Pictet–Spengler-Based Multicomponent Domino Reactions to Construct Polyheterocycles

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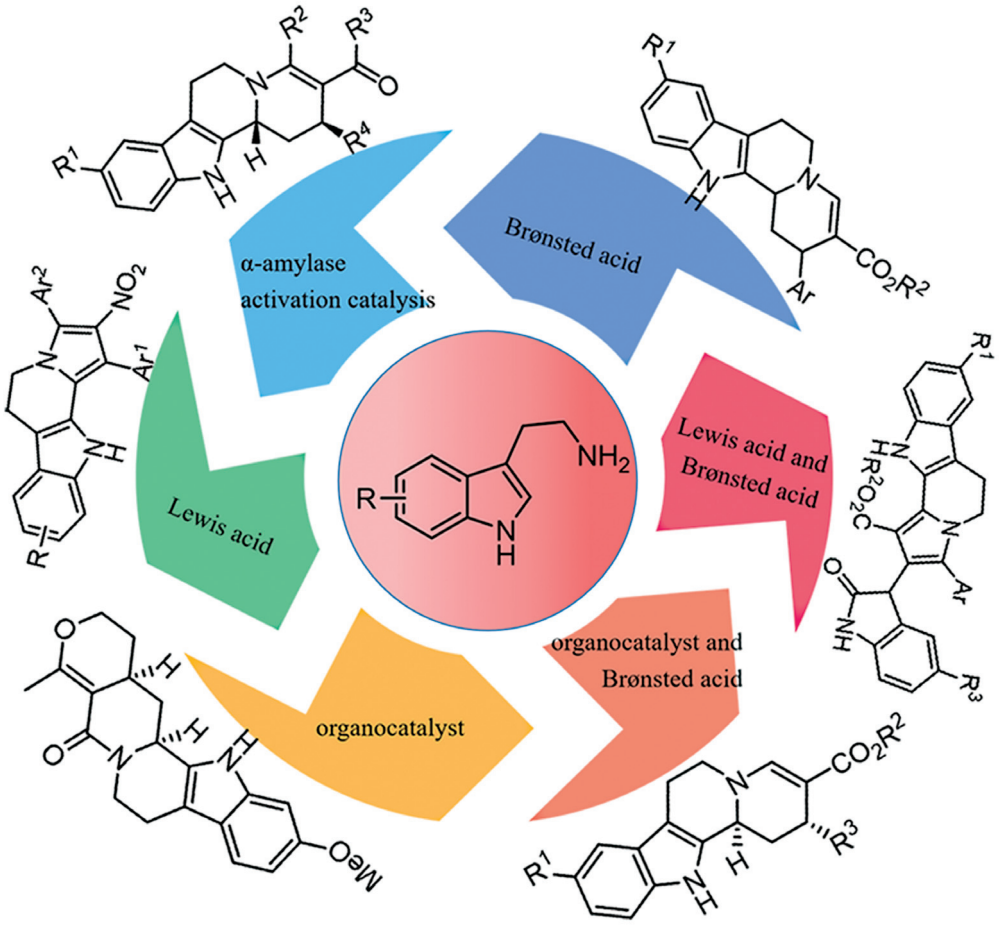

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Abstract

The Pictet–Spengler reaction is one of the important methodological arsenals in synthetic and medicinal chemistry, acting as an amenable tool for preparing tetrahydroisoquinoline, tetrahydro-β-carbolines, polycyclic skeletons, and value-added products. More than 100 years after its initial discovery, the Pictet–Spengler reaction's response has not withdrawn from the stage, but it has once again become the focus of attention with new features. The review summarizes recent advances in Pictet–Spengler-based multicomponent reactions from 2007 to 2022, including three-component and four-component Pictet–Spengler cyclization reactions in the presence of metal catalysts, organocatalysts, biological enzyme catalysts, and so on. These Pictet–Spengler-based multicomponent protocols provide an atom-/step economic approach for the synthesis of a library of new chemical entities.

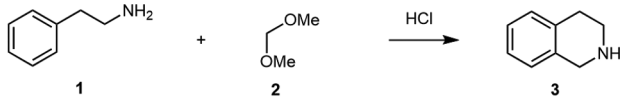
Keywords

- Pictet–Spengler reaction
- multicomponent reactions
- domino reactions
- cyclization
- heterocycles

Introduction

The Pictet–Spengler reaction, discovered in 1911 by Amé Pickett and Theodore Spengler, is originally a cyclization of a phenethylamine **1** and a formaldehyde dimethyl acetal **2** to produce 1,2,3,4-tetrahydroisoquinoline **3** in the presence of hydrochloric acid (►**Scheme 1**).[1] After that, a variety of modified reaction systems for the Pictet–Spengler reaction have been developed for the construction of valuable heterocyclic scaffolds,[2] such as Brønsted acids,[3–38] Lewis acids,[39–41] transition metal catalysts,[42–46] organocatalysts,[26,27,47,48] and enzyme strictosidine synthases.[13,49] Meanwhile, the use of suitably substituted amine derivatives such as β-arylethylamines, tryptamines, or functionalized aromatic amines with an aldehyde or ketone is essential for the progress of the Pictet–Spengler reaction.[50] Furthermore, the post-Pictet–Spengler cyclization strategy has been extensively employed in the preparation of stereochemically and structurally complex polycyclic heterocycles which have been found to exhibit significant biological activities.[51–54]

In addition, the development of synthetic platforms to prepare compounds with minimum effort and exceptional synthetic efficiency is crucial for the discovery of new bioactive molecules. In this context, multicomponent reactions that significantly reduce the step of synthetic operations and diminish the generation of waste provide an alternative method to give complex and diverse products.[55–58] Over the past decades, great effort has been devoted to the design and development of multicomponent reactions, in particular in the field of the synthesis of heterocycles.[59–62] Although there are many literature reviews involving multicomponent reactions and Pictet–Spengler reactions,[63] the use of Pictet–Spengler cyclization-based multicomponent reactions in the generation of polyheterocycles has rarely been touched in previous reviews.



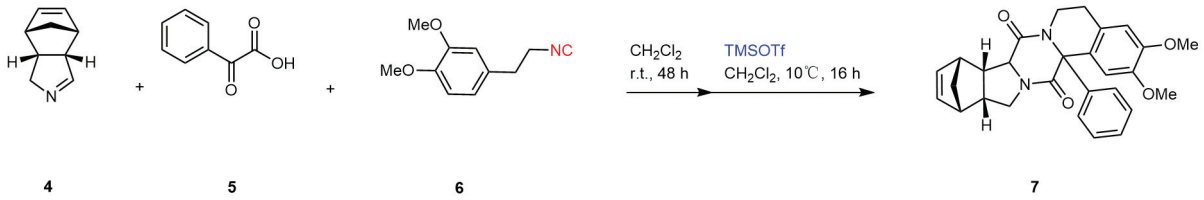
Scheme 1 The Pictet–Spengler reaction.

In 2020, Calcaterra and coworkers published a review on the construction of polycyclic β-carboline-derived natural products and bioactive *N*-heterocycles using post-Pictet–Spengler cyclization strategies.[64–67] Considering significant progress of Pictet–Spengler cyclization-based multicomponent reactions has been made and still no related review has been documented, this review is devoted to a discussion of this research area, covering mainly the literature from 2007 to 2022, and is divided into two categories: three-component and four-component Pictet–Spengler cyclization-based domino reactions including the Brønsted acid and Lewis acid-promoted, transition metal-catalyzed and organo-catalyzed methodologies.

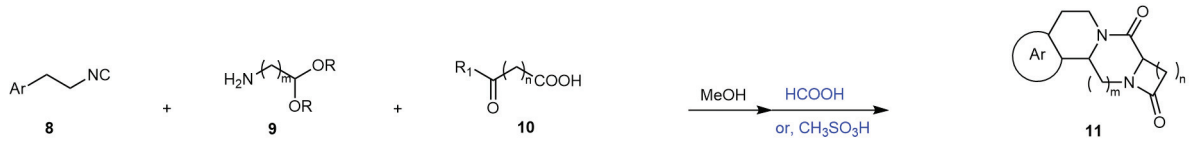
Three-Component Pictet–Spengler Cyclization-Based Domino Reactions

As known, the classic Pictet–Spengler reaction involving two-component cyclization is not beneficial for the exploration of the chemical space of target products. The combination of the Pictet–Spengler reaction with the multicomponent reaction has been proven to be an economic and practical approach for the construction of highly complex and diverse scaffolds in a single operation. For example, in 2010, Znabet and coworkers demonstrated the domino Ugi-type multicomponent reaction/Pictet–Spengler cyclization strategy using a bridged imine **4**, a phenylglyoxylic acid **5**, and an isonitrile **6** for the construction of alkaloid-like polycyclic compound **7** (►**Scheme 2**).[68] In the reaction, the Ugi-type adduct was first formed in dichloromethane at room temperature for 48 hours, then the mixture reacted at 10°C for 16 hours under trimethylsilyl fluorosulfonic acid conditions to obtain the desired product in good yield.

In 2011, Wang and coworkers developed an alternative approach to access polycyclic compounds through a concise two-step procedure including an Ugi-type reaction and subsequent Pictet–Spengler reaction (►**Scheme 3**).[69] The first step was the Ugi-type reaction of phenylethylamine-derived isonitriles **8**, aminoacetaldehyde dimethyl acetal **9**, and a suitable bifunctional oxocarboxylic acid **10**, followed by the Pictet–Spengler reaction in the presence of formic acid at room temperature or methanesulfonic acid at 70°C.



Scheme 2 Ugi-type/Pictet–Spengler-type cyclization sequence.



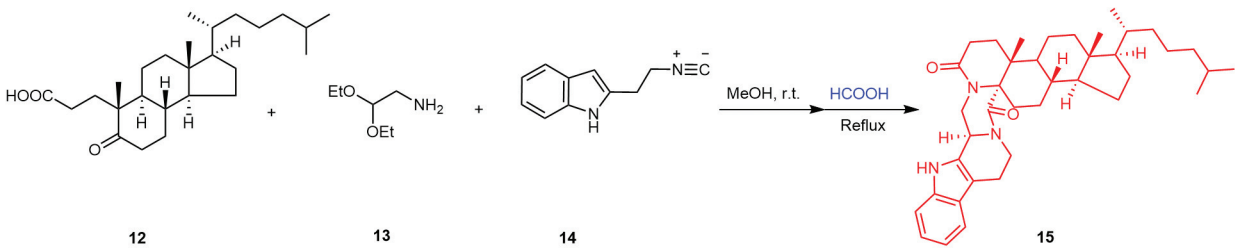
Scheme 3 Ugi-type/Pictet–Spengler sequence to polycyclic compounds.

Recently, Alonso et al also used formic acid as a catalyst to promote the three-component domino Ugi-type/Pictet–Spengler reaction.[70] As shown in ►**Scheme 4**, the steroidal pyrazinoisoquinolines **15** were obtained from cholesterol-based oxalic acid **12**, 2,2-diethoxyethylamine **13**, and 3-(2-isocyanatoethyl)-1*H*-indole **14** by applying a synthetic sequence comprising the Ugi reaction followed by a Pictet–Spengler cyclization using formic acid at reflux conditions to generate the compound **15**.

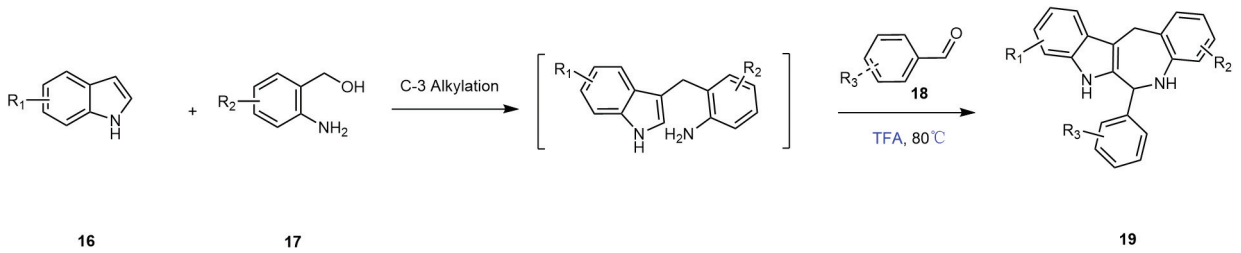
Furthermore, Kundu's group described a one-pot method for the synthesis of benzazepino-indoles from indoles **16**, 2-aminobenzyl alcohols **17**, and benzaldehydes **18** (►**Scheme 5**).[71] In this reaction, alkylation and subsequent Pictet–Spengler reaction in trifluoroacetic acid (TFA; 30% in DCE) at 80°C afforded the target products **19** in moderate to good yields. Interestingly, when 2-alkynylbenzaldehydes were introduced, the product benzazepino-indole then underwent a second consecutive ring closure through intramolecular hydroamination to access indole-based annulated polyheterocycles.

In 2018, Yan's group reported a trifluoromethanesulfonic acid-promoted one-pot domino reaction of tryptamines **20**, alkyl propionates **21**, and 2-aryl-3-nitro-2H-chromenes **22**, which can conveniently yield the functionalized tetrahydrochromeno [4′,3′:2,3]indolizino [8,7-*b*]indoles **23** in high yields (►**Scheme 6**).[72] Using nitroolefins instead of 2-aryl-3-nitro-2H-chromenes, the corresponding tetrahydroindolizino[8,7-*b*]indoles were obtained under similar conditions. In this one-pot three-step reaction, the domino process of double Michael addition, Pictet–Spengler reaction, and annulation was performed, which has the advantages of high atomic economy.

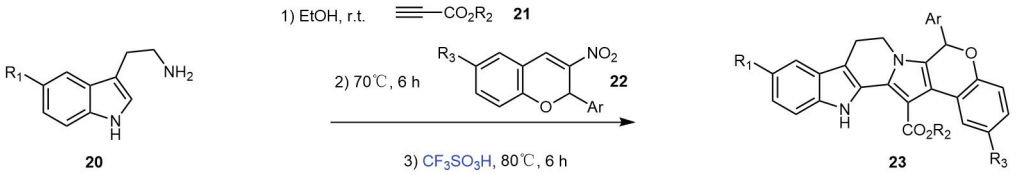
In 2019, Ali et al reported a one-pot two-step approach for the generation of pyrrolo[1,2-*a*][1,4]benzodiazepines under



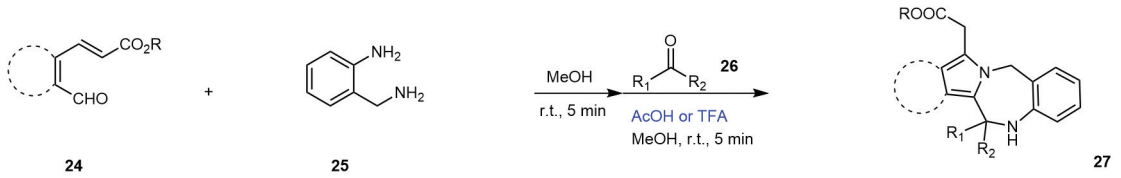
Scheme 4 Sequential Ugi-type/Pictet–Spengler reaction.



Scheme 5 Tandem alkylation/Pictet–Spengler reaction.



Scheme 6 One-pot double Michael addition/Pictet–Spengler/annulation.

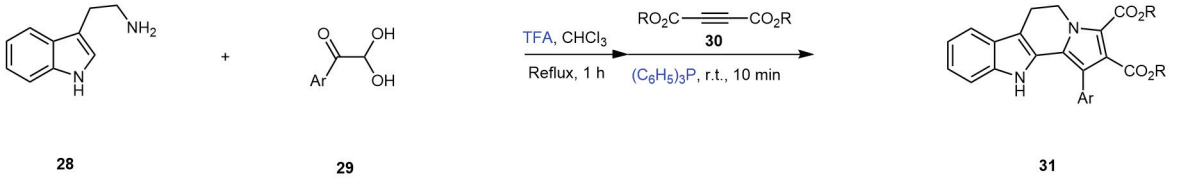


Scheme 7 One-pot domino annulation/Pictet–Spengler reaction.

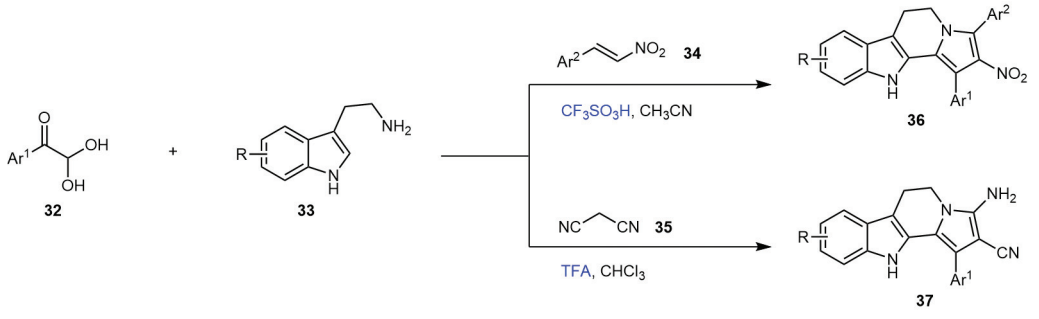
mild conditions (►**Scheme 7**).[73] First step of the reaction was that the 3-(3-formyl cycloalkenyl)-acrylate derivatives **24** were reacted with amino benzylamines **25** in methanol for 5 minutes to give pyrrole intermediates (up to 95% yield). Then, aldehydes or ketones **26** were added to the reaction system, and the desired products were obtained in 70 to 92% yields by acetic acid or TFA-promoted Pictet–Spengler cyclization. This method has several advantages, such as a very short time, step and atom economic, and environmentally benign.

Subsequently in the year 2021, Peytam et al reported an efficient one-pot two-step reaction of tryptamine **28**, arylglyoxal monohydrates **29**, and acetylenic esters **30**, which led to the formation of 18 dihydroindolizino[8,7-*b*]indole derivatives **31** with good to excellent yields (►**Scheme 8**).[74] First, the TFA-promoted Pictet–Spengler cyclization of tryptamine and arylglyoxal monohydrates was conducted in chloroform for 1 hour to from an intermediate. Then, the 1,3-dipolar cycloaddition reaction of the intermediate with acetylenic esters afforded the target compounds, which were evaluated as new α-glucosidase inhibitors.

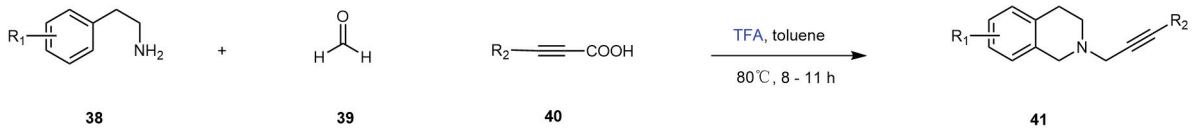
Compared with a one-pot multi-step reaction, the multi-component one-step strategy has drawn widespread attention as it offers several advantages such as operational simplicity and convergent nature. In 2016, Cai and coworkers developed an acid-catalyzed, multi-component tandem reaction for the generation of polyfunctional dihydroindolizino [8,7-*b*]indoles from an arylglyoxal monohydrate **32**, a tryptamine **32**, and a trans-β-nitrostyrene **33** or a malonitrile **34** under mild, metal-free conditions (►**Scheme 9**).[75] This reaction was based on utilizing the trifluoromethanesulfonic acid (CF_3SO_3H) and TFA as a catalyst and the domino Pictet–Spengler cyclization/Michael addition/intramolecular cyclization and oxidative aromati-



Scheme 8 One-pot two-step reaction to dihydroindolizino[8,7-*b*]indole derivatives.



Scheme 9 Acid-catalyzed multi-component tandem cyclization.



38 39 40 41

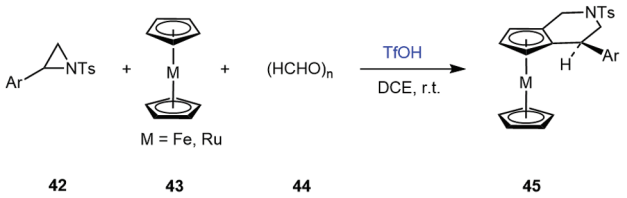
Scheme 10 A^3-Coupling/Pictet–Spengler cascade.

zation to obtain the desired products **36** and **37** in 62 to 72% yields and 72 to 85% yields, respectively.

In 2020, Hu and coworkers discovered that using toluene as a solvent in the presence of TFA, the multi-component of a 2-phenylethanamine, formaldehyde, and a propiolic acid gave the bicyclic *N*-propargyl tetrahydroisoquinoline in moderate to good yields (►**Scheme 10**).[32] Metal-free decarboxylative A^3-coupling provided the propargylamine intermediate, followed by the Pictet–Spengler cyclization to access target products. Meanwhile, a set of *N*-propargyl thienotetrahydropyridine and benzodiazepine skeletons could be obtained using the same protocol.

In 2021, González-Pelayo and coworkers accomplished the construction of a set of metallocene analogs of the relevant tetrahydroisoquinoline motif **45** by TfOH-catalyzed three-component reactions of 2-aryl-*N*-sulfonyl aziridines **42** with ferrocene (or ruthenocene) **43** and formaldehyde **44** (►**Scheme 11**).[76] Initially, the amino-functionalized metallocene derivatives were formed from a regioselective ring opening of the aziridine. Later, an intermolecular Pictet–Spengler cyclization of the formed intermediate and formaldehyde led to target products.

In the aforementioned methods, strong acids were employed, and, in some cases, trifluoromethanesulfonic anhydride was available for such a multi-component Pictet–Spengler reaction. For example, in 2019, Magyar and



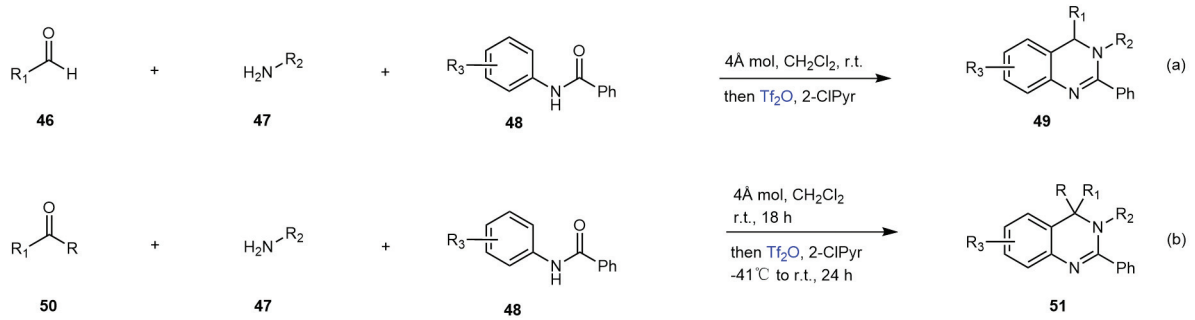
42 43 44 45

Scheme 11 Ring opening of 2-aryl-*N*-sulfonyl aziridines.

coworkers reported the three-component tandem reaction of amides **48**, aldehydes **46**, and amines **47** in the presence of trifluoromethanesulfonic anhydride, providing the corresponding 3,4-dihydroquinazolines **49** in moderate to good yields (►**Scheme 12a**).[77] The reaction was first performed in CH_2Cl_2 for 18 hours with a 4 Å molecular sieve under room temperature conditions, then treated with Tf_2O and 2-ClPyr for 24 hours at room temperature to afford the desired compounds by Pictet–Spengler-type cyclization. This report showed great advantages including the wide scope of the substrate to afford extensive diversity about the heterocyclic scaffold. The following year, Campbell et al documented a similar tandem assembly procedure for the generation of diverse C4-quaternary 3,4-dihydroquinazolines **51** using ketones **50** instead of aldehydes (►**Scheme 12b**).[78] This one-pot cascade reaction, involving the Tf_2O-mediated amide dehydration/ketimine addition/Pictet–Spengler cyclization, produced the corresponding products in moderate to excellent yields.

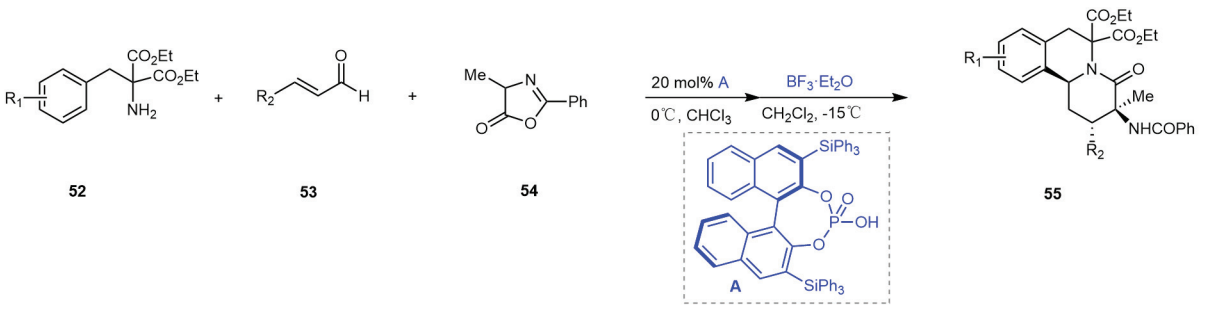
In addition to the Brønsted acid-promoted three-component domino Pictet–Spengler reaction, great advances in organocatalytic and Brønsted acid-promoted Pictet–Spengler reaction have been achieved. For example, in 2009, the group of Gong reported the first asymmetric three-component [4 + 2] cycloaddition reaction of aryl ethylamine **52,** cinnamaldehydes **53**, and azlactones **54** in the presence of the phosphoric acid catalyst and trifluoroborane, providing the benzo[*a*]quinolizidines in 65 to 76% yields with 90 to 97% *ee* (►**Scheme 13**).[79] They found that the 3-aminopiperidinone intermediates could be smoothly generated from **52**, **53**, and **54** under the catalysis of 20 mol% of **A**. Treatment of these intermediates with $BF_3{\cdot}Et_2O$ resulted in the generation of target products by Pictet–Spengler-type cyclization reactions.

In 2010, Wu et al reported a chiral amine-catalyzed and benzoic acid-promoted three-component reaction of a β-



46 47 48 49 50 47 48 51

Scheme 12 Trifluoromethanesulfonic-mediated three-component tandem procedure.

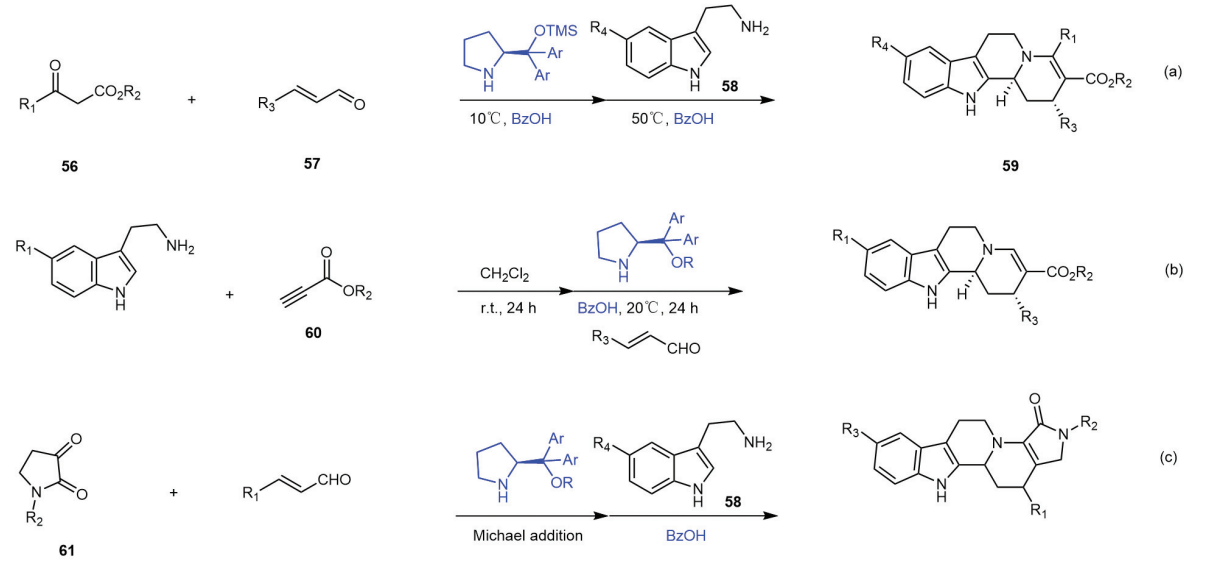


Scheme 13 Formal [4 + 2] cycloaddition involving Pictet–Spengler reaction.

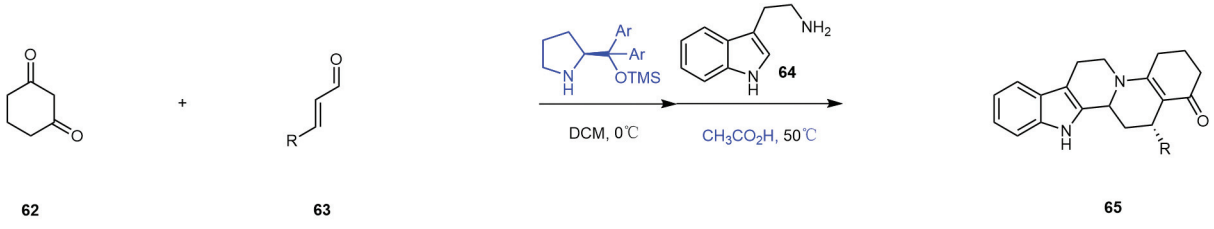
keto ester **56**, an α,β-unsaturated aldehyde **57**, and a tryptamine **58**, affording the indoloquinolizidines **59** in one pot (►**Scheme 14a**).[63] The reaction was first conducted with benzoic acid as an additive and toluene as a solvent at 10° C, then substrate **56** was added with **57**, followed by the addition of **58** and stoichiometric benzoic acid. The mixture was reacted at 50°C for 24 hours to give 88 to 95% yields of products.

In the following year, Wu and coworkers explored the domino Michael addition/Pictet–Spengler reaction employing the same reaction systems (►**Scheme 14b**).[64] Using propionates **60** instead of β-keto esters **56**, a similar process was performed to access the indoloquinolizidine derivatives in moderate to good yields. In addition, the Xu's group described the domino Michael addition/Pictet–Spengler reaction of α-oxo-γ-butyrolactams **61**, α,β-unsaturated aldehydes, and tryptamines, delivering the butyrolactam-fused indoloquinolizidine compounds in the presence of the same Jørgensen–Hayashi catalyst and benzoic acid (►**Scheme 14c**).[80] These methods provided an efficient and novel synthetic route for the construction of indole-based alkaloids.

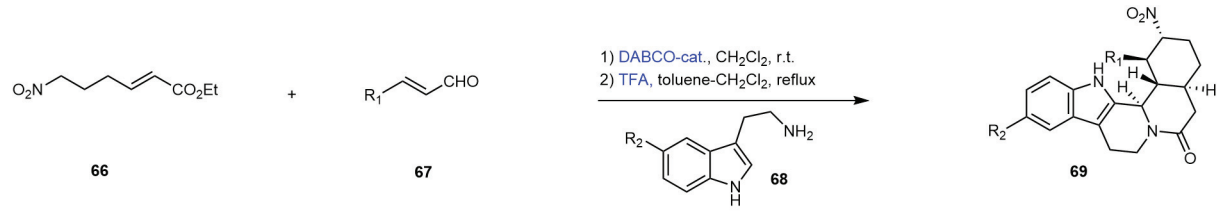
Besides using benzoic acid as a promotor, other Brønsted acids such as acetic acid and TFA were also disclosed with the combination of the organocatalyst. For example, in 2011, Rueping et al developed an asymmetric Michael addition of 1,3-dicarbonyl compounds **62** and α,β-unsaturated aldehydes **63**, and subsequent diastereoselective Pictet–Spengler cyclization (►**Scheme 15**).[81] Michael addition was performed



Scheme 14 Domino Michael addition/Pictet–Spengler reaction.



Scheme 15 Domino Michael addition/acetic acid-promoted Pictet–Spengler reaction.



66 67 68 69

Scheme 16 Domino double-Michael addition and Pictet–Spengler-lactamization reaction.

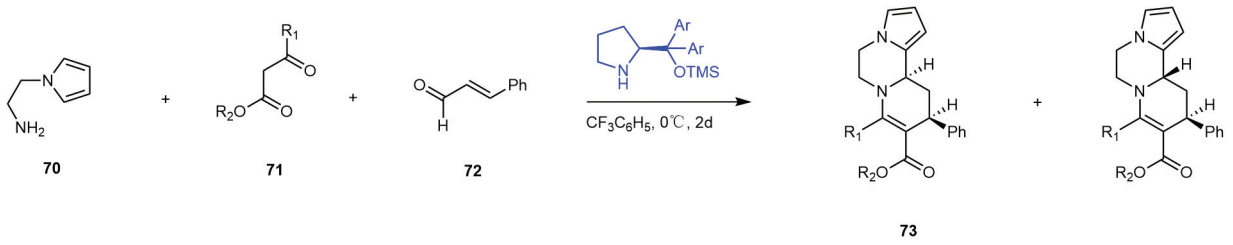
in the presence of the Jørgensen–Hayashi catalyst, followed by the acetic acid-promoted Pictet–Spengler cyclization of tryptamine at 50°C, giving the corresponding products **65** in 68 to 85% yields.

In 2013, Hong et al performed a one-pot organocatalytic enantioselective double-Michael addition/Pictet–Spengler-lactamization domino reaction (►**Scheme 16**).[82] This reaction represents an atom-economical pathway to delivering dodecahydrobenz[a]indolo[3,2-*h*]quinolizines with five contiguous stereogenic centers. The process of the reaction is that the double Michael reaction of (*E*)-ethyl 6-nitrohex-2-enoate **66** and α,β-unsaturated aldehydes **67** in CH_2Cl_2 under mild ambient temperature conditions, followed by TFA-promoted Pictet–Spengler and lactamization with 2-(1*H*-indol-3-yl)ethanamine provided the "inside yohimbine" **69** in good yields with high enantioselectivities.

The three-component Pictet–Spengler reactions, only using the organocatalyst without any other acids, represent an alternative method. In this field, in 2014, Du et al reported the first organocatalytic multicomponent reaction for the synthesis of enantioenriched pyrrolopiperazines **73** through an enantioselective Michael addition/Pictet–Spengler cyclization sequence (►**Scheme 17**).[83] In the reaction, various *N*-(2-aminoethyl)pyrroles **70**, cinnamyl aldehydes **71**, and β-keto esters **72** were evaluated in trifluorotoluene as a solvent at 0°C for 2 days, providing the desired products in 53 to 70% yields with excellent enantioselectivities.

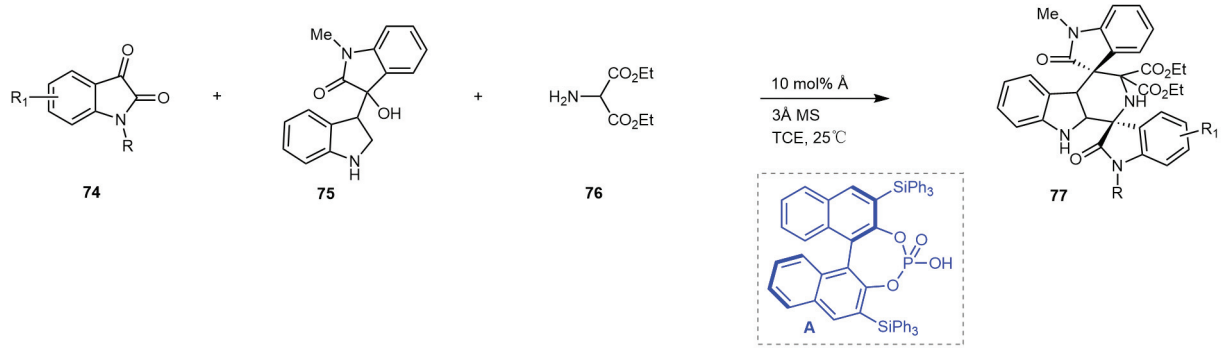
In the same year, Dai et al discovered a three-component reaction of isatins **74**, isatin-derived 3-indolylmethanols **75**, and an amino ester **76** by chiral phosphoric acid-catalyzed cascade Michael addition/Pictet–Spengler cyclization, which was the first catalytic asymmetric multicomponent Pictet–Spengler reaction using chiral phosphoric acid **A** as a catalyst (►**Scheme 18**).[84] Under the catalysis of **A**, the Michael addition of the in-situ-formed isatin-derived azomethine ylide from **75** and amino ester with **76** gave a transient intermediate. Subsequently, this intermediate underwent a Pictet–Spengler cyclization facilitated by the chiral phosphoric acid **A** to deliver the structurally complex and diverse bispirooxindoles **77** in excellent stereoselectivities.

In 2018, Yu et al disclosed the total synthesis of strychnofoline from commercially available 6-methoxytryptamine **78**. In the reaction, the first step was the generation of the quinolizidine derivative **81** (►**Scheme 19**).[85] By sequential addition of



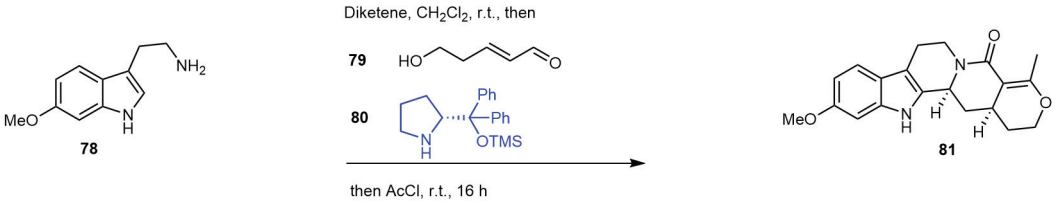
70 71 72 73

Scheme 17 Organocatalytic Michael addition/Pictet–Spengler sequence.



74 75 76 77 A

Scheme 18 Chiral phosphoric acid-catalyzed asymmetric Michael addition/Pictet–Spengler sequence.



Scheme 19 Application of domino Pictet–Spengler reaction to (−)-strychnofoline.

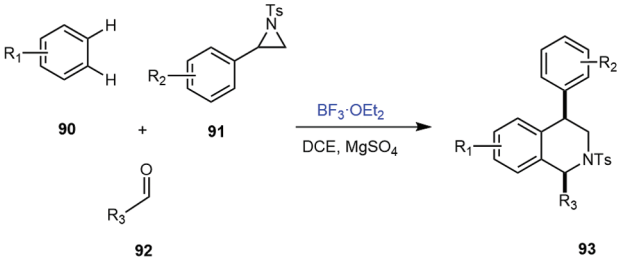
6-methoxytryptamine, diketene, acrolein derivative **80**, and acyl chloride in the presence of the Jørgensen–Hayashi catalyst, 67% yield of product **81** was obtained by one-pot acylation/asymmetric Michael addition/Pictet–Spengler reaction.

As known, the Pictet–Spengler reactions are generally realized by Brønsted acid or Lewis acid catalysis. In 2013, the group of Menéndez described a sequential multi-component reaction of tryptamines **82**, α,β-unsaturated aldehydes **83**, and β-dicarbonyl compounds **84** catalyzed by ammonium cerium nitrate (CAN), providing the indoloquinolizines **85** in good yields (►**Scheme 20**).[86] The process of reaction involved the initial formation of an enamine from the tryptamines and β-dicarbonyl components, followed by Michael addition of α,β-unsaturated aldehyde and 6-*exo*-*trig* cyclization to form a vinylimide cation, then a Pictet–Spengler cyclization to access the target products.

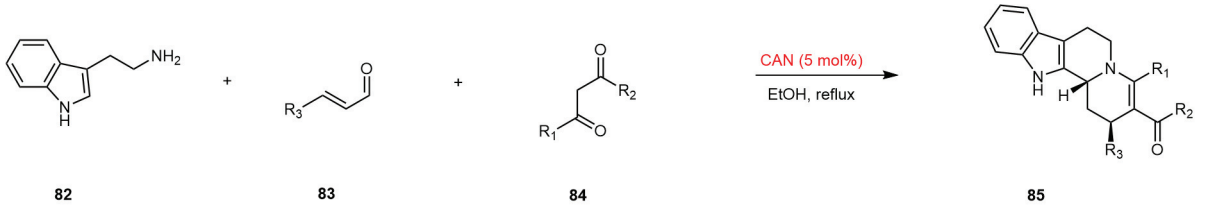
In the same year, the group of Yan published a report on the construction of hexahydroindolo[2,3-*a*]quinolizine framework by utilizing a one-pot three-component reaction of tryptamines **86**, propiolates **87**, and α,β-unsaturated aldehydes **88** (►**Scheme 21**).[87] The reaction involved the Michael addition of tryptamines and propiolates to generate β-enamino ester at room temperature, followed by the Pictet–Spengler reaction in the presence of anhydrous $ZnCl_2$, leading to the generation of desired products **89** in moderate to high yields and with high diastereoselectivity.

In 2015, Xing et al reported a new Lewis acid-promoted three-component reaction of arenes **90**, aziridines **91**, and aldehydes **92**, through a sequential ring opening of aziridine and Pictet–Spengler cyclization (►**Scheme 22**).[88] This reaction provided a rapid and convergent approach for the synthesis of a library of *cis*-1,4-disubstituted tetrahydroisoquinolines **93** in 50 to 75% yields under mild conditions. Aziridines were treated with arenes in the presence of $BF_3{\cdot}OEt_2$ to gain ring-opening adducts, followed by Pictet–Spengler cyclization with aldehydes to furnish desired tetrahydroisoquinoline derivatives.

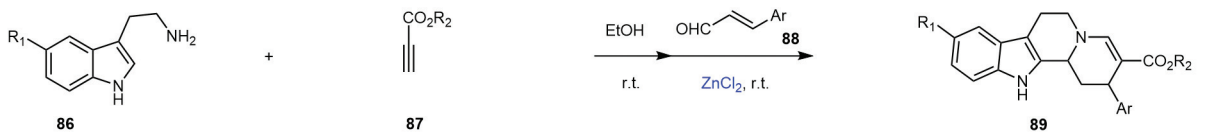
In 2020, Ghashghaei et al published an article in which the α-aminopyridines, indole 3-carbonaldehydes, and ethyl isocyanoacetate were reacted in the presence of $Yb(OTf)_3$ as a Lewis acid catalyst (►**Scheme 23**).[89] This alternative method involved a cascade process of Groebke–Blackburn–Bienaymé reaction to form the fused adduct, acid-catalyzed Pictet–Spengler cyclization to obtain dihydropyridine, and oxidation by atmospheric O_2 to finally afford a series of



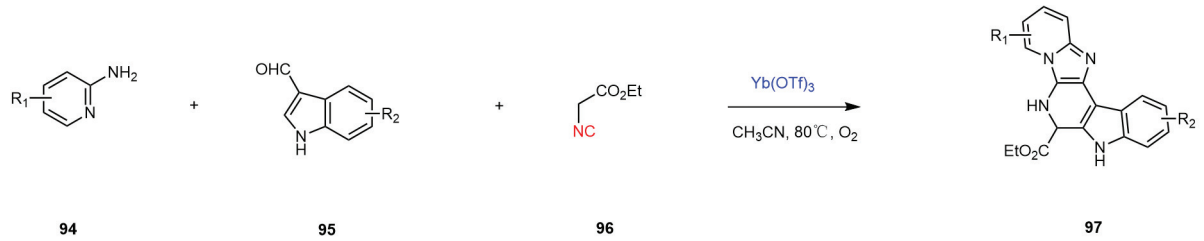
Scheme 22 Lewis acid-promoted ring-opening/Pictet–Spengler sequence.



Scheme 20 Michael addition/6-*exo*-*trig* cyclization/Pictet–Spengler reaction sequence.

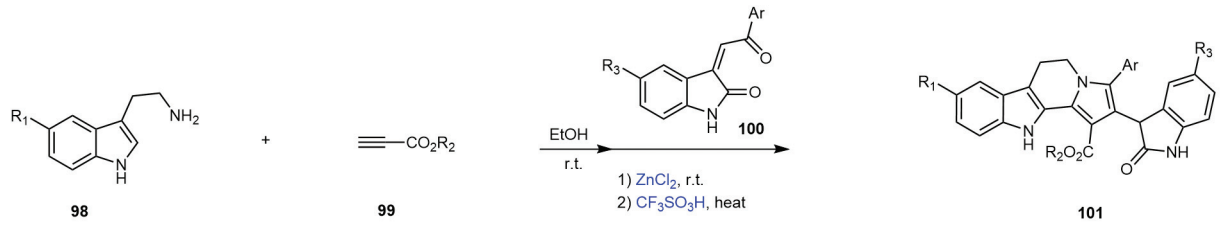


Scheme 21 Domino Michael addition and $ZnCl_2$-catalyzed Pictet–Spengler reaction.



94 95 96 97

Scheme 23 Extended Pictet–Spengler-based multi-component reaction.

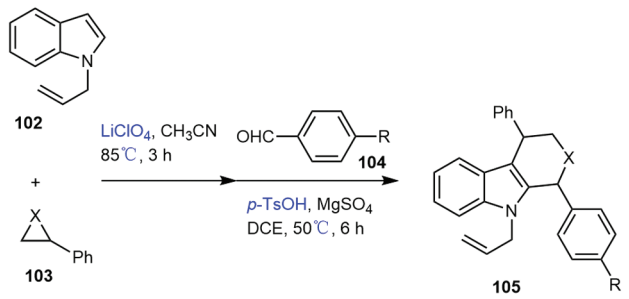


98 99 100 101

Scheme 24 One-pot sequential formation of β-enamino ester/Michael addition/Pictet–Spengler reaction.

polyheterocyclic compounds using acetonitrile as a solvent at 80°C in open air. Meanwhile, the processes can be performed in parallel and the products with fused, linked, and bridged scaffolds displayed remarkable bioactivity as potent ligands of the aryl hydrocarbon receptor.

On the other hand, following the Lewis acid-mediated Pictet–Spengler reactions, the combined Lewis acid and Brønsted acid catalysis systems were developed to explore the Pictet–Spengler-based multi-component reactions. In 2014, Zhu and coworkers applied $ZnCl_2$ and CF_3SO_3H in the three-component reaction of tryptamines **98**, alkyl propiolates **99**, and 3-phenacylideneoxindoles **100**, providing a series of 6,11-dihydro-5*H*-indolizino[8,7-*b*]indoles **101** with high efficiency (►**Scheme 24**).[90] First, the 2-pyrrolo-3′-yloxindole intermediate was obtained through a sequential formation of β-enamino ester and Michael addition in the presence of anhydrous $ZnCl_2$. Then, the 2-pyrrolo-3′-yloxindoles were converted to the corresponding products **101** by a CF_3SO_3H-catalyzed Pictet–Spengler cyclization process.

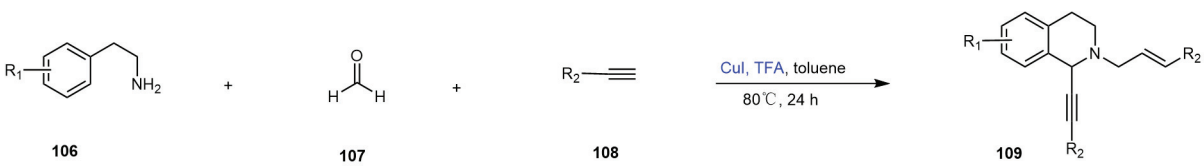


102 103 104 105

Scheme 25 Domino ring-opening/Pictet–Spengler reaction.

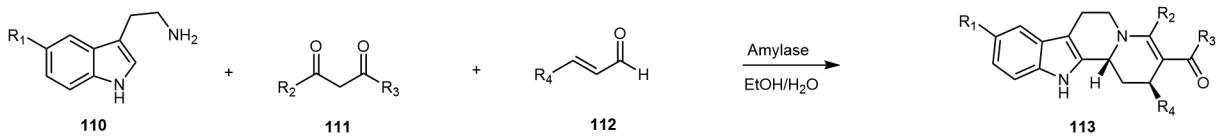
In 2020, Wani and coworkers reported that the 1,4-disubstituted tetrahydro-β-carbolines and tetrahydropyrano[3,4-*b*]indoles **105** could be obtained in high yields and stereoselectivity by a simple and efficient method using indoles **102**, aziridines or epoxides **103**, and benzaldehydes **104** (►**Scheme 25**).[91] In this report, $LiClO_4$-catalyzed ring opening of aziridines and epoxides with indoles was performed in acetonitrile at 85°C for 3 hours, followed by *p*-toluenesulfonic acid-catalyzed Pictet–Spengler cyclization with benzaldehydes. To improve the efficiency of the Pictet–Spengler cyclization, various reaction parameters were screened. The results showed that when using 20 mol% of *p*-toluenesulfonic acid as a catalyst in DCE at 50°C for 6 hours, 60 to 85% yields of the desired products were obtained.

In addition, Feng and coworkers reported a CuI/TFA catalysis system to catalyze the domino Pictet–Spengler reaction/A^3-type coupling/1,5-hydride transfer/alkynylation in 2022 (►**Scheme 26**).[92] The mechanism studies showed that TFA promoted the Pictet–Spengler reaction of 2-arylethan-1-amines **106** and formaldehyde to form tetrahydroisoquinolines, followed by a reaction with another molecule of formaldehyde to give iminium ion, then Cu-catalyzed intermolecular hydride transfer and alkynylation with two molecules of



106 107 108 109

Scheme 26 Synthesis of nitrogen-tethered 1,6-enynes through CuI/TFA catalysis.



110 111 112 113

Scheme 27 Biocatalytic one-pot three-component Pictet–Spengler reaction.

terminal alkyne **108** to deliver nitrogen-tethered 1,6-enynes **109** with high selectivity.

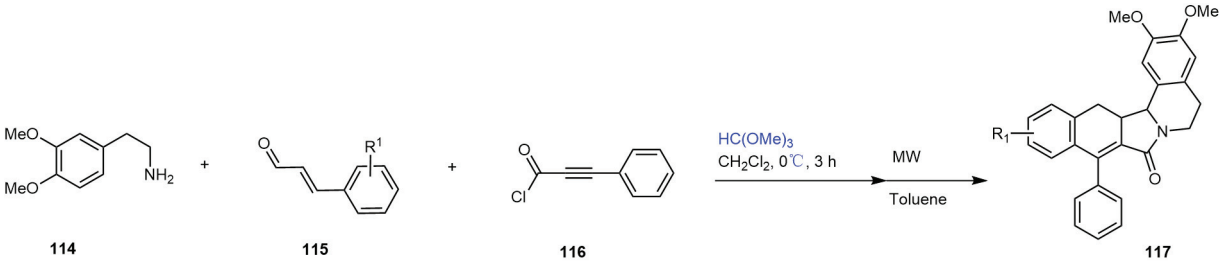
To make the three-component Pictet–Spengler reaction greener, in recent years, enzyme catalysis, Brønsted acid, and Lewis acid-free strategies have received considerable attention. For example, α-amylase activation catalysis is an alternative protocol for the generation of highly substituted indoquinolines **113**, which was uncovered by He and coworkers in 2019 (►**Scheme 27**).[93] The reaction using tryptamines **110,** β-keto esters **111**, and α,β-unsaturated aldehydes **112** as starting materials afforded a variety of products in moderate to good yields.

In addition, the field of acid-free Pictet–Spengler cyclization was also dominated. In 2010, Ruijter and Orru found that a domino *N*-acyliminium Pictet–Spengler/Diels–Alder reaction of β-arylethylamine **114**, cinnamaldehyde derivatives **115**, and alkynyl chloride **116** afforded the polycyclic alkaloid-type compounds **117** in high yield (►**Scheme 28**).[94] The first procedure of the reaction used $HC(OMe)_3$ and dichloromethane as a solvent at 0°C for 3 hours to obtain the Pictet–Spengler adducts in 72 to 85% yields, then toluene was added as a solvent under microwave irradiation, providing the corresponding products in good yields by intramolecular Diels–Alder reaction.

In 2021, Deng et al reported the selective synthesis of benzothiophene-fused polycyclic and eight-membered *N*-heterocycles **122** and **121** via the Pictet–Spengler reaction under catalyst-free conditions, where the selectivity depended on the R_3-substituted group (►**Scheme 29**).[95] Using thioisatin **118**, bromoacetophenone **119**, and a tryptamine **120**, the benzothiophene-fused polycycles **121** were obtained in 61 to 79% yields. When the *D*-tryptophan methyl ester hydrochloride was used instead of tryptamine, the corresponding products were switched to benzothiophene-fused eight-membered polycyclic compounds **122** (60–78% yields).

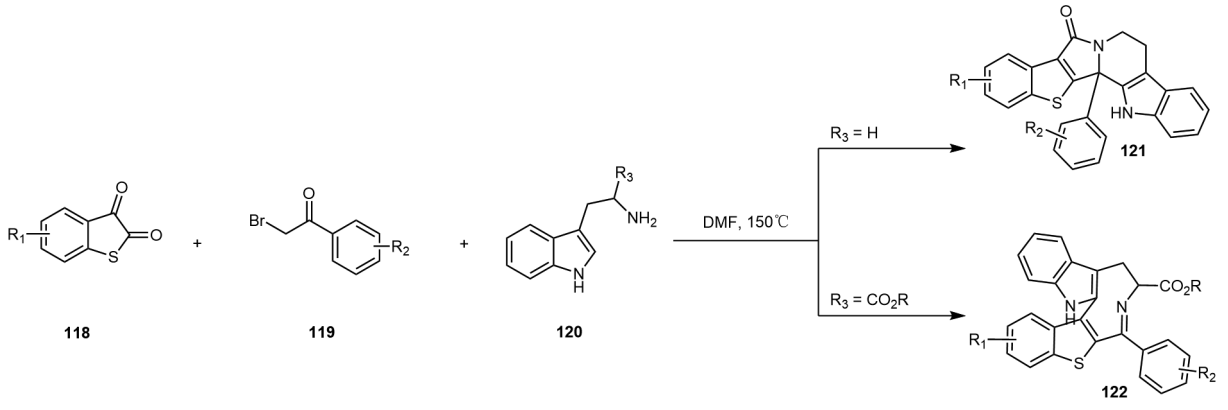
Four-Component Pictet–Spengler Cyclization-Based Domino Reactions

Brønsted acids, Lewis acids, organocatalysts, and catalyst-free reaction systems have been well developed in the domino Pictet–Spengler reactions. In addition to the



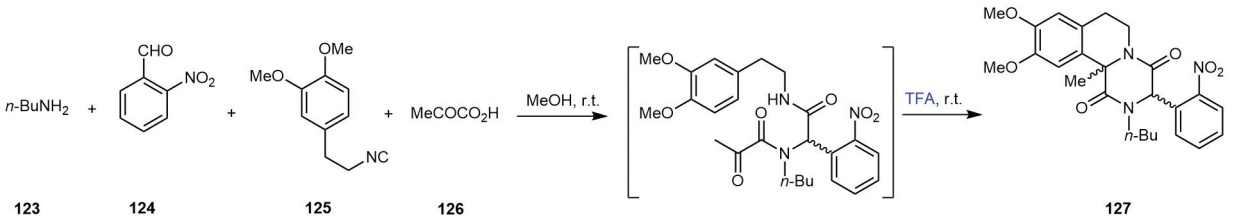
114 115 116 117

Scheme 28 Pictet–Spengler/Diels–Alder sequence.



118 119 120 121 122

Scheme 29 Catalyst-free strategy for Pictet–Spengler reaction.



Scheme 30 New Ugi4-CR/Pictet–Spengler domino reaction.

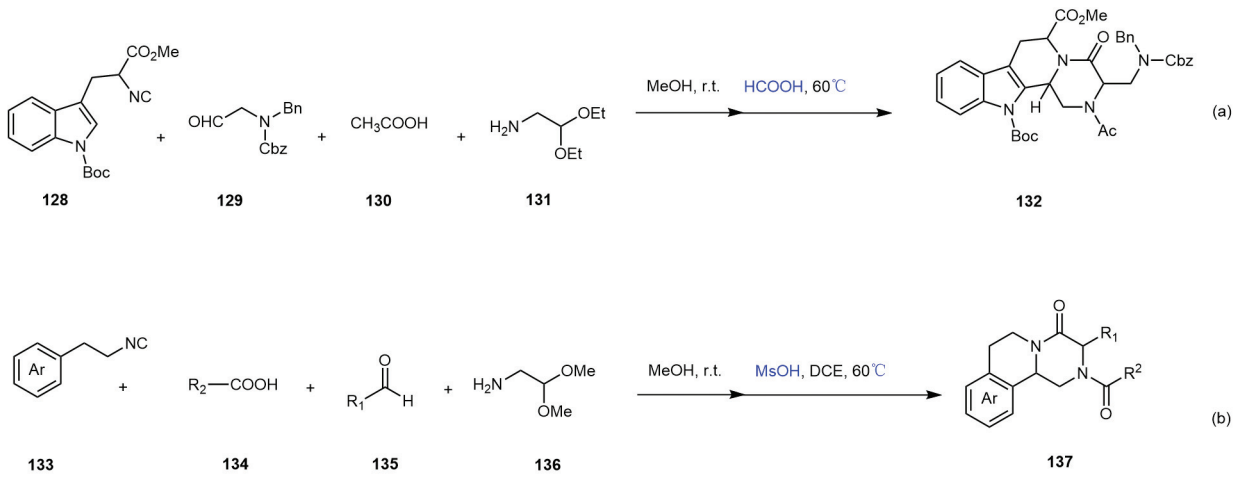
above-mentioned three-component Pictet–Spengler reactions, some researchers have investigated the four-component Pictet–Spengler reactions in the past decade. In the case of this field, domino Ugi/Pictet–Spengler cyclization reactions have reached impressive levels. For example, in 2007, Gageat and coworkers described a one-pot two-step Ugi 4-CR/Pictet–Spengler reaction of a primary amine **123**, an aldehyde **124**, an α-keto acid **126**, and an isocyanide **125** (►**Scheme 30**).[96] When the α-keto acid was added to the aldehyde, primary amine, and isocyanide in methanol, the Uig adduct was produced at room temperature for 2 hours. The reaction mixtures just evaporated the solvent, then treated with TFA to generate a tricyclic 2,5-diketopiperazine **127** through a Pictet–Spengler-type cyclization.

Similarly, Lesma and coworkers later reported a one-pot two-step reaction of isocyanide **128**, *N*-protected 2-aminoacetaldehyde **129**, functionalized amine **131**, and acetic acid for the synthesis of tryptophan-derived peptidomimetics **132** by an Ugi 4-CR/Pictet–Spengler reaction sequence (►**Scheme 31a**)[97] The first step: Ugi 4-CR was performed in methanol as a solvent at room temperature for 24 hours. The second step: the Pictet–Spengler reaction was performed at 60°C for 30 minutes in the presence of HCOOH, giving the final products. It was important to note that *N*-protected 2-aminoacetaldehyde was for the first time used as the carbonyl component in the Ugi 4-CR.

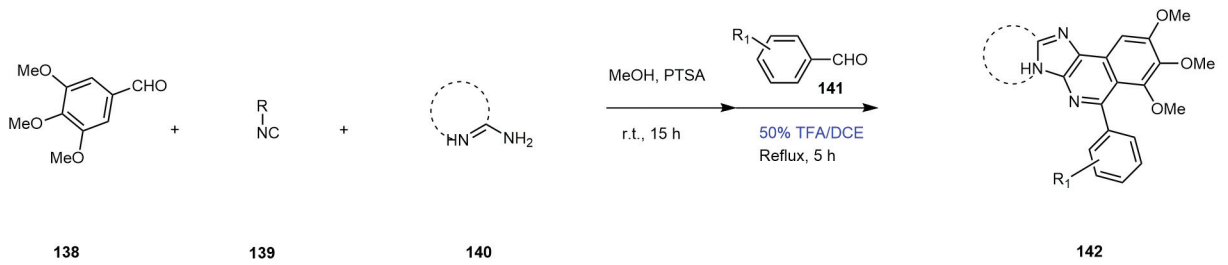
In addition, Liu and coworkers described an Ugi 4-CR followed by the Pictet–Spengler reaction in a one-pot two-step procedure (►**Scheme 31b**).[98] This reaction gave a series of tetrahydroisoquinoline drug praziquantel derivatives **137** in moderate to good yields from isocyanides with aromatic group **133**, aldehydes **135**, amines **136**, and carboxylic acids **134** using DCE as a solvent at 80°C in the presence of MsOH.

Diversity-oriented syntheses of *N*-fused polycyclic heterocycles were reported by Tyagi and coworkers in 2012.[99] They developed a new protocol for the construction of two kinds of polycyclic skeletons by an Ugi-type reaction followed by a tandem Pictet–Spengler reaction or copper-catalyzed coupling reaction. Taking the domino Ugi-type/Pictet–Spengler reaction as an example, first, the Ugi-type reaction of aldehydes **138**, isonitriles **139**, and 2-amino aromatic heterocycles **140** was performed in methanol in the presence of PTSA. Then 50% TFA in DCE and another aromatic aldehyde were added and the desired products **142** were obtained in good yields by tandem Pictet–Spengler reaction ►**Scheme 32**.

In 2013, Sinha and coworkers developed the shortest scalable synthesis of the schistosomiasis drug praziquantel **147** through an Ugi 4-CR/Pictet–Spengler sequence (►**Scheme 33**).[100] In this reaction, an α-amino acid **144**, a ketone **146**, an isocyanide **143**, and an aminoacetaldehyde dimethyl acetal **145** were introduced for the first step to give the Ugi 4-CR adduct in MeOH/H_2O (4:1) at room temperature. Then concentrated formic acid was added and the mixture was stirred at room temperature for 16 hours, providing the corresponding Pictet–Spengler cyclization



Scheme 31 Ugi 4-CR/Pictet–Spengler reaction sequence.



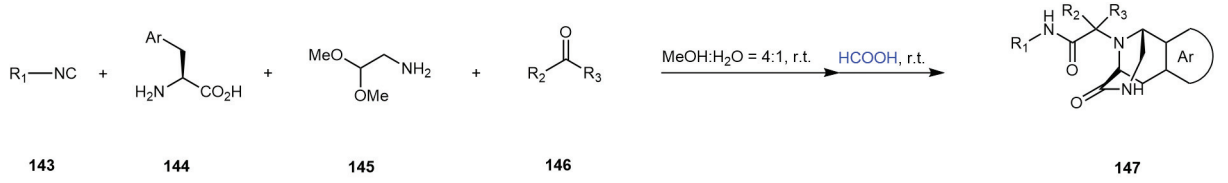
138 139 140 142

Scheme 32 Sequence of Ugi-type and Pictet–Spengler reaction.

products in good to acceptable yields. In general, the reaction is compatible with many functional groups and different fragments.

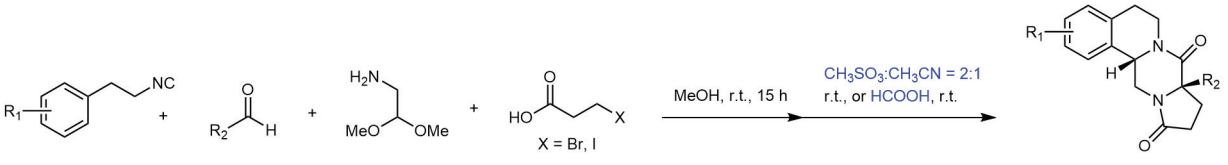
Very recently, Zhang et al found that the privileged scaffold dihydropyrrolo[1,2-*a*]pyrazine-dione **152** could be constructed by an Ugi 4-CR and Pictet–Spengler reaction sequence (►**Scheme 34**).[101] Taking isonitriles **148**, aldehydes **149**, 2,2-dimethoxyethane-1-amines **150**, and 3-bromopropanoic acid **151** as starting materials in the presence of methanol, the Ugi 4-CR adducts were produced at room temperature. Posttransformation of Ugi 4-CR adducts led to novel fused tricyclic systems under different acidic conditions. This approach also gave the alkaloid-type polycyclic scaffold with potential bioactivity.

A combined Brønsted acid and Lewis acid catalysis system has been proven to be an effective tool for domino Ugi 4-CR/Pictet–Spengler reactions. In 2011 Cano-Herrera and coworker applied a sequential Ugi 4-CR/Pictet–Spengler/reductive methylation reaction protocol for the synthesis of a piperazinohydroisoquinoline ring system (►**Scheme 35**).[102] They employed *N*-Boc amino acids **156** for the $InCl_3$-promoted Ugi reaction of aldehydes **153**, 2,2-dimethoxyethane-1-amines **154**, and isonitriles **155**, followed by an *N*-Boc-deprotection process and iminium formation. The iminium intermediate then afforded the desired products **157** via the Pictet–Spengler reaction and reductive *N*-methylation in the presence of formic acid. All these processes were performed in the same reaction flask.



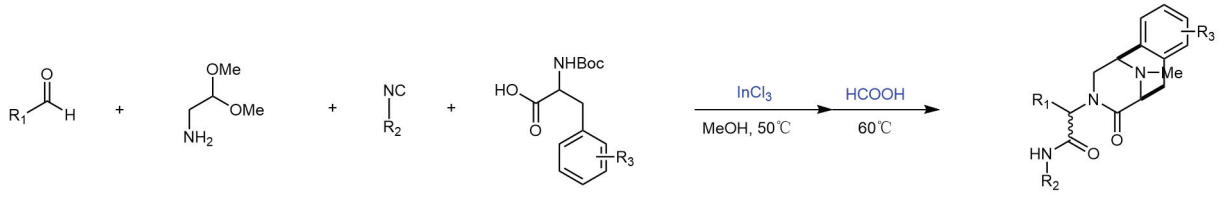
143 144 145 146 147

Scheme 33 New Ugi variation and Pictet–Spengler reaction in one pot.



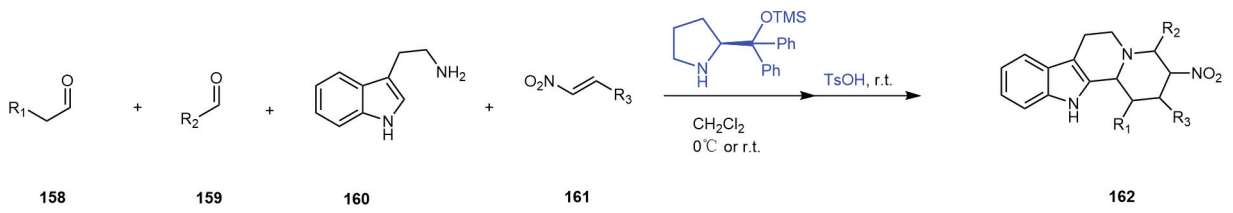
148 149 150 151 152

Scheme 34 Highly stereoselective Ugi 4-CR/Pictet–Spengler sequence.

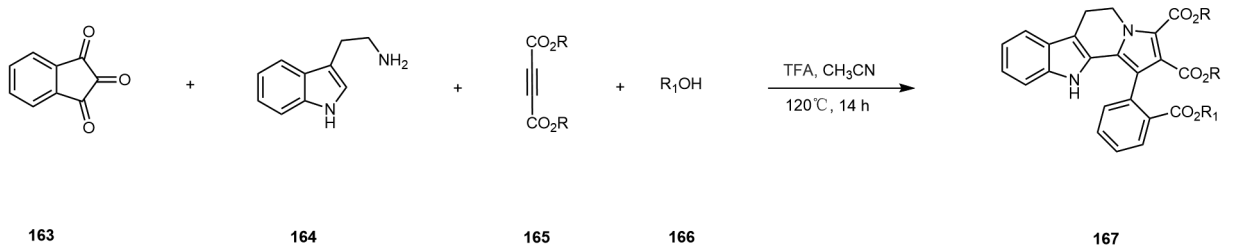


153 154 155 156 157

Scheme 35 Sequential Ugi/Pictet–Spengler/reductive methylation reaction.



Scheme 36 Organocatalytic TsOH-promoted cascade reaction.



Scheme 37 Acid-catalyzed four-component tandem double cyclizations.

In addition, an organocatalytic TsOH-promoted cascade reaction of aliphatic aldehydes **159** and **158**, nitroethylenes **161**, and tryptamine **160** was reported by Tan et al in 2014 (►**Scheme 36**).[103] This one-pot two-step reaction involved Michael addition, aza-Henry reaction, hemiaminalization, and dehydration sequence in the presence of the Jørgensen–Hayashi catalyst at 0°C or room temperature for 12 hours, followed by TsOH-promoted Pictet–Spengler cyclization to afford the indoloquinolizidine derivatives **162** in 30 to 55% overall yields with excellent d.r. (>20:1 in all cases) and *ee* (91–98%) at room temperature for 4 hours.

In 2019, the group of Kumbhare reported a novel one-pot four-component cyclization reaction for constructing dihydroindolizino[8,7-*b*]indoles **167** from ninhydrin **163**, tryptamine **164**, dimetylene acetylene dicarboxylates **165**, and aliphatic alcohols **166** in the presence of TFA (►**Scheme 37**).[104] In this reaction, the tandem Pictet–Spengler cyclization reaction and construction of C–C and C–N bonds could be produced under transition metal-free conditions at 120°C for 14 hours, finally providing the desired fused-indole derivatives in good yields.

Conclusion and Prospects

In the nearly two decades since the centenary of the Pictet–Spengler cyclization, a pile of chaotic papers has proved that the reaction has not withdrawn from the historical stage, but has once again attracted attention with new characteristics. In this review, we have highlighted the recent developments in multi-component Pictet–Spengler-based reactions including the three-component and four-component reactions. These reactions represent the most useful tool for the efficient and straightforward construction of polyheterocycles from readily available starting materials, such as tetrahydroisoquinolines, quinoline-indole derivatives, tetrahydro-β-carbolines, and so on. In addition to the importance of Brønsted acid in this field, researchers have widely explored several other catalysis systems such as Lewis acid, organocatalysts, combined Lewis acid and Brønsted acid, and synergistic organocatalyst and Brønsted acid. The major advantage of these reactions is that the complex and diverse molecular structures can be easy to obtain with a wide scope, modularity, high atom economy, good scalability, and high yields. Although multi-component Pictet–Spengler-based reactions have become a useful tool for obtaining complex scaffolds and new chemical entities in one pot, the extension of the Pictet–Spengler cyclization to more diverse domino reactions and the application of other types of organocatalysts are expected to be developed.

Conflict of Interest

None declared.

Acknowledgments

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