Natural Product Reports

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Nat. Prod. Rep.*, 2024, **41**, 1060

Recent advances in the total synthesis of galantamine, a natural medicine for Alzheimer's disease

Bichu Cheng, [ac] Qi Wang,[c] Yi An [a] and Fener Chen *[abc]

Received 5th January 2024

DOI: 10.1039/d4np00001c

rsc.li/npr

Covering: 2006 to 2023

(−)-Galantamine is a natural product with distinctive structural features and potent inhibitory activity against acetylcholine esterase (AChE). It is clinically approved for the treatment of Alzheimer's disease. The clinical significance and scarcity of this natural product have prompted extensive and ongoing efforts towards the chemical synthesis of this challenging tetracyclic structure. The objective of this review is to summarize and discuss recent progress in the total synthesis of galantamine from 2006 to 2023. The contents are organized according to the synthetic strategies for the construction of the quaternary center. Key features of each synthesis have been highlighted, followed by a summary and outlook at the end.

1. Introduction

(−)-Galantamine (**1**) is a natural product of the Amaryllidaceae alkaloid family. It was first isolated from the plant Caucasian snowdrop in the 1950s by scientists from the Soviet Union, and later from the bulbs of several different species of the Amaryllidaceae family.[1,2] These plants have been used in traditional herbal medicine for centuries. (−)-Galantamine (**1**) was found to be the major active component and has a dual mechanism of action on the cholinergic system.[3] It is a centrally acting,

[a]*Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, China. E-mail: rfchen@fudan.edu.cn*
[b]*College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, China*
[c]*School of Science, Green Pharmaceutical Engineering Research Center, Harbin Institute of Technology, Shenzhen 518055, China*

selective, reversible, and competitive acetylcholinesterase (AChE) inhibitor and an allosteric modulator of the nicotinic receptor for acetylcholine (Fig. 1). It has 50-fold greater selectivity for human erythrocyte AChE than for plasma BuChE (AChE $IC_{50} = 0.35$ μM; BuChE $IC_{50} = 18.6$ μM).[4] In 2001, after half a century of investigation, (−)-galantamine hydrobromide, commercially known as Razadyne, was approved by the FDA as a drug for the treatment of mild to moderate confusion (dementia) related to Alzheimer's disease (AD). A meta-analysis of randomized controlled trials of galantamine showed that it significantly improved cognitive, behavioral, and global performance in patients with AD.[5]

(−)-Galantamine (**1**) has a fascinating and synthetically challenging structure containing a strained tetracyclic framework and three stereocenters. The fused tetracyclic structure consists of an aromatic A ring, a heterocyclic B ring, a cyclohexenol C ring and an azepine D ring. The three stereocenters, including a spiro benzylic quaternary center,[6–8] are embedded in the tetracyclic structure (Fig. 2). The structure of (−)-galantamine (**1**) and its close relatives narwedine (**5**) and lycoramine (**6**) is similar to that of morphine (**7**). These structural challenges, and the demand for an economical and sustainable supply of the natural product to the market have stimulated extensive and ongoing interest in the chemical synthesis of galantamine (**1**).

Numerous synthetic studies of (−)-galantamine (**1**) and its analogues have been performed and dozens of total syntheses have been reported.[9–12] This review aims to summarize the recent synthetic achievements of this fascinating natural product and to discuss the evolution of the synthetic strategies employed during different periods.[13–43] Special focus is placed on the construction of the key benzylic quaternary center and the asymmetric synthesis. For the sake of brevity and completeness of this review, only a few selected key early discoveries prior to 2006 will be summarized, followed by more recent developments.

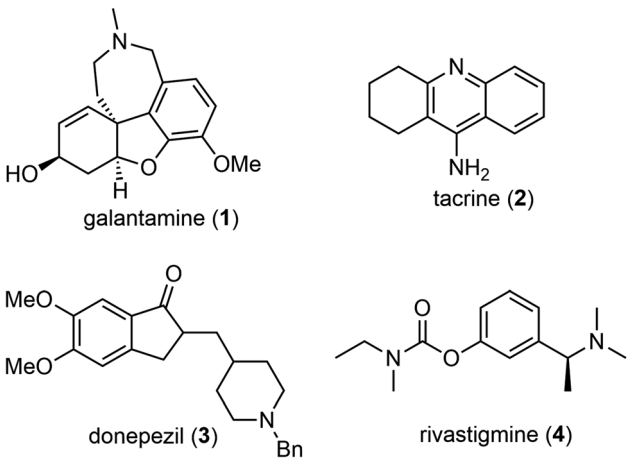


Fig. 1 Structure of (−)-galantamine and AChE inhibitors.

2. Biomimetic oxidative coupling reactions

The biosynthesis of galantamine with oxidative *ortho–para* phenol coupling as the key step was first proposed by Barton and coworkers and later supported by their own biomimetic synthesis. Since then, oxidative coupling of phenols[44] has become the most extensively studied method for the total synthesis of galantamine. The early efforts have been summarized in a previous review.[9]

2.1 Biosynthesis of galantamine

Barton and co-workers recognized that Amaryllidaceae alkaloids, including galantamine (**1**), could be derived from a common precursor, 4′-*O*-methylnorbelladine (**8**) (R═H, or its *N*-methyl congener) (Scheme 1).[45] Oxidative *ortho–para* phenol coupling of **8** forms the central C–C bond, with simultaneous generation of the quaternary center and the azepine ring. An intramolecular oxa-Michael addition of the phenol to the quinoid system generates product **10** with the tetracyclic scaffold. Further reduction of the keto group and methylation of the

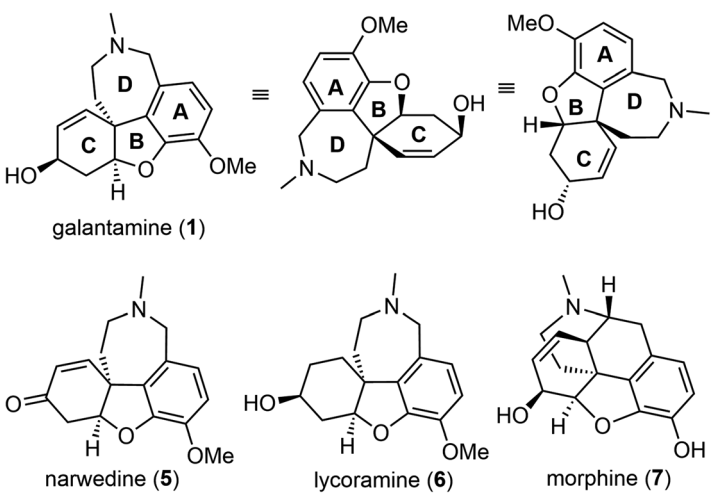
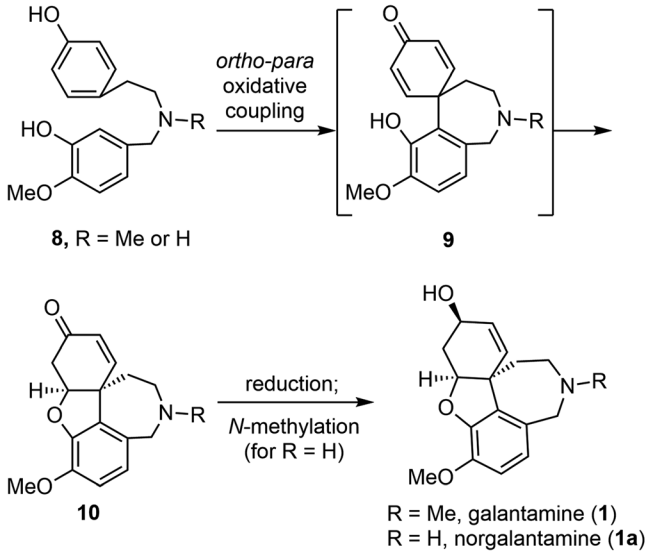


Fig. 2 Structure of (−)-galantamine from different perspectives and related natural products.

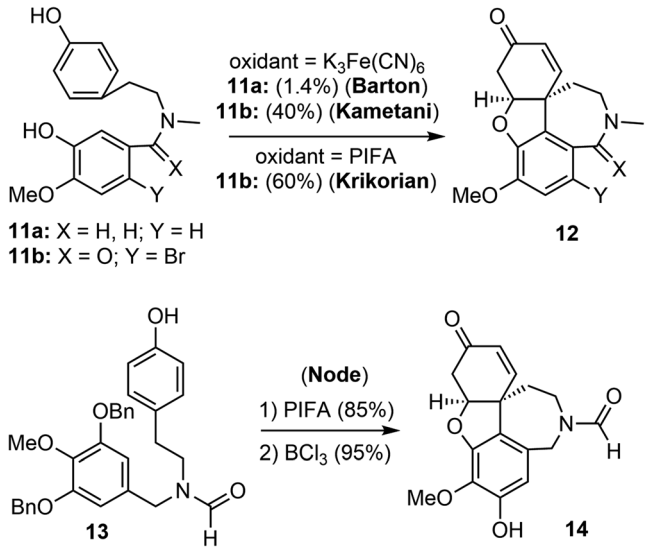


Scheme 1 Possible biosynthetic pathway for galantamine.

amine would afford galantamine (**1**). The biosynthesis of Amaryllidaceae alkaloids has been investigated biochemically using labelled precursors and intermediates.[45–47] More recently, genomic studies have identified several biosynthetic genes that encode enzymes involved in these steps.[48,49]

2.2 Previous results of oxidative phenol coupling

Barton and Kirby were the first to report the biomimetic intramolecular oxidative coupling of **11a** with potassium ferricyanide ($K_3Fe(CN)_6$) as the oxidant, resulting in the desired product **12a**, albeit in very low yield (Scheme 2). Subsequent ketone reduction with lithium aluminium hydride ($LiAlH_4$) led to a mixture of (±)-galantamine and (±)-epigalantamine.[50] This landmark biomimetic synthesis inspired many groups to make significant contributions to improve the performance of



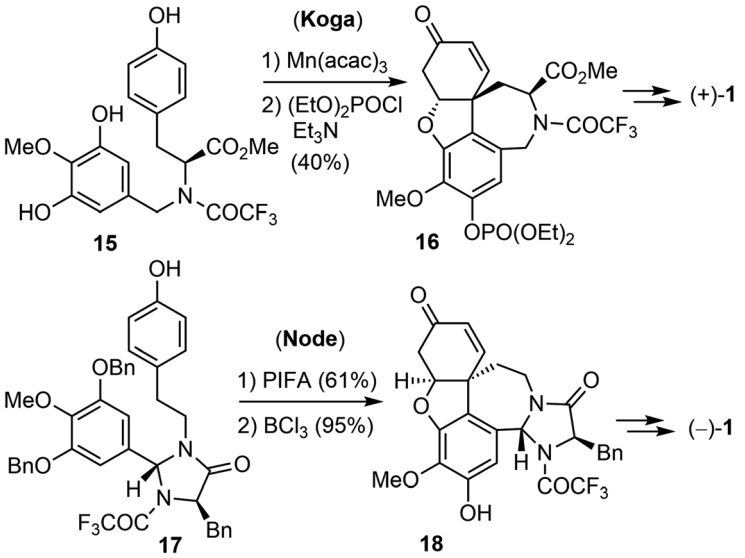
Scheme 2 Racemic oxidative coupling reactions.

Barton's synthesis in the following years. Subsequent modifications were made to the substrate structure, and alternative oxidants were employed to enhance the efficacy of the intramolecular oxidative phenol coupling reaction.

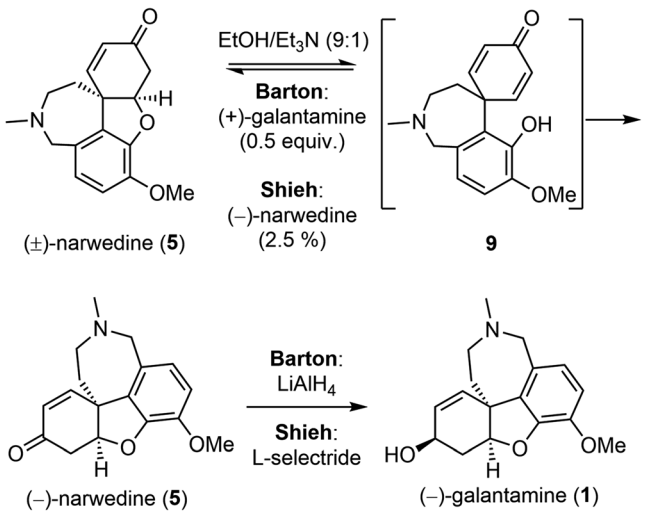
Kametani and co-workers found that by blocking the *para* position of the phenol with a bromide and using a lactam instead of an amine significantly increased the yield of the oxidative phenol coupling (**11b**).[51,52] In 1998, Kita and co-workers reported that [bis(trifluoroacetoxy)iodo]benzene (PIFA) was a suitable oxidant for promoting the diphenol coupling.[53] Krikorian and co-workers then applied PIFA to the key oxidative coupling reaction of amide **11b** and obtained the tetracyclic derivative **12b** in 60% yield.[54] In 2001, Node and co-workers reported a synthesis of galantamine using the symmetric *N*-formamide **13** as the substrate.[55] The PIFA-promoted oxidative coupling reaction of **13** in trifluoroethanol at room temperature afforded a dienone in 85% yield, a selective *O*-debenzylation using BCl_3 and *in situ* oxa-Michael addition provided the narwedine-type product **14** in a high yield. The use of the symmetrical substrate **13** as a precursor avoided the use of bromide as a blocking group at the *para*-phenol position. The extra hydroxy group was later removed by a palladium-catalyzed reduction of the corresponding triflate.

The first asymmetric synthesis of enantiomerically pure (+)- and (−)-galantamine was reported by Koga's laboratory (Scheme 3).[56] Compound **15** was derived from L-tyrosine methyl ester. The phenol oxidative *ortho–para* coupling reaction was carried out with 5 equiv. of manganic tris(acetylacetonate) ($Mn(acac)_3$) in acetonitrile. The resulting tetracyclic compound was protected as the diethyl phosphonate to give **16** in 81% yield. Compound **16** was then converted to (+)-galantamine. Node and co-workers reported in 2004 a creative synthesis of (−)-galantamine based on the concept of remote asymmetric induction.[57] Compound **17** was readily obtained from tyramine with (*R*)-*N*-BOC-D-phenylalanine. The oxidative phenol coupling reaction of **17** afforded a dienone. *O*-debenzylation and *in situ* oxa-Michael addition delivered product **18**, which was converted to (−)-galantamine.

Barton and Kirby also investigated the interconversion of galantamine and narwedine (Scheme 4).[50] Oxidation of (−)-galantamine (**1**) with manganese dioxide, and crystallization from acetone led to (−)-narwedine (**5**). Serendipitously, they discovered that crystallization from ethanol (EtOH) led to (+)-narwedine. The apparently spontaneous formation of (+)-narwedine during crystallization was most likely due to the presence of small amounts of unoxidized (−)-galantamine. The process must proceed through the symmetrical dienone intermediate **9**. Eventually, they obtained (−)-narwedine (**5**) by crystallization of (±)-narwedine with 0.5 equiv. of (+)-galantamine in a mixture of EtOH/Et_3N. Further reduction of the ketone group in **5** with $LiAlH_4$ completed a relay synthesis of (−)-galantamine. Shieh and coworkers reinvestigated this crystallization-induced dynamic resolution of narwedine.[58,59] They found that resolution of (±)-narwedine in EtOH/Et_3N worked equally well with a catalytic amount of (−)-narwedine (2.5%) or (+)-galantamine (1%). This process is highly efficient, as evidenced by the conversion of 10 g of (±)-narwedine into



Scheme 3 Asymmetric oxidative coupling reactions.



Scheme 4 Crystallization-induced dynamic chiral resolution and ketone reduction.

9.02 g of (−)-narwedine in just two cycles. Shieh and coworkers also solved the issue of stereoselectivity in the final ketone reduction. The desired product was stereoselectively obtained by employing L-selectride as the reducing agent instead of $LiAlH_4$. These two key improvements are crucial for the pilot scale synthesis of (−)-galantamine (*vide infra*).

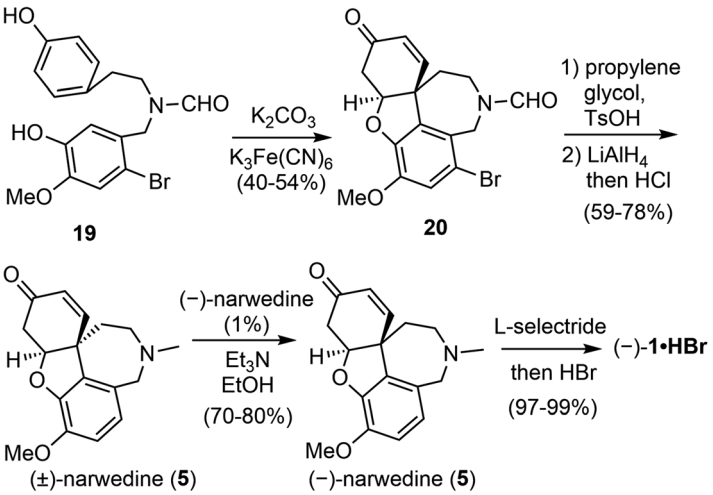
In the late 1990s, a collaboration between the pharmaceutical company Sanochemia and Vienna University of Technology (Johannes Fröhlich and Ulrich Jordis) resulted in a pilot-scale process for the production of (−)-galantamine (Scheme 5).[60,61] The phenol **19** was prepared from veratraldehyde in 4 steps on a 100 kg scale. The oxidative phenol coupling reaction was optimized by a multifactorial analysis of reaction parameters, and 40–42% yield of **20** were consistently obtained on scales up to 12 kg. Compound **20** was transformed to racemic narwedine ((±)-**5**) in 2 steps. Racemic narwedine is then resolved according to Shieh's procedure to give enantiomerically pure (−)-narwedine.[58] Using a catalytic amount of seed crystals of (−)-**5**, a consistently reproducible procedure has been developed for the crystallisation-induce chiral transformation of (±)-**5** to (−)-**5** on scales up to 7 kg. (−)-Narwedine was stereoselectively reduced with L-selectride to afford (−)-galantamine (**1**), which was isolated as the salt of hydrobromide in nearly quantitative yield. More than 5 kg of the final product was obtained by this process in 12.4% overall yield.

From Barton's biomimetic synthesis to Sanochemia's pilot scale synthesis of galantamine, it took generations of chemists and almost four decades of effort to optimize a low-yielding but landmark reaction to an industrial scale reaction with practical values. There are continuous and ongoing interest in this biomimetic intramolecular oxidative coupling reaction, especially with the advent of new technologies. The clinical demand for (−)-galantamine also requires a sustainable and economical supply to complement the isolation of (−)-galantamine from its natural source.[62]

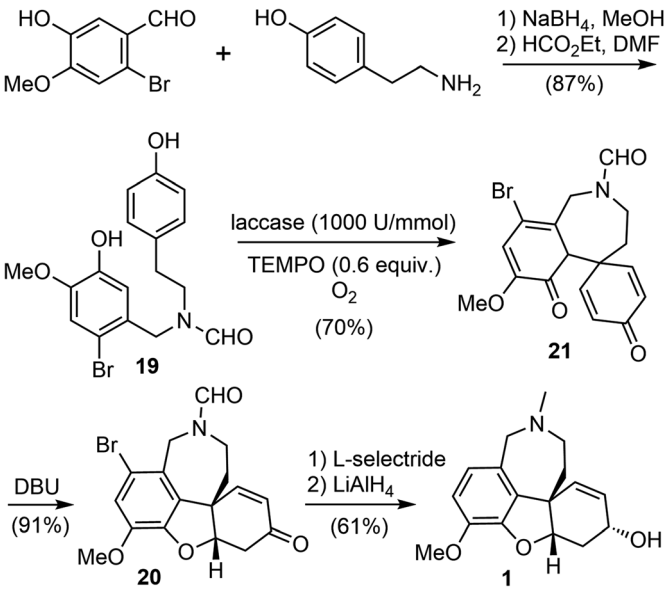
2.3 Chemoenzymatic approach (Saladino)

Biocatalysis is especially useful for the preparation of novel building blocks or the late-stage modification of complex molecules, due to the high selectivity profiles of enzymes. Chemoenzymatic synthesis allows the organic chemists to combine the versatility of synthetic organic transformations with the unparalleled selectivity of biocatalysis, providing efficient access to important bioactive small molecules.[63]

Laccases (EC 1.10.3.2) are a class of multicopper-containing oxidoreductase that catalyze the one-electron oxidation in nature (E^0 = 0.5 to 0.8 V *vs.* normal hydrogen electrode NHE), using air as the primary oxidant.[64,65] In 2020, Saladino and coworkers reported a novel and biomimetic synthesis of galantamine (Scheme 6).[36] They developed a laccase catalyzed *para*–



Scheme 5 Industrial synthesis of (−)-galantamine by Sanochemia.



Scheme 6 Saladino's chemoenzymatic synthesis of galantamine.

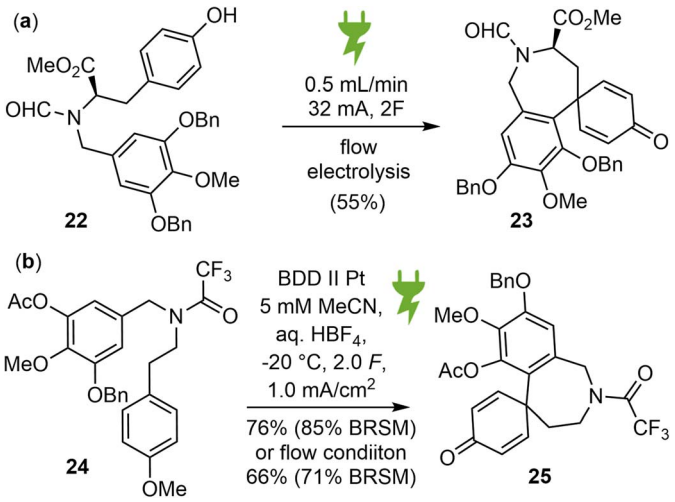
ortho oxidative radical coupling of a norbelladine derivative **19** to a spirocyclohexadienone **21** in the presence of the redox mediator 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). The phenol **19** was prepared in two steps from commercially available tyramine and 2-bromoisovanillin *via* reductive amination and *N*-formylation. Treatment of **19** with laccase from *Trametes versicolor* (1000 U $mmol^{-1}$) and 0.6 equivalents of TEMPO as the redox mediator and oxygen as the primary oxidant led to the oxidative radical coupling product **21** in 70% yield. Product **21** is a tricyclic fused system, containing the azepine D ring and two hexadienone rings. Surprisingly, in contrast to the spontaneous oxa-Michael addition to form the B ring in the biomimetic chemical synthesis of galantamine (*vide supra*),[60,61] this enzyme catalyzed reaction stopped at the oxidative coupling stage, reflecting the mildness of the reaction conditions. Tautomerization of **21** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) induced an intramolecular oxa-Michael addition to give the tetracyclic product **20** in 91% yield. Final sequential reduction of the ketone with L-selectride and reduction of the amide and debromination with $LiAlH_4$ afforded galantamine in 61% yield.

The entire process of this total synthesis required only 6 steps from commercial compounds, with an overall yield of 34%. Further optimization of the reaction conditions, *e.g.*, reducing the amount of TEMPO and using supported laccase for recycling, would make this route a potential candidate for scaling up the synthesis of galantamine.

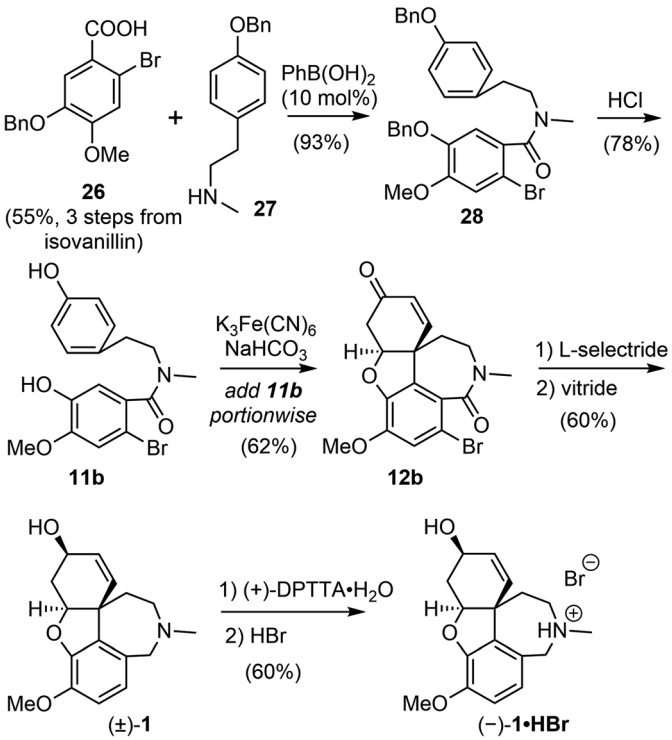
2.4 Electrosynthesis approach (Wirth, Opatz and Waldvogel)

Organic electrosynthesis is an old and rich discipline that has experienced a significant renaissance in recent years. It provides a customizable, cost effective and environmentally benign alternative for conducting redox reactions using only electrons as traceless reagents, thereby eliminating the need for dangerous and toxic stoichiometric oxidants.[66] With the recent renaissance of the field, two independent reports on the electrochemical synthesis of galantamine were published almost simultaneously.[39,40]

In 2022, Wirth and coworkers reported a new biomimetic total synthesis of (−)-galantamine (**1**), using an anodic aryl–aryl coupling as the key synthetic step, which was further optimized in a flow electrochemical setup (Scheme 7a).[39] The substrate **22** was synthesized from methyl D-tyrosine and methyl gallate in 6 steps. Various parameters of the electrolysis were screened and optimized. It was found that RVC anode and platinum cathode is the best electrode material combination, trifluoroethanol with 0.1 M nBu_4NClO_4 as supporting electrolyte is a very good solvent, the addition of an acidic additive such as trifluoroacetic acid successfully increased the yield of the electrolysis product **23** to 40% in batch mode. This reaction was then examined using a flow electrochemical reactor. After optimizing the flow system, the yield of **23** increased to 55%. Subsequently, product **23** was converted to (−)-galantamine by adapting the strategy from Koga's synthesis.[56]



Scheme 7 Electro-synthesis of galantamine. (a) Wirth and (b) Opatz and Waldvogel's work.



Scheme 8 Bandichhor's chemical resolution approach.

In the same year, Opatz and Waldvogel reported a biomimetic approach towards the synthesis of Amaryllidaceae alkaloids using a highly versatile anodic key transformation to spirodienones (Scheme 7b).[40] The substrate **24** for the electro oxidative coupling was prepared from methyl gallate in 11 steps. The metal-free, high performance boron-doped diamond (BDD) electrode was found to be the anode material of choice. Acetonitrile with an acid additive gave the most promising results. To prevent the rearrangement of the sensitive spirodienone moiety, a continuous flow setup was refined to neutralize the electrolyte immediately after electrolysis. Product **25** was then converted to Node's intermediate,[55] which represents a formal total synthesis of galantamine.

Electrosynthesis provided an alternative approach to traditional oxidants for this key biomimetic oxidative coupling in the total synthesis of galantamine. However, both the substrates and the reaction parameters for this key reaction required a lot of effort for careful optimization in the above two cases, making the overall syntheses less efficient.

2.5 Chemical resolution (Bandichhor)

The process for the scalable chemical synthesis of (−)-galantamine by Sanochemia[60,61] was adapted or modified on certain steps for further improvement by all subsequent production procedures. In 2008, Bandichhor and coworkers reported an alternative scalable synthesis of (−)-galantamine *via* Kametani's intermediate **11b** (Scheme 8).[17] The acid **26** and amine **27** were both obtained in 3 steps from readily available starting materials. Coupling of these two fragments with 10 mol% of ecofriendly phenyl boronic acid afforded the amide **28** in 93% yield.[67] The *O*-benzyl groups was removed under acidic condition to give the known phenol **11b**.[51,52] The incremental addition of **11b** to Kametani's conditions ($K_3Fe(CN)_6$, $NaHCO_3$) led to the key intramolecular oxidative coupling followed by a spontaneous oxa-Michael addition to give the tetracyclic product **12b** in 62% yield, much higher than those reported by Kametani and the Sanochemia process. The enone was reduced with L-selectride to afford an alcohol in good yield (80%) and diastereoselectivity (de 99.6%). The reduction of the lactam and concomitant debromination with vitride led to the racemic galantamine ((±)-**1**). The racemic mixture was resolved using (+)-di-*p*-tolyl tartaric acid ((+)-DPTTA) to produce the enantiomerically pure product (−)-galantamine (**1**) with good yield (70%, based on available enantiomer in the racemate) and chiral purity (99.91%).[68] The HBr salt of (−)-galantamine was formed conventionally using aq. HBr. All reactions in the process were performed on a decagram scale, and an overall yield of 9% was obtained from isovanillin.

By modifying the substrate and reaction conditions, they were able to obtain a good yield for the key intramolecular oxidative coupling reaction. However, half of the valuable late-stage product was lost using the classical resolution method, and they did not demonstrate the recycling of the other enantiomer, which makes the route less cost effective for scalable production of (−)-galantamine.

3. Transition metal catalyzed reactions

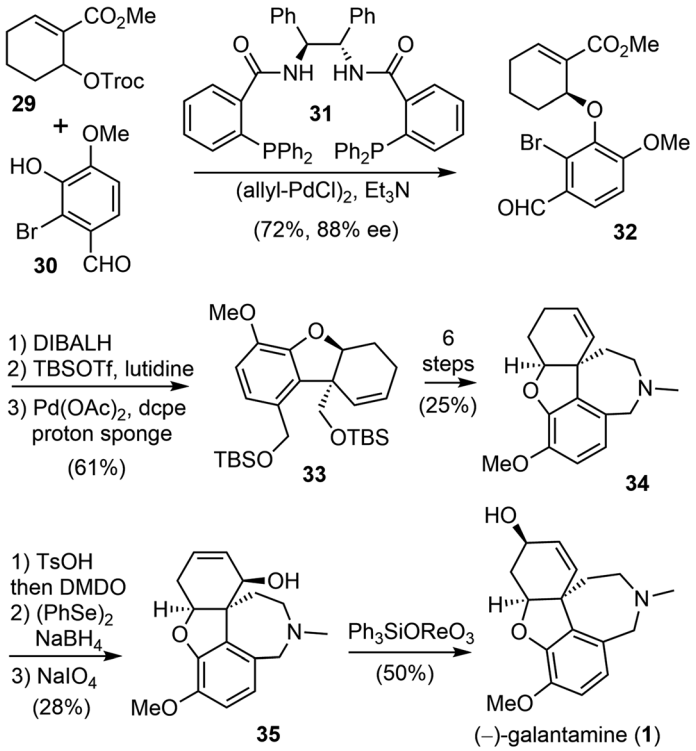
Transition metal catalyzed reactions play an indispensable role in modern synthetic chemistry. They have been awarded the Nobel Prize in Chemistry three times in the 21st century. For decades, oxidative phenol coupling was the only way to construct the benzylic quaternary center in the total synthesis of galantamine. Trost and coworkers were the first to break this paradigm and use a palladium catalyzed intramolecular

Heck reaction.[69–71] Since then, numerous applications of transition metal catalyzed reactions, including all three Nobel Prize-winning reactions (the Heck coupling reaction, asymmetric hydrogenation reaction[22] and olefin metathesis reaction[14,23,41]), have been employed in the total synthesis of galantamine.[14,23,24,28,29]

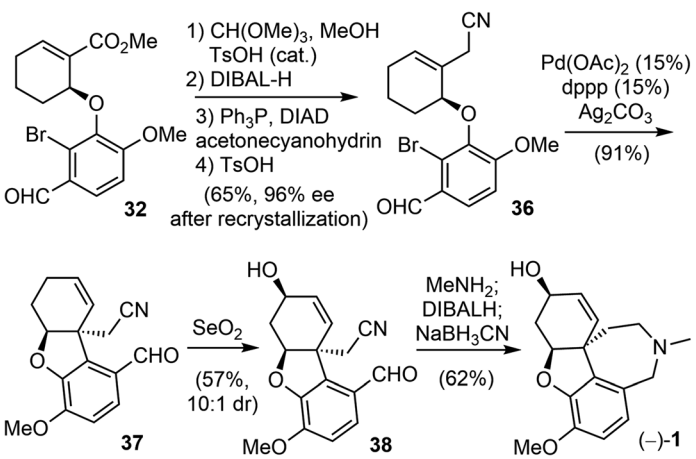
3.1 Heck reaction (Trost and Guillou)

In 2000, Trost and Toste reported the first catalytic asymmetric synthesis of (−)-galantamine (Scheme 9).[69] They used sequential palladium-catalyzed asymmetric allylic alkylation (AAA) and intramolecular Heck reaction to build the key vicinal stereocenters with high enantioselectivity. This is the first total synthesis that does not use an oxidative phenol coupling to construct the quaternary center of (−)-galantamine (**1**).

First, a palladium-catalyzed AAA reaction of allylic carbonate **29** with 2-bromovanillin (**30**) in the presence of the chiral ligand **31** afforded the required chiral aryl ether **32** in 72% yield and with 88% enantiomeric excess (ee). The attempted intramolecular Heck reaction of the electron-poor olefin **32** to construct the crucial quaternary center failed. Therefore, **32** was



Scheme 9 Trost and Toste's total synthesis of (−)-galantamine.

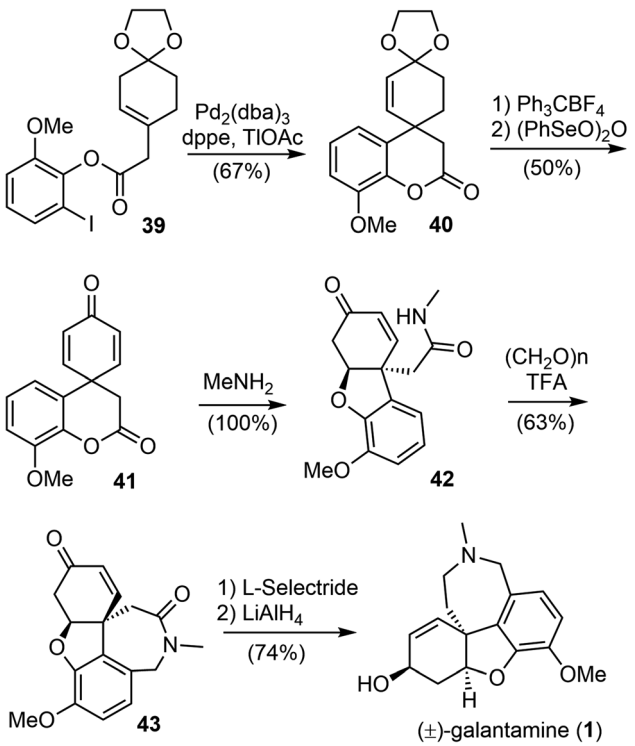


Scheme 10 Trost and Tang's total synthesis of (−)-galantamine.

transformed to an electron-rich bis-TBS ether. This compound underwent the palladium-catalyzed intramolecular Heck reaction smoothly with the electron-rich bidentate ligand 1,2-bis(-dicylohexylphosphino)ethane (dcpe). The reaction yielded benzofuran **33** in good yield, together with some mono-deprotected product. Both the olefin isomerization reaction and the phenol ionization reaction were suppressed under this condition. Compound **33** was then converted to **34** in 6 steps, including a reductive amination to form the azepine D ring. Compound **34** was converted to allylic alcohol **35** in a further 3 steps, through an epoxide to allylic alcohol isomerization. Finally, a 1,3-transposition of the allylic alcohol provided (−)-galantamine (**1**).

Two years later, Trost and Tang improved the total synthesis of (−)-galantamine (**1**) to an 8-step process (Scheme 10).[72] The same arylether **32** was used in their second generation total synthesis. The α,β-unsaturated ester was homologated to a β,γ-unsaturated nitrile **36** in four steps, including a Mitsunobu reaction with acetone cyanohydrin. The enantiomeric excess of **36** was improved to 96% ee after recrystallization. The palladium-catalyzed intramolecular Heck cyclization proceeded smoothly in the presence of silver carbonate (Ag_2CO_3) and provided the product **37** in high yield (91%). An allylic oxidation mediated by SeO_2 introduced the allylic hydroxy group and selectively delivered the product **38** (dr 10 : 1). The condensation of aldehyde **38** with methylamine, followed by subsequent reduction and intramolecular cyclization, formed the hydrobenzazepine D ring and gave (−)-galantamine (**1**) in a one-pot process.

In 2001, Guillou and Thal reported an efficient synthesis of (±)-galantamine from a readily available ester **39** (Scheme 11).[73]



Scheme 11 Guillou and Thal's total synthesis of (±)-galantamine.

The palladium-catalyzed intramolecular Heck cyclization of **39** afforded the tricyclic compound **40** in 67% yield. Removal of the dioxolane group, followed by oxidation with $(PhSeO)_2O$ afforded the key spirocyclohexadienone intermediate **41** in 50% yield. The ester amidation reaction of **41** with 40% aqueous methylamine was carried out at room temperature and resulted in the spontaneous phenolic oxa-Michael addition to cyclohexadienone to afford amide **42**. Compound **42** was then subjected to Pictet–Spengler cyclization with paraformaldehyde to form the azepine D ring and give tetracyclic product **43** in 63% yield. Successive stereoselective reduction of the enone **43** with L-selectride and reduction of the lactam with $LiAlH_4$ afforded (±)-galantamine in good yield.

The above three total syntheses of galantamine formed the basis for many subsequent total syntheses. The intramolecular Heck reaction has been used many times to construct the quaternary center. The reductive amination method of Trost and the Pictet–Spengler cyclization method of Guillou were employed to form the azepine D ring. The key intermediates in their total syntheses became the targets of later syntheses.

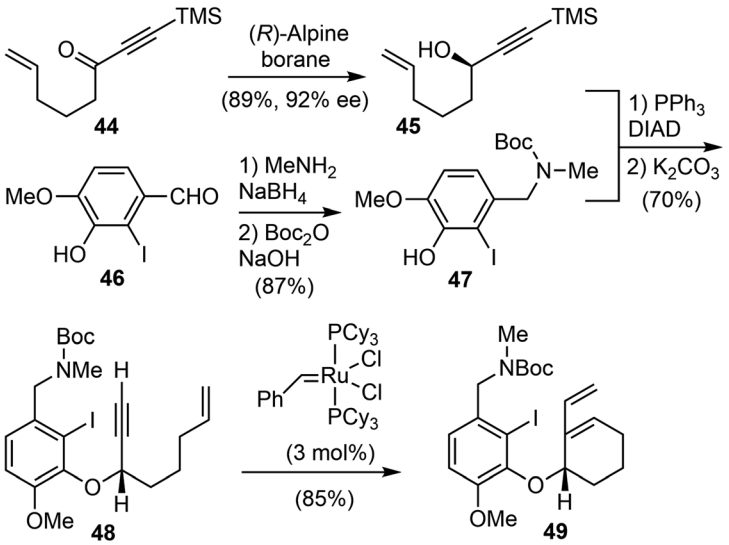
3.2 Enyne RCM and Heck reaction (Brown)

In 2007, Brown and coworkers reported their first-generation enantioselective total synthesis of (−)-galantamine in 11 linear steps from commercially available materials.[14] An enantioselective reduction of a propargylic ketone **44** with (*R*)-alpine borane afforded the chiral alcohol **45**. Coupling of the alcohol **45** with phenol **47** *via* Mitsunobu reaction afforded enyne **48**. The C ring was closed by an efficient enyne metathesis reaction of **48** in the presence of 3 mol% of the first-generation Grubbs' catalyst, generating the diene product **49** in 85% yield at ambient temperature (Scheme 12).

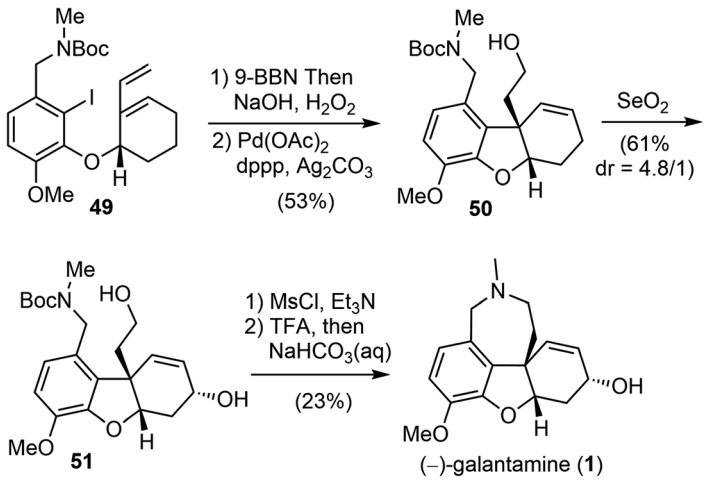
The terminal olefin of **49** was selective hydroborated and oxidized to yield a homoallylic alcohol (Scheme 13). Subsequently, an intramolecular Heck reaction successfully formed the central heterocyclic five-membered B ring to give tricyclic compound **50**. Allylic oxidation of **50** using Trost's procedure led to the desired (*R*)-allylic alcohol **51** with modest selectivity.[69] The azepine D ring was generated by selectively activating the primary hydroxyl group through mesylation, followed by a one-pot Boc deprotection/*N*-alkylation process by sequential treatment with TFA and neutralization with $NaHCO_3$ (aq). (−)-Galantamine and its epimer were obtained after separation by column chromatography.

Fifteen years later, Brown and coworkers reported their second-generation asymmetric synthetic route to (−)-galantamine with very high levels of stereocontrol. Several transition-metal mediated reactions were pivotal in achieving high levels of chemo and stereo-control, including the use of an enyne ring closing metathesis (RCM), two asymmetric allylation reactions and an intramolecular Heck reaction.[41]

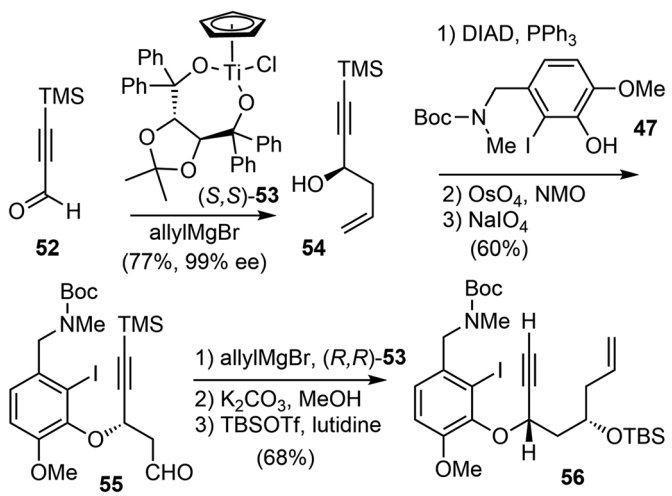
Asymmetric allylation of aldehyde **52** with Hafner's titanium-TADDOL reagent (*S*,*S*)-**53** provided the chiral homoallylic alcohol **54** with excellent enantioselectivity (Scheme 14).[74] The Mitsunobu coupling of phenol **47** and alcohol **54** afforded an olefin as a single enantiomer in high yield. A two-step



Scheme 12 Enyne metathesis reaction.



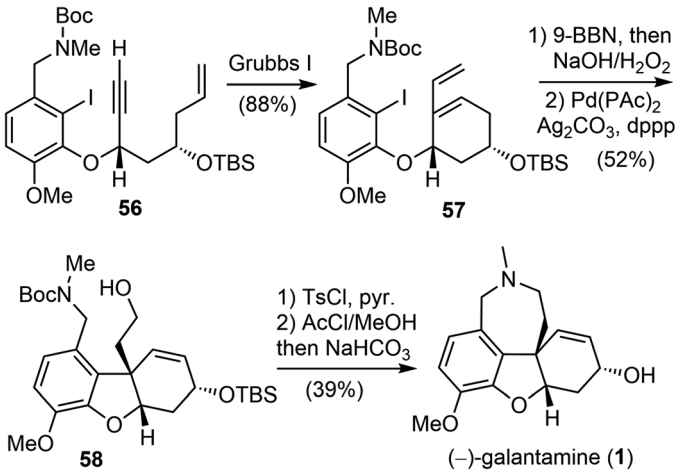
Scheme 13 Brown's first-generation total synthesis of (–)-galantamine.



Scheme 14 Synthesis of **48** by two asymmetric allylation reactions.

dihydroxylation/oxidative cleavage process transformed the terminal olefin to aldehyde **55**. A second aldehyde allylation reaction with TADDOL reagent (*R*,*R*)-**53** gave another homoallylic alcohol in good yield and excellent diastereoselectivity. Functional group manipulation provided enyne **56**, which contained the full scaffold of the alkaloid and the necessary stereochemical information, ready for the key reactions.

In the presence of Grubbs' first-generation catalyst, enyne **56** underwent an RCM reaction to generate the C ring and afforded the cyclized product **57** (Scheme 15). Selective hydroboration of the terminal olefin with 9-BBN and oxidation, followed by an intramolecular Heck cyclization generated the tricyclic compound **58**.[70] Finally, formation of the azepine D ring by an *N*-alkylation reaction and *in situ* deprotection delivered (–)-galantamine (**1**). The overall process of their total synthesis of (–)-galantamine is 11 steps with 7.3% overall yield from the known enantiomerically enriched alcohol **54**.



Scheme 15 Brown's second-generation total synthesis of (−)-galantamine.

3.3 Dynamic kinetic resolution and reductive Heck (Zhou and Xie)

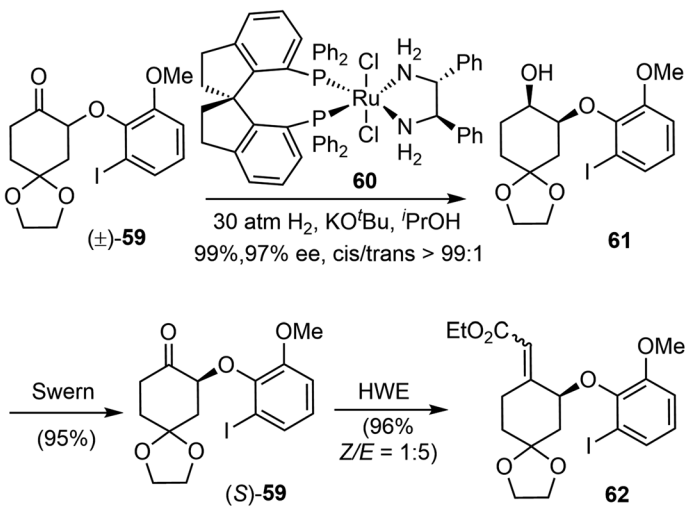
In 2012, Zhou and Xie reported an asymmetric total synthesis of (−)-galantamine (20.1%, 12 steps).[22] Their synthetic strategy features an efficient ruthenium-catalyzed asymmetric hydrogenation of a racemic α-aryloxy cyclic ketone *via* dynamic kinetic resolution (DKR), and a palladium-catalyzed intramolecular reductive Heck cyclization to construct the benzylic quaternary center.

Previously, they developed a highly efficient ruthenium-catalyzed asymmetric hydrogenation of racemic α-aryloxy cyclohexanones *via* DKR to produce chiral β-aryloxy cycloalkanols with excellent enantioselectivity.[75] Using this methodology, the racemic α-aryloxy cyclic ketone **59** was hydrogenated with the chiral ruthenium catalyst $RuCl_2$-(*S*)-SDP/(*R*,*R*)-DPEN (**60**) to afford the chiral β-aryloxy cyclohexanol **61** in high yield (99%), excellent enantioselectivity (97% ee) and *cis*-selectivity (*cis*/*trans* > 99 : 1) (Scheme 16). The aryloxy cyclohexanol **61** was then converted by Swern oxidation and Horner–Wadsworth–Emmons reaction (HWE) to give the α, β-unsaturated ester **62** as an inconsequential olefin mixture (*Z*/*E* 1 : 5).

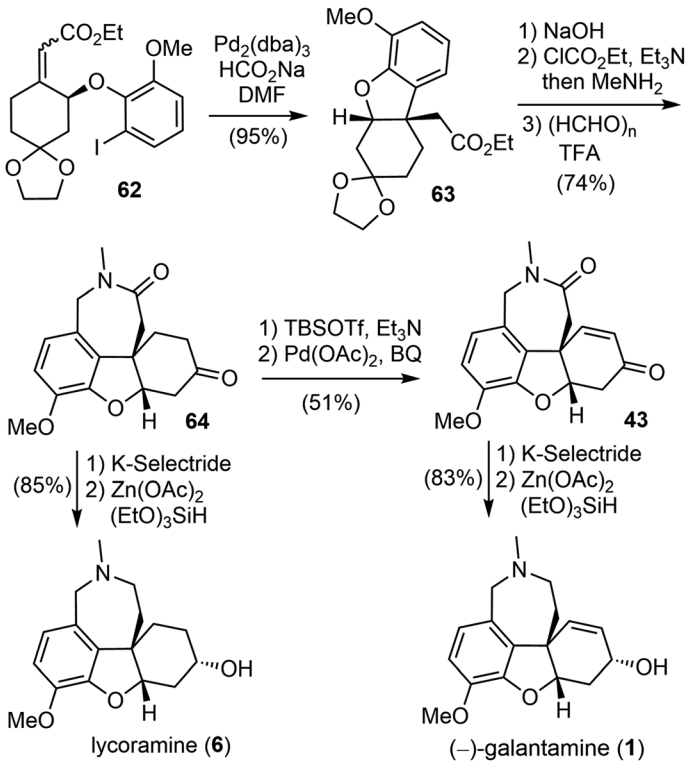
The construction of the key quaternary center *via* the intramolecular Heck reaction of aryl allyl ethers is often impeded by a competitive palladium-catalyzed ionization of the aryloxy group, leading to the formation of a phenol.[69] To address this issue, a reductive Heck reaction was investigated. After screening and optimization, it was found that the intramolecular reductive Heck cyclization successfully formed the desired product **63** in 95% yield when the *Z*, *E*-mixture of ester (*S*)-**62** was subjected to the catalyst $[Pd_2(dba)_3]$ in the presence of sodium formate (HCO_2Na) (Scheme 17). The ester **63** was then transformed to an amide, followed by Pictet–Spengler cyclization with paraformaldehyde according to Guillou's procedure[73] to give the tetracyclic intermediate **64**. Stereoselective reduction of the ketone group to the alcohol with K-selectride and a further reduction of the lactam to the amine by Beller's method[76] (triethoxysilane ($(EtO)_3SiH$)/$Zn(OAc)_2$) afforded the natural product lycoramine (**6**). On the other hand, a Sagusa oxidation of the ketone **64** gave the known enone product **43**,[73] and successive reduction with K-selectride and $(EtO)_3SiH$)/$Zn(OAc)_2$ gave the natural product (−)-galantamine (**1**). (−)-Galantamine (**1**) was synthesized in twelve steps with 20.1% overall yield and lycoramine (**6**) was synthesized in ten steps with 40.2% overall yield from commercially available starting materials.

3.4 Alder-ene, Diels–Alder and Heck reaction (Banwell)

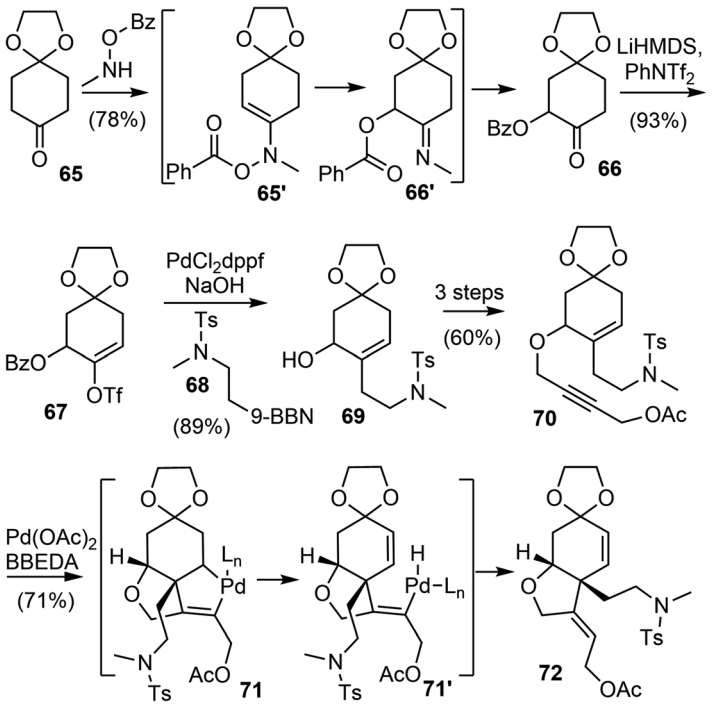
The Banwell group has been working on the total synthesis of galantamine for a long time, and has published several generations of total syntheses with different strategies.[19,27,28,42,77] In 2015, they reported a new and distinct total synthesis of galantamine,[27] in which the aromatic A ring was made by a Diels–Alder reaction, the heterocyclic B ring and associated



Scheme 16 A DKR reaction to generate the oxygenated stereocenter.



Scheme 17 Zhou and Xie's total synthesis of (–)-galantamine.



Scheme 18 Palladium-catalyzed intramolecular Alder-ene reaction.

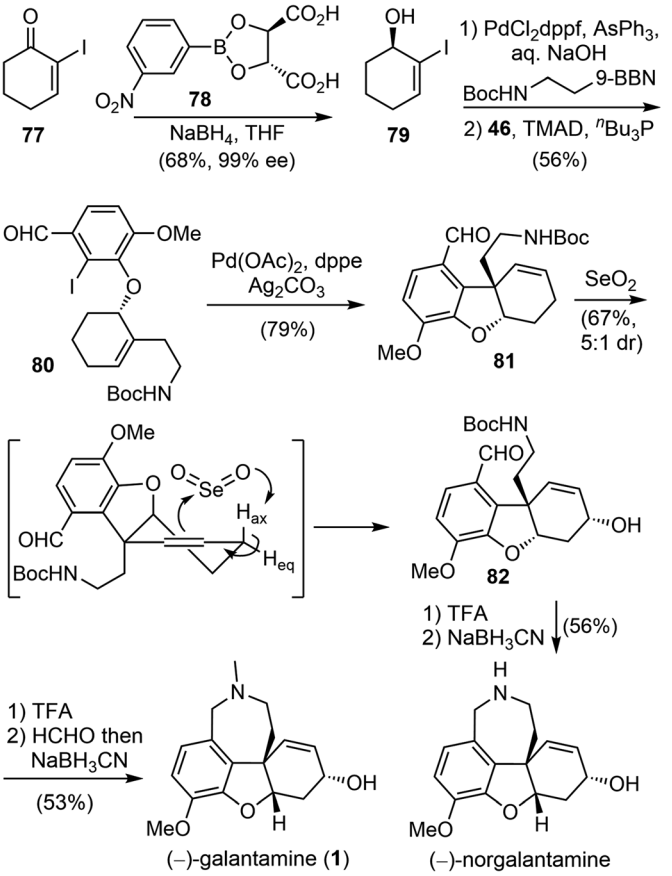
quaternary carbon center were constructed by a palladium-catalyzed intramolecular Alder-ene (IMAE) reaction, and the seven-membered D ring was then formed by a modified Bischler–Napieralski reaction.

Following a literature method,[78] the commercial ketone **65** underwent an α-acyloxylation reaction with *N*-methyl-*O*-benzoylhydroxylamine (MeNHOBz) at room temperature to give the product **66** (Scheme 18). This reaction presumably proceeds *via*

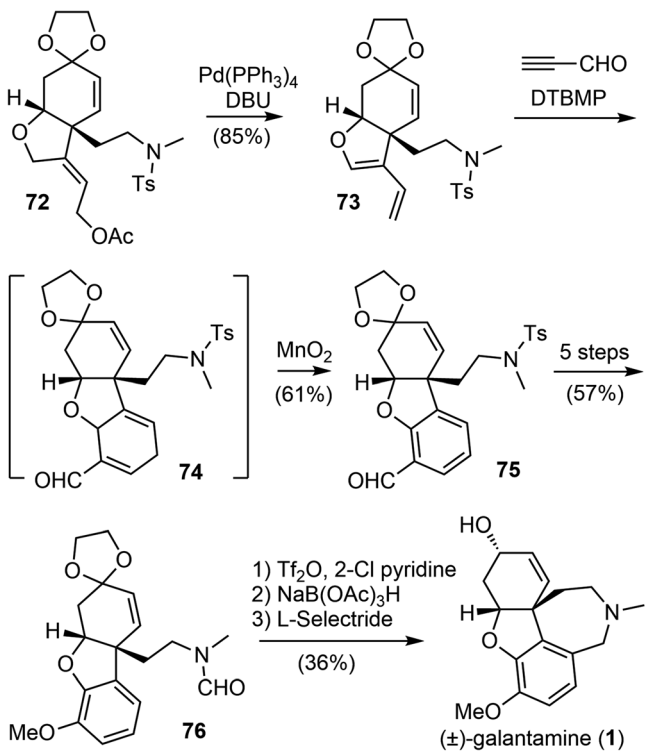
a concerted pericyclic rearrangement of the intermediate **65′** to give the α-benzoyloxy imine **66′**, with further *in situ* hydrolysis to give the observed product. The ketone **66** was regioselectively converted to an enol triflate **67**, which underwent a *B*-alkyl Suzuki coupling reaction with the *in situ* generated boron reagent **68** to afford the coupling product alcohol **69** after ester hydrolysis. The incorporation of the alkyne moiety was completed in 3 steps to give the enyne **70**. The palladium-catalyzed IMAE reaction of enyne **70** was best performed with a strong σ-donating ligand *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA), to successfully form the heterocyclic B ring and the quaternary center and provide the desired cyclization product **72**.[79,80]

The allylic acetate **72** underwent a palladium-catalyzed elimination reaction under basic conditions to give a diene **73** (Scheme 19). Compound **73** then participated in a regioselective Diels–Alder cycloaddition reaction with propynal, followed by immediate oxidation with manganese dioxide (MnO_2) to form the aromatic A ring and afford the aldehyde **75**. Compound **75** was converted in 5 steps to formamide **76**. A modified Bischler–Napieralski cyclodehydration reaction of **76** under Movassaghi's conditions (Tf_2O/2-Cl pyridine) formed the D ring,[81] and subsequent reduction of the resulting iminium with sodium triacetoxyborohyride ($NaBH(OAc)_3$) afforded narwedine. A diastereoselective reduction of the ketone group with L-selectride afforded (±)-galantamine (**1**). The longest linear sequence of the total synthesis is 18 steps from commercial compound **66**.

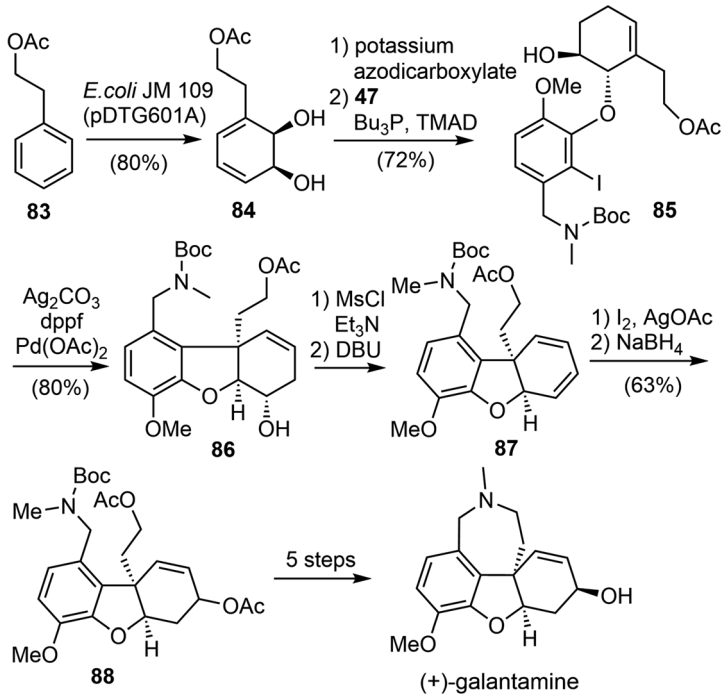
Although several distinctive strategies were used, the installation of the aromatic moiety in the above synthesis was laborious, making the overall process less efficient. After several generations of evolution,[19,28] Banwell and coworkers published a concise total synthesis of (−)-galantamine in 2022 (Scheme 20).[42] The synthesis commenced from the known chiral allylic alcohol **79**, which was readily available from an asymmetric ketone reduction reaction with (L)-TarB-NO_2 reagent (**78**) derived from (L)-tartaric acid.[82] Compound **79** was then subjected to a *B*-alkyl Suzuki cross-coupling reaction to introduce the alkyl side chain and a Mitsunobu reaction with commercial iodoisovanillin **46** to afford the coupling product **80**, containing all the carbons of the natural product. An intramolecular Heck reaction of **80** under the standard conditions afforded the cyclohexene derivative **81**, with concomitant formation of the quaternary center and the heterocyclic B ring. Allylic oxidation under Trost's conditions with SeO_2 diastereoselectively generated the allylic alcohol **82**.[72] It was proposed that SeO_2 reacted with the olefin and the axial proton H_{ax} through an ene mechanism, with H_{ax} perfectly aligned with the π-system. Finally, closure of the azepine D ring *via* a double reductive amination reaction in the presence of formaldehyde afforded the final target (−)-galantamine (**1**). In the absence of formaldehyde, a related natural product (−)-norgalantamine was obtained. The whole process for the total synthesis of (−)-galantamine (**1**) took only 6 steps from the known chiral compound **79**.



Scheme 20 Banwell's improved total synthesis of (−)-galantamine.



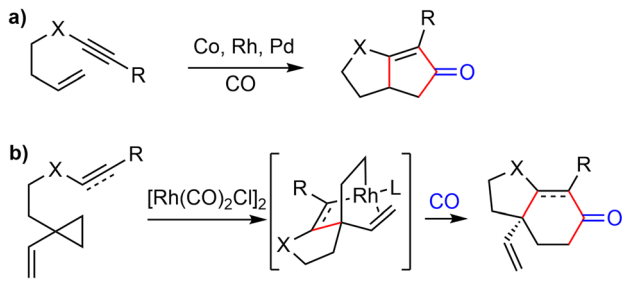
Scheme 19 Banwell's total synthesis of (±)-galantamine.



Scheme 21 Hudlicky's total synthesis of (+)-galantamine.

3.5 Microbial dihydroxylation/Heck reaction (Hudlicky)

In 2016, Hudlicky and coworkers reported a ten-step chemoenzymatic synthesis of *ent*-galantamine from phenethyl acetate (Scheme 21).[29] The synthesis began with the microbial dihydroxylation of phenethyl acetate **83** to afford an intermediate cyclohexadiene diol **84**. The less hindered alkene was selective reduced, followed by a selective Mitsunobu reaction of the more reactive allylic alcohol with phenol **47**, resulting in the coupling product **85**. The tricyclic ABC rings of galantamine was assembled by a subsequent intramolecular Heck reaction of **85**. The alcohol **86** was converted to the diene **87** by mesylation, followed by elimination with DBU. A Prevost reaction of the diene **87** gave a diastereomeric mixture of iodoacetates, which were immediately subjected to reduction with sodium borohydride in DMSO to give a 2 : 1 mixture of diastereomeric acetates **88**. Formation of the azepine D ring and adjustment of the stereochemistry of the allylic alcohol was achieved in 5 steps from **88**, resulting in the synthesis of (+)-galantamine.

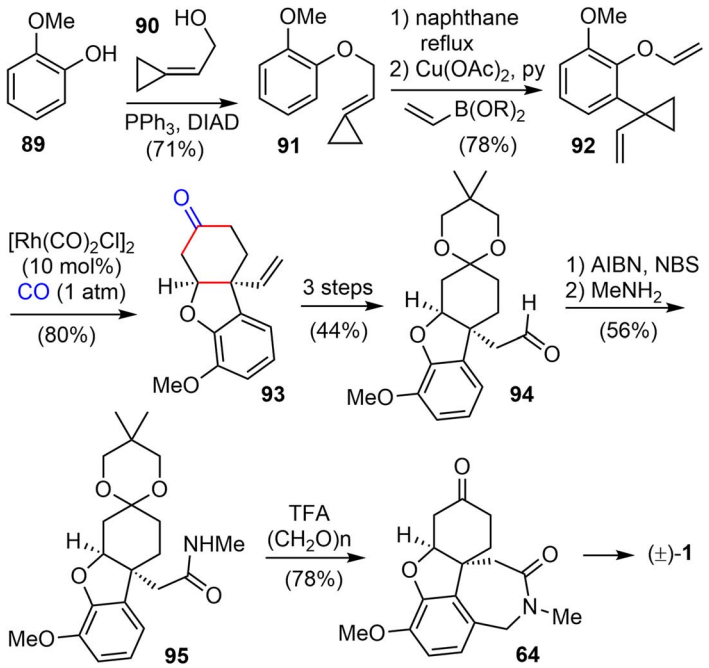


Scheme 22 (a) An intramolecular Pauson–Khand reaction; (b) Rh-catalyzed [(3 + 2) + 1] cycloaddition reaction.

3.6 3.6 Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition (Yu)

Vinylcyclopropanes (VCPs) have been widely used in transition-metal-catalyzed cycloaddition reactions.[83] The presence of an olefin ligand directs the transition-metal for the selective C–C bond cleavage of the highly strained cyclopropane ring. In 2010, Yu and coworkers developed a Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition reaction,[84] which could be regarded as a homologous Pauson–Khand reaction (Scheme 22). Highly substituted bicyclic cyclohexenones and cyclohexanones could be obtained by this method.

In 2015, they extended the scope of this methodology further and reported a Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition reaction of 1-ene–vinylcyclopropane and CO to build the *cis*-hydrodibenzofuran skeleton. This strategy was then applied to the formal synthesis of (±)-galantamine and (±)-lycoramine (Scheme 23).[26] The substituted vinylcyclopropane substrate **92** was prepared from **89** in 3 steps. The phenol **89** and alcohol **90** underwent a Mitsunobu reaction to form the allylic ether **91** in 71% yield. A Claisen rearrangement in naphthane transformed **91** to a phenol, which underwent a Cu- catalyzed *O*-vinylation with 2,4,6-trivinylcyclotriboroxane–pyridine complex[85] to give the 1-ene-VCP **92**. The key Rh-catalyzed [(3 + 2) + 1] cycloaddition reaction under 1 atm of CO gas generated the desired tricyclic *cis*-hydrodibenzofuran product **93**. The yield dropped slightly when the reaction was scaled up. Compound **93** was transformed to aldehyde **94** in 3 steps. Following Tu's precedent,[13,86] aldehdye **94** was converted to amide **95** under radical oxidation conditions (*vide infra*). Install the D ring by a Pictet–Spengler cyclization using Guillou's procedure generated the tetracyclic compound **64**,[73] which is a key intermediate in Zhou and Xie's total synthesis of galantamine.[22]



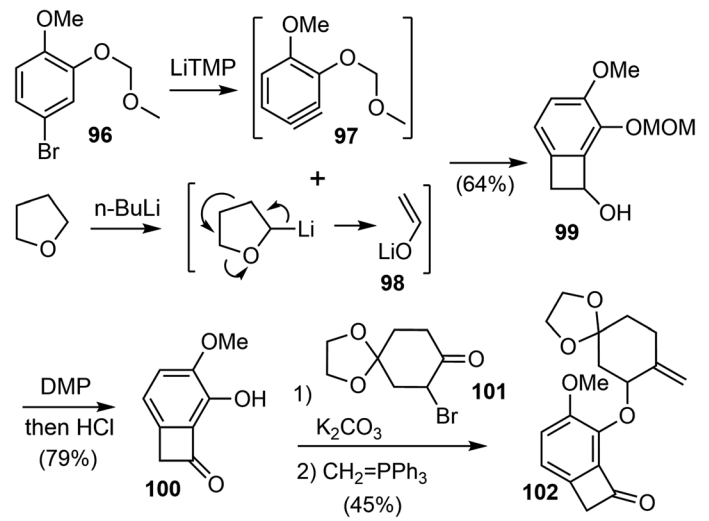
Scheme 23 Yu's formal total synthesis of galantamine.

3.7 "Cut and sew" carboacylation reaction (Xu)

Transition metal-catalyzed carbon–carbon bond activation has been increasingly used as a powerful tool for devising unusual bond-disconnecting strategies. The "cut and sew" strategy uses strained rings (benzocyclobutenones and cyclobutanones) with a tethered unsaturated moiety as substrates. It starts with the oxidative addition of a transition metal into the cyclic C–C bond (the "cut" step) to give a reactive metallacycle, followed by intramolecular migratory insertion of the unsaturated unit and reductive elimination to furnish the ring (the "sew" step) (Scheme 25).[87,88]

In 2020, Xu and coworkers reported a novel strategy for the formal total synthesis of galantamine and lycoramine.[35] The concise synthesis was enabled by a Rh-catalyzed intramolecular "cut and sew" carboacylation reaction for the formation of the tetracyclic framework and a regioselective Pd-catalyzed C–H activation for double-bond introduction.

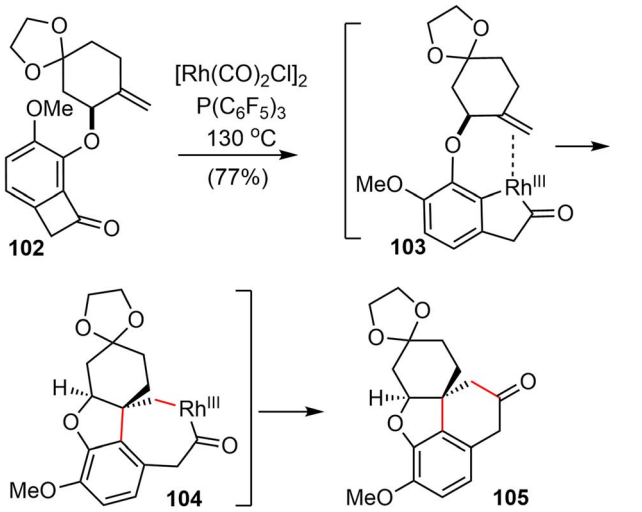
Their synthesis commenced with the preparation of substituted benzocyclobutenone **102** (Scheme 24). Lithium enolate **98** was first prepared *in situ* from THF and *n*-BuLi. Slow addition of a freshly prepared solution of lithium tetramethylpiperidide (LiTMP) to a mixture of aryl bromide **96** and lithium enolate **98** generated the highly reactive substituted aryne **97**, which underwent the [2 + 2] cycloaddition reaction with **98** to afford the benzocyclobutanol **99** regioselectively in 64% yield on a decagram scale.[89] The adjacent methoxymethyl ether (MOM) group on benzyne allowed the



Scheme 24 Preparation of benzylcyclobutenone **102**.

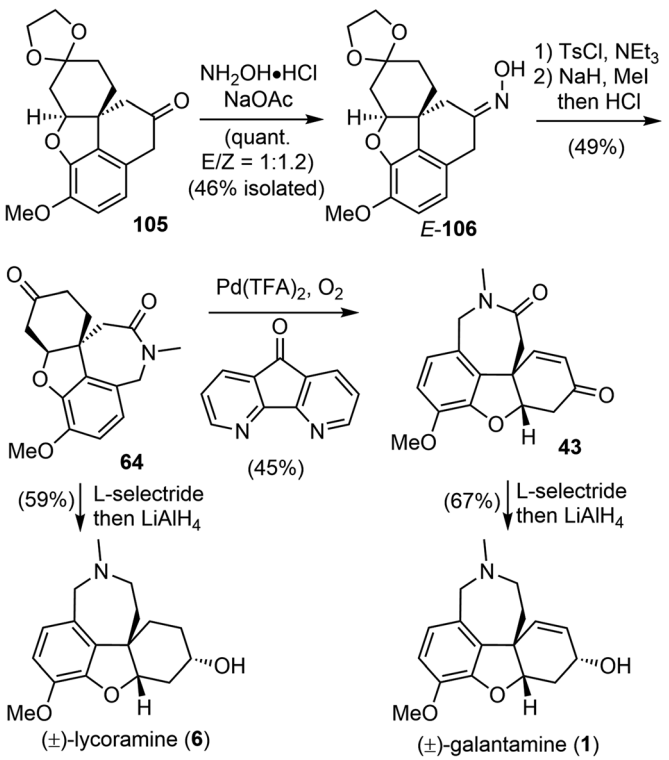
production of **99** as a single regioisomer through the negative inductive effect.[90] Dess–Martin oxidation of the alcohol followed by removal of the MOM group under acidic conditions afforded benzocycloubutenone **100** in 79% overall yield on a decagram scale. Alkylation of **100** with the known bromide **101** followed by a selective Wittig olefination provided the key C–C activation precursor **102** in 45% yield over 2 steps.

After screening and optimization of the reaction parameters, it was found that the key "cut and sew" carboacylation reaction[87] of **102** was best performed with the catalysis of $[Rh(CO)_2Cl]_2$ (5 mol%) in combination with an electronically poor monodentate phosphine ligand $P(C_6F_5)_3$ (22 mol%). Ring opening of the strained cyclobutenone *via* C–C bond cleavage, followed by cyclization with the tethered olefin generated the desired product **105** in 77% yield on a gram scale (Scheme 25).



Scheme 25 The "cut and sew" carboacylation reaction of **102**.

Having successfully established the core structure of the target, the next goal was to form the azepine D ring by an *N*-insertion reaction of the tetracyclic ketone **105** (Scheme 26). They first tried the Schmidt rearrangement, but it was unsuccessful. Instead, condensation of **105** with hydroxylamine gave the corresponding oxime quantitatively as a separable mixture of *E*/*Z* isomers (*E*/*Z* = 1 : 1.2). The *E*-isomer **106** was isolated and tosylated, and the Beckmann rearrangement occurred spontaneously at 30 °C in THF/water without any additives to give the desired amide. Subsequent *N*-methylation generated Zhou and Xie's intermediate **64**,[22] which underwent a Pd-catalyzed regioselective dehydrogenation reaction according to Stahl's procedure[91] to give Guillou's enone **43**.[73] Sequential reduction of the ketone and lactam groups with L-selectride and $LiAlH_4$ successfully elaborated intermediates **64** and **43** to (±)-lycoramine (**6**) and (±)-galantamine (**1**), respectively. The longest linear sequences of the total synthesis of galantamine and lycoramine are 11 and 10 steps, respectively.

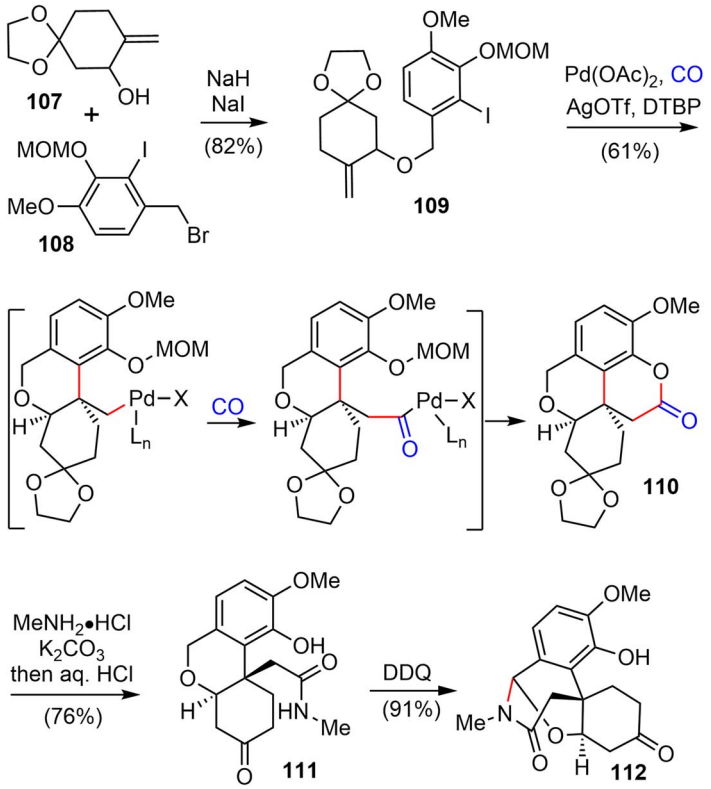


Scheme 26 Xu's formal total synthesis of (±)-galantamine and (±)-lycoramine.

3.8 Olefin carbonylative annulation (Zhao)

In 2021, Zhao and coworkers reported a highly efficient formal total synthesis of galantamine and lycoramine.[37] A two-phase approach was used in their total synthesis, with a palladium-catalyzed carbonylative cascade annulation and a DDQ-mediated regioselective intramolecular oxidative lactamization to generate the tetracyclic skeleton in the early phase, followed by a $BF_3 \cdot OEt_2$-promoted selective reorganization of the bridged tetracyclic skeleton in the late phase.

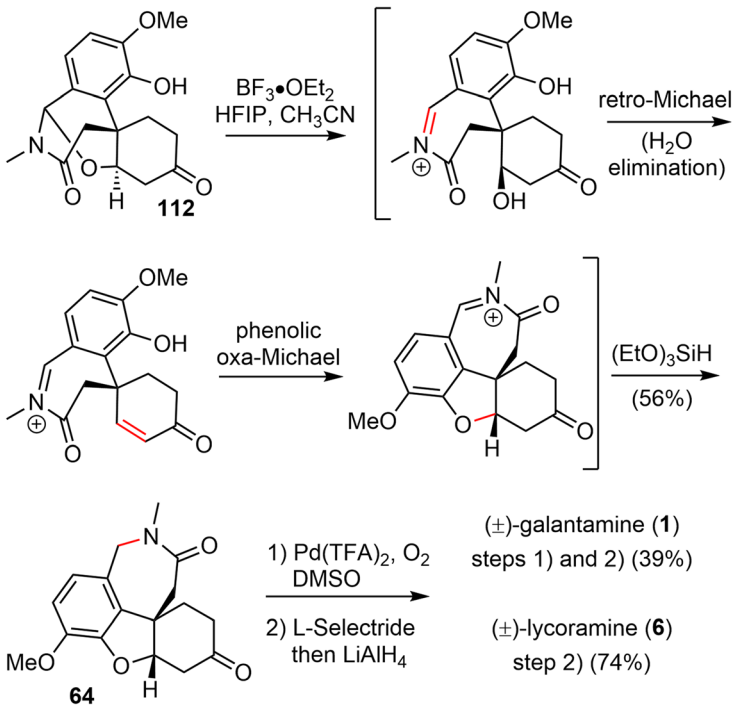
Their synthesis started with the deprotonation of racemic allylic alcohol **107**, followed by intermolecular *O*-alkylation with freshly prepared benzylic bromide **108** in the presence of a catalytic amount of NaI to provide the desired **109** in 82% yield (Scheme 27). The crucial palladium catalyzed carbonylative lactonization reaction was then investigated under a variety of conditions.[92,93] It was found that the reaction could be catalyzed by $Pd(OAc)_2$ without additional ligand, in the presence of AgOTf and a sterically hindered base 2,6-di-*tert*-butylpyridine (DTBP) under 1 atm of carbon monoxide. Loss of the MOM group *in situ* under the reaction conditions led directly to the desired lactonization product **110** in 61% yield. In contrast to the *cis*-5,6-bicyclic products obtained in the previous total syntheses, only the *trans*-6,6-bicyclic product was obtained in this case. Treatment of **110** with $MeNH_2 \cdot HCl$ in the presence of K_2CO_3, followed by one-pot deprotection of the ketal, afforded the amide **111** in 76% yield. The X-ray crystal structure of **111** confirmed the *trans*-6,6-bicyclic structure of **110**. Although there are many precedents for similar transformations, the structural rearrangement of compound **111** to the galantamine skeleton was unsuccessful under a variety of conditions. Instead, oxidation of **111** with DDQ proceeded



Scheme 27 Palladium catalyzed carbonylative esterification.

smoothly to afford the bridged tetracyclic aza-acetal **112** in excellent yield.

Compound **112** was found to be a suitable substrate for the desired skeletal rearrangement reaction (Scheme 28). They were pleased to find that treatment of **112** with $BF_3 \cdot Et_2O$, followed by the addition of $(EtO)_3SiH$ as the reductant, successfully converted **112** to the desired tetracyclic lactam **64** in 56% yield. Presumably, the Lewis acid $BF_3 \cdot Et_2O$ initiated the aza-acetal



Scheme 28 Zhao's formal total synthesis of (±)-galantamine and (±)-lycoramine.

cleavage, a retro-oxa-Michael addition and a phenolic oxa-Michael addition cascade to afford the tetracyclic iminium, followed by reduction with $(EtO)_3SiH$ to give the known lactam **64**.[22] Remarkably, this sequence allowed the preparation of hundreds of milligrams of late intermediate **64** in 19% overall yield in five steps from compounds **107** and **108** in a single batch. As in the previous total synthesis, further oxidation state adjustment of **64** completed the seven- and six-step syntheses of (±)-galantamine (**1**) and (±)-lycoramine (**6**), respectively.

4. Rearrangement reactions

Intramolecular rearrangement reactions are efficient ways to build sterically hindered quaternary centers. Stereospecific rearrangement reactions, such as the sigmatropic rearrangement, can transfer the chirality from a less hindered stereocenter to a sterically congested one with high fidelity. These reactions have been extensively employed in the total syntheses of natural products with quaternary centers. Several rearrangement reactions have been successfully applied in the synthesis of galantamine.[13,15,19,38,43]

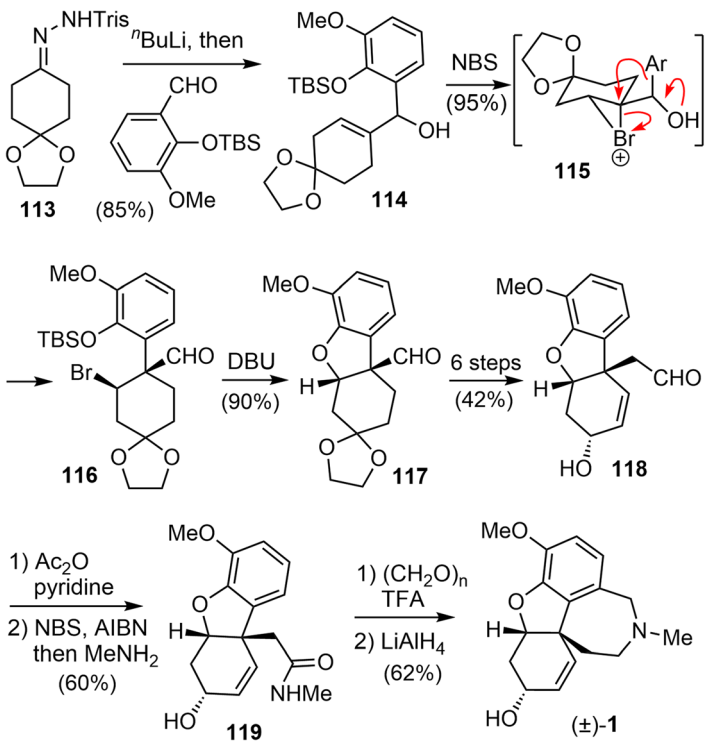
4.1 Semipinacol rearrangement (Tu)

In 2006, Tu and coworkers reported their total synthesis of (±)-galantamine in 13 steps from the commercially available compounds.[13] The overall yield of their synthesis is 12%. Similar to their previous work on the total synthesis of lycoramine,[94] a semi-pinacol rearrangement reaction of an allylic alcohol was used to build the benzylic quaternary center.

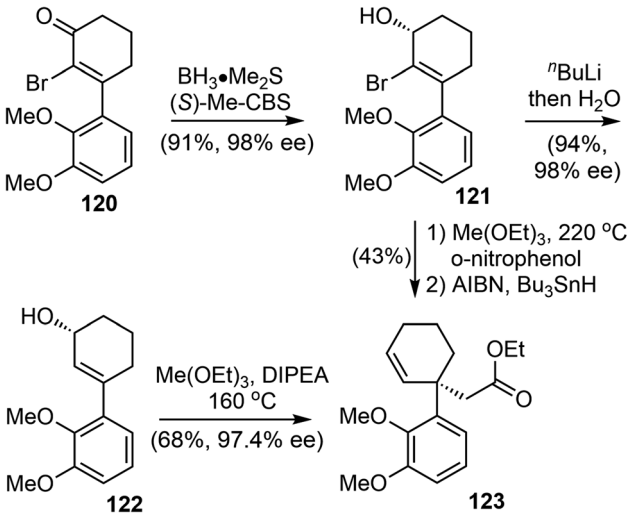
A modified Shapiro reaction of hydrazone **113** with *n*-BuLi generated a vinyl lithium,[95] which reacted a *o*-vanillin derivative to give an allylic alcohol **114** in 85% yield (Scheme 29). Upon treatment of **114** with NBS in DCM at 0 °C, the aldehyde **116** with a quaternary center was obtained in 95% yield as a single isomer. Presumably, a bromonium ion **115** was formed first, followed by a stereospecific semipinacol rearrangement of the aromatic group to generate the quaternary center. Reaction of **116** with DBU in DMSO initiated a one-pot desilylation and intramolecular S_N2 type cyclization reaction to form the B ring and gave the tricyclic product **117** in 90% yield.[94] Compound **117** was then transformed into aldehyde **118** in 6 steps, including a one-carbon homologation of the aldehyde and oxidation state adjustment of the C ring. A radical oxidation of the aldehyde generated the corresponding acid bromide, which reacted with $MeNH_2$ to give an amide **119**.[86] A further Pictet–Spengler reaction of **119** with paraformaldehyde gave the known lactam,[73] and reduction of the lactam afforded (±)-galantamine.

4.2 Johnson–Claisen rearrangement (Bisai)

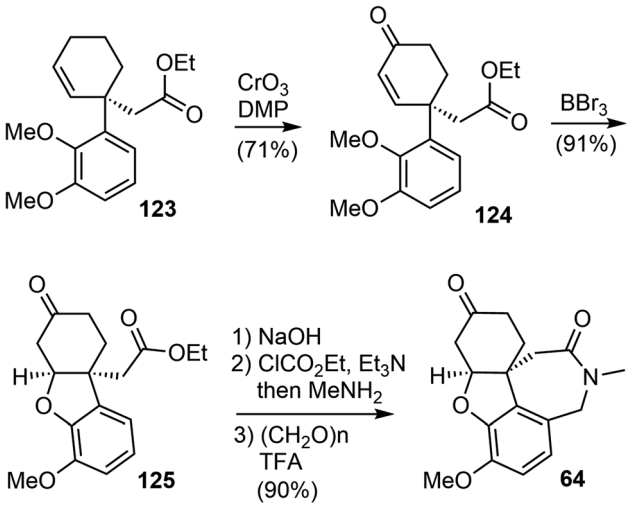
In 2022, Bisai and coworkers reported asymmetric total synthesis of naturally occurring Amaryllidaceae alkaloids sharing dihydrobenzofuran scaffolds, including (−)-galantamine (**1**), (−)-lycoramine (**6**), and (−)-narwedine (**5**).[38] The synthesis used a key catalytic enantioselective Corey–Bakshi–Shibata (CBS) reduction of α-bromoenone (99% ee), the chirality of the resulting secondary alcohol was transferred to an all-carbon quaternary center *via* an orthoester Johnson–Claisen rearrangement.



Scheme 29 Tu's total synthesis of (±)-galantamine.



Scheme 30 The orthoester Johnson–Claisen rearrangement.



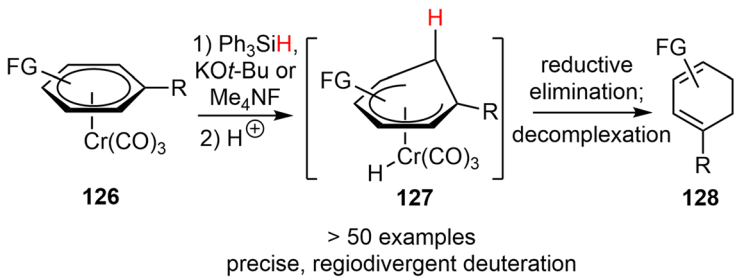
Scheme 31 Bisai's formal total synthesis of (−)-galantamine *via* **64**.

The α-bromo-3-arylcyclohexenone **120** was synthesized by a Stork–Danheiser reaction over a 10 g scale.[96] CBS reduction of **120** was carried out using the 20 mol% (*S*)-Me-CBS catalyst at 25 °C for 3 h to afford allyl alcohol **121** in 99% ee on gram scale (Scheme 30).[97] The bromo atom at the α-position was essential for the high enantioselectivity. Two sets of conditions were identified for the crucial Johnson–Claisen rearrangement.[98,99] In the first approach, debromination with *n*-BuLi afforded the allylic alcohol **122**, Conventional weak acidic conditions for the Johnson–Claisen rearrangement of **122** led to the product with decreased ee. Further optimization revealed that reaction in a basic medium suppressed the loss of optical purity. Under the optimized conditions, heating a solution of **122** (98% ee) and triethyl orthoacetate in DIPEA promoted the orthoester Johnson–Claisen rearrangement to produce the desired ester **123** in 68% yield in 48 h without the loss of optical purity (97.4% ee). Microwave irradiation shortened the reaction time to 20 min at 210 °C. In the second approach, the orthoester Johnson–Claisen rearrangement of **121** was carried out in the presence of *o*-nitrophenol using 20 equivalents of triethyl orthoacetate at 220 °C for 36 h. This reaction afforded the desired product without the loss of optical purity. A radical-initiated debromination with tributyltin hydride (Bu_3SnH) in the presence of catalytic AIBN provided product **123**.

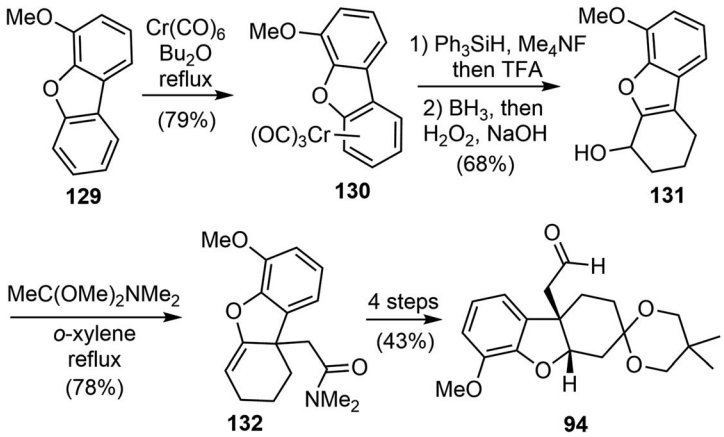
An allylic oxidation of **123** using CrO_3 in the presence of 3,5-dimethylpyrazole (DMP) afforded the enone **124** in 71% yield (Scheme 31).[100] A chemoselective demethylation of **124** with 1.05 equivalent of BBr_3 resulted in a concomitant oxa-Michael cyclization to form the tricyclic structure and delivered **125** in 91% yields in a one-pot fashion. The ester was transformed to an amide, which underwent a Pictet–Spengler reaction with paraformaldehyde to generate the azepine D ring and gave compound **64**, an intermediate in Zhou and Xie's total synthesis.[22] The tetracyclic compound **64** was a versatile intermediate and was converted to four Amaryllidaceae alkaloids in 2–5 steps, including (−)-galantamine.

4.3 Eschenmoser–Claisen rearrangement (Li)

In 2023, Li and coworkers reported a chemo- and regioselective 1,2-reduction of arenes *via* η^6-coordination to chromium (**126**), providing rapid access to 1,3-cyclohexadienes **128** (Scheme 32).[43] The process begins with the *in situ* generation of the hydride ion from Ph_3SiH and KOt-Bu or Me_4NF. This ion then attacks the arene ring to form the η^5-cyclohexadienyl anion intermediate. Protonation of this intermediate results in the formation of the Cr–H species **127**. Reductive elimination completes the 1,2-reduction process, and the resulting η^4-cyclohexadiene complex quickly undergoes solvolysis to release the final 1,3-cyclohexadiene product. The reaction conditions are mild and can tolerate various reduction-sensitive functional groups. More than 50 examples



Scheme 32 Selective 1,2-reduction of chromium-bound arenes.



Scheme 33 Li's formal total synthesis of (±)-galantamine *via* **94**.

have been developed to demonstrate the versatility of the reaction. Additionally, it allows for regiodivergent deuteration, with precise control over the position of deuteration and the degree of deuterium incorporation by using different sequences of (non)deuterated hydride and acid reagents.

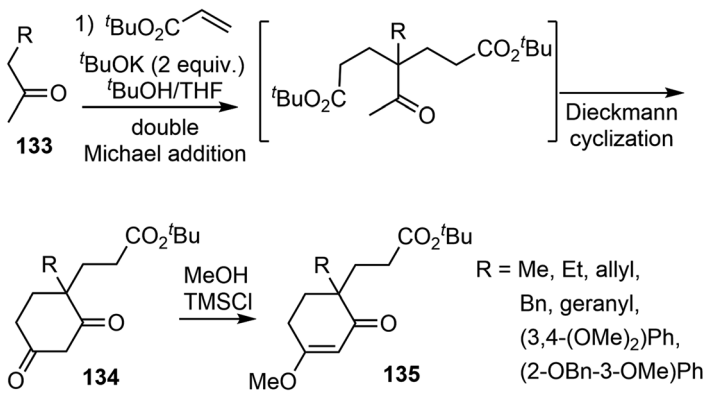
The reaction was then applied in a formal total synthesis of galantamine (Scheme 33). The η^6-coordinated chromium complex **130** was prepared by refluxing 4-methoxydibenzo[*b*,*d*]furan **129** with chromium hexacarbonyl. Following the standard conditions developed above, the chromium-bound complex **130** was reduced to a diene on a gram-scale. The crude 1,2-reduction product was subjected to a hydroboration/oxidation process to give the alcohol product **131**. A novel dearomative Eschenmoser–Claisen rearrangement was used to convert **131** to amide **132** with a quaternary center in 78% yield. Compound **132** was further transformed to compound **94**, an intermediate in Yu's synthesis of (±)-galantamine.[26]

5. Alkylation reactions

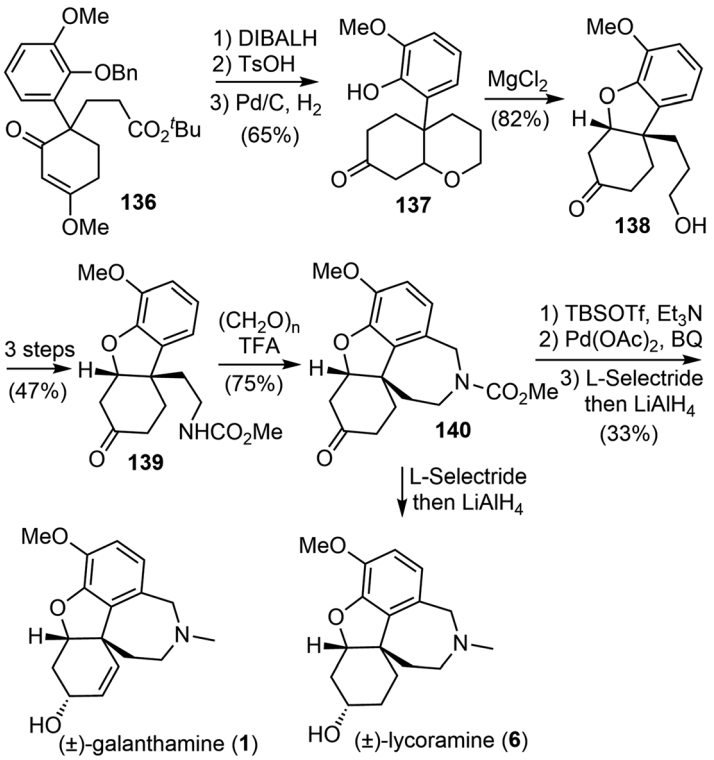
The enolate alkylation reaction is a fundamental and well-established process for C–C bond formation, including the creation of bonds involving highly congested quaternary centers. The control of the stereoselectivity of enolate alkylation using chiral auxiliaries, chiral bases, and chiral catalysts has received considerable attention, resulting in many innovative methodologies. The enolate alkylation reaction has been successfully implemented in the construction of the congested quaternary center and C ring of galantamine. Highly efficient asymmetric enolate alkylation reactions with organocatalysts and Lewis acid catalyst were identified for the asymmetric total synthesis of (−)-galantamine.

5.1 Cascade double Michael addition and Dieckmann reaction (Ishikawa)

In 2008, Ishikawa and Saito developed a practical method for synthesizing 4,4-disubstituted cyclohexane-1,3-diones from nonactivated simple ketones (Scheme 34).[16] The process involved a double Michael addition of substituted acetone derivatives **133** with excess acrylic acid ester under basic conditions, followed by a Dieckmann cyclization, resulting in the formation of 4,4-disubstituted cyclohexane-1,3-diones **134** in a single pot. Interestingly, only highly substituted enolates participate as Michael donors in the cascade process. Enol ethers **135** were selectively formed from diketones **134** under acidic conditions. Alkyl and aryl groups were successfully



Scheme 34 The cascade double Michael addition and Dieckmann reaction.



Scheme 35 Ishikawa and Saito's synthesis of (±)-galantamine and (±)-lycoramine.

introduced at the quaternary stereogenic center, which is typically challenging to achieve.

Enol ethers **135** were found to be useful intermediates for the synthesis of sterically congested natural products (Scheme 35). A hydroxy enone was obtained by reduction of the ester and ketone groups of **136**. When treated with TsOH, it underwent an intramolecular oxy-Michael addition reaction, and the olefin was temporarily protected. Subsequent *O*-debenzylation under hydrogenolysis conditions gave a phenol derivative **137**. A $MgCl_2$-mediated retro-Michael and a phenolic hydroxy-Michael addition reaction of **137** afforded the thermodynamically more stable dihydrobenzofuran **138**. The primary hydroxy group of **138** was transformed to a carbamate **139** in 3 steps. A Pictet–Spengler cyclization of **139** with paraformaldehyde generated the D ring and gave the key tetracyclic product **140**.[73] As in the previous total syntheses, compound **140** served as a common intermediate for the total syntheses of (±)-galantamine and (±)-lycoramine.

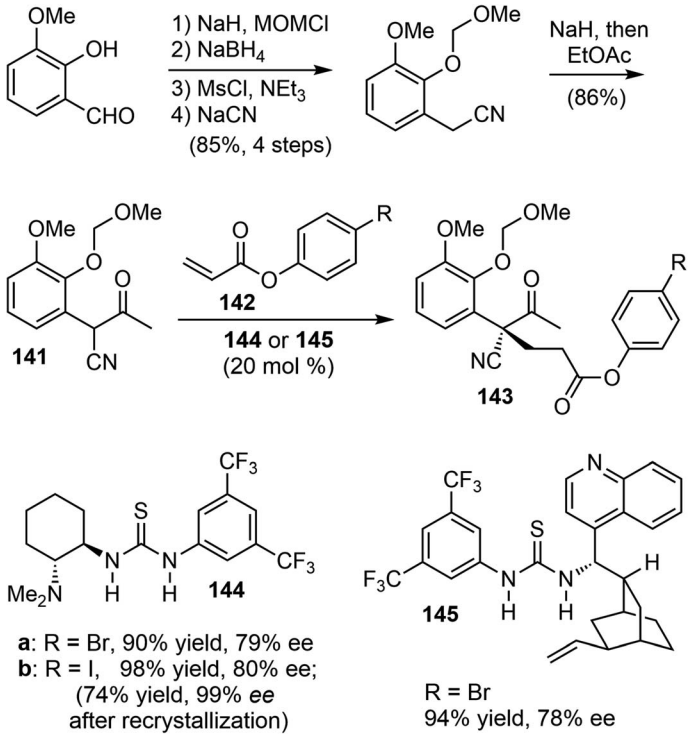
Ishikawa's work opened up a new avenue for the total synthesis of galantamine. In the majority of previous total syntheses, the C ring of galantamine was obtained from commercial supplies. Ishikawa's work was one of the earliest examples to generate the C ring during the total synthesis, and it was also the first example to create the quaternary center by the classic enolate alkylation reaction. The new synthetic strategy provides many opportunities for the development of asymmetric total synthesis of galantamine. Following their racemic synthesis, several groups successfully identified highly efficient asymmetric catalytic systems for similar reactions and completed the enantioselective total synthesis of (−)-galantamine.

5.2 Organocatalyzed asymmetric intermolecular Michael addition (Fan)

In 2011, Fan and coworkers reported total syntheses of several hydrodibenzofuran alkaloids.[21] They first developed a method to set up the key sterically congested aryl-substituted quaternary carbon center through an organocatalytic asymmetric intermolecular Michael addition of α-aryl-α-cyanoketones **141** with acrylates **142** (Scheme 36). Compound **141** was readily prepared in 5 steps from *o*-vanillin in a good overall yield. The Takemoto catalyst **144** (ref. 101) and the cinchonidine-derived bifunctional catalyst **145** (ref. 102) gave the best results and allowed for tuning of the enantioselectivity. Among the solvents tested, *p*-xylene was found to be the optimal choice with respect to both enantioselectivity as well as the reactivity of the catalyst.

Using **144** as the catalyst, the Michael addition of **141** and **142b** yielded the functionalized δ-keto ester **143b** with an aryl-substituted all-carbon quaternary center. Iodide **143b** was selected for the final synthesis because of its ease of crystallization. An optical purity of 99% ee was obtained with a yield of 74% after a single recrystallization. The absolute configuration of the chiral all-carbon quaternary stereocenter was confirmed by X-ray crystallography.

Following Ishikawa's racemic total synthesis, compound **143b** underwent a Dieckmann condensation reaction under basic conditions. The resulting 1,3-diketone was regioselectively transformed to enol ether **146** under acidic conditions (Scheme

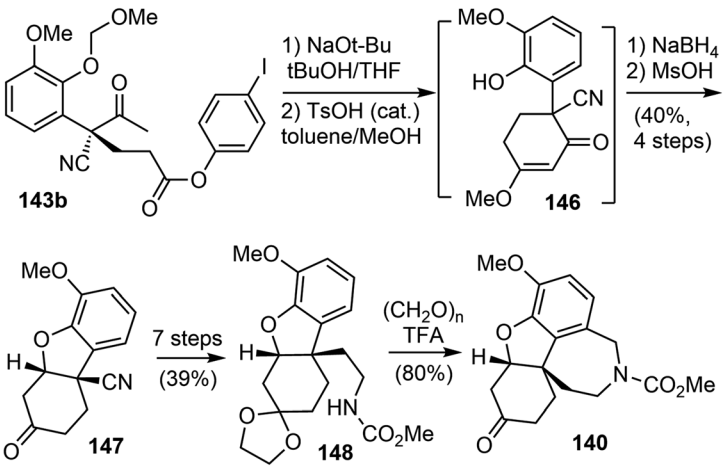


Scheme 36 Intermolecular asymmetric Michael addition to form the quaternary center.

37). The subsequent Luche reduction of **146**, followed by acidic workup led to the formation of an enone that underwent a further intramolecular oxa-Michael addition reaction. The tricyclic intermediate **147** with the key *cis*-hydrodibenzofuran skeleton was obtained in 40% yield over 4 steps. Subsequently, a one-carbon homologation of the nitrile group was performed in 7 further steps, converting **147** into the carbamate **148**. Compound **148** underwent a Pictet–Spengler reaction with paraformaldehyde to form the tetracyclic compound **140**, which is a key intermediate in Ishikawa's racemic total synthesis.[16] Following similar reaction sequences, **140** was converted to (−)-galantamine and (−)-lycoramine after the oxidation state adjustment.

5.3 Lewis acid catalyzed asymmetric intermolecular Michael addition (Jia)

In 2015, Jia and coworkers disclosed a catalytic asymmetric total synthesis of (−)-galantamine (**1**) and (−)-lycoramine (**6**).[25] Two metal catalyzed reactions were developed to build the core structure of the natural products. Specifically, a palladium-catalyzed intramolecular Larock annulation reaction was employed to construct the 3,4-fused benzofuran,



Scheme 37 Fan's formal synthesis of (−)-galantamine and (−)-lycoramine *via* **140**.

while a Sc(III)/*N*,*N*′-dioxide complex catalyzed enantioselective conjugate addition of a 3-alkyl-substituted benzofuranone to methyl vinyl ketone was used to set up the quaternary carbon center.

They first investigated the synthesis of 3,4-fused benzofuran by an intramolecular Larock annulation reaction of an *ortho*-iodophenol tethered with an internal alkyne.[103] The reaction of **149** under the catalysis of $[Pd_2(dba)_3]$ (5 mol%) and $P(t\text{-}Bu)_3\cdot HBF_4$ (20 mol%) afforded the desired product **150** in 95% yield (Scheme 38). This transformation was found to be quite general, with more than 15 examples of 3,4-fused benzofurans containing either carbon, oxygen, or nitrogen tethers were obtained in reasonable yields.

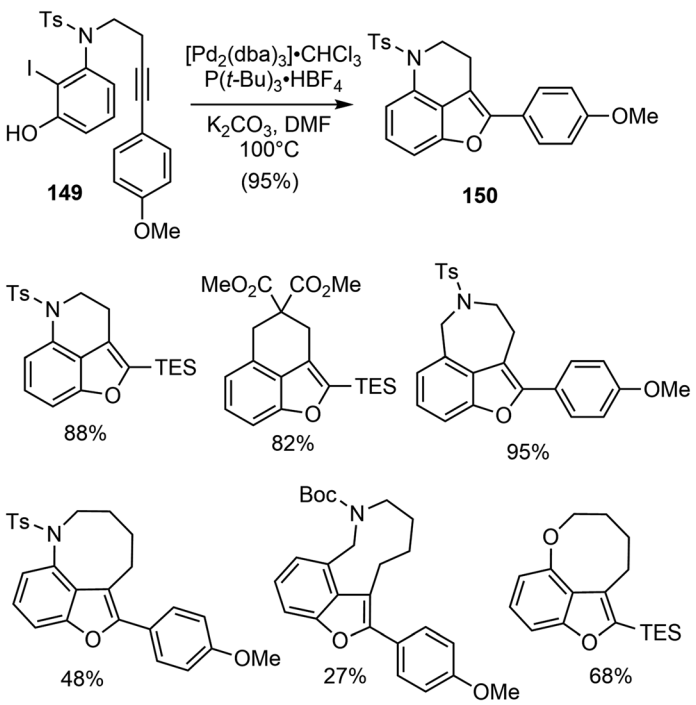
Having developed this method, they applied it to the total synthesis of galantamine. The substrate **151** was obtained in 2 steps from readily available materials. Under the reaction conditions developed above, the 3,4-fused benzofuran **152** was obtained from **151** in 89% yield. Removal of the TES group with TBAF followed by oxidation with *m*-CPBA afforded the lactone **153**. They then explored the construction of the chiral all-carbon quaternary stereocenter. They first examined a number of organocatalysts for the reaction of **153** with methyl vinyl ketone (MVK). However, the highest enantioselectivity obtained was 55% ee. Alternatively, other catalytic reaction systems were explored, and it was discovered that a combination of the Lewis acid $Sc(OTf)_3$ with the chiral *N*,*N*′-dioxide ligand **154** catalyzed the asymmetric Michael addition reaction of **153** to MVK.[104] The reaction proceeded smoothly at room temperature to afford the desired product **155** in 85% yield with 93% ee. An intramolecular cyclization reaction of **155** yielded a hemiketal and generated the tetracyclic core structure **156**. Ionic reduction of the hemiketal with Et_3SiH resulted in simultaneous reduction of the ketone and removal of the Boc group. Protection of the amine with methyl chloroformate and oxidation of the alcohol delivered **140**, the key intermediate in Ishikawa's racemic total synthesis[16] and Fan's asymmetric synthesis (Scheme 39).[21]

5.4 Organocatalyzed asymmetric Robinson annulation (Tu)

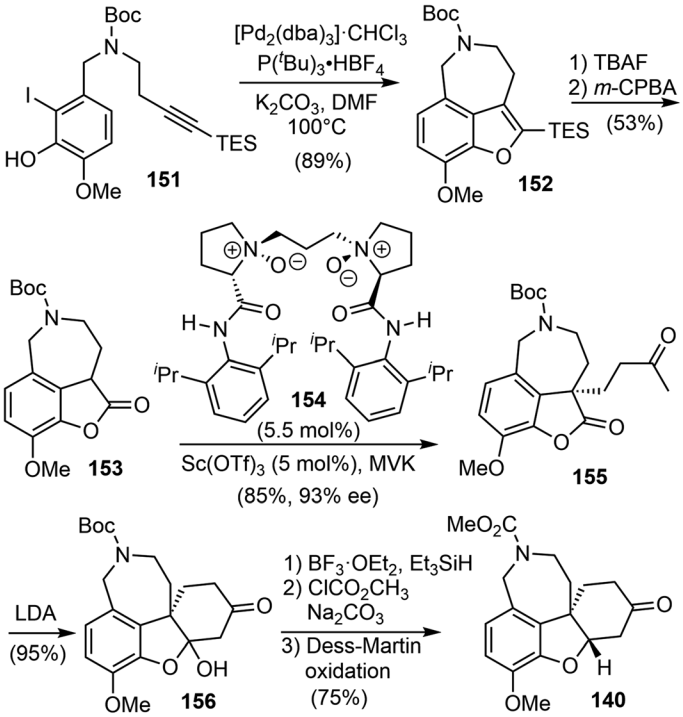
In 2019, Tu and coworkers reported catalytic asymmetric total syntheses of (−)-galantamine (**1**) and (−)-lycoramine (**6**).[33] They developed a spirocyclic pyrrolidine (SPD)-catalyzed enantioselective Robinson annulation reaction to construct the key *cis*-hydrodibenzofuran core with the all-carbon quaternary stereocenter.[105]

Their synthesis commenced from 3-butyn-1-ol **157** (Scheme 40). A one-pot double transformation of **157** led to an internal alkyne **158**. A copper catalyzed regioselective and stereoselective hydroboration reaction of alkyne **158**, followed by a Pd-catalyzed Suzuki coupling reaction with aryl bromide **159**, selectively afforded the trisubstituted olefin **160**. Compound **160** was then converted to the α, β-unsaturated ketone **161**.

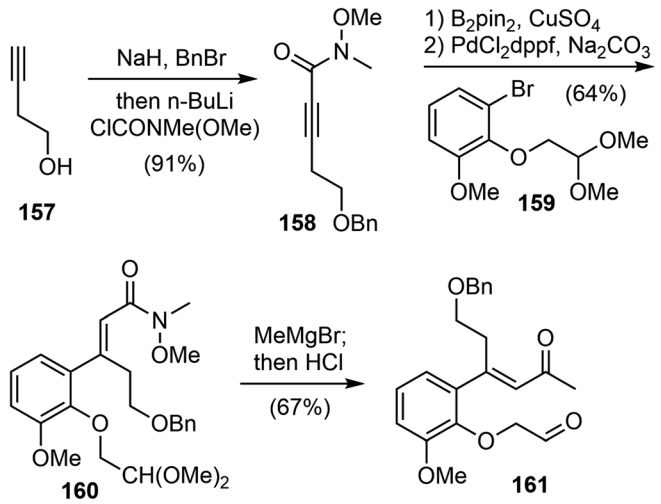
An initial effort was made to produce the tricyclic compound **164** through a direct intramolecular Robinson annulation of **161**. However, the transformation stopped at the Michael addition stage, despite numerous experimental conditions screening. The product was isolated as **163** after a Wittig olefination. Among the reaction conditions screened, it was discovered that the Michael addition/Wittig olefination product **163** was obtained in good yield and selectivity in the presence of the SPD catalyst **C** and 2,4,6-triisopropylbenzoic acid as an additive. The outcome of the reaction was further improved by decreasing the reaction temperature to −30 °C,



Scheme 38 Larock-type annulation for the synthesis of 3,4-fused benzofurans.



Scheme 39 Jia's formal total synthesis of (−)-galantamine *via* **140**.



Scheme 40 Synthesis of α, β-unsaturated ketone **161**.

resulting in the product **163** being obtained in 87% yield with 96% ee (Scheme 41).

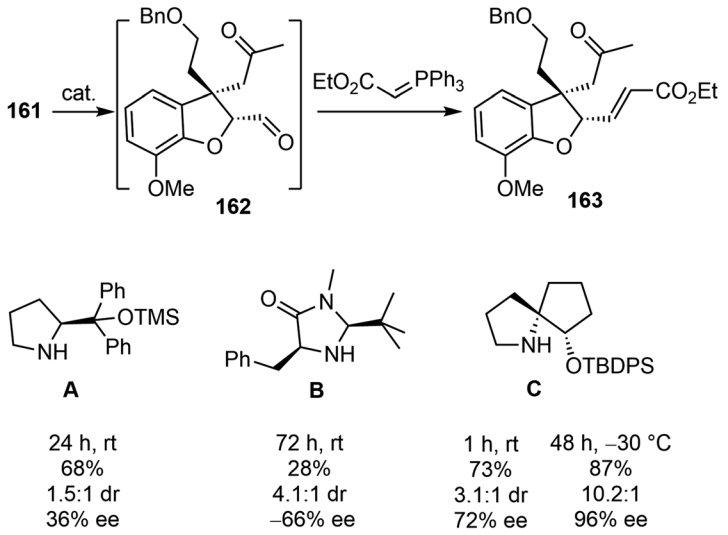
As a direct intramolecular Robinson annulation of **161** to generate the tricyclic compound **164** was not successful, it was discovered that an acid catalyzed aldol cyclization reaction of crude Michael product **163** afforded the tricyclic compound **164** (>99% ee) (Scheme 42). Compound **164** was used as a key intermediate in their total synthesis of morphine.[105] A Rubottom oxidation reaction installed the hydroxy group of **165** in 3 steps from compound **164**. Followed by a further oxidation state adjustment, the aldehyde **166** was generated in 5 steps. The tetracyclic product **167** was produced by oxidative amidation of the aldehyde and a Pictet–Spengler reaction with paraformaldehyde, following the protocol from their previous racemic total synthesis,[13] Stereo inversion of the alcohol was achieved by Dess–Martin oxidation of the alcohol and L-selectride reduction of the ketone. A final lactam reduction with $LiAlH_4$ completed the total synthesis of (−)-galantamine (**1**).

5.5 Aryne insertion reaction (Chandrasekhar)

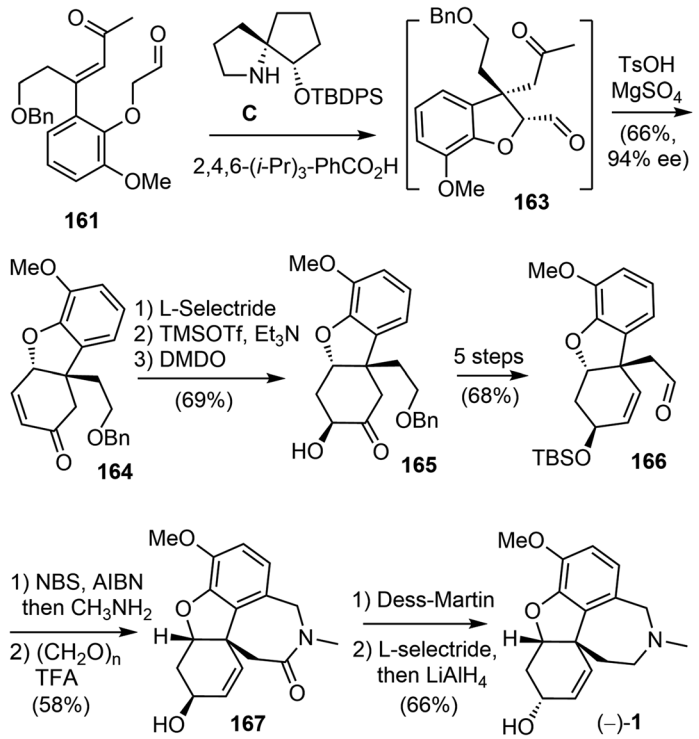
In 2019, Chandrasekhar and coworkers reported a racemic total synthesis of (±)-galantamine (**1**).[34] The process involved only two sub-critical temperature reactions and less than five chromatographic purifications. The synthesis used a key regioselective aryne insertion reaction into a GABA (γ-amino butyric acid) derivative to form the substituted aromatic A ring of galantamine.

Aryne is a highly reactive intermediate, it allows rapid functionalization of an aromatic ring by forming multiple carbon–carbon or carbon–heteroatom bonds in a single operation. The acyl–alkylation reaction of aryne with β-ketoester represents a mild and direct aryne insertion into a carbon–carbon bond (Scheme 43). The use of *o*-silyl aryl triflates, *e.g.*, **168**, as aryne precursors has allowed generation of the reactive intermediate under almost neutral conditions. The acyl-alkylation product **170** is the net result of aryne insertion into the α,β C–C single bond of the β-ketoester **169**, presumably by a formal [2 + 2] cycloaddition/fragmentation cascade.[106]

The synthesis began with the β-formyl ester **171**, which was synthesized from GABA in four steps. Upon treatment with the methoxy benzyne precursor **172** and cesium fluoride (CsF), the trisubstituted aryl compound **173** was regioselectively obtained



Scheme 41 Intramolecular Michael addition/Wittig olefination of α, β-unsaturated ketone **161**.



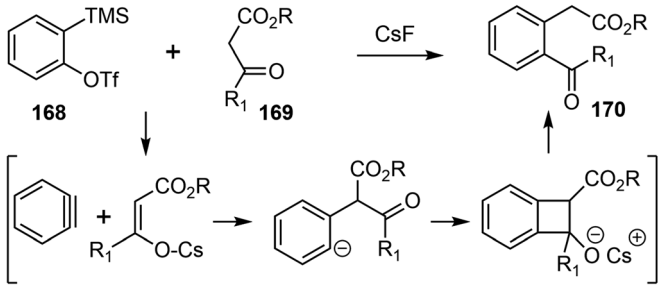
Scheme 42 Tu's total synthesis of (–)-galantamine.

in 62% yield (Scheme 44). The methoxy group on benzyne, through the negative inductive effect,[90] provided **173** as a single regioisomer. The product was transformed to the lactone **174** in 3 steps. The lactone was α-alkylated with methyl vinyl ketone, and the azepine D ring was installed with a Pictet–Spengler reaction to generate compound **175**. A further intramolecular condensation reaction gave the tetracyclic product **176**, which is a close analogue of Jia's intermediate **156**.[25] By carrying out similar transformations to those in Jia's synthesis, compound **176** was converted to galantamine in a further seven steps.

5.6 Intramolecular phenol alkylation (Magnus)

In 2009, Magnus and coworkers reported a distinct total synthesis of (±)-narwedine (**5**).[18] The synthesis used the *para*-alkylation of a substituted phenol as the key reaction.[31] This reaction generated the cross-conjugated 2,5-cyclohexadienone **179** with a quaternary center and avoided the phenolic oxidation reaction.

Their synthesis commenced from a Suzuki cross coupling reaction of commercially available 2-bromovanillin (**30**) with the

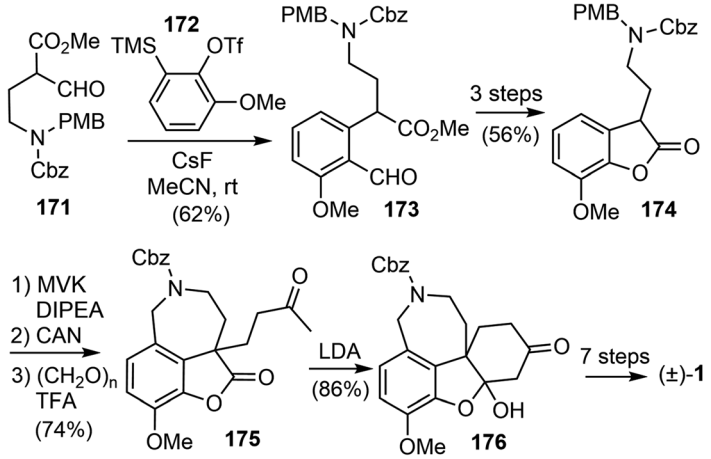


Scheme 43 Acyl-alkylation of aryne with β-ketoester.

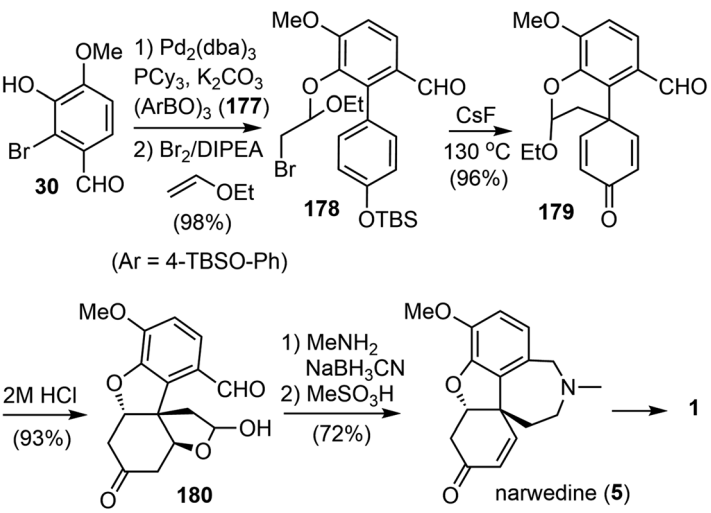
boronic acid anhydride **177** (Scheme 45). The resulting biaryl phenol was treated with ethyl vinyl ether and Br_2 in the presence of *N*,*N*-diisopropylethylamine at 0 °C. The bromoetherification product **178** was obtained in excellent yield (98%). Exposure of **178** to CsF (3 equiv.) in *N*,*N*-dimethylformamide (DMF) at 130 °C resulted in a clean desilylation and intramolecular alkylation reaction. The 2,5-cyclohexadienone **179** was obtained in high yield, and thus confirming the viability of this strategy. Acid catalyzed hydrolysis of the acetal in **179** resulted in two oxa-Michael addition reactions to give product **180**. Reductive amination of **180** with $MeNH_2$ generated the azepine D ring, which was converted into narwedine (**5**) by treatment with $MeSO_3H$. The overall process was completed with an impressive yield of 63%, which is approximately five times the yield of the current commercial process.[60,61] Since (±)-narwedine (**5**) has been converted into (−)-galantamine (**1**) by a crystallization-induced dynamic chiral resolution, and a diastereoselective reduction with L-selectride,[58] this completes an eight-step formal total synthesis of (−)-galantamine (**1**).

6. Miscellaneous approaches

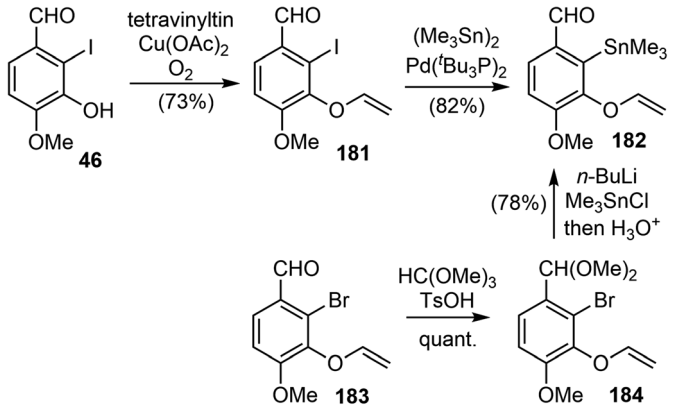
Other than the above four general approaches to the total synthesis of galantamine, there are several other miscellaneous approaches reported. Yu and coworkers reported a formal synthesis with a radical cyclization to form the quaternary



Scheme 44 Chandrasekhar's total synthesis of (±)-galantamine.



Scheme 45 Magnus' total synthesis of (±)-narwedine.



Scheme 46 Two approaches to aryltin fragment **182**.

center,[30] Cho and coworkers reported a synthesis of (±)-galantamine by a tandem C3-selective Stille coupling-intramolecular Diels–Alder (IMDA) cascade reaction.[20] Nagase and coworkers finished a semi synthesis from naltrexone,[32] which will not be discussed in this review.

6.1 Tandem Stille/IMDA (Cho)

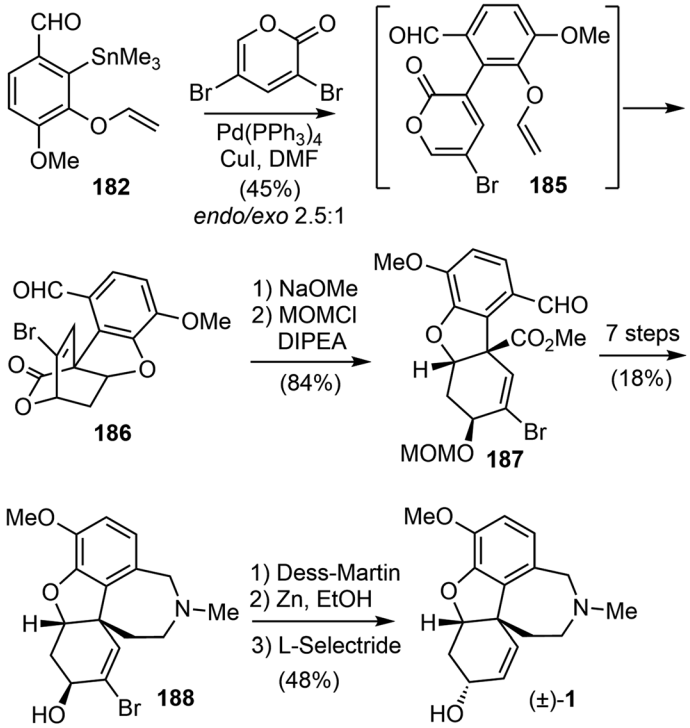
In 2010, Cho and coworkers reported their synthesis of (±)-galantamine by using a tandem C3-selective Stille coupling-intramolecular Diels–Alder (IMDA) cascade of 3,5-dibromo-2-pyrone as a key strategy, which was a novel strategy and a valuable addition to the galantamine synthesis predominated by the approaches involving either oxidative phenol coupling or an intramolecular Heck reaction.[20]

A Cu(II)-promoted *O*-vinylation of the iodophenol **46** provided the aryl vinyl ether **181** in good yield.[107] The Pd-catalyzed stannylation of iodide in **181** proceeded smoothly to afford the aryltin fragment **182**. Alternatively, compound **182** could be made in 2 steps from the bromo analogue **183** in a more economical way (Scheme 46).

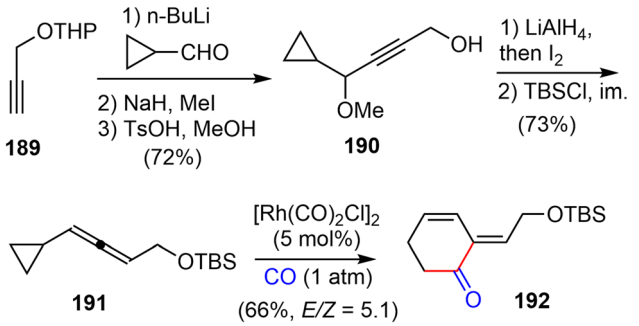
A C3-selective Stille coupling reaction of **182** with 3,5-dibromo-2-pyrone was best performed with 5 mol% of $Pd(PPh_3)_4$ and 10 mol% of CuI in DMF (Scheme 47). The reaction did not afford the Stille coupling product **185**, but instead gave the tandem Stille/IMDA cascade product **186** directly in modest yield and selectivity. The lactone ring opening of 6-*endo* product **186** with NaOMe and protection of the resultant secondary hydroxyl group as a MOM ether furnished ester **187** in 84% yield over two steps. From this point, they converted compound **187** to the tetracyclic intermediate **188** in 7 steps, adapting the procedures developed by Trost and co-workers for the synthesis of galantamine on the basis of the structural similarity with their tricyclic intermediate.[69] Final epimerization of the alcohol and reductive removal of the bromide afforded galantamine (**1**).

6.2 Radical cyclization (Yu)

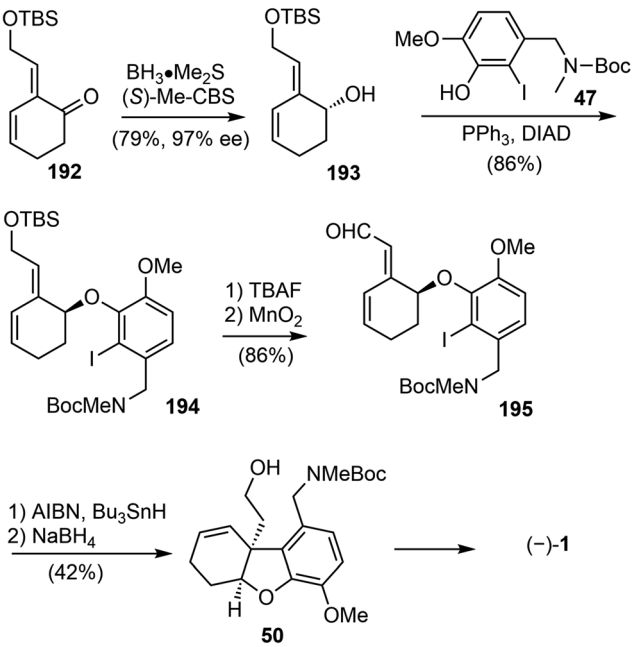
In 2016, Yu and coworkers reported another formal total synthesis of (−)-galantamine,[30] shortly after the first generation.[26] They first investigated a Rh-catalyzed [5 + 1] cycloaddition of di- and tri-substituted allenylcyclopropanes with CO (Scheme 48). The allene derivative **191** was prepared in 5 steps



Scheme 47 Cho's total synthesis of galantamine.



Scheme 48 Rh-catalysed [5 + 1] cycloaddition of allenylcyclopropanes and CO.



Scheme 49 Yu's formal total synthesis of (−)-galantamine *via* **50**.

from the propargylic alcohol **189**. Under the optimized conditions, the Rh-catalyzed cycloaddition reaction of **191** with CO afforded the functionalized 2-methylidene-3,4-cyclohexenone **192**.

CBS reduction of enone **192** led to the chiral alcohol product **193** in 79% yield and 97% ee (Scheme 49). Then alcohol **193** and the known phenol underwent the Mitsunobu reaction to form ether **194** in 86% yield. The TBS group was deprotected using TBAF and then the alcohol intermediate was oxidized to aldehyde **195** by activated MnO_2 in 86% yield over two steps. The initial attempts to form the five-membered ring in the natural product (−)-galantamine with Heck reaction of **194** or its deprotected alcohol was not successful. It was found that the starting materials decomposed slowly under the reaction conditions. Instead, ring closing cyclization of **195** under the radical conditions led to the desired product in 60% yield. Finally, reduction of the aldehyde led to Brown's intermediate **50** in total synthesis of galantamine,[14] which constituted a formal total synthesis of (−)-galantamine.

7. Summary of the total syntheses

Prior to 2006, there were only two synthetic strategies available for constructing the quaternary center in the total synthesis of galantamine: oxidative phenol coupling and the intramolecular Heck reaction.[9] The asymmetric total synthesis of galantamine relied on chiral auxiliaries or chemical resolution, with only one example of catalytic asymmetric total synthesis coming from the Trost group. However, substantial progress has been made in the synthetic chemistry of galantamine since then, with over 30 new syntheses reported (Table 1).

7.1 Evolution of synthetic strategy for the quaternary center

For almost half a century, the field has been dominated by the classical oxidative phenol coupling method, during which time some landmark achievements were discovered. The biomimetic oxidative phenol coupling reaction evolved from a low-yield, proof-of-concept experiment[50] to a high-yield, reliable synthetic strategy.[53,55] Asymmetric versions of total synthesis were achieved with chiral auxiliary control,[56,57] and more significantly, with the discovery of crystallization-induced dynamic resolution of (±)-narwedine.[58] Finally, based on these early discoveries, an impressive pilot scale chemical synthesis of (−)-galantamine was developed.[60,61] Recent progress on this strategy involves the implementation of new synthetic technologies, including chemoenzymatic synthesis[36] and electrosynthesis.[39,40]

The situation changed at the beginning of this century with the advent of transition metal catalyzed reactions.[69–72] These reactions not only introduced new synthetic strategies, but also provided new ways for the asymmetric synthesis of (−)-galantamine, which coincides with the rapid development in the field of transition metal catalyzed asymmetric reactions. Since these pioneering works, in addition to the use of the Heck coupling strategy in new circumstances,[14,23,24,28,29,41,42] novel transition metal catalyzed reactions, such as the reductive Heck reaction,[22] rhodium-catalyzed C–C bond activation,[26,30,35] and palladium-catalyzed cyclization reactions,[27,37] have been successfully applied in the total synthesis of galantamine.

In addition to the advances in the two classical approaches mentioned above, several more diverse synthetic strategies have emerged in the recent total synthesis of galantamine, including enolate and phenolate alkylation reactions, several types of rearrangement reactions and other miscellaneous approaches. Highly efficient asymmetric total syntheses have been developed based on either traditional stoichiometric chiral reagents[38] or asymmetric Lewis acid catalysis[25] and organocatalysis.[21,33]

7.2 Assembly of the tetracyclic structure

The aromatic A ring was obtained from commercial sources and was used as the starting material in most total syntheses of galantamine. The only exception was the total synthesis reported by Banwell in 2015.[27] They used a regioselective Diels–Alder reaction of a diene with propynal, followed by oxidation to form the A ring.

The heterocyclic B ring was formed either by C–O bond linkage *via* an intramolecular phenolic oxa-Michael addition in

Table 1 Tabulated summary of highlighted syntheses of galantamine since 2006

Strategy	Main author/Year	Key reactions	Ring forming sequence	Source of chirality	Ref.
Oxidative phenol coupling	Bandichhor/2008	Phenol oxidative coupling	A + C → DB	Chemical resolution	17
	Wirth/2022	Electrosynthesis	A + C → D → B	Chiral pool	39
	Opatz, Waldvogel/2022	Electrosynthesis	A + C → D → B	Racemic	40
	Saladino/2022	Chemoenzymatic phenol oxidative coupling	A + C → D → B	Racemic	36
Transition metal catalyzed reaction	Zhou, Xie/2012	Dynamic kinetic resolution and reductive Heck	A + C → B → D	Dynamic kinetic resolution	22
	Brown/2007	Enyne RCM and Heck reaction	A → C → B → D	Asymmetric ketone reduction	14
	Brown/2022	Enyne RCM and Heck reaction	A → C → B → D	Asymmetric aldehyde allylation	41
	Banwell/2015	Alder-ene, Diels–Alder *B*-alkyl Suzuki	C → B → A → D	Racemic	27
	Banwell/2022	*B*-alkyl Suzuki, Heck	A + C → B → D	Asymmetric ketone reduction	42
	Hudlicky/2016	Microbial dihydroxylation/Heck	A + C → B → D	Microbial dihydroxylation	29
	Yu/2015	Rh-catalyzed [(3 + 2) + 1] cycloaddition	A → BC → D	Racemic	26
	Xu/2020	Rh-catalyzed "cut and sew" reaction	A + C → B → D	Racemic	35
	Zhao/2021	Pd-catalyzed olefin carbonylative cyclization	A + C → BD	Racemic	37
Enolate alkylation	Ishikawa/2008	Cascade double Michael addition and Dieckmann reaction	A → C → B → D	Racemic	16
	Fan/2011	Organocatalyzed asymmetric Michael addition	A → C → B → D	Organocatalysis	21
	Jia/2015	Lewis acid catalyzed asymmetric Michael addition	A → BD → C	Lewis acid catalysis	25
	Tu/2019	Organocatalyzed asymmetric Michael addition	A → B → C → D	Organocatalysis	33
	Chandrasekhar/2019	Aryne insertion	A → B → D → C	Racemic	34
	Magnus/2009	Intramolecular phenol alkylation	A + C → B → D	Racemic	18
Rearrangement reaction	Tu/2006	Semipinacol rearrangement	A + C → B → D	Racemic	13
	Bisai/2022	Johnson–Claisen rearrangement	A + C → B → D	Catalytic asymmetric ketone reduction	38
	Li/2023	Eschenmoser–Claisen rearrangement	ABC → D	Racemic	43
Miscellaneous approaches	Cho/2010	Tandem Stille coupling/IMDA	A → B + C → D	Racemic	20
	Yu/2016	Rh-catalyzed [5 + 1] cycloaddition, radical cyclization	A + C → B → D	Catalytic asymmetric ketone reduction	30

the oxidative coupling strategy and was the last ring formed for the tetracyclic structure, or alternatively, by C–C bond linkage *via* intramolecular Heck cyclization. Recent developments include the formation of the C–O bond by intramolecular phenolic substitution reaction,[13] or the formation of the C–C bond *via* intramolecular reductive Heck reaction,[22] Alder-ene reaction[27] or radical cyclization reaction.[30] The B ring has also been formed in intramolecular annulation reactions with concomitant formation of D or C ring.[25,26,33]

The cyclohexene C ring has been obtained from commercial sources in many total syntheses. However, disconnection at the C ring provides new options for diverse and innovative strategies in the total synthesis of galantamine. Recent progress in the synthesis of C ring include Robinson type annulation reactions,[16,21,25,33,34] metal catalyzed[14,26,30,41] or thermal cycloaddition reactions,[20] and arene dearomatization.[43]

The azepine D ring is typically the last ring to be formed in most total syntheses. Methods for the synthesis of this ring were mostly developed before 2006. The A and C rings were united in the intramolecular oxidative phenol coupling reaction, with simultaneous formation of the D ring. Other methods were the intramolecular C–N bond formation *via* reductive amination or *N*-alkylation reaction developed by Trost,[69,72] and C–C bond formation *via* the Pictet–Spengler reaction first used in Guillou's total synthesis.[73] A recent development came from Jia's synthesis,[25] in which the D ring was formed by a Pd-catalyzed intramolecular Larock annulation reaction with simultaneous formation of the B ring to give 3,4-fused benzofuran. In Xu' total synthesis, a ring expansion reaction *via* Beckman rearrangement was used to form the D ring.

7.3 Source of chirality

The industrial production of (−)-galantamine currently relies on a highly efficient crystallization-induced dynamic chiral resolution of a racemic intermediate (±)-narwedine (**5**) with a catalytic amount of chiral mediator. This process may reduce the importance of asymmetric synthesis for (−)-galantamine, but it remains a valuable platform for its application. Various methodologies have been used in the asymmetric total synthesis of (−)-galantamine and its enantiomer. These include chemical resolution,[17] biocatalysis,[19,29] asymmetric ketone reduction with catalytic[30,38] or stoichiometric[14,42] chiral reagents, asymmetric aldehyde allylation reaction,[41] and asymmetric catalysis with chiral transition metal complexes,[22] chiral Lewis acid[25] and organocatalysis.[21,33]

8. Conclusions

Galantamine is a bioactive natural product that was isolated from a herbal medicine and developed into a clinically approved drug for Alzheimer's disease. It is another gift of nature to mankind.[108–110] Because of its important bioactivities, scarcity of the natural resources and intriguing structural features, galantamine has attracted a lot of interest from the synthetic organic chemistry community, and even more so after it became a generic drug. The development of synthetic strategies for the total synthesis of galantamine parallels the advances in modern synthetic organic chemistry. It provides a good opportunity to demonstrate the interplay between target-oriented synthesis and synthetic methodology by summarizing and analyzing the total synthesis of galantamine. It is anticipated that galantamine will remain as a source of inspiration and a test for new synthetic methods and strategies.

The demand for galantamine has outstripped its natural supply. Currently, the natural product is synthesized industrially using the classic work of oxidative phenol coupling and crystallization-induced dynamic resolution. While this method is elegant and practical, there is still room for improvement. Several routes in the previously mentioned total syntheses have already surpassed the current industrial pilot-scale synthesis in terms of both step count and overall yield. The development of new chemistry and technology, as well as the pursuit of sales and profit, may lead to newer and more creative total syntheses of the natural product, potentially including a more efficient and scalable route.[111,112]

9. Author contributions

B. Cheng wrote the manuscript with the assistance from Q. Wang and Y. An. F. Chen supervised the project.

10. Conflicts of interest

There are no conflicts to declare.

11. Acknowledgements

Financially support from Shenzhen Fundamental Research Program (GXWD20201230155427003-20200822151253001) was acknowledged.

12. Notes and references

1 D. A. Cozanitis, *Wien. Med. Wochenschr.*, 2021, **171**, 205–213.
2 B. Janssen and B. Schäfer, *ChemTexts*, 2017, **3**, 7.
3 S. Lilienfeld, *CNS Drug Rev.*, 2002, **8**, 159–176.
4 A. L. Harvey, *Pharmacol. Ther.*, 1995, **68**, 113–128.
5 D. Jiang, X. Yang, M. Li, Y. Wang and Y. Wang, *J. Neural Transm.*, 2015, **122**, 1157–1166.
6 K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191.
7 C. Li, S. S. Ragab, G. Liu and W. Tang, *Nat. Prod. Rep.*, 2020, **37**, 276–292.
8 P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou and J. Zhou, *ACS Catal.*, 2019, **9**, 1820–1882.
9 J. Marco-Contelles, M. do Carmo Carreiras, C. Rodríguez, M. Villarroya and A. G. García, *Chem. Rev.*, 2006, **106**, 116–133.
10 U. Rinner, C. Dank and T. Hudlicky, *Targets Heterocycl. Syst.*, 2016, **20**, 283.
11 W. Haiming, C. Peng and T. Meng, *Chin. J. Org. Chem.*, 2014, **34**, 852.

12 F. Lei, G. O. U. Shao-Hua and Z. Yi-Hua, *Chin. J. Org. Chem.*, 2011, **31**, 286.
13 X.-D. Hu, Y. Q. Tu, E. Zhang, S. Gao, S. Wang, A. Wang, C.-A. Fan and M. Wang, *Org. Lett.*, 2006, **8**, 1823–1825.
14 V. Satcharoen, N. J. McLean, S. C. Kemp, N. P. Camp and R. C. D. Brown, *Org. Lett.*, 2007, **9**, 1867–1869.
15 H. Tanimoto, T. Kato and N. Chida, *Tetrahedron Lett.*, 2007, **48**, 6267–6270.
16 T. Ishikawa, K. Kudo, K. Kuroyabu, S. Uchida, T. Kudoh and S. Saito, *J. Org. Chem.*, 2008, **73**, 7498–7508.
17 J. M. Reddy, K. V. Kumar, V. Raju, B. V. Bhaskar, V. Himabindu, A. Bhattacharya, V. Sundaram, R. Banerjee, G. M. Reddy and R. Bandichhor, *Synth. Commun.*, 2008, **38**, 2138–2149.
18 P. Magnus, N. Sane, B. P. Fauber and V. Lynch, *J. Am. Chem. Soc.*, 2009, **131**, 16045–16047.
19 M. G. Banwell, X. Ma, O. P. Karunaratne, A. C. Willis, M. G. Banwell, X. Ma, O. P. Karunaratne and A. C. Willis, *Aust. J. Chem.*, 2010, **63**, 1437–1447.
20 J. H. Chang, H.-U. Kang, I.-H. Jung and C.-G. Cho, *Org. Lett.*, 2010, **12**, 2016–2018.
21 P. Chen, X. Bao, L.-F. Zhang, M. Ding, X.-J. Han, J. Li, G.-B. Zhang, Y.-Q. Tu and C.-A. Fan, *Angew. Chem., Int. Ed.*, 2011, **50**, 8161–8166.
22 J.-Q. Chen, J.-H. Xie, D.-H. Bao, S. Liu and Q.-L. Zhou, *Org. Lett.*, 2012, **14**, 2714–2717.
23 J. Choi, H. Kim, S. Park and J. Tae, *Synlett*, 2013, **24**, 379–382.
24 Y. Zang and I. Ojima, *J. Org. Chem.*, 2013, **78**, 4013–4018.
25 L. Li, Q. Yang, Y. Wang and Y. Jia, *Angew. Chem., Int. Ed.*, 2015, **54**, 6255–6259.
26 Y. Feng and Z.-X. Yu, *J. Org. Chem.*, 2015, **80**, 1952–1956.
27 J. Nugent, E. Matoušová and M. G. Banwell, *Eur. J. Org Chem.*, 2015, 3771–3778.
28 J. Nugent and M. G. Banwell, *Eur. J. Org Chem.*, 2016, 5862–5867.
29 M. A. A. Endoma-Arias and T. Hudlicky, *Chem.–Eur. J.*, 2016, **22**, 14540–14543.
30 C.-H. Liu and Z.-X. Yu, *Org. Biomol. Chem.*, 2016, **14**, 5945–5950.
31 B. Dong, B. Zhou, J. Ren, L. Lu, G. Lu, P. Hu and B.-B. Zeng, *Tetrahedron*, 2017, **73**, 4719–4722.
32 N. Yamamoto, T. Okada, Y. Harada, N. Kutsumura, S. Imaide, T. Saitoh, H. Fujii and H. Nagase, *Tetrahedron*, 2017, **73**, 5751–5758.
33 Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *J. Org. Chem.*, 2019, **84**, 12664–12671.
34 T. Venkatesh, P. S. Mainkar and S. Chandrasekhar, *Org. Biomol. Chem.*, 2019, **17**, 2192–2198.
35 Y. Zhang, S. Shen, H. Fang and T. Xu, *Org. Lett.*, 2020, **22**, 1244–1248.
36 C. Zippilli, L. Botta, B. M. Bizzarri, M. C. Baratto, R. Pogni and R. Saladino, *RSC Adv.*, 2020, **10**, 10897–10903.
37 Y.-P. Chang, X. Ma, H. Shao and Y.-M. Zhao, *Org. Lett.*, 2021, **23**, 9659–9663.
38 S. Majumder, A. Yadav, S. Pal, A. Khatua and A. Bisai, *J. Org. Chem.*, 2022, **87**, 7786–7797.
39 Z. Xiong, F. Weidlich, C. Sanchez and T. Wirth, *Org. Biomol. Chem.*, 2022, **20**, 4123–4127.
40 D. Pollok, L. M. Großmann, T. Behrendt, T. Opatz and S. R. Waldvogel, *Chem.–Eur. J.*, 2022, **28**, e202201523.
41 I. R. Miller, N. J. McLean, G. A. I. Moustafa, V. Ajavakom, S. C. Kemp, R. K. Bellingham, N. P. Camp and R. C. D. Brown, *J. Org. Chem.*, 2022, **87**, 1325–1334.
42 N. Hu, Y.-T. He, P. Lan, M. G. Banwell, L. V. White, N. Hu, Y.-T. He, P. Lan, M. G. Banwell and L. V. White, *Aust. J. Chem.*, 2022, **75**, 974–982.
43 J.-Y. Qiu, W.-L. Zeng, H. Xie, M.-Y. Wang and W. Li, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218961.
44 M. C. Carson and M. C. Kozlowski, *Nat. Prod. Rep.*, 2024, **41**, 208–227.
45 D. H. R. Barton, G. W. Kirby, J. B. Taylor and G. M. Thomas, *J. Chem. Soc.*, 1963, 4545–4558.
46 A. M. Takos and F. Rook, *Int. J. Mol. Sci.*, 2013, **14**, 11713–11741.
47 J. Eichhorn, T. Takada, Y. Kita and M. H. Zenk, *Phytochemistry*, 1998, **49**, 1037–1047.
48 B. B. Majhi, S.-E. Gélinas, N. Mérindol, S. Ricard and I. Desgagné-Penix, *Front. Plant Sci.*, 2023, **14**, 1231809.
49 T. U. Jayawardena, N. Merindol, N. S. Liyanage and I. Desgagné-Penix, *Nat. Prod. Rep.*, 2024, DOI: **10.1039/D3NP00044C**.
50 D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806–817.
51 T. Kametani, K. Yamaki, H. Yagi and K. Fukomuto, *J. Chem. Soc. Chem. Commun.*, 1969, 425–426.
52 T. Kametani, K. Yamaki, H. Yagi and K. Fukumoto, *J. Chem. Soc. C*, 1969, 2602–2605.
53 Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma and T. Takada, *J. Org. Chem.*, 1998, **63**, 6625–6633.
54 D. Krikorian, V. Tarpanov, S. Parushev and P. Mechkarova, *Synth. Commun.*, 2000, **30**, 2833–2846.
55 M. Node, S. Kodama, Y. Hamashima, T. Baba, N. Hamamichi and K. Nishide, *Angew. Chem., Int. Ed.*, 2001, **40**, 3060–3062.
56 K. Koga, K. Shimizu, K. Tomioka and S. Yamada, *Heterocycles*, 1977, **8**, 277.
57 S. Kodama, Y. Hamashima, K. Nishide and M. Node, *Angew. Chem., Int. Ed.*, 2004, **43**, 2659–2661.
58 W.-C. Shieh and J. A. Carlson, *J. Org. Chem.*, 1994, **59**, 5463–5465.
59 N. G. Anderson, *Org. Process Res. Dev.*, 2005, **9**, 800–813.
60 L. Czollner, W. Frantsits, B. Küenburg, U. Hedenig, J. Fröhlich and U. Jordis, *Tetrahedron Lett.*, 1998, **39**, 2087–2088.
61 B. Küenburg, L. Czollner, J. Fröhlich and U. Jordis, *Org. Process Res. Dev.*, 1999, **3**, 425–431.
62 1.64–1.75 kg of galantamine was isolated per hectare of *N. pseudonarcissus*: M. D. Fraser, H. E. Vallin, J. R. T. Davies, G. E. Rowlands and X. Chang, *Sci. Rep.*, 2021, **11**, 1389.

63 J. Li, A. Amatuni and H. Renata, *Curr. Opin. Chem. Biol.*, 2020, **55**, 111–118.
64 M. Mogharabi and M. A. Faramarzi, *Adv. Synth. Catal.*, 2014, **356**, 897–927.
65 N. Cardullo, V. Muccilli and C. Tringali, *RSC Chem. Biol.*, 2022, **3**, 614–647.
66 S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 6018–6041.
67 R. K. Mylavarapu, K. GCM, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya and R. Bandichhor, *Org. Process Res. Dev.*, 2007, **11**, 1065–1068.
68 D. A. Chaplin, N. B. Johnson, J. M. Paul and G. A. Potter, *Tetrahedron Lett.*, 1998, **39**, 6777–6780.
69 B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 2000, **122**, 11262–11263.
70 P. J. Parsons, M. D. Charles, D. M. Harvey, L. R. Sumoreeah, A. Shell, G. Spoors, A. L. Gill and S. Smith, *Tetrahedron Lett.*, 2001, **42**, 2209–2211.
71 C. Pilger, B. Westermann, U. Flörke and G. Fels, *Synlett*, 2000, 1163–1165.
72 B. M. Trost and W. Tang, *Angew. Chem., Int. Ed.*, 2002, **41**, 2795–2797.
73 C. Guillou, J.-L. Beunard, E. Gras and C. Thal, *Angew. Chem., Int. Ed.*, 2001, **40**, 4745–4746.
74 A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit and F. Schwarzenbach, *J. Am. Chem. Soc.*, 1992, **114**, 2321–2336.
75 W.-J. Bai, J.-H. Xie, Y.-L. Li, S. Liu and Q.-L. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 81–84.
76 S. Das, D. Addis, S. Zhou, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 1770–1771.
77 M. G. Banwell, J. N. Buckler, C. J. Jackson, P. Lan, X. Ma, E. Matoušová and J. Nugent, in *Strategies and Tactics in Organic Synthesis*, ed. M. Harmata, Academic Press, 2015, vol. 11, pp. 29–50.
78 C. S. Beshara, A. Hall, R. L. Jenkins, K. L. Jones, T. C. Jones, N. M. Killeen, P. H. Taylor, S. P. Thomas and N. C. O. Tomkinson, *Org. Lett.*, 2005, **7**, 5729–5732.
79 L. Petit, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2011, **13**, 5800–5803.
80 B. M. Trost and C. Pedregal, *J. Am. Chem. Soc.*, 1992, **114**, 7292–7294.
81 M. Movassaghi and M. D. Hill, *Org. Lett.*, 2008, **10**, 3485–3488.
82 S. Eagon, C. DeLieto, W. J. McDonald, D. Haddenham, J. Saavedra, J. Kim and B. Singaram, *J. Org. Chem.*, 2010, **75**, 7717–7725.
83 J. Wang, S. A. Blaszczyk, X. Li and W. Tang, *Chem. Rev.*, 2021, **121**, 110–139.
84 L. Jiao, M. Lin, L.-G. Zhuo and Z.-X. Yu, *Org. Lett.*, 2010, **12**, 2528–2531.
85 N. F. McKinley and D. F. O'Shea, *J. Org. Chem.*, 2004, **69**, 5087–5092.
86 I. E. Markó and A. Mekhalfia, *Tetrahedron Lett.*, 1990, **31**, 7237–7240.
87 Y. Xue and G. Dong, *Acc. Chem. Res.*, 2022, **55**, 2341–2354.
88 P. Chen, B. A. Billett, T. Tsukamoto and G. Dong, *ACS Catal.*, 2017, **7**, 1340–1360.
89 P.-H. Chen, N. A. Savage and G. Dong, *Tetrahedron*, 2014, **70**, 4135–4146.
90 P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550–3577.
91 T. Diao and S. S. Stahl, *J. Am. Chem. Soc.*, 2011, **133**, 14566–14569.
92 K. Ma, B. S. Martin, X. Yin and M. Dai, *Nat. Prod. Rep.*, 2019, **36**, 174–219.
93 P. H. Gehrtz, V. Hirschbeck, B. Ciszek and I. Fleischer, *Synthesis*, 2016, **48**, 1573–1596.
94 C.-A. Fan, Y.-Q. Tu, Z.-L. Song, E. Zhang, L. Shi, M. Wang, B. Wang and S.-Y. Zhang, *Org. Lett.*, 2004, **6**, 4691–4694.
95 A. R. Chamberlin, J. E. Stemke and F. T. Bond, *J. Org. Chem.*, 1978, **43**, 147–154.
96 G. Stork and R. L. Danheiser, *J. Org. Chem.*, 1973, **38**, 1775–1776.
97 E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551–5553.
98 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741–743.
99 R. A. Fernandes, A. K. Chowdhury and P. Kattanguru, *Eur. J. Org Chem.*, 2014, **2014**, 2833–2871.
100 W. G. Salmond, M. A. Barta and J. L. Havens, *J. Org. Chem.*, 1978, **43**, 2057–2059.
101 T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672–12673.
102 J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481–4483.
103 R. C. Larock, *J. Organomet. Chem.*, 1999, **576**, 111–124.
104 X. Liu, L. Lin and X. Feng, *Acc. Chem. Res.*, 2011, **44**, 574–587.
105 Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *Nat. Commun.*, 2019, **10**, 2507.
106 U. K. Tambar and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 5340–5341.
107 M. Blouin and R. Frenette, *J. Org. Chem.*, 2001, **66**, 9043–9045.
108 A. G. Atanasov, S. B. Zotchev, V. M. Dirsch and C. T. Supuran, *Nat. Rev. Drug Discovery*, 2021, **20**, 200–216.
109 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2020, **83**, 770–803.
110 Y. Tu, *Angew. Chem., Int. Ed.*, 2016, **55**, 10210–10226.
111 C. A. Kuttruff, M. D. Eastgate and P. S. Baran, *Nat. Prod. Rep.*, 2014, **31**, 419–432.
112 X.-Y. Liu and Y. Qin, *Nat. Prod. Rep.*, 2023, **40**, 1694–1700.

