BIOMIMETIC CASCADE STRATEGIES TOWARDS 2-AMINOINDOLINES FROM ALKALOIDS

DOI: http://dx.medra.org/10.17374/targets.2022.25.256

Timo van Schaik,[a] Jordy M. Saya,[b] Eelco Ruijter,[a] Romano V. A. Orru*[a]

[a]*Department of Chemistry and Pharmaceutical Sciences and Amsterdam Institute for Molecular and Life Sciences (AIMMS), Vrije Universiteit Amsterdam, De Boelelaan 1108, 1081 HZ Amsterdam, The Netherlands*

[b]*Aachen-Maastricht Institute for Biobased Materials (AMIBM), Faculty of Science and Engeneering, Maastricht University, Organic Chemistry of Bio-based Building Blocks, Brightlands Chemelot Campus, Center Court, Urmonderbaan 22, 6167 RD Geleen, The Netherlands*

(e-mail: r.orru@maastrichtuniversity.nl)

Abstract. *The 2-aminoindoline scaffold is abundant in natural alkaloids with antibacterial, antitumor and anti-inflammatory activities. Synthetic organic chemists have developed various elegant strategies towards this heterocyclic core. These strategies often entail a cascading sequence, where two or more bonds are formed simultaneously. Potentially, these approaches drastically decrease the number of reaction steps required typically minimizing waste generation and energy consumption. These features are a requisite for the present development of new and accessible more greener pharmaceuticals. This review will uncover the synthetic cascade toolbox towards the 2-aminoindolines core focussing on synthetic applicability and discussing the different reaction mechanisms involved.*

Contents

1. Introduction

Although chemical space is nearly infinite, natural products (NPs) evolved in a rather economical fashion, adding functional groups to limited common scaffolds.[1] Herein *N*-heterocycles take an important position (Figure 1). Since the beginning of life on Earth, they co-evolved with proteins, sustaining a continuous feedback-loop towards the relevant biological activity space. This delivers a much more confined area in the on-going quest towards finding new biologically active small molecules.

Indolines and, specifically, 2-aminoindolines occupy a prominent position in the natural product scaffold tree diagram, especially in alkaloids. As the name implies, their structure entails a heterocyclic

2,3-fused indoline moiety resulting in an aminal functionality. One of the earliest discovered NPs containing such a backbone is physostigmine, found in the Calabar bean (Figure 2).[2] At the time, physostigmine was known for its toxicity; however, nowadays it is an FDA approved drug for the treatment of the eye-condition glaucoma.[3]

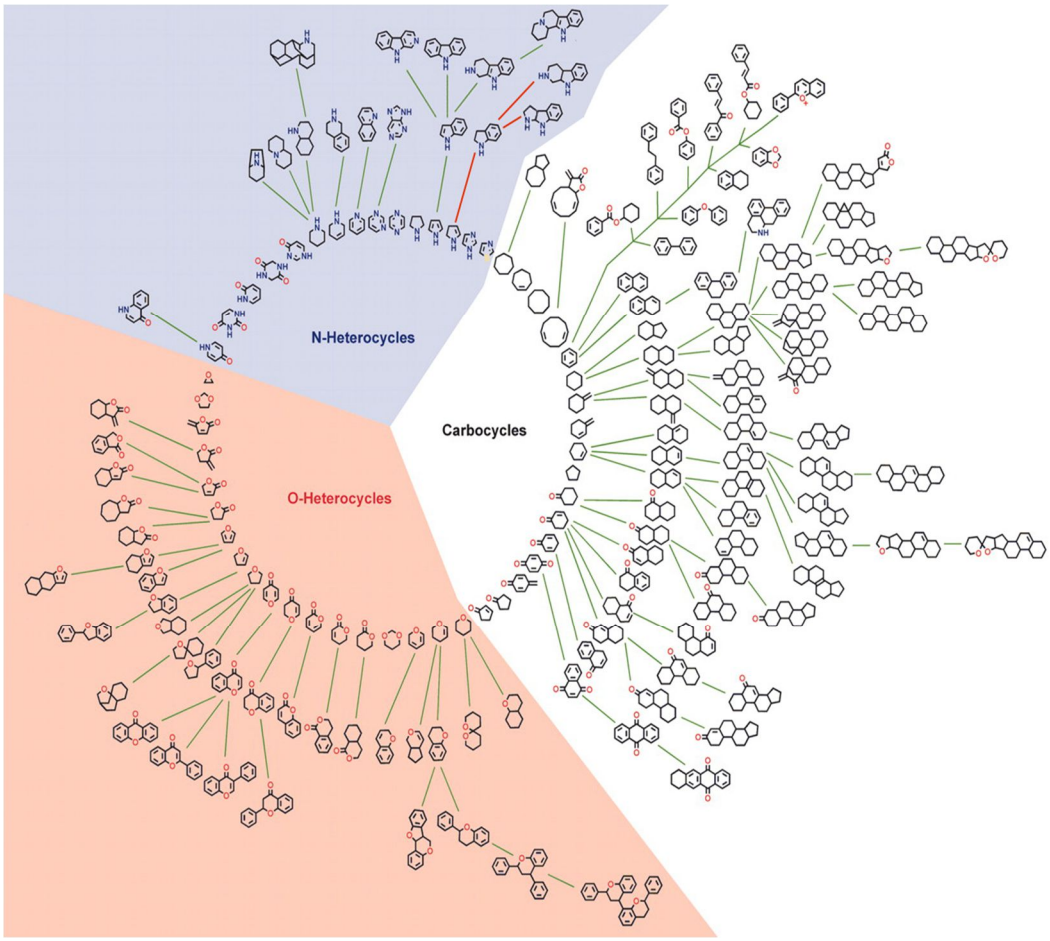


Figure 1. The natural product scaffold tree with abundancy of at least 0.5%.
(taken from Waldmann *et al. J. Am. Chem. Soc.* **2014**).[1]

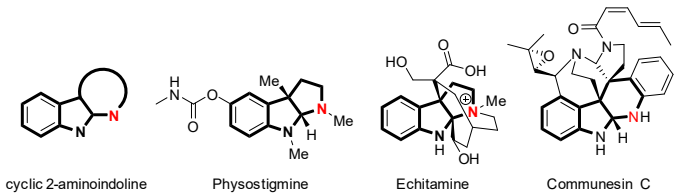


Figure 2. Interesting examples containing the cyclic 2-amino pyrroloindoline backbone.

The pyrroloindolines and pyridonoindolines found in nature can be very complex as seen in echitamine and communesin C with promising in vivo anti-tumor and anti-proliferative properties towards leukemia cells, respectively.[4] The biosynthesis of these alkaloids starts from tryptophan and tryptamine building blocks, often forming multiple new bonds at once,[4] which inspired chemists to pursue elegant the biomimetic approaches. This review focuses on the diversity in approaches towards polycyclic 2-aminoindolines *via* dearomatization of indoles in order to juxtapose the currently available synthetic tools. Recently, Lu *et al.* published a review on asymmetric transformations towards pyrroloindolines.[5] Therefore, we discuss the synthetic relevance and underlying reaction mechanisms of these, mostly biomimetic, cascade strategies based on their common structural motif: pyrroloindolines **I**, pyridinoindolines **II**, 2,3-fused pyrroloindolines **III**, and 3,3-spiro pyrroloindolines **IV** (Figure 3).

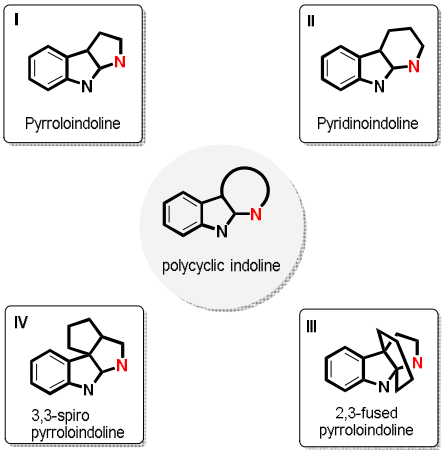
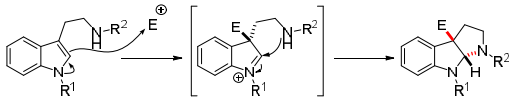


Figure 3. Division into four chapters: pyrroloindolines **I**, pyridinoindolines **II**, 2,3-fused pyrroloindolines **III**, and 3,3-spiropyrroloindolines **IV**.

2. Synthesis of pyrroloindolines

2.1. Electrophilic addition

Perhaps the most straightforward strategy towards the construction of pyrroloindolines is the dearomative electrophilic addition to a tryptamine (Scheme 1).



Scheme 1. General mechanism for the electrophilic addition and subsequent imine interception.

In Figure 4, a range of different classes of electrophiles that can be incorporated at C3 of a tryptamine moiety are summarized. Conceptually, the electrophile first adds to the C3 position of the indole core, producing an indoleninium intermediate. Subsequent intramolecular capture of the reactive iminium species then effectively results in two newly formed bonds (Figure 4, indicated in red). The intermediate pyrroloindolines in their turn are used in the total synthesis of a range of alkaloids. Although this is a very effective strategy to quickly afford the pyrroloindoline backbone and a considerable number of impressive (asymmetric) syntheses have been reported,[6-124] we are more interested in the different mechanistic aspects of its assembly as are discussed below.

To highlight one example, Corey and co-workers explored an interesting protection-deprotection strategy involving the indole 2,3-double bond (Scheme 2).[97] They show that triazoline **2** forms an urazole adduct quantitatively with 1,2,3,4-tetrahydrocarbazole, within minutes under very mild conditions. Extension to a tryptophan derivative proved however more challenging although pyrroloindoline **3** could still

be formed in 62%. This was then converted back to indole **1** in vacuo at elevated temperatures. Although this approach works here, it would likely not be a practical indole protecting group for many other substrates.

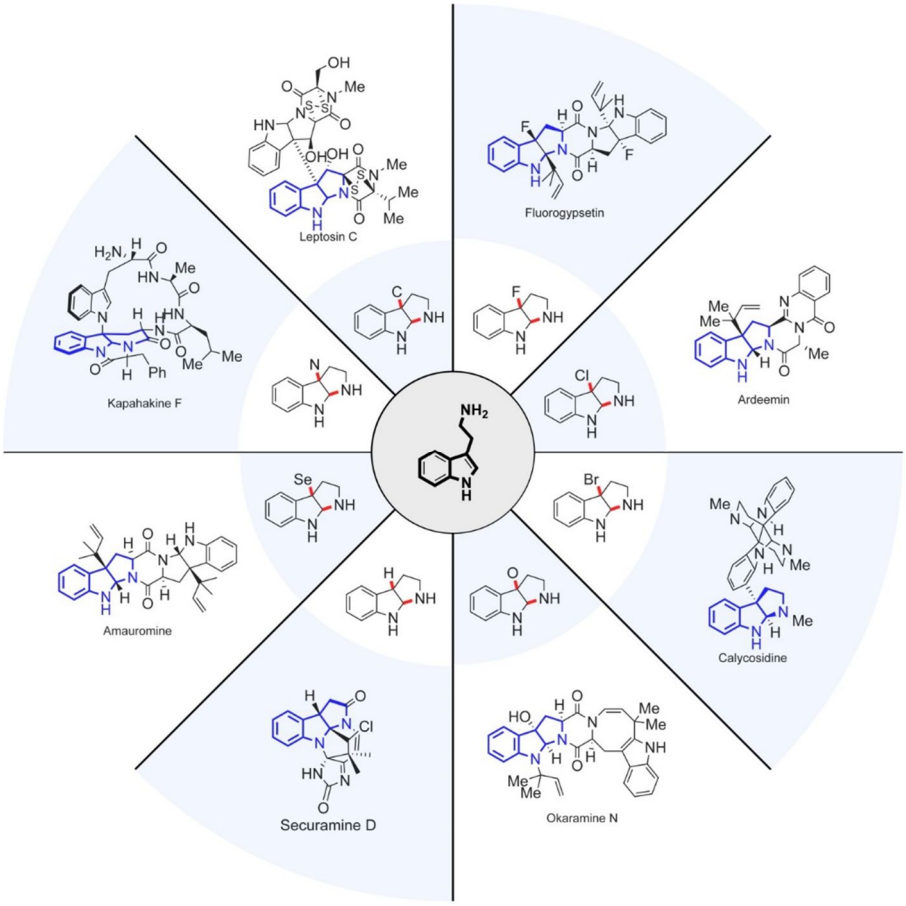
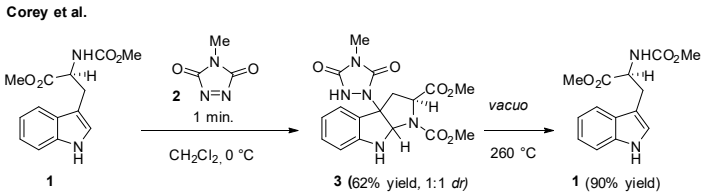


Figure 4. Electrophilic addition-imine interception cascades to access pyrroloindolines.

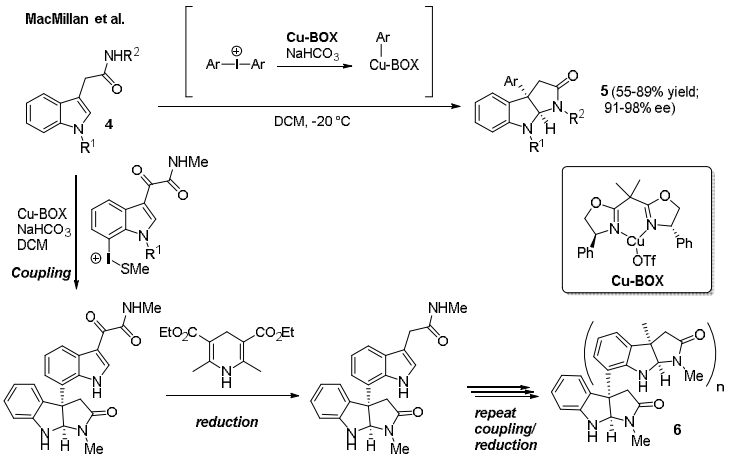


Scheme 2. Protection and deprotection of a tryptophan moiety.

2.2. Metal catalyzed arylation

The C3-aryl pyrroloindoline unit is present in several natural alkaloids. Synthetic strategies mainly involve C3 halogenation of the indole **4**, to generate the pyrolloindoline **5**, after which it can undergo a cross coupling reaction with an aryl donor (*e.g.* Heck reaction). For example, MacMillan *et al.* were able to achieve this transformation in a one-step asymmetric procedure using a Cu-BOX complex (Scheme 3).[125]

The authors later demonstrated the power of this procedure by making several oligomeric pyrolloindoline natural products **6**, by applying this procedure in a controlled iterative sequence.

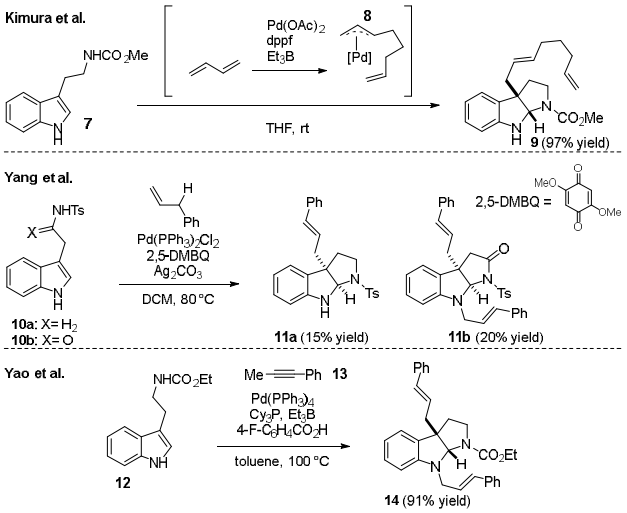


Scheme 3. Cu catalyzed one step C(3)-arylation of indoles.

2.3. Addition to π-allyl complex

Another commonly employed approach towards the construction of pyrroloindolines involves the addition of π-allyl intermediates to the indole C3 position. Subsequently, the resulting indolenine is intramolecularly trapped by the nucleophilic amine. A major advantage of this approach over more classical strategies is the potential to induce effectively the desired chemo-, as well as diastereo- and enantio-selectivity.

In this respect, Kimura and co-workers were first to exploit a Tsuji-Trost type allylation (Scheme 4).[126] Under the given catalytic system, two equivalents of butadiene initially dimerize to afford π-allyl complex **8**, followed by electrophilic allylation to the indole C3 position of **7** affording pyrroloindoline **9**. Interestingly, this methodology does not work for *N*-methyl substituted indoles, where the starting material was recovered exclusively.



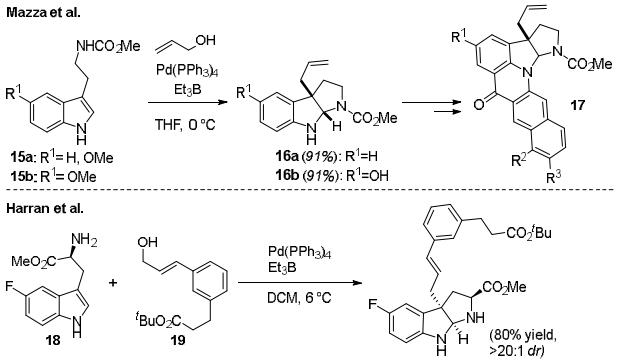
Scheme 4. Pyrroloindoline synthesis *via* addition to π-allyl complex. Part 1.

Coordination of triethylborane with the amine forms a *N*-indolyltriethyl borate species, which enhances the nucleophilicity of the C3 position (Scheme 4).

Related work by Yang and co-workers discusses a palladium catalyzed allylic C-H activation in the presence of stoichiometric amounts of silver carbonate and 2,5-dimethoxybenzoquinone (2,5-DMBQ).[127] The authors tested a variety of nucleophiles for their methodology including tryptamine derivatives. However, *N*-tosyltryptamine **10a** and indolylcarboxamide **10b** gave poor yields of **11a** and **11b** (15% and 20%, respectively). Competing reactions like N-alkylation and C-H amination leads to branched products. Likely, the chemoselectivity can be greatly enhanced by selecting the appropriate Lewis acid or additive as Yang mainly focus was the synthesis of aliphatic 3,3-disubstituted indolenines, leaving the pyrroloindoline synthesis unoptimized (Scheme 4).

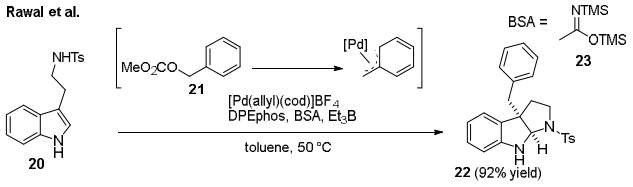
In a similar fashion, Yao and co-workers used an alkyne moiety together with indole **12** as precursors for the reactive π-allyl species.[128] The transformation comprises two catalytic cycles. In the first cycle alkyne **13** is converted to the corresponding phenylallene *via* hydropalladation and subsequent reductive elimination, generating **14**. The second cycle delivers the desired π-allyl complex. Once again, the addition of triethylborane proved to be pivotal for successful C3 alkylation (Scheme 4).

Mazza and co-workers applied allyl alcohol to construct an alkaloid-inspired hexacyclic scaffold **17** that was tested subsequently for antiproliferative properties (Scheme 5).[129] The reaction works equally well for tryptamine **15a** and **15b**, respectively generating **16a** and **16b** in both 91% yield. This approach was further elaborated by Harran and co-workers, who employed a more complex allylic alcohol **19** in combination with tryptophan derivative **18**, describing the first diastereoselective (*dr*≥20:1) allylation of this type.[130] Surprisingly, the Tsuji-Trost reaction is compatible with the highly nucleophilic free amine under relatively general reaction conditions.



Scheme 5. Pyrroloindoline synthesis *via* addition to π-allyl complex. Part 2.

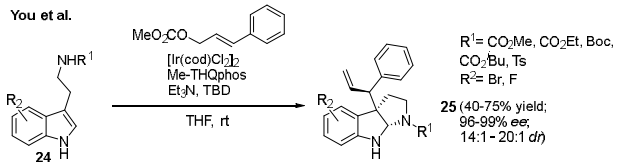
Next, Rawal and co-workers showed that benzylation *via* an unusual dearomatized π-benzyl complex is possible as well. (Scheme 6).[131] The authors explain that the additive *N,O*-bis(trimethylsilyl)acetamide (BSA) **23** serves as scavenger of the released methoxide anion originating from decarboxylation of methyl carbonate **21** to form MeOTMS. The resulting negatively charged TMS-acetamide in turn deprotonates the indole **20** giving **22** in an excellent overall yield of 92%.



Scheme 6. Pyrroloindoline synthesis *via* addition to benzylic π-allyl complex.

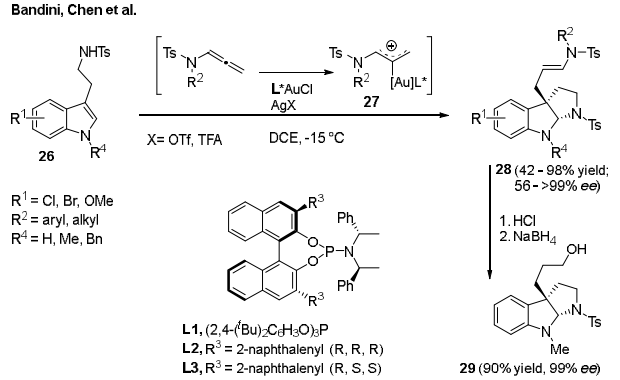
However, since the authors did not document a control experiment omitting the BSA additive, it is unclear if triethylborane alone would have been sufficient for the reaction to proceed.

A further highlight is the work of You and co-workers in this area. They were the first to report a highly enantioselective Tsuji-Trost cascade reaction involving an indole **24** (Scheme 7).[132,133] Interestingly, they focused on developing a methodology to exclusively afford the branched allylated products **25**, which results in an additional stereocenter. Especially phosphoramidite ligands gave an excellent *ee*. However, the stereocontrol of the branched stereocenter proved to be difficult. Ultimately, Me-THQPhos accommodated a good catalytic fit and furnished the product in a high *dr*. The resulting vinyl group was swiftly functionalized to a terminal alcohol *via* hydroboration.



Scheme 7. Synthesis *via* branched Tsuji-Trost reaction.

A more exotic route was explored by Bandini and co-workers using a gold catalyzed aminoallylation *via* a π-allyl species **27** (Scheme 8).[134] Ligand **L1** in combination with a silver(I) salt was selected to optimize their reactions. The nature of the chosen silver salt proves pivotal for the selectivity of the reaction. For example, using AgOTf gave 95:5 selectivity in favour of *N*-alkylation, while with AgTFA desired product **28** was afforded with a 98:2 selectivity. Noteworthy, Chen and co-workers attempted an asymmetric approach of the same system by using the ligands **L2** and **L3**.[135] In combination with the phosphoramidite catalysts, AgOTf was in fact effective in giving the correct *C*-alkylation of indoles **26** product even though this particular silver salt gave the undesired selectivity in the work of Bandini. In order to show the applicability of this methodology, the enamine functionality **28** was readily hydrolyzed to the corresponding aldehyde and then reduced in the presence of sodium borohydride to the concomitant alcohol **29**.

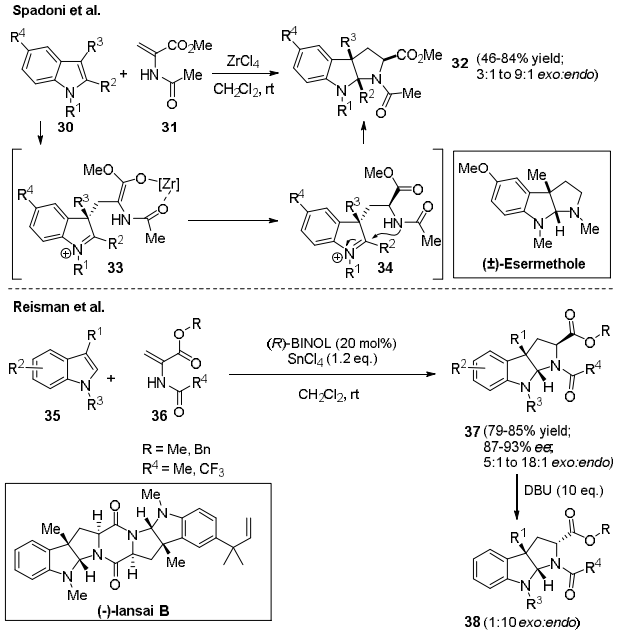


Scheme 8. Gold catalyzed aminoallylation.

2.4. Michael type reaction

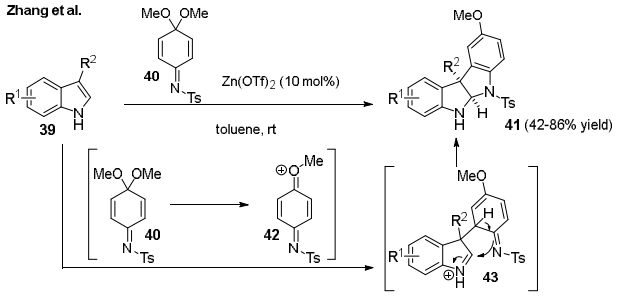
Starting from indoles **30** another quite straightforward strategy to afford the pyrroloindolines **32** skeleton involves a 1,4-conjugate addition towards **33**, followed by a ring-closure of **34**. In an effort to develop a concise methodology for the synthesis of (±)-esermethole, Spadoni and co-workers explored this using zirconium-based catalysis (Scheme 9).[136] Stoichiometric amounts of zirconium salts were, however, required for any conversion at all. Interestingly, free *NH*-indole **30** as well as the alkylated amine were tolerated in the reaction, whereas electron-withdrawing protecting groups (-Boc, -Ac, -Ts) prevented any reaction. In the same year and independently, Reisman and co-workers established the asymmetric total

synthesis of (-)-lansai B using a very similar enantioselective approach.[137,138] Although Michael acceptors of type **31** are usually not very reactive due to the electron-donating nature of the enamide functionality, the combination with a strong Lewis acid in this reaction provided good yields of **37**, especially when $SnCl_4$ was used. The *ee* could be significantly increased by making the Michael acceptor **36** more electrophilic, employing an electron-withdrawing trifluoroacetamide group and substituting the methyl ester for a benzyl ester. As expected, electron-rich aromatic substituents gave better yields by increasing the initial nucleophilicity of indoles **35**. Lastly, **37** could be epimerized reliably towards the apparently more stable thermodynamic *endo* product **38** in a 10:1 ratio.



Scheme 9. Michael type reactions.

Next, Zhang *et al.* presented a new strategy involving an in situ generated quinone imine ketal **40** in combination with an indole **39** (Scheme 10).[139] The reactant **40** was readily obtained by $PhI(OAc)_2$ oxidation of the concomitant *N*-tosyl anisidine. Evidently, this Michael acceptor is much more electrophilic compared to **31** and **36** described above and thus only requires a mild Lewis acid for efficient 1,4-conjugate addition to occur. Cleavage of one the methoxy groups of the acetal in **40** is facilitated by $Zn(OTf)_2$, generating the highly electrophilic oxonium ion **42**, which is then attacked by indole **39**.



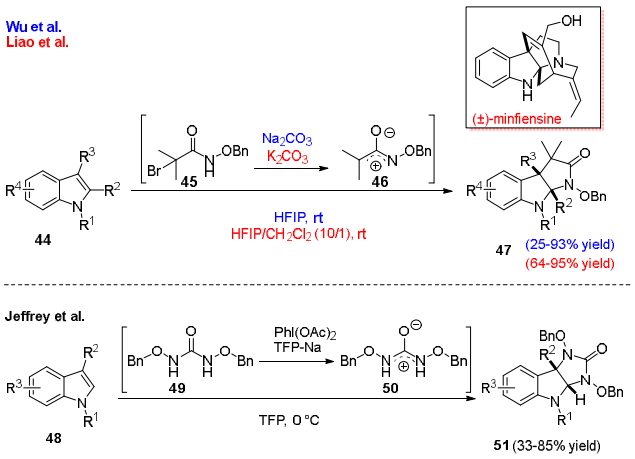
Scheme 10. Quinone imine ketal cascade reaction.

Rearomatization and intramolecular trapping of intermediate iminium species **43** yields pyrroloindoline **41**. Position R^2 tolerates (bulky) aliphatic substituents, but an aryl group at that position gave no reaction at all. So far, an asymmetric version of this reaction trying several chiral ligands like BINOL and PYBOX gave **41** in only poor *ee* (Scheme 10).

2.5. 1,3-Dipolar cycloaddition

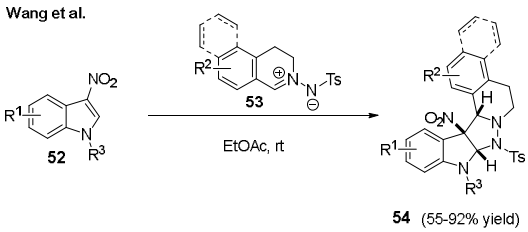
A very efficient way of connecting another 5-membered ring to indoles **44** core to arrive at pyrroloindolines is a 1,3-dipolar cycloaddition. Under basic conditions, Wu and co-workers could liberate the bromide of **45** in order to generate dipole **46** (Scheme 11).[140] Subsequently, a formal [2+3] cycloaddition takes place. It should be noted that apolar and aprotic solvents gave no reaction and only the protic solvents TFE and HFIP were effective towards the desired heterocycle **47**.

Only a few months later, Liao and co-workers independently reported almost the same reaction with similar optimization conditions and scope examples.[141] However, they were able to systematically increase the yield with seemingly only minor changes. Firstly, a small volumetric fraction of DCM was added to resolve any solubility issues. Furthermore, the slightly more basic potassium carbonate was used instead of sodium carbonate. Moreover, the effective reaction concentration was higher compared to Wu's reaction conditions, boosting the yields averaging from 60-70% to >90%. Lastly, a racemic formal synthesis of a key intermediate toward minfiensine was realized, demonstrating the potential of this methodology. Next, Jeffrey and co-workers reported a hetero variation of this formal [2+3] cycloaddition, involving indoles **48** dibenzyloxy urea **49**.[142] The reactive zwitterionic species was generated by oxidation mediated by phenyliodine(III) diacetate (PIDA). Based on precedent experiences with 1,3-dipole **50** in different contexts, the uncommon solvent 2,2,3,3-tetrafluoro propanol (TFP) was chosen. Initially, the reaction only produced **51** in low yield (21%). However, addition of 1.2 equivalents of the basic sodium alkoxide of TFP (TFP-Na) boosted the yield to 79%. Optionally, molybdenum hexacarbonyl ($Mo(CO)_6$) could be used to cleave both *N*-OBn bonds, producing the free urea.



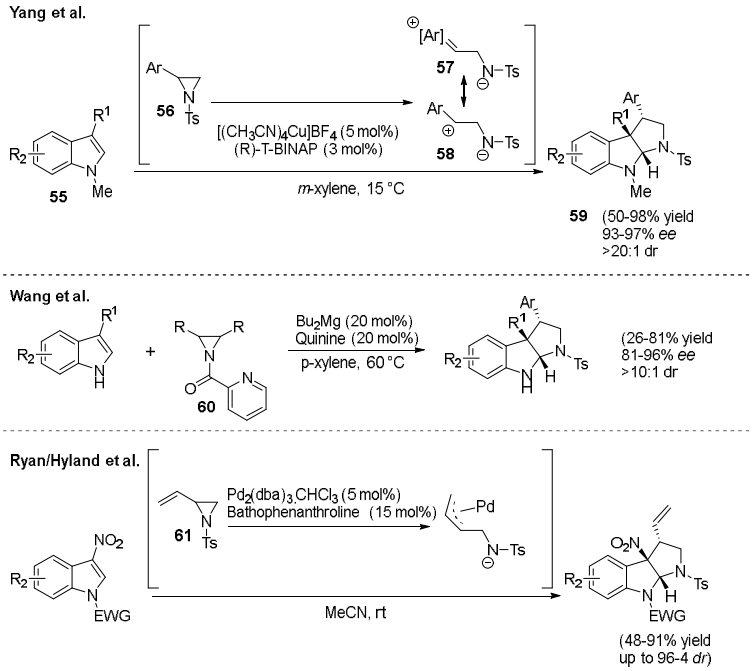
Scheme 11. 1,3-Dipolar addition to indoles.

Recently, Wang and co-workers described an intriguing 1,3-dipolar addition involving 3-nitroindoles **52** and azomethine ylides **53** (Scheme 12).[143] When exploring initial reaction conditions, they employed various Lewis acids. However, and to their surprise, the absence of any catalyst at all improved the conversion dramatically. Ultimately, excellent yields of **54** were accomplished under environmentally friendly conditions, using ethyl acetate as solvent. The resulting *endo*-stereo selectivity was dictated by π–π-stacking interactions of the aromatic rings. Notably, the R^3-substituent only tolerates electron-withdrawing groups. Already a very weak electron-donating methyl substituent showed no conversion towards the corresponding heterocyclic product, possibly inducing lower electrophilicity at C2.



Scheme 12. Azomethine ylide as 1,3-dipole.

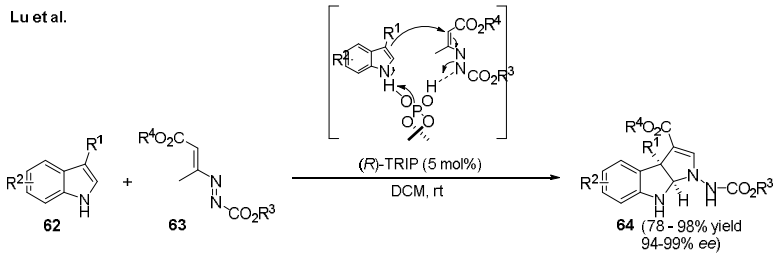
Also, Yang and co-workers showed that activated aziridines could function as masked 1,3-dipoles (Scheme 13) in this type of transformations.[144] The aziridine **56** was selected, as the aryl-group effectively stabilizes the benzylic cation while the electron-withdrawing tosyl group stabilizes the *N*-anion in the zwitterionic species **57**↔**58** generated in situ. This rationale was supported by the observation that the electron-rich 4-methoxyphenyl derivative of **56** dramatically increased the reaction rate, while the corresponding 4-nitrophenyl derivative leads to a sluggish conversion of **55** to form **59**. Interestingly, when optically pure (*S*)-**56** was employed, the reaction still proceeds with retention of configuration even in the absence of the chiral catalyst. However, there was a catalytic mismatch in case (*S*)-T-BINAP was used instead of (*R*)-T-BINAP, obtaining an *ee* of only 53% (97% *ee* originally). This indicates that a slow kinetic resolution of the aziridine takes place. Later, similar transformations were reported using aziridines *via* Lewis acid catalysis of non activated aziridines **60** and vinyl aziridines **61** using a palladium catalyst.[145,146]



Scheme 13. Ring-opening aziridine as 1,3-dipole.

Noteworthy is that the group of Lu recently reported a chiral phosphoric acid catalyzed [3+2] cycloaddition with azoalkenes **63** (Scheme 14).[147] The phosphoric acid both activates the indole **62** and azoalkenes, thereby pre-organizing it perfectly and hence giving pyrroloindolines **64** in generally high *ee's*

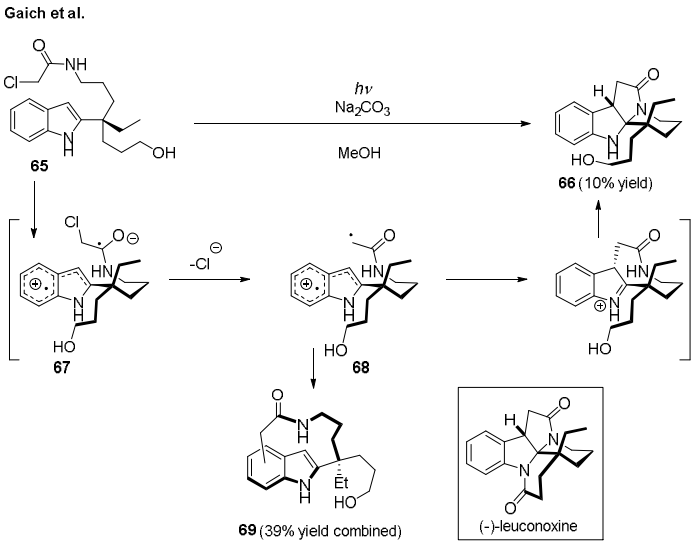
of around 99%. The authors demonstrated that it was possible to later break the N-N bond, generating biomimetic pyrroloindolines.



Scheme 14. Chiral phosphoric acid catalyzed enantioselective [3+2] cycloaddition of indoles and azoalkenes.

2.6. Radical cyclization

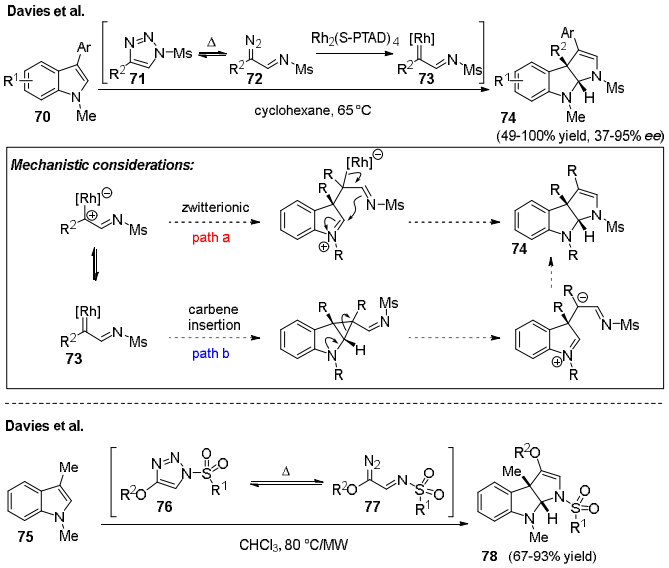
Radical cyclization processes offer great opportunities in the type of chemistry we are discussing in this section. For example, Gaich and co-workers reported an interesting strategy inspired by the Witkop cyclization of indole **65** to access pyrroloindolines of type **66** (Scheme 15).[148] The generally accepted mechanism involves photon-induced electron transfer from the excited indole chromophore onto the chloroacetamide functionality, which forms intermediate **67**. Then, radical fragmentation of the C-Cl bond produces key acetamide radical **68**. Intramolecular recombination of the two radicals produced mainly Witkop cyclization products **69**, where substitution occurred at indole position C4 and C7. The desired product **66** was only recovered in a yield of 10%. Remarkably, the authors stated that in the absence of sodium carbonate **66** was not formed, which raises the question whether its formation proceeds *via* a radical mechanism at all. Alternatively, an intramolecular S_N2 reaction at C-3 could also account for the observed products. Ultimately, this key-transformation was used to finalize the total synthesis of Aspidosperma alkaloid (–)-leuconoxine after oxidative lactamization.[149]



Scheme 15. Radical cascade reaction.

2.7. Carbene insertion

A creative way to attach an amino allyl moiety to the indole ring **70** *via* a carbene insertion reaction was discovered by Davies and co-workers.[150] Under thermal conditions, triazole **71** ring opens, resulting in diazopropylidene species **72** (Scheme 16). Then, in the presence of a rhodium catalyst, dinitrogen is expelled and carbene **73** is formed. There are two generally accepted mechanistic pathways for the ensuing carbene addition. Pathway **a** essentially represents a stepwise formal [2+3] addition rather similar to the reactivity of a Fischer carbene. On the other hand, pathway **b** represents a typical carbenoid cyclopropanation, followed by a two-step ring expansion. Interestingly, performing the reaction in moderately polar solvents such as chloroform and ethyl acetate gave no reaction at all, while pyrroloindolines **74** were obtained in excellent yields and *ee*'s in cyclohexane and toluene. A year later, the same group reported the synthesis of pyrroloindolines **78** *via* a similar methodology involving indoles **75** and 4-alkoxytriazole **76** slightly above ambient temperatures.[151] The alkoxy group may destabilize diazo intermediate **77**, yet stabilizes the formation of the free carbenoid.

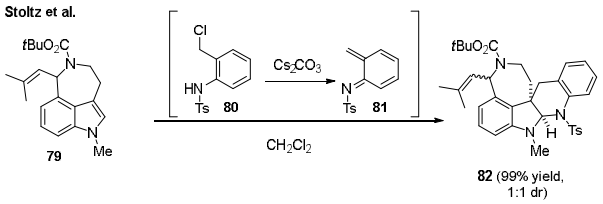


Scheme 16. Triazole opening carbene formation and subsequent addition.

3. Synthesis of pyridinoindolines

3.1. Diels-Alder type reaction

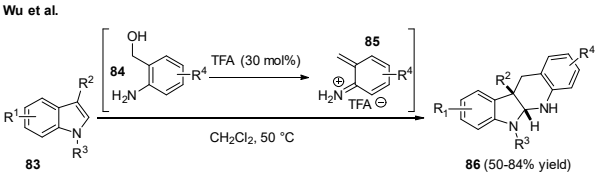
Possibly the most popular strategy towards pyridinoindolines is the inverse demand hetero Diels-Alder reaction, which was first reported by Stoltz and co-workers. They employed indole **79** as dienophile and the *aza*-quinone methide **81** as diene (Scheme 17).[152,153]



Scheme 17. Diels-Alder reaction with aza-quinone methides.

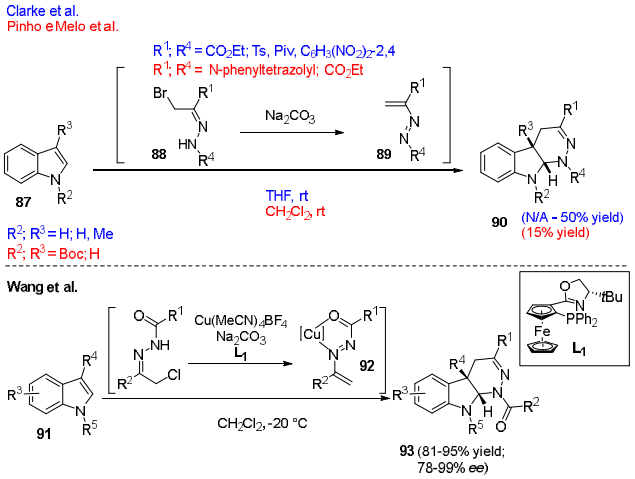
These were generated *in situ* by chloride elimination of **80** under basic conditions. Although the diene **81** proved exceptionally reactive in a Diels-Alder process, unfortunately the desired pyridinoindoline **82** was formed as a 1:1 diastereomeric mixture. Apparently, the bulky isobutylene group was too far from the reacting centres to impact the diastereoselectivity (Scheme 17).

In a similar approach, Wu and co-workers generate the *aza*-quinone methide **85** by acidic hydrolysis of benzyl alcohol **84** (Scheme 18).[154] Initial screening of reaction conditions showed that the catalytic $Ga(OTf)_3$ in combination with *N*-methylskatole as substrate gave the desired pyridinoindoline, yet other electron-withdrawing *N*-protecting groups were not tolerated. After further optimization studies TFA, as an organic Brønsted acid, gave the most consistent formation of **86** in reasonable yields. With C3-unsubstituted indoles **83** the resulting aminal in **86** tautomerized to the corresponding indole. The group of Wei later reported a similar strategy using $In(OTf)_3$ as the catalyst, which allowed also 2,3-disubstituted indoles as an alternative input.[155]



Scheme 18. TFA catalyzed DA reaction with an aza-quinone methide intermediate.

Next, Clarke and co-workers explored vinyldiazenes **89** (*i.e. in situ* derived from bromohydrazones **88**) in combination with different potential dienophiles (Scheme 19).[156] They studied the effect of three different R^4-substituents in **89** using indole and skatole as a substrate. Only with R^4=2,4-dinitrophenyl and skatole a moderate yield of desired **90** was obtained, while reactions with indole led to quick tautomerization of the aminal to yield an aromatic indole moiety again. Remarkably, when **89** with a pivaloyl R^4-group was used together with indole, a stable *aza*-pyridinoindoline was formed and no tautomerization was observed, despite the acidic proton present at C3. Also Pinho e Melo and co-workers observed this when they employed a Boc-protected indole **87** with different vinyldiazenes.[157] Recently, Wang and co-workers rediscovered this inverse-electro-demand *aza*-Diels-Alder reaction to access pyridinoindolines **93** via indoles **91** and diazenes **92**.[158] The reaction follows the same mechanism, however, an active chiral copper catalyst chelates between the carbonyl functionality and the diazene **92**, creating a chiral environment for the ensuing enantioselective Diels-Alder reaction.

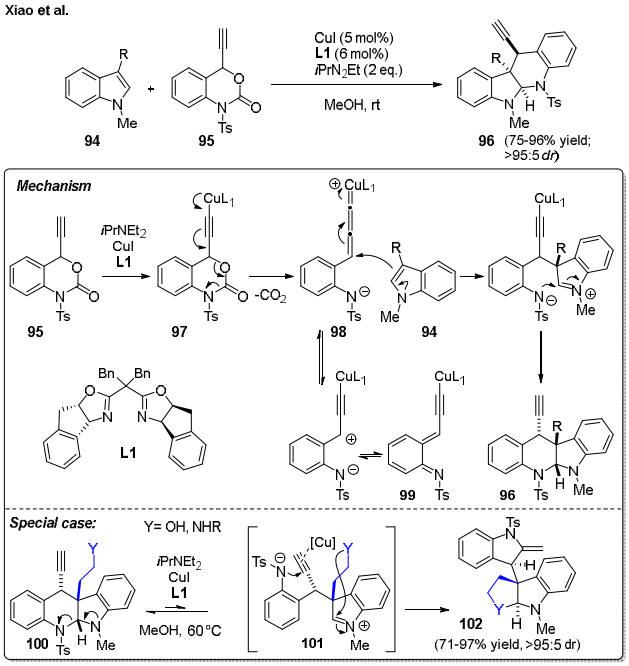


Scheme 19. Heterocyclic DA reactions towards pyridinoindolines.

3.2. Copper catalyzed cascade reaction

In an alternative approach to access pyridinoindolines **96**, Xiao and co-workers reported an intriguing cascade reaction involving carbamate **95** (Scheme 20).[159,160] Mechanistically, the copper catalyst is believed to undergo an oxidative insertion on the terminal end of the alkyne **95**, followed by copper allenylidene formation **97** accompanied by successive decarboxylation. The thus formed intermediate **98** is reminiscent of an *ortho* azo-quinone methide **99** and further reacts accordingly with indoles **94**. Finally, reductive elimination of the copper catalyst furnishes the pyridinoindolines **96** in reasonable to excellent yields. Attempts to induce enantioselectivity using several different chiral ligands failed, but chiral ligand **L1** did furnish high *dr*'s relative to the acetylene bearing stereocenter.

Interestingly, when the temperature is increased to 60 °C and R^2 comprises a tethered nucleophile (-OH, -NHR), the proximate aliphatic nucleophile intercepts the indolenine moiety in intermediate **101** instead. The now free aniline functionality attacks the copper-activated alkyne to afford product **102**. Pyridinoindoline **100** even converts to product **102** retrospectively, by exposure to the same catalytic reaction conditions with an elevated temperature (60 °C).



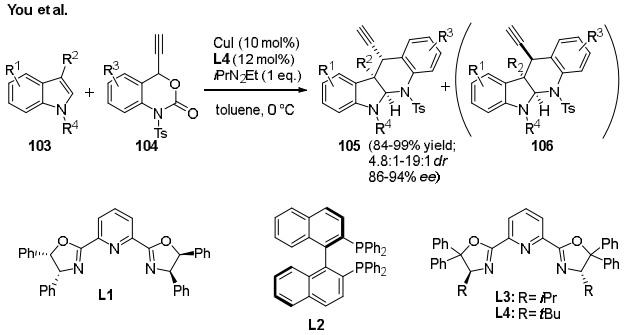
Scheme 20. Copper catalyzed decarboxylic propargylic dearomatization of indoles.

Intriguingly, only a month later You and co-workers independently reported the asymmetric version of the same reaction, employing almost identical reaction conditions (Scheme 21).[160]

During reaction scouting with benchmark substrate 1,3-dimethylindole even Xiao's original reaction conditions were initially implemented. However, a different ligand was used and the catalyst loading was doubled (Table 1). Unfortunately, the product only gave an *ee* of 1%, but the minor *cis*-diastereomer showed an encouraging *ee* of 43%. Upon changing the solvent from methanol to toluene, instead of *trans*-product **106**, the *cis*-product **105** now became the major product with a *dr* of 5.5:1 and a more pronounced *ee* of -57%.

Employing the bulkier PYBOX-ligand (**L4**), the yield and *ee* for the benchmark substrate increases to 95% and 89%, respectively. The group then showed that, perhaps surprisingly, both electron-withdrawing and donating substitutions were compatible at R^1 (indoles **103**) and R^3 (carbamates **104**), furnishing excellent

yields of corresponding pyridinoindolines **105**. However, at R^4 only electron-rich alkyl groups were tolerated. In all examples, the obtained *trans*-diastereomer produces very poor *ee*'s. Evidently, the *trans*-product is barely affected by the chiral environment employed, which explains why Xiao could not successfully develop an asymmetric version.



Scheme 21. Enantioselective copper catalyzed decarboxylic propargylic dearomatization of indoles.

Table 1. Optimization conditions for 1,3-dimethylindole.

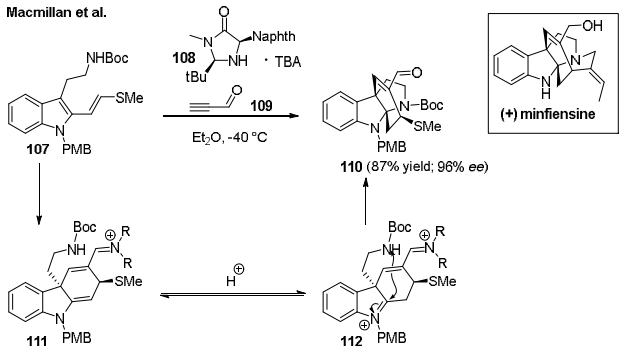
Entry	Ligand	Solvent	Yield [%]	d.r.	ee 127 [%]	ee 128 [%]
1	**L1**	MeOH	56	1:12.5	43	1
2	**L1**	toluene	67	5.5:1	-57	-9
3	**L2**	toluene	83	>1:19	-4	15
4	**L3**	toluene	85	14.3:1	84	4
5	**L4**	toluene	88	19:1	88	6
6[a]	**L4**	toluene	95	>19:1	89	9

[a]Amount of *i*PrNEt was reduced from 2.0 to 1.0 equiv. and reaction temperature was reduced from rt to 0 °C.

4. Synthesis of 2,3-fused pyrroloindolines

4.1. Diels-Alder type reaction

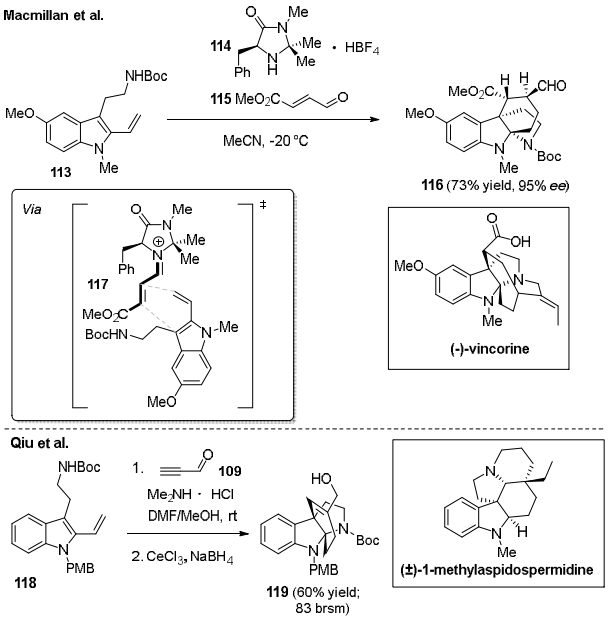
Generally, as discussed in section 3, the approaches based on a Diels-Alder reaction are very straightforward for the construction of pyridinoindolines. In addition to this, Macmillan and co-workers showed that the DA reaction can be used in an ingenious manner to access the 2,3-fused pyrroloindoline core (Scheme 22).[161] In their approach, the enamine **111** formed by an initial DA reaction of indole **107** and 2-propynal **109** tautomerizes to the corresponding iminium **112**. Subsequent nucleophilic interception of the tethered amine leads to efficient and stereoselective formation of the desired 2,3-fused pyrroloindoline **110**.



Scheme 22. Enantioselective DA cascade reaction towards minfiensine.

The key ingredient for success in this reaction cascade was the organocatalytic use of imidazolidinone **108**. The catalyst temporarily condenses with propynal creating a chiral environment while at the same time activating the aldehyde. The bulky naphthyl substituent gave optimal enantioselectivity due to the large shielding effect. Notably, the methodology was applied for a total synthesis of (+)-minfiensine in only 9 steps. (Scheme 22)

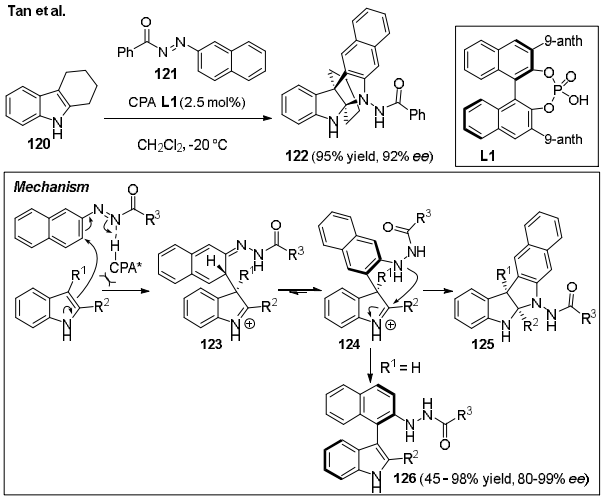
Somewhat later, an impressive total synthesis of (−)-vincorine was reported employing a similar strategy.[162] Four stereocenters were installed in a single operation including an all-carbon quaternary center (Scheme 23). This impressive cascade starts again with iminium formation **117**, derived from imidazolidinone **114** and aldehyde **115**. The imidazolidinonium group from the dienophile likely points outwards with respect to the indole species of diene **113**, which avoids an unfavorable clash of the bulky *gem*-dimethyl group with the aromatic system. The benzyl group of the organocatalyst then effectively shields one π-face from reacting, affording the *endo*-product **116** in good yield and stereoselectivity. Surprisingly, the counterion used for the ammonium organocatalyst salt, affected both the yield and *ee* dramatically. For example, employing the imidazolidinone hydrogenchloride salt (instead of HBF_4) resulted in much lower yields and *ee*. Likely, the less coordinating BF_4^- anion increases the electrophilicity of the dienophile. Later, Qiu and co-workers employed the same methodology in an attempt to prepare (±)-1-methylaspidospermidine. However, with the same organocatalyst pyrroloindoline **119** was obtained only poor yields and no enantioselectivity, even in the presence of various Lewis acids, were obtained. This is quite peculiar, since substrates **113** and **118** are structurally very close.



Scheme 23. DA cascade reactions towards complex alkaloids.

4.2. Nucleophilic aromatic substitution

In another approach, Tan and co-workers showed that a chiral phosphoric acid (CPA) can catalyze a nucleophilic aromatic substitution towards the 2,3-fused pyrroloindoline core of **122** (Scheme 24).[163] The initial dearomatization of **120** and **121** gives intermediate **123**. The large flat 9-anthracene groups in the CPA confine a space where the reaction can take place, effectively shielding one π-face. After re-aromatization the proximate amine then traps the iminium moiety of **124** and generate 2,3-alkylated pyrroloindolines **125** with execellent yields and *ee*. Remarkably, when R^1=H, indoleninium intermediate **124** re-aromatized, producing an aromatic 3-substititued indole bearing axial chirality **126** in excellent yield and *ee*.



Scheme 24. Nucleophilic aromatic substitution cascade reaction.

4.3. Transition-metal-catalyzed dearomatization

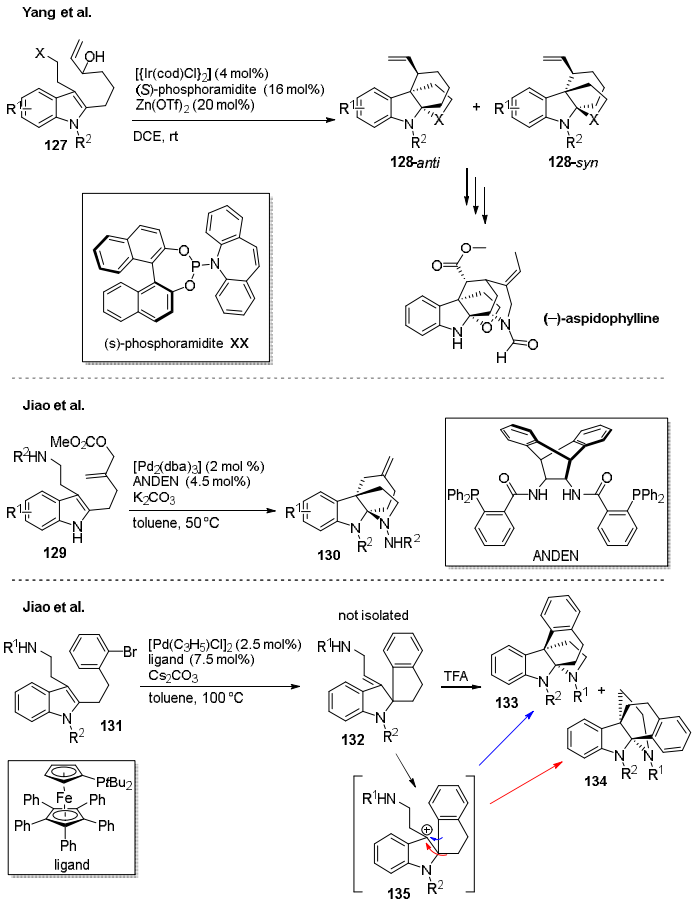
Transition metal based catalysts have been reliably used to dearomatize indoles and Yang and coworkers recognized the potential in asymmetric allyl substitutions.[164] With an allyl alcohol on a spacer at C2, the polycyclic indoline **128** was formed in high *ee* (generally >99%), albeit with poor diastereoselectivity (Scheme 25). This methodology was used in the total synthesis of natural (−)-aspidophylline. For this substrate **127** was dearomatized to a 5:1 diasteromeric mixture of **128** (*syn*:*anti*) in 98% and 95% *ee,* repectively. Surprisingly, the oxidative cleavage of the vinyl in this mixture provided a single diastereoisomer. A similar intramolecular allylation, with allyl-X tethered indole **129**, by Jiao and coworkers proved successful in forming pyrroloindoline **130**. Although the authors used a different catalytic system, they accomplished a total synthesis of (+)-minfiensine.[165]

The same authors demonstrated that a Heck coupling using C2 tethered arylbromides **131** is a feasible approach as well. This Heck coupling selectively cyclizes on the C2 position, rather than the C3 position. The resulting C2 spiroindoline **132** subsequently converts to pyrroloindolines **133** and **134** *via* cation **135** after treatment with TFA *via* an aza-semipinacol rearrangement, although the two regioisomers were obtained in low selectivity. The authors also attempted an asymmetric catalytic system, however, with poor *ee* (22%).[166]

4.4. Radical based dearomatizations

Next to these, Deng and Zhou *et al.* developed a radical dearomatization methodology using readily available indoles **136** and (*E*)-ferulic acid **137** under oxidative Cu(II) catalysis (Scheme 26). Unlike most mechanisms discussed in this review, the electron-rich indole double bond oxidizes to generate the pyrrolidine core bearing a radical at C3 **139**. This then reacts with the activated double bond of (*E*)-ferulic acid to give **140**. After subsequent pyrrolidine ring opening, the COO·radical closes to the C2 position yielding intermediate **141**. In the final step, another oxidation to **142** facilitates cyclization to form pyrroloindoline **138**.[167]

Recently, the group of Ding investigated a photo-Fries rearrangement in their cascade towards the pyrroloindolines **145**. By using a 300 W high-pressure mercury lamp (365 nm) the N–CO bond in indoles **143** is broken, followed by a cyclization of biradical **144** at the indole C3 position. When changing from a batch procedure to continuous flow, yields were significantly increased. The authors explored several substitutions patterns on several locations and utilized the methodology in the first total synthesis of (+)-alsmaphorazine C and a formal synthesis of (+)-strictamine.[168]



Scheme 25. Transition-metal-catalyzed dearomatization of indoles.

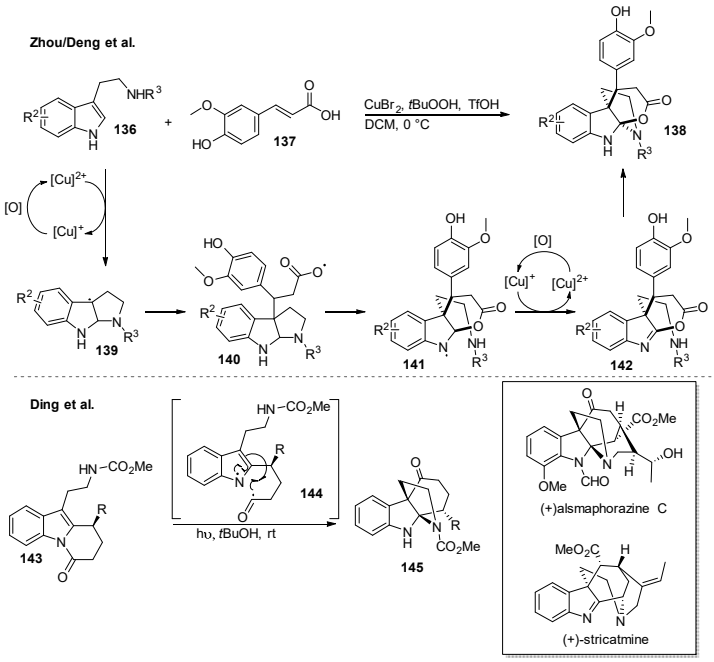
5. Synthesis of 3,3-spiropyrroloindolines

5.1. Gold alkyne catalysis

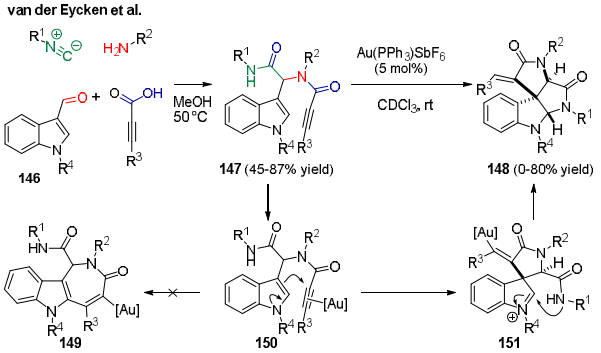
Rather complex 3,3-spiropyrroloindolines **148** were produced by Van der Eycken and co-workers *via* an elegant serendipitous cascade.[169] They first exploited the Ugi reaction indole-3-carboxaldehydes **146** to rapidly set the stage for a follow-up gold-catalyzed reaction (Scheme 27). Interestingly, they expected the formation of product **149** from conjugate addition to the propyolamide **150**. However, the gold catalyst activates the α-position instead, leading to a 5-*exo*-dig attack and forming intermediate **151**. Finally, the nearby amide functionality intramolecularly traps the imine moiety. The substitution pattern on Ugi products **147** proves flexible, which effectively results in a different location of the acyl group marked in blue.[170] The subsequent gold-catalyzed reaction is similar to earlier work, however, this time the amide functionality R^2 is positioned exocyclic. The yield could be increased significantly with the addition of one equivalent of TFA. The same group later demonstrated that AgOTf performed even better, as it accepted an even wider scope of substrates.[171]

5.2. Oxidative coupling

The Ugi reaction is a popular and effective strategy to set up a cascade reaction towards 3,3-spiropyrroloindolines. El Kaïm and co-workers also employed the Ugi reaction towards dipeptide **152** and provoked a subsequent oxidative coupling cascade in one-pot (Scheme 28).



Scheme 26. Radical based dearomatizations.

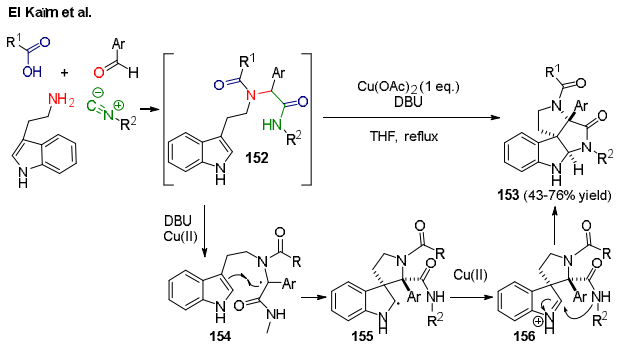


Scheme 27. Gold catalyzed addition to alkynes.

As a base, DBU can deprotonate the acidic α-hydrogen.[172] The accompanying stoichiometric copper acetate then induces a single electron oxidation of the enolate, leaving free radical **154** behind. The reactive radical propagates onto the indole ring to form spiroindoline **155** after which it is oxidized a second time to **156**. Finally, ring-closure of the amide provides product **153**. The aromatic substituent was required for the reaction to proceed, as aliphatic substituents would not render the α-proton acidic enough. Electron-withdrawing aromatic groups increase the yield of **153**. For *p*-nitrophenyl the reaction could even be carried out under acidic conditions at rt (Scheme 28).

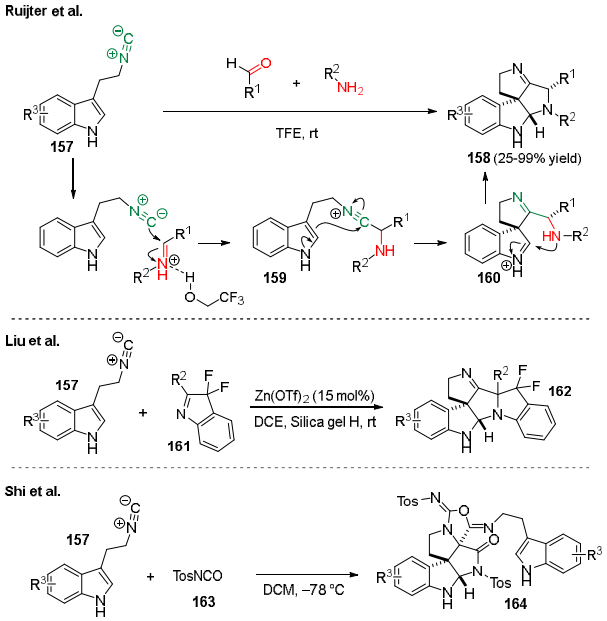
5.3. Interrupted Ugi type reaction

Next, our group contributed to a unique synthesis of a 3,3-spiropyrroloindolines as well.[173] Instead of relying on a two-step reaction sequence, a one-pot *interrupted* Ugi reaction was developed to generate the complex molecule in one chemical operation.



Scheme 28. Ugi-Oxidative coupling cascade to access 3,3-spiropyrroloindolines.

Usually, for the Ugi reaction an aldehyde, amine, isocyanide and a carboxylic acid are needed. However, instead of the carboxylic acid, the indole functionality of tryptamine-derived isocyanides **157** were used to intercept the nitrilium ion **159**, resulting in intermediate **160** (Scheme 29). The resulting indoleninium species is then intramolecularly trapped by the proximate amine to furnish tetracycle **158** as a single diastereoisomer. To compensate for the absence of a carboxylic acid, the imine was activated by the mildly acidic 2,2,2-trifluorethanol solvent. Liu *et al*. later showed that indolinenes **161** were also tolerated using $Zn(OTf)_2$ as the catalyst to give spiroindolines **162**.[174] The group of Shi reported that tosylisocyanates **163** are also tolerated in DCM at -78 °C. Unexpectedly, a second equivalent of isocyanide and isocyanate reacts with the newly formed imine to generate an extra heterocycle in product **164**.[175]



Scheme 29. Tryptamine derived isocyanides towards spiropyrroloindolines.

6. Conclusion and outlook

In this overview we discussed a range of creative and elegant syntheses towards cyclic 2-aminoindolines, which are complex heterocyclic scaffolds that occur in many alkaloids and other (poly)-heterocyclic products. By far the most popular approach comprises the dearomative cascade sequence

that initiates from the indole or tryptamine starting core. However, several interesting *bottom up* methodologies have been developed as well, including the interrupted Fischer type indolization. Moreover, multicomponent reactions in combination with a subsequent cascade reaction proved to be a powerful methodology to arrive at the desired (poly)-heterocycles. The initial multicomponent reaction is effective at setting in place functional groups for an ensuing domino reaction, which otherwise would take extensive additional synthetic steps.

Although many different routes towards cyclic 2-aminoindolines have been explored, we feel there is still room for improvement. Generally, total syntheses towards the complex akuammiline class of compounds are still relatively tedious. Macmillan made great progress in this field and exploited the imine/enamine tautomerization optimally. We personally think this cascading imine/enamine manipulation is the way to go for future endeavors in the synthesis of cyclic 2-aminoindolines.

References

1. Van Hattum, H.; Waldmann, H. *J. Am. Chem. Soc.* **2014**, *136* (34), 11853-11859.
2. Proudfoot, A. *Toxicological Reviews*. 2006, 99-138.
3. Realini, T. *Optometry and Vision Science*. 2011, 36-38.
4. Trost, B. M.; Osipov, M. *Chem. Eur. J.* **2015**, *21*, 16318-16343.
5. Mei, G.-J.; Koay, W. L.; Tanbc, C. X. A.; Lu, Y. *Chem. Soc. Rev.*, **2021**, *50*, 5985-6012.
6. Cao, Y.; Han, F.; Yang, D.; Zhao, D.; Kong, W.; Ma, Y.; Wang, L.; Sun, Q.; Li, D.; Wang, R. *Chem. Eur. J.* **2014**, *20*, 16478-16483.
7. Lin, T. Y.; Wu, H. H.; Feng, J. J.; Zhang, J. *ACS Catal.* **2017**, *7*, 4047-4052.
8. Shibata, N.; Tarui, T.; Doi, Y.; Kirk, K. L. *Angew. Chem. Int. Ed.* **2002**, *40*, 4461-4463.
9. Fujiwara, T.; Seki, T.; Yakura, T.; Takeuchi, Y. *J. Fluor. Chem.* **2014**, *165*, 7-13.
10. Lozano, O.; Blessley, G.; Martinez Del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 8105-8109.
11. Liang, X. W.; Liu, C.; Zhang, W.; You, S. L. *Chem. Commun.* **2017**, *53* (40), 5531-5534.
12. Yakura, T.; Nambu, H.; Fujiwara, T.; Nishimura, Y.; Yasuda, H. *RSC Adv.* **2014**, *5*, 5464-5473.
13. Matinkhoo, K.; Pryyma, A.; Todorovic, M.; Patrick, B. O.; Perrin, D. M. *J. Am. Chem. Soc.* **2018**, *140*, 6513-6517.
14. Pryyma, A.; Bu, Y. J.; Wai, Y.; Patrick, B. O.; Perrin, D. M. *Org. Lett.* **2019**, *21*, 8234-8238.
15. Egami, H.; Hotta, R.; Otsubo, M.; Rouno, T.; Niwa, T.; Yamashita, K.; Hamashima, Y. *Org. Lett.* **2020**, *22*, 5656-5660.
16. Wang, X.; Wang, S.; Xue, W.; Gong, H. *J. Am. Chem. Soc.* **2015**, *137* 36, 11562-11565.
17. Luo, S.; Zhang, S.; Shao, W.; Lu, Y.; Teng, F. Preparation method for physostigmine precursor compound, CN107129495 (A), September 5, 2017.
18. Horibe, T.; Ohmura, S.; Ishihara, K. *Org. Lett.* **2017**, *19*, 5525-5528.
19. Tu, D.; Ma, L.; Tong, X.; Deng, X.; Xia, C. *Org. Lett.* **2012**, *14*, 4830-4833.
20. Iwaki, T.; Yamada, F.; Funaki, S.; Somei, M. *Heterocycles* **2005**, *65*, 1811-1815.
21. Hakamata, H.; Sato, S.; Ueda, H.; Tokuyama, H. *Org. Lett.* **2017**, *19*, 5308-5311.
22. Zhang, D.; Song, H.; Liu, X.-Y.; Xiao, T.; Chen, Z.-T.; Qin, Y.; Deng, L.-F. *Chem. Commun.* **2017**, *53*, 12665-12667.
23. Xie, W.; Jiang, G.; Liu, H.; Hu, J.; Pan, X.; Zhang, H.; Wan, X.; Lai, Y.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12924-12927.
24. López, C. S.; Pérez-Balado, C.; Rodríguez-Graña, P.; De Lera, Á. R. *Org. Lett.* **2008**, *10*, 77-80.
25. Peng, Y.; Luo, L.; Yan, C. S.; Zhang, J. J.; Wang, Y. W. *J. Org. Chem.* **2013**, *78*, 10960-10967.
26. Wada, M.; Murata, T.; Oikawa, H.; Oguri, H. *Org. Biomol. Chem.* **2014**, *12*, 298-306.
27. Welch, T. R.; Williams, R. M. *Tetrahedron* **2013**, *69*, 770-773.
28. Iwasa, E.; Hamashima, Y.; Fujishiro, S.; Hashizume, D.; Sodeoka, M. *Tetrahedron* **2011**, *67*, 6587-6599.
29. Feng, X.; Jiang, G.; Xia, Z.; Hu, J.; Wan, X.; Gao, J. M.; Lai, Y.; Xie, W. *Org. Lett.* **2015**, *17*, 4428-4431.
30. Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238-241.

31. Sato, S.; Tokuyama, H.; Kawauchi, D.; Hirayama, A.; Adachi, T.; Ueda, H. *Heterocycles* **2017**, *94*, 1940.
32. Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 9655-9659.
33. Sun, Y.; Li, R.; Zhang, W.; Li, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9201-9204.
34. Lindovska, P.; Movassaghi, M. *J. Am. Chem. Soc.* **2017**, *139*, 17590-17596.
35. Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940-14943.
36. Loach, R. P.; Fenton, O. S.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 1057-1064.
37 Denizot, N.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Eur. J.* **2015**, *21*, 18953-18956.
38. Lathrop, S. P.; Pompeo, M.; Chang, W. T. T.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 7763-7769.
39. Olaizola, I.; Abdine, R. A. A.; Dhimane, H.; Dalko, P. I. *Synthesis* **2017**, *49*, 391-396.
40. Xua, J.; Tong, R. *Green Chem.* **2017**, *19*, 2952-2956.
41. Movassaghi, M.; Lindovska, P. Diazene Directed Modular Synthesis of Compounds With Quaternary Carbon Centers WO2017205539 (A1), November 30, 2017.
42. Liu, K.; Jiang, H.-J.; Li, N.; Li, H.; Wang, J.; Zhang, Z.-Z.; Yu, J. *J. Org. Chem.* **2018**, *83*, 6815-6823.
43. Grubbs, A. W.; Artman, G. D.; Tsukamoto, S.; Williams, R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2257-2261.
44. Beniddir, M. A.; Martin, M. T.; Tran Huu Dau, M. E.; Grellier, P.; Rasoanaivo, P.; Guéritte, F.; Litaudon, M. *Org. Lett.* **2012**, *14*, 4162-4165.
45. May, J. P.; Fournier, P.; Pellicelli, J.; Patrick, B. O.; Perrin, D. M. *J. Org. Chem.* **2005**, *70*, 8424-8430.
46. Rominger, F.; Yu, Y.; Yang, W.; Hashmi, A. S. K.; Pflästerer, D.; Huang, L. *Chem. Eur. J.* **2014**, *20*, 3927-3931.
47. Adhikari, A. A.; Chisholm, J. D. *Org. Lett.* **2016**, *18*, 4100-4103.
48. Pedras, M. S.; Okanga, F. I. *Can. J. Chem.* **2011**, *78*, 338-346.
49. Yamada, F.; Goto, A.; Hasegawa, M.; Kobayashi, K.; Somei, M. *Heterocycles* **2017**, *95*, 844-861.
50. Molęda, Z.; Wojtasiewicz, K.; Panasiewicz, M.; Czarnocki, Z. *J. Pineal Res.* **2010**, *49*, 55-59.
51. Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629.
52. Galli, R.; Dobler, M.; Güller, R.; Stahl, R.; Borschberg, H. J. *Helv. Chim. Acta* **2002**, *85*, 3400-3413.
53. Yamada, F.; Fukui, Y.; Iwaki, T.; Ogasawara, S.; Okigawa, M.; Tanaka, S.; Somei, M. *Heterocycles* **2006**, *67*, 129-134.
54. Itakura, K.; Uchida, K.; Kawakishi, S. *Tetrahedron Lett.* **1992**, *33*, 2567-2570.
55. Yamaguchi, K.; Nakagawa, M.; Ito, M.; Sodeoka, M.; Hino, T.; Taniguchi, M. *Heterocycles* **2009**, *21*, 406-406.
56. Ghosh, S. K.; Nagarajan, R. *RSC Adv.* **2014**, *4*, 63147-63149.
57. Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964-11975.
58. Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2995-2998.
59. Liu, Z.; Zhang, K.; Chen, G.; Ding, H.; Zhu, C. *Angew. Chem. Int. Ed.* **2014**, *54*, 879-882.
60. Liu, Z.; Zhang, K.; Chen, G.; Ding, H.; Zhu, C. *Angew. Chem. Int. Ed.* **2014**, *54*, 879-882.
61. Kanai, M.; Oisaki, K.; Sohma, Y.; Ishiyama, T.; Sasaki, D.; Seki, Y.; Abe, J. *J. Am. Chem. Soc.* **2016**, *138*, 10798-10801.
62. Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199-3202.
63. Żytek, M.; Zawadzka, A.; Czarnocki, Z.; Pluciński, F.; Molęda, Z.; Madej, D.; Maurin, J. K. *Comptes Rendus Chim.* **2013**, *16*, 807-813.
64. An, J.; Zou, Y. Q.; Yang, Q. Q.; Wang, Q.; Xiao, W. J. *Adv. Synth. Catal.* **2013**, *355*, 1483-1489.
65. Luo, S. P.; Peng, Q. L.; Xu, C. P.; Wang, A. E.; Huang, P. Q. *Chinese J. Chem.* **2014**, *32*, 757-770.
66. Deng, X.; Liang, K.; Tong, X.; Ding, M.; Li, D.; Xia, C. *Tetrahedron* **2015**, *71*, 3699-3704.
67. Deng, X.; Liang, K.; Tong, X.; Ding, M.; Li, D.; Xia, C. *Org. Lett.* **2014**, *16*, 3276-3279.
68. Yongxin, Z. R.; Qingliang, Y.; Yuanyuan, H.; Shun, G.; Hangbo, Y.; Chengyu, Y.; Huihui, G.; Xiaomai, Z.; Hongsheng, X.; Qianqian, T.; Minjun, C.; Linyao, Z.; Junxiang, J.; Wenjun, L.; Xiaotao, Z.; Chen, L.; Yifang, X; Zixiang, G. Derivatives of Amanita Toxins and Their Conjugation To a Cell Binding Molecule, WO2017046658 (A1), March, 23, 2017.

69. May, J. P.; Patrick, B. O.; Perrin, D. M. *Synlett* **2006**, *2006*, 23403-3406.
70. Blanc, A.; Xia, F.; Todorovic, M.; Perrin, D. M. *Amino Acids* **2017**, *49*, 407-414.
71. Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 3394-3402.
72. Ding, M.; Liang, K.; Pan, R.; Zhang, H.; Xia, C. *J. Org. Chem.* **2015**, *80*, 10309-10316.
73. Yang, Z.-P.; He, Q.; Ye, J.-L.; Huang, P.-Q. *Org. Lett.* **2018**, *20*, 4200-4203.
74. Cheng, Y.-Z.; Zhao, Q.-R.; Zhang, X.; You, S.-L. *Angew. Chem. Int. Ed.* **2019**, *58*, 18069-18074.
75. Quintero, L.; Vázquez, A. B.; Meza-León, R. L.; Ortíz, A.; Bernès, S. *Tetrahedron Lett.* **2009**, *50*, 1539-1541.
76. Xiao, J.; Lu, Y. P.; Liu, Y. L.; Wong, P. S.; Loh, T. P. *Org. Lett.* **2011**, *13*, 876-879.
77. Burgaud, B. G. M.; Horwell, D. C.; Pritchard, M. C.; Bernad, N.; Martinez, J. *Tetrahedron Asymmetry* **1995**, *6*, 1081-1084.
78. Xiao, J.; Loh, T.-P. *Tetrahedron Lett.* **2008**, *49*, 7184-7186.
79. Ashwood, V. A.; Field, M. J.; Horwell, D. C.; Julien-Larose, C.; Lewthwaite, R. A.; McCleary, S.; Pritchard, M. C.; Raphy, J.; Singh, L. *J. Med. Chem.* **2001**, *44*, 2276-2285.
80. Hernández, F.; Avendaño, C.; Söllhuber, M. *Tetrahedron Lett.* **2003**, *44*, 3367-3369.
81. Coste, A.; Toumi, M.; Wright, K.; Razafimahaléo, V.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 3841-3844.
82. Taniguchi, M.; Hino, T. *Tetrahedron* **2002**, *37*, 1487-1494.
83. Bourne, G. T.; Crich, D.; Davies, J. W.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **2004**, 1693-1699.
84. Ruiz-Sanchis, P.; Savina, S. A.; Acosta, G. A.; Albericio, F.; Álvarez, M. *Eur. J. Org. Chem.* **2012**, *2012*, 67-73.
85. Bergman, J.; Tilstam, U.; Törnroos, K.-W. *J. Chem. Soc., Perkin Trans. 1* **2004**, 519-527.
86. Caballero, E.; Avendaño, C.; Menéndez, J. C. *Tetrahedron Asymmetry* **1998**, *9*, 967-981.
87. Pfaffenbach, M.; Roller, A.; Gaich, T. *Chem. Eur. J.* **2016**, *22*, 8444–8447.
88. Tayu, M.; Suzuki, Y.; Higuchi, K.; Kawasaki, T. *Synlett* **2016**, *27*, 941-945.
89. Hewitt, P. R.; Cleator, E.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 2415-2417.
90. Ley, S. V.; Cleator, E.; Hewitt, P. R. *Org. Biomol. Chem.* **2003**, *1*, 3492-3494.
91. Wei, Q.; Wang, Y.-Y.; Du, Y.-L.; Gong, L.-Z. *Beilstein J. Org. Chem.* **2013**, *9*, 1559-1564.
92. Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1999**, *121*, 11953-11963.
93. Beaumont, S.; Pons, V.; Retailleau, P.; Dodd, R. H.; Dauban, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 1634-1637.
94. Nelson, H. M.; Reisberg, S. H.; Shunatona, H. P.; Patel, J. S.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5600-5603.
95. Stephens, D. E.; Larionov, O. V. *Eur. J. Org. Chem.* **2014**, *2014*, 3662-3670.
96. Shen, Z.; Xia, Z.; Zhao, H.; Hu, J.; Wan, X.; Lai, Y.; Zhu, C.; Xie, W. *Org. Biomol. Chem.* **2015**, *13*, 5381-5384.
97. Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999-2001.
98 Mori, I.; Baran, P. S.; Newhouse, T.; Foo, K.; Takayama, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716-2719.
99. Zhang, P.; Sun, W.; Li, G.; Hong, L.; Wang, R. *Chem. Commun.* **2015**, *51*, 12293-12296.
100. Tayu, M.; Ishizaki, T.; Higuchi, K.; Kawasaki, T. *Org. Biomol. Chem.* **2015**, *13*, 3863-3865.
101. Li, Q; Xia, T.; Yao, L.; Deng, H.; Liao, X. *Chem. Sci.* **2015**, *6*, 3599-3605.
102. Zhang, Z.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 11778-11782.
103. Yi, J.-C.; You, S.-L.; Zheng, Z.-B.; Liu, C.; Tang, Y.; Dai, L.-X. *Angew. Chem. Int. Ed.* **2015**, *55*, 751-754.
104. Cai, Z. J.; Wang, S. Y.; Ji, S. J. *Org. Lett.* **2013**, *15*, 5226-5229.
105. Guo, J.; Chen, S.; Liu, J.; Guo, J.; Chen, W.; Cai, Q.; Liu, P.; Sun, P. *Eur. J. Org. Chem.* **2017**, *2017*, 4773-4777.
106. Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119-7137.

107. Liu, C.; Yi, J.-C.; Zheng, Z.-B.; Tang, Y.; Dai, L.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2016**, *55*, 751-754.
108. Zhang, G.-Y.; Peng, Y.; Xue, J.; Fan, Y.-H.; Deng, Q.-H. *Org. Chem. Front.* **2019**, *6*, 3934-3938.
109. Nakagawa, M.; Kato, S.; Kataoka, S.; Kodato, S.; Watanabe, H.; Okajima, H.; Hino, T.; Witkop, B. *Chem. Pharm. Bull.* **1981**, *29*, 1013-1026.
110. Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675-678.
111. Yi, J. C.; Liu, C.; Dai, L. X.; You, S. L. *Chem. Asian J.* **2017**, *12*, 2975-2979.
112. Liu, C.; Yi, J.-C.; Dai, L.-X.; You, S.-L. *Asian J. Org. Chem.* **2017**, *6*, 1201-1204.
113. Liu, C.; Yin, Q.; Dai, L. X.; You, S. L. *Chem. Commun.* **2015**, *51*, 5971-5974.
114. Kandukuri, S. R.; Bahamonde, A.; Chatterjee, I.; Jurberg, I. D.; Escudero-Adán, E. C.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 1485-1489.
115. Dix, A. V.; Meseck, C. M.; Lowe, A. J.; Mitchell, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2522-2524.
116. May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203-1205.
117. Menozzi, C.; Dalko, P. I.; Cossy, J. *Chem. Commun.* **2006**, *44*, 4638-4640.
118. Olaizola, I.; Abdine, R. A. A.; Dhimane, H.; Dalko, P. I. *Synthesis* **2017**, *49*, 391-396.
119. Han, S. J.; Vogt, F.; May, J. A.; Krishnan, S.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *J. Org. Chem.* **2015**, *80*, 528-547.
120. Herrera, L.; Stephens, D. E.; D'Avila, A.; George, K. G.; Arman, H.; Zhang, Y.; Perry, G.; Lleonart, R.; Larionov, O. V.; Fernández, P. L. *Org. Biomol. Chem.* **2016**, *14*, 7053-7060.
121. Muthusubramanian, P.; Carlé, J. S.; Christophersen, C. *Acta Chem. Scandinavica B* **1983**, *37*, 803-807
122. Lin, A.; Yang, J.; Hashim, M. *Org. Lett.* **2013**, *15*, 1950-1953.
123. a) Liu, C.; Yi, J.-C.; Liang, X.-W.; Xu, R.-Q.; Dai, L.-X.; You, S.-L. *Chem. Eur. J.* **2016**, *22*, 10813-10816. b) Yi, J.-C.; Liu, C.; Dai, L.-X.; You, S.-L. *Chem. Asian J.* **2017**, *12*, 2975-2979.
124. Rose, T. E.; Curtin, B. H.; Lawson, K. V.; Simon, A.; Houk, K. N.; Harran, P. G. *Chem. Sci.* **2016**, *7*, 4158-4166.
125. Jamison, C. R.; Badillo, J. J.; Lipshultz, J. M.; Comito, R. J.; MacMillan, D. W. C. *Nat. Chem.* **2017**, *9*, 1165-1169.
126. Kimura, M.; Tohyama, K.; Yamaguchi, Y.; Kohno, T. *Heterocycles* **2010**, *80*, 787-797.
127. Zhang, H.; Hu, R. Bin; Liu, N.; Li, S. X.; Yang, S. D. *Org. Lett.* **2016**, *18*, 28-31.
128. Gao, S.; Wu, Z.; Fang, X.; Lin, A.; Yao, H. *Org. Lett.* **2016**, *18*, 3906-3909.
129. Mazza, A.; Beccalli, E. M.; Contini, A.; Garcia-Argaez, A. N.; Dalla Via, L.; Gelmi, M. L. *Eur. J. Med. Chem.* **2016**, *124*, 326-339.
130. Rose, T. E.; Curtin, B. H.; Lawson, K. V.; Simon, A.; Houk, K. N.; Harran, P. G. *Chem. Sci.* **2016**, *7*, 4158-4166.
131. Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111-114.
132. Zhang, X.; Han, L.; You, S.-L. *Chem. Sci.*, **2014**, *5*, 1059-1063.
133. Zhang, X.; Liu, W. B.; Tu, H. F.; You, S. L. *Chem. Sci.* **2015**, *6*, 4525-4529.
134. Jia, M.; Cera, G.; Perrotta, D.; Monari, M.; Bandini, M. *Chem. Eur. J.* **2014**, *20*, 9875-9878.
135. Shen, Z. Q.; Li, X. X.; Shi, J. W.; Chen, B. L.; Chen, Z. *Tetrahedron Lett.* **2015**, *56*, 4080-4083.
136. Battistoni, F.; Piersanti, G.; Lucarini, S.; Diamantini, G.; Spadoni, G.; Bartoccini, F.; Righi, M. *Org. Lett.* **2010**, *12*, 3844-3847.
137. Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418-14420.
138. Wang, H.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2014**, *53*, 6206-6210.
139. Shu, C.; Liao, L. H.; Liao, Y. J.; Hu, X. Y.; Zhang, Y. H.; Yuan, W. C.; Zhang, X. M. *Eur. J. Org. Chem.* **2014**, *2014*, 4467-4471.
140. DiPoto, M. C.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14861-14864.
141. Ji, W.; Yao, L.; Liao, X. *Org. Lett.* **2016**, *18*, 628-630.
142. Anumandla, D.; Acharya, A.; Jeffrey, C. S. *Org. Lett.* **2016**, *18*, 476-479.
143. Liu, X.; Yang, D.; Wang, K.; Zhang, J.; Wang, R. *Green Chem.* **2017**, *19*, 82-87.
144. Chai, Z.; Zhu, Y.-M.; Yang, P.-J.; Wang, S.; Wang, S.; Liu, Z.; Yang, G. *J. Am. Chem. Soc.* **2015**, *137*, 10088−10091.

145. Wang, L.; Yang, D.; Han, F.; Li, D.; Zhao, D.; Wang, R. *Org. Lett.* **2015**, *17*, 176-179.
146. Rivinoja, D. J.; Gee, Y. S.; Gardiner, M. G.; Ryan, J. H.; Hyland, C. J. T. *ACS Catal.* **2017**, *7*, 1053-1056.
147. Mei, G.-J.; Tang, X.; Tasdan, Y.; Lu, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 648-652.
148. Yonemitsu, O.; Cerutti, P.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 3941-3945.
149. Pfaffenbach, M.; Gaich, T. *Chem. Eur. J.* **2015**, *21*, 6355-6357.
150. Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6802-6805.
151. Alford, J. S.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 10266-10269.
152 Bunders, C.; Cavanagh, J.; Melander, C. *Org. Biomol. Chem.* **2011**, *9*, 5476-5481.
153. May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 5262-5271.
154. Robertson, F. J.; Kenimer, B. D.; Wu, J. *Tetrahedron* **2011**, *67*, 4327-4332.
155. Luo, M.; Chen, J.; Yu, L. Wei, W. *Eur. J. Org. Chem.* **2017**, *2017*, 2652-2660.
156. Clarke, S. J.; Gilchrist, T. L.; Lemos, A.; Roberts, T. G. *Tetrahedron* **1991**, *47*, 5615-5624.
157. Lopes, S. M. M.; Brigas, A. F.; Palacios, F.; Lemos, A.; Pinho E Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, *2012*, 2152-2160.
158. Huang, R.; Tong, M.-C.; Chen, X.; Li, J.; Wang, C.-J.; Tao, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 4680-4684.
159. Li, T. R.; Lu, L. Q.; Wang, Y. N.; Wang, B. C.; Xiao, W. J. *Org. Lett.* **2017**, *19*, 4098-4101.
160. Shao, W.; You, S. L. *Chem. Eur. J.* **2017**, *23*, 12489-12493.
161. Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606-13607.
162. Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442-6445.
163. Qi, L. W.; Mao, J. H.; Zhang, J.; Tan, B. *Nat. Chem.* **2018**, *10*, 58-64.
164. Jiang, S.-Z.; Zeng, X.-Y.; Liang, X; Lei, T.; Wei, K.; Yang, Y.-R. *Angew. Chem. Int. Ed.* **2016**, *55*, 4044-4048.
165. Zhang, Z.-X.; Chen, S.-C.; Jiao, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 8090-8094.
166. Gao, D.; Jiao, L. *J. Org. Chem.* **2021**, *86*, 5727-5743.
167. Cao, W.; Fan, J.; Yan, L.; Zeng, G.; Ma, J. Wang, Y.; Zhou, Y.; Deng, X. *Org. Lett.* **2019**, *21*, 9506-9511.
168. Gao, B.; Yao, F.; Zhang, Z.; Ding, H. *Angew. Chem. Int. Ed.* **2021**, *60*, 10603-10607
169. Modha, S. G.; Kumar, A.; Vachhani, D. D.; Jacobs, J.; Sharma, S. K.; Parmar, V. S.; Van Meervelt, L.; Van Der Eycken, E. V. *Angew. Chem. Int. Ed.* **2012**, *51*, 9572-9575.
170. Kumar, A.; Vachhani, D. D.; Modha, S. G.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *Beilstein J. Org. Chem.* **2013**, *9*, 2097-2102.
171. Zaman, M.; Hasan, M.; Peshkov, A. A.; Van Hecke, K.; Van der Eycken, E. V.; Pereshivko, O. P.; Peshkova, V. A. *Adv. Synth. Catal.* **2020**, *362*, 261-268.
172. El Kaïm, L.; Grimaud, L.; Le Goff, X. F.; Menes-Arzate, M.; Miranda, L. D. *Chem. Commun.* **2011**, *47*, 8145-8147.
173. Saya, J. M.; Oppelaar, B.; Cioc, R. C.; van der Heijden, G.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. *Chem. Commun.* **2016**, *52*, 12482-12485.
174. Liu, Y.-L.; Mao, X.-Y.; Lin, X.-T.; Chen, G.-S. *Org. Chem. Front.* **2018**, *5*, 2303-2307.
175. Li, L.; Liu, J.; Shi, M. *Org. Lett.* **2018**, *20*, 7076-7079.