Title: Recent Progress in Steroid Synthesis Triggered by the Emergence of New Catalytic Methods

Authors: Hem Raj Khatri, Ph.D.; Nolan Carney; Ryan Rutkoski; Bijay Bhattarai; Pavel Nagorny

To be cited as: 10.1002/ejoc.201901466

Link to VoR: https://doi.org/10.1002/ejoc.201901466

Recent Progress in Steroid Synthesis Triggered by the Emergence of New Catalytic Methods

Hem Raj Khatri, Nolan Carney, Ryan Rutkoski, Bijay Bhattarai and Pavel Nagorny*[a]

Abstract: The rich biology associated with steroids dictates a growing demand for the new synthetic strategies that would improve the access to natural and unnatural representatives of this family. The recent advances in the field of catalysis have greatly impacted the field of natural product synthesis including the synthesis of steroids. This article provides a short overview of the recent progress in the synthesis of steroids that was enabled by the advances in catalysis.

1. Introduction

Due to the fact that steroidal hormones are of great importance for the regulation of a wide range of cellular functions in eukaryotic organisms, and humans in particular, this large and diverse family of natural products has played a central role in the fields of medicine and drug discovery.[1] Historically, chemists have played an important role in both helping to understand the vital biological processes regulated by steroids as well as in developing steroid-based medicines for the treatment of diseases or improvement of the quality of human life. Needless to say, these advances would not be possible without breakthroughs in synthetic chemistry and catalysis, including transition metal mediated catalysis, asymmetric catalysis and organocatalysis. Synthesis of steroids requires addressing many challenges including the installation of all-carbon quaternary stereocenters,[2] multiple redox manipulations,[3] and assembly of polycyclic ring systems with defined stereochemistries at the ring junctions.[4] In this review, we summarize some of the recent advances in the synthesis of steroids that have been enabled by the advances in catalysis. It is primarily focused on the studies that have emerged since 2014 and have not been reviewed elsewhere,[5] and does not cover some of the important advances in closely related areas of asymmetric non-steroidal terpene natural product syntheses.[6,7]

2. Syntheses Enabled by Transition Metal Catalysis

2.1. Enantioselective Palladium-Catalyzed Dearomatizative Cyclization for the Synthesis Steroid Boldenone Core[8]

Chiral phenanthrenone derived tricyclic cores bearing all-carbon quaternary centers are present in numerous complex terpenes and steroid natural products.[9] An asymmetric intramolecular Heck reaction[10] is a conventional approach to construct these

Dr. Hem Raj Khatri has obtained his B.S. degree in chemistry from Tri-Chandra Campus in Nepal in 2002, and his M.Sc. Degree in organic chemistry from Tribhuvan University in Nepal in 2005. In 2010 he joined the group of Professor Jianlong Zhu at the University of Toledo where he worked on the synthesis of derhodinosylurdamycin A and synthetic methodology. In 2015 he completed his Ph.D. and joined the group of Pavel Nagorny at the University of Michigan as a postdoctoral fellow. His postdoctoral work has been focused on the synthesis of cardiotonic steroids ouabagenin, 19-sarmentologenin and trewianin aglycone. In 2019, he joined Astex Pharmaceuticals as a process chemist.

Nolan Carney obtained a B.S. in Chemistry and Biology from Jacksonville University, Florida in 2018. Since then he has moved to Ann Arbor, Michigan to pursue a Ph.D. in the Program of Chemical Biology at University of Michigan under the supervision of Professor Pavel Nagorny. His research interests include total synthesis of natural products and analogs with a focus on cardiotonic steroids.

Ryan Rutkoski obtained his B.S. degree in chemical engineering from Rowan University, New Jersey at 2018. Upon completion of these studies, he joined the Medicinal Chemistry Program at the University of Michigan. In 2019 he joined the Nagorny group where he currently explores the synthesis and medicinal chemistry of cardiotonic steroids and develops new methods for the glycosylation of natural products.

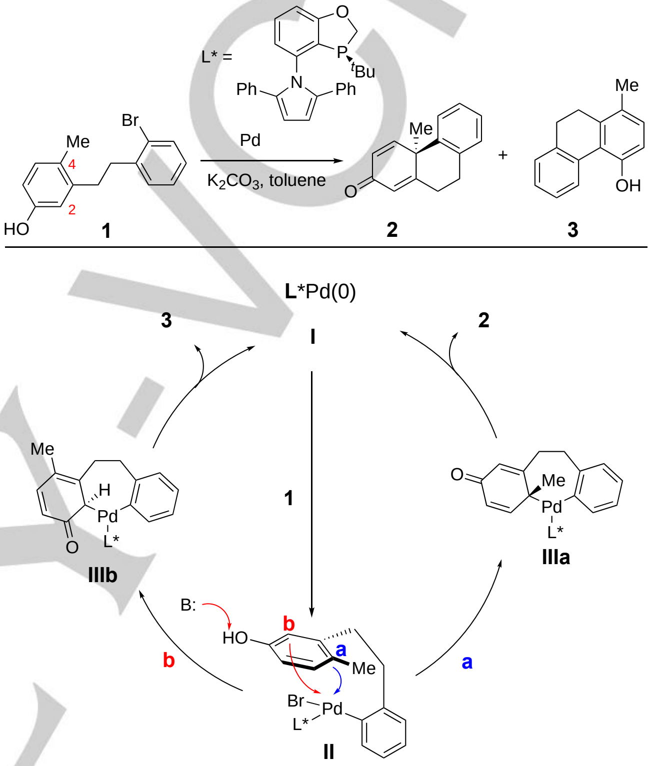
---

[a] Dr. Hem Raj Khatri, Nolan Carney, Ryan Rutkoski, Bijay Bhattarai, and Prof. Dr. Pavel Nagorny*
Chemistry Department
University of Michigan
930. N. University Ave. Ann Arbor, MI 48109
E-mail: nagorny@umich.edu
Homepage: http://umich.edu/~nagornyp/index.html

Bijay Bhattarai obtained B.S. in chemistry from Southeastern Louisiana University in 2013 where he conducted research in organic synthesis and methodology. In 2013 he joined the Nagorny group at the University of Michigan where he carried research on hydrogen bond catalysis and total synthesis of cardiotonic steroid cannogenol and its derivatives. After completing his Ph.D. in 2018, he joined Wave Life Sciences as a medicinal chemist.

Dr. Pavel Nagorny received his B.S. degree in chemistry in 2001 from the Oregon State University where he conducted research in the laboratory of Professor James. D. White. After earning his Ph.D. degree in chemistry under the mentorship of professor David A. Evans from Harvard University in 2007, he spent three years as a postdoctoral fellow with Professor Samuel J. Danishefsky at the Memorial Sloan-Kettering Cancer Center. In 2010, Pavel joined the faculty of the University of Michigan as a Robert A. Gregg Assistant Professor in Chemistry. From 2014-2017 he was appointed as a William R. Roush Assistant Professor in Chemistry, and in 2017 he was promoted to the rank of Associate Professor. Pavel's research group interests range from natural product synthesis to asymmetric catalysis, organocatalysis and carbohydrate chemistry.

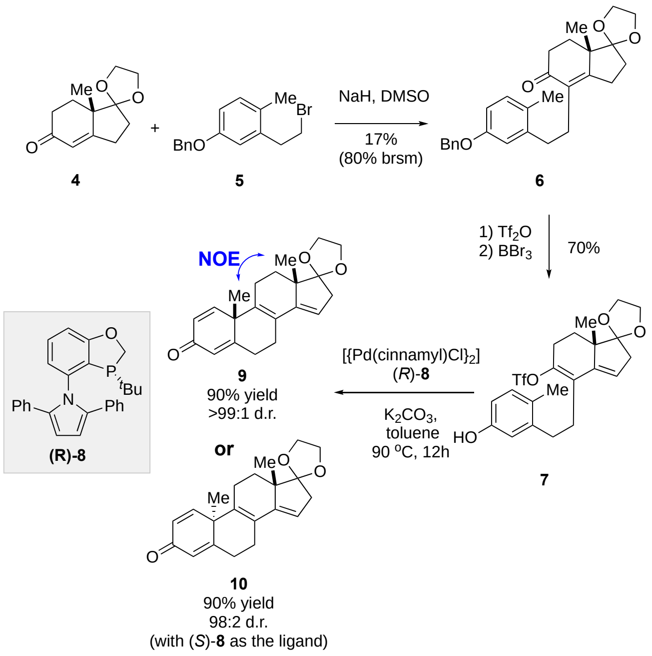
polycyclic cores bearing all-carbon quaternary centers. Alternatively, in 2015, Tang et.al.[8] reported an efficient palladium-catalyzed asymmetric intramolecular dearomatizative cyclization[11] based on the earlier studies of the Buchwald group[12] to afford various chiral phenanthrenones, some of which containing many key features of the steroidal and terpenoid frameworks (Scheme 1). They envisioned that bromoaryl-tethered phenol **1** would undergo dearomatizative cyclization in the presence of a chiral palladium catalyst to provide chiral product **2** and its achiral congener **3**. The tentative mechanism for the formation of products **2** and **3** is depicted in Scheme 1. Initially formed through the oxidative addition to aryl bromide, intermediate **II** could potentially undergo two competing pathways in the presence of a base: 1) nucleophilic attack via the C4 position of phenol leading to the formation of palladacycle **IIIa** and eventually resulting in product **2** and 2) nucleophilic attack via the C2 position of phenol providing the regioisomeric achiral product **3**. The intramolecular dearomatizative cyclization of **1** was optimized by screening various chiral palladium catalysts. The use of novel P-chiral ligand containing diphenylpyrrole substituent provided the best outcome with 94% yield and 92% ee of the desired product **2**. The substrate scope study of this useful transformation revealed that the reaction is compatible with the fluoro-, chloro-, and methoxy- substituents in the aryl-bromide portion of the substrate.



Scheme 1. Competitive cyclization pathways for oxidative dearomatization[8]

The reaction was also compatible with the presence of biaryl and heteroaryl groups such as naphthalene, quinoline, and furan in aryl bromide end. The variation in tether length allowed to construct both 5- as well as 7-membered rings. The reaction outcome was not affected by varying the alkyl substituent at the C4 position as both ethyl and butyl substituted substrates provided favorable outcome; however, the phenyl substituted at the C4 (a) position substrate did not give any desired product. The versatility and efficiency of this method was also used to quickly set the core of the anabolic steroid boldenone (Scheme 2). The key precursor **7** was prepared from Hajosh-Parrish ketone-derived ketal **4** and bromide **5** following a three-step sequence consisted of alkylation, triflation, and debenzylation. The subsequent asymmetric dearomatization reaction with [{Pd(cinnamyl)Cl}$_2$]/(*R*)-**8** smoothly provided boldenone skeleton **9** in high yield (90%) and high diastereoselectively (>99:1). Remarkably, the use of [{Pd(cinnamyl)Cl}$_2$]/(*S*)-**8** granted access to diastereomeric skeleton **10** (90% yield, 98:2 d.r.)

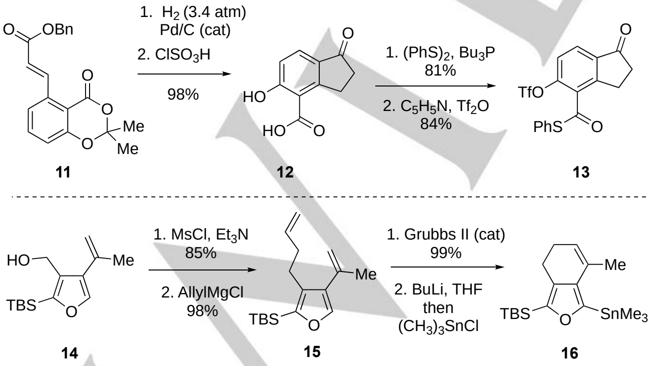
demonstrating the efficiency of this catalyst-controlled transformation.



Scheme 2. Dearomatizative cyclization in the synthesis of boldenone skeleton[8]

2.2. Enantioselective Total Syntheses of Furanosteroids (–)-Viridin and (–)-Viridiol by Guerrero's Group[13]

Recently in 2017, the Guerrero group reported an elegant approach to furanosteroids, (-)-viridin and (-)-viridiol based on an enantioselective intramolecular Heck reaction approach[13]. While the racemic synthesis of viridin[14] and viridiol[15] was accomplished by Sorensen in 2004[16], this late stage fragment coupling based strategy may be amenable to the synthesis of viridin analogs with modifications in D ring.



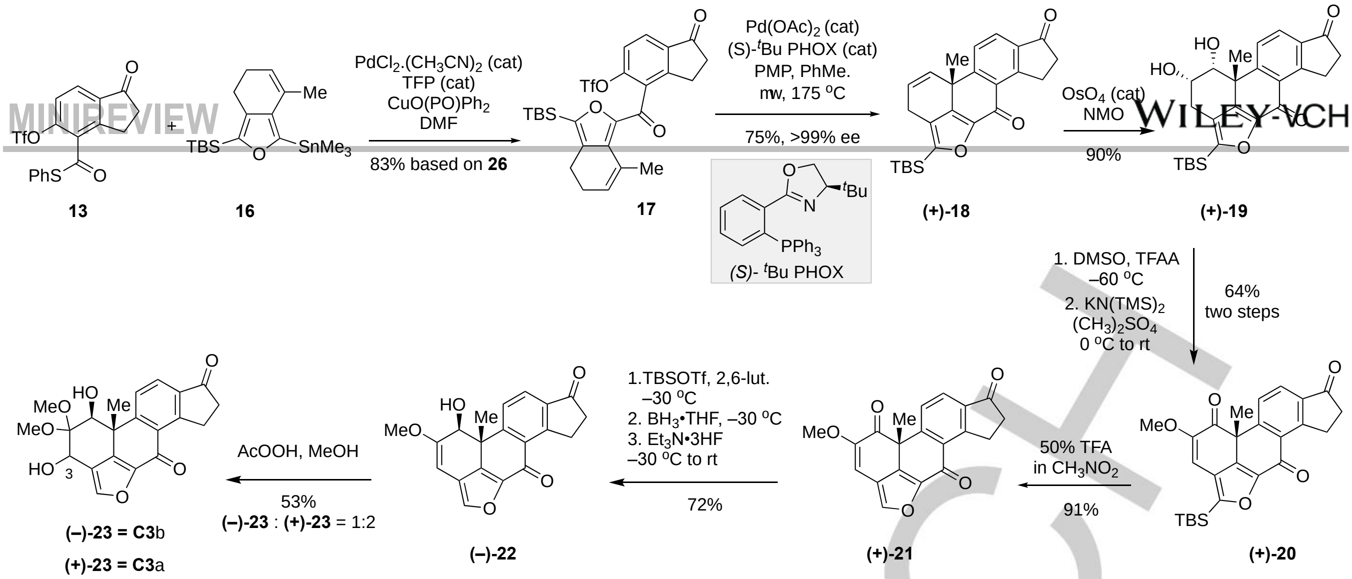
Scheme 3. Synthesis of the key intermediates for the (–)-viridin and (–)-viridiol synthesis[13]

The synthesis began with the access of thioester **13** and stannane **16** (Scheme 3). A known aryl triflate[17] was subjected to a Heck alkenylation to get compound **11**. Hydrogenation of alkene and concomitant removal of benzyl group followed by treating the resulting cinnamic acid with neat chlorosulfonic acid led to indanone **12**. Finally, the functionalized indanone **13** was obtained after thioesterification and triflation of **12**. On the other hand, a known furan derivative[18] **14** was converted to the A-ring furan fragment **16** in a 4-step sequence involving 1) chlorination of a primary alcohol using methanesulfonyl chloride and triethylamine, 2) displacement of chloride by allyl group using allyl magnesium chloride to get **15**, 3) ring closing metathesis using Grubb's second-generation catalyst and 4) lithiation followed by stannylation.

Next, the fragment coupling between **13** and **16** was executed under Liebeskind stannane-thioester coupling conditions[19] remarkably to get diketone **17** with aryl triflate intact in good yields and on multigram scale (Scheme 4). The coupled product **17** was then subjected for the stereodefining enantioselective intramolecular Heck reaction using Pd(0)-*S*-^{t}BuPHOX complex in presence of 1,2,2,6,6-pentamethylpiperidine (PMP) to furnish **(+)-18** in 75% yield and high enantioselectivity (>99% ee). This reaction proceeds via the classical Heck reaction mechanism (Scheme 5), and the facial selectivity for the conversion of **17A** into **17B** is determined by the chiral ligand *S*-^{t}BuPHOX. It is noteworthy that the use of PMP was required to complete the conversion and reduce the alkene isomerization which was otherwise observed with diphosphine ligands.

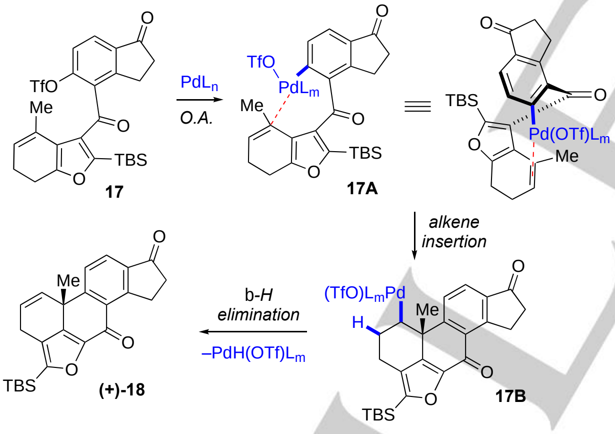
Compound **18**, though contains the complete carbon skeleton of viridin, still lacks the required oxidation of the A-ring. To install it, Upjohn dihydroxylation was carried out to get diol **19** diastereoselectively from α-face biased by the angular methyl group. The following Swern oxidation and methylation led to the methoxyketone **20** providing the required oxidation at C-3 via indirect means as the direct means of oxidation of this position on **18** were unsuccessful. The TBS group in **20** was cleanly removed by stirring in TFA to get compound **21** which was then subjected for a three-step sequence involving 1) a temporary protection of the D-ring ketone as a TBS-silyl-enol ether, 2) stereoselective reduction of the A-ring ketone using BH_3•THF, and 3) desilylation by using Et_3N•HF to reveal the D-ring ketone, to deliver keto alcohol **22** in 72 % isolated yields for three steps. Even though allylic alcohol **22** may potentially be advanced to (–)-viridin by hydroboration and selective alcohol oxidation, the former step was unsuccessful. Consequently, enol-ether **22** was epoxidized using AcOOH in methanol to give a mixture of diastereomers (–)-**23** and (+)-**23**.

The seemingly challenging diastreoselective monodemethoxylation of dimethoxyacetals (–)-**23** and (+)-**23** was then successfully performed using TMSOTf and hydride donor to respectively give viridiol and epi-viridiol, albeit in low

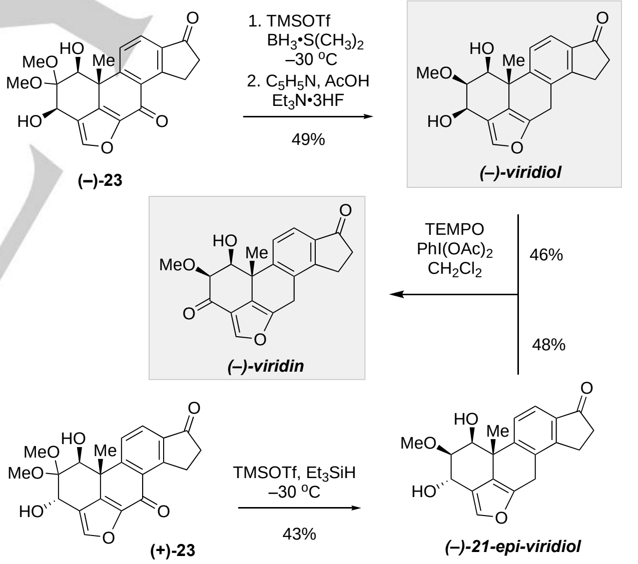


yields due either to decomposition of reactant or product (Scheme 6). Both epimers were then converted to viridin after TEMPO oxidation completing an 18-step synthesis starting from commercial materials.

Scheme 4. Fragment assembly and synthesis of the precursor **23** to (–)-viridin and (–)-viridiol[13]



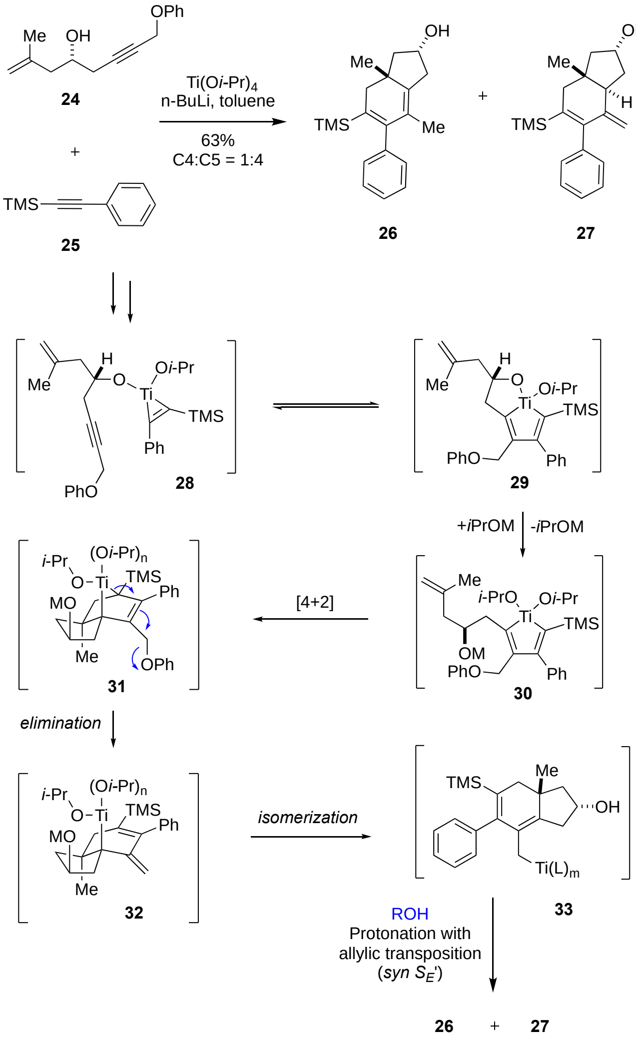
Scheme 5. Mechanism of the Heck reaction leading to **(+)-18**



Scheme 6. Elaboration of (–)-**23** and (+)-**23** into (–)-viridin and (–)-viridiol[13]

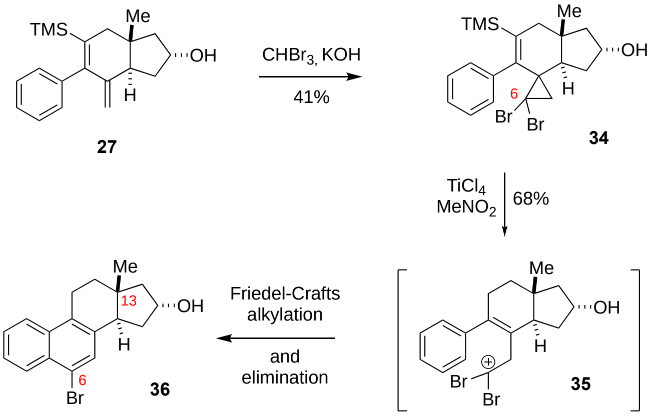
2.3. Synthesis of natural and enantiomeric steroids via metallacycle-mediated annulative cross-couplings[20]

In 2017, Micalizio group reported an interesting and concise approach based on the metallacycle-mediated cross coupling to access a series of natural and enantiomeric steroids.[20c] The strategy involves the early construction of the C/D ring system via a metallacycle-mediated annulative cross coupling[21] between an alkyne and a suitably functionalized chiral enyne followed by a strategic formation of the C5-C6 bond after a suitable functionalization and activation of ACD tricycle. The enyne **24** was synthesized from (–)-epichlorohydrin either via a low yielding two-step protocol involving 1) S_N2 displacement of the chloride by alkynyl lithium derived from phenylpropargyl ether and 2) opening of the epoxide by propenyl cuprate or a more

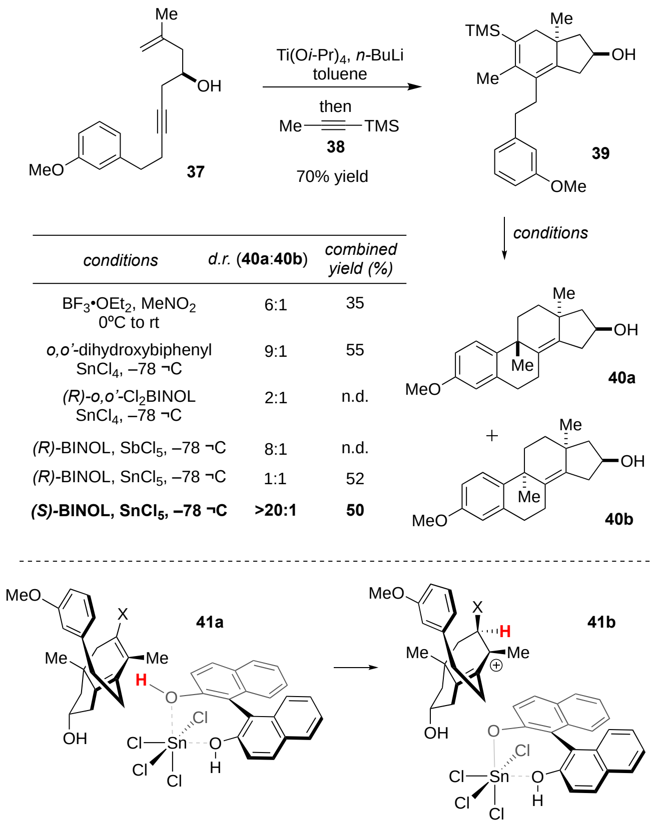


Scheme 7. Titanium(IV)-mediated formation of the steroidal C/D-ring system[20]

efficient three-step protocol involving 1) opening of the epoxide by alkynyl lithium in presence of $BF_3•Et_2O$, 2) treating with KO^tBu and 3) S_N2 displacement with propenyl cuprate. The enyne **24** was then subjected for a unique titanium-mediated annulative cross coupling with trimethylsilyl-phenylacetylene (**25**) to deliverhydrindane **26** along with the *exo*-diene **27** (Scheme 7). This powerful transformation constructs three C-C σ bonds and two stereocenters including one quarternary center leading to an angularly substituted *trans*-fused hydrindane from acyclic precursors. Mechanistically, this transformation was proposed to proceed via a series of cascade events as depicted in Scheme 7, which include 1) formation of titatanocycle intermediate **28**; 2) an alkoxide-directed formation of metallacycle **29** followed by alkoxide exchange to generate **30** in high regioselectivity (>20:1 r.s.);[22] 3) diastereoselective intramolecular [4+2] cycloaddition to give bridged metallacyclopentene **31** (>20:1 d.r.), 4) elimination to furnish tertiary allylic metal species **32**, 5) isomerization to provide primary allylic metal species **33** and 6) stereoselective protonation via an allylic transposition to furnish hydrindanes **26** and **27**. After the key cyclization transformation, the introduction of the C6 carbon and subsequent construction of the B ring was investigated (Scheme 8). Thus, the exocyclic methylene in **27** was cyclopropanated to give vinylcyclopropane intermediate **34**. It should be noted that the yields of this reaction could be improved when the C-16 alcohol is protected.



Scheme 8. Elaboration of **27** into steroidal core **36**[20c]



conditions	d.r. (**40a**:**40b**)	combined yield (%)
BF_3•OEt_2, $MeNO_2$ 0ºC to rt	6:1	35
o,o'-dihydroxybiphenyl $SnCl_4$, –78 ¬C	9:1	55
(R)-o,o'-Cl_2BINOL $SnCl_4$, –78 ¬C	2:1	n.d.
(R)-BINOL, $SbCl_5$, –78 ¬C	8:1	n.d.
(R)-BINOL, $SnCl_5$, –78 ¬C	1:1	52
***(S)*-BINOL, $SnCl_5$, –78 ¬C**	**>20:1**	**50**

Scheme 9. Application to the synthesis of euphane analogs by Micalizio and coworkers[20a]

The initial attempts to ionize **34** with the expectation that it would undergo an electrocyclic ring opening followed by an intramolecular Friedel-Crafts alkylation were deemed unsuccessful. However, it was found that the treatment of **34** with $TiCl_4$ in nitromethane led to the steroidal product **36** in 68% yield.This process presumably proceeds via homoallylic cationic intermediate **35**, which is formed after protodesilylation, protonation of resulting double bond and regioselective cyclypropane fragmentation[23] triggered by the *in situ* generated protic acid arising from the reaction between the C-16 alcohol and $TiCl_4$. The subsequent intramolecular Friedel-Crafts alkylation reaction and the loss of HBr led to **36**.[24]This strategy was later adopted to the synthesis of terpenoid euphane analogs and investigated them as potential selective agonists of the estrogen receptor beta (ERβ).[20a] The homopropargylic alcohol **37** underwent Ti(IV)-mediated annulation with alkyne **38** to provide the functionalized hydrindane **39** (Scheme 9).

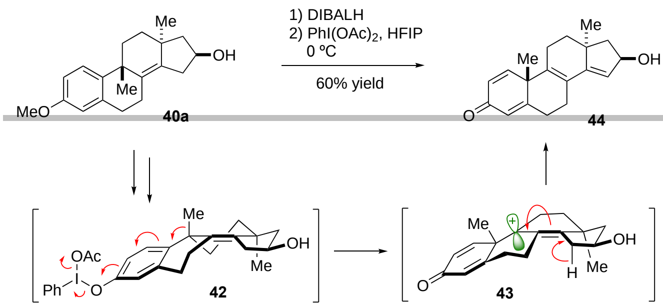
Scheme 10. Dearomatizative rearrangement leading to the formation of steroidal skeleton with C19 methylation by the Micalizio group[20a]

This intermediate was then subjected to various Lewis and Br∅nsted acids to obtain diastereomeric steroid cores **40a** and **40b**. While the diastereomer **40a** is favored under the achiral Lewis acid catalysis with BF_3•OEt_2 (entry 1), the authors decided to further improve the selectivity by utilizing combinations of chiral Br∅nsted acids obtained by complexation of Lewis acids and BINOL or its methylation of the C16 hydroxyl group of the D-ring did not lead to the erosion in the reaction dr. Such catalysts were previously explored by the Yamamoto[27] and Corey[28] to achieve enantioselective polyene cyclization reactions, and turned out to be of particular utility in enhancing the formation of the diastereomer **40a**. Thus, the combination of (*S*)-BINOL and $SnCl_4$ at –78 ºC resulted in the conversion of **39** to **40a** in 50% yield and >20:1 dr. This transformation proceeds through the protonation of **41a** and follows by the intramolecular Friedel-Crafts reaction through the intermediacy of **41b** (Scheme 9). This remarkable reaction is dependent on the chirality of BINOL, and the use of the (*R*)-BINOL as the ligand instead led to 1:1 dr. In addition, the methylation of the C16 hydroxyl group of the D-ring did not lead to the erosion in the reaction dr.

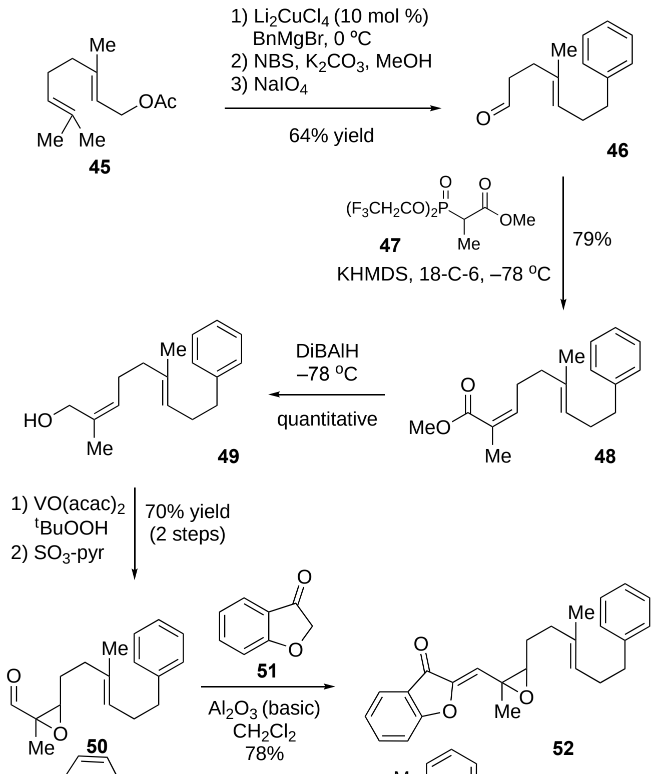
The diastereomer **40a** and related compounds were subjected to the oxidative dearomatizative rearrangement leading to the steroidal cores containing the C19 methylation. Thus, the treatment of **40a** led to the formation of the deprotected C3 hydroxyl (Scheme 10). The reaction of this resultant intermediate with phenyliodine(III) diacetate (PIDA) results in intermediate **42** that undergoes subsequent rearrangement to provide the dearomatized carbocation **43**, deprotonation of which leads to **44**.

2.4. Pd-catalyzed intramolecular alkenylation to form 4,5-spirocyclic skeleton of phainanoid A[29]

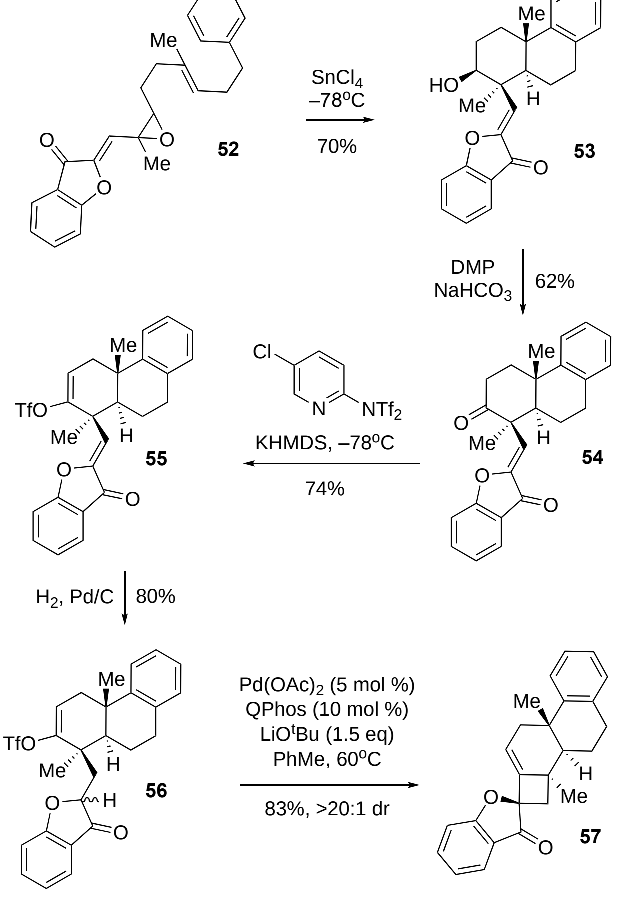
In 2017, Dong and coworkers published a palladium-catalyzed intramolecular alkenylation approach to access the strained cyclobutane-containing 4,5-spirocycle of the western part of phainanoids.[29] This approach featured Pd-catalyzed intramolecular alkenylation of an enolate that provided the spirocyclic cyclobutane-containing portion of phainoids.

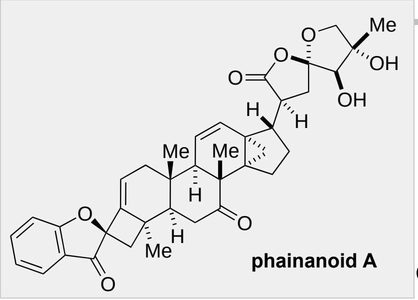


Scheme 11. Synthesis of precursor **52** for the model studies toward the synthesis of phainanoid A by the Dong group[29]



Scheme 12. Completion of the synthesis of the western portion of phainanoid A by the Dong group[29]





These model studies began by first developing a scalable route to allylic epoxide **52** (Scheme 11). This compound was generated from the commercially available geranyl acetate **45**. Thus, **45** was subjected to a three-step sequence involving copper-catalyzed allylic coupling, chemoselective epoxidation, and oxidative cleavage of the epoxide that resulted in aldehyde **46** in 64% yield. Subsequently, the Still-Gennary variant of the Horner-Wadsworth-Emmons olefination was employed to afford *Z*-olefin-containing **48** in 79% yield. The reduction of the ester moiety in **48** with DIBAL-H and subsequent two step oxidation of the resultant alcohol **49** afforded aldehyde **50** in 70% yield over 3 steps. Finally, basic-alumina-promoted aldol condensation between **50** and 3-coumaranone (**51**) afforded allylic epoxide **52** with *Z*-selectivity.

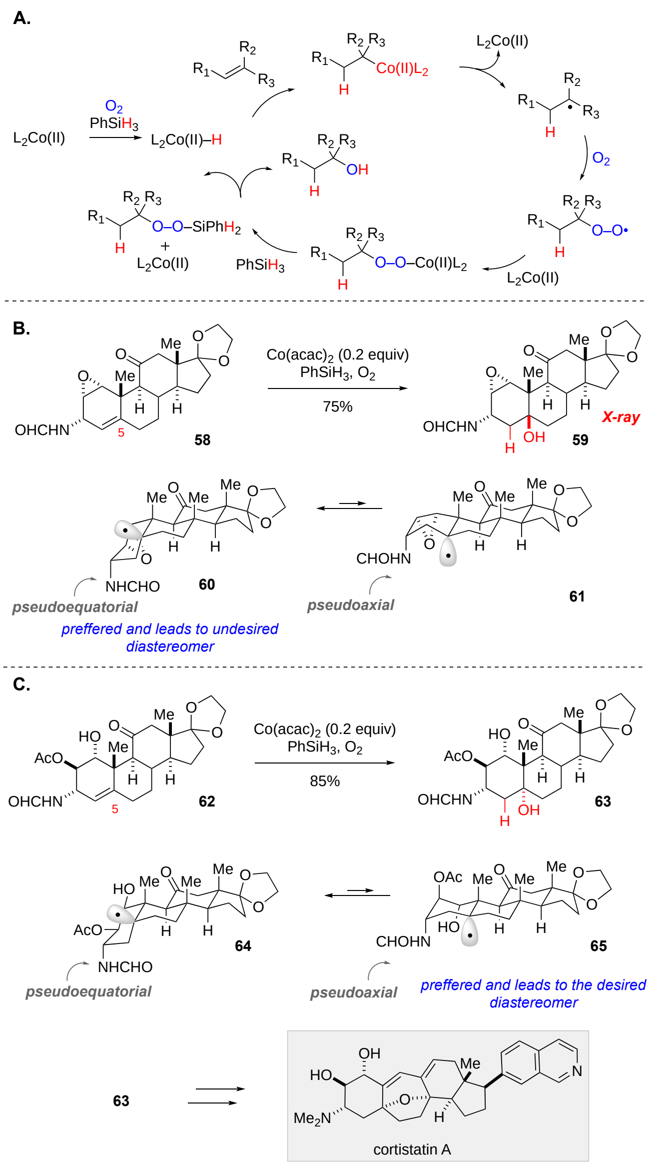
With the efficient, scalable synthesis of **52** in hand, the synthesis of the western part of phainanoids was completed (Scheme 12). Lewis acid mediated polyene cyclization with $SnCl_4$ was employed to obtain tricyclic alcohol **53** with a *trans*-decaline core in 70% yield. Subsequent DMP oxidation and triflation of ketone **54** with Comins' reagent afforded vinyl triflate **55** in 46% yield over 2 steps. Previous studies showed that the challenging selective reduction of a trisubstituted olefin in the presence of a vinyl triflate could be obtained via Pd/C-catalyzed hydrogenation with an H_2-balloon. This method was utilized to obtain vinyl triflate **56** in 80% yield. Finally, they attempted to form the benzofuranone-based 4,5-spirocyclic motif with and exocylic olefin. Previous work by Helquist and coworkers indicated that *tert*-butyl substituted phosphine ligands could promote palladium-catalyzed intermolecular alkenylation of ketones.[30] Based on these findings Dong attempted the intramolecular alkenylation of vinyl triflates with $Pd(OAc)_2$ and QPhos. They observed the base had a significant effect on the reaction, and LiO^{t}Bu was superior compared to LiHMDS, KHMDS, NaHMDS, KO^{t}Bu, NaO^{t}Bu, and Cs_2CO_3. They also found that the reaction performed best under moisture free conditions. Utilizing the optimized conditions from the model studies, they successfully performed the intramolecular alkenylation of **56** to afford the hexacyclic western part of the phainanoids (**57**).

2.5. Application of the transformations involving transition metal-catalyzed hydrogen atom transfer (HAT) to the synthesis of steroids

Transition metal catalyzed reactions involving HAT have been of great utility to the synthesis of steroids and terpenoids. While many applications of HAT reactions are focused on introduction of oxygenation via olefin hydration under mild conditions, several recent applications feature the application of HAT reaction for the C-C bond constructions that result in the formation of challenging motifs present in various steroids. Below we provide a brief overview of the recent applications of such transformations and highlight their use in the synthesis of aplysiasecosterol by the Li group[31] and construction of (–)-nodulisporic acid C by the Pronin group.[32]

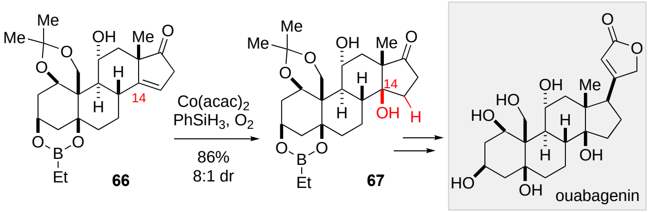
2.5.1 Mukayiama's hydration for the diastereoselective introduction of tertiary alcohols in the syntheses of steroids cortistatin A,[35] ouabagenin[36] and linckosides A and B[37]

Transition metal-catalyzed transformations resulting in the net Markovnikov's hydration of the alkenes represent powerful and mild methods for the introduction of hydroxyl groups into complex substrate.[33] These transformations typically proceed in the presence of Co(II) or Mn(II) salts and require molecular oxygen and silane. The mechanism of Mukayiama hydration[34] is not completely understood; however, it is believed to proceed through the formation of transition metal hydrides, that react with alkenes to accomplish hydrogen atom transfer (HAT) that results in the species with radical-like properties (Scheme 13A). These species undergo further reaction with molecular oxygen and the resultant peroxide species are being reduced by silane and Co(II). Importantly, these conditions may result in different stereoselectivities then what is observed in more traditional hydration reactions that proceed through the carbocationic intermediates.



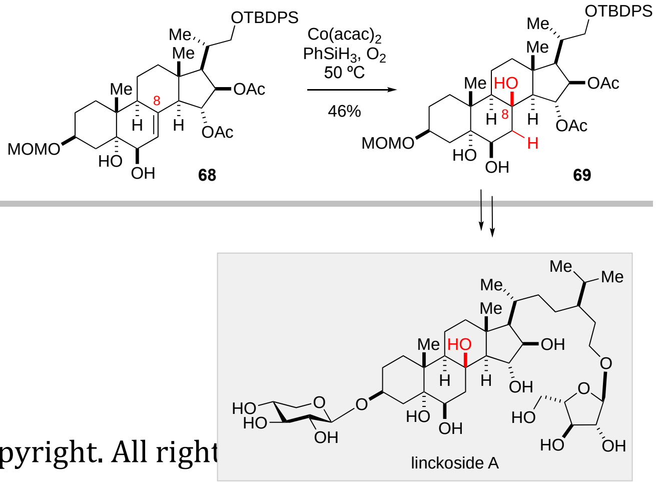
Scheme 13. A. The mechanism of Mukayiama hydration. **B. C.** Application of the Mukayiama hydration in the synthesis of cortistatin A by Baran and coworkers[35]

This feature has been explored by the Baran group for the installation of the C5 oxygenation in their synthesis of cortisatin A (Scheme 13B and C).[35] In order to introduce the α-C5 oxygen required for the synthesis of cortistatin A, Baran group first explored the hydration of the intermediate **58**. However, the undesired β-C5 hydroxylated product **59** was formed instead. The authors rationalized this selectivity by proposing that the reaction mechanism involves a C5 radicals or a related species denoted by **60** and **61** (Scheme 13B). These radical intermediates differ by the configuration of the radical containing C5 carbon.



Scheme 14. Application of the Mukayiama hydration in the synthesis of ouabagenin by Baran and coworkers[36]

Due to the presence of the α-C1/ α-C2 epoxide moiety, the intermediate **61** containing pseudoaxial –NHCHO group is less favored and the reaction happens through **60** that contains *cis*-A/B ring junction. This mechanistic hypothesis prompted the authors to examine other substituents at the A ring. As a result of this studies, the hydration of compound **62** leading to intermediate **63** with the desired α-C5 configuration was identified (Scheme 13C). The formation of **63** may potentially happen through different conformers **64** and **65**. The absence of the α-C1/ α-C2 epoxide allows now to achieve *trans*-AB ring



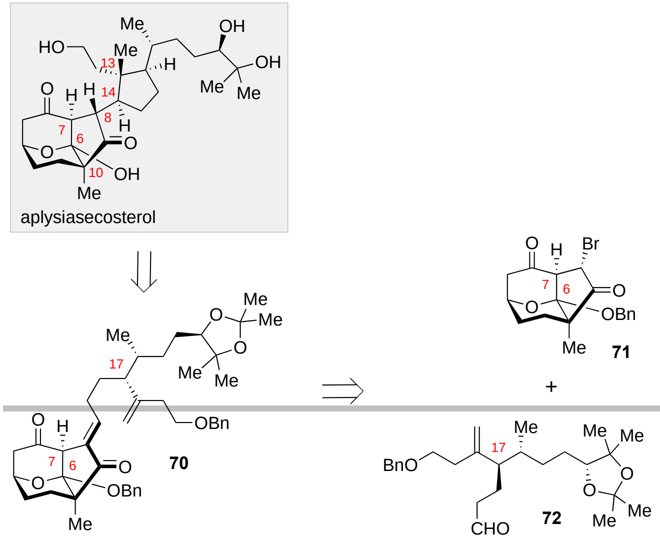
junction in **65**, which is the reactive intermediate, through which the formation of **63** happens. Importantly, the facile formation of **65** enabled the completion of the synthesis of cortistatin A.

Scheme 15. Application of the Mukayiama hydration in the synthesis of linckosides A and B by Yu and coworkers[37]

Subsequently, the Baran group successfully implemented this strategy in the synthesis of polyoxygenated cardiotonic steroid ouabagenin from progesterone.[36] As progesterone does not contain the β-C14 hydroxyl group, Baran and coworkers installed this moiety using Δ^{14}-alkene-containing intermediate **66** (Scheme 14). Thus, treatment of **66** with molecular oxygen, phenylsilane and $Co(acac)_2$ as the reaction promoter resulted in the formation of **67** as the 8:1 mixture of β : α isomers. The selective formation of the β-isomer may be explained by the higher stability of the *cis*-hydrindane conformer of the C14-radical intermediate than the corresponding *trans*-hydrindane one.This strategy for the diastereoselective installation of the tertiary alcohols at the ring junction of the steroid skeleton was recently utilized by the Yu and coworkers in their synthesis of linckosides A and B (Scheme 15).[37] Surmising that the Δ^7-alkene of precursor **68** would preferentially react to form the β-C8 hydroxyl group, Yu and coworkers successfully carried the hydration of **68** to form advanced intermediate **69** that was later elaborated into linckosides A and B.

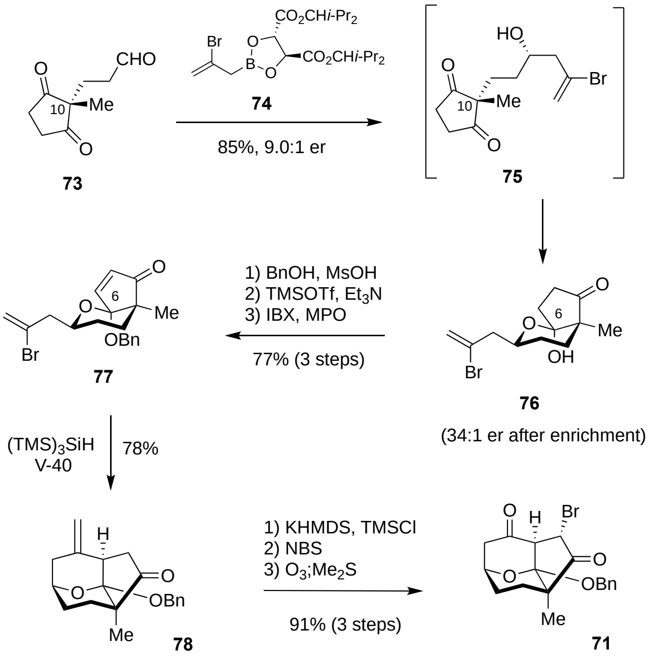
2.5.2 Application of the transformations involving iron-catalyzed hydrogen atom transfer (HAT) to the synthesis of aplysiasecosterol by Li and coworkers[31]

Aplysiasecosterol is a natural steroid derivative with a highly reorganized skeleton. While this molecule features many functionalities present in steroids, its assembly required the development of new synthetic strategy, in particular, for the construction of the highly substituted cyclopentane ring. Li's group performed the first asymmetric total synthesis of the 9,11-secosteroid aplysiasecosterol in 2018[31]. A convergent synthesis was accomplished to establish the stereocenters shown in Scheme 16 prior to a HAT based radical cyclization to construct the cyclopentane ring of aplysiasecosterol in a selective manner.



Scheme 16. Retrosynthesis of aplysiasecosterol[31]

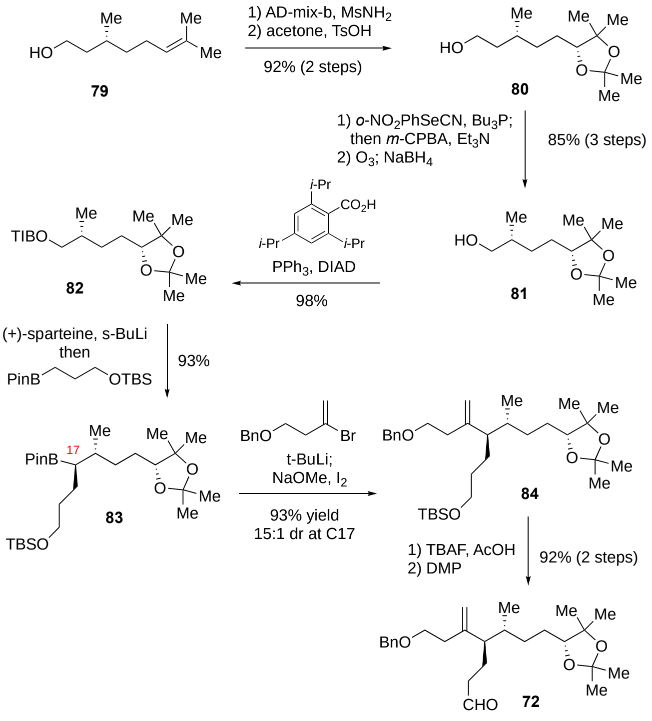
The Li group found that a desymmetrizing lactolization reaction could be performed using the Roush enantioselective allylation of symmetric aldehyde **73** with boronic ester **74** to bypass the traditional Corey-Bakshi-Shibata reduction and streamline the synthesis providing **75** in 85% yield and 9:1 er as determined by Mosher esterification followed by the ^{19}F NMR analysis (Scheme 17). After the subsequent enantioenrichment of **76**, the benzyl acetal formation was accomplished with BnOH and MsOH. This intermediate was then converted into α,β-unsaturated enone **77** using Nicolaou's protocol (silyl enol ether formation then IBX/MPO oxidation) in 77% yield from **76**. The left-hand segment synthesis was finished with annulation initiated with V-40 and$(TMS)_3SiH$ (78% yield), subsequent silyl enol ether formation, NBS bromination, and ozonolysis to give **71**. (91% yield over 3 steps).



Scheme 17. Synthesis of the key intermediate **71** in the synthesis of aplysiasecosterol[31]

For the synthesis of the right-hand segment **72**, Li and coworkers initially utilized Myer's alkylation; however, the process was tedious thus decreasing the efficiency. Therefore, a different route commencing with the formation of **80** from **79** using Sharpless asymmetric dihydroxylation was developed (*cf.* Scheme 18). This followed by the Grieco elimination/ozonolysis sequence to derive one carbon shorter homologue **81** (85%, 3 steps). The primary alcohol moiety of **81** was esterified under the Mitsunobu conditions to provide **82** (98% yield), which set stage for the Aggarwal's lithiation-borylation chemistry that involved a stereoselective lithiation with (+)-sparteine. The resultant organolithium species was alkylated with alkyl pinacolborane to provide **83** with the desired configuration of the C17 stereocenter in 93% yield. Treating **83** with *t*-BuLi allowed for a Zweifel-Evans olefination to give **84** (93%, 15:1 dr at C17). This compound was further elaborated to the corresponding aldehyde by a sequence involving silyl deprotection and Dess-Martin oxidation to provide aldehyde **72** for the coupling with **71**.

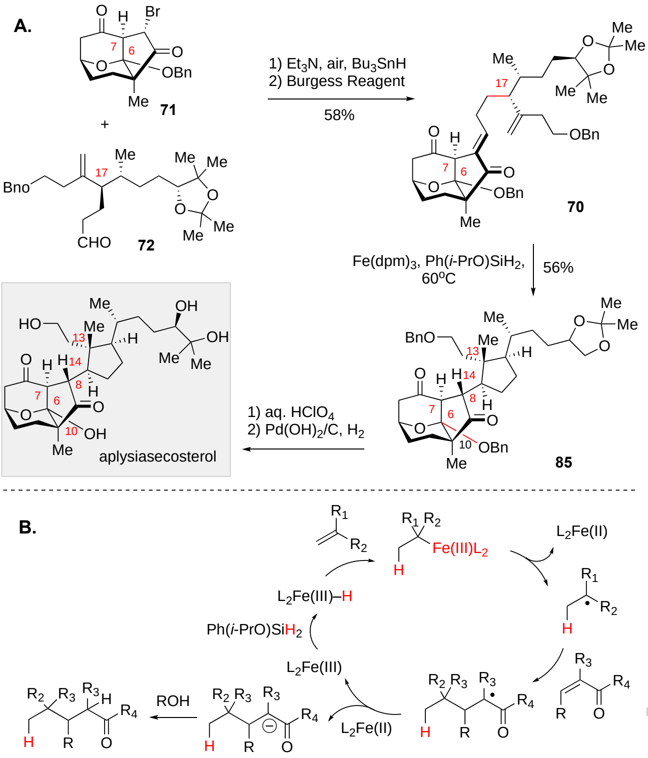
Subsequently, **71** and **72** were linked by a radical Reformatsky type of aldol addition reaction that provided the *anti*-aldol product in 70% yield (Scheme 19A). This aldol addition product was converted to the corresponding aldol condensation product **70** by the elimination of water using Burgess reagent (58%, 2 steps). From here, the Li group envisioned that the key highly functionalized cyclopentane moiety of aplysiasecosterol could be installed using Fe(III)-catalyzed radical cyclization developed by the Baran group. The tentative mechanism of this transformation is depicted in Scheme 19B and is likely to involve a HAT resulting in a radical intermediate.[38] Upon screening various ligands for the Fe(III) catalyst (acac, ox, dibm, and dpm, etc.) the optimal conditions were identified to provide **85** in 56% yield. This compound was subsequently subjected to deprotection that provided aplysiasecosterol in 92% yield (2 steps). It is of note that the cyclization conditions were extended to produce analogues with similar yield. From this work, Li and coworkers have provided an advantageous route that can be used to synthesize 9,11-secosteroids in a convergent fashion.



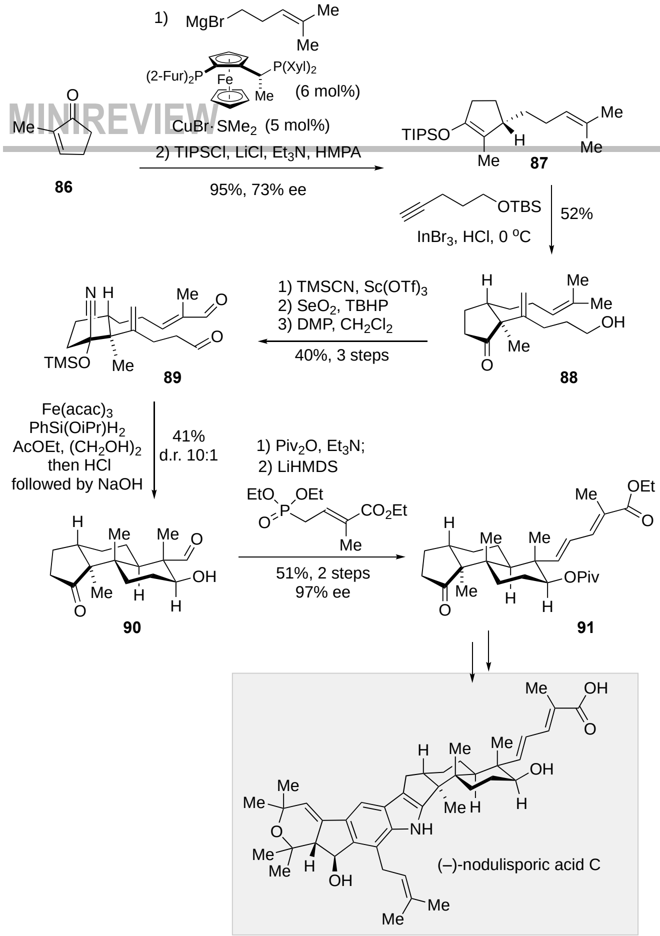
Scheme 18. Synthesis of the intermediate **72** by Li and coworkers[31]

2.5.3 Application of the transformations involving iron-catalyzed hydrogen atom transfer (HAT) to the synthesis of aplysiasecosterol by Pronin and coworkers[39]

Pronin's group recently applied iron-catalyzed HAT cyclization/aldol addition sequence to establish the eastern portion of indole diterpenoid, (–)-nodulisporic acid C (Scheme 20).[39] The synthesis began with the copper-catalyzed asymmetric conjugate addition to **86** using the JosiPhos derivative SL-J015-1 to prepare the silyl-enol ether **87** in 95% yield and 73% ee. This silyl enol ether underwent an indium (III) bromide catalyzed addition to the TBS-protected pent-4-yn-1-ol,[40] and the following acid work up provided access to **88** containing a quaternary stereocenter. This intermediate was subjected to a three-step sequence that included the formation of cyanohydrin, Sharpless allylic oxidation and primary alcohol oxidation by Dess-Martin periodane to provide the dialdehyde **89** in 40% yield over 3 steps. Subjecting **89** to Fe(acac)$_3$ with PhSi(O*i*Pr)H$_2$[38] resulted in diastereoselective formation of two vicinal quaternary centers and concomitant aldol addition.This followed by the acidic work up with HCl and then base to cleave



Scheme 19. A. Fragment coupling and completion of the synthesis of aplysiasecosterol. **B.** Proposed mechanism for the iron(III)-promoted HAT cyclization.[31]

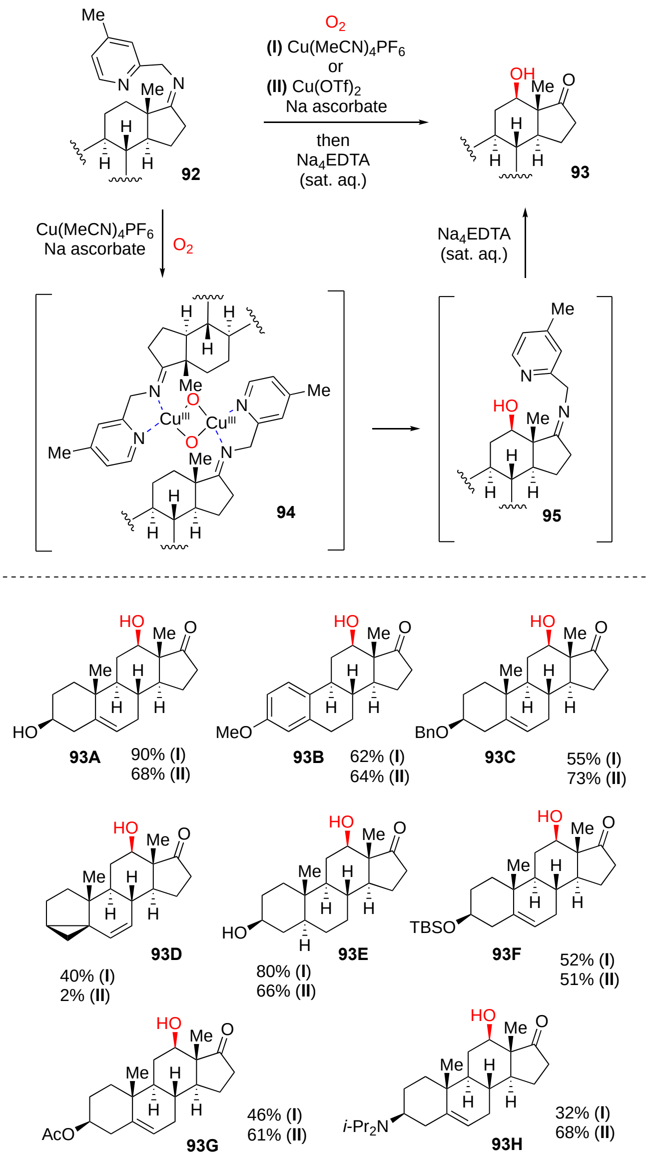


the cyanohydrine moiety and provided **90** in 41% yield and 10:1 d.r. The high diastereoselectivity of this reaction is attributed to the pseudoaxial substituent at the C2 position. The substrate **90** was esterified (Piv_2O, Et_3N) and then subjected to Horner-Wadsworth-Emmons olefination to provide the fully functionalized eastern portion of (–)-nodulisporic acid C (**91**), which was subsequently elaborated to the natural product itself.

Scheme 20. Application of iron(III)-promoted HAT cyclization/aldol addition cascade in the synthesis of (–)-nodulisporic acid C by Pronin and coworkers[39]

2.5. Application of the directed copper-catalyzed C-H oxidation in the synthesis of pergularin, utendin and tomentogenin by the Baran group[41]

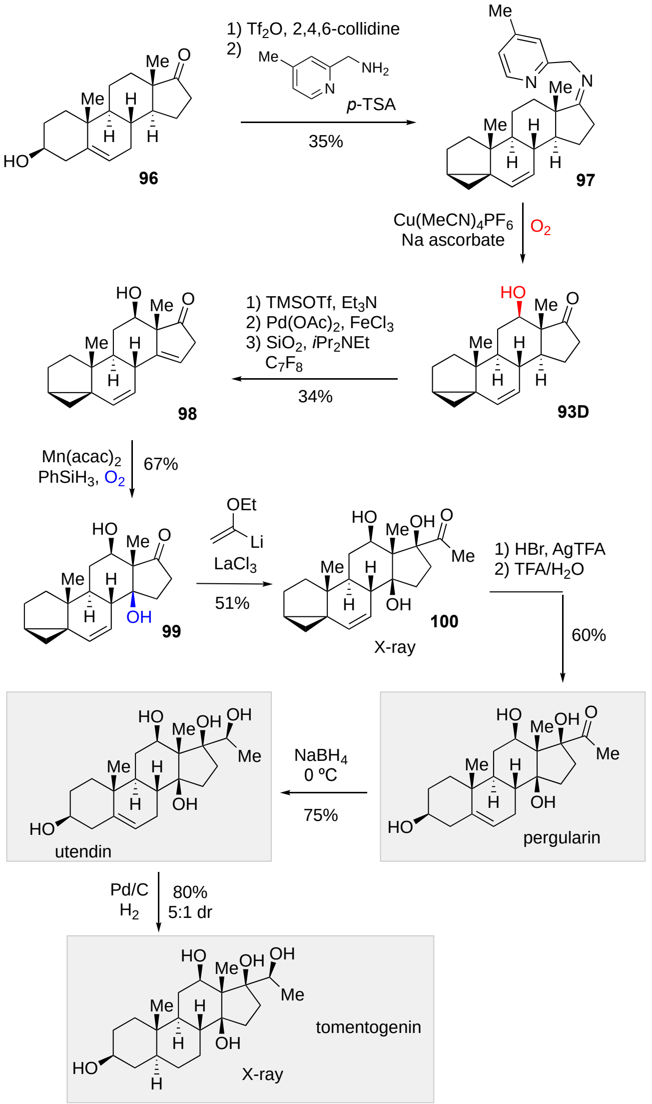
While many steroids carry significant degree of skeletal oxidation, synthesis of steroids with high degree of oxidation represents a significant challenge. Recently, new approaches based on the late stage selective C-H oxidation started to emerge and be applied to complex steroid synthesis. Thus, based on the promising results obtained by the Schonecker group, Baran and coworkers have developed a powerful method for the introduction of the β-C12 hydroxylation at steroid skeleton under aerobic conditions (Scheme 21). This approach requires the presence of the C17 ketone that is then being converted to an imine functionalized with a 4-methylpyridyl moiety. This auxiliary is required for achieving chelation with Cu to form dimer **94** and for directing the oxidation to the β-C12 position resulting in **95**. The imine moiety of **95** could be subsequently removed by the work up with saturated solution of Na_4TMEDA. The Baran group was able to demonstrate that this oxidation protocol is rather general and could be applied to a variety of substrates to obtain the corresponding oxidized products **93A-93H** in preparatively useful yields (40-90%).



Scheme 21. Cu-catalyzed C-H auxiliary-directed C-H oxidation of the C12 position of steroidal skeleton by the Baran group[41]

This protocol was subsequently applied to the synthesis of steroids utendin, pergularin and tomentogenin that feature β-

C12 oxidation of the C ring and contain highly oxidized D-ring (*cf.* Scheme 22). This synthesis commenced with inexpensive DHEA (**96**) that was subjected a 2 step sequence to provide auxiliary-containing product **97** (35% yield). This substrate was subjected to the aerobic oxidation in the presence of $Cu(MeCN)_4PF_6$ and sodium ascorbate to provide β-C12 oxidized product **93D** in 40% yield. This trans-C/D ring-containing intermediate was converted to **98** in 34% yield via a 3 step sequence that involved the formation of silyl enol ether (TMSOTf, Et_3N), and subsequent Saegusa oxidation ($Pd(OAc)_2$, $FeCl_3$) followed by the silica gel promoted deconjugation of the resultant enone moiety. Intermediate **98** was next subjected to Mn(II)-promoted Mukayiama hydration conditions that afforded **99** in 67% yield.

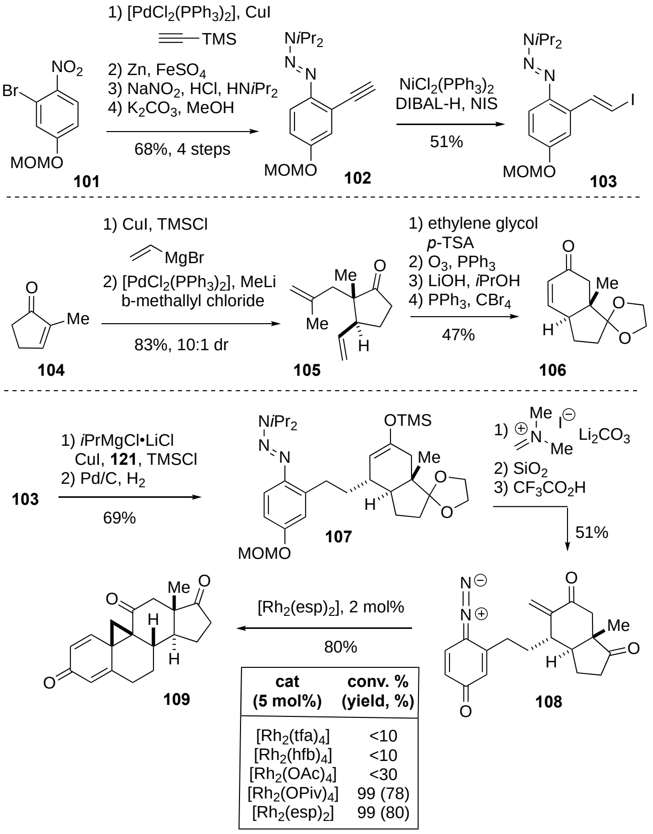


Scheme 22. Directed C-H oxidation in the synthesis of pergularin, utendin and tomentogenin by the Baran group[41]

It is noteworthy that despite the fact that substrate **98** contains two alkenes, only the trisubstituted Δ^{14}-alkene moiety reacted under these conditions. The diastereoselectivity of this reaction was consistent with the observations made by the Baran group in their studies on the synthesis of ouabagenin (*cf.* Scheme 14).[38] The resultant product **99** was reacted with lithiated ethyl vinyl ether in the presence of $LaCl_3$ to provide **100** upon hydrolysis of the vinyl ether moiety (51% yield). The allylic cyclopropane functionality of **100** was cleanly converted to the homoallylic bromide by the treatment with HBr. The subsequent silver(I)-assisted solvolysis of this intermediate resulted in the corresponding homoallylic trifluoroacetate that was hydrolyzed to form pergularin by the treatment with aqueous trifluoroacetic acid (60% yield). This followed by the stereoselective reductions that were used to convert pergularin to utendin ($NaBH_4$, 75% yield) and then utendin to tomentogenin (Pd/C, H_2, 80% yield).

2.6. Rh-catalyzed cyclopropanation with quinone diazides in the synthesis of cycloartenol core by the Baran group[45]

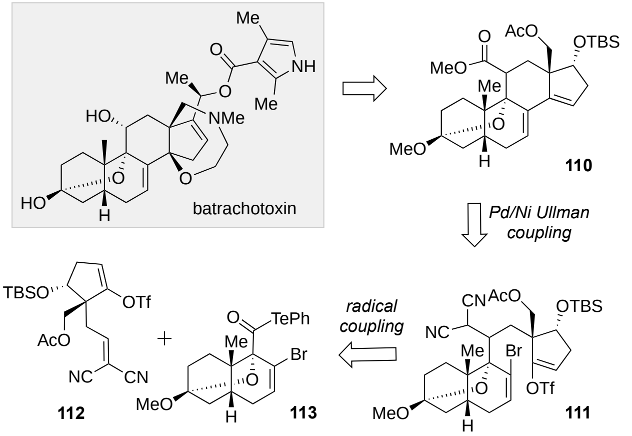
Cyclopropane-containing steroids such as cycloartenols represent challenging synthetic targets. In 2014, Baran and coworkers reported a new approach to the synthesis of such steroids that is based on an intramolecular cylopropanation with quinone diazides using Rh(II)-based catalysts and provided steroidal core **109** that may serve as the intermediate for the synthesis of cycloartenols and other classes of steroids.[43]



cat (5 mol%)	conv. % (yield, %)
$[Rh_2(tfa)_4]$	<10
$[Rh_2(hfb)_4]$	<10
$[Rh_2(OAc)_4]$	<30
$[Rh_2(OPiv)_4]$	99 (78)
$[Rh_2(esp)_2]$	99 (80)

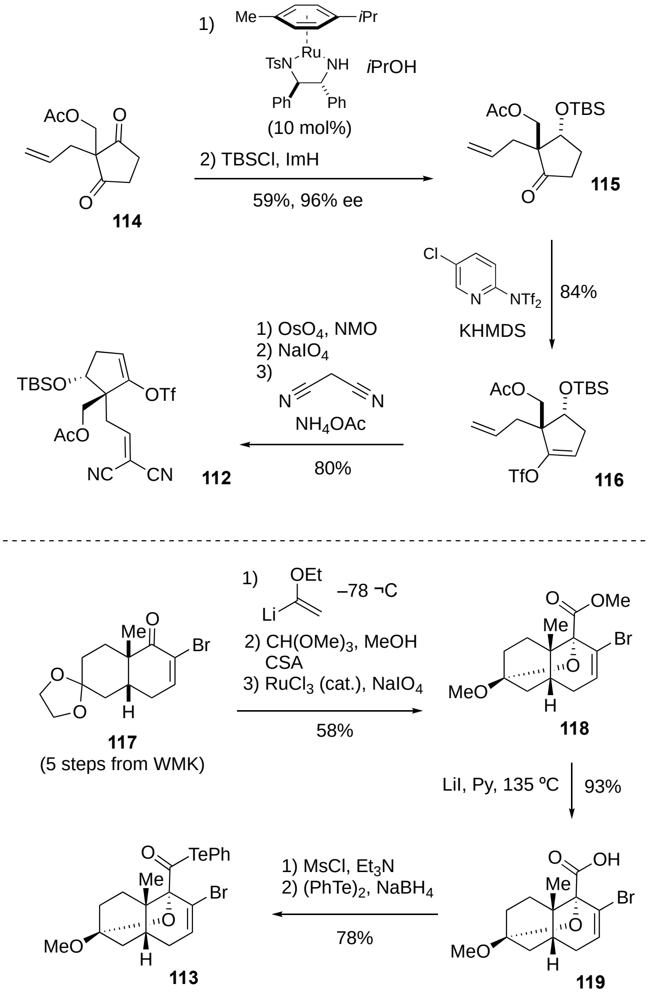
Scheme 23. Rh(II)-catalyzed intramolecular cyclopropanation in the synthesis of the cycloartenol core by the Baran group[43]

These studies commenced with the preparation of the fragments **103** and **106** (Scheme 23). Thus, bromophenol derivative **101** was subjected to a 4 step sequence that involved Sonagashira coupling with TMS-protected acetylene ($PdCl_2(PPh_3)_2$, CuI), reduction of the nitro group (Zn, $FeSO_4$), and subsequent installation of the triazene moiety via the intermediacy of the diazonium salt ($NaNO_2$, HCl then HN*i*Pr_2). This sequence culminated by base-promoted cleavage of the silane protection (K_2CO_3, MeOH) to provide triazene **102** in 68% yield (4 steps). Compound **102** was then subjected to Ni(0)-catalyzed hydroalumination of the alkyne moiety ($NiCl_2(PPh_3)_2$, DIBAL-H) that followed by the conversion of the organoaluminum intermediate to vinyl iodide **103** (51% yield) by its reaction with NIS. The synthesis of intermediate **106** commenced with 2-methyl-2-cyclopentenone **104** (Scheme 23). This compound was subjected to conjugate addition of vinyl cuprate followed by the capture of the enolate as the TMS-enol ether. After purification, this silyl enol ether was converted to the corresponding lithium enolate, which was cross-coupled with β-methallyl chloride ([$PdCl_2(PPh_3)_2$], MeLi, β-methallyl chloride) resulting in compound **105** (83% yield, 10:1 dr). This intermediate was subjected to protection to install 1,3-dioxalane moiety (ethylene glycol, *p*-TSA), ozonolysis (O_3, PPh_3) and aldol condensation (LiOH, iPrOH followed by PPh_3, CBr_4) to provide key intermediate **106** in 47% yield over 4 steps.



Scheme 24. Retrosynthetic analysis of Inoue's approach to batrachotoxin [44]

With both intermediates in hand, their coupling was accomplished next. Thus, **103** was subjected to Mg/halogen exchange with *i*PrMgCl•LiCl, and the resultant Grignard reagent was employed as a nucleophile for the Cu(I)-catalyzed 1,4-conjugate addition to **106** followed by the capture of the resultant enolate with TMSCl to form the corresponding silyl enol ether. The subsequent reduction of the styrene moiety (Pd/C, H_2) provided intermediate **107** in 69% yield over 2 steps. This compound reacted with Eschenmoser's salt and Li_2CO_3 to install the exocyclic enone moiety and subjected to deprotection of 1,3-dioxalane (SiO_2). The resultant compound was treated with trifluoroacetic acid, which resulted in the deprotection of the MOM group and formation of the quinone diazide **108**. Quinone diazide was then treated with various Rh(II) salts to accomplish intramolecular diastereoselective cyclopropanation proceeding through Rh-based carbenoid and leading to steroidal core **109**. The evaluation of various catalysts helped to identify [$Rh_2(esp)_4$] as the best catalyst of this transformation that afforded **109** in 80% yield.

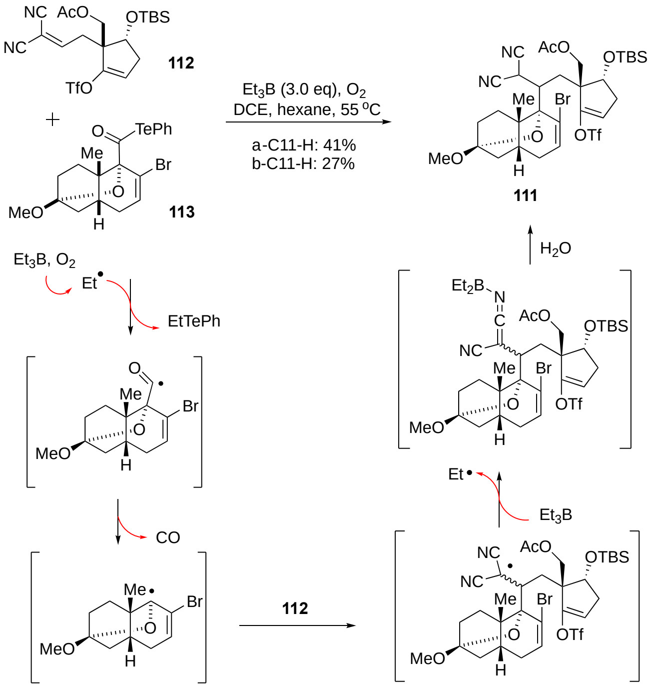


Scheme 25. Synthesis of the key intermediates[44]

2.7. Pd/Ni-promoted Ulman coupling in the synthesis of the batrachotoxin core by the Inoue group[44]

Batrachotoxin is a steroidal alkaloid with neurotoxic properties isolated in 1968 from the skin of Columbian poison-arrow frogs.[45] Batrachotoxin features multiple fused rings and high level of skeletal oxidation, and represents a formidable synthetic target.[7k,46] In 2018 Inoue's group disclosed a new approach that allowed for the synthesis of batrachotoxin's steroidal core **110** (Scheme 24), which could potentially be expanded to the synthesis of batrachotoxin.[44] Intermediate **110** was generated from **111** through the intramolecular Pd/Ni-catalyzed Ullman coupling reaction. Compound **111**, in turn, was prepared by the radical addition of **113** to **112**, which represents another the key step in the synthesis of **110**.

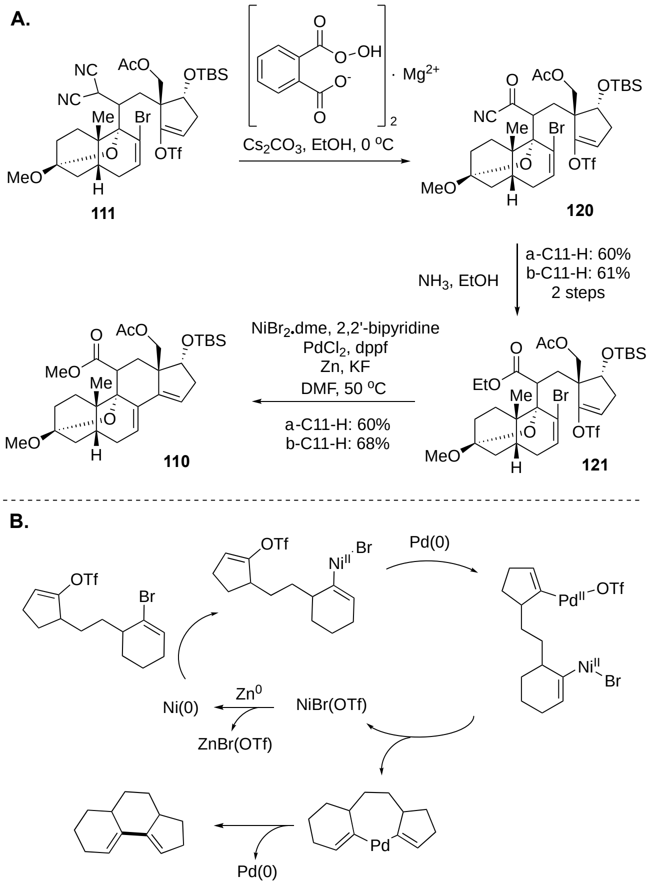
The synthesis of intermediate **112** commenced with the asymmetric Noyori transfer hydrogenation of prochiral substrate **114** resulting in the desymmetrized reduction product in 96% ee (Scheme 25). The following TBS protection resulted in **115** (59% yield, 2 steps). This product was enolized in the pesence of the Commins' reagent to provide **116** (84%), which was converted to **112** in 3 steps via the oxidative cleavage of the terminal alkene followed by the aldol condensation with malononitrile (80%, 3 steps). The synthesis of **113** commenced with **117** that was derived from Wieland-Miescher ketone. This compound was reacted with lithiated vinyl ethyl ether, and the resultant product was subjected to 1,3-dioxolane hydrolysis/intramolecular acetalization ($CH(OMe)_3$, MeOH, CSA) followed by the oxidative cleavage of the vinyl ether moiety ($RuCl_3$, $NaIO_4$) to provide **118** in 58% yield.



Scheme 26. Coupling of intermediates **112** and **113** leading to **111**[44]

With both fragments **112** and **113** in hand, the subsequent coupling was attempted (Scheme 26) using Et_3B and molecular oxygen. The mechanism of this transformation is depicted in Scheme 26 and commences with Et_3B reacting with oxygen and producing ethyl radical. Ethyl radical then abstracts Te from the C-Te bond of **113**. The resultant acyl radical undergoes a subsequent decarbonylation to provide an α-alkoxy radical with fixed stereochemical configuration.[47] The following addition to the electron deficient alkylidenemalonitrile **112** provides a stabilized radical that is subsequently trapped with Et_3B to form boron enolate, which hydrolyses upon work up and provides **111** (α-C11-H, 41% yield; β-C11-H, 27% yield).

With this in hand, the intermediate **111** was elaborated to batrachotoxin core **110** (Scheme 27A). These studies commenced with the oxidation of the malononitrile moiety with monoperoxyphthalate to provide **120**, which was subjected to ethanolysis under the basic conditions (NH_3, EtOH) leading to **121** (α-C11-H, 60% yield; β-C11-H, 61% yield). This substrate contains both vinyl bromide and vinyl triflate moieties that provide handles for the subsequent reductive cyclization.



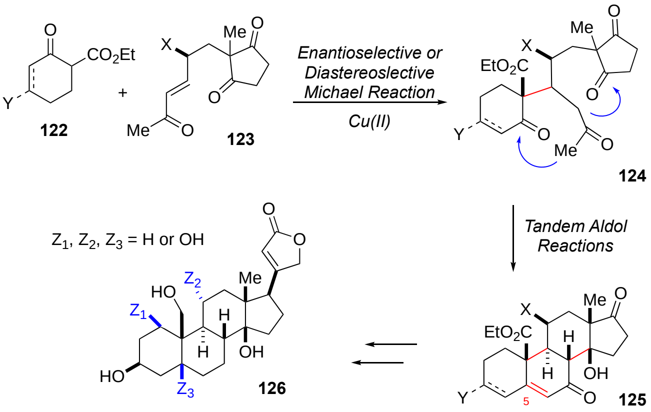
Scheme 27. A. Synthesis of batrachotoxin core **110**. **B.** Potential mechanism for the Pd/Ni-catalyzed Ullman coupling[44,48]

The Inoue group first employed Ni-catalyzed Ullman coupling ($NiCl_2$, 2,2'-bipyridine, Zn, CH_3CN, Py, 50 °C); however, this transformation did not lead to high yields of **110** due to the slow oxidative insertion into C-OTf bond. Subsequently, a modified protocol developed by the Weix group and utilizing dual Pd/Ni catalytic system was employed.[48] Low yields were observed when the transformation was attempted catalytically; however, the use of stoichiometric metal complexes tripled the yields of **110**. While the actual reaction mechanism is yet to be clarified, based on the Weix group proposal, a catalytic cycle depicted in Figure 27B and potentially involving a bimetallic intermediate could be envisioned.

3. Syntheses Enabled by the Lewis Acid Catalysis

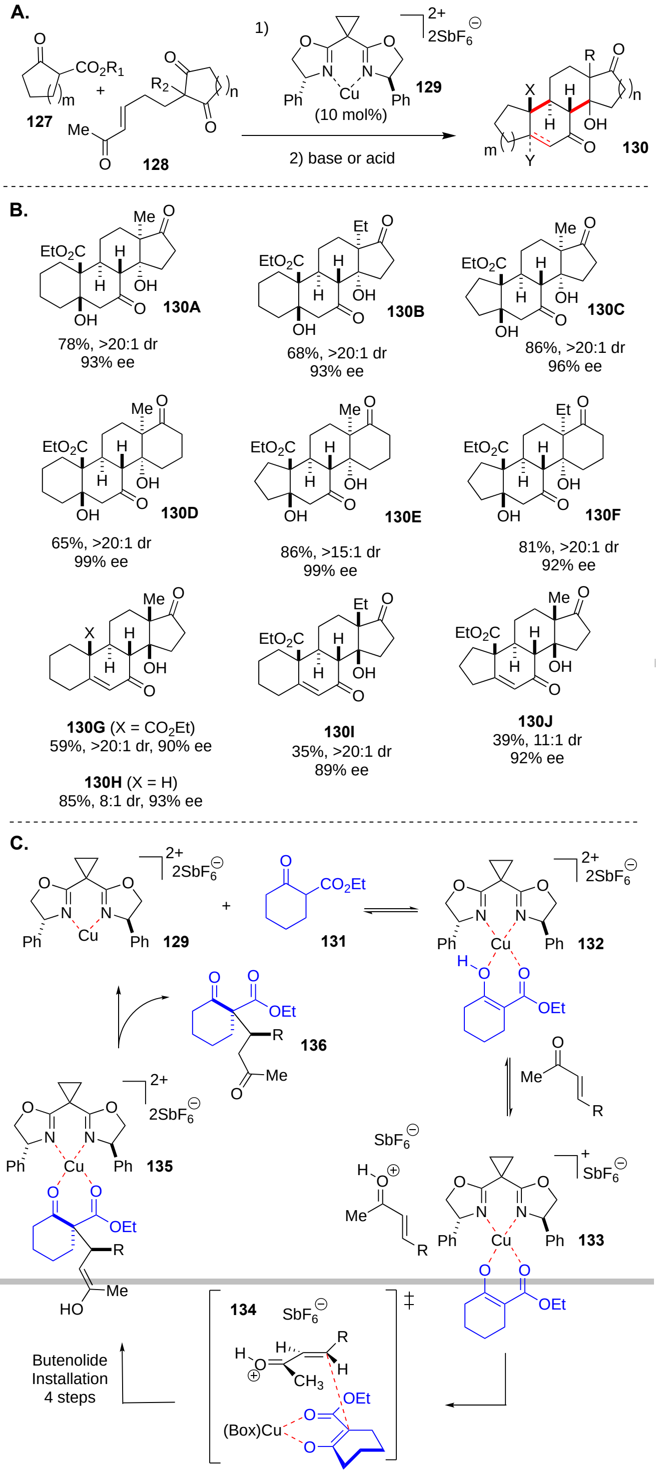
3.1. Cu(II)-catalyzed enantioselective tandem Michael/Aldol reactions in the synthesis of cardiotonic steroids by Nagorny and coworkers[49]

Cardiotonic steroids represent a large family of steroids with unique structural features such as characteristic β–C14 alcohol, β-C17 heterocyclic ring, and an unusual *cis*-C/D ring junction pattern, which imparts a rigid "U" shape to the molecule. Around a thousand of different natural cardenolides have been isolated to date from various plant and animal sources. Considering that cardenolides are involved in regulating vital biological processes and for centuries have been used as therapeutic agents, the total synthesis of cardenolides has attracted considerable attention. Despite these numerous studies, the synthesis of highly oxygenated cardenolides, such as ouabagenin, represents a significant challenge, and only recent advances in catalysis and synthetic methodology allowed to overcome some of these challenges. Such landmark efforts include the recently disclosed syntheses of ouabagenin and 19-hydroxysarmentogenin by the Deslongchamps,[50] Baran[36] and Inoue[51] groups as well as the studies by the Nagorny group that will be the focus of this mini-review.[49]



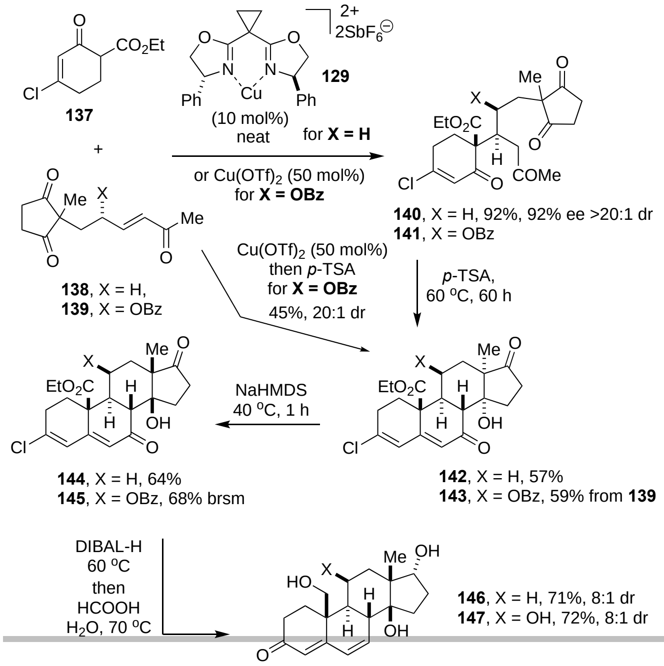
Scheme 28. Cu(II)-catalyzed tandem Michael/aldol reaction approach to the synthesis of cardiotonic steroids[49]

The tandem Michael/aldol reaction approach to cardiotonic steroids is summarized in Scheme 28. This approach is based on the presumption that enones **123** and β-ketoesters **122** could undergo a stereoselective Michael reaction to provide **124**. Subjecting **124** to tandem aldolization under acidic or basic conditions would lead to **125**, which represents a fully functionalized cardenolide skeleton that could be further elaborated into steroids **126** featuring various oxidation patterns. Michael reactions are sensitive to the substrate sterics, and the transformations leading to products like **124** that contain vicinal quaternary/tertiary all-carbon stereocenters are very rare. After screening a variety of conditions, Nagorny and coworkers identified Cu(II) salts as unique catalysts for this transformation under no solvent conditions. Based on these findings, in 2015 Nagorny group demonstrated that the formation of **130** is possible in a highly enantioselective and diastereoselective fashion from simple and readily available building blocks **127** and **128** (Scheme 29).[49g] Thus, it was demonstrated that readily available chiral *bis*(oxazoline) copper(II) complex **129** could promote



Scheme 29. Enantioselective Cu(II)Box-catalyzed Michael/aldol cascade approach to cardenolide core. **A.** Overall transformation. **B.** Substrate scope. **C.** Tentative reaction mechanism[49c,g]

Michael reactions with high levels of stereocontrol and the stereochemistry required for their subsequent elaboration to natural cardiotonic steroids (Scheme 29A). These Michael adducts could be subjected to various acidic or basic conditions that promote the intramolecular aldolization and provide various steroid-like cores **130A-J**. The choice of the cyclization conditions was of particular importance for establishing the stereochemistry of the CD ring junction. By using DBU as base in THF, the Michael adducts were converted into products **130A-F** with unnatural α-configuration of the C13/C14 stereocenters in good to excellent yields and selectivities. Alternatively, treating the substrate with Cs_2CO_3 in DMF at 140 ºC led to the product **130G** possessing natural β-C13/β-C14 configuration. Similarly, subjecting the Michael adducts to 2 step conditions involving pre-cyclization of the B-ring using pyrolidinium acetate followed by the formation of the C-ring with LiHMDS or NaHMDS led to products **130I-J**. Finally, the reaction with β-ketocarboxylic acid instead of ester (i.e. **142**, R_1=H), led to the formation of nor-steroid skeleton **130H** in good yield and selectivity (85%, 8:1 dr, 93% ee, gram scale).[51c] The tentative mechanism of this transformation is depicted in Scheme 29C. Unlike the majority of other Cu(II)Box-catalyzed reactions, **129** is proposed to bind and activate nucleophile **131** rather than enone electrophile. The chelation of **129** and **131** leads to the formation of complex **132** that then transfers a proton to the enone and results in Cu(II)-based chiral enolate **133**. The subsequent Michael reactions presumably happens through an open transition state **134** and results in the corresponding product **136**.



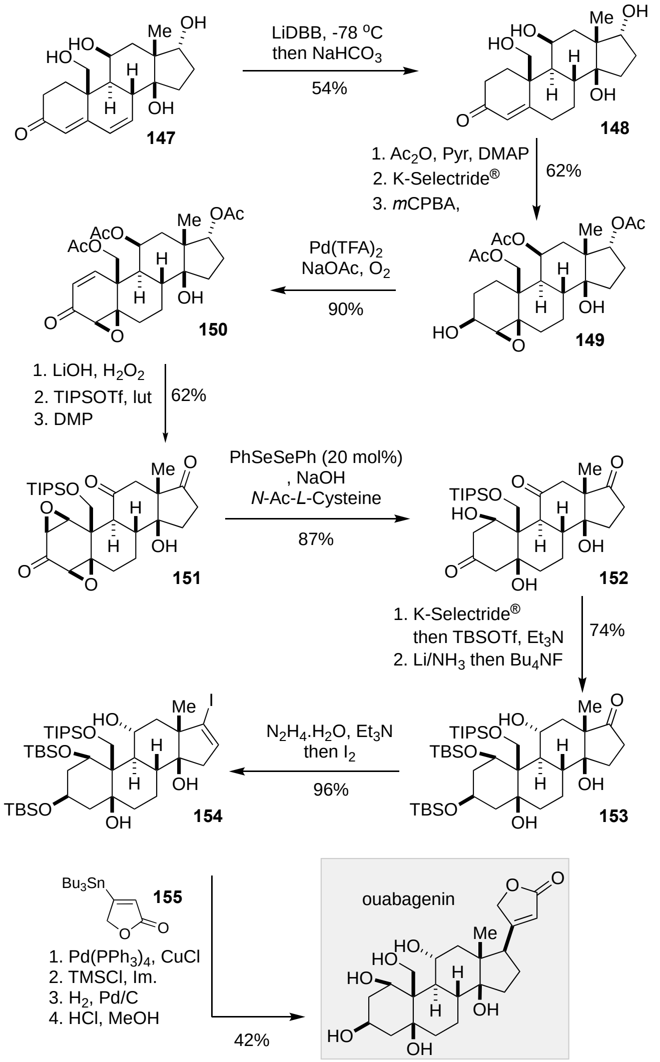
Scheme 30. Enantioselective and diastereoselective Cu(II)-catalyzed Michael/aldol cascade reactions for the synthesis of functionalized cardenolides cores 1**46** and **147**[49a,d,e]

These studies were subsequently translated into the synthesis of more complex cardenolide cores **146** and **147** (Scheme 30) that were later elaborated to a variety of natural cardenolides.[49a,d,e] The modified approach required adjusting the oxidation state of both the β-ketoester and enone fragments in order to install the C3 and, optionally, C11 oxygenation. To address the problems associated with the installation of the C3 stereochemistry, vinylchloride-containing β-ketoester **137** was employed. β-Ketoester **137** reacted with either the achiral enone **138** or prepared in 3 steps OBz-containing chiral enone **139** (Scheme 30). In the former case, the reaction was catalyzed by chiral catalyst **129** that promoted the formation of Michael adduct **140** in 92% yield, 92%ee, >20:1 dr. This compound was then cyclized with *p*-TSA to provide functionalized steroidal core **142** (57% yield, >20:1 dr).

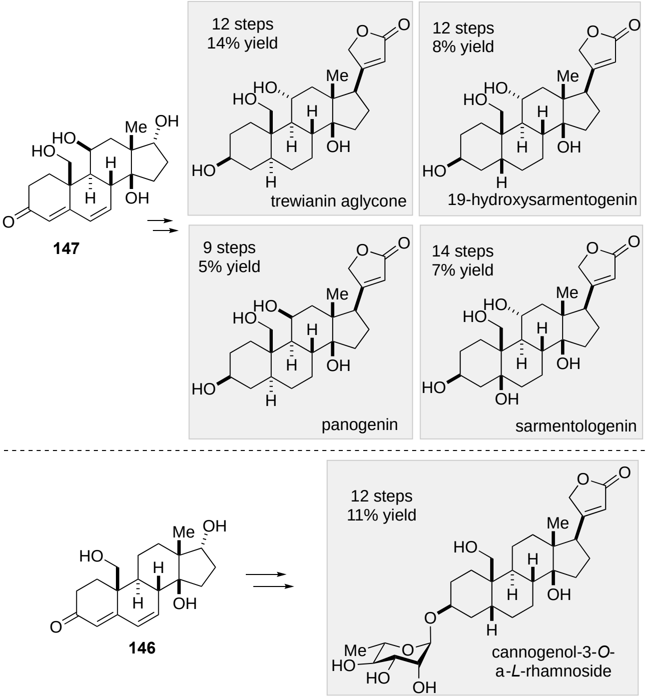
In the case of chiral enone **139**, the Michael reaction with **137** was catalyzed by $Cu(OTf)_2$ (50 mol%), and resulted in the diastereoselective formation of product **141** in 70% yield as well as a monocyclized aldol product resulting from **141** (20% yield). Subjection of both of these compounds to *p*-TSA in the subsequent step resulted in the formation of aldol adduct **143** (59% yield from **139**). Alternatively, the formation of **143** from **139** and **137** could be executed in a single operation (45% yield, 20:1 dr) by carrying both steps in one pot. In both cases the stereoselective formation of all 5 new stereocenters was imposed by the C11-OBz group-containing stereocenter.

The aforementioned protocols enabled concise formation of the steroidal cores **142** and **143** on multigram scale. Both of these intermediates contained the desired stereochemistry and oxygenation with the exception of the α-C13/α-C14 stereocenters at the CD ring junction. However, our DFT calculations indicated that the natural β-C13/β-C14 configuration present in **144** and **145** has higher thermodynamic stability. Therefore, **142** and **143** were subjected to retro-Aldol/Aldol sequence resulting in the net epimerization of the C13/C14 stereocenters and providing **144** and **145** in 64% and 68% (brsm) respectively. These products underwent the global reduction with DIBAL-H followed by the solvolysis of vinyl chlorides to generate unsaturated C3 ketones in an efficient one pot transformation (71% yield, 8:1 dr and 72% yield, 8:1 dr for **146** and **147**, correspondingly). Both advanced intermediates were produced in only 6 steps (LLS) on a multigram scale and contained all of the necessary functionalization to be advanced to various cardiotonic steroids (Schemes 31 and 32).

More advanced intermediate **147** contains oxygenations at the C3, C11, C14, C17, and C19 positions as well as the unsaturation at the C-5 position, which is critical for its rapid elaboration to various highly oxygenated cardenolide ouabagenin (Scheme 31).[51a] The presence of the additional C1/C5 oxygenation in ouabagenin makes this important natural product to be one of the most complex targets among the cardiotonic steroids. The synthetic studies towards ouabagenin commenced with the reduction of the Δ^7-olefin of **147** with LiDBB, followed by a basic work-up with $NaHCO_3$ to provide **148**. Polyol **148** was then subjected to a 3 step sequence that included acetylation of the C11, C17, and C19 positions (Ac_2O, Py, DMAP), diastereoselective reduction of the C3 ketone with K-Selectride®, and C3-directed epoxidation of the Δ^4-olefin with *m*-CPBA (6:1 dr for epoxidation step) to afford **149** in 62% yield. The following oxidation of **149** with Pd(TFA)$_2$ and NaOAc under molecular oxygen atmosphere afforded **150** in 90% yield. Enone **150** was subjected to another 3 step sequence to furnish **151** (62% yield) as a single diastereomer. This was accomplished by deacetylation followed by the Δ^1-epoxidation with LiOH and H_2O_2 to generate the C1/C2 epoxide, as a single diastereomer. The C19 hydroxyl of this *bis*-epoxide underwent selective protection as the TIPS ether (TIPSCl, 2,6-lutidine) that followed by the oxidation of the C11 and C17 hydroxyls to afford **151**. The reduction of the epoxide moieties of **151** represented a significant challenge due to the propensity of the resultant product to undergo dehydration leading to a complex mixture of enones. After extensive screening, the conditions that involved the reduction of **151** with PhSeSePh (20 mol%) and *N*-Ac-*L*-Cys-OH under basic conditions resulted in the desired product **152** in 87% yield. Careful control of the *N*-Ac-*L*-Cys and NaOH stoichiometry was required to avoid water elimination and subsequent aromatization of the A ring. Then **152** was subjected to a single pot diastereoselective reduction of the C3 ketone with K-Selectride® followed by the protection of the C3 and C17 alcohols as the TBS ether and enol ether, respectively (TBSOTf, 2,6-lutidine). The resultant product was subjected to another single pot procedure that involved the C11 ketone reduction under dissolving metal conditions to obtain the equatorial C11 alcohol, followed by work up with TBAF that provided ouabagenin core **153** in 74% yield over two steps. Vinyl iodide moiety at C17 was then installed using Barton's protocol to give **154** in 96% yield. The final installation of the C-17 butenolide was achieved via a four-step sequence involving: 1) a Stille coupling of vinyl iodide **154** with stannane **155**, 2) TMS protection of the C11 and C14 alcohols, 3) diastereoselective hydrogenation of Δ^{16}- double bond, and 4) global deprotection of silyl-protecting groups with aqueous HF to afford ouabagenin in 42% over the final four steps.



Scheme 31. Elaboration of core **147** into cardenolide ouabagenin[49a]



Scheme 32. Elaboration of cores **146**/**147** into various cardiotonic steroids[49]

The aforementioned strategy for the assembly of ouabagenin could be generally applied to a variety of other cardiotonic steroids (Scheme 32).[49c,d] Thus, key intermediate **147** was successfully elaborated to diastereomeric cardenolides trewianin aglycone (12 steps, 14% yield), [49a,d] 19-hydroxysarmentogenin (12 steps, 8% yield), [49a,d] panogenin (9 steps, 5% yield) [49a] and 5-*epi*-panogenin (9 steps, 23% yield)[49a,d] that have different configurations at the C5 and C11 stereocenters. In addition, these efforts provided sarmentologenin (14 steps, 7% yield) that lacks C1-oxygenation in comparison to ouabagenin.

Similar strategy was used to convert the intermediate **146** lacking the C11 stereocenter into glycosylated cardiotonic steroid cannogenol-3-*O*-α-*L*-rhamnoside (12 steps, 11% yield) and its analogs with modified sugar.[49d]

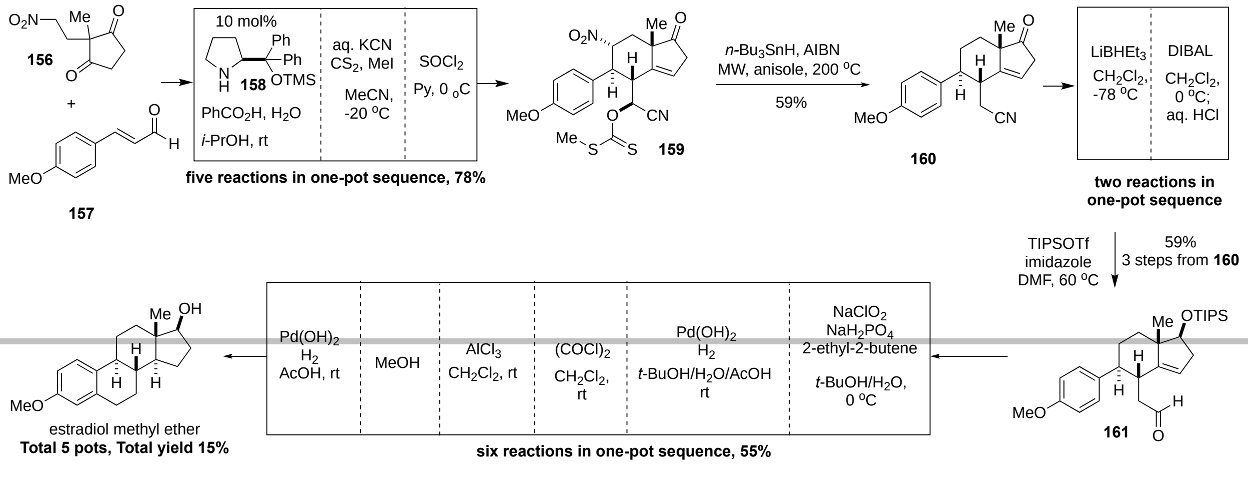
4. Syntheses Enabled by the Organocatalysis

The seminal studies of Hajos, Parrish, Eder, Sauer and Wiechert revolutionized the synthesis of steroids and terpenoids and helped to reveal the power of organocatalysis for the synthesis of complex natural products.[52] Not surprisingly, the development of new organic catalysts and organocatalyzed tandem reactions is still of great importance to the synthesis of steroids. While many modern studies are focused on improving the synthesis and formation of functionalized Hajosh-Parrish and Wieland-Miescher ketones, the developments in organocatalysis allow to achieve rapid formation of significantly more complex intermediates. This subsection of the mini review highlights some of such studies that emerged from the groups of Hayashi,[53] Hong[54] and List.[55]

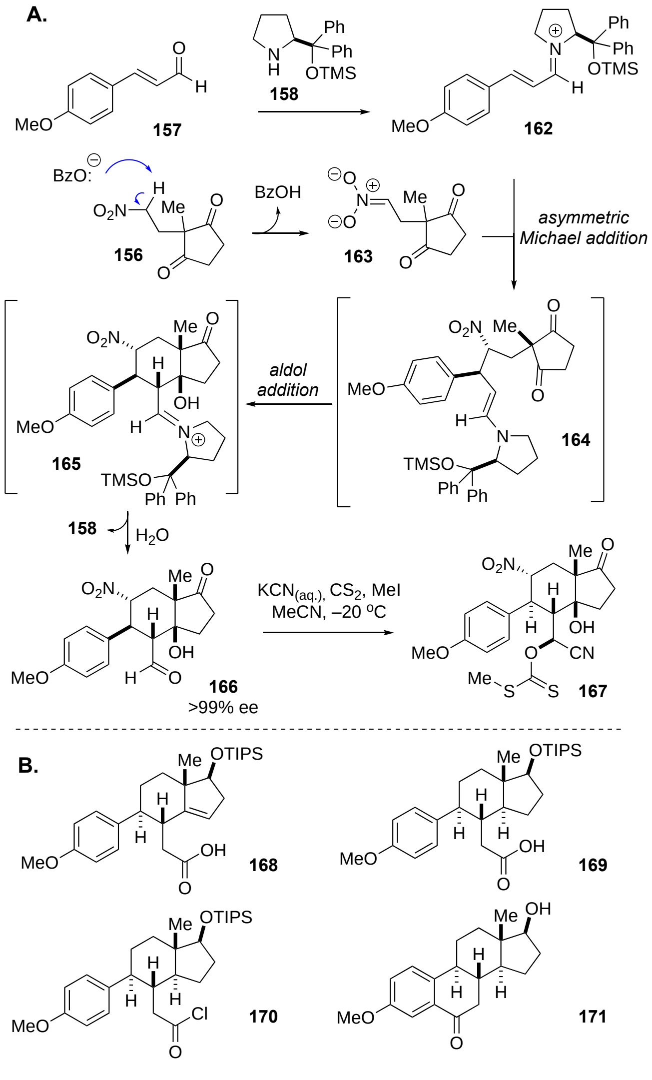
4.1. Pot-economical total synthesis of estradiol methyl ether by the Hayashi group[53]

Interested in developing rapid and economical ways for the synthesis of pharmaceutically important natural products,[56] Hayashi and co-workers recently reported a highly pot-economical synthesis[53] of estradiol methyl ether using proline-derived organocatalyst **158** (*cf.* Scheme 33).[57] The highlight of their synthesis involves an expedient stereo-controlled construction of the intermediate **159** with all carbons necessary for installing the steroid framework within the first pot. The reaction involves diphenylprolinol trimethylsilylether (**158**) catalyzed asymmetric reaction between nitroalkane **156** and 3-(*p*-methoxyphenyl)-propenal **157**. The mechanism of this transformation is depicted in Scheme 34A. The condensation of **157** and **158** leads to the formation of iminium ion **162**, which undergoes an asymmetric Michael reaction with nitronate anion **163** derived from **156**. This results in an enamine-containing product **164** that undergoes highly selective addition to one of the ketone moieties of the 1,3-cyclopentanedione linked to the enamine. Upon hydrolysis of the resultant iminium ion **165**, the bicyclic structure **166** containing five contiguous stereocenters is obtained. The selectivity of this domino reaction is remarkable and provides essentially a single diastereomer with very high enantioselectivity (>99% ee). This reaction was successfully telescoped with two other subsequent reactions: 1) stereoselective addition of cyanide followed by the formation of xanthate ester **167** (*cf.* Scheme 34A), and 2) dehydration using $SOCl_2$ and pyridine to afford intermediate **159** in 78% yield from **156** and **157** in the first pot (*cf.* Scheme 33). The simultaneous removal of nitro-group and xanthate in **159** was carried out reductively using Bu_3SnH and AIBN under microwave condition and resulted in **160**. This intermediate was subjected a two-step one pot sequence involving diastereoselective reduction of the ketone and nitrile via sequential addition of $LiBHEt_3$ at -78 ^oC and DIBAL at 0^{o}C. The resulting hydroxyl aldehyde after TIPS protection (TIPSCl, imidazole) affords aldehyde **161** in 59% yield from **160**. What follows next is a remarkable six-step one-pot sequence depicted in Scheme 33 that includes 1) Krauss-Pinnick oxidation yielding **168** (Scheme 34B), 2) *trans*-hydrindane-selective hydrogenation controlled by OTIPS group and leading to **169**, 3) acyl chloride **170** formation, 4) Friedel-Crafts acylation 5), deprotection of the silyl group by the addition of MeOH leading to **171**, and 6) reduction of benzyl ketone to give estradiol methyl ether in 55% yield. The synthesis highlights the idea of compatibility in one-pot transformations and accomplishes the synthesis of estradiol methyl ether in five reaction pots involving four purification steps.

Scheme 33. Hayashi's pot-economical synthesis of estradiol methyl ether[53]



The key domino reaction of diphenylprolinol silyl-ether mediated Michael reaction of nitroalkane and intramolecular aldol reaction is quite general in terms of aryl group at 3-position of propenal as various electron rich (*p*-methoxy-, *p*-methyl-) as well as electron deficient (*p*-fluoro-, *p*-bromo-, *p*-chloro-, *o*-fluoro-) aryl group containing enals afford bicycle [3,3,0] nonane frameworks with excellent enantioselectivity.



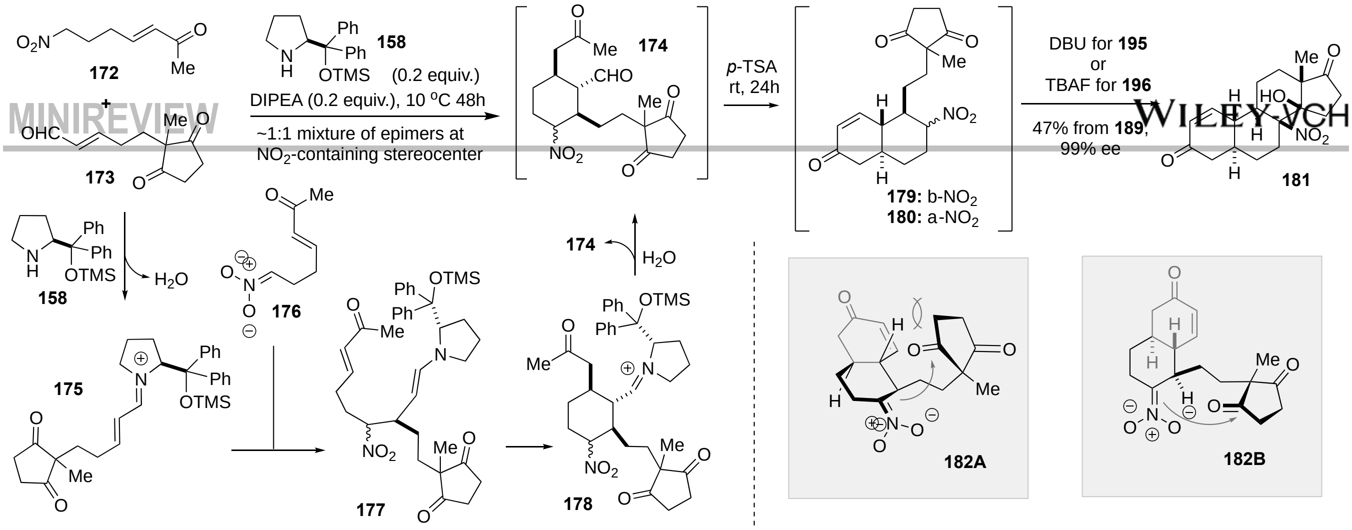
Scheme 34. A. Mechanism for the formation of intermediate **167**. **B.** Synthetic intermediates for the pot-economical synthesis of estradiol methyl ether[53]

4.2. Organocatalytic enantioselective Michael-Michael-Aldol-Henry reaction cascade for the one pot synthesis of *nor*-steroid skeleton by Hong and coworkers[54]

In 2014, Hong and coworkers reported a one pot organocatalytic enantioselective double Michael/aldol/Henry cascade reactions to assemble enantiomerically enriched *nor*-steroid **181** from simple precursors **172** and **173**.[54] This approach is based on the organocatalytic union of **172** and **173** catalyzed by the organocatalyst **158** (Scheme 35). This transformation represents the key step in the sequence leading to **181** and proceeds through the initial formation of iminium ion **175** from **173** and prolinol derivative **158**.[57] Iminium **175** undergoes a subsequent Michael reaction with nitronate anion **176** derived from **172**. This transformation proceeds with high levels of stereocontrol at the newly formed carbon stereocenter; however, a ~1:1 mixture of diastereomers at the stereocenter containing the nitro- group is formed. The chiral prolinol portion of the resultant adduct **177** is of great importance for controlling the stereochemistry of the subsequent intramolecular Michael addition of enamine into enone to provide intermediate **178**, which subsequently undergoes hydrolysis to form aldehyde **174** as a 1:1 mixture of epimers at the nitro- group containing stereocenter. This transformation was followed by *in situ* addition of *p*-TSA that led to intramolecular aldol condensation to form the mixture of **179** and **180** epimeric at the NO_2-containing stereocenter. The one pot sequence leading to **181** was then completed by the sequential addition of DBU followed by TBAF. Both reagents promoted the intramolecular Henry reaction by deprotonation leading to nitronate intermediate **182**; however, the addition of DBU triggered the cyclization of **179** while TBAF was required for the reaction of **180** to happen. The cyclization presumably proceeds through the transition state **182B** (rather than **182A**) and leads to the natural configuration of the CD ring junction. The desired product **181** was obtained in 47% yield over the entire single pot sequence as a single isomer. Its absolute and relative configurations corresponded to the stereochemistry observed for the natural cardiotonic steroids.

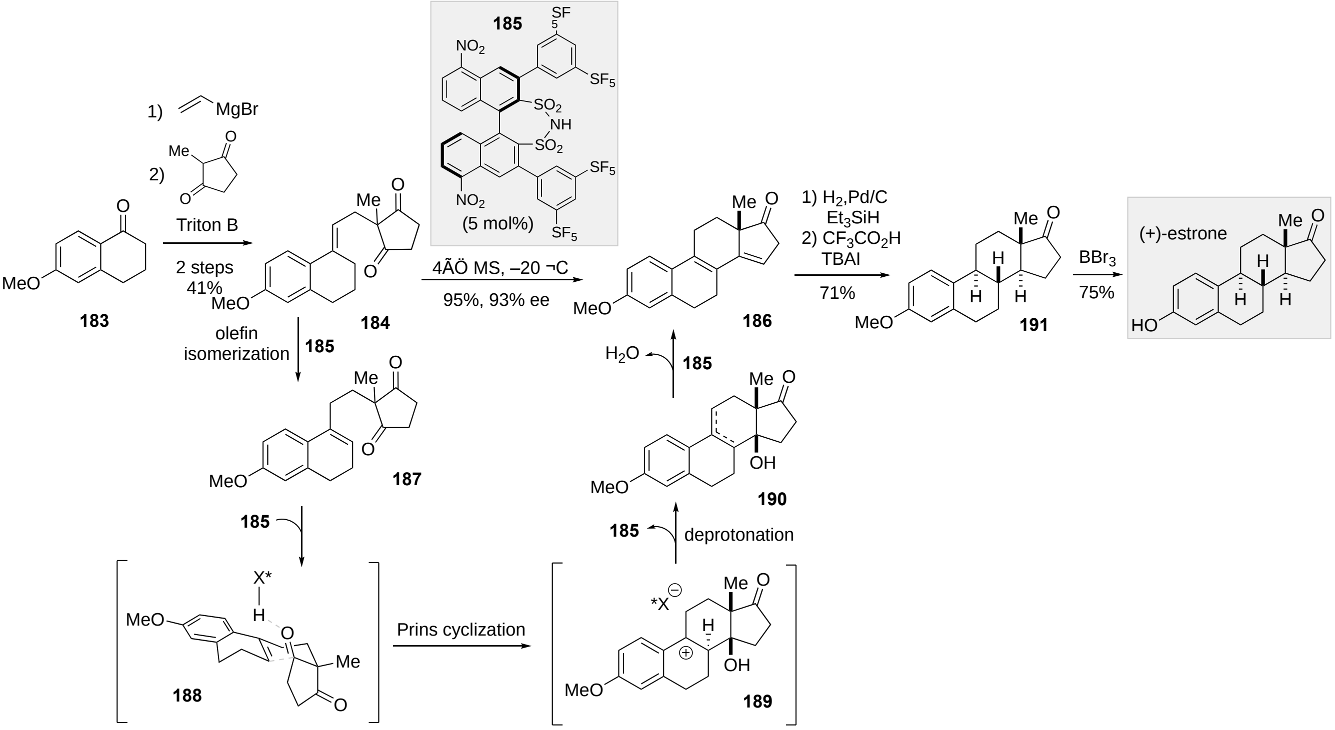
4.3. Organocatalytic chiral Br∅nsted acid-catalyzed synthesis of estrogen by List and coworkers[55]

While many applications of organocatalysis in synthesis of steroids are based on the exploration of chiral amine catalysis, other applications started to immerge in the recent years. Thus, in 2014, Benjamin List's group reported an asymmetric synthesis of (+)-estrone that was enabled by the chiral Br∅nsted acid catalysis (*cf.* Scheme 36).[55] This synthesis was based on the racemic approach by Torgov, who in 1963, described an acid catalyzed cyclization of easily available diketone **184** into a steroidal $\Delta^{8,14}$-dienone **186**, which is a useful precursor to various steroids including estrone.[58] Even though Torgov's cyclization-represents an efficient way to generate racemic steroidal scaffolds, the development of the corresponding enantioselective variants has always been elusive.[59] Mechanistically, the developed Torgov's cyclization involves four sequential acid catalyzed steps: 1) isomerization of exocyclic $\Delta^{9,11}$-olefin in compound **184** to the endocyclic $\Delta^{8,9}$-isomer **187**; 2) intramolecular Prins-type cyclization through **188** leading to a stabilized carbocation **189**; 3) deprotonation of carbocation **189** to give isomeric mixture of olefins **190**, and 4) isomerization and dehydration of **190** to furnish Torgov's diene **186**. List's group realized that the likely stereo-determining step, the cyclization of



Scheme 35. One pot construction of nor-cardenolide core **181** by Hong and coworkers[54]

Scheme 36. Synthesis of (+)-estrone by enantioselective Torgov's cyclization using chiral acid **201**[55]



188 to **189**, could potentially be catalyzed by using chiral Br∅nsted acid.[60] In fact, upon screening of various chiral Br∅nsted acids, a unique chiral disulfonamide (DSI) catalyst **185** containing SF_5- and NO_2- substituents was found to catalyze the cyclization in high yield and high enantioselectivity (95% yields, 93% ee). A single recrystallization essentially provided enantiopure compound **186** (>99.8% ee). It is noteworthy that precious DSI catalyst **185** could be recovered in 88% yield and reused following the acidification with similar efficacy. Diene **186** was then successfully converted to (+)-estrone by using two-step diastereoselective reduction protocol developed by E.J. Corey.[61] This sequence included stepwise reduction of first Δ^{14}- (Pd/C, H_2, Et_3SiH) and then Δ^{8}- (CF_3CO_2H, TBAI, Et_3SiH) alkene moieties followed by the deprotection of (+)-estrone methyl ether with BBr_3.

5. Conclusion and Outlook

This mini review has highlighted some recent progress in the synthesis of steroids that was enabled by the advances in catalysis. The rapid progression of the field of catalysis has greatly expanded the toolbox of a synthetic organic chemist and provided new powerful transformations that allow to install complex functionalities in a highly selective and mild manner. This has resulted in many new and creative approaches to complex steroidal skeletons that feature high efficiency and allow to accomplish multiple steps in a single reaction pot. Such approaches provide robust platforms for the subsequent medicinal chemistry exploration of steroids and other related natural products and their derivatives.

Acknowledgments

The authors are grateful to NIH (R01GM111476) for the financial support.

Keywords: steroid • terpenoid • synthesis • catalysis • review

---

[1] E. J. Corey, B. Czako, L. Kurti *Molecules and Medicine*, Hoboken, NJ: Wiley-VCH **2007**.

[2] a) J. Feng, M. Holmes, M. J. Krische, *Chem. Rev.* **2017**, *117*, 12654; b) E. A. Peterson, L. E. Overman, *Proc. Nat. Acad. Sci. U. S. A.* **2004**, *101*, 11943; c) M. Buschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem. Int. Ed.* **2016**, *55*, 4156.

[3] a) N. A. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed*. **2009**, *48*, 2854; *Angew. Chem.* **2009**, *121*, 2896; b) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010.

[4] a) J. W. Lehmann, D. J. Blair; M. D. Burke, *Nature Rev. Chem.* **2018**, *2*, 0115; b) J.-L. Shih, P.-A. Chen, J. A. May, *Beilstein J. Org. Chem*. **2016**, *12*, 985; c) R. Ardkhean, D. F. J. Caputo, S. M. Morrow, H. Shi, Y. Xiong, E. A. Anderson, *Chem. Soc. Rev.* **2016**, *45*, 1557.

[5] Selected reviews related to the synthesis of steroids: a) M. T. C. Pessoa, L. A. Barbosa, J. A. F. P. Villar, *Stud. Nat. Prod. Chem.* **2018**, *57*, 79; b) H. Mizoguchi, *J. Synth. Org. Chem. Japan* **2017**, *75*, 253; c) M. Michalak, K. Michalak, J. Wicha, *Nat. Prod. Rep.* **2017**, *34*, 361; d) P. Gupta, G. Panda, *Eur. J. Org. Chem.* **2014**, 8004; e) R. Singh, G. Panda, *Tetrahedron* **2013**, *69*, 2853; f) B. Heasley, *Chem. Eur. J*. **2012**, *18*, 3092; g) M. Kotora, F. Hessler, B. Eignerova, *Eur. J. Org. Chem.* **2012**, 29; h) J. R. Hanson, *Nat. Prod. Rep.* **2010**, *27*, 887; i) D. F. Covey, *Steroids* **2009**, *74*, 577; j) J. Wolfling, *ARKIVOC (Gainesville, FL, U.S.)* **2007**, 210; g) M. Ibrahim-Quali, *Steroids* **2008**, *73*, 375; k) M. Ibrahim-Quali, *Steroids* **2007**, *72*, 475; M. Ibrahim-Quali, M. Santelli, *Steroids* **2006**, *71*, 1025; l) A. S. Chapelon, D. Moraléda, R. Rodriguez, C. Ollivier, M.Santelli, *Tetrahedron* **2007**, *63*, 11511; m) L. F. Tietze, H. P. Bell, S. Chandrasekhar, *Angew. Chem. Int. Ed*. **2003**, *42*, 3996; *Angew. Chem*. **2003**, *115*, 4128; n) R. Skoda-Foldes, L. Kollar, *Chem. Rev.* **2003**, *103*, 4095; o) J.F. Biellmann, *Chem. Rev.* **2003**, *103*, 2019; p) G. Mehta, V. Singh, *Chem. Soc. Rev.* **2002**, *31*, 324.

[6] For the selected reviews on the synthesis of terpenoids refer to: a) K. Hung, X. Hu, T J. Maimone, *Nat. Prod. Rep*. **2018**, 35, 174; b) Y. Zou, A. B. Smith III, *J. Antibiot.* **2018**, *71*, 185; c) Z. G. Brill, M. L. Condakes, C. P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753; d) M. A. Corsello, J. Kim, N. K. Garg, *Chem. Sci.* **2017**, *8*, 5836; e) J. E. Zweig, D. E. Kim, T. R. Newhouse, *Chem. Rev*. **2017**, *117*, 11680; f) C. N. Ungarean, E. H. Southgate, D. Sarlah, *Org. Biomol. Chem.* **2016**, *14*, 5454; g) Urabe, D.; Asaba, T.; Inoue, M. *Chem. Rev.* **2015**, *115*, 9207; h) P. S. Riehl, Y. C. DePorre, A. M. Armaly, E. J. Groso, C. S. Schindler, *Tetrahedron* **2015**, *71*, 6629; i) Yoshimura, T. *Tetrahedron Lett.* **2014**, *55*, 5109; j) E. C. Cherney, P. S. Baran, *Is. J. Chem.* **2011**, 51, 391.

[7] For the selected examples of the studies in the area of steroid total synthesis published since 2014 and not covered in this review refer to: a) Y. Wang, W. Ju, H. Tian, S. Sun, X. Li, W. Tian, J. Gui, *J. Am. Chem. Soc.* **2019**, *141*, 5021; b) R. C. Heinze, P. Heretsch, *J. Am. Chem. Soc.* **2019**, *141*, 1222; c) D. E. Kim, J. E. Zweig, T. R. Newhouse, *J. Am. Chem. Soc.* **2019**, *141*, 1479; d) A. Nagata, Y. Akagi, S. S. Masoud, M. Yamanaka, A. Kittaka, M. Uesugi, M. Odagi, K. Nagasawa, *J. Org. Chem*. **2019**, *84*, 7630; e) Y. Zou, X. Li, Y. Yang, S. Berrit, J. Melvin, S. Gonzales, M. Spafford, A. S. Smith III, *J. Am. Chem. Soc*. **2018**, *140*, 9502; f) J. Liu, J. Wu, J.-H. Fan, X. Yan, G. Mei, C.-C. Li, *J. Am. Chem. Soc.* **2018**, *140*, 5365; g) Y. Wang, W. Ju, H. Tian, W. Tian, J. Gui, *J. Am. Chem. Soc.* **2018**, *140*, 9413; h) J. Danielsson, D. X. Sun, X.-Y. Chen, A. L. Risinger, S. L. Mooberry, E. J. Sorensen, *Org. Lett*. **2017**, *19*, 4892; i) G. Xu, M. Elkin, D. Tantillo, T. R. Newhouse, T. Maimone, *Angew. Chem. Int. Ed*. **2017**, *56*, 12498; *Angew. Chem*. **2017**, *129*, 12672; j) A. Nakazaki, K. Hashimoto, A. Ikeda, T. Shibata, T. Nishikawa, *J. Org. Chem.* **2017**, *82*, 9097; k) M. M. Logan, T. Toma, R. Thomas-Tran, J. Du Bois, *Science* **2016**, *354*, 865; l) R. J. Sharpe, J. S. Johnson,. *J. Am. Chem. Soc.* **2015**, *137*, 4968; m) A. M. Camelio, T. C. Johnson, D. Siegel, *J. Am. Chem. Soc.* **2015**, *137*, 11864.

[8] K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang, W. Tang, *Angew. Chem. Int. Ed*. **2015**, *54*, 3033.

[9] a) A.-S. Chapelon, D. Moraléda, R. Rodriguez, C. Ollivier, M. Santelli, *Tetrahedron* **2007**, *63*, 11511; b) T. J. Maimone, P. S. Baran, *Nat. Chem. Biol.* **2007**, *3*, 12. C; c) J. Gershenzon, N. Dudareva, *Nat. Chem. Biol.* **2007**, *3*, 408; d) R. A. Yoder, J. N. Johnston, *Chem. Rev.* **2005**, *105*, 4730.

[10] a) M. Mori, K. Chiba, Y. Ban, *Tetrahedron Lett.* **1977**, *18*, 1037; b) Y. Sato, M. Soeoka, M. Shibasaki, *J. Org. Chem.* **1989**, *54*, 4738; c) N. E. Carpenter, D. J. Kucera, L. E. Overman, *J. Org. Chem*. **1989**, *54*, 5846; d) A. B. Dounay, L. E. Overman, *Chem. Rev*. **2003**, *103*, 2945; e) S. P. Maddaford, N. G. Andersen, W. A. Cristofoli, B. A. Keay, *J. Am. Chem. Soc.* **1996**, *118*, 10766.

[11] For overview of this topic, see: a) A. R. Pape, K. P. Kaliappan, E. P. Kundig, *Chem. Rev.* **2000**, *100*, 2917; b) S. Quideau, L. Pouys_gu, D. Deffieux, *Synlett* **2008**, 467; c) L. Pouys_gu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235; d) L. Pouys_gu, T. Sylla, T. Garnier, L. B. Rojas, J. Charris, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 5908; e) S. P. Roche, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068; *Angew. Chem.* **2011**, *123*, 4154; f) C.-X. Zhuo,W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Angew. Chem.* **2012**, *124*, 12834; g) Q. Ding, Y. Ye, R. Fan, *Synthesis* **2013**, 1.

[12] S. Rousseaux, J. Garcia-Fortanet, M. A. D. Aguela Sanchez, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 9282.

[13] M. Del Bel, A. R. Abela, J. D. Ng, C. A. Guerrero, *J. Am. Chem. Soc*. **2017**, *139*, 6819.

[14] P. W. Brian, J. C. McGowan, *Nature* **1945**, *156*, 144.

[15] J. S. Moffatt, J. D. Bu'Lock, T. H. Yuen, *J. Chem. Soc. D: Chem. Commun.* **1969**, 839.

[16] E. A. Anderson, E. J. Alexanian, E. J. Sorensen, *Angew. Chem. Int. Ed*. **2004**, *43*, 1998.

[17] A. Fürstner, O. Thiel, G. Blanda, *Org. Lett.* **2000**, *2*, 3731.

[18] W. A. Cristofoli, B. A. Keay, *Synlett* **1994**, 625.

[19] R. Wittenberg, J. Srogl, M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 3033.

[20] a) W. S. Kim, Z. A. Shalit, S. Nguyen, E. Schoepke, A. Eastman, T. P. Burris, A. B. Gaur, G. C. Micalizio, *Nature Commun.* **2019**, *10*, 2448; b) H. T. Wai, K. Du, J. Anesini, W. S. Kim, A. Eastman, G. C. Micalizio, *Org. Lett.* **2018**, *20*, 6220; c) Kim, W. S.; Du, K.; Eastman, A.; Hughes, R. P.; Micalizio, G. C. *Nat. Chem.* **2017**, *10*, 70.

[21] a) H. A. Reichard, M. McLaughlin, M. Z. Chen, G. C. Micalizio, *Eur. J. Org. Chem.* **2010**, 391; b) H. A. Reichard, G. C. Micalizio, *Chem. Sci.* **2011**, *2*, 573; c) G. C. Micalizio, H. Mizoguchi, *Isr. J. Chem*. **2017**, *57*, 228.

[22] J. Ryan, G. C. Micalizio, *J. Am. Chem. Soc.* **2006**, *128*, 2764.

[23] a) T. Sasaki, S. Eguchi, T. Kiriyama, *J. Org. Chem*. **1973**, *38*, 2230; b) R. L. Danheiser, J. M. Jr. Morin, M. Yu, A. Basak, A. *Tetrahedron Lett.* **1981**, *22*, 4205; c) P. G. Gassman, L. Tan, T. R. Hoye, *Tetrahedron Lett*. **1996**, *37*, 439; d) M. G. Banwell, J. E. Harvey, D. C. R. Hockless, A. W. Wu*, J. Org. Chem.* **2000**, *65*, 4241.

[24] a) G. A. Olah, J. M. Bollinger, *J. Am. Chem. Soc*. **1968**, *90*, 6082; b) C. D. Poulter, S. Winstein, *J. Am. Chem. Soc.* **1969**, *91*, 3649; c) C. D. Poulter, S. Winstein, *J. Am. Chem. Soc.* **1969**, *91*, 3650; d) T. S. Sorensen, K. Ranganayakulu, *Tetrahedron Lett.* **1970**, *11*, 659.

[25] a) S. Seko, Y. Tanabe, G. Suzukamo, *Tetrahedron Lett*. **1990**, *31*, 6883; b) Y. Tanabe, Y. *et al. J. Chem. Soc. Perkin Trans. 1*, **1996**, 2157.

[26] W. S. Kim, C. Aquino, H. Mizoguchi, G. C. Micalizio, *Tetrahedron Lett.* **2015**, *56*, 3557.

[27] a) H. Ishibashi, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc*. **2004**, *126*, 11122; b) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 1505; c) K. Ishihara, S. Nakamura, H. Yamamoto*, J. Am. Chem. Soc.* **1999**, *121*, 4906.

[28] K. Surendra, E. J. Corey, *J. Am. Chem. Soc*. **2012**, *134*, 11992.

[29] J. Xie, J. Wang, G. Dong, *Org Lett.* **2017**, *19*. 3017.

[30] M. Grigalunas, T. Anker, P.-O. Norrby, O. Wiest, P. Helquist. *Org Lett.* **2014**, *16*. 397.

[31] Z. Lu, X. Zhang, Z. Guo, Y. Chen, T. Mu, A. Li, *J. Am. Chem. Soc.* **2018**, *140*, 9211.

[32] N. A. Godfrey, D. J. Schatz, S. V. Pronin*, J. Am. Chem. Soc*. **2018**, *140*, 12770.

[33] a) S. Isayama, T. Mukaiyama, *Chem. Lett*. **1989**, 1071; b) T. Mukaiyama, S. Isayama, S. Inoki, K. Kato, T. Yamada, T. Takai, *Chem. Lett*. **1989**, 449; c) I. Isayama, T. Mukaiyama, *Chem. Lett*. **1989**, 569; d) S. Isayama, T. Mukaiyama, *Chem. Lett*. **1989**, 573.

[34] S. W. M. Crossley, C. Obradors, R. M. Martinez, R. A. Shenvi, *Chem. Rev*. **2016**, *116*, 8912.

[35] a) J. Shi, G. Manolikakes, C.-H. Yeh, C. A. Guerrero, R. A. Shenvi, H. Shigehisa, P. S. Baran, *J. Am. Chem. Soc*. **2011**, *133*, 8014; b) R. A. Shenvi, C. A. Guerrero, J. Shi, C.-C. Li, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 7241.

[36] a) H. Renata, Q. Zhou, G. Dunstl, J. Felding, R. R. Merchant, C.-H. Yeh, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 1330; b) H. Renata, Q. Zhou, P. S. Baran, *Science*, **2013**, *339*, 59.

[37] D. Zhu, B. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 15098.

[38] a) J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutierrez, J. Giacoboni, M. W. Smith, P. L. Holland, P. S. Baran, *J. Am. Chem.* **2017**, *139*, 2484; b) J. C. Lo, J. Gui, Y. Yabe, C.-M. Pan, P. S. Baran, *Nature* **2014**, 343.

[39] N. A. Godfrey, D. J. Schatz, S. V. Pronin, *J. Am. Chem. Soc*. **2018**, *140*, 12770.

[40] S. D. Holmbo, N. A. Godfrey, J. J. Hirner, S. V. Pronin, *J. Am. Chem. Soc.* **2016**, *138*, 12316.

[41] Y. Y. See, A. T. Herrmann, Y. Aihara, P. S. Baran*, J. Am. Chem. Soc.* **2015**, *137*, 13776.

[42] a) B. Schonecker, C. Lange, T. Zheldakova, W. Gunther, H. Gorls, G. Vaughan, *Tetrahedron* **2005**, *61*, 103; b) B. Schonecker, T. Zheldakova, C. Lange, W. Gunther, H. Gorls, M. Bohl, *Chem.-Eur. J.* **2004**, *10*, 6029; c) B. Schonecker, T. Zheldakova, Y. Liu, M. Kotteritzsch, W. Gunther, H. Gorls, *Angew. Chem. Int. Ed***.** **2003**, *42*, 3240; *Angew. Chem*. **2003**, *115*, 3361.

[43] H. T. Dao, P. S. Baran, *Angew. Chem. Int. Ed.* **2014**, *53*, 14382; *Angew. Chem*. **2014**, *126*, 14610.

[44] K. Sakata, Y. Wang, D. Urabe, M. Inoue, *Org. Let.* **2018**, *20*, 130.

[45] a) T. Tokuyama, J. Daly, B. Witkop, *J. Am. Chem. Soc.* **1969**, *91*, 3931; b) T. Tokuyama, J. Daly, B. Witkop, I. L. Karle, J. Karle, *J. Am. Chem. Soc.* **1968***, 90*, 1917.

[46] a) M. Kurosu, L. R. Marcin, T. J. Grinsteiner, Y. Kishi, *J. Am. Chem. Soc.* **1998**, *120*, 6627; b) R. Imhof, E. Gossinger, W. Graf, H. Berner, L. Berner-Fenz, H. Wehrli, *Helfv. Chem. Acta* **1972**, *55*, 1151; c) R. Imhof, E. Gossinger, W. Graf, L. Berner-Fenz, H. Berner, R. Schaufelberger, H. Wehrli, *Helv. Chim. Acta* **1973**, *56*, 139.

[47] a) H. Fujino, M. Nagatomo, A. Paudel, S. Panthee, H. Hamamoto, K. Sekimizu, M. Inoue, *Angew. Chem. Int. Ed*. **2017**, *56*, 11865; *Angew. Chem*. **2017**, *129*, 12027; b) S. Matsumura, Y. Matsui, M. Nagatomo, M. Inoue, *Tetrahedron* **2016**, *72*, 4859; c) M. Nagatomo, H. Nishiyama, H. Fujino, M. Inoue, *Angew. Chem. Int. Ed.* **2015**, *54*, 1537; *Angew. Chem*. **2015**, *127*, 1557; d) M. Nagatomo, D. Kamimura, Y. Matsui, K. Masuda, M. Inoue, *Chem. Sci*. **2015**, *6*. 2765.

[48] L. K. G. Ackerman, M. M. Lovell, D. J. Weix, *Nature* **2015**, *524*, 454.

[49] a) H. R. Khatri, B. Bhattarai, W. Kaplan, Z. Li, M. J. C. Long, Y. Aye, P. Nagorny, *J. Am. Chem. Soc.* **2019**, *141*, 4849; b) J.-H. Tay, V. Dorokhov, S. Wang, P. Nagorny, *J. Antibiotics* **2019**, *72*, 437; c) J. Lee, S. Wang, M. Callahan, P. Nagorny, *Org. Lett*. **2018**, *20*, 2067; d) B. Bhattarai, P. Nagorny, *Org. Lett*. **2018**, *20*, 154; e) W. Kaplan, H. R. Khatri, P. Nagorny, *J. Am. Chem. Soc*. **2016**, *138*, 7194; f) P. Nagorny, N. Cichowicz, *Strategies and Tactics in Organic Synthesis* **2016**, *12*, 237; g) N. Cichowicz, W. Kaplan, I. Khomutnyk, B. Bhattarai, Z. Sun, P. Nagorny, *J. Am. Chem. Soc*. **2015**, *137*, 14341.

[50] a) M. S. Reddy, H. Zhang, S. Phoenix, P. Deslongchamps, C*hem. Asian J.* **2009**, *4*, 725; b) H. Zhang, M. S. Reddy, S. Phoenix, P. Deslongchamps, *Angew. Chem., Int. Ed*. **2008**, *47*, 1272; *Angew. Chem.* **2008**, *120*, 1292.

[51] a) D. Urabe, Y. Nakagawa, K. Mukai, K. Fukushima, N. Aoki, H. Itoh, M. Nagatomo, M. Inoue, *J. Org. Chem*. **2018**, *83*, 13888; b) K. Mukai, S. Kasuya, Y. Nakagawa, D. Urabe, M. Inoue, M. *Chem. Sci.* **2015**, *6*, 3383; c) K. Mukai, D. Urabe, S. Kasuya, N. Aoki, M. Inoue, *Angew. Chem., Int. Ed.* **2013**, *52*, 5300; *Angew. Chem*. **2013**, *125*, 5408.

[52] a) Z. G. Hajos, D. R. Parrish, *German Patent DE 2102623*, July 29, **1971;** b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; c) U. Eder, G. Sauer, R. Wiechert, *German Patent DE 2014757*, Oct 7, **1971**; d) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed*. **1971**, *10*, 496; *Angew. Chem*. **1971**, *83*, 492.

[53] Y. Hayashi, S. Koshino, K. Ojima, E. Kwon, *Angew. Chem. Int. Ed.* **2017**, *56*, 11812; *Angew. Chem*. **2017**, *129*, 11974.

[54] D.-H. Jhuo, B.-C. Hong, C.-W. Chang, G.-H. Lee, *Org. Lett.* **2014**, *16*, 2724.

[55] S. Prevost, N. Dupre, M. Leutzsch, Q. Wang, V. Wakchaure, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 8770; *Angew. Chem*. **2014**, *126*, 8915.

[56] Y. Hayashi, *Chem. Sci.,* **2016**, *7*, 866.

[57] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Joergensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794; *Angew. Chem*. **2005**; *117*, 804; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44,* 4212; *Angew. Chem*. **2005**, *117*, 4284.

[58] S. N. Ananchenko, I. V. Torgov, *Tetrahedron Lett*. **1963**, *4*, 1553.

[59] a) V. S. Enev, J. Mohr, M. Harre, K. Nickisch, *Tetrahedron: Asymmetry* **1998**, *9*, 2693; b) M. Braun, R. Fleischer, B. Mai, M.-A. Schneider, S. Lachenicht, *Adv. Synth. Catal*. **2004**, *346*, 474; c) For other asymmetric syntheses of the Torgov diene: d) G. Quinkert, M. Del Grosso,A. Bucher,M. Bauch,W. Dcring, J. W. Bats, G. Drner, *Tetrahedron Lett.* **1992**, *33*, 3617; e) K. Tanaka, H. Nakashima, T. Taniguchi, K. Ogasawara, *Org. Lett.* **2000**, *2*, 1915; f) Y.-Y. Yeung, R.-J. Chein, E. J. Corey, *J. Am. Chem. Soc*. **2007**, *129*, 10346; g) D. Soorukram, P. Knochel, *Org. Lett*. **2007**, *9*, 1021; h) E. Canales, E. J. Corey, *Org. Lett.* **2008**, *10*, 3271.

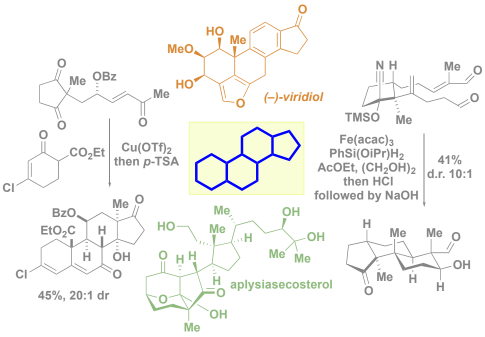
[60] T. James, M. van Gemmeren, B. List, *Chem. Rev*. **2015**, *115*, 9388.

[61] Y.-Y. Yeung, R.-J. Chein, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 10346.

Entry for the Table of Contents

MINIREVIEW

This mini review discusses the recent progress in the synthesis of steroids that was enabled by the advances in the transition metal catalysis, Lewis acid catalysis and organocatalysis.



Steroid, Natural Products, Total Synthesis, Catalysis

*Hem Raj Khatri, Nolan Carney, Ryan Rutkoski, Bijay Bhattarai, and Pavel Nagorny**

Page 1. – Page 24.

Recent Progress in Steroid Synthesis Triggered by the Emergence of New Catalytic Methods