

REVIEW

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Progresses in organocatalytic asymmetric dearomatization reactions of indole derivatives

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Chiral indole derivatives such as indolines and indolenines are important heterocyclic frameworks which constitute the core structures of many natural products and bioactive molecules. So, intensive attentions from chemists have been paid to the construction of such frameworks. Among different approaches, organocatalytic asymmetric dearomatization (organo-CADA) reactions of indole derivatives have become powerful methods toward this goal. Consequently, a variety of enantioenriched heterocyclic frameworks containing indoline, indolenine and the related cores have been constructed *via* organo-CADA reactions of indole derivatives, and a series of important natural products with structural complexity and enantio-purity have been synthesized based on these methodologies. This review summarizes the progresses in organo-CADA reactions of indole derivatives since 2004 and their applications in total synthesis of natural products, and gives some insights into challenging issues in this research field, which will enlighten the future development of this field.

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1. Introduction

Chiral indole derivatives such as indolines and indolenines are important heterocyclic frameworks, which contain a tetra-

substituted chiral center. Particularly, the framework of chiral indoline exists in a number of natural alkaloids and bioactive compounds (Fig. 1).¹ Consequently, chemists have given intensive attention to the construction of chiral indoline-related frameworks.^{2,3}

In this context, catalytic asymmetric dearomatization (CADA) reactions^{4,5} have proven to be important methods for constructing chiral indoline-related frameworks. This is because CADA reactions are competent in transforming planar

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Feng-Tao Sheng was born in 1996 in Lianyungang, Jiangsu province, China. He received his Bachelor's degree from Xuzhou University of Technology in 2018. In the same year, he joined the group of Prof. Feng Shi to pursue his M.S. degree. His current research interests focus on organocatalytic asymmetric construction of axially chiral indole-based frameworks. He has published 4 research papers in international peer-

reviewed journals including *J. Am. Chem. Soc.*, *Angew. Chem., Int. Ed.*, *Chin. J. Chem.* and *Org. Biomol. Chem.*



Jing-Yi Wang

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reactions for the synthesis of enantioenriched indole derivatives. She has published 4 research papers in international peer-reviewed journals including *Org. Chem. Front.*, *J. Org. Chem.* and *Eur. J. Org. Chem.*

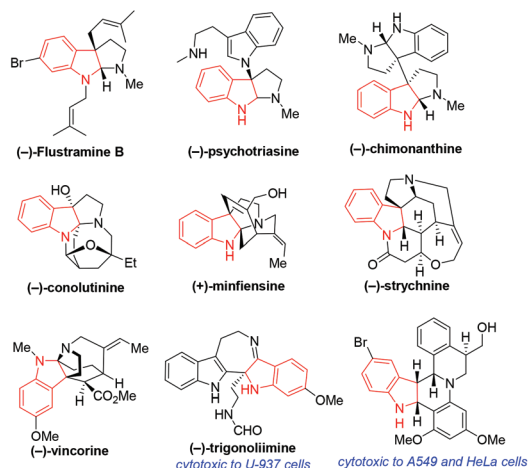


Fig. 1 Selected natural alkaloids and bioactive molecules containing a chiral indoline core.

aromatic structures into stereoselective chiral frameworks. In particular, due to the advantages of asymmetric organocatalysis in synthesizing enantioenriched molecules with potential bioactivity,^{6,7} organocatalytic asymmetric dearomatization (organo-CADA) reactions of indole derivatives have become powerful methods for constructing optically pure indoline and indolenine frameworks.

As summarized in Scheme 1, organo-CADA reactions of indole derivatives are classified into four categories based on different indole derivatives. This scheme summarizes the main characteristics and reaction types of the four kinds of indole derivatives in organo-CADA reactions.

The first type is organo-CADA reactions of tryptamines, tryptophols and their analogues (Scheme 1a), which can utilize the C3-nucleophilicity of the indole ring to attack elec-

trophiles (E) and initiate a cascade cyclization, thus accomplishing the organo-CADA reactions (eqn (1)). In addition, in the presence of some oxidants, oxidative cascade cyclization would occur (eqn (2)). Clearly, the organo-CADA reactions of tryptamines or tryptophols provided an easy access to enantioenriched pyrroloindoline or furoindoline scaffolds, which are widely found in natural alkaloids.

The second type is vinylindole-involved organo-CADA reactions (Scheme 1b), which mainly include tryptamine-derived 2-vinylindoles (eqn (3)) and 3-vinylindoles (eqn (4)). Both of them acted as electron-rich dienes to undergo [4 + 2] cycloadditions with electronically poor alkenes or alkynes under organocatalysis, which constructed chiral indoline skeletons fusing a six-membered ring. More importantly, tryptamine-derived 2-vinylindoles can further undergo a cascade cyclization after the [4 + 2] cycloaddition due to the existence of the tryptamine functionality, thus constructing structurally complex bridged-cyclic pyrroloindoline frameworks (eqn (3)). This type of organo-CADA reactions provided important protocols for the total synthesis of related natural products.

The third type is organo-CADA reactions of C3- and/or C2-substituted indoles (Scheme 1c). In a very simple way, this class of indole derivatives can use their C3-nucleophilicity to attack electrophiles (E), thus realizing organo-CADA reactions and constructing indolenine scaffolds with optical purity (eqn (5)). If a nucleophilic site (Nu) is linked to the electrophiles, a [2 + n] cycloaddition could occur to construct chiral indoline-fused cyclic skeletons (eqn (6)).

The last type is organo-CADA reactions of C3-functionalized indoles which are incorporated with an electrophilic site (Scheme 1d). This class of indole derivatives utilized their C3-nucleophilicity to undergo intramolecular addition reaction with the inner electrophilic site, thus constructing enantioenriched spiro-indolenine frameworks.



Wei Tan

Wei Tan was born in 1989 in Huai'an, Jiangsu province, China. He received his Bachelor's degree and M.S. degree from Jiangsu Normal University in 2012 and 2015, respectively, under the supervision of Prof. Feng Shi. Then he obtained his Ph.D. degree from East China Normal University in 2019 under the supervision of Prof. Xue-Feng Jiang. He joined Jiangsu Normal University as a researcher in 2019. His current

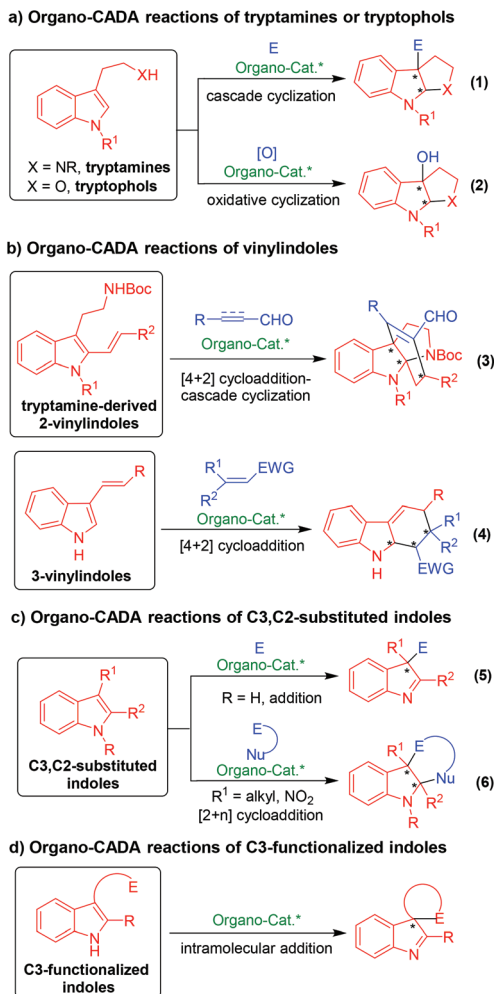
research interests focus on catalytic asymmetric synthesis of axially chiral five-membered heterobiaryls. He has published over 10 research papers in international peer-reviewed journals.



Yu-Chen Zhang

Yu-Chen Zhang was born in 1989 in Xuzhou, Jiangsu province, China. He received his Bachelor's degree from China Pharmaceutical University in 2011. Then he obtained his M.S. and Ph.D. degrees from Jiangsu Normal University and University of Science and Technology of China in 2016 and 2019 under the supervision of Prof. Feng Shi and Prof. Liu-Zhu Gong, respectively. He joined Jiangsu Normal University

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Scheme 1 Organo-CADA reactions of indole derivatives.



Feng Shi

Feng Shi was born in 1976 in Nantong, Jiangsu province, China. She received her Master's degree at Jiangsu Normal University in 2004 and then worked at this university as a lecturer. She obtained her Ph.D. degree at Soochow University in 2013 and worked as a visiting scholar at Nanyang Technological University from 2012 to 2013. She started her independent career from 2013 at Jiangsu Normal University and

was appointed to a Full Professor in 2015. Her research interests focus on catalytic asymmetric synthesis of enantioenriched heterocycles, especially indole derivatives. She has published over 120 research papers in international peer-reviewed journals.

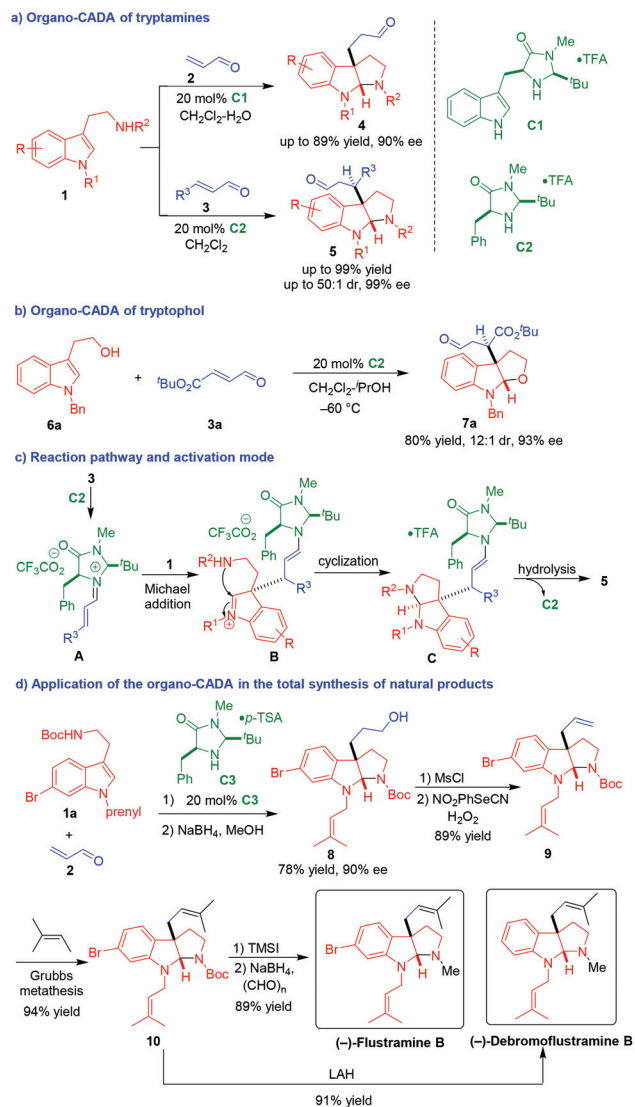
Based on the organo-CADA reactions of these indole derivatives, a variety of enantioenriched heterocyclic frameworks containing the indoline and indolenine cores were constructed, and a series of important natural products with structural complexity and enantiopurity were synthesized based on these methodologies. Although CADA reactions have received great attention from the chemistry community,^{4,5} a summarization on the topic of organo-CADA reactions of indole derivatives has not appeared which requires a timely and systematic summary, thus enlightening the future development of this research field. For clarity, the organization of this review is based on the types of indole derivatives which are involved in organo-CADA reactions.

2. Organo-CADA reactions of tryptamines, tryptophols and their analogues

2.1 Organo-CADA reactions of tryptamines, tryptophols and their analogues with C,N-centered electrophiles

In 2004, MacMillan and coworkers utilized chiral imidazolidinone catalysts as competent amine-type organocatalysts to realize the first organo-CADA reaction of tryptamines and tryptophol (Scheme 2).⁸ In the presence of organocatalysts **C1** or **C2**, tryptamines **1** underwent CADA reactions with α,β -unsaturated aldehydes **2** and **3**, constructing pyrroloindoline architectures **4–5** in high yield and excellent stereoselectivities (Scheme 2a). Additionally, the organo-CADA reaction of tryptophol **6a** with α,β -unsaturated aldehyde **3a** could smoothly occur to construct a furanoindoline framework with good results (Scheme 2b). In the suggested reaction pathway and activation mode (Scheme 2c), α,β -unsaturated aldehydes **3** were activated by catalyst **C2** to generate iminiums **A**, which were attacked by tryptamines **1** to undergo a Michael addition. Then, the generated intermediates **B** performed an intramolecular cyclization to give intermediates **C**. Finally, the hydrolysis of intermediates **C** gave rise to products **5** and released catalyst **C2**.

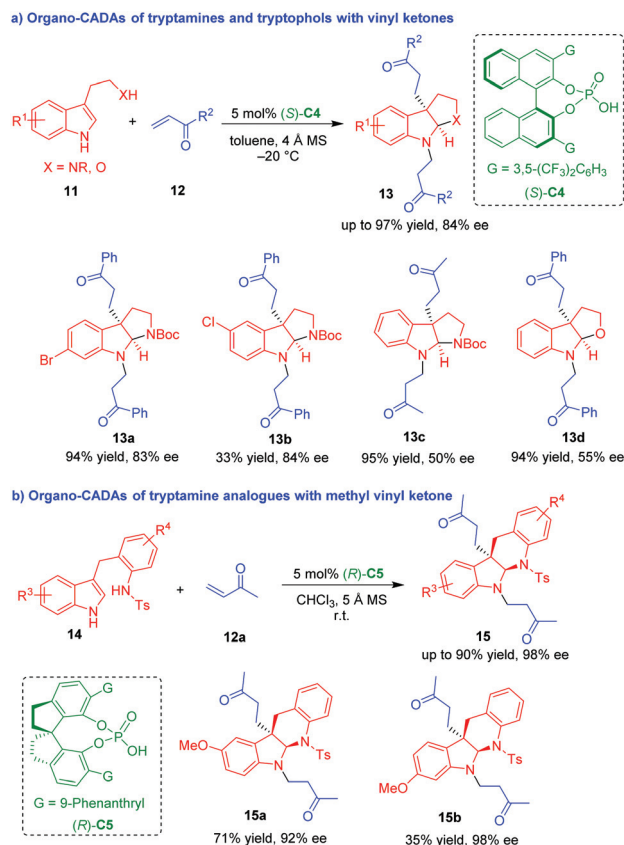
More importantly, they realized the application of this organo-CADA reaction in the total synthesis of natural products (Scheme 2d). Namely, the CADA reaction of tryptamine **1a** with α,β -unsaturated aldehyde **2** under the catalysis of chiral amine **C3** generated the key compound **8** with a high enantioselectivity of 90% ee after reduction of the aldehyde group. Then, compound **8** was subjected to mesylation and elimination to give compound **9** bearing a terminal alkenyl group, which underwent a metathesis to generate compound **10** as a precursor of natural products. Finally, in the presence of lithium aluminum hydride (LAH), compound **10** underwent both carbamate reduction and dehalogenation to generate (–)-debromoflustramine **B**. Instead, the selective removal of the Boc-group from compound **10** followed by reductive *N*-methylation resulted in the generation of (–)-flustramine **B**. This seminal work explored the potential of organo-CADA



Scheme 2 Organo-CADA reactions of tryptamines and tryptophol and their application in natural products synthesis by MacMillan and coworkers.⁸

reactions of tryptamines for the total synthesis of indoline-related natural alkaloids.

Chiral phosphoric acids (CPAs) have been recognized as a versatile organocatalysts in asymmetric catalysis for the enantioselective synthesis of nitrogenous and oxygenous heterocycles, especially enantioenriched indole derivatives.⁹ This is because the NH group in the indole moiety is easily activated by CPAs *via* hydrogen-bonding interactions.¹⁰ In 2012, You and coworkers utilized CPA (S)-C4 as a suitable organocatalyst to promote the CADA reaction of NH-unprotected tryptamines and tryptophol **11** with vinyl ketones **12** (Scheme 3a).¹¹ Interestingly, this CADA reaction involved double Michael addition to vinyl ketones **12**, which afforded *N*-alkylated pyrroloindolines **13** in overall high yields and moderate to good enantioselectivities.

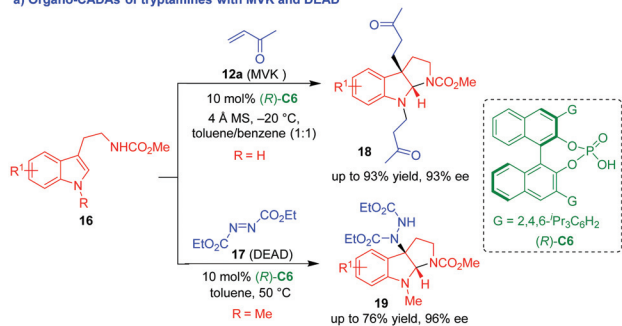


Scheme 3 Organo-CADA reactions of tryptamines, tryptophol and analogues with vinyl ketones by You and coworkers.^{11,12}

To expand the applicability of this strategy, in 2014, the same group devised tryptamine analogues **14** as competent substrates to undergo CADA reactions with methyl vinyl ketone (MVK) **12a** in the presence of CPA (R)-C5, which constructed indolinoquinoline frameworks **15** in moderate to high yields and good enantioselectivities (Scheme 3b).¹² Notably, both of the two approaches involved a cascade Michael addition/cyclization/*N*-Michael addition sequence, and the second *N*-Michael addition of *in situ* generated indoline to vinyl ketones should be ascribed to the strong nucleophilicity of the NH group in the structure of indoline.

Nearly at the same time, Antilla and coworker described CPA (R)-C6-promoted CADA reactions of tryptamines **16** with MVK **12a** and diethyl diazene-1,2-dicarboxylates (DEAD) **17**, respectively, which constructed enantioenriched pyrroloindoline frameworks **18** and **19** in good yields and high stereoselectivities (Scheme 4a).¹³ Notably, the authors performed NMR experiments to investigate the possible activation mode of CPA to substrates. In the reaction involving MVK **12a**, they proposed that (R)-C6 simultaneously formed two hydrogen bonds with the indole NH group and the ester carbonyl group of tryptamines **16**, and the amide NH group of tryptamines **16** formed another hydrogen bond with MVK **12a**, thus controlling the enantioselectivity in the first step of Michael addition (Scheme 4b). The similarly activation mode was suggested for

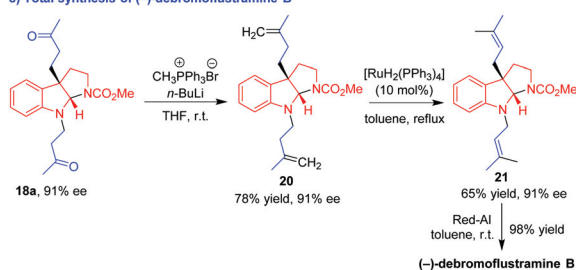
a) Organo-CADAs of tryptamines with MVK and DEAD



b) Proposed activation mode



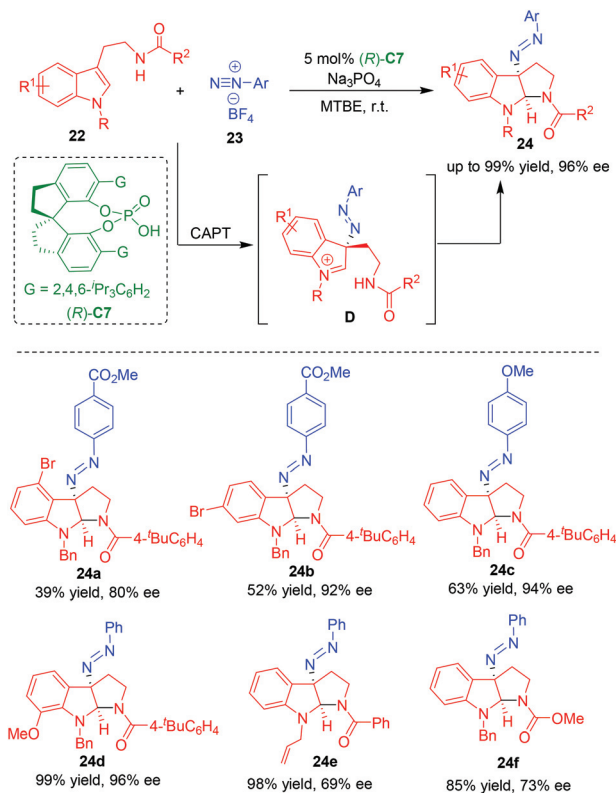
c) Total synthesis of (–)-debromoflustramine B



Scheme 4 Organo-CADA reaction of tryptamines and its application in the total synthesis of (–)-debromoflustramine B by Antilla and coworker.¹³

the reaction involving DEAD **17**, and the difference is that (*R*)-**C6** just formed one hydrogen bond with the ester carbonyl group of tryptamines **16** due to the existence of indole *N*-methyl group. More importantly, they applied the CADA reaction of tryptamines **16** with MVK **12a** in the total synthesis of (–)-debromoflustramine B *via* a very concise synthetic route (Scheme 4c). Namely, the pyrroloindoline product **18a** with 91% ee generated from CADA reaction was subjected to a Wittig olefination to give compound **20** with a retained enantioselectivity. Catalyzed by a Ru complex, the terminal olefin **20** isomerized into the internal alkene **21**, which further underwent a reduction reaction to afford (–)-debromoflustramine B in an excellent yield.

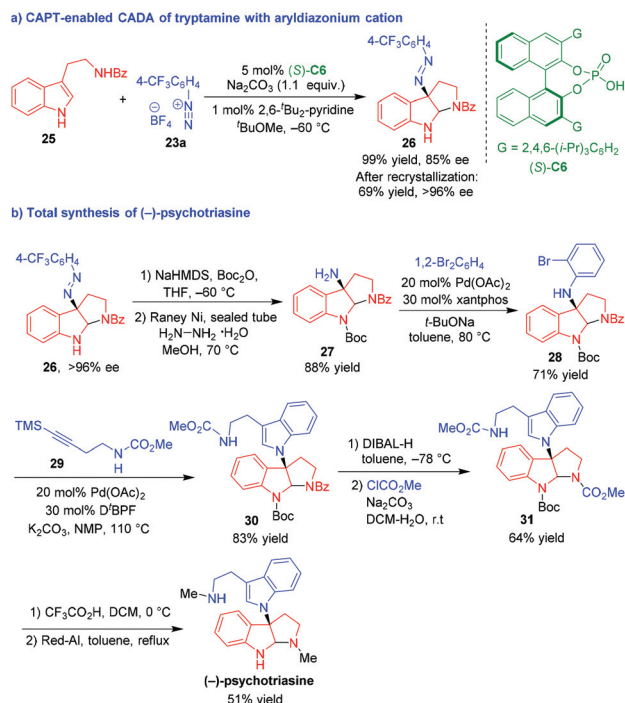
In 2014, under the catalysis of chiral anion phase-transfer (CAPT), Toste and coworkers realized the CADA reaction of tryptamines **22** using aryldiazonium cations as a source of electrophilic nitrogen, which was *in situ* generated from aryldiazonium tetrafluoroborates **23** (Scheme 5).¹⁴ By this approach, a series of C3-diazinated pyrroloindolines **24** were synthesized in overall high yields and excellent enantioselectivities. The authors suggested that the interaction of CPA (*R*)-**C7** with aryldiazonium tetrafluoroborates **23** provided a soluble chiral ion pair, which controlled the enantioselectivity in the step of nucleophilic addition of tryptamines **22** to aryl-



Scheme 5 Organo-CADA reaction of tryptamines with aryldiazonium cations by Toste and coworkers.¹⁴

diazonium, thus generating an enantioenriched intermediate **D** to undergo the subsequent intramolecular cyclization to give products **24**.

Shortly after, Liao, Deng and coworkers established the application of CAPT-enabled CADA reaction of tryptamine with aryldiazonium cation in the total synthesis of (–)-psychotriasine (Scheme 6).¹⁵ Initially, they developed the CAPT-enabled CADA reaction of tryptamine **25** with aryldiazonium cation **23a** in the presence of (*S*)-**C6**, affording pyrroloindoline **26** bearing an azo group in a quantitative yield and a good enantioselectivity (Scheme 6a). The enantioselectivity of product **26** could be further improved to >96% ee after recrystallization. Then, compound **26** was utilized as a starting material for the total synthesis of (–)-psychotriasine (Scheme 6b). After protecting the NH group with Boc, the azo group of compound **26** was transformed into an amino group with the action of hydrazine hydrate and RANEY® Ni to generate an important intermediate compound **27**. The Buchwald–Hartwig amination of 1,2-dibromobenzene with compound **27** afforded compound **28**, which underwent Larock cyclization with alkyne **29** to give compound **30** bearing a newly generated tryptamine moiety. The subsequent removal of the *N*-Bz group of compound **30** and the re-protection of the free NH group with ClCO₂Me gave rise to compound **31** bearing two *N*-CO₂Me groups. Finally, the *N*-Boc group of compound **31** was removed with TFA and the two *N*-CO₂Me groups were

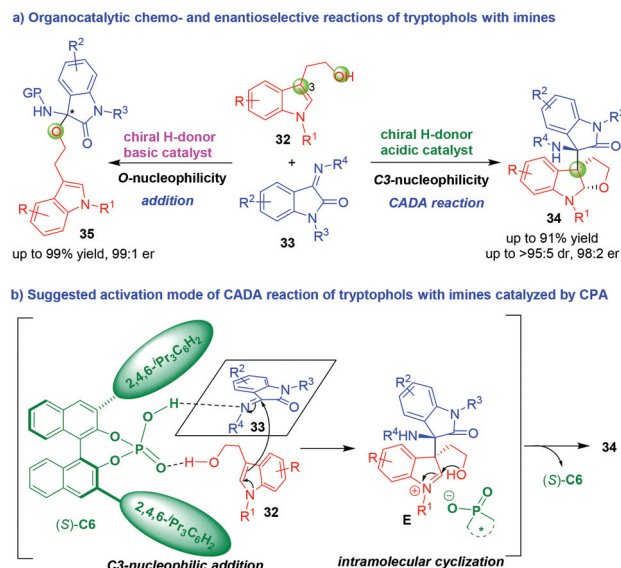


Scheme 6 Application of organo-CADA reaction in the total synthesis of (–)-psychotriasine by Liao, Deng and coworkers.¹⁵

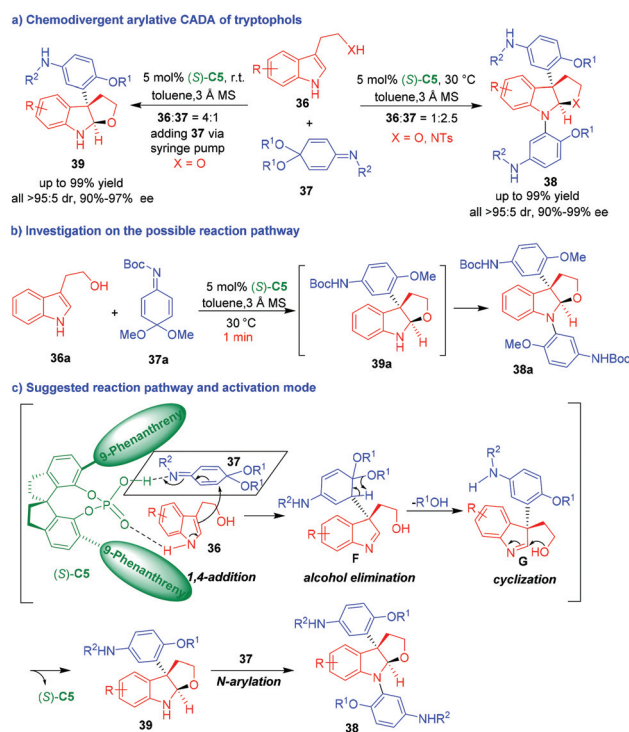
reduced into *N*-Me groups by Red-Al, leading to the total synthesis of (–)-psychotriasine.

Under asymmetric catalysis, tryptophols always displayed the C3-nucleophilicity to undergo cascade addition–cyclization reactions with various electrophiles, thus realizing the CADA reactions. On the contrary, tryptophols rarely displayed the *O*-nucleophilicity in catalytic asymmetric reactions. In 2017, Shi and coworkers established catalyst-controlled chemo- and enantioselective CADA reaction of tryptophols **32** with isatin-derived imines **33** (Scheme 7).¹⁶ As illustrated in Scheme 7a, in the presence of chiral H-donor acidic catalyst such as CPA, tryptophols **32** displayed the C3-nucleophilicity to undergo CADA reaction with imines **33**, affording dihydrofuroindoline derivatives **34** in high yields, excellent diastereo- and enantioselectivities. However, in the presence of chiral H-donor basic catalyst such as chiral squaramide-tertiary amine, tryptophols **32** displayed the *O*-nucleophilicity to undergo addition reaction with imines **33**, generating 3-substituted 3-aminooxindoles **35** in good yields and high enantioselectivities. In the suggested activation mode of CADA reaction (Scheme 7b), CPA (*S*)-C6 simultaneously activated both tryptophols **32** and imines **33** via hydrogen-bonding interactions, which facilitated an enantioselective C3-nucleophilic addition of tryptophols **32** to imines **33** to generate chiral intermediates **E**. The intermediates **E** rapidly underwent an intramolecular cyclization reaction to give dihydrofuroindoline products **34**.

Shortly after, the same group reported a CPA-enabled chemodivergent arylative CADA reaction of tryptophols **36** by using quinone imine ketals (QIKs) **37** as aryl group surrogates



Scheme 7 Organo-CADA reaction of tryptophols with isatin-derived imines by Shi and coworkers.¹⁶



Scheme 8 Organo-CADA reactions of tryptophols with QIKs by Shi and coworkers.¹⁷

(Scheme 8a).¹⁷ By modulating the reaction conditions, two series of dihydrofuroindoline products **38** and **39** could be generated in a chemoselective manner with generally high yields, and excellent diastereo- and enantioselectivities. The investigation on the possible reaction pathway (Scheme 8b) revealed that product **39a** was initially generated after stirring **36a** and

37a for just one minute. However, product **39a** was rapidly transformed into *N*-aryl-substituted product **38a** in the reaction mixture. To make the reaction stop at the stage of forming **39**, the authors utilized the operation of slowly adding QIK **37** to an excess amount of tryptophols **36** by a syringe pump (Scheme 8a, left). Based on the experimental results, the authors suggested a possible reaction pathway and activation mode of CPA (*S*)-**C5** to the two substrates (Scheme 8c). The two substrates of **36** and **37** were simultaneously activated by (*S*)-**C5**, thus facilitating an enantioselective 1,4-addition between them to generate chiral intermediates **F**, which promptly underwent alcohol elimination to give intermediates **G**. The subsequent intramolecular cyclization of intermediates **G** gave rise to *N*-unprotected dihydrofuroindoline products **39**. If there were excess amount of QIK **37** in the reaction system, products **39** would perform *N*-arylation reaction with QIKs **37** to afford *N*-aryl-protected dihydrofuroindoline products **38**.

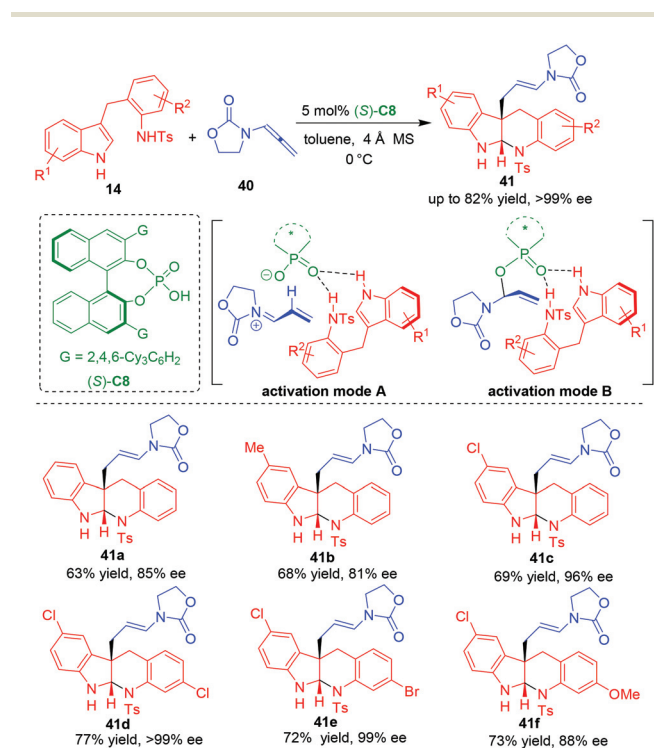
In 2020, Shin and coworkers reported a CADA reaction of tryptamine analogues **14** by using allenamides **40** as suitable electrophilic precursors in the presence of CPA (*S*)-**C8**, which constructed indoloquinolone scaffolds in moderate to good yields and generally high enantioselectivities (Scheme 9).¹⁸ Based on the control experiments, it was discovered that the two NH groups in tryptamine analogues **14** are crucial for controlling the enantioselectivity. So, they proposed that the P=O group of CPA should simultaneously form two hydrogen bonds with both of the two NH groups. But there are two possible activation modes of CPA on allenamides **40**. The first one is the ion-pairing interaction between the anion of CPA and the

α,β -unsaturated iminium ion *in situ* generated by the protonation of allenamides **40** (activation mode A), while the second one is the covalent interaction generated from the addition reaction of CPA anion to the α,β -unsaturated iminium (activation mode B). The authors believed that activation mode B was more favorable than activation mode A based on a previously reported DFT calculation.¹⁹

2.2 Organo-CADA reactions of tryptamines, tryptophols and their analogues with halogen-centered electrophiles

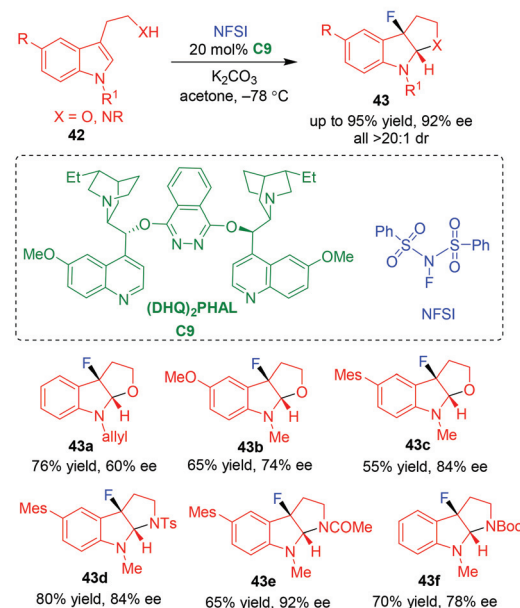
Although organo-CADA reactions of tryptamines or tryptophols with C,N-centered electrophiles have developed rapidly, halogen-centered electrophiles were not employed to such reactions until 2011. In that year, Gouverneur and coworkers established the first organo-CADA reaction of tryptamines or tryptophols **42** with a fluorinating reagent (NFSI) in the presence of catalytic amount of hydroquinine 1,4-phthalazinediyl diether [(DHQ)₂PHAL] **C9**, which afforded fluorinated pyrroloindolines or furoindolines **43** in moderate to good yields and acceptable enantioselectivities (Scheme 10a).²⁰ Furthermore, indole derivative **44** could undergo organocatalytic asymmetric dearomative difluorocyclization under the same reaction conditions, offering product **45** in a moderate enantioselectivity (Scheme 10b).

Apart from catalytic asymmetric fluorination, catalytic asymmetric selenofunctionalization is also an important transform-

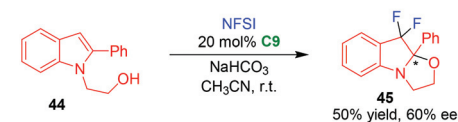


Scheme 9 Organo-CADA reaction of tryptamine analogues with allenamides by Shin and coworkers.¹⁸

a) Organo-CADA reaction of tryptamines and tryptophols with NFSI



b) Organocatalytic asymmetric dearomative difluorocyclization



Scheme 10 Organo-CADA reaction of tryptamines or tryptophols with a fluorinating reagent by Gouverneur and coworkers.²⁰

ation. In 2013, the first organocatalytic asymmetric selenofunctionalization of tryptamines was realized by Gong and co-workers in the presence of CPA, which constructed C3-selenyl-substituted pyrroloindoline frameworks in high yields (up to 85%) and good enantioselectivities (up to 89% ee).²¹

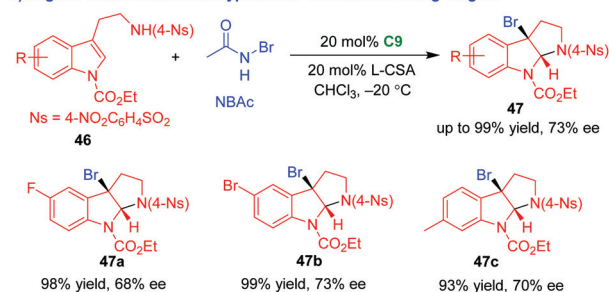
In 2014, You's group established organo-CADA reactions of tryptamines and their analogues with brominating or chlorinating reagents, thus realizing the bromocyclization and chlorocyclization of tryptamine derivatives (Scheme 11).^{22,23} In the presence of chiral amine catalyst **C9** and L-(–)-camphorsulfonic acid (CSA), tryptamines **46** underwent CADA reaction with *N*-bromoacetamide (NBAC), giving rise to C3-bromo-substituted pyrroloindolines **47** in high yields and moderate enantioselectivities (Scheme 11a).²² The CADA reaction of tryptamine analogues **48** was realized by using DCDMH as a chlorination reagent under the catalysis of (DHQD)₂PHAL **C10**, which constructed enantioenriched oxazinoindoline scaffolds **49** in high yields and excellent enantioselectivities (Scheme 11b).²³

Among different halogenating dearomative cyclizations of indole derivatives, catalytic asymmetric bromocyclization is highly valuable because the C–Br bond is easier to cleavage,

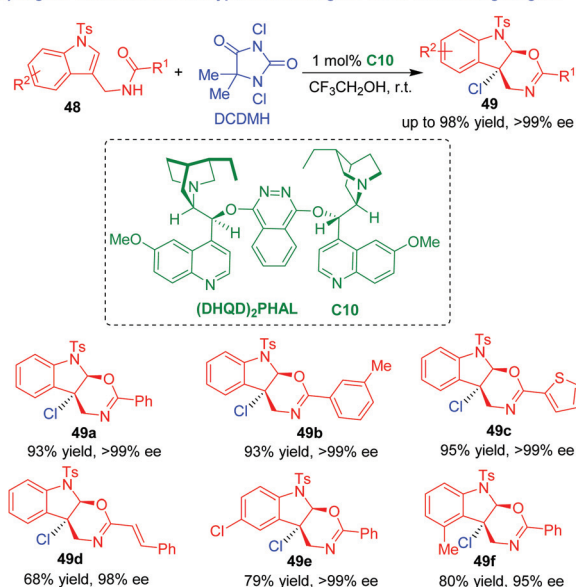
thus ensuring useful transformations. To this end, Ma, Xie, Lai and coworkers successfully devised organo-CADA bromocyclizations of tryptamines and tryptophols and realized their application in total synthesis of natural alkaloids (Scheme 12).^{24–26} In 2013, they developed catalytic asymmetric dearomative bromocyclization of tryptamines **50** in the presence of CPA (*R*)-**C11** by using bromine salt **51** as a brominating reagent, providing an easy access to optically pure brominated pyrroloindolines **52** in high yields and excellent enantioselectivities (Scheme 12a).²⁴

More importantly, this methodology was applied in the brief, enantioselective synthesis of natural alkaloid (–)-chimonanthine. In brief, the CADA reaction of tryptamine **50a** with **51** afforded brominated product **52a** with optical purity, which underwent a homodimerization in the presence of Co(PPh₃)₃Cl to generate bispyrroloindoline **53**. Finally, the removal of *N*-Boc group with TMSOTf and the reduction of *N*-CO₂Me group with Red-Al accomplished the total synthesis of (–)-chimonanthine. Furthermore, the methodology of organocatalytic

a) Organo-CADA reaction of tryptamines with a brominating reagent

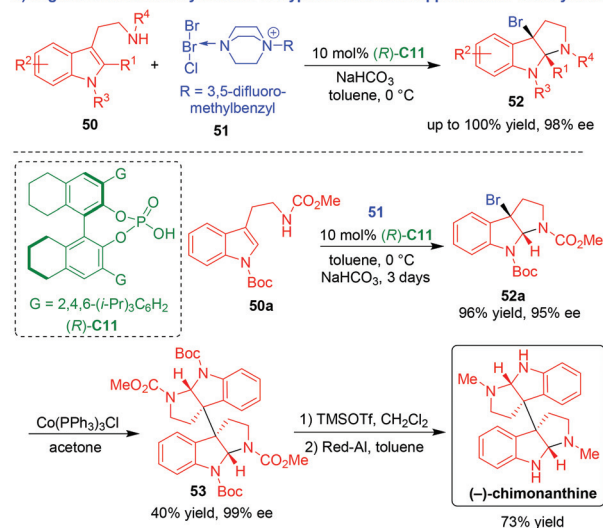


b) Organo-CADA reaction of tryptamine analogues with a chlorinating reagent

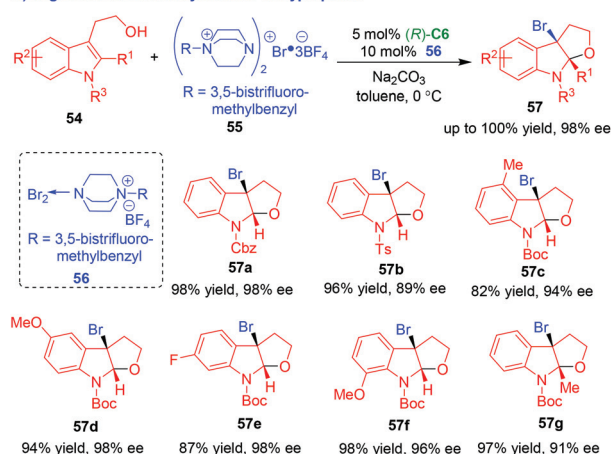


Scheme 11 Organo-CADA reactions of tryptamines and analogues with brominating or chlorinating reagents by You and coworkers.^{22,23}

a) Organo-CADA bromocyclization of tryptamines and its application in total synthesis



b) Organo-CADA bromocyclization of tryptophols



Scheme 12 Organo-CADA bromocyclizations of tryptamines and tryptophols by Ma, Xie, Lai and coworkers.^{24–26}

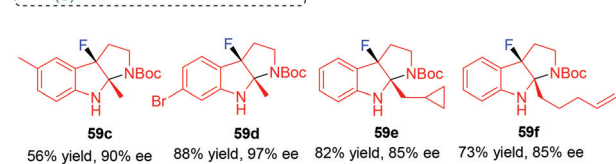
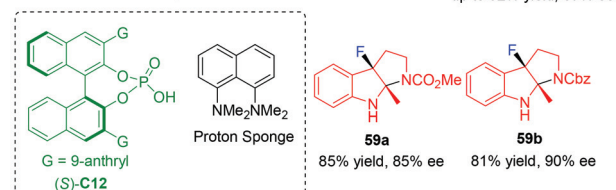
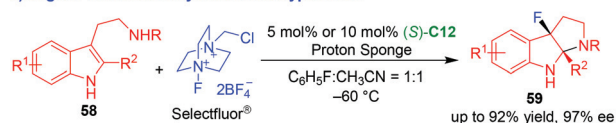
asymmetric dearomative bromocyclization of tryptamine was also employed for the first enantioselective total synthesis of (–)-conolutinine in ten steps.²⁵

Soon after, the same group developed catalytic asymmetric dearomative bromocyclization of tryptophols **54** in the presence of CPA (*R*)-**C6** by using bromine salt **55** as a brominating reagent. Interestingly, they discovered that the addition of catalytic amount of DABCO-derived bromine salt **56** increased the enantioselectivity of the product (Scheme 12b).²⁶ By this protocol, a series of 3-bromofuroindolines **57** were synthesized in high yields and excellent enantioselectivities.

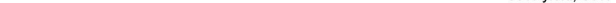
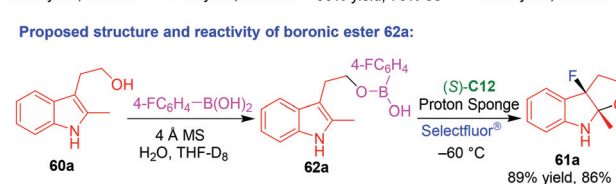
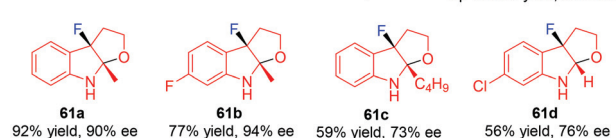
Although chiral amine-catalyzed asymmetric dearomative fluorocyclizations of tryptamines and tryptophols have been established in 2011 by Gouverneur and coworkers,²⁰ highly enantioselective fluorocyclizations of tryptamines and tryptophols are still highly desired. To achieve this goal, in 2017 and 2018, based on the strategy of asymmetric fluorination using anionic chiral phase-transfer catalyst,²⁷ You and coworkers successfully devised CPA (*S*)-**C12** catalyzed asymmetric dearomative fluorocyclizations of NH-protected tryptamines **58** and tryptophols **60** by using Selectfluor® as a fluorating reagent (Scheme 13),^{28,29} which afforded C3-fluoropyrroloindolines **59** and C3-fluorofuroindolines **61**, respectively, in a highly enantioselective manner. Notably, the authors performed control experiments to investigate the reaction mechanism. In organo-CADA fluorocyclization of tryptamines **58** (Scheme 13a),²⁸ they discovered there was a significant background reaction in the absence of CPA (*S*)-**C12** or proton sponge. Additionally, it was revealed that the addition of HBF₄ accelerated the reaction, while the addition of proton sponge would slow down the reaction. Therefore, they deduced that the role of proton sponge was to neutralize HBF₄ released *in situ* from Selectfluor®, thus inhibiting the background reaction. In organo-CADA fluorocyclization of tryptophols **60** (Scheme 13b),²⁹ they investigated the role of 4-fluorophenyl boronic acid by treating tryptophol **60a** with boronic acid together, and the reaction generated boronic ester **62a** which was detected by *in situ* NMR, ¹³C NMR and HRMS. Moreover, the reaction of boronic ester **62a** with Selectfluor® in the presence of (*S*)-**C12** could give rise to product **61a** in similar results with those under standard conditions, thus confirming boronic ester **62a** was a key intermediate for the fluorocyclization reaction.

In 2020, Hamashima and coworkers utilized chiral dicarboxylic acid **C13** as a precatalyst in the organo-CADA fluorocyclization of tryptamine analogues **63** by using Selectfluor® as a fluorating reagent (Scheme 14).³⁰ The utilization of the catalytic system is based on the consideration that the dicarboxylate ion of **C13** could act as a chiral anionic phase-transfer catalyst to bring Selectfluor® into the organic phase, thus controlling the reactivity and enantioselectivity of the dearomative fluorocyclization. By this reaction, a series of C3-fluoropyrroloindoline derivatives **64** were generated in good yields and high enantioselectivities. Furthermore, the authors discovered that the addition of a small amount of water played an important role in the reaction, which might facilitate the formation of **C13** anion and mediate the hydrogen-bonding interaction between the catalyst and the anion of substrates **63**.

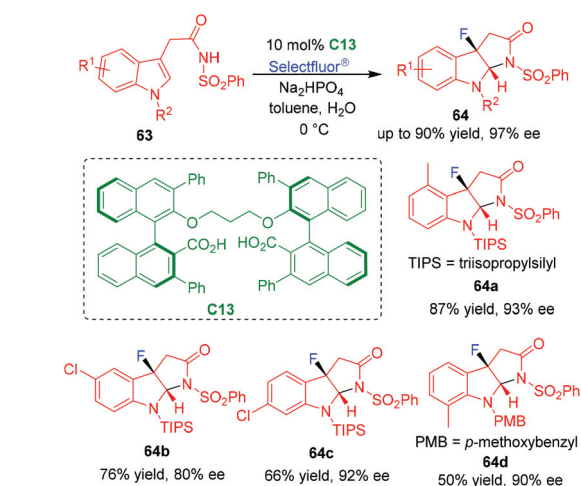
a) Organo-CADA fluorocyclization of tryptamines



b) Organo-CADA fluorocyclization of tryptophols



Scheme 13 Organo-CADA fluorocyclizations of tryptamines and tryptophols by You and coworkers.^{28,29}



Scheme 14 Organo-CADA fluorocyclization of tryptamine analogues by Hamashima and coworkers.³⁰

2.3 Organo-CADA reactions of tryptamines, tryptophols and their analogues with O-centered reagents

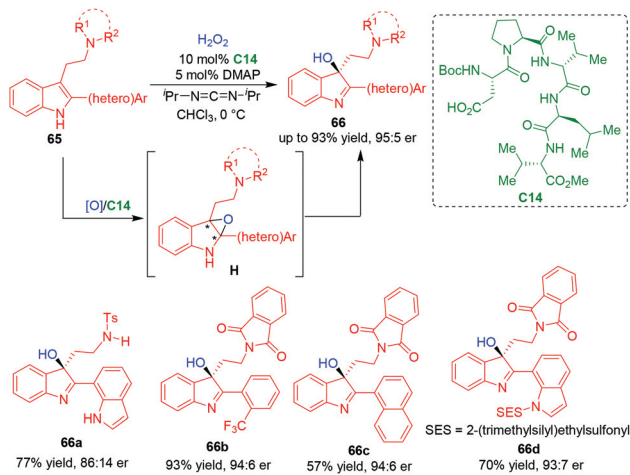
Compared to well-developed organo-CADA reactions of tryptamines, tryptophols and their analogues with C-, N-, halogen-centered electrophiles, such reactions with O-centered reagents are rather underdeveloped, which might be ascribed to the formidable challenge in controlling the chemoselectivity and enantioselectivity of catalytic asymmetric indole oxidation. This challenge was firstly confronted in 2011 by Miller, Movassaghi and coworkers (Scheme 15).³¹ In that year, they reported a highly chemo- and enantioselective CADA oxidation of tryptamine analogues **65** by using hydrogen peroxide as an oxidant and peptide **C14** as a chiral organocatalyst, delivering 3-hydroxy-indolenines **66** in good yields and moderate to high enantioselectivities (Scheme 15a). It was suggested that products **66** might be derived from the intermediate indole oxides **H**. Moreover, enantioenriched hydroxy-indolenine **66e** could be utilized in stereospecific rearrangements to give 2-oxindole **67** with a retained enantiopurity (Scheme 15b).

Later, Movassaghi and coworkers established the total synthesis of (–)-trigonolimine A–C on the basis of asymmetric dearomative oxidation of bis-tryptamines in the presence of equivalent chiral oxidant,^{32,33} and they investigated the anticancer activities of these compounds.³³

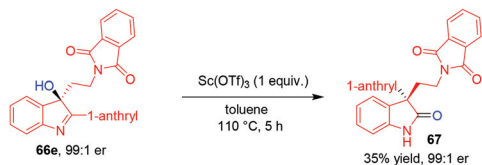
Organo-CADA reactions of indole derivatives scarcely involved the generation of radical intermediates in spite of the fact that the catalytic asymmetric radical chemistry has become an emerging area.³⁴ Therefore, the development of radical-involved CADA reactions is highly valuable and the

control of the enantioselectivity in such reactions remains a great challenge. In 2018, Knowles and coworkers established an organo-CADA oxidation of tryptamines *via* noncovalent stabilization of indole radical cations and realized the application of this methodology to the synthesis of several natural alkaloids (Scheme 16).³⁵ In the presence of a photocatalyst and chiral phosphate base (S)-**C15**, tryptamines **68** underwent a catalytic asymmetric dearomative proton-coupled electron transfer (PCET) reaction with TEMPO[•] radical, affording alkoxyamine-substituted pyrroloindolines **69** in good yields and high enantioselectivities (Scheme 16a). In this reaction, an oxidative PCET process provided an ionic hydrogen-bonded intermediate **I** between the radical cation of tryptamine **69** and the CPA anion of (S)-**C15**. Then, TEMPO[•] radical rapidly captured the radical cation of tryptamine and generated intermediate **J** in an enantioselective manner due to the ion-pairing interaction and the hydrogen-bonding interaction of CPA

a) Organo-CADA oxidation of tryptamine analogues

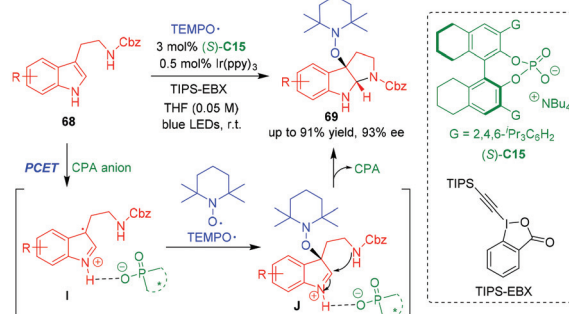


b) Stereoselective rearrangement of C3-hydroxy indolenine into 2-oxindole

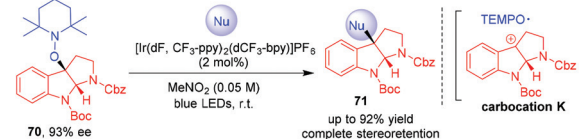


Scheme 15 Organo-CADA oxidation of tryptamine analogues by Miller, Movassaghi and coworkers.³¹

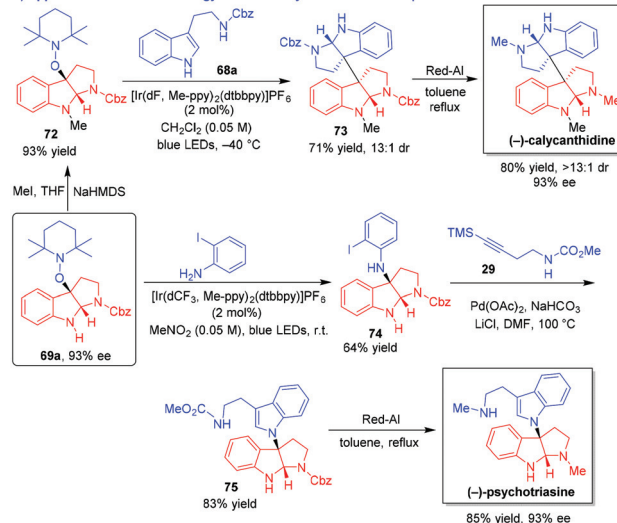
a) Catalytic asymmetric dearomative PCET reaction of tryptamines



b) Mesolytic bond cleavage induced nucleophilic substitution



c) Application of the methodology in the total synthesis of natural products



Scheme 16 Organo-CADA oxidation of tryptamines with TEMPO[•] radical by Knowles and coworkers.³⁵

anion. The subsequent intramolecular cyclization of intermediate **J** generated product **69** and released the CPA catalyst.

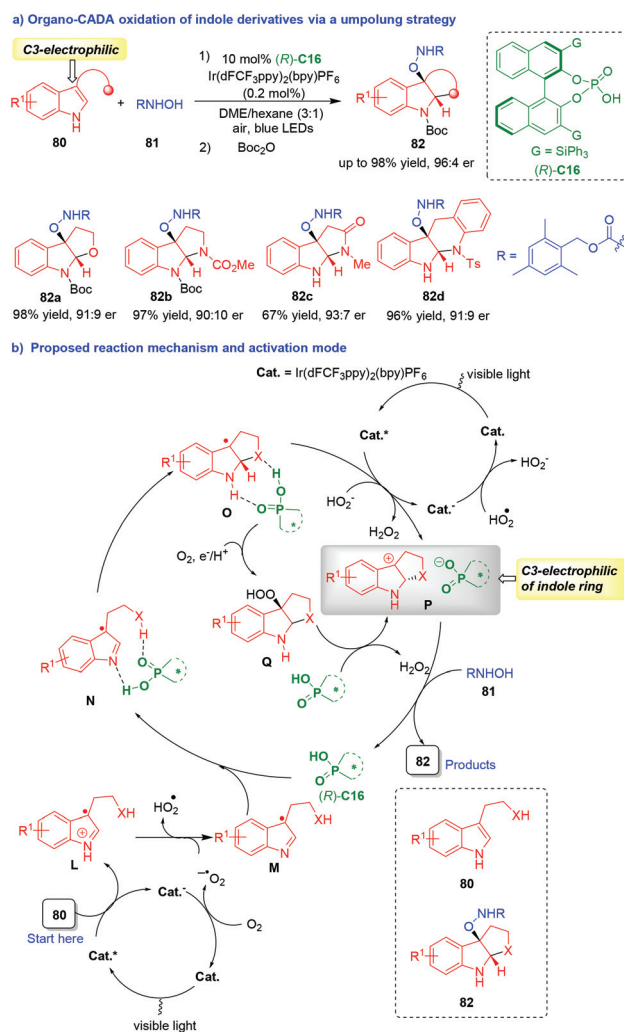
Furthermore, enantioenriched alkoxyamine-substituted pyrroloindolines **70** could undergo single-electron oxidation/mesolytic cleavage sequence to give transient carbocation intermediates **K**, which were readily attacked by a wide range of nucleophiles to give C3-nucleophile-substituted pyrroloindolines **71** in high yields with complete stereoretention (Scheme 16b).

More importantly, starting from alkoxyamine-substituted pyrroloindoline **69a** with 93% ee, the authors successfully accomplished the total synthesis of (–)-calycanthidine, (–)-psychotriasine and (–)-chimonanthine with very concise synthetic routes. As illustrated in Scheme 16c, *N*-methylation of **69a** afforded pyrroloindoline **72**, which was subjected to nucleophilic substitution with tryptamine **68a** via the process of single-electron oxidation/mesolytic cleavage, accompanying by the dearomative intramolecular cyclization of **68a** to generate compound **73**. Then, the reduction of the two Cbz groups in compound **73** by Red-Al led to the production of (–)-calycanthidine with complete enantioselectivity. The synthetic route for (–)-psychotriasine also involved a nucleophilic substitution of **69a** by using *ortho*-iodoaniline as a nucleophile, and the reaction offered *N*-aryl pyrroloindoline **74** as a suitable substrate to undergo Larock annulation with alkyne **29**, thus generating the core structure **75** of the target natural product. Finally, the reduction of the *N*-ester groups in compound **75** resulted in the production of (–)-psychotriasine with a maintained enantioselectivity of 93% ee. This work not only contributed greatly to the research field of organo-CADA reactions of indole derivatives, but also provided a powerful method for enantioselective total synthesis of related natural alkaloids.

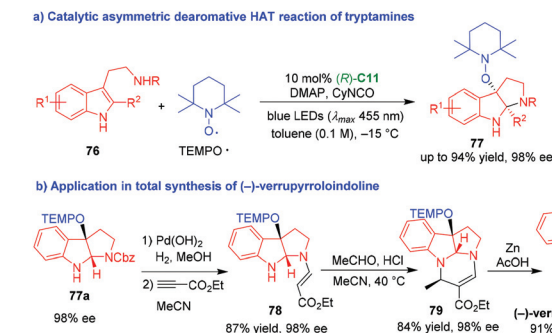
Nearly at the same time, Xia and coworkers also reported an organo-CADA oxidation of tryptamines **76** via a radical process (Scheme 17).³⁶ Different with the strategy of Knowles,³⁵ the authors discovered that visible light could directly excite TEMPO and tryptamines **76** could convert into tryptamine radicals via a hydrogen atom transfer (HAT) process without the photocatalyst of iridium. Catalyzed by CPA (*R*)-**C11**, the asymmetric dearomative HAT reaction of tryptamines **76** with TEMPO[•] radical smoothly afforded TEMPO-sub-

stituted pyrroloindolines **77** in high yields and excellent enantioselectivities (Scheme 17a). Notably, this methodology could be applicable in the total synthesis of natural product (–)-verrurpyrroloindoline in five steps (Scheme 17b). Compound **77a** with 98% ee could conveniently transform into compound **78** via deprotection of *N*-Cbz group and Michael addition with alkynyl ester. The condensation of compound **78** with acetaldehyde, followed by an intramolecular cyclization, afforded compound **79** bearing the core structure of natural product. At last, the removal of TEMP group under a reductive condition gave rise to (–)-verrurpyrroloindoline without the erosion of the enantioselectivity.

The C3-nucleophilicity is a common reactivity of indole derivatives, but the C3-electrophilicity is a “new world” of indole chemistry,³⁷ which has rarely been disclosed.³⁸ In 2019, You, Zhang and coworkers established an innovative organo-CADA oxidation of tryptamines, tryptophols and their analogues **80** via an umpolung strategy (Scheme 18).³⁹ In this reac-



Scheme 18 Organo-CADA oxidation of tryptamines, tryptophols and their analogues via an umpolung strategy by You, Zhang and coworkers.³⁹



Scheme 17 Organo-CADA oxidation of tryptamines with TEMPO[•] radical by Xia and coworkers.³⁶

tion, indole derivatives **80** displayed C3-electrophilicity to react with *N*-hydroxycarbamate **81** as nucleophiles in the presence of a photocatalyst and CPA (*R*)-**C16**, offering a variety of C3-oxyamine-substituted indoline derivatives **82** in high yields and good enantioselectivities (Scheme 18a).

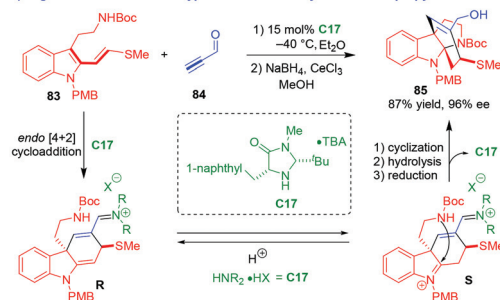
In the proposed reaction mechanism and activation mode (Scheme 18b), two sequential single-electron-transfer (SET) oxidation of indole derivatives **80** were involved under the dual catalysis of photocatalyst (Cat.) and CPA (*R*)-**C16**, which inverted the reactivity of indole derivatives **80** from C3-nucleophilic to C3-electrophilic. In brief, the first SET oxidation of substrates **80** generated the radical cations **L**, which were deprotonated to give radicals **M**. Then, with the aid of CPA (*R*)-**C16**, radicals **M** underwent the sequence of cyclization/second SET oxidation *via* the formation of intermediates **N** and **O** to give carbocations **P** as key intermediates. In the structure of carbocations **P**, the C3-position of the indole ring had a positive charge, thus displaying C3-electrophilicity. Additionally, there was an electrostatic interaction between the tertiary pyrroloindoline carbocations **P** and the CPA anion, which played an important role in controlling the enantioselectivity of the subsequent nucleophilic addition of *N*-hydroxycarbamates **81** to carbocations **P**, leading to the generation of enantioenriched products **82** and the completion of the catalytic cycle. It should be noted that an alternative reaction pathway from intermediates **O** to carbocations **P** *via* the formation of intermediates **Q** could not be fully excluded. This work has not only provided a robust method for the synthesis of enantioenriched C3-oxyamine-substituted indoline derivatives, but also offered an umpolung strategy for designing organo-CADA reactions of indole derivatives, which will greatly advance the development of CADA reactions and indole chemistry.

3. Organo-CADA reactions of vinylindoles

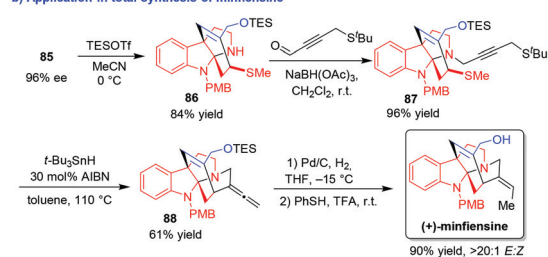
Vinylindoles are versatile building blocks in cycloadditions.⁴⁰ Among them, tryptamine-derived vinylindoles are competent substrates for cascade reactions due to the existence of both tryptamine and vinylindole moieties. In 2009, MacMillan and coworkers designed an innovative organo-CADA reaction of tryptamine-derived vinylindole **83** with propynal **84** in the presence of chiral amine catalyst **C17**, which constructed a bridged tetracyclic carbazole framework **85** in a high yield and excellent enantioselectivity (Scheme 19a).⁴¹ This cascade reaction started with **C17**-catalyzed asymmetric [4 + 2] cycloaddition of vinylindole **83** and propynal **84** to give a chiral intermediate **R**, which rapidly isomerized into intermediate **S** bearing an iminium group. Then, by making avail of the tryptamine functionality, an intramolecular cyclization of intermediate **S** occurred to give the tetracyclic pyrroloindoline structure, which transformed to final product **85** *via* hydrolysis to release **C17** and reduction of the formyl group.

More importantly, this methodology could be successfully used for the asymmetric total synthesis of natural product

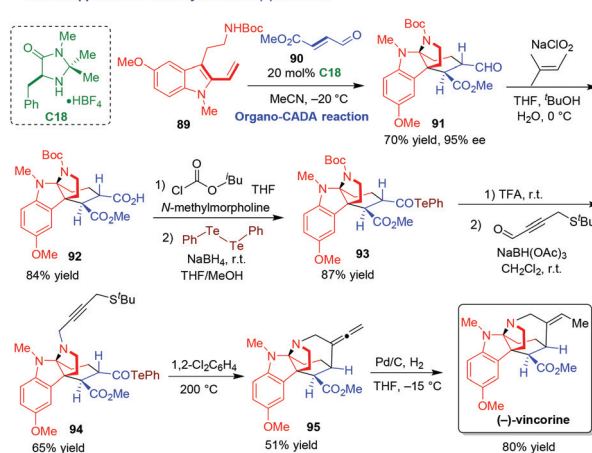
a) Organo-CADA reaction of tryptamine-derived vinylindoles with propynal



b) Application in total synthesis of minfiensine



c) Organo-CADA reaction of tryptamine-derived vinylindoles with enal and its application in total synthesis of (–)-vincorine



Scheme 19 Organo-CADA reaction of tryptamine-derived vinylindoles with propynal or enal and its application in natural products synthesis by MacMillan and coworkers.^{41,42}

(+)-minfiensine in a rather concise way (Scheme 19b).⁴¹ Compound **85** with 96% ee was subjected to simultaneous deprotection of *N*-Boc group and protection of the OH group with TESOTf, which afforded compound **86** in 84% yield. Then, compound **86** underwent a reductive amination with 4-(*tert*-butylthio)but-2-ynal to generate *N*-alkynyl-substituted compound **87**, which further underwent intramolecular alkyne radical cyclization to give compound **88** bearing an allene group. Finally, the hydrogenation of the allene group in compound **88** occurred in a highly (*E/Z*)-selective manner, and the deprotection of the OTES group accomplished the total synthesis of (+)-minfiensine.

Furthermore, the same group also developed an organo-CADA reaction of tryptamine-derived vinylindole **89** with enal **90**, and realized its application in the total synthesis of (–)-vincorine (Scheme 19c).⁴² Similarly, the CADA reaction of vinylin-

dole **89** with enal **90** in the presence of chiral amine catalyst **C18** involved the cascade sequence of asymmetric $[4 + 2]$ cycloaddition and intramolecular cyclization, which offered tetracyclic pyrroloindoline **91** in 70% yield and 95% ee. Then, the oxidation of the formic group in compound **91** led to the generation of carboxylic acid **92**, which was converted into telluride **93** *via* a sequence involving the generation of a mixed anhydride followed by the reaction with 1,2-diphenylditellane. In the next step, the deprotection of *N*-Boc group with TFA gave NH group, which underwent *N*-alkylation with 2-butylnal-4-*tert*-butyl sulfide *via* reductive amination to give compound **94** as an alkyl radical precursor. Under a high temperature (200 °C), compound **94** underwent an intramolecular radical cyclization of the acyl telluride with the thermally initiated alkyl radical, offering the allene compound **95**. Finally, the selective hydrogenation of the allene functionality in compound **95** resulted in the synthesis of (–)-vincorine as a single (*E/Z*)-isomer.

In 2011, MacMillan and coworkers further demonstrated the art of synthesis *via* the combination of organocascade catalysis with collective natural product synthesis, which provided a robust method for the total synthesis of a series of natural alkaloids from a common intermediate (Scheme 20).^{43,44} The key reaction was an organo-CADA cascade reaction of tryptamine-derived vinylindole **96** with propynal **84** in the presence of chiral amine catalyst *ent*-**C17**, which generated enantioenriched tetracyclic spiroindoline **97** as a common intermediate for versatile synthesis of natural products (Scheme 20a).⁴³

In the proposed mechanism for the generation of spiroindoline **97** (Scheme 20b), propynal **84** was activated by *ent*-**C17** to generate an iminium intermediate, which underwent a stereoselective $[4 + 2]$ cycloaddition with vinylindole **96** to give intermediate **T**. Then, intermediate **T** transformed into unsaturated iminium **U** *via* β -elimination of methyl selenide. In the next transformation of intermediate **U** to tetracyclic intermediate **V**, there were two possible pathways A and B. In pathway A, intermediate **U** directly underwent an intramolecular conjugate addition to generate intermediate **V**. In pathway B, intermediate **U** underwent another type of intramolecular cyclization at the indole C2-position to give bridged intermediate **W** after hydrolysis. In the presence of Brønsted acid (involved in *ent*-**C17**), intermediate **W** could undergo the sequence of ring-opening/conjugate addition *via* intermediates **X** and **Y** to give intermediate **V**. Finally, intermediate **V** isomerized into intermediate **Z**, which led to the generation of product **97** as a common structure for the total synthesis.

Based on this key reaction and the formation of the common intermediate **97**, the authors accomplished asymmetric total syntheses of six natural alkaloids including strychnine, aspidospermidine, vincadifformine, akuammicine, kopsanone and kopsinine. Herein, the total synthesis of (–)-strychnine was selected as a representative example to demonstrate the power of this methodology (Scheme 20c).⁴³ The common intermediate **97a** with 97% ee was subjected to deformylation by using Wilkinson's catalyst $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ and a subsequent introduction of a carbomethoxy group *via* the reaction with

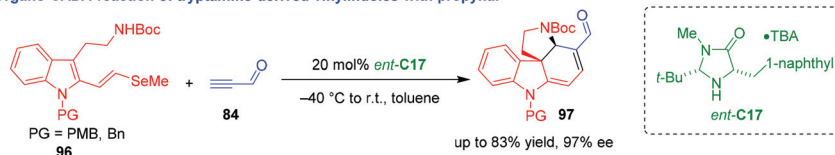
phosgene and methanol. The subsequent reduction with DIBAL-H afforded unsaturated ester **98** as a mixture of alkene isomers in 61% total yield for the three steps. Then, compound **98** underwent allylation with substituted allyl bromide and simultaneous alkene isomerization, followed by the reduction of both ester functionalities in the presence of DIBAL-H. The resulted compound **99** performed Jeffery–Heck cyclization/lactol formation to generate compound **100**, which further underwent deprotection of *N*-PMB group to give Wieland–Gumlich aldehyde **101**. Finally, an intramolecular cyclization of compound **101** occurred in the presence of malonic acid, acetic anhydride and sodium acetate to complete the total synthesis of (–)-strychnine.

Two years later, the same group expanded the strategy of organocatalytic asymmetric $[4 + 2]$ cycloaddition/ β -elimination/conjugate addition cascade to the total synthesis of (–)-minovincine (Scheme 20d).⁴⁴ The key step was also an organo-CADA cascade reaction of tryptamine-derived vinylindole **96a** with 3-butyln-2-one **102** in the presence of chiral amine catalyst **C19**, leading to the generation of tetracyclic spiroindoline **103** with 91% ee as a key intermediate compound for the total synthesis. Under the catalysis of palladium complex, spiroindoline **103** underwent carbomethoxylation to give compound **104**, which was subjected to a regioselective 1,4-conjugate reduction and *N*-Boc removal to generate compound **105**. Then, compound **105** performed *N*-alkylation with 1,3-diiodopropane and intramolecular cyclization with the help of potassium *tert*-butoxide, thus producing compound **106** as a single diastereomer. The final deprotection of *N*-PMB group in compound **106** led to the total synthesis of (–)-minovincine.

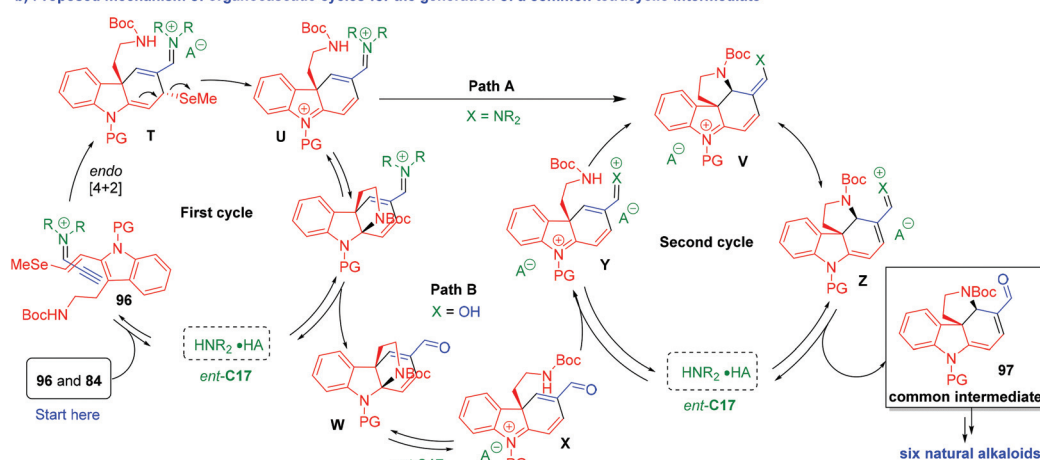
3-Vinylindoles can act as electron-rich dienes in Diels–Alder reactions.⁴⁰ In 2009, Ricci, Bernardi and coworkers established the first organocatalytic asymmetric Diels–Alder reaction of 3-vinylindoles **107** with electronically poor dienophiles such as maleimides **108** and quinones **109** in the presence of bifunctional thiourea-tertiary amine **C20** (Scheme 21).⁴⁵ Very interestingly, this organocatalytic asymmetric $[4 + 2]$ cycloaddition gave rise to dearomative products **110** in high yields and excellent enantioselectivities, and the newly formed carbon–carbon double bond did not isomerize into aromatic indole ring. In the suggested transition state, thiourea-tertiary amine catalyst **C20** simultaneously activated both 3-vinylindole **107a** and *N*-phenylmaleimide **108a** *via* forming multiple hydrogen bonds, thus controlling the diastereo- and enantioselectivity of the $[4 + 2]$ cycloaddition.

In 2011, Barbas and coworkers utilized C_2 -symmetric bithiourea **C21** as a suitable organocatalyst to enable CADA $[4 + 2]$ cycloaddition of 3-vinylindoles **107** with methyleneindolinones **111**, constructing carbazolespirooxindole frameworks **112** in high yields, excellent diastereo- and enantioselectivities (Scheme 22).⁴⁶ Notably, this reaction has a wide substrate scope, and a variety of substituted 3-vinylindoles **107** could serve as competent substrates, which provided a practical method for the synthesis of spirooxindoles with potential bioactivities. Moreover, the chiral catalyst and solvent could be recycled. The authors also suggested a hydro-

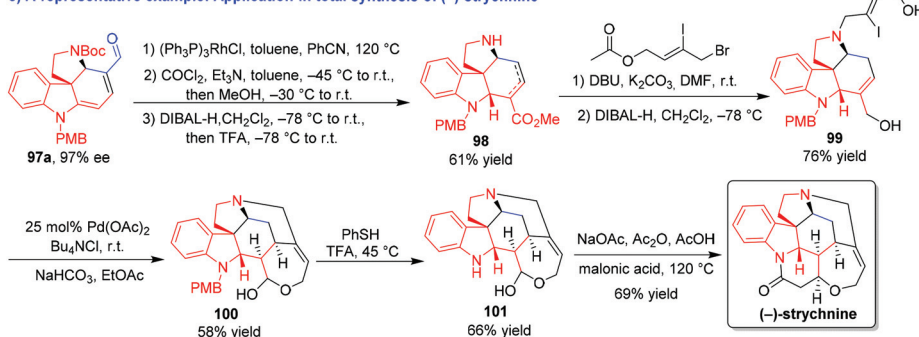
a) Organo-CADA reaction of tryptamine-derived vinylindoles with propynal



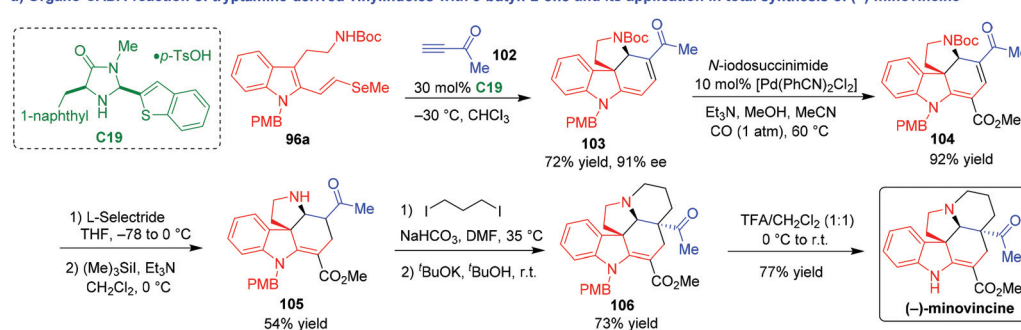
b) Proposed mechanism of organocascade cycles for the generation of a common tetracyclic intermediate



c) A representative example: Application in total synthesis of (–)-strychnine



d) Organo-CADA reaction of tryptamine-derived vinylindoles with 3-buten-2-one and its application in total synthesis of (–)-minovincine

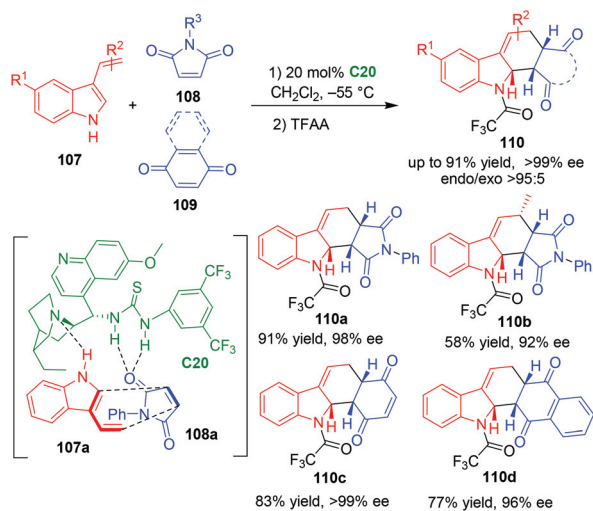


Scheme 20 Organo-CADA reaction of tryptamine-derived vinylindoles with propynal or 3-buten-2-one and its application in natural products synthesis by MacMillan and coworkers.^{43,44}

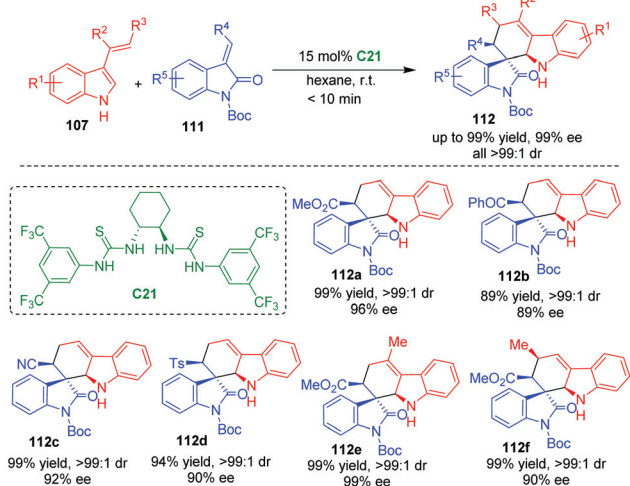
gen-bonding interaction between the catalyst and the substrates.

In 2013, Enders and coworkers reported an organo-CADA cascade reaction of 3-vinylindoles **107** with α,β -unsaturated aldehydes **3** in the presence of proline-derived catalyst **C22**, which constructed tetracyclic pyridocarbazole scaffolds **113** in good yields and excellent stereoselectivities (Scheme 23).⁴⁷

This reaction occurred *via* iminium–iminium–enamine activation sequence. Namely, the first step was asymmetric Diels–Alder reaction of 3-vinylindoles **107** with vinyl iminiums **A'** generated *in situ* from α,β -unsaturated aldehydes **3** and **C22**, resulting in the formation of tetrahydrocarbazole intermediates **B'**. Then, another molecule of aldehydes **3** was activated by **C22** to yield vinyl iminiums **A'**, which underwent aza-



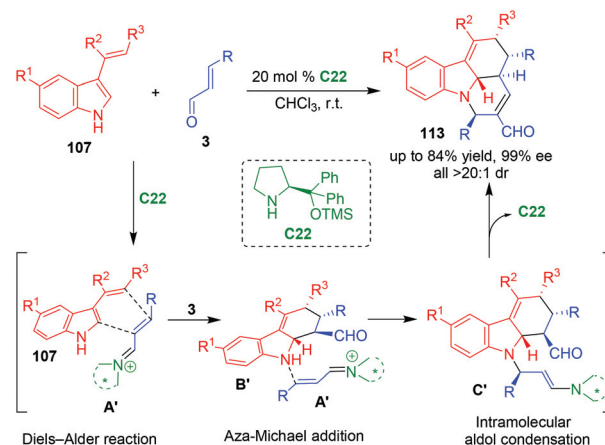
Scheme 21 Organo-CADA [4 + 2] cycloaddition of 3-vinylindoles with dienophiles by Ricci, Bernardi and coworkers.⁴⁵



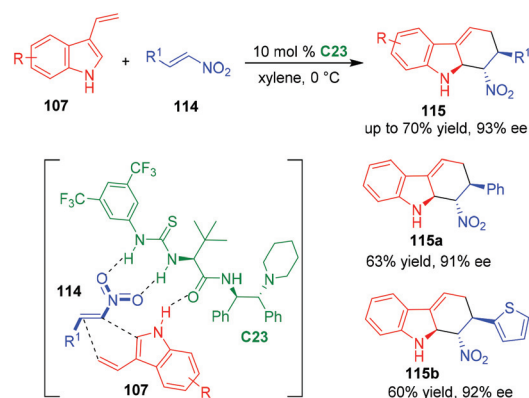
Scheme 22 Organo-CADA [4 + 2] cycloaddition of 3-vinylindoles with methyleneindolinones by Barbas and coworkers.⁴⁶

Michael addition with intermediates **B'** to give intermediates **C'**. Due to the enamine activation mode, the intermediates **C'** underwent an intramolecular aldol condensation to generate the final products **113**.

In 2019, Guo and coworkers expanded the electronically poor dienophiles to nitroolefins **114**, and established an organo-CADA [4 + 2] cycloaddition of 3-vinylindoles **107** with nitroolefins **114** in the presence of chiral thiourea-tertiary amine catalyst **C23**, delivering tetrahydrocarbazole derivatives **115** in moderate to good yields and excellent enantioselectivities (Scheme 24).⁴⁸ In addition, the authors performed theoretical calculations to investigate the possible activation mode of **C23** to the substrates. It was revealed that **C23** was more likely to utilize its carbonyl group, rather than the tertiary amine



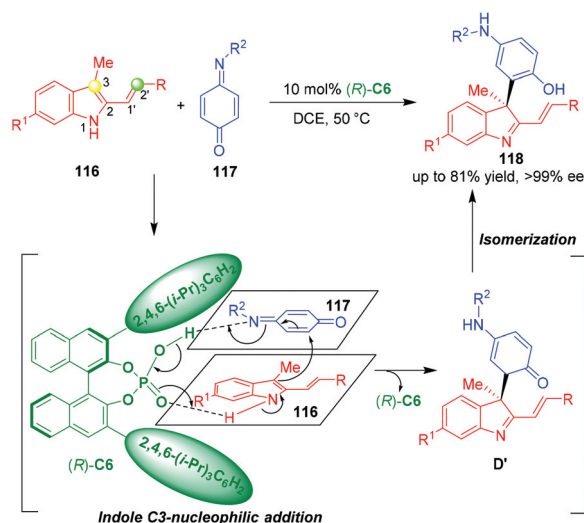
Scheme 23 Organo-CADA cascade reaction of 3-vinylindoles with α,β -unsaturated aldehydes by Enders and coworkers.⁴⁷



Scheme 24 Organo-CADA [4 + 2] cycloaddition of 3-vinylindoles with nitroolefins by Guo and coworkers.⁴⁸

group, in forming a hydrogen bond with the indole NH group, thus activating 3-vinylindoles **107** to participate in the reaction.

Apart from 3-vinylindoles, Shi and coworkers reported that 3-methyl-2-vinylindoles **116** could also undergo organo-CADA reaction with quinone monoimides **117** under the catalysis of CPA (*R*)-**C6**, which generated indolenines **118** bearing a quaternary stereogenic center in high yields and excellent enantioselectivities (Scheme 25).⁴⁹ Very interesting, in this reaction, the reactivity of 3-methyl-2-vinylindoles **116** was switched from C2'-nucleophilicity to indole C3-nucleophilicity, which was different from previously reported [2 + *n*] cycloadditions of 3-methyl-2-vinylindoles,⁵⁰ thus enabling the CADA reaction with quinone monoimides **117** in a chemospecific fashion. In the suggested activation mode, (*R*)-**C6** simultaneously formed two hydrogen bonds with the NH group of **116** and C=N group of **117**, thus activating both of the substrates to undergo an enantioselective indole C3-nucleophilic addition. The generated intermediates **D'** rapidly underwent an isomerization to give final products **118**.



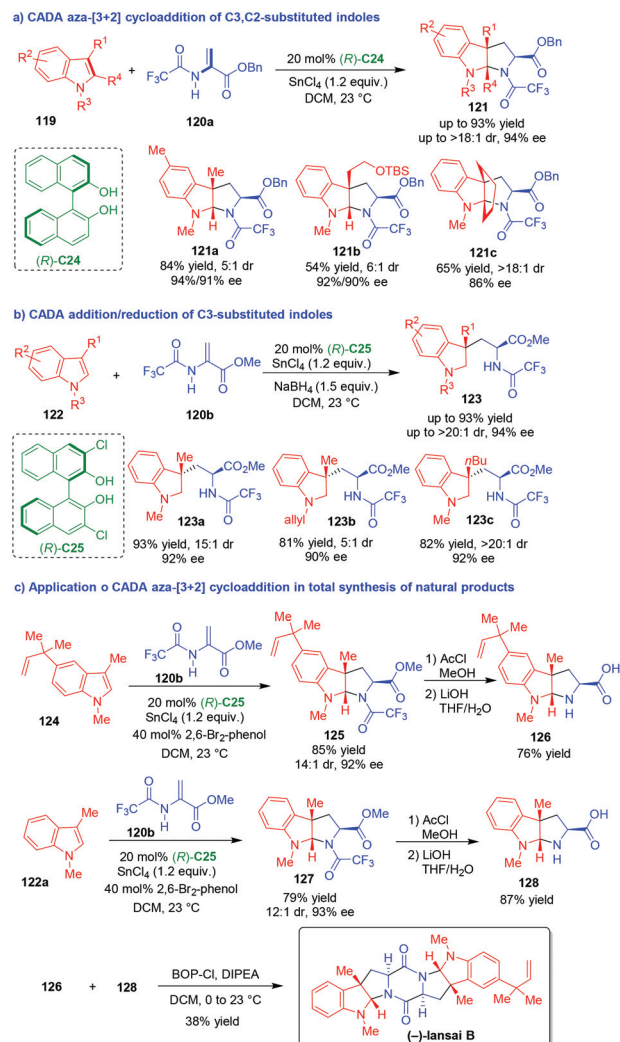
Scheme 25 Organo-CADA reaction of 3-methyl-2-vinylindoles with quinone monoimides by Shi and coworkers.⁴⁹

4. Organo-CADA reactions of C3,C2-substituted indoles

4.1 Organo-CADA cycloadditions of C3,C2-substituted indoles

4.1.1 Dearomative [3 + 2] cycloadditions. C3,C2-Substituted indoles could serve as electron-rich two-carbon (2C) building blocks in catalytic asymmetric [2 + *n*] cycloadditions, thus realizing the CADA reactions of C3,C2-substituted indoles along with the construction of a new ring system. Reisman and coworkers not only established catalytic asymmetric dearomative aza-[3 + 2] cycloadditions of C3,C2-substituted indoles, but also successfully utilized this strategy in the total synthesis of natural alkaloids (Scheme 26).^{51–53} In 2010, Reisman's group accomplished a formal [3 + 2] cycloaddition between C3,C2-substituted indoles **119** and 2-amidoacrylate **120a** in the presence of (*R*)-BINOL **C24** and SnCl₄, which constructed pyrroloindoline frameworks **121** in high yields, excellent enantioselectivities and moderate to good diastereoselectivities (Scheme 26a).⁵¹ Notably, based on the control experiment, the authors suggested that the system of (*R*)-C24 and SnCl₄ imposed a cooperative Lewis acid-Brønsted acid activation on the substrates. In a later study,⁵² they gave a detailed suggestion on the activation mode and optimized the reaction with improved diastereoselectivity. Moreover, they realized a one-pot CADA addition/reduction of C3-substituted indoles **122** with 2-amidoacrylate **120b** under the cooperative catalysis of (*R*)-C25 and SnCl₄, generating enantioenriched indoline derivatives **123** in good results (Scheme 26b).

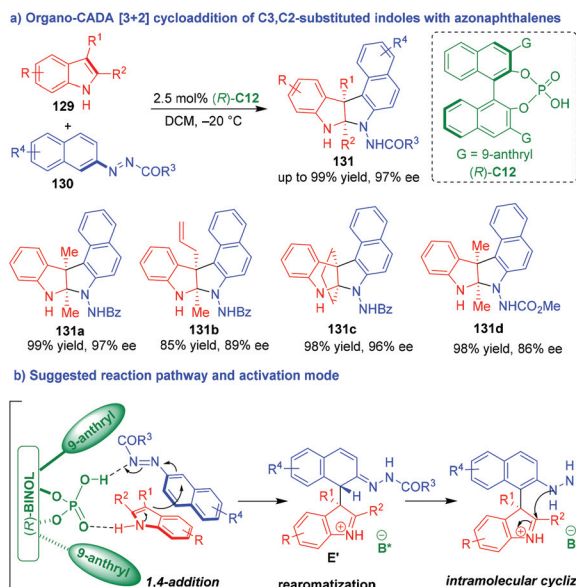
More importantly, this methodology was conveniently used in the total synthesis of natural alkaloids including (–)-lansai B, (+)-nocardioazines A and B.⁵³ As exemplified by the synthesis of (–)-lansai B (Scheme 26c), the CADA aza-[3 + 2] cycloaddition of C3-substituted indole **124** with 2-amidoacrylate



Scheme 26 CADA reactions of C3,C2-substituted indoles and the application in total synthesis of natural products by Reisman and coworkers.^{51–53}

120b afforded pyrroloindoline **125** in a high yield, good diastereoselectivity and excellent enantioselectivity. The subsequent cleavage of the TFA group in compound **125**, followed by hydrolysis of the methyl ester with LiOH, led to the generation of compound **126**. Accordingly, compound **122a** underwent similar transformations to give compound **128** via the formation of **127**. Finally, the condensation of compounds **126** and **128** with BOPCl accomplished the total synthesis of (–)-lansai B.

In 2018, Tan and coworkers established an organo-CADA aza-[3 + 2] cycloaddition of C3,C2-substituted indoles **129** with azonaphthalenes **130** under the catalysis of CPA (*R*)-C12, which constructed enantioenriched pyrroloindole skeletons **131** bearing two contiguous quaternary stereogenic centers in high yields and excellent stereoselectivities (Scheme 27a).⁵⁴ It's worth-noting that the azo group in substrates **130** played an important role as a directing and activating group in this reaction. Additionally, the different R¹ and R² groups of C3,C2-sub-

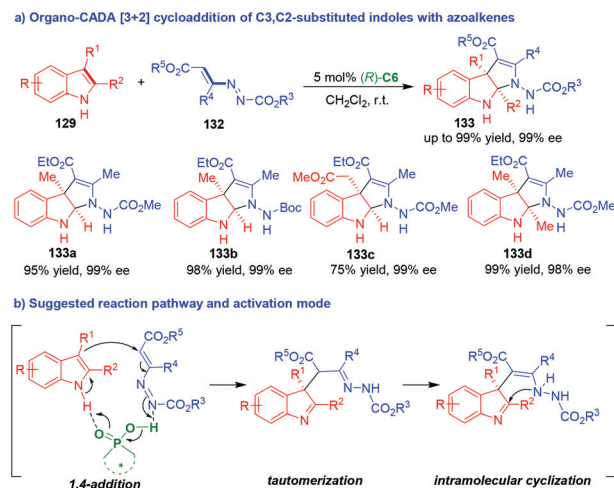


Scheme 27 Organo-CADA aza-[3 + 2] cycloaddition of C3,C2-substituted indoles with azonaphthalenes by Tan and coworkers.⁵⁴

stituted indoles **129** were crucial to control the chemoselectivity of the reaction because axially chiral arylindole frameworks were constructed instead of the pyrroloindole skeletons in other cases. In the suggested reaction pathway and activation mode (Scheme 27b), CPA (*R*)-**C12** acted as a bifunctional catalyst to form two hydrogen bonds with both substrates, thus facilitating an enantioselective 1,4-addition between them to generate intermediates **E'**, which underwent an rearomatization of the phenyl ring and a subsequent intramolecular cyclization to complete the aza-[3 + 2] cycloaddition.

Very recently, Lu and coworkers discovered azoalkenes **132** could act as suitable carbon-carbon-nitrogen (CCN) building blocks in organo-CADA aza-[3 + 2] cycloadditions with C3,C2-substituted indoles **129** in the presence of CPA (*R*)-**C6** owing to the hydrazine-enamine tautomerization of azoalkenes **132**, which delivered optically pure pyrroloindolines **133** in excellent yields and perfect enantioselectivities (Scheme 28a).⁵⁵ The activation mode of CPA (*R*)-**C6** to the substrates was still a dual activation mode *via* hydrogen-bonding interactions (Scheme 28b), which promoted the enantioselective reaction sequence of 1,4-addition/tautomerization/intramolecular cyclization to obtain enantioenriched pyrroloindolines **133**.

Compared with rapidly developed organo-CADA aza-[3 + 2] cycloaddition of C3,C2-substituted indoles, the corresponding oxa-[3 + 2] cycloadditions are rather underdeveloped, which might be ascribed to the lack of suitable oxygen-containing three-atom building blocks. In 2014, Zhang and coworkers discovered that quinone monoimines **117** could act as competent oxygen-containing three-atom building blocks in CPA (*R*)-**C6**-catalyzed dearomative oxa-[3 + 2] cycloadditions of C3,C2-substituted indoles **129**, constructing benzofuroindoline frameworks **134** in moderate to good yields and excellent enantioselectivities (Scheme 29a).⁵⁶ In the suggested reaction pathway,



Scheme 28 Organo-CADA aza-[3 + 2] cycloaddition of C3,C2-substituted indoles with azoalkenes by Lu and coworkers.⁵⁵

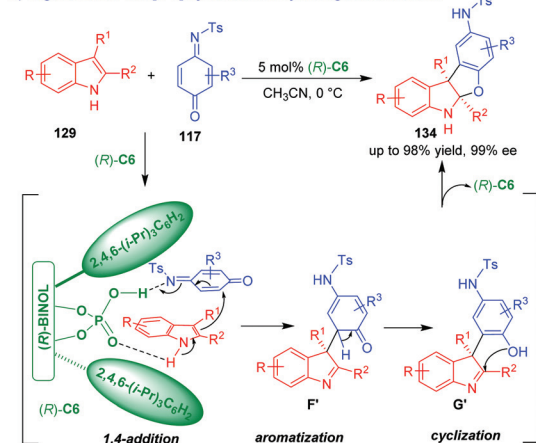
(*R*)-**C6** simultaneously activated both **129** and **117** *via* hydrogen-bonding interactions, thus promoting an enantioselective 1,4-addition between them to give intermediates **F'**, which rapidly underwent aromatization to generate intermediates **G'**. At last, the intramolecular cyclization of intermediates **G'** gave rise to benzofuroindolines **134**.

In 2019, Zhong, Wu and coworkers employed the strategy of Mn(III)/Brønsted acid relay catalysis in the asymmetric dearomative oxa-[3 + 2] cycloaddition of C3,C2-substituted indoles **129** with aminophenols **135** in the presence of Mn-complex and CPA (*R*)-**C6** by using TBHP as an oxidant, which offered benzofuroindolines **136** in good yields and high stereoselectivities (Scheme 29b).⁵⁷ There are two catalytic cycles in the reaction process. One is oxidative catalysis of Mn-catalyst to convert aminophenols **135** into quinone monoamine intermediates **H'**, which is a slow step. Another is chiral Brønsted acid catalysis of (*R*)-**C6** to facilitate the [3 + 2] cycloadditions of C3,C2-substituted indoles **129** with intermediates **H'**, which is a fast step. So, different from Zhang's method,⁵⁶ this synthetic method could directly utilize aminophenols **135** as starting substrates, which is atom-economy and step-economy.

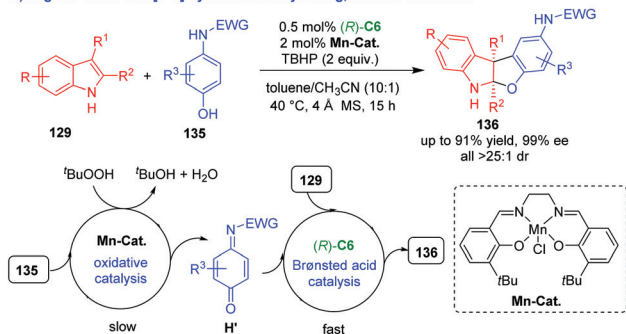
Nearly at the same time, Zhong, Zeng and coworkers employed 1,4-quinone **137** as a suitable oxygen-containing three-atom building blocks in (*R*)-**C6**-catalyzed dearomative oxa-[3 + 2] cycloaddition of C3,C2-substituted indoles **129** under mild reaction conditions (Scheme 29c).⁵⁸ This approach also constructed benzofuroindolines **138** in moderate to good yields, excellent diastereoselectivities and considerable enantioselectivities.

4.1.2 Dearomative [4 + 2] and [3 + 3] cycloadditions. Although organo-CADA [3 + 2] cycloadditions of C3,C2-substituted indoles have been intensively investigated, in sharp contrast, organo-CADA [4 + 2] cycloadditions of C3,C2-substituted indoles have scarcely been reported. Nevertheless, such transformations could construct enantioenriched indoline scaffolds fusing a six-membered ring. To achieve this goal, in 2012, You

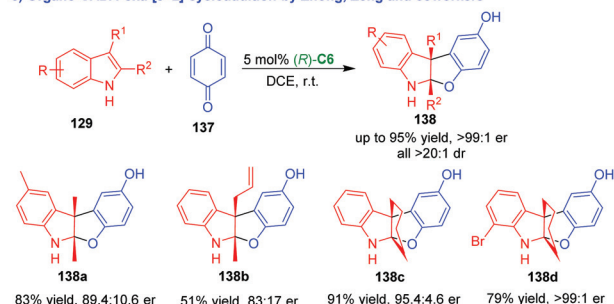
a) Organo-CADA oxa-[3+2] cycloaddition by Zhang and coworkers



b) Organo-CADA oxa-[3+2] cycloaddition by Zhong, Wu and coworkers



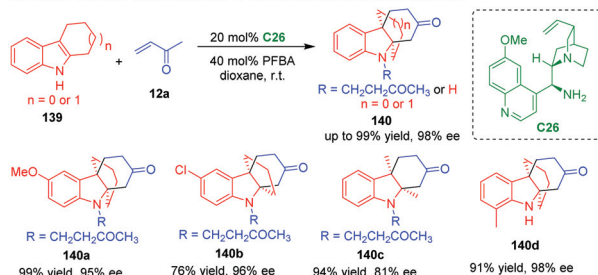
c) Organo-CADA oxa-[3+2] cycloaddition by Zhong, Zeng and coworkers



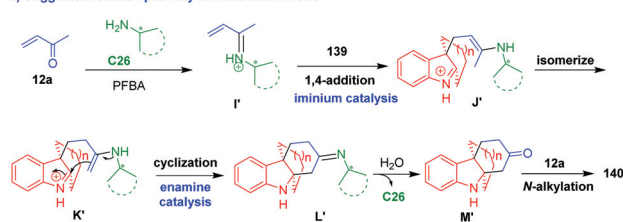
Scheme 29 Organo-CADA oxa-[3 + 2] cycloaddition of C3,C2-substituted indoles with quinone derivatives.^{56–58}

and coworkers utilized methyl vinyl ketone (MVK) **12a** as a suitable four-carbon building blocks to undergo CADA [4 + 2] cycloaddition with C3,C2-substituted indoles **139** under the catalysis of quinine-derived primary amine **C26** and pentafluorobenzoic acid (PFBA), which constructed bridged polycyclic indoline scaffolds **140** in high yields and excellent enantioselectivities (Scheme 30a). Notably, in most cases, products **140** were *N*-alkylated by aza-1,4-addition with another molecule of MVK **12a**. However, in the case of product **140d**, no aza-1,4-addition occurred, which might be attributed to the fact that the 7-methyl group hindered the NH group of the indole ring to undergo aza-1,4-addition. In the suggested reaction pathway and activation mode (Scheme 30b), MVK **12a** was activated by chiral primary amine **C26** to generate chiral iminium

a) Organo-CADA [4+2] cycloaddition of C3,C2-substituted indoles with MVK



b) Suggested reaction pathway and activation mode

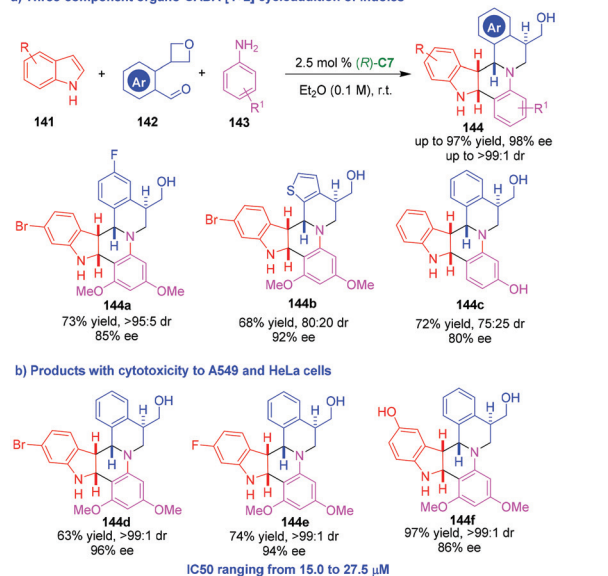


Scheme 30 Organo-CADA [4 + 2] cycloaddition of C3,C2-substituted indoles with MVK by You and coworkers.⁵⁹

intermediates **I'**, which were attacked by C3,C2-substituted indoles **139** to undergo 1,4-addition under iminium catalysis. The generated intermediates **J'** rapidly isomerized into **K'**, which underwent an intramolecular cyclization under enamine catalysis to give cyclic intermediates **L'**. Finally, the hydrolysis of **L'** offered intermediate products **M'** and released catalyst **C26**, and the subsequent aza-1,4-addition of **M'** with another molecule of MVK **12a** afforded products **140**.

The Povarov reaction is an inverse electron-demand aza-Diels–Alder reaction between electron-rich dienophiles with *in situ* generated aldimines, but indoles were scarcely used as dienophiles in such reactions. In 2013, Sun, Zhu and coworkers innovatively utilized a three-component Povarov reaction to realize an organo-CADA reaction of indoles (Scheme 31a). In this reaction, indoles **141** were employed as the dienophiles, and well-designed aromatic aldehydes **142** bearing an oxetane moiety were employed as reaction partners for generating aldimines with anilines **143** in the presence of CPA (R) -**C7**. The oxetane moiety in substrates **142** was discovered to be a superb directing group which played a crucial role in controlling both the reactivity and the enantioselectivity of the three-component Povarov reaction. Based on this design, a series of polycyclic molecules **144** with structural complexity were synthesized in overall high yields and good stereoselectivities. In addition, the evaluation of the bioactivity of some products discovered products **144d–144f** were cytotoxic to human lung carcinoma (A549) and human cervical carcinoma (HeLa) cells with IC_{50} ranging from 15.0 to 27.5 μM (Scheme 31b). This three-component CADA [4 + 2] cycloaddition was suggested to occur in a stepwise manner (Scheme 31c). Namely, the condensation of aldehydes **142** with anilines **143** generated aldimines **N'**, which underwent a stepwise [4 + 2] cycloaddition with indoles **141** under the activation of (R) -**C7**. Notably, it is suggested that the oxetane moiety might serve as

a) Three-component organo-CADA [4+2] cycloaddition of indoles



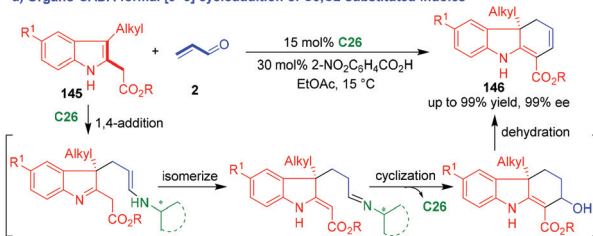
Scheme 31 Three-component organo-CADA [4 + 2] cycloaddition of indoles by Sun, Zhu and coworkers.⁶⁰

a hydrogen-bonding acceptor to form a hydrogen bond with (R)-C7 in the reaction process, thus controlling the reactivity and the enantioselectivity of the reaction.

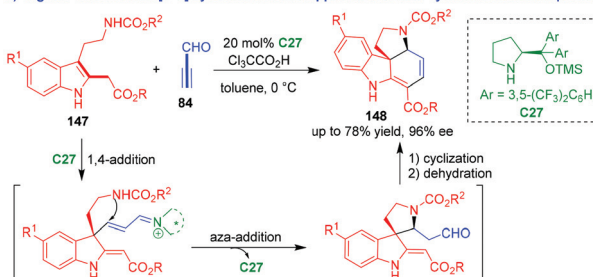
Normally, C3,C2-substituted indoles act as two-carbon (2C) building blocks in [2 + *n*] cycloaddition. In 2013, Wu and co-workers utilized C3,C2-substituted indoles **145** with a unique structure as three-carbon (3C) building blocks in formal [3 + 3] cycloaddition (Scheme 32a).⁶¹ In this organo-CADA formal [3 + 3] cycloaddition, acrolein **2** was utilized as another 3C reaction partner, and the reaction in the presence of chiral primary amine catalyst **C26** smoothly afforded tricyclic hydrocarbazoles **146** in high yields and excellent enantioselectivities. This reaction occurred *via* a cascade sequence of 1,4-addition/isomerization/intramolecular cyclization/dehydration, which was enabled by chiral iminium catalysis.

Shortly after, the same group developed another organo-CADA formal [3 + 3] cycloaddition and realized its application in total synthesis of natural products (Scheme 32b).⁶² They utilized tryptamine-derived C3,C2-substituted indoles **147** as 3C building blocks to react with propynal **84** in the presence of chiral amine catalyst **C27**, which constructed tetracyclic frameworks **148** in moderate yields and high enantioselectivities *via*

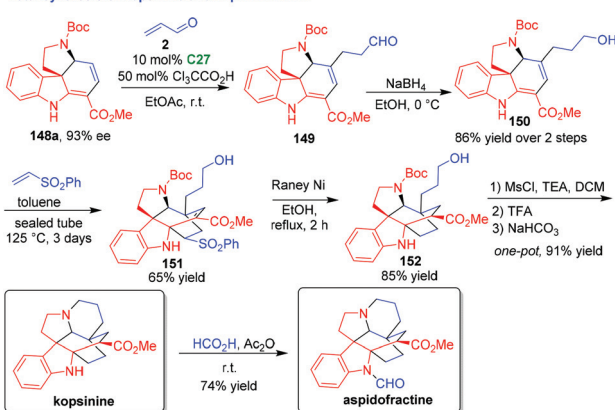
a) Organo-CADA formal [3+3] cycloaddition of C3,C2-substituted indoles



b) Organo-CADA formal [3+3] cycloaddition and application in total synthesis of natural products



Total synthesis of kopsinine and aspidofractine:



Scheme 32 Organo-CADA formal [3 + 3] cycloadditions of C3,C2-substituted indoles by Wu and coworkers.^{61–63}

a cascade process. More importantly, they employed this methodology in the total synthesis of kopsinine and aspidofractine. The Michael addition of **148a** with 93% ee to acrolein **2** in the presence of **C27** afforded aldehyde **149**, which was reduced into alcohol **150**. Then, the Diels–Alder reaction of compound **150** with vinyl phenylsulfone generated bridged pentacyclic compound **151**. The sulfone moiety of compound **151** was removed by the action of RANEY® Ni to give compound **152**. Subsequently, compound **152** was subjected to the mesylation of the OH group and the removal of the *N*-Boc group, thus facilitating an intramolecular cyclization to accomplish the synthesis of kopsinine. Finally, the *N*-formylation of kopsinine gave rise to another natural product, aspidofractine.

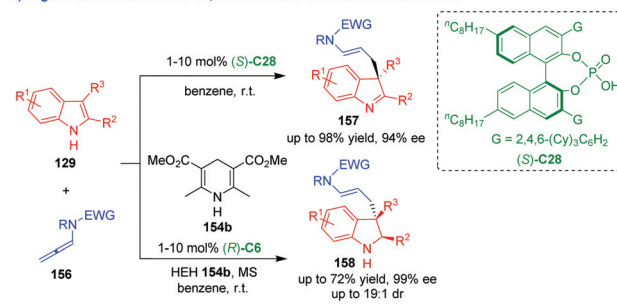
Additionally, they extended this methodology to organo-CADA formal [3 + 3] cycloadditions of tryptamine-derived 2-vinylindoles with propynal under the catalysis of chiral imidazolidinone catalyst, which also constructed tetracyclic frameworks similar to **148**.⁶³

4.2 Organo-CADA additions of C3,C2-substituted indoles

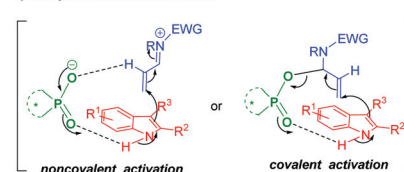
Organo-CADA addition of C3,C2-substituted indoles with electrophiles is the most convenient method for the synthesis of enantioenriched indolenines. So, chemists have employed different electrophiles to react with C3,C2-substituted indoles under organocatalysis. In 2014, Shi and coworkers established two organocatalytic asymmetric aryative dearomatizations of C3,C2-substituted indoles **129** with quinone imine ketals (QIKs) **37** under the catalysis of CPA (*R*)-**C6**, which synthesized two series of optically pure indolenines **153** and **155** in high yields and excellent stereoselectivities (Scheme 33a).⁶⁴ The two CADA reactions occurred *via* a tandem process. As illustrated in Scheme 33b, (*R*)-**C6** activated both substrates **129** and **37** at the same time *via* forming hydrogen bonds, which facilitated an enantioselective 1,4-addition between them to give intermediates **O'**. Then, intermediates **O'** rapidly underwent alcohol elimination to accomplish the first CADA reaction and generate indolenines **153**. In the second CADA reaction, the addition of Hantzsch ester (HEH) **154a** led to a stereoselective transfer hydrogenation between HEH **154a** and indolenines **153** by the activation of CPA (*R*)-**C6**, thus affording indolenines **155** in excellent enantio- and diastereoselectivities.

Nearly at the same time, Bandini and coworkers utilized allenamides **156** as competent electrophiles to perform organo-CADA addition with C3,C2-substituted indoles **129** in the presence of (*S*)-**C28**, which generated a series of indolenines **157** in moderate to good yields and high enantioselectivities (Scheme 34a).⁶⁵ In addition, they also established

a) Organo-CADA additions of C3,C2-substituted indoles with allenamides



b) Two possible activation modes



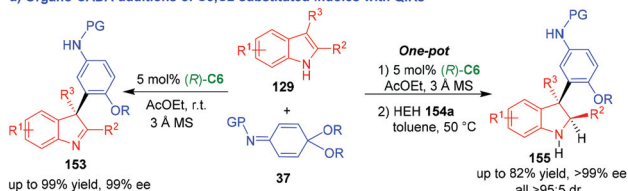
Scheme 34 Organo-CADA addition of C3,C2-substituted indoles with allenamides by Bandini and coworkers.⁶⁵

a cascade sequence of dearomatization/hydrogen transfer by adding HEH **154b** to the reaction system under the catalysis of (*R*)-**C6**, which delivered indolenines **158** in moderate yields and good stereoselectivities. The authors suggested two possible activation modes (Scheme 34b). One is noncovalent activation of CPA to allenamides *via* forming a hydrogen bond; another is covalent activation of CPA to allenamides *via* forming a covalent bond. To find out the more possible activation mode, Bandini, Miscione and coworkers carried out density functional theory (DFT) calculations and ESI-MS analysis to investigate the reaction mechanism, and it was discovered that allenamides formed adducts with CPA through a proton transfer and generated a covalent bond at the beginning of the reaction.¹⁹

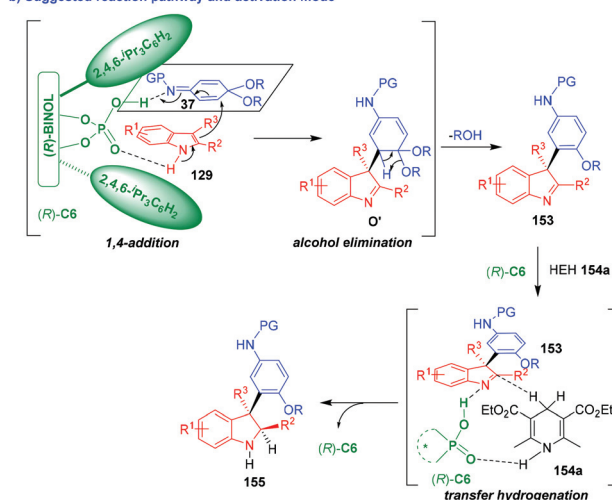
In 2014, Wu and coworkers realized an organo-CADA addition of indoloazepines **159** by using propargyl aldehydes or ketone **160** as electrophiles in the presence of the MacMillan's catalyst **C29**, affording C3-alkenyl-substituted indolinoazepines **161** in generally good yields and high enantioselectivities (Scheme 35).⁶⁶ Notably, apart from propargyl aldehydes, propargyl ketone could also participate in the reaction to give product **161f** in a high enantioselectivity albeit with a low yield. In the suggested activation mode, propargyl aldehydes or ketone **160** were activated by catalyst **C29** to generate chiral alkynyl iminium intermediates, which were readily attacked by indoloazepines **159** from the terminal position of the alkynyl group, thus initiating the CADA addition.

Recently, Wang, Sun and coworkers employed β,γ -alkynyl- α -imino esters **162** as electrophiles to react with C3,C2-substituted indoles **129** in the presence of CPA (*S*)-**C30**, thus realizing an organo-CADA addition of C3,C2-substituted indoles (Scheme 36).⁶⁷ More importantly, this dearomative reaction occurred with a selectivity of γ -addition, thus generating products **163** bearing a quaternary stereogenic center with central chirality and a moiety of tetrasubstituted α -aminoallenoate

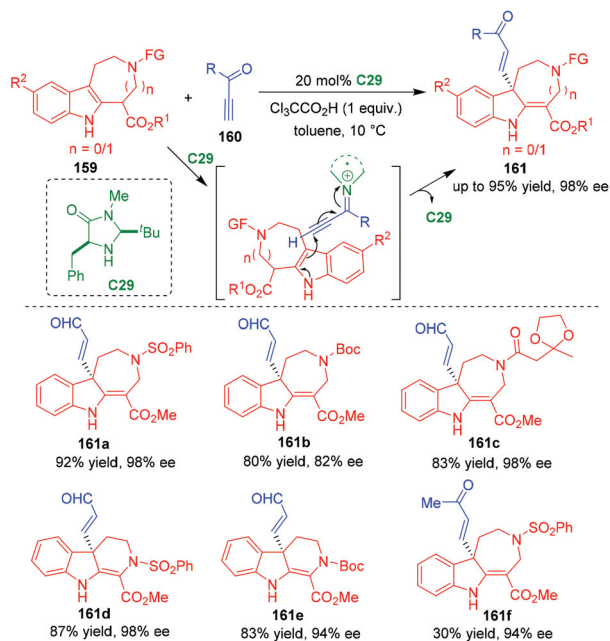
a) Organo-CADA additions of C3,C2-substituted indoles with QIKs



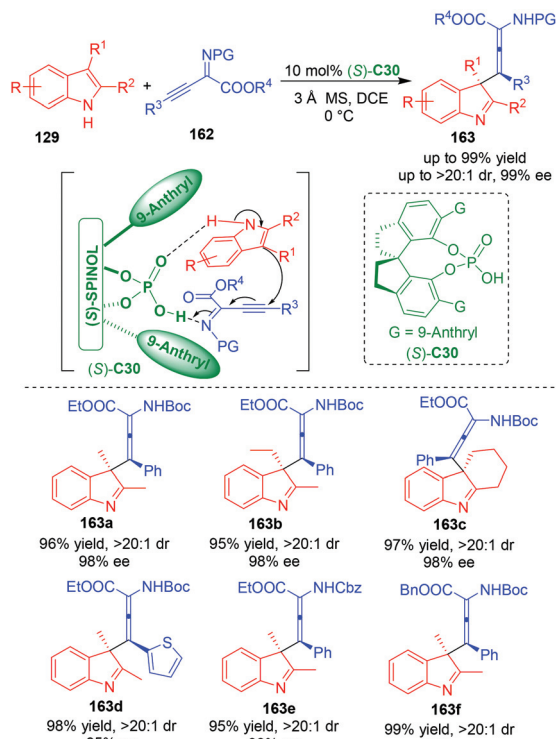
b) Suggested reaction pathway and activation mode



Scheme 33 Organo-CADA addition of C3,C2-substituted indoles with QIKs by Shi and coworkers.⁶⁴



Scheme 35 Organo-CADA addition of indoloazepines with propargyl aldehydes or ketone by Wu and coworkers.⁶⁶



Scheme 36 Organo-CADA addition of C3,C2-substituted indoles with β,γ -alkynyl- α -imino esters by Wang, Sun and coworkers.⁶⁷

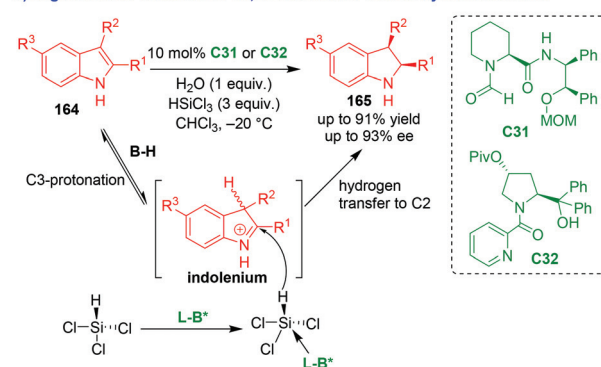
with axial chirality. In fact, the simultaneous construction of two elements of chirality has become a hot topic in catalytic asymmetric synthesis.^{68,69} So, this approach has not only con-

tributed to the research field of CADA, but also added a good example for simultaneously controlling two different elements of stereogenicity. Moreover, the authors performed DFT calculations to investigate the possible activation mode. They discovered that CPA still acted as a bifunctional catalyst to activate both of the two substrates *via* hydrogen-bonding interactions, thus promoting the addition of 129 to the γ -position of 162 and controlling the stereoselectivity *via* steric effect and π - π interaction between the catalyst and the substrates.

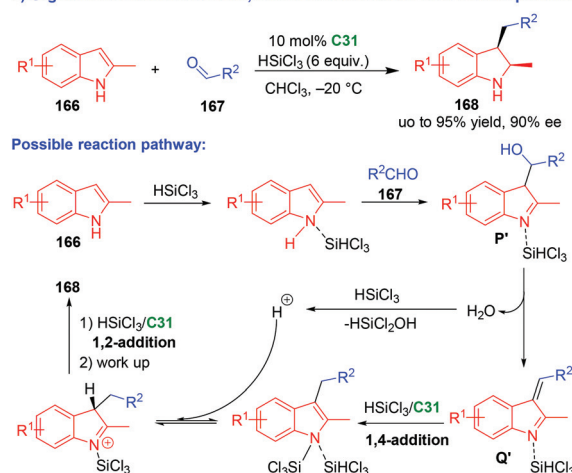
4.3 Organo-CADA reductions and oxidations of C3,C2-substituted indoles

In 2011, Chen, Sun and coworkers realized an organo-CADA reduction of C3,C2-substituted indoles 164 by trichlorosilane in the presence of chiral Lewis base C31 or C32, which afforded enantioenriched indolines 165 in high yields, good enantioselectivities and exclusive diastereoselectivity (Scheme 37a).⁷⁰ This reaction took advantage of the combined catalysis of an achiral Brønsted acid (B-H) and a chiral Lewis base (L-B*). Namely, the C3-protonation of indoles 164 in the presence of B-H (*in situ* generated from water and trichlorosilane) would give rise to electrophilic indolenium ions. The indolenium intermediates could be attacked by HSiCl₃ assisted

a) Organo-CADA reduction of C3,C2-substituted indoles by trichlorosilane



b) Organo-CADA reduction of C3,C2-substituted indoles via a tandem process



Scheme 37 Organo-CADA reduction of C3,C2-substituted indoles by Chen, Sun, Wang and coworkers.^{70,71}

by L-B*, which was followed by a hydrogen transfer to give final products **165**. This reaction opened a new avenue for direct CADA reduction of indoles under organocatalysis.

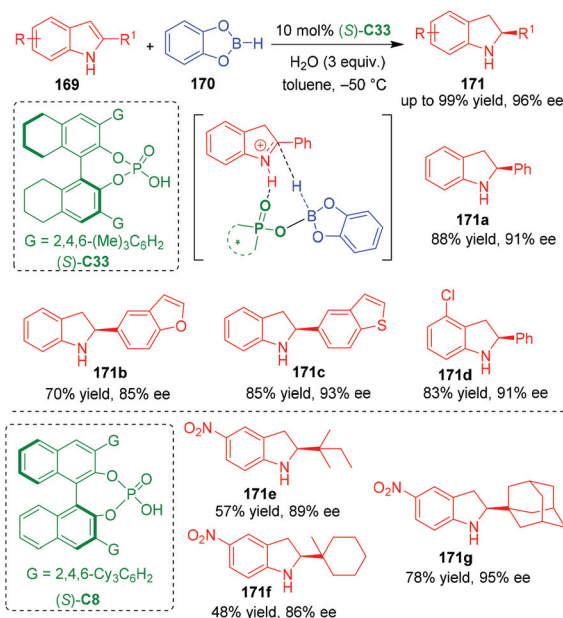
Three years later, Sun, Wang and coworkers expanded the application of this strategy to organo-CADA reduction of C3, C2-substituted indoles *via* a tandem process (Scheme 37b).⁷¹ In detail, the three-component reaction of 2-methylindole **166**, aldehydes **167** and trichlorosilane in the presence of chiral Lewis base **C31** offered 2-methyl-3-alkylindolines **168** in high yields and good stereoselectivities. In the possible reaction pathway, 2-methylindole **166** was activated by trichlorosilane and underwent an addition reaction with aldehydes **167** to form 3-indolylmethanol analogous **P'**, which were readily transformed into vinyl imine intermediates **Q'** after dehydration. Subsequently, in the presence of **C31**, intermediates **Q'** underwent tandem process of 1,4-addition/1,2-addition with trichlorosilane to give products **168** after work up.

In 2020, Song, Yu and coworkers established an organo-CADA reduction of C2-substituted indoles **169** in the presence of catecholborane **170**, water and CPA (*S*)-**C33**, which generated C2-substituted indolines **171** in moderate to good yields and high enantioselectivities (Scheme 38).⁷² In this reaction, the authors suggested that a new chiral B-H was generated *in situ* from CPA boron complex and water, whose acidity is higher than TsOH estimated by DFT calculations. Additionally, they performed DFT calculations on the possible reaction pathways and activation mode of the new chiral B-H on the substrate. In the key transition state leading to the generation of the chiral center, it is suggested that the new chiral B-H formed a hydrogen-bonding interaction with the NH group of the iminium intermediate, thus facilitating an enantioselective hydrogen transfer to give optically pure product. Moreover, several

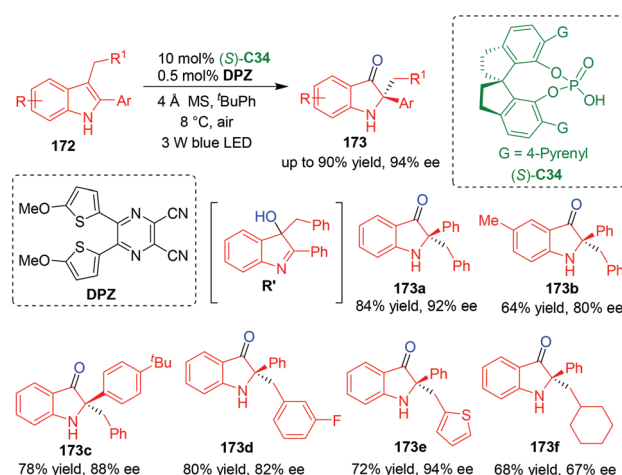
C2-alkyl-substituted indoles **169** could also undergo the organo-CADA reduction in the presence of CPA (*S*)-**C8**, which gave rise to indolines **171e–171g** bearing bulky C2-substituents in moderate yields and considerable enantioselectivities.

In contrast to reduction reactions, catalytic asymmetric oxidation of indole derivatives is also a method for realizing the CADA reactions. In 2018, Jiang, Zhao and coworkers established an organo-CADA reaction of C3,C2-substituted indoles **172** *via* a cascade reaction involving aerobic oxidation and semipinacol rearrangement under visible-light-driven cooperative catalysis of CPA (*S*)-**C34** and organophotoredox catalyst DPZ (dicyanopyrazine-derived chromophore),⁷³ which was developed by their group.⁷⁴ By this approach, chiral oxindole derivatives **173** were obtained in high yields and moderate to good enantioselectivities (Scheme 39). Based on the control experiments, the authors suggested that the first step of aerobic oxidation would generate a chiral intermediate of 3-hydroxy indolenine **R'**, which acted as a chiral promoter for the second step of semipinacol rearrangement.

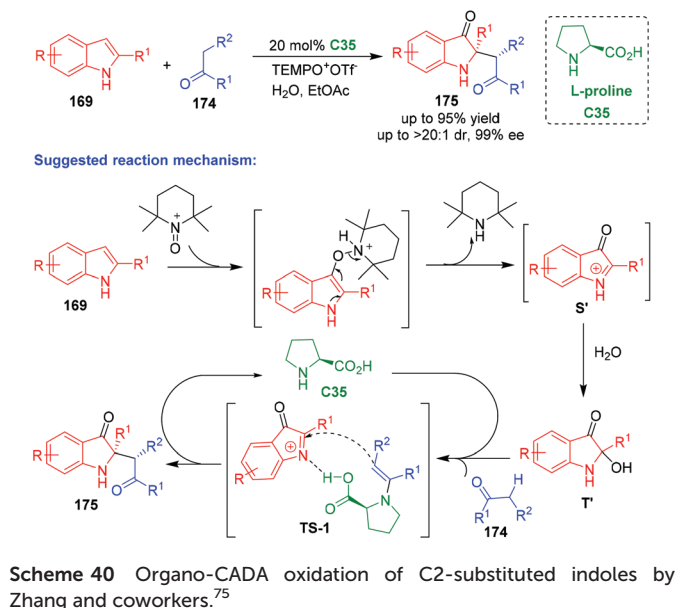
In 2019, Zhang and coworkers reported an organo-CADA oxidation of C2-substituted indoles **169** *via* the reaction with aldehydes or ketones **174** and TEMPO oxoammonium salt in the presence of L-proline **C35**, which provided oxindole derivatives **175** bearing a C2-quaternary stereogenic center in high yields and excellent stereoselectivities (Scheme 40).⁷⁵ Notably, this reaction was not only applicable to C2-aryl indoles **169**, but also to C2-alkyl indoles. In the suggested reaction mechanism, C2-substituted indoles **169** reacted with TEMPO oxoammonium to give a complex, which rapidly transformed into oxindol-1-ium intermediates **S'** through an electron-transfer process. Then, intermediates **S'** reacted with water to give 2-hydroxyoxindoles **T'**. In the proposed transition state (**TS-1**), L-proline **C35** acted as a bifunctional catalyst, which not only activated aldehydes or ketones **174** *via* enamine catalysis but also activated oxindol-1-ium intermediates *via* hydrogen-bonding catalysis, thus facilitating a stereoselective addition



Scheme 38 Organo-CADA reduction of C2-substituted indoles by Song, Yu and coworkers.⁷²



Scheme 39 Organo-CADA oxidation of C3,C2-substituted indoles by Jiang, Zhao and coworkers.⁷³



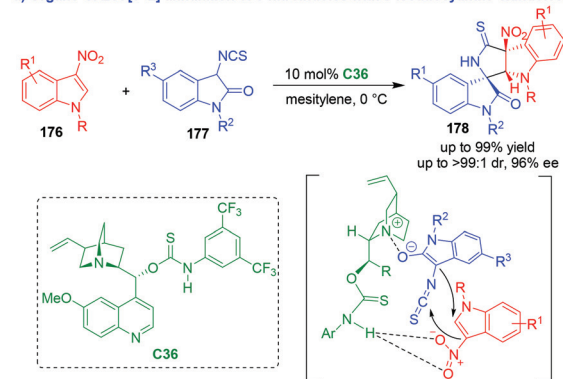
reaction between the two reaction partners to give products 175 after hydrolysis.

5. Organo-CADA reactions of 3-nitroindoles

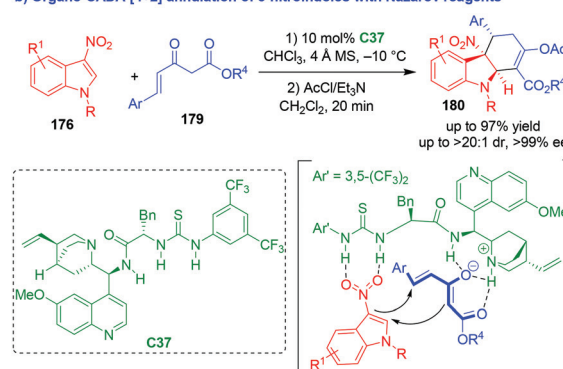
Normally, C3- and/or C2-substituted indoles are electron-rich reactants in organo-CADA reactions. In sharp contrast, electron-poor indole derivatives have scarcely been utilized in organo-CADA reactions. In recent years, 3-nitroindoles have been utilized as electron-poor indole derivatives in organo-CADA annulations and cycloadditions. Although Chataigner and coworkers reported a CADA [4 + 2] cycloaddition of 3-nitroindole with electron-rich alkenes under the catalysis of a chiral thiourea catalyst in 2015,⁷⁶ highly enantioselective reactions of 3-nitroindoles were not achieved until Yuan's group established a CADA [3 + 2] annulation of 3-nitroindoles **176** in the same year (Scheme 41a).⁷⁷ They utilized 3-isothiocyanato oxindoles **177** as three-atom reaction partners to undergo an organo-CADA [3 + 2] annulation with 3-nitroindoles **176** in the presence of chiral bifunctional catalyst **C36**, which offered indoline-based spirooxindoles **178** bearing multiple chiral centers in high yields and excellent stereoselectivities. In the suggested activation mode, substrates **177** were activated by the tertiary amine moiety of **C36** to form enolates, and the nitro group of 3-nitroindoles **176** was activated by the NH group of **C36** via hydrogen-bonding interaction, thus facilitating a stereoselective addition of enolates to **176** and a subsequent cyclization to accomplish the [3 + 2] annulation.

In 2017, the same group utilized Nazarov reagents **179** as four-atom reaction partners to undergo an organo-CADA [4 + 2] annulation with 3-nitroindoles **176** in the presence of chiral thiourea-tertiary amine catalyst **C37**, constructing hydro-

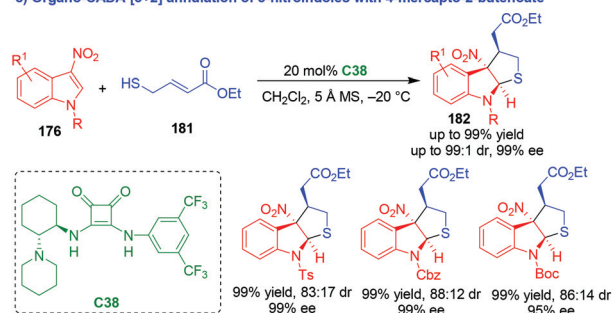
a) Organo-CADA [3+2] annulation of 3-nitroindoles with 3-isothiocyanato oxindoles



b) Organo-CADA [4+2] annulation of 3-nitroindoles with Nazarov reagents



c) Organo-CADA [3+2] annulation of 3-nitroindoles with 4-mercapto-2-butenolate



Scheme 41 Organo-CADA [2 + *n*] annulations of 3-nitroindoles by Yuan's group.^{77–79}

carbazole frameworks **180** in good yields, high diastereo- and enantioselectivity (Scheme 41b).⁷⁸ In the possible transition state, Nazarov reagents **179** were activated by the tertiary amine moiety of **C37** to form enolates, and the nitro group of 3-nitroindoles **176** was activated by the thiourea functionality of **C37** via forming two hydrogen bonds. Then, the enolates of Nazarov reagents **179** attacked the C2-position of 3-nitroindoles **176** followed by an intramolecular cyclization to realize the enantioselective [4 + 2] annulation.

Recently, this group also developed organo-CADA [3 + 2] annulation of 3-nitroindoles **176** with ethyl 4-mercapto-2-butenolate **181** under the catalysis of chiral squaramide-tertiary amine **C38**, constructing tetrahydrothiophene-fused indoline skeletons **182** in high yields, moderate diastereoselectivities and excellent enantioselectivities (Scheme 41c).⁷⁹ It should be noted that they also utilized 3-nitrobenzothiophenes in the

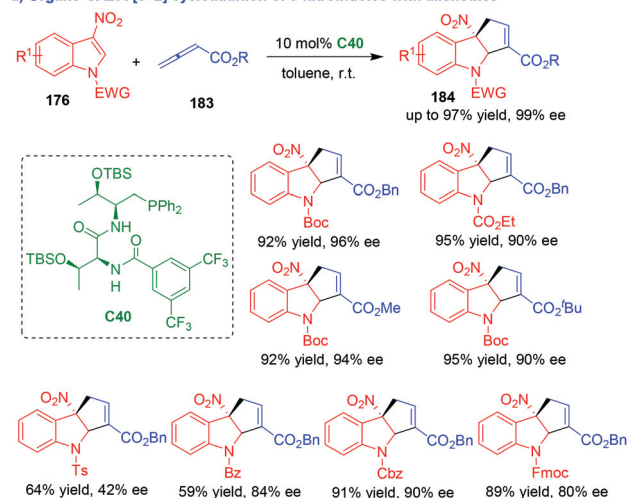
[3 + 2] annulation with **181**, which realized the CADA reaction of 3-nitrobenzothiophenes.

In 2019, nearly at the same time, the two groups of Zhang⁸⁰ and Lu⁸¹ independently accomplished organo-CADA [3 + 2] cycloaddition of 3-nitroindoles **176** with allenates **183** under the catalysis of chiral phosphine catalysts **C39** and **C40**, which were respectively developed by their own group (Schemes 42 and 43). By these two approaches, a wide range of cyclopentaindoline scaffolds **184** were constructed in uniformly high yields and excellent enantioselectivities.

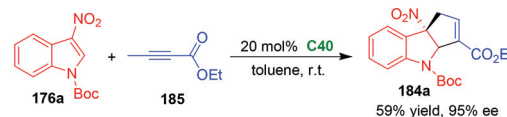
The two approaches have a similar reaction mechanism. As exemplified by **C39**-catalyzed CADA [3 + 2] cycloaddition (Scheme 42b),⁸⁰ the addition of **C39** to allenates **183** generated phosphonium intermediates **U'**, which attacked the C2-position of 3-nitroindoles **176** via TS-2 to form intermediates **V'**. In TS-2, a possible activation mode of chiral phosphine **C39** to the substrates was suggested, which played an important role in controlling the enantioselectivity of the reaction. Then, intermediates **V'** underwent an intramolecular cyclization to give intermediates **W'**, which further underwent proton shift to generate intermediates **X'**. Finally, intermediates **X'** underwent elimination to give products **184** and regenerate catalyst **C39**.

Notably, in the work of Lu's group, the *N*-protecting group of 3-nitroindoles **176** could be extended from Boc to other electron-withdrawing groups such as Ts, Bz, Fmoc, Cbz and ester groups (Scheme 43a).⁸¹ In addition, 2-butynoate **185** could serve as a suitable reaction partner in the CADA [3 + 2] cycloaddition with 3-nitroindole **176a**, which afforded product **184a**

a) Organo-CADA [3+2] cycloaddition of 3-nitroindoles with allenates



b) Organo-CADA [3+2] cycloaddition of 3-nitroindole with 2-butynoate



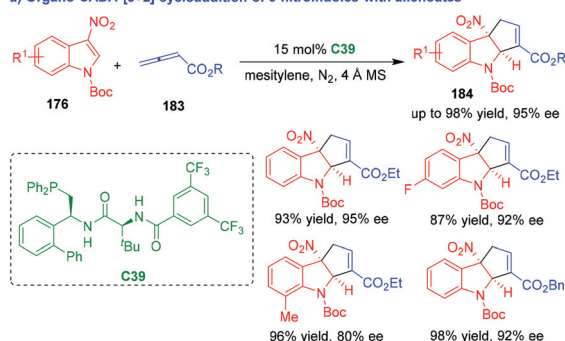
Scheme 43 Organo-CADA [3 + 2] cycloaddition of 3-nitroindoles with allenates by Lu's group.⁸¹

in a moderate yield with an excellent enantioselectivity (Scheme 43b).

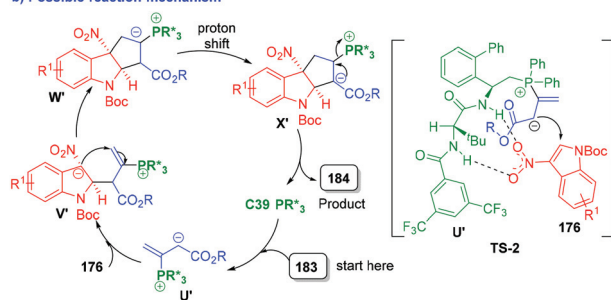
It should be noted, in the work of Zhang's group, organo-CADA [3 + 2] cycloaddition of 2-nitrobenzofurans with Morita-Baylis-Hillman (MBH) carbonates have also been established under chiral phosphine catalysis, which constructed enantio-enriched cyclopentadihydrobenzofuran scaffolds in excellent results.⁸⁰ Moreover, Shi's group also reported a similar CADA [3 + 2] cycloaddition of 3-nitroindole in the presence of commercially available chiral phosphines, which gave rise to cyclopentaindoline product in a moderate enantioselectivity.⁸²

Apart from the above mentioned three-atom building blocks, MBH carbonates could also serve as suitable three-carbon reaction partners in organo-CADA [3 + 2] annulations with 3-nitroindoles. In 2016, Chen and coworkers reported the first example of organo-CADA [3 + 2] annulation of 3-nitroindole **176b** with isatin-derived MBH carbonate **186a** under the catalysis of chiral DMAP-type Lewis base catalyst **C41**, generating cyclopentaindoline-based spirooxindole **187a** in moderate enantioselectivity (Scheme 44a).⁸³ In 2020, to solve the issue of controlling the enantioselectivity of the reaction, Tian, Lin, Ge, Gao and coworkers utilized a chiral DMAP-thiourea **C42** as a bifunctional catalyst to enable a highly enantioselective CADA [3 + 2] annulation of 3-nitroindoles **176** with MBH carbonates **186**, which synthesized a series of cyclopentaindoline-based spirooxindoles **187** in high yields and excellent stereoselectivities (Scheme 44b).⁸⁴ Furthermore, preliminary biological evaluation discovered that product **187b** displayed promising inhibition activity against pancreatic lipase.

a) Organo-CADA [3+2] cycloaddition of 3-nitroindoles with allenates

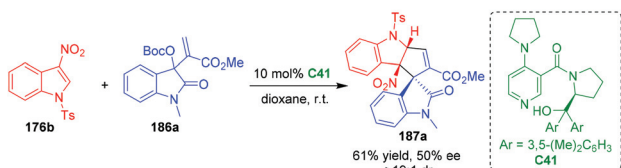


b) Possible reaction mechanism

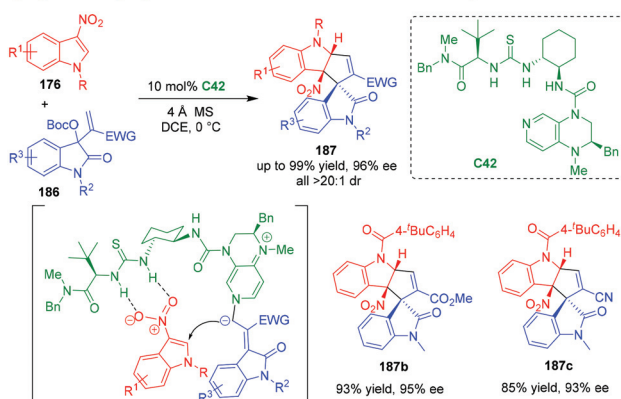


Scheme 42 Organo-CADA [3 + 2] cycloaddition of 3-nitroindoles with allenates by Zhang's group.⁸⁰

a) Organo-CADA [3+2] annulation of 3-nitroindole with MBH carbonate by Chen and coworkers



b) Organo-CADA [3+2] annulation of 3-nitroindoles with MBH carbonates by Tian, Lin, Ge, Gao et al



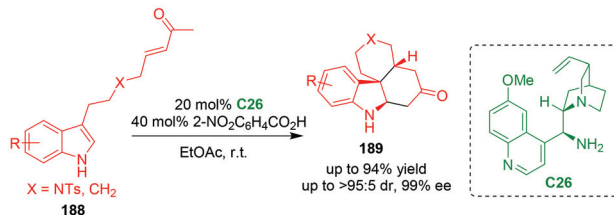
Scheme 44 Organo-CADA [3 + 2] annulation of 3-nitroindoles with MBH carbonates.^{83,84}

6. Organo-CADA reactions of other substituted indoles

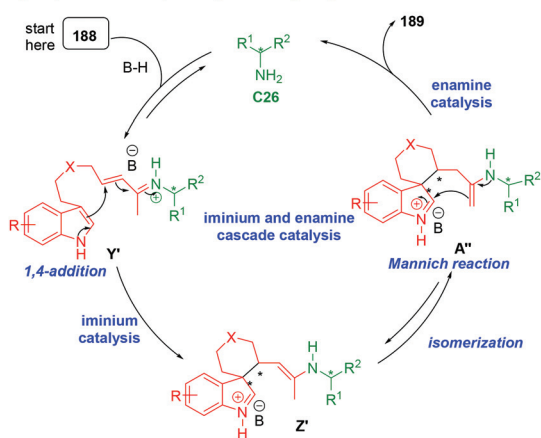
In addition to the above mentioned organo-CADA reactions of indole derivatives, some other substituted indoles bearing well-designed functional groups could also undergo organo-CADA reactions, particularly spirocyclizations, to construct enantioenriched spiro-indole-based frameworks. In 2011, You and coworkers realized an organo-CADA spirocyclization of C3-functionalized indoles **188** in the presence of chiral primary amine **C26** and 2-nitrobenzoic acid, which constructed tetracyclic indoline-containing skeletons **189** in generally high yields, good diastereoselectivities and excellent enantioselectivities (Scheme 45a).⁸⁵ In the proposed reaction pathway and catalytic cycle (Scheme 45b), this CADA reaction occurred *via* a cascade process. Initially, C3-functionalized indoles **188** were activated by chiral primary amine **C26** to generate iminium intermediates **Y'**, which rapidly underwent an enantioselective intramolecular 1,4-addition *via* iminium catalysis to give spirocyclic intermediates **Z'**. Subsequently, **Z'** isomerized into **A''**, which underwent an intramolecular Mannich reaction *via* enamine catalysis to give final tetracyclic products **189** after hydrolysis to regenerate **C26**.

More importantly, this CADA methodology could be applied in the synthesis of ACNO analogue **192** of the natural product (+)-kreysiginine (Scheme 45c). In brief, compound **189a** with 98% ee underwent Huang Minlon reduction to convert the ketone group into methylene group. Then, the oxidation of compound **190** afforded compound **191** bearing an imine group. Finally, the oxidation of **191** with NaNO_2 and

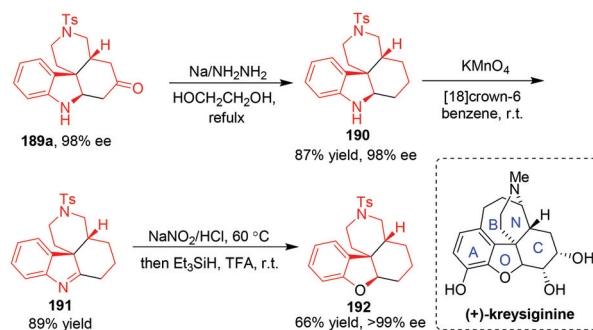
a) Organo-CADA spirocyclization of C3-functionalized indoles



b) Proposed reaction pathway and catalytic cycle



c) Application in the synthesis of the ACNO analogue of (+)-kreysiginine

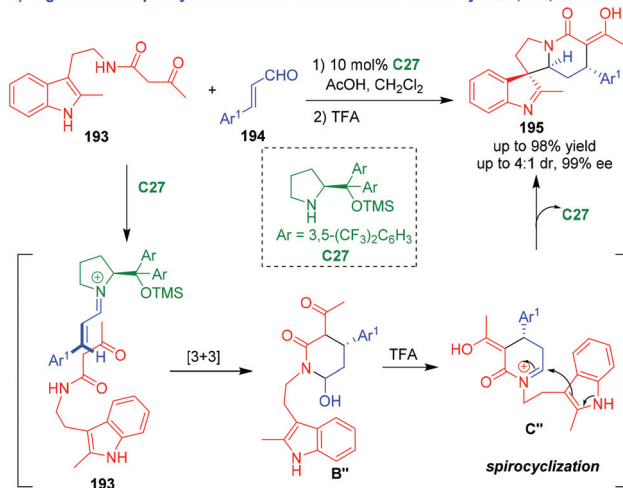


Scheme 45 Organo-CADA spirocyclization of C3-functionalized indoles *via* cascade catalysis by You and coworkers.⁸⁵

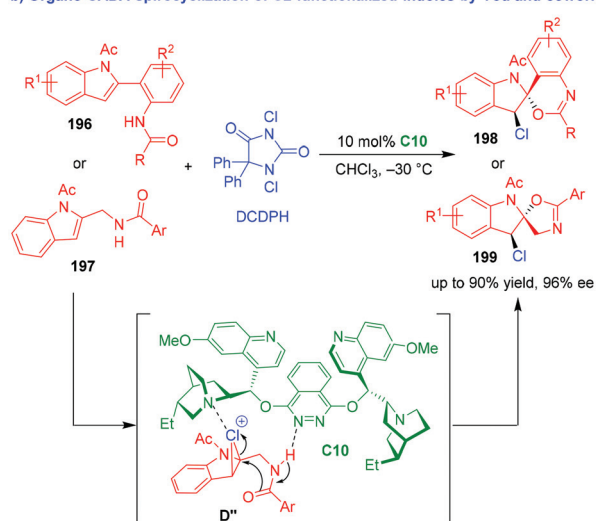
subsequent reduction with Et_3SiH gave rise to compound **192** as an analogue of (+)-kreysiginine.

Apart from intramolecular reactions, intermolecular reactions could also provide opportunities for CADA spirocyclizations of indole derivatives. In 2012, Zhao, Wu, Cao and coworkers reported an organo-CADA spirocyclization of indole derivatives **193** bearing a C3-ketoamide group with α,β -unsaturated aldehydes **194** in the presence of chiral secondary amine **C27**, which offered spiro-indolenines **195** in good yields, moderate diastereoselectivities and excellent enantioselectivities (Scheme 46a).⁸⁶ The reaction involved a cascade process, which started with the activation of aldehydes **194** by **C27** to generate chiral iminium intermediates. Then, a stereoselective formal [3 + 3] cyclization occurred between chiral iminium intermediates and indole derivatives **193** to form six-membered intermediates **B''**, which transformed into another iminium intermediates **C''** with the action of TFA.

a) Organo-CADA spirocyclization of C3-functionalized indoles by Zhao, Wu, Cao et al



b) Organo-CADA spirocyclization of C2-functionalized indoles by You and coworkers



Scheme 46 Organo-CADA intermolecular spirocyclizations of functionalized indoles.^{86,87}

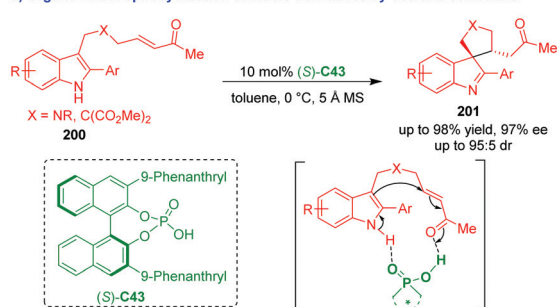
Finally, an intramolecular dearomative cyclization occurred, which realized the spirocyclization and afforded products **195**.

Another organo-CADA intramolecular spirocyclization of functionalized indoles was established by You and coworkers in 2013 (Scheme 46b).⁸⁷ They applied the strategy of chlorocyclization in the CADA reaction of C2-functionalized indoles **196** or **197** by using DCDPH as a chlorinating reagent in the presence of (DHQD)₂PHAL **C10**, which gave rise to spiroindoline derivatives **198** or **199** in high yields and excellent enantioselectivities. In the suggested reaction pathway and activation mode, the chlorination of C2-functionalized indoles such as **197** with DCDPH would generate three-membered cyclic chloronium species **D''**, which could be activated by **C10** via forming hydrogen bonds. Thus, intermediates **D''** underwent an enantioselective intramolecular nucleophilic addition and ring-opening reaction to generate spiro-products **199**.

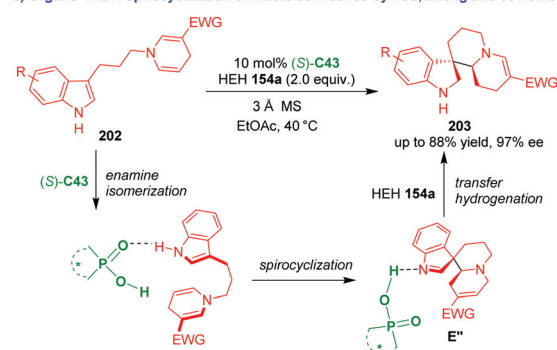
In addition to chiral amine catalysts, chiral phosphoric acids (CPAs) have proven to be suitable organocatalysts, which enabled a series of CADA spirocyclizations of C3-functionalized indoles (Scheme 47).^{88–90} In 2017, You and coworkers established an organo-CADA spirocyclization of indole derivatives **200** under the catalysis of CPA (*S*)-**C43**, generating spiroindolenines **201** in good yields and moderate to high enantioselectivities (Scheme 47a).⁸⁸ In the suggested activation mode, CPA (*S*)-**C43** simultaneously activated both the NH group of the indole ring and the carbonyl group of the enone moiety, which promoted an enantioselective intramolecular Michael addition between the indole C3-position and the enone moiety, thus realizing the dearomative spirocyclization.

Based on this reaction, one year later, the same group devised a class of C3-functionalized indoles **202** bearing a dihydropyridine moiety to accomplish organo-CADA spirocycli-

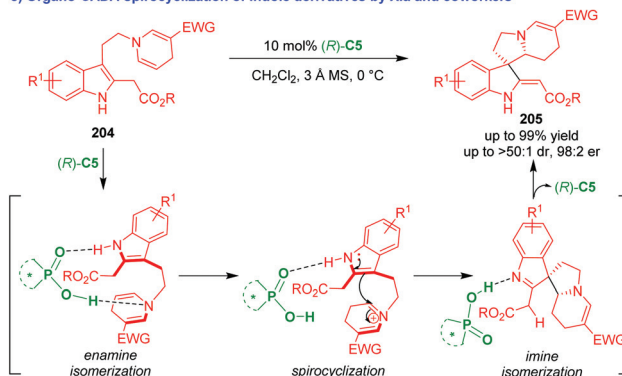
a) Organo-CADA spirocyclization of indole derivatives by You and coworkers



b) Organo-CADA spirocyclization of indole derivatives by You, Zheng and coworkers



c) Organo-CADA spirocyclization of indole derivatives by Xia and coworkers



Scheme 47 Organo-CADA spirocyclizations of C3-functionalized indoles via CPA catalysis.^{88–90}

zation (Scheme 47b).⁸⁹ In the presence of CPA (*S*)-**C43**, C3-functionalized indoles **202** underwent an enantioselective spirocyclization to give chiral spiro-indolenine intermediates **E'**, which further underwent transfer hydrogenation with HEH **154a**, thus affording spiroindolines **203** in good yields and excellent enantioselectivities. Furthermore, the authors performed DFT calculations to give some insights into the reaction mechanism and the origin of stereochemistry.

Very recently, Xia and coworkers also reported an organo-CADA spirocyclization of indole derivatives **204** bearing both a C3-dihydropyridine moiety and a C2-ester group, which delivered enantioenriched spiroindolines **205** with excellent results under the catalysis of CPA (*R*)-**C5** (Scheme 47c).⁹⁰ The reaction process was similar to You's approach,⁸⁹ which involved an enamine isomerization/spirocyclization/dearomatization cascade. But the most important difference is that Xia's approach utilized a C2-ester group to facilitate an imine isomerization in the last step, thus stabilizing products **205** after spirocyclization. So, the C2-ester group in indole derivatives **204** played a crucial role in this CADA spirocyclization reaction.

7. Conclusions and outlook

In summary, organo-CADA reactions of indole derivatives have developed rapidly in recent decades, which provided efficient and enantioselective approaches for accessing optically pure heterocycles containing indoline, indolenine and other related cores, which are widely found in natural products and bioactive molecules. However, there are still some challenging issues to be solved in this research field. These issues include but are not limited to the following. (1) The organo-CADA reaction types of indole derivatives are confined to intramolecular cyclization, addition, [3 + 2], [4 + 2] and [3 + 3] cycloadditions, which resulted in the limitation of the constructed scaffolds, mainly including indoline, indolenine and five-membered-ring or six-membered-ring fused indolines. In contrast, other organo-CADA reaction types such as [4 + 3], [4 + 4], [5 + 2] cycloadditions of indole derivatives for the construction of indole-fused medium-size rings have not yet been established, which require specific design of indole-based building blocks and their involved CADA reactions. (2) In the reaction pathways of organo-CADA reactions of indole derivatives, the formation of imine, iminium, vinyl iminium and other ion-type intermediates is commonly suggested. However, radical intermediates have scarcely been involved in the reaction pathways in spite of the fact that the catalytic asymmetric radical chemistry has become an important area. Although controlling the enantioselectivity in such reactions remains a great challenge, it is highly valuable to develop radical-involved CADA reactions of indole derivatives, perhaps by the combination of asymmetric organocatalysis with visible light photoredox catalysis and electrochemical synthesis. (3) Although the frameworks of indole, indoline and indolenine exist in lots of natural alkaloids, the application of organo-CADA reactions of indole

derivatives in the total synthesis of natural products are still rather limited, which only included several organo-CADA reactions of tryptamines, tryptamine-derived 2-vinylindoles and C3,C2-substituted indoles. The power and potential of organo-CADA reactions of indole derivatives in the total synthesis of natural products should be further explored and demonstrated. Therefore, great efforts are highly needed to address these challenging issues, and we have enough reason to believe that this research field will rise to a new level with the persistent endeavors of organic chemists.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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