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Insights

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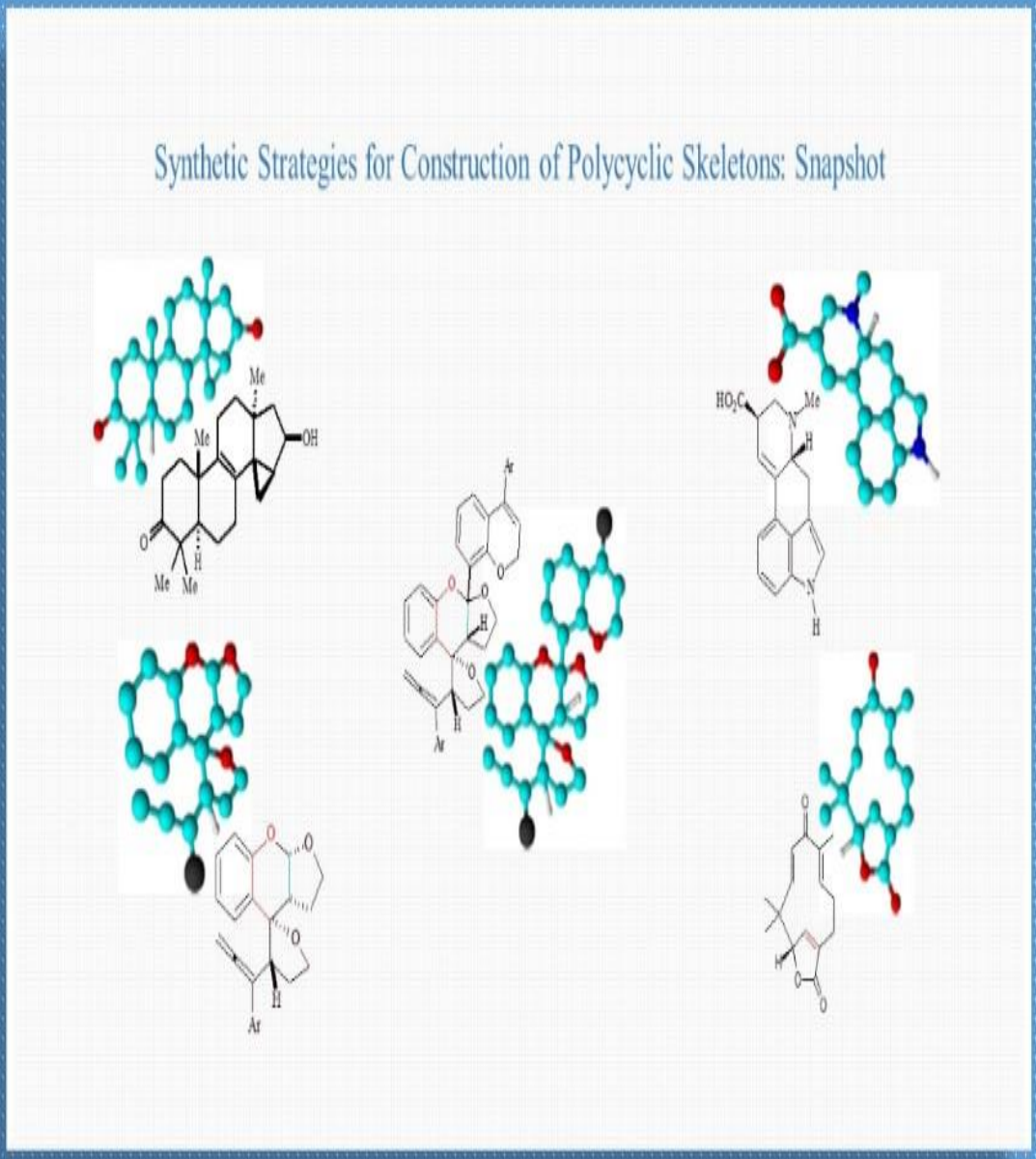

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Synthetic Strategies for Construction of Polycyclic Skeletons: Snapshot

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Natural products are a wealthy source of therapeutics, that their total synthesis has, to a large degree, been dependent on the ability to construct their molecular architectures, which are typically quite challenging. Certainly, in the past couple decades, transition-metal-catalyzed their construction has played a key role in the development of the chemical synthesis, and has become an indispensable tool in this field. Various synthetic strategies have been developed, and have the ability to forge their molecular complexity from relative simple building blocks. This snapshot provides illustrative examples of the total synthesis of a number of natural products, that features one or more of metal-catalyzed multi-ring-forming reactions. The aim of this snapshot is to describe some impressive tactics, as well as to inspire future development and new applications.

KEYWORDS: Cascade reactions, Deconstructive synthesis, Total synthesis, TM Catalysis, Polycycles.

1. Introduction

Natural products, especially alkaloids and terpenoids, are an important source of pharmaceutical agents, because they have a large spectrum of biological activities.[1-3] These compounds possess polycyclic frameworks embedded in complex structures. Typically, the architecture of these compounds requires access to various processes in chemical synthesis to construct carbon frameworks through carbon-carbon or carbon-heteroatom bond-forming reactions that overcome many challenges, such as difficult ring-forming with "anti-Bredt" backbones. In addition, the development of highly efficient atom- and step-economic process is an important element in total synthesis. Remarkable progress has been made in this field and in all its various guises has arguably enriched the landscape of synthetic organic chemistry. Herein, a number of total syntheses is highlighted, that features one or more of transition-metal-catalyzed multi-ring-forming reactions. The present snapshot does not intend to be a comprehensive review of the subject, but rather aims to provide

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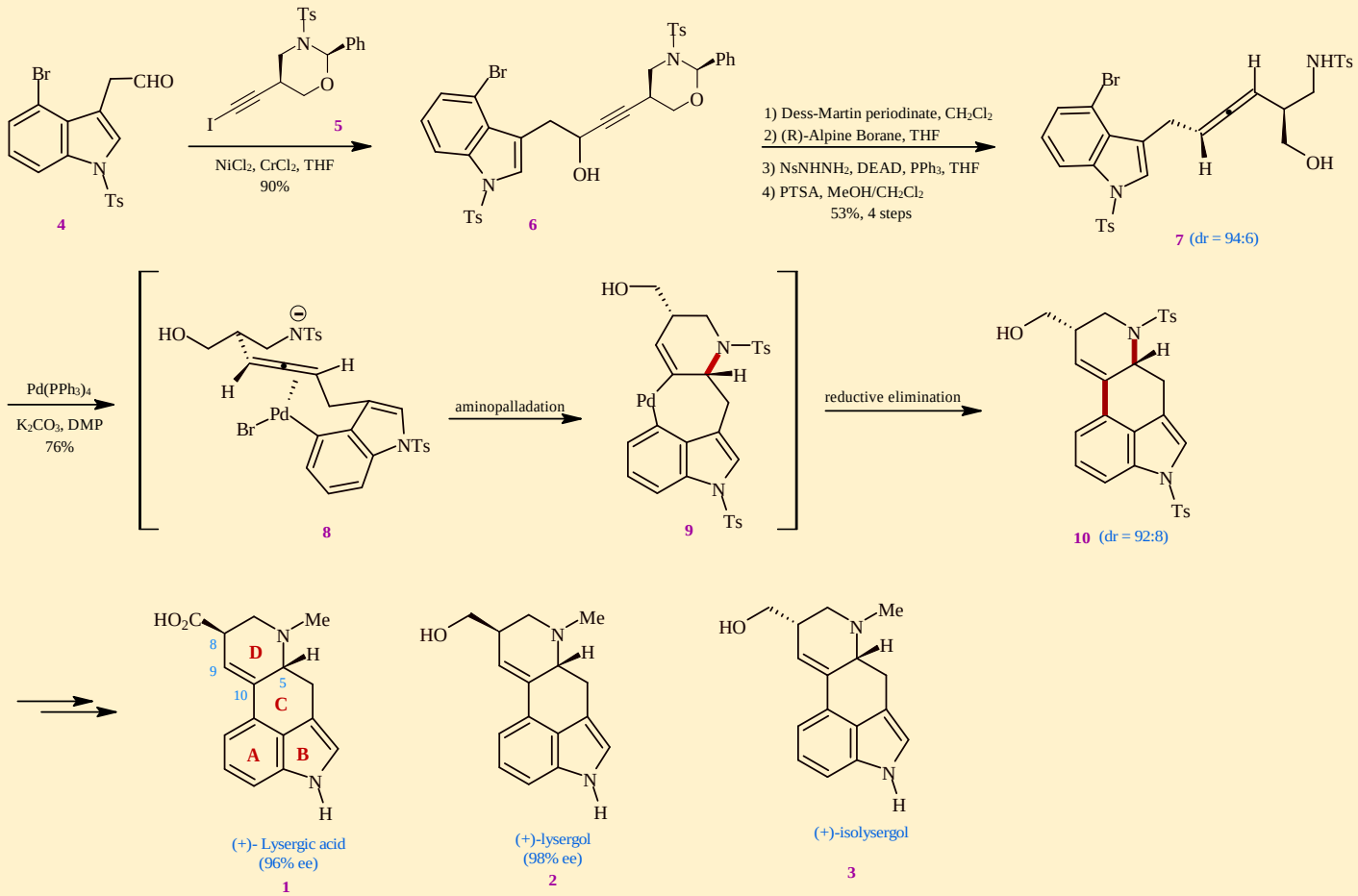
illustrative examples of some impressive tactics, as well as to inspire future development and new applications. I hope to underscore the power of these approaches in chemical syntheses.

2. Cascade reactions

Cascade (domino) reactions are among the most efficient and powerful tools for the formation of several new bonds sequentially in a single process with a rapid increase in the molecular complexity as a result of their intramolecular nature, but also display high atom economy and synthetic elegancy.[4]
The use of transition-metal-catalyzed cascade polycyclization is an extraordinary technique, which promotes a variety of different processes, such as insertion, nucleophilic substitution, and direct arylation/C-H bond functionalization, due to high functional group tolerance, and orthogonality to other reaction manifolds. In addition, metal-catalyzed reactions have the ability to architect a wide variety of complex structure *via* highly selective mechanistic pathways as a result of the preorganization of the reactive intermediates around the metallic center.

Palladium-catalyzed cascade reactions have probably affected the landscape of synthetic chemistry due to their highly atom-economical (that is, the increase in molecular complexity in a single operation, while in most cases no by-product is released during the process). Smart use of these zipper-mode cascade reactions in a complex setting was made by Ohno and co-workers in their total synthesis of Ergot skeleton **1**-**3** (Scheme 1).[5,6] The significance of this indole alkaloid is due to partly to its biological activity, but also to its rather remarkable [*cd*]-fused indole skeleton containing the $\Delta^{9,10}$ double bond and the chiral centers at the C5 and C8 positions. The key cyclization precursor of these tetracyclic natural products is the amino allene derivative **7**, which was prepared by the Nozaki-Hiyama-Kishi (NHK) reaction of indole-3-acetaldehyde **4** with the L-serine-derived iodoalkyne **5** to give **6**, followed by building the axially chiral allene **7** *via* an Alpine-Borane-mediated reduction and Myers allene formation. The palladium(0)-catalyzed cascade cyclization of **7** allowed the direct construction of the C/D ring system of the ergot alkaloid skeleton as well as the creation of the C5 stereogenic center to provide the tetracyclic indole **10** with transfer of the allenic axial chirality to the central skeleton. The impressive results obtained with **7** exhibit the preferred cyclization mode through aminopalladation rather than carbopalladation, in which the aminopalladation of the indolyl-palladium halide, that formed by the oxidative addition of **7** to palladium(0), proceeded *via* conformation **8**. Stereoselective aminopalladation yielded **9**, followed by reductive elimination led to **10**, which was recognized as a common synthetic intermediate for the ergot alkaloids. Thus, functional group modification of **10** allowed the enantioselective total synthesis of (+)-lysergic acid **1**, (+)-lysergol **2**, and (+)-isolysergol **3**.



Scheme 1. Total synthesis of ergot alkaloids. DEAD = diethyl azodicarboxylate; PTSA = *para*-toluenesulfonic acid; Ts = toluene-sulfonyl.

There also has been a burgeoning interest in recent years in gold catalysis. The motif behind this interest is illustrative by the total synthesis of three aromadendrane natural products reported by the Echavarren group, which shows the elegant control over the strereochemical outcome of the gold-catalyzed cascade through a simple variation of reaction conditions (Scheme 2).[7,8] Consequently, reaction of dienyne **11** with catalyst **12** (neat) led, *via* carbenoid **13**, to an intramolecular transfer of the benzyloxy group to provide carbenoid **14** (path a), and then tricycle **15**, a precursor to (-)-4β,7α-aromadendranediol and (-)-epiglobulol. Alternatively, equivalent reaction in the presence of an excess of allyl alcohol resulted in intermolecular ring-opening of **13** to the epimeric carbenoid **16**/tricycle **17** (path b), a pathway to (-)-4α,7α-aromadendranediol.

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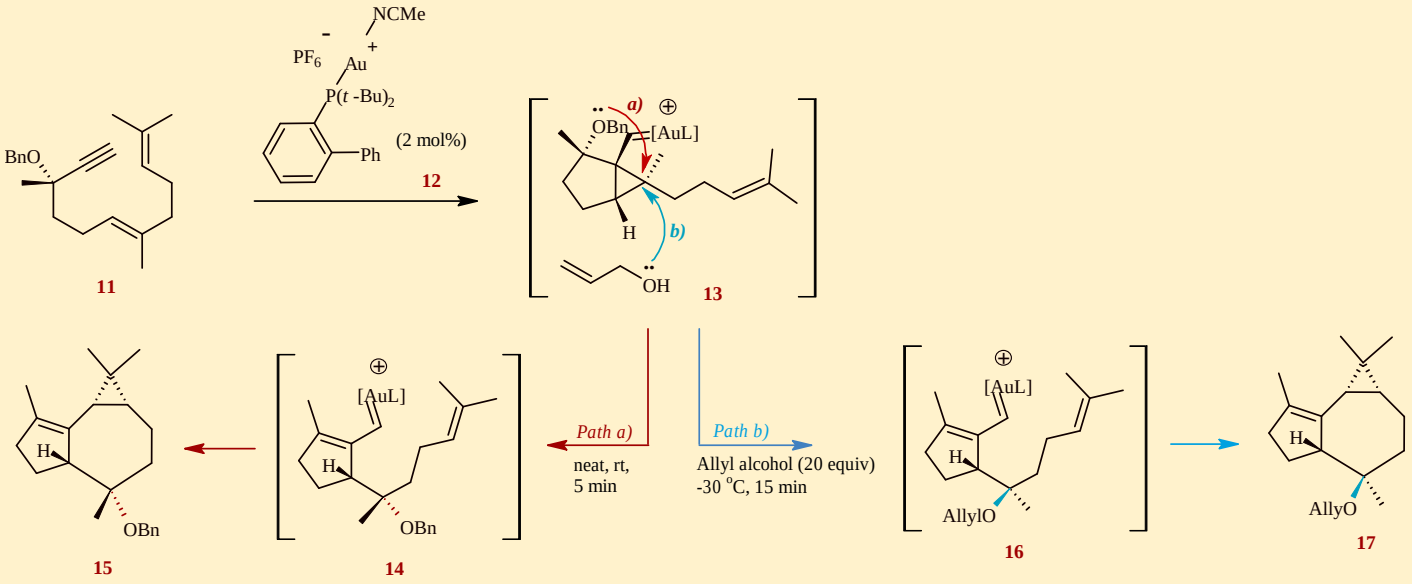
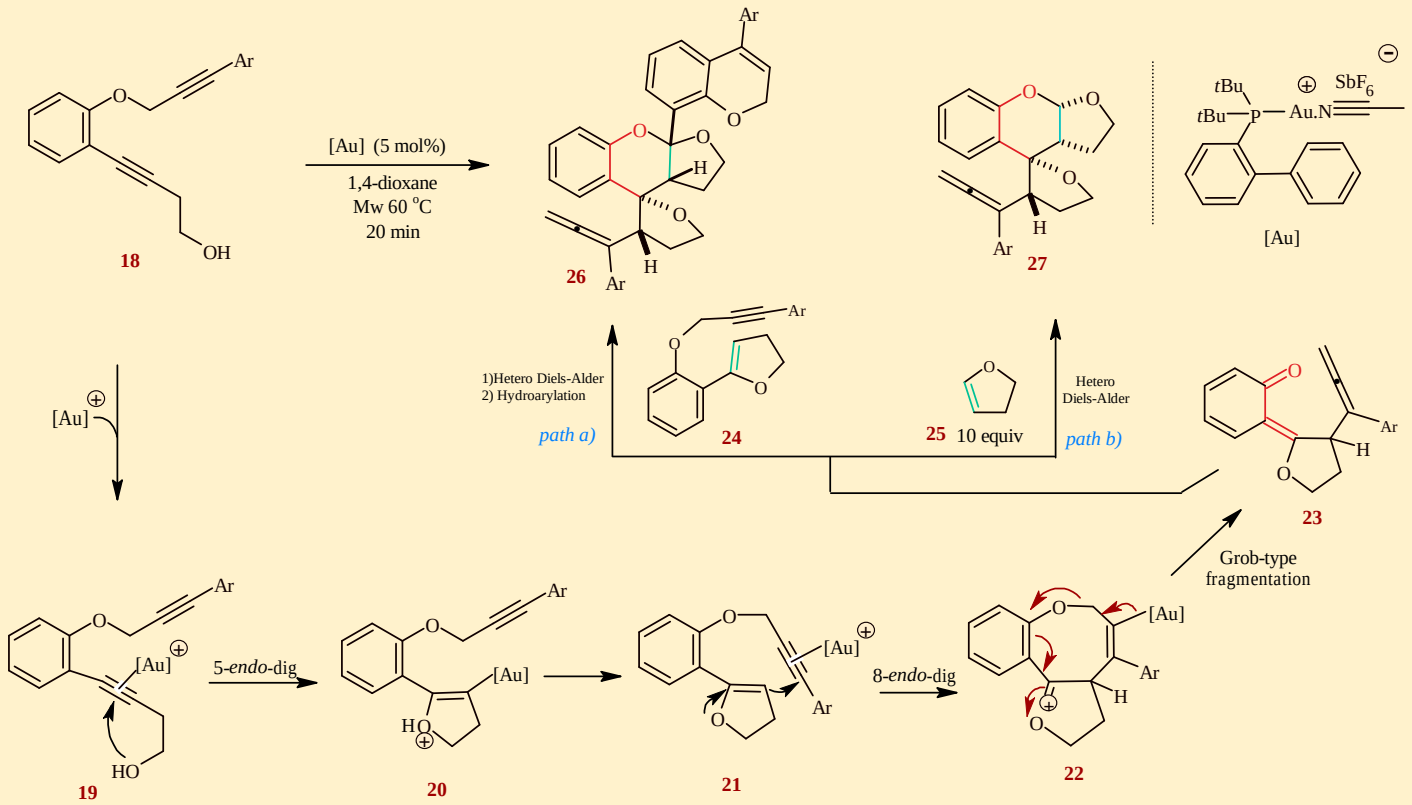


Scheme 2. Nucleophile-tuned approach to three aromadendrane natural products.

Another impressive gold-catalyzed cascade reaction has been reported by the Blond group, in which the synthesis of polycyclic molecules comprising furopyran cores bearing fused bicyclic *O,O*-acetals is achieved. [9] In fact, these heterocyclic motifs are present in a wide range of biological active products. The key step of this cascade reaction is the hetero Diels-Alder reaction, in which the gold(I)-triggered the reaction to construct such scaffolds behaves through concomitantly generating *in situ* the diene and the dienophile (Scheme 3). Thus, the sequence starts with two regioselective cyclization: a 5-*eno*-dig and a 8-*endo*-dig cyclization to provide the 8-membered ring **22**, followed by the Grob-type fragmentation to produce the diene intermediate **23**. The formation of both the intermediate diene **23** and the dienophile **24** are concomitantly produced through the hetero Diels-Alder reaction (path a), in which the dienophile **24** comes from the protodeauration of intermediary **20**. Finally, the gold-catalyzed hydroarylation forges *4H*-furo[2,3-*b*]pyrans **26** in good yield. Alternatively, equivalent reaction in the presence of an excess of the dienophile dihydrofuran **25** results in the formation of new *4H*-furo[2,3-*b*]pyrans **27**, with 28-80% yield (path b).[10]



Scheme 3. Gold(I)-catalyzed cascade reaction.

A divergent approach to the daunting asymmetric synthesis of 11-membered ring core and bridged butenolide moietes of the remarkable anticancer targets “humulanolide natural products” has been reported by the Li group, in which a ruthenium-catalyzed metathesis cascade has been employed.[8,11] For instance, the brilliant strategy adapted by the Li group harnesses the ring strain of a cyclobutene to control formation of these two rings in (-)-asteriscunolide D **28** (Scheme 4). Two possible mechanisms are shown, with the catalyst having a choice of initiation sites at the unhindered terminal alkene in **29**, or the strain (but electron-deficient) cyclobutene. The authors proposed the former route, with a subsequent strain release-driven ring-opening metathesis (ROM) reaction of the cyclobutene **30** resulting in the butenolide unit **31**, with the ruthenium carbenoid transferred to the ring-opening side chain. Subsequently, this undergoes RCM with the 1,1-disubstituted alkene, yielding (-)-asteriscunolide D in moderate yield. Alternatively, initial reaction *via* cyclobutene ring opening **32**, and metathesis with the terminal alkene, could give intermediate **33** prior to a

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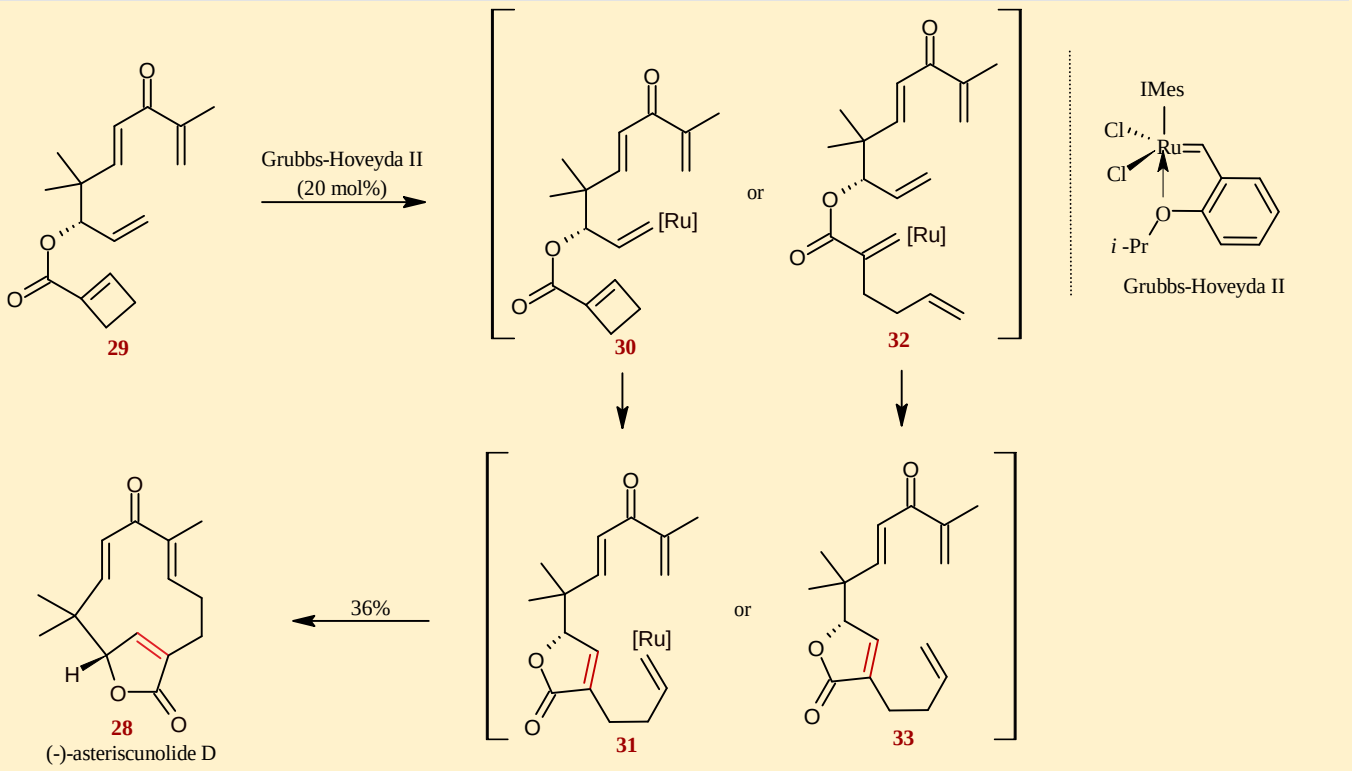
separate ring-closing macrocyclization. Both strategies pave the path for transformation of asteriscunolide D into several other natural products.



Scheme 4. Metathesis cascades in the synthesis of (-)-asteriscunolide D.

3. Deconstructive functionalization of ketones strategy "*Cut-and-Sew*"

Deconstructive of cyclic molecules employing transition-metal (TM)-catalyzed carbon-carbon activation has emerged as an excellent strategy for scaffold hoping modifications of such molecules. This strategy mainly involves cyclic ketones with a tethered unsaturated moiety as substrates, in which the oxidative addition of a TM into the ketone C-C bond (the "cut" step) affords a reactive metallacycle intermediate, followed by intra-molecular migratory insertion of the unsaturated unit and reductive elimination to forge the ring (the "sew" step). This strategy allows the construction of diverse bridged and fused ring scaffolds through changing the ring sizes of the cyclic ketones, the length of the linkers, and different unsaturated coupling partners.

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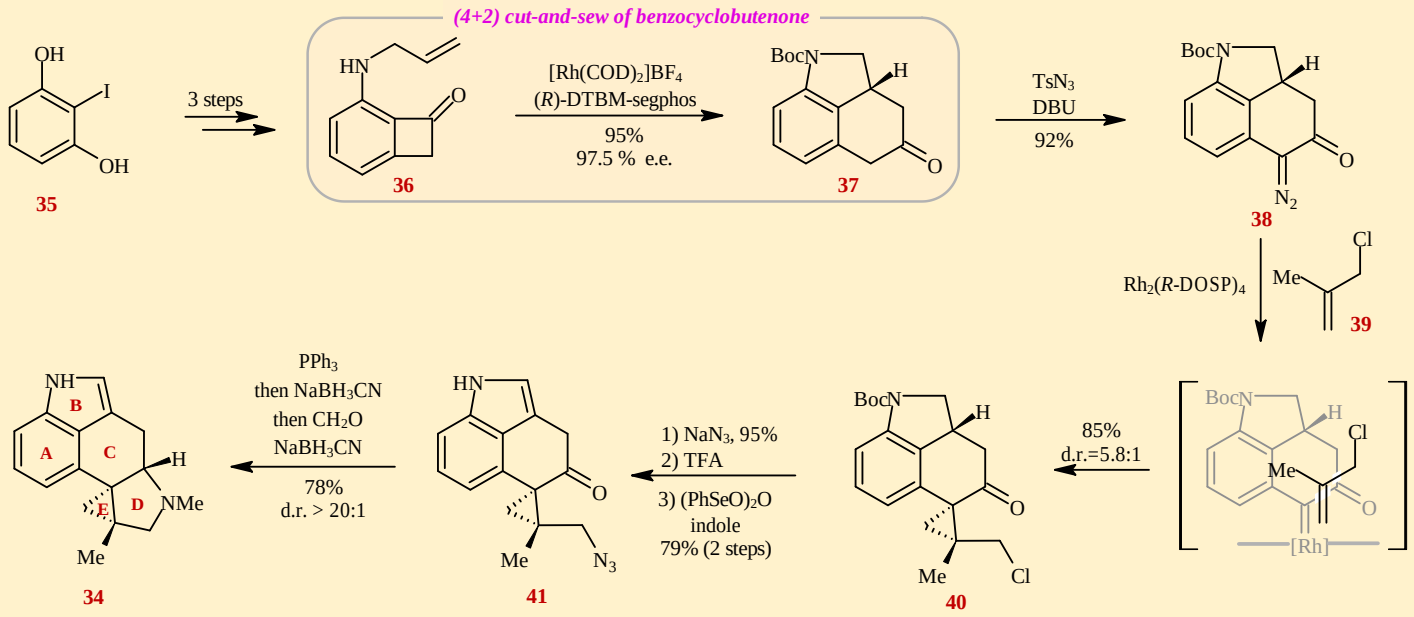
As an illustrative example, the asymmetric total synthesis of (-)-cyclocalvine **34** is a member of the ergot alkaloid family, which processes a penta-cyclic core with a unique [3.1.0] structural motif. The structure contains a sterically congested cyclopropane ring and three contiguous chiral centers including two adjacent quaternary carbons. In an insightful piece of retrosynthetic analysis, the Dong group proposed that the 6-6-5 fused A/B/C core skeleton could arise from the benzocyclobutenone **36** though the cut-and-sew strategy, which **36** can be formed from commercially available diphenol **35** *via* [2+2] cycloaddition (Scheme 5).[12,13] Whereas, the cyclopropane ring (E) can be formed through rhodium-catalyzed cyclopropanation. Indeed, a combination of cationic rhodium $[Rh(COD)_2]BF_4$ and DTBM-segphos was efficient, giving the desired ketone **37** in 95% yield and 97.5 % e.e. Subsequent the cut-and-sew step, the diazo-transfer followed by a Rh-catalyzed diastereoselective cyclopropanation of 2-methylallyl chloride **39** delivered the desired cyclo-propane product **40** with good diastereoselectivity. The indole **41** was obtained by the S_N2-substitution with azide, Boc deprotection and indoline oxidation. Finally, a one-pot aza-Wittig/reduction/reductive amination furnished (-)cyclocalvine **34** in 78% yield and > 20:1 diastereoselectivity.



Scheme 5. Enantioselective total synthesis of (−)-cyclocalvine.

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4. Miscellaneous approaches

4.1. Synthetic strategy for tetracyclic terpenoids

Tetracyclic terpenoids are a rich source of bioactive compounds, that leads to drug discovery and development across a diverse therapeutic landscape. In this context, a unified asymmetric access to tetracyclic systems **42** related to the large and diverse class tetracyclic terpenoids has been reported by the Gaur and Micalizio group, which have been shown to be capable of accessing the euphane system; delivering potent agonists of the estrogen receptor beta (ERβ), and selective anticancer properties against glioblastoma (Scheme 6).[14]

Thus, the formation of the precursor hydrindane **48** is achieved by alkoxide-directed metallacycle-mediated annulative cross-coupling of the enyne **46**, which is realized from the coupling epoxide **44** to alkyne **45**. This path enables and controls the regio- and stereochemical course of the metallacycle-mediated annulation reaction. Then, the double-asymmetric Brønsted acid-promoted cyclization process allows the conversion of **48** to the tetracycle **49** (78% yield; ds ≥ 25:1), followed by demethylation and oxidative rearrangement affords the tetraene **50** as a single isomer. The authors proposed that it would be prudent to establish the stereochemical relationship between C14 and C16 before the installation of the additional quaternary center at C14, and that the latter task could be accomplished though hydroxyl-directed Simmons-Smith cyclopropanation. Indeed, this tactic proved to be highly effective in realizing the *trans*-fused hydrindane system affording adjacent quaternary centers at C13 and C14. Subsequent treatment with $Co_2(CO)_8$ and H_2O affords site-selective A-ring enone reduction, and provides the stereodefined intermediate **51** in 69% yield. Finally, a one-pot Birch reduction and alkylation provides the full functionalized and differentiated product **42** in 52% yield as a single stereoisomer.

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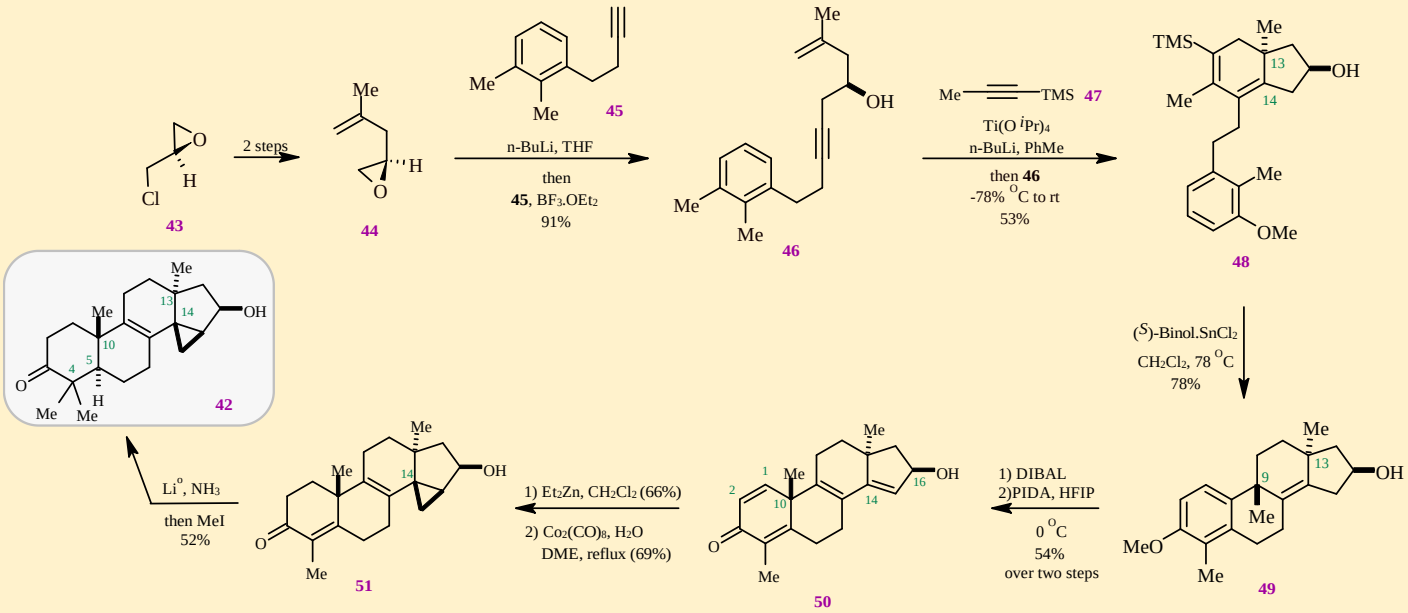


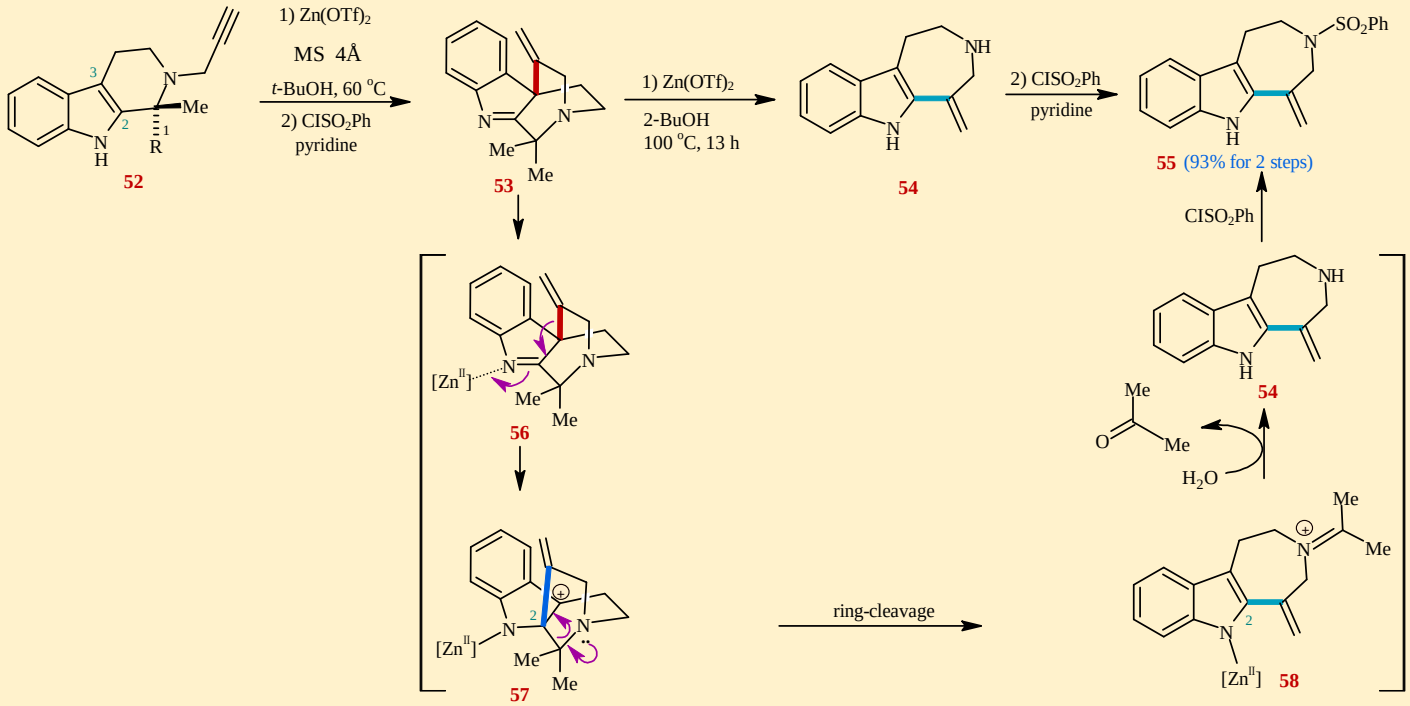
Scheme 6. An asymmetric synthesis of tetracyclic terpenoid skeletons from epichlorohydrin.

4.2. Zn(II)-mediated hydroarylations

The hydroarylation of alkynes with transition metal mediators serving as "π-acids" is an efficient tool for carbon-carbon or carbon-heteroatom bond-forming reactions. Unlike the use of expensive or toxic transition metals, zinc-mediated intramolecular hydroarylation of alkyne reactions has distinct catalytic abilities and could provide sustainable and environment benign reactions.

Smart use of a unique combination of $Zn(OTf)_2$ with *t*-BuOH mediated divergent cyclization of *N*-propargylated tetrahydrocarbolines **52** under neutral condition was made by the Maeda and Oguro team in their programmable divergent synthesis of indole alkaloidal scaffolds.[15] The intriguing solvent effects of *t*-BuOH as a proton donor facilitate protodezincation of alkenyl zinc species without the addition of Brønsted acid promoters. $Zn(OTf)_2$-mediated annulation of substrate **52** bearing a terminal alkyne group proceeded *via* kinetic formation of the spiroindole **53** involving a quaternary center (*i.e. via* 6-*exo* dearomatizing spirocyclization (Scheme 7). Moreover, treatment of **53** with $Zn(OTf)_2$ under thermodynamic conditions leads to cascade reactions through migration of the alkenyl group from the C3 to the C2 position to generate a tertiary cation at the benzylic C3 position **57** and concomitant retro-Mannich-type fragmentation of the tertiary cation **57** would entail ring-cleavage and formation of iminium cation intermediate **58** and regeneration of the indole system. Hydrolysis of the resulting iminium cation **58** would liberate secondary amine to furnish

azeppino[4,5-*b*]indole **54** framework and acetone, followed by sulfonylation of **54** to provide **55.** The study has revealed that substituents on substrate **52** in the vicinity of the reaction sites greatly influence the mode of the divergent annulations. Thus, rational choices of the substituents, solvent and reaction conditions could allow programmable divergent synthesis of such skeletons.



Scheme 7. $Zn(OTf)_2$-mediated intramolecular hydroarylation of *N*-propargylated tetrahydrocarbolines.

5. Conclusions

The rich and diverse paradigm of natural products has served as a motivation for the molecular architecture and achievement of a new chemical synthesis capable of designing pivotal motifs for cyclic backbones. Among the many elegant strategies, metal-catalyzed reactions provide an extremely powerful means to engineer cascade processes realizing high functional tolerance, orthogonality to other reaction variations, and the ability to construct complex structures *via* highly selective mechanistic routes, as well as synonymous

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with high atom economy. Moreover, deconstructive strategy based on metal-catalyzed C-C bond activation of cyclic ketones has the capability to access diverse bridged- and fused ring-scaffolds, which are nontrivial to construct otherwise. Clearly, these brilliant strategies result in the ongoing development of versatile synthetic methodologies for the flexible and greener synthesis of skeletally diverse and densely-functionalized polycyclic molecules to address challenges in natural product synthesis, and to render unique opportuneities for medicinal exploration.

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