diastereomer. Macrocycle **40** could be advanced to (–)-spinosyn A in four additional steps, requiring 23 total steps (15 in the longest linear sequence). This synthesis expanded the scope of the carbopalladation/carbonylative macrolactonization cascade, demonstrating its efficacy in forming fused macrocyclic ring systems. Furthermore, the smooth transition from the model system to the fully functionalized system is a promising indicator that homologous complex



Scheme 6 Strategic approach to (+)-perseanol.

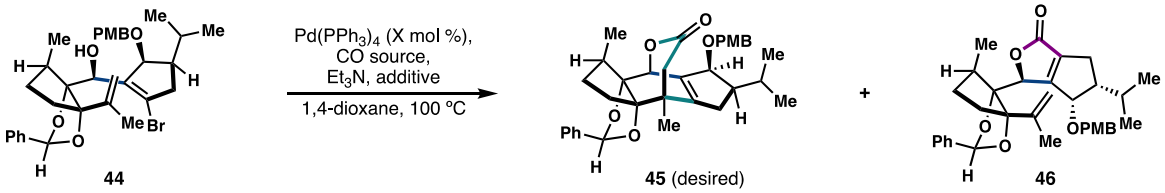
substrates may be tolerated in the reaction, enabling the preparation of analogs of **34**.

Total synthesis of (+)-perseanol

A carbopalladation/carbonylative lactonization cascade was also employed in Reisman and coworkers' synthesis of (+)-perseanol (**2**), an isoryanodane diterpene with potent antifeedant and insecticidal properties (Scheme 6a).[17] Reisman and coworkers proposed formation of the E ring at a late stage, disconnecting **2** to **41**. A two-part convergent fragment coupling strategy was designed to efficiently access **41**. First, two fragments of similar size and complexity would be united via 1,2-addition of alkenyl iodide **43** to aldehyde **42** (Scheme 6b). Next, a palladium-catalyzed carbo-palladation/carbonylative lactonization cascade of the resulting alcohol **44** would close the B and D rings to afford **41**.

To that end, cyclopentene fragments **42** and **43** were each prepared in six steps from commercially available substrates and coupled to give secondary alcohol **44** in 75% yield. With substrate **44** in hand, the carbopalladation/carbonylative lactonization cascade was investigated (Table 1). Initial attempts resulted in recovery of significant amounts of unreacted starting material (entry 1). Hypothesizing that coordination of CO to palladium inhibited the rate of oxidative addition, the reaction mixture was stirred at 100 °C for 60 minutes before addition of CO (entry 2). In this case, the desired product **45** was obtained in modest yield alongside premature carbonylation product **46**. The yield of **45** could be further improved by increasing the palladium loading to 120 mol % and the prestir time to 90 minutes as well as changing the palladium source (entry 3). Reagents that generate CO in situ were also tested, in hopes that maintaining low concentration of CO would enable the use of catalytic amounts of palladium (entries 4–7). The use of *N*-formylsaccharin in combination with KF ultimately afforded **45** in 57% yield using 50 mol % catalyst (entry 8). Cascade product **45** was advanced to **2** in 8 additional steps, completing the first total synthesis of (+)-perseanol in 16 steps (longest linear sequence) from (*R*)-pulegone.

Table 1 Optimization of carbopalladation/carbonylative lactonization cascade.



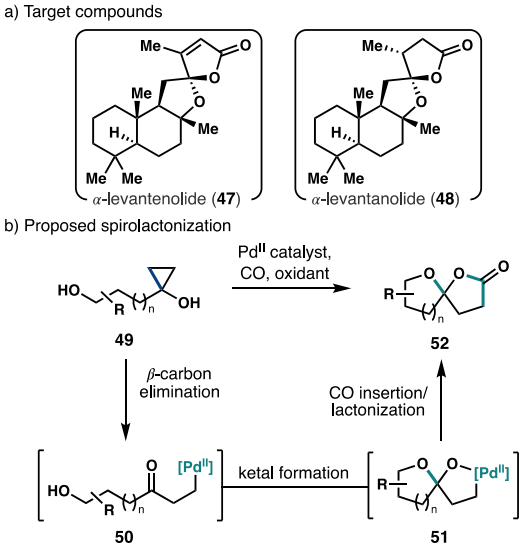
entry	Pd loading (mol %)	CO source	additive	**44** (%)	**45** (%)	**46** (%)
1	50[a]	CO (1 atm), 5 min prestir	-	75	10	5
2	50[a]	CO (1 atm), 60 min prestir	-	50	34	9
3	120	CO (1 atm), 90 min prestir	-	23	48	13
4	50	$Mo(CO)_6$	DBU	85	0	8
5	50	*t*-BuNC	-	90	0	0
6	50	phenyl formate	-	14	7	4
7	50	*N*-formylsaccharin	-	22	31	10
8	50	*N*-formylsaccharin	KF	1	57	14

[a]$Pd(P(t\text{-}Bu)_3)_2$ with 2X mol % P(*p*-F-Ph)$_3$ was used as Pd source

C. Carbonylative spirolactonization of hydroxycyclopropanols: Total synthesis of α-levantenolide and α-levantanolide

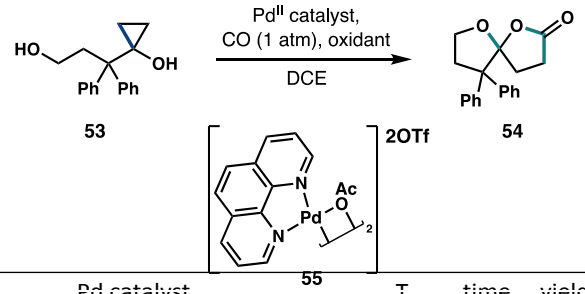
A final example of a carbonylative PCC in natural product synthesis is Dai's synthesis of α-levantenolide (**47**) and α-levantanolide (**48**, Scheme 7a).[18] Motivated by a lack of methods to efficiently synthesize oxaspirolactones, the authors envisioned that readily available hydroxycyclopropanols could be used to access these valuable materials (Scheme 7b). The authors hypothesized that hydroxycyclopropanol **49** could first engage with a Pd^{II} catalyst, undergoing β-carbon elimination to form Pd-homoenolate **50**. Ketal formation with a pendant alcohol and hydroxyl coordination would give rise to **51**, which could form the desired oxaspirolactone (**52**) after CO insertion and lactonization. An oxidant would then be required to regenerate Pd^{II}.

The proposed cascade was developed using model substrate **53** (Table 2). $Pd(TFA)_2$ and $[(cinnamyl)PdCl]_2$ were effective in combination with CO and 2 equivalents of benzoquinone



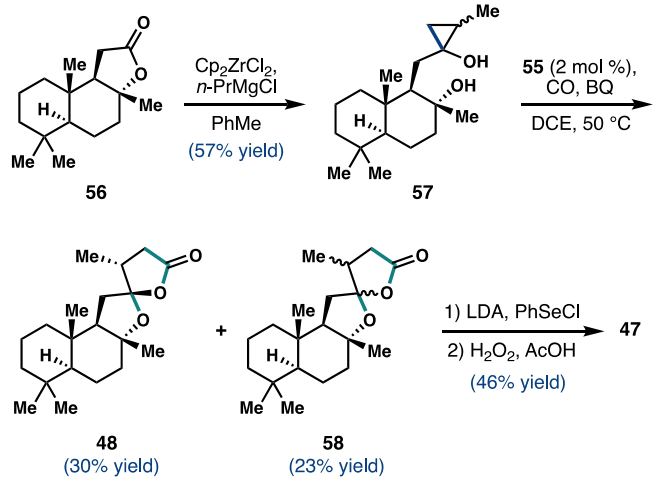
Scheme 7 Spirolactonization strategy toward □-levantanolide and □-levantenolide.

Table 2 Development of spirolactonization cascade.



entry	Pd catalyst (mol %)	oxidant	T (°C)	time (h)	yield (%)
1	$Pd(TFA)_2$ (10)	BQ	23	14	30
2	$[(cinnamyl)PdCl]_2$ (10)	BQ	23	60	66
3	**55** (10)	BQ	23	60	85
4	**55** (10)	O_2	23	60	60
5	**55** (5)	BQ	50	18	89

(entries 1 and 2). Hypothesizing that an electron-deficient palladium species would facilitate coordination of the cyclopropanol [$Pd(neoc)(OAc)]_2(OTf)_2$ (**55**) was tested, and the yield improved to 85% (entry 3). A balloon of oxygen could be used in place of benzoquinone, though the yield was significantly reduced (entry 4). Increasing the temperature to 50 °C allowed the catalyst loading and reaction time to be reduced, affording product in 89% yield after only 18 h with 5 mol % catalyst (entry 5). The efficacy of this reaction was further demonstrated using a set of hydroxycyclopropanol substrates, with yields ranging from 50 to 99%. Having developed a robust method for the carbonylative spirocyclization of hydroxycyclopropanols, the authors applied this reaction to the syntheses of **47** and **48** (Scheme 8). Commercially available (+)-



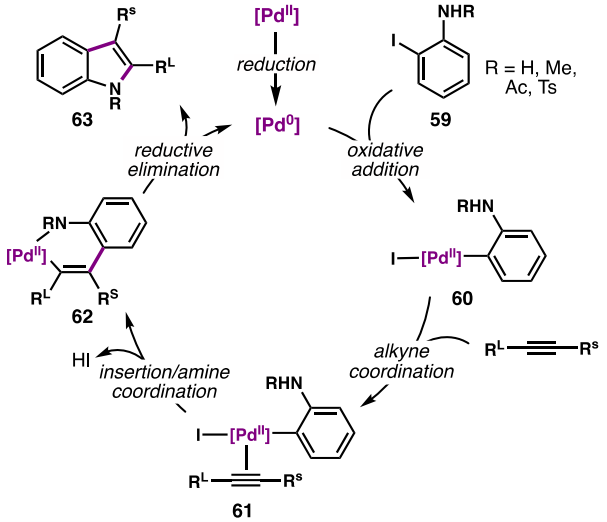
Scheme 8 Total synthesis of α-levantanolide and α-levantenolide.

sclareolide (**56**) was converted to cyclopropanol **57** in 57% yield. The spirolactonization cascade proceeded in 53% total yield and required only 2 mol % catalyst; however, a mixture of diastereomers was obtained. The desired diastereomer, **48**, was isolated in 30% yield. This was consistent with the substrate scope, in which spiro[4.4] ring systems were generally synthesized in poor dr, but spiro[4.5] systems were generally obtained with good dr. Nevertheless, α-levantanolide (**48**) was obtained in 17% overall yield across two steps. Both diastereomers of spirocyclization product (**48** and **58**) could be carried forward in a two-step sequence, affording α-levantenolide (**47**) in four steps and 14% overall yield.

2. C–C and C–O or C–N bond formation: Larock heteroannulations

Providing access to distinct chemical space from the previously described carbonylative cascades, the Larock heteroannulation reaction enables the one-step synthesis of 2,3-disubstituted indoles, benzofurans, and related heterocycles. Multistep versions of this transformation involving initial cross-coupling of an alkynyl tin or thallium species onto the aryl ring and then subsequent cyclization to form a 3-substituted indole were originally established by Taylor, McKillop and Stille.[19] The widely used single-step heteroannulation method was developed by Larock soon after these initial reports.[20] The method was later expanded for the synthesis of 1,2-dihydroisoquinolines, benzofurans, benzopyrans, and isocoumarins.

The proposed mechanism for these reactions involves initial reduction of the Pd^{II} source to Pd^0, subsequent oxidative addition of the aryl iodide **59**, alkyne coordination and insertion to give alkenyl Pd species **62**, and reductive elimination to release the indole product (**63**, Scheme 9).[21] If the difference in size between alkyne substituents is large enough, the annulation occurs with high regioselectivity. Given that the



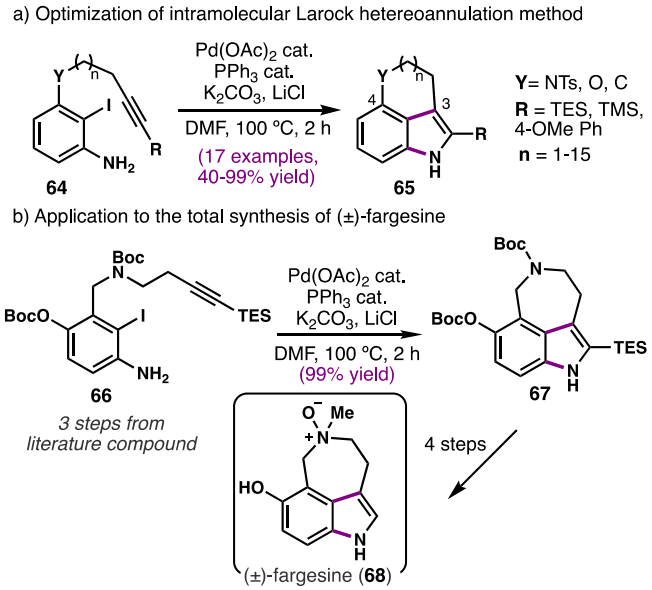
Scheme 9 Proposed catalytic cycle for the Larock heteroannulation cascade

interaction between the larger substituent (R^L) and a developing Pd–C bond will be less than that between R^L and a shorter C–C bond, R^L is placed at the 2-position of the indole.

Total synthesis of eight ergot alkaloids

The 3,4-fused indole motif is present in many bioactive natural products, necessitating streamlined methods for the construction of these scaffolds (Scheme 10a). Striving to

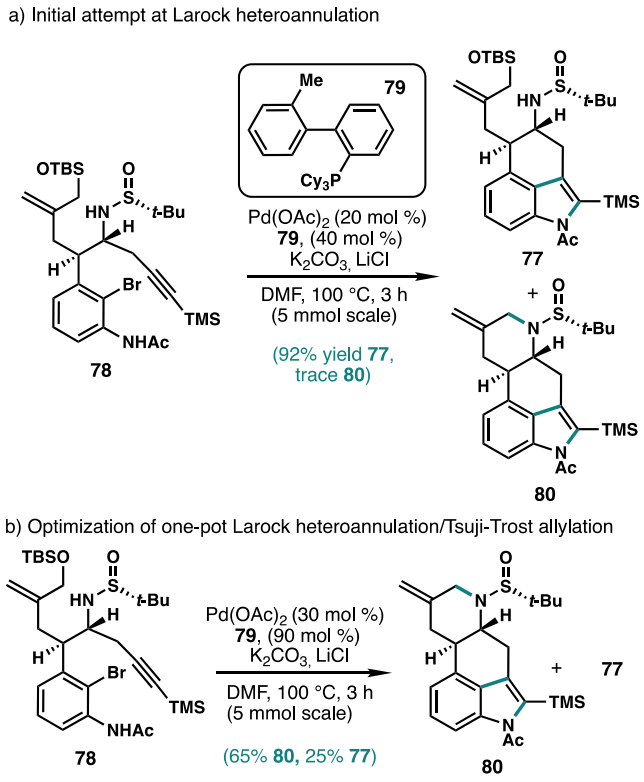
establish a general strategy for the single-step construction of this moiety, Jia and coworkers developed an intramolecular Larock heteroannulation reaction. They aimed to apply the method to the natural product fargesine (**68**) as a proof of concept.[22] To the authors' delight, the optimization of this method proved simpler than anticipated, as the standard conditions for the Larock indole synthesis furnished the desired 3,4-fused indoles in good to excellent yields (Scheme 10a). Furthermore, this method could be used to form both medium-sized rings as well as macrocycles. Additionally, 2-bromoanilines could be employed as substrates in the presence of a MePhos (**79**) or dppp ligand in place of the traditional PPh_3 ligand. Finally, the application of this method enabled the 8-step total synthesis of (±)-fargesine (Scheme 10b).



Scheme 10 Development and application of intramolecular Larock hetereoannulation method

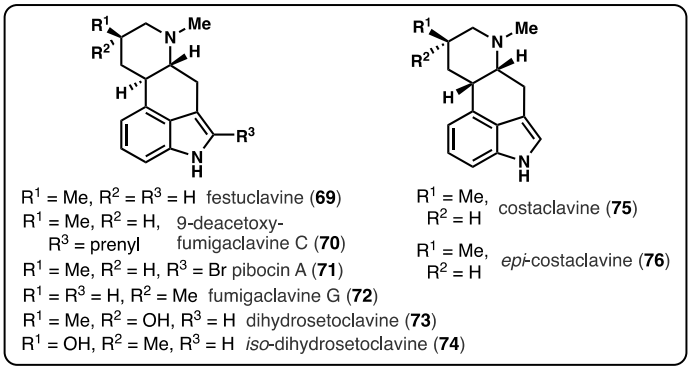
Many natural products produced by ergot fungi also contain the 3,4-fused indole scaffold, and members of this class display diverse and medicinally relevant bioactivities. In fact, several ergot alkaloids are used in the clinical treatment of migraines and Parkinson's disease, rendering natural products in this class attractive synthetic targets.[23] Demonstrating the synthetic utility of their previously established intramolecular Larock heteroannulation method, Jia and coworkers designed a highly divergent synthetic route for the total syntheses of (±)-festuclavine (**69**), (±)-9-deacetoxy-fumigaclalvine C (**70**), (±)-pibocin A (**71**), (±)-fumigaclavine G (**72**), (±)-dihydrosetoclavine (**73**), (±)-*iso*-dihydrosetoclavine (**74**), (±)-costaclavine (**75**), and (±)-*epi*-costaclavine (**76**) from common intermediate **77** (Scheme 11).[24] Larock heteroannulation precursor **78** was accessed in 6 steps from commercially available 2-bromo-1-methyl-3-nitrobenzene.

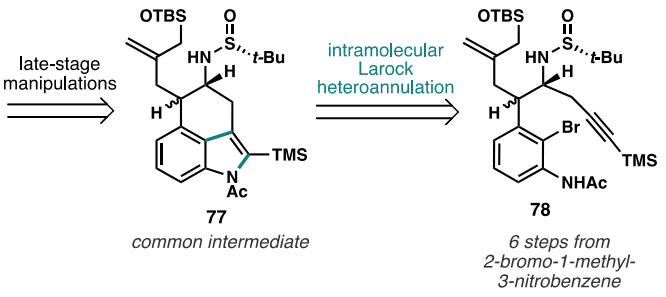
When **78** was subjected to the previously established PCC conditions, the expected heteroannulation product was obtained in 92% yield on gram scale (Scheme 12a). Surprisingly, tetracyclic product **80**, the result of an unexpected one-pot



Scheme 12 One-pot Larock heteroannulation cascade/Tsuji-Trost allylation

Larock heteroannulation/Tsuji–Trost allylation, was also isolated in a trace amount. Because the requisite functionality for the Tsuji–Trost allylation was already present in the starting material, this reaction is most accurately described as a "one-



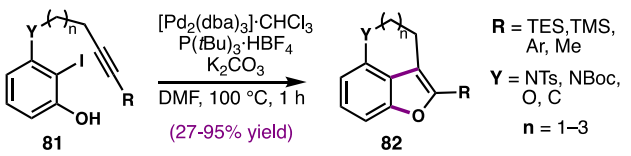


Scheme 11 Abbreviated retrosynthetic strategy for the synthesis of eight ergot alkaloids.

pot" transformation rather than a cascade. By simply increasing the Pd and ligand loadings, tetracyclic product **80** was obtained in 65% yield, along with 25% of the Larock heteroannulation product, **77** (Scheme 12b). Impressively, this one-pot transformation established the tetracyclic framework shared by the target ergot alkaloids and forged two C–N bonds and one C–C bond in a single synthetic step. Furthermore, this constituted the first example of Tsuji–Trost allylation utilizing a TBS-protected allylic alcohol. Each ergot alkaloid target was subsequently accessed from tetracyclic indole **80** in five or fewer steps, demonstrating the synthetic efficiency and versatility of this divergent synthetic route.

Catalytic asymmetric total synthesis of (–)-galanthamine and (–)-lycoramine

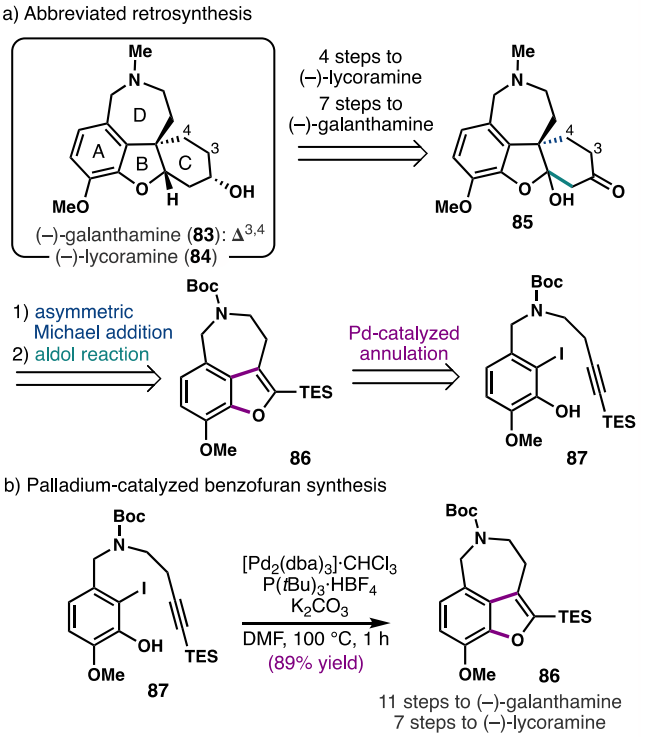
In pursuit of (–)-galanthamine and (–)-lycoramine, two benzofuran-containing Amaryllidaceae alkaloids, the Jia group aimed to expand their intramolecular Larock heteroannulation methodology for the synthesis of 3,4-fused benzofurans.[25] Screening of multiple ligands and Pd sources revealed that $Pd_2(dba)_3{\cdot}CHCl_3$ and $P(t\text{-}Bu)_3{\cdot}HBF_4$ were the optimal reagents (Scheme 13). The substrate scope was quite general, enabling



Scheme 13 Substrate scope of Larock heteroannulation method

the construction of 6–9-membered rings containing O or N heteroatoms and tolerating various substitutions at the 2-position. Notably, the desire to utilize the Larock heteroannulation cascade to construct (–)-galanthamine (**83**) and (–)-lycoramine (**84**) resulted in the expansion of the substrate scope for this reaction, demonstrating that strategic applications can have impacts beyond the realm of natural product synthesis.

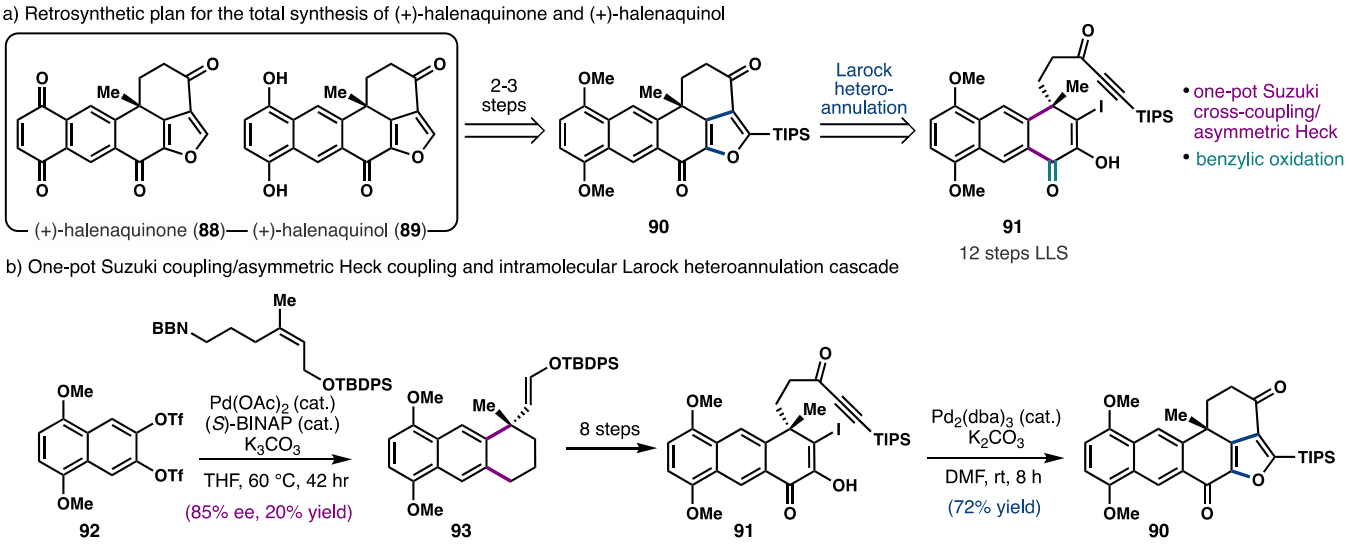
Amaryllidaceae alkaloids **83** and **84** are medicinally relevant targets that have demonstrated inhibition of acetyl-cholinesterases; in fact, (–)-galanthamine has been used clinically to treat Alzheimer's disease. Previous approaches aimed to form the "B" or "D" ring at a late stage in the synthesis. In contrast, Jia and coworkers aimed to construct the ABD ring system in a single synthetic operation through a palladium-catalyzed Larock heteroannulation reaction. Retrosynthetically, a late-stage asymmetric Michael addition/aldol sequence would be used to forge the C ring from benzofuran **86**, which would be prepared via PCC of iodophenol **87** (Scheme 14a). The optimized heteroannulation cascade translated well to the fully elaborated system, enabling the catalytic asymmetric total synthesis of (–)-galanthamine and (–)-lycoramine, which were completed in 14 and 10 steps, respectively (Scheme 14b). Although it was two steps longer than the shortest catalytic asymmetric synthesis of (–)-galanthamine achieved by Zhou and Xie, the unique retrosynthetic strategy developed by Jia and coworkers led to an expansion of the substrate scope for the Larock heteroannulation reaction, laying the groundwork for future applications to the synthesis of medicinally important benzofuran natural products.



Scheme 14 Total synthesis of (–)-galanthamine and ()-lycoramine

Asymmetric total synthesis of (+)-halenaquinone and (+)-halenaquinol

Shibasaki and coworkers' total synthesis of (+)-halenaquinone (**88**) and (+)-halenaquinol (**89**), completed in 1996, was an early application of PCC in natural product synthesis (Scheme 15a).[26,27] This approach featured two key palladium-catalyzed reactions: a one-pot Suzuki cross-coupling/asymmetric Heck coupling and a Larock heteroannulation cascade. The combination of these two palladium-catalyzed cyclization reactions was a creative strategy that enabled the rapid assembly of the pentacyclic core of **88** and **89**.



Scheme 15 Asymmetric total synthesis of (+)-halenaquinone and (+)-halenaquinol. BBN = borabicyclo(3.3.1)nonane, LLS = Longest linear sequence

Retrosynthetically, both targets were derived from compound **90**, the product of the key Larock heteroannulation cascade. The Larock heteroannulation substrate **91** was accessed in 8 step sequence involving multiple oxidations and functional group manipulations of **93**. Compound **93** was accessed via a novel one-pot Suzuki coupling/Heck coupling reaction. Although the authors denote this process as a "cascade", we disagree with this nomenclature, as the requisite functionality for the second Heck coupling is already present in the substrate and is not generated as a result of the first Suzuki coupling. This one-pot reaction installed the benzylic quaternary center of both natural products in 85% ee and 20% yield from triflate **92** (Scheme 15b). Tricyclic product **93** was then advanced to PCC precursor **91** in an eight-step sequence. The key Larock heteroannulation cascade occurred in a 72% yield. Notably, this was the first published example of intramolecular Larock annulation, and it was also the first application to utilize an iodinated diosphenol. This synthetic effort enabled the short and enantioselective construction of both **88** and **89**, and it demonstrates how the strategic combination of multiple palladium-catalyzed cyclizations can be utilized to build complex carbocyclic frameworks from simple starting materials.

The intramolecular Larock heteroannulation cascade has been applied in several additional total syntheses (Chart 4). The Boger group successfully applied the cascade for the construction of ergot alkaloids (±)-dihydrolysergic acid (**94**) and (±)-dihydrolysergol (**95**).[28] In addition, the total syntheses of macrocyclic peptides (±)-chloropeptin I (**96**) and (±)-chloropeptin II (**97**) were enabled by an intramolecular Larock macrocyclization using stoichiometric palladium.[29] More recently, Boger and coworkers completed the total synthesis of macrocyclic peptide (±)-streptide (**98**) using a similar transformation, which gave the indole product in 60% yield.[30] These examples demonstrate the robust and highly selective nature of the intramolecular Larock heteroannulation reaction, enabling the formation of 20-membered macrocycles from complex polypeptide substrates.

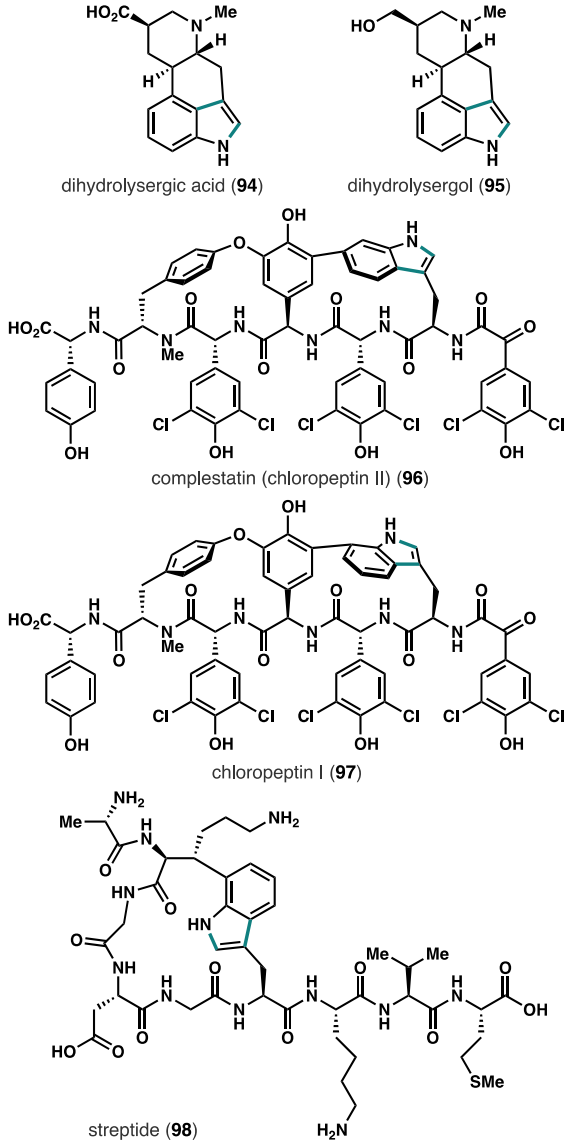
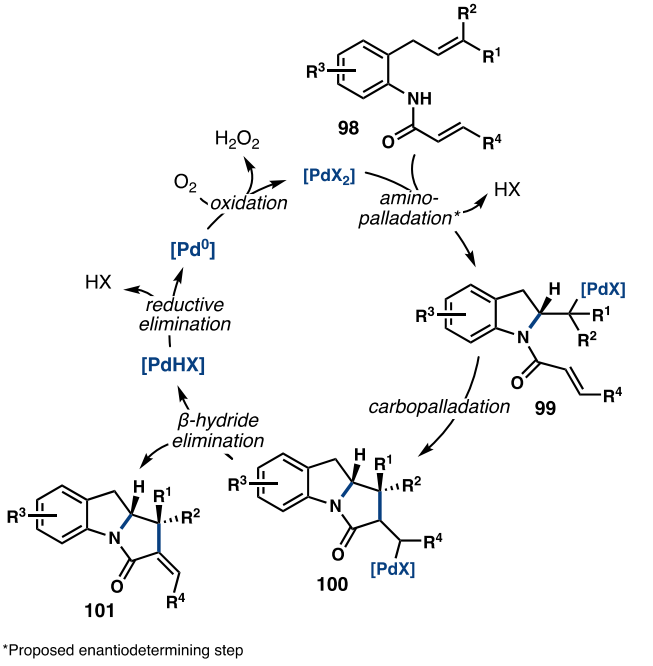


Chart 4 Additional targets completed via Larock hetereoannulation cascade

3. C–C and C–N bond formation: nucleopalladation/carbopalladation/β-hydride elimination cascades

Although redox-neutral C–C and C–N bond-forming PCCs have been widely developed and applied, oxidative cascades have received significantly less attention. C–C and C–O bond-forming cascades involving nucleopalladation and subsequent carbopalladation and *β*-hydride elimination were initially discovered by Larock, although these early examples required stoichiometric palladium.[31] A catalytic, oxidative version of this transformation was established by Semmelhack, and

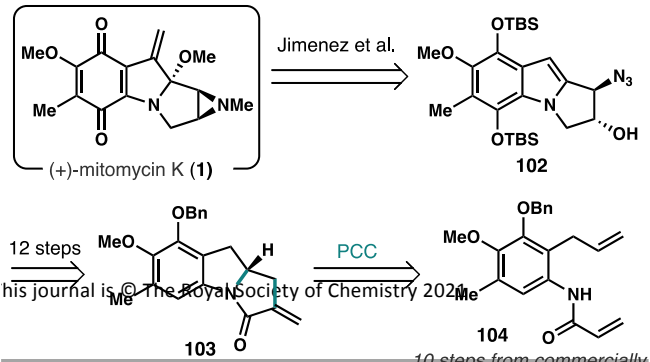


Scheme 16. Proposed catalytic cycle for nucleopalladation/carbopalladation/ *β*-hydride elimination cascades

enantioselective variants were developed soon after.[32,33] The analogous transformation with nitrogen nucleophiles was first reported in the context of chiral indoline synthesis and later applied to the total synthesis of (+)-mitomycin K (**1**).[34] The proposed mechanism of this PCC is initiated by aminopalladation to afford alkylpalladium species **99** (Scheme 16). Subsequent carbopalladation of the pendant alkene forms an additional ring, and *β*-hydride elimination from **100** releases the polycyclic product (**101**). Reductive elimination and oxidation regenerate the Pd^{II} catalyst.

Asymmetric total synthesis of (+)-mitomycin K

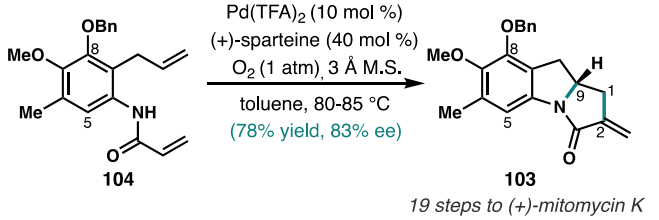
The mitomycins are an iconic class of natural products, well known for their small but highly functionalized structure



Scheme 17 Retrosynthetic plan for the synthesis of (+)-mitomycin K.

and potent antitumor activity. Mitomycins have a long synthetic history, but the first enantioselective synthesis of (+)-mitomycin K (**1**) was only recently achieved (Scheme 17). Retrosynthetically, the authors envisioned the completion of target **1** from precursor azide **102**, which had previously been employed in a racemic synthesis of (±)-mitomycin K. They aimed to derive azide **102** from PCC product **103** via a sequence of functional group manipulations. A key palladium-catalyzed oxidative cascade cyclization of **104** would establish the 6/5/5 fused polycyclic core and constitute the first successful strategic application of their previous established enantioselective oxidative cyclization method.

Prior investigations of the key oxidative PCC did not explore arene substituent effects. In this case, substitution at C8 and C5 was desired in order to reduce the number of subsequent oxidation state manipulations (Scheme 18). Therefore, the authors aimed to elucidate substituent effects on reaction yield

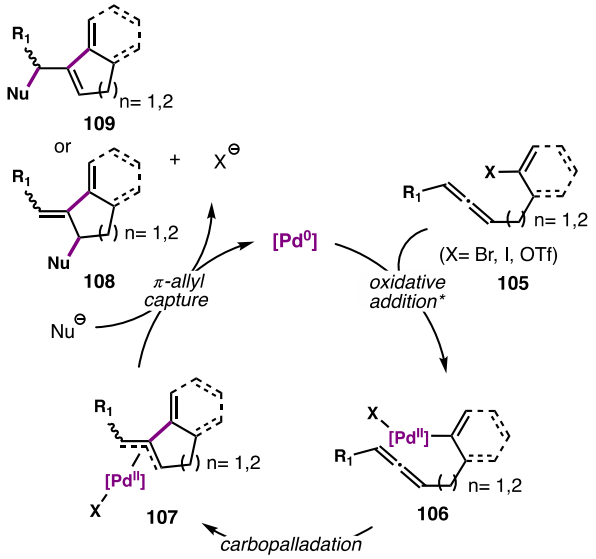


Scheme 18 Key palladium-catalyzed oxidative cascade cyclization

and enantioselectivity. Interestingly, substitution at C5, vicinal to the acrylamide moiety, was found to be detrimental to *ee*, whereas benzyl ether substitution at C8, vicinal to the allyl group, was somewhat beneficial, although the rationale for these substituent effects is unclear. The authors obtained cyclization product **103** in 83% *ee*, which was subsequently advanced to azide **102** in 12 steps. Although the absolute configuration at C9 established by the cyclization was subsequently ablated via oxidation, it was first used to relay the correct absolute configurations at both C1 and C2. Finally, azide **102** was advanced to (+)-mitomycin K using a procedure established by Jimenez et al.

The application of this oxidative PCC enabled the first enantioselective total synthesis of (+)-mitomycin K, demonstrating that PCCs can be a powerful tool for asymmetric synthesis. In addition, the aforementioned oxidative PCC enabled the single-step construction of the polycyclic 6/5/5 scaffold from a much simpler precursor. Unfortunately, the need for multiple oxidation state manipulations and functional group interconversions to obtain desired azide intermediate **102** added many steps to the synthesis. Nevertheless, the authors persevered and successfully constructed enantiopure (+)-mitomycin K in 33 steps from commercial starting materials, completing the first asymmetric total synthesis of this natural product.

4. C–C and C–N bond formation: carbopalladation/π-allyl capture

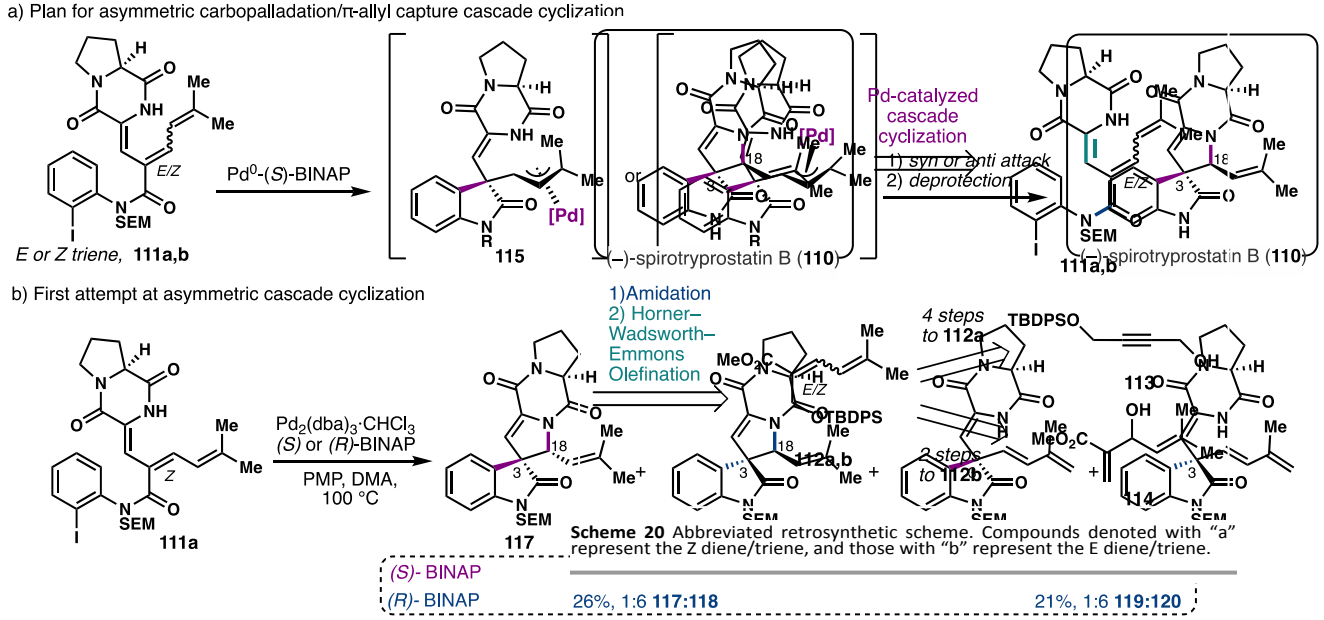


Scheme 19 Proposed catalytic cycle for carbopalladation/π-allyl capture cascades.

The carbopalladation/π-allyl capture cascade is one of the most widely developed and frequently applied PCCs, accepting a variety of diene or allene substrates and O, C, and N-centered nucleophiles. In the literature, this cascade is often referred to as the Heck insertion/anion capture cascade or the Heck/Tsuji–Trost cascade. We consider it more accurate to refer to these reactions as carbopalladation/π-allyl capture cascades, as their proposed mechanism does not contain all the elementary steps of the Heck coupling or the Tsuji–Trost allylation. The suggested mechanism for these transformations commences with oxidative addition of an alkenyl or aryl halide electrophile, such as **105**, to a Pd^0 complex (Scheme 19). The resulting Pd^{II} complex (**106**) participates in the carbopalladation of a diene or allene to give π-allylpalladium^{II} intermediate **107**. This intermediate can then be trapped by a variety of internal or external nucleophiles. This PCC was initially disclosed and extensively developed by Grigg and coworkers, who found that π-allylpalladium^{II} complexes generated from allene or diene insertion could be successfully trapped by hydrides, organozincs, organoborons, organotins, *C*-, *O*-, and *N*-centered nucleophiles.[35] Subsequently, Shibasaki and coworkers developed an enantioselective variant that utilized a $Pd(OAc)_2$ catalyst and chiral (*S*)-BINAP ligand to promote asymmetric diene insertion followed by stereoselective π-allyl capture by acetate anions or benzylamines.[36,37] They later applied this cascade to the asymmetric total synthesis of natural product (–)-**Δ**$^{9(12)}$-capnellene.[38]

Total synthesis of (–)-spirotryprostatin B

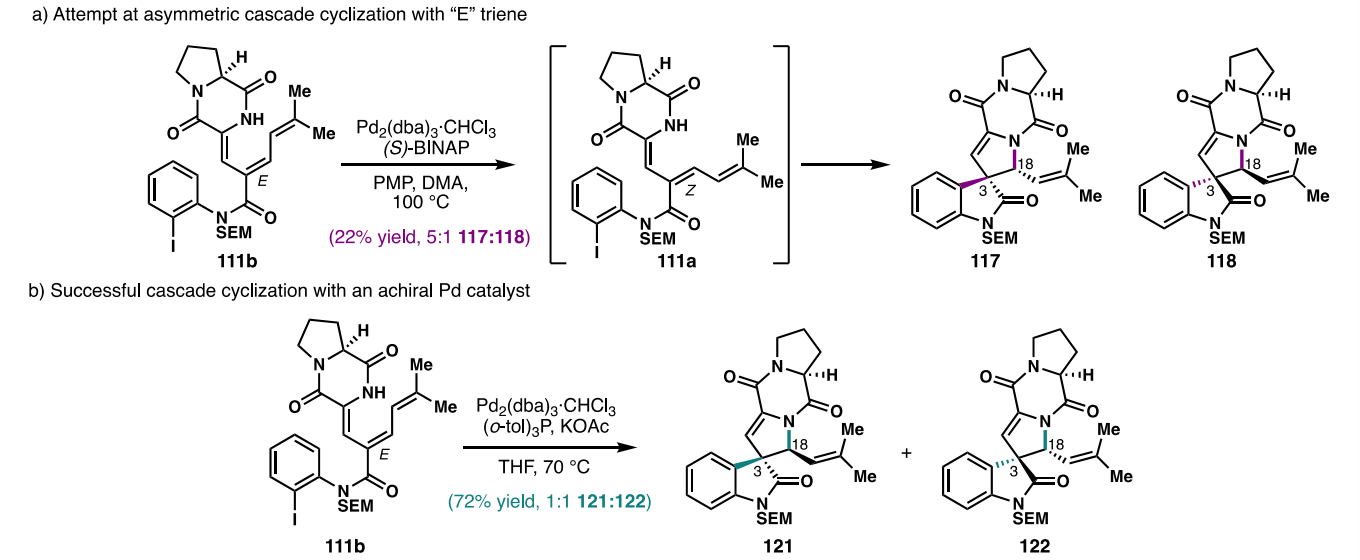
In 2000, the Overman group employed the carbopalladation/π-allyl capture cascade to synthesize the marine natural product (–)-spirotryprostatin B (**110**, Scheme 20).[39,40] Their original strategy was to employ this PCC in an asymmetric fashion to establish the correct absolute configurations of both the oxindole C3 all-carbon quaternary



Scheme 20 Abbreviated retrosynthetic scheme. Compounds denoted with "a" represent the Z diene/triene, and those with "b" represent the E diene/triene.

Scheme 21 Studies toward the total synthesis of (–)-spirotryprostatin B. SEM = 2-(trimethylsilyl)ethoxymethyl

center and the adjacent C18 stereocenter of the spiropyrrolidine ring in a single step. The requisite *Z* and *E* trienes for this key PCC, **111a** and **111b**, respectively, were synthesized via amidation and Horner–Wadsworth–Emmons olefination of aldehydes derived from **112a** and **112b**.



Scheme 22 Additional studies toward the total synthesis of (–)-spirotryprostatin B.

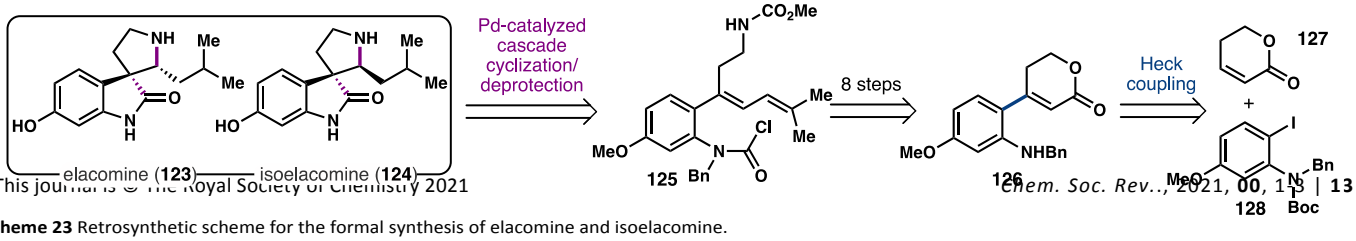
Unfortunately, upon exposure of cyclization precursor **111a** to $Pd_2(dba)_3$ and either (*R*) or (*S*)-BINAP, only SEM protected (–)-18-*epi*-spirotryprostatin B (**117**) and (–)-3-*epi*-spirotryprostatin B (**118**) were obtained, along with byproducts **119** and **120** resulting from elimination of palladium hydride from the π-allylpalladium intermediate (Scheme 21b).

Based on the stereochemical implications of their first attempt, the authors prepared the (2*E*)-2,4-hexadienamide precursor **111b**, expecting it to yield SEM-protected (–)-spirotryprostatin B. Frustratingly, **111b** isomerized under the reaction conditions to the more stable (2*Z*) cyclization precursor, yielding products **117** and **118** as before (Scheme 22a). To complete their synthesis, the authors performed the cascade cyclization with an achiral Pd catalyst, allowing the reaction to occur at lower temperature and thereby preventing isomerization. A 1:1 mixture of SEM protected (–)-spirotryprostatin B (**121**) and (–)-3,18-*epi*-spirotryprostatin B (**122**) was obtained in 72% yield (Scheme 22b).

Although the asymmetric variant of this cascade cyclization failed to produce the desired epimer, the synthetic efficiency of this strategy should not be overlooked. This palladium-catalyzed cascade installed two of the five rings of the natural product and established the correct relative configuration of stereocenters C3 and C18 in a single synthetic operation, allowing the authors to access (–)-spirotryprostatin B in just 11 steps from a known compound.

Formal synthesis of elacomine and isoelacomine

Following Overman's application of the carbopalladation/π-allyl capture cascade to the synthesis of (–)-spirotryprostatin B, Takemoto and coworkers applied a related strategy for the synthesis of elacomine (**123**), a hemiterpene spirooxindole alkaloid (Scheme 23).[41] Although elacomine itself does not exhibit biological activity, the spiro(pyrrolidine-3,3'-oxindole) scaffold is a common motif in medicinally relevant natural products. The application of the carbopalladation/π-allyl capture cascade was inspired by their previously established cycloamidation of carbamoyl chlorides with dienes. Compound **125** was identified as the requisite PCC precursor to the natural product, and it was prepared from Heck coupling product **126** in eight steps, including reductive lactone opening, Wittig olefination, and amide installation.

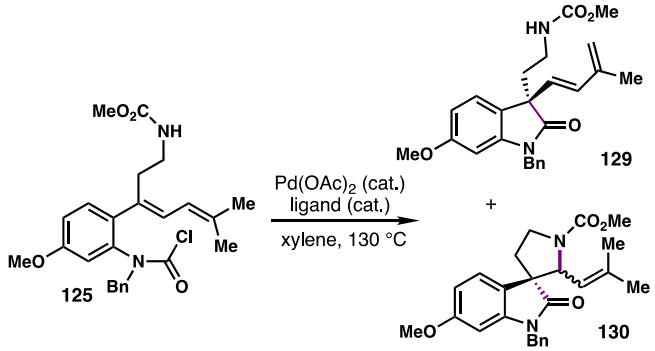


Scheme 23 Retrosynthetic scheme for the formal synthesis of elacomine and isoelacomine.

Surprisingly, subjection of carbamoyl chloride **125** to the conditions previously optimized for domino cyclization did not result in the expected cascade product (entry 1, Table 3). Instead, **129** was isolated, the product of β-hydride elimination from the π-allylpalladium intermediate. When Bu_4NI was used as an additive, desired PCC product **130** could be isolated, albeit in low yield (entry 2). Changing the ligand to DPPF did not improve the yield of **130** (entry 3), but byproduct **129** was not observed in the absence of Cs_2CO_3 (entry 4), inspiring a screen of acidic conditions. In the presence of catalytic $Bi(OTf)_3$, cyclization product **130** was obtained in 52% yield but with poor dr (entry 7), presumably the result of a palladium-catalyzed Heck/bismuth-catalyzed hydroamination cascade. Although the authors propose this transformation proceeds via a carbopalladation/π-allyl capture cascade in the absence of Bi, one cannot rule out a palladium-catalyzed Heck/hydroamination cascade as the operative mechanism.

Ultimately, the Heck reaction and hydroamination were performed separately to improve the yield and dr of spirooxindole **130** formation. When elimination product **129** was subjected to catalytic $Bi(OTf)_3$ and KPF_6, the hydroamination product (**130**) was obtained in 83% yield and 3:1 dr (Scheme 24). The diastereomeric reaction products were separately converted to elacomine and isoelacomine in just two steps. Despite its practical challenges, the late-stage PCC greatly simplified the synthetic strategy for the total synthesis of elacomine and isoelacomine.

Table 3 Optimization of carbopalladation/π-allyl capture strategy.

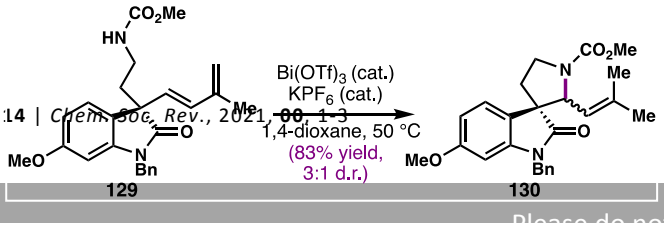


entry	ligand	additives	% **130** (dr)	% **129**
1	PPh_3	Cs_2CO_3	0	86
2	PPh_3	Cs_2CO_3, Bu_4NI	11 (1:1)	28
3	DPPF	Cs_2CO_3	0	84
4	DPPF	–	37 (1:1)	0
5	DPPF	TfOH	17 (1:1)	0
6	DPPF	$Hf(OTf)_4$	33 (5:4)	0
7	DPPF	$Bi(OTf)_3$ *	52 (5:4)	0

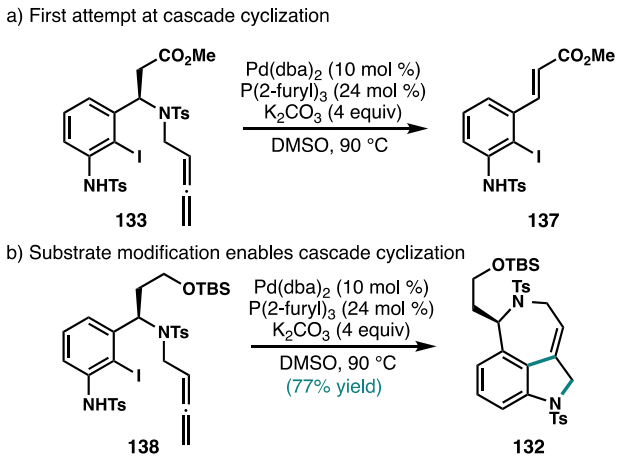
*$Pd(TFA)_2$ was used instead of $Pd(OAc)_2$

Enantioselective formal synthesis of (–)-aurantioclavine

Nemoto and coworkers were the first to apply the carbopalladation/π-allyl capture PCC to the construction of 3,4-fused tricyclic indoles.[42] This skeleton is ubiquitous in bioactive natural products, including the clavine alkaloids, communesins, and lysergic acid derivatives.[23,43,44] To illustrate proof of concept, the group initially applied the cascade to synthesize the core of dragamacidin E.[45] Soon after, the group published an enantioselective formal synthesis of the ergot alkaloid (–)-aurantioclavine (**131**) realizing their first completed synthesis involving the cascade (Scheme 25).[46] Their key retrosynthetic disconnections included a palladium-catalyzed carbopalladation/π-allyl capture cascade to establish the 3,4-fused tricyclic indole scaffold and an organocatalytic asymmetric aziridination to establish the absolute configuration of the single stereogenic center in the natural product.

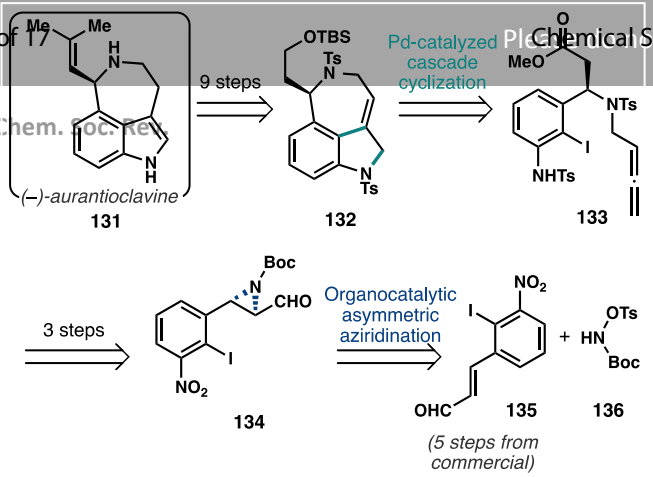


Scheme 24 Bi-catalyzed hydroamination.



Scheme 26 Optimization of carbopalladation/π-allyl capture cascade.

Their first attempt at PCC with substrate **133** unfortunately failed to yield the desired product; instead, compound **137** was isolated due to elimination of the tosylamido moiety (Scheme 26a). In order to circumvent this undesired reactivity, the authors reduced the methyl ester to obtain TBS ether **138**, hypothesizing that the lack of an acidic proton in this substrate would prevent tosylamido elimination. Subjecting **138** to their established reaction conditions provided the desired product (**132**) in good yield (Scheme 26b). Elaboration of **132** to a known intermediate enabled the completion of their 22-step formal synthesis.

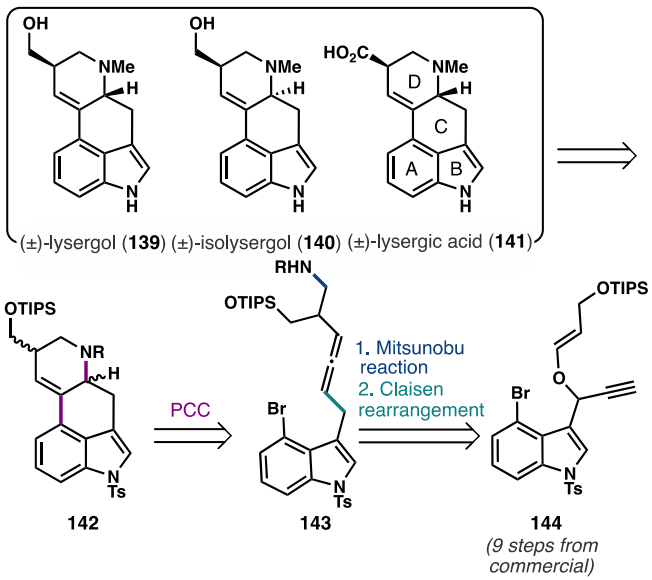


Scheme 25 Retrosynthetic plan for the formal synthesis of (–)-aurantioclavine.

Although mechanistically distinct, this cascade can be strategically similar to the intramolecular Larock heteroannulation cascade, with the allene acting as an alkyne surrogate. Because the carbopalladation/π-allyl capture cascade tolerates terminal allenes, this method may be more useful for the synthesis of indoles lacking substitution at the 2-position, whereas the Larock heteroannulation cascade is best suited to indoles with functionality at the 2-position.

Total synthesis of (±)-lysergic acid, (±)-lysergol, and (±)-isolysergol

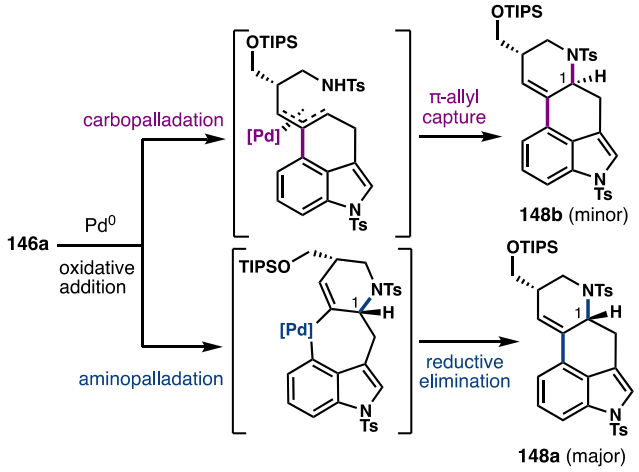
Ergot alkaloids have a rich history as targets for total synthesis, inspiring elegant strategies for the construction of the 3,4-fused tetracyclic indole core. Ohno and coworkers' divergent total synthesis of (±)-lysergic acid (**141**), (±)-lysergol (**139**), and (±)-isolysergol (**140**) via carbopalladation/π-allyl capture cascade constitutes a primary example (Scheme 27).[47]



Scheme 27 Retrosynthetic plan for the total synthesis of lysergic acid and analogues.

The authors aimed to install both the C and D rings of the target alkaloids concurrently through the application of the aforementioned PCC. The allenic amide cyclization substrate **143** would be prepared in a 13-step sequence utilizing a Claisen rearrangement to install the allene and a Mitsunobu reaction to furnish the sulfonamide. The authors encountered their first major challenge when they obtained cyclization substrates **145** and **146** as a mixture of inseparable diastereomers. Therefore, they subjected a 4:1 ratio of diastereomers to a screen of Pd sources, ligands, bases, and solvents (Table 4). Although the diastereoselectivity of the reaction could not be improved without a reduction in yield, it was found that the tosylamide substrates **146a** and **146b** provided slightly higher dr than the nosylamides **145a** and **145b** (entries 1 and 4). HPLC separation of nosylamide substrates **145a** and **145b** showed that dr improved slightly when a diasteromerically pure substrate was used (entries 2 and 3).

In a demonstration of perseverance, the authors utilized the lack of diastereoselectivity to their advantage. Nosyl deprotection and *N*-methylation of **147a** and **147b** yielded a separable mixture of diastereomers from which (±)-isolysergol and (±)-lysergol were derived. Similarly, alcohol deprotection of **148b** and conversion to the methyl ester gave a separable mixture of diastereomers, the major of which was advanced to (±)-lysergic acid.

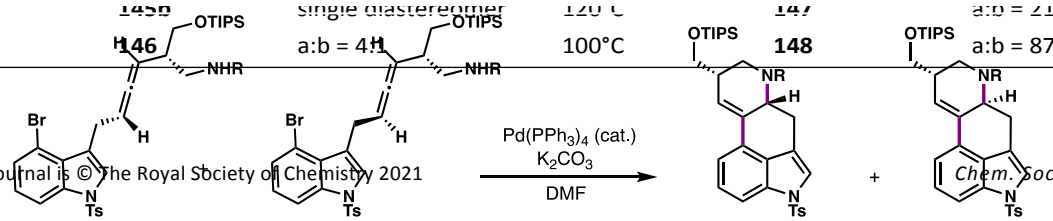


Scheme 28 Proposed mechanistic pathways leading to major and minor diasteromers.

The authors proposed that the major cyclization product (**148a**) could arise from a pathway involving oxidative addition, aminopalladation, and reductive elimination (Scheme 28). This mechanistic pathway is reminiscent of palladium-catalyzed carboamination reactions developed by the Wolfe group.[48–50]. The minor diastereomer was proposed to arise from a carbopalladation/π-allyl capture pathway that involved *anti* capture of the π-allyl Pd intermediate by nitrogen

entry	substrate	substrate d.r.	temperature	product	product d.r.	yield (%)
3	**145b**	single diastereomer	120 °C	**147**	a:b = 21:79	67
4	**146**	a:b = 4:1	100°C	**148**	a:b = 87:13	65

Table 4 Optimization of the key carbopalladation/π-allyl capture cascade



145a: R = Ns **146a:** R = Ts **145b:** R = Ns **146b:** R = Ts **147a:** R = Ns **148a:** R = Ts **147b:** R = Ns **148b:** R = Ts

Conclusions

We have highlighted a number of natural product syntheses that utilize palladium-catalyzed cascade cyclizations, focusing on cascades that close multiple rings and form both C–X (X = O,N) and C–C bonds in a single synthetic step. Three key strategic approaches have emerged in our analysis. First, a PCC can be employed early in the synthesis to rapidly build complexity and establish the core structure of the natural product. This approach is exemplified in the synthesis of (–)-kumausallene (**15**), in which a gram-scale Semmelhack reaction is the fourth step. Second, a PCC can be used at a late stage to construct the final few rings of a natural product. This strategy requires particularly robust and functional group-tolerant cascades. Notable examples highlighted in this review include the syntheses of (±)-schindilactone A (**3**), (–)-spinosyn A (**34**), and (+)-halenaquinone/halenaquinol (**88** and **89**). Third, a PCC can support a convergent synthetic strategy. In this case, an initial fragment coupling step joins two fragments of similar size and complexity. The PCC is then used to forge additional rings between these fragments, tailoring the natural product scaffold. This strategy was employed in the syntheses of (+)-perseanol (**2**) and (–)-spirotryprostatin B (**110**).

Despite the success of PCCs in natural product synthesis, there are some areas which invite further development. Some of the syntheses required lengthy functional group interconversion sequences following the key PCC. This may be avoidable in some cases with improved route design; however, it could also indicate a lack of functional group tolerance in the PCC itself. Another interesting extension of the current technology would be the development and application of intermolecular PCCs. Such a cascade could be applied toward a convergent total synthesis, in which the PCC would encompass both the fragment coupling and the scaffold tailoring steps. Finally, expansion of the scope of ring systems accessible via PCCs could enable their use toward a broader variety of natural products. Cyclization to form medium, large, or otherwise strained rings, carbonylative lactamization or thioesterification, and incorporation of heterocyclic sp^2 coupling partners would be particularly valuable. Overall, palladium-catalyzed cascades have been used effectively in the total synthesis of a multitude of natural products. We anticipate that these reactions will continue to be successfully leveraged in natural product synthesis due to their power, breadth, and versatility.

Conflicts of interest

There are no conflicts to declare.

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