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Recent advances on the synthesis and application of tetrahydro-γ-carbolines☆

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ABSTRACT

Tetrahydro-γ-carbolines (THγCs) constitute one of the most important subtypes of indole alkaloids. In addition to being substructures of natural products, these structural motifs and moieties can often be found in pharmaceuticals due to their diverse bioactivities such as antiviral, antibacterial, antifungal, antiparasitic, antitumor, anti-inflammatory, and neuropharmacological activities. Beyond the pharmacological and biological aspects of these scaffolds, they have considerable synthetic applications for the construction of further bioactive compounds, too. The aim of this review is to summarize recent developments in the synthesis of this compound class.

1. Introduction

Amongst the nitrogen heterocycles indole-fused pyridine ring-containing systems, commonly known as pyridoindoles or carbolines, have received considerable attention over the past decades. The tetrahydro derivatives of carbolines, constituting one of the most attractive motifs of indole-containing heterocycles, are classified as α-, β-, γ- or δ-tetrahydrocarbolines depending on the position of the nitrogen atom on the pyridine ring (C ring of ABC skeleton) (Fig. 1) [1,2]. Out of these diverse structures, tetrahydro-γ-carbolines have been found to possess a wide range of advantageous characteristics and beneficial effects, therefore can be considered as core scaffolds in various pharmaceutical compounds with a diversity of biological activities [3].

Several THγC structures are known for their diverse bioactivities including mostly neuropharmacological, antifungal, antiparasitic or antitumor activities, some of them are therapeutically used pharmaceuticals.

Amongst the THγCs, one of the most-known leading compounds with no doubt is the drug molecule *Dimebon* (Fig. 2), owing to a broad neuropharmacological activity profile: it is used as an antihistamine agent, moreover, it has cardioprotective, antiarrhythmic and even neuroprotective effects [4].

Within the neuropharmacological activies, concerning the neurodegenerative disorders, another THγC-containing bioactive compound, *Tubastatin A* (Fig. 2) and its analogues were found to act as a neuroprotective HDAC6 inhibitor [5]. Furthermore, some *N*-modified carbolines as neuronal *N*-methyl-D-aspartate (NMDA) receptors [6,7] and also conjugates as acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and carboxylesterase (CaE) inhibitors (Fig. 2) [8,9] were also reported.

According to the neuropathic and antipsychotic aspects of neuropharmacological activity, *Gevotroline* and *Alosetron* (Fig. 2) are both 5-HT receptor antagonist THγC-containing pharmaceuticals – while the former serves as an antipsychotic drug, the latter is used for the management of severe diarrhea-predominant irritable bowel syndrome (IBS) [10,11]. In addition, *Flutroline* (Fig. 2) is known by its antipsychotic and neuroleptic effects [12]. The synthesis of some 5-HT receptor antagonist THγC derivatives [13] was also accomplished.

In contrast to the large number of neuropharmacological activities of THγCs, only one example for the antifungal activity exists: compound C38 (Fig. 2) showed comparable *in vitro* antifungal activity to fluconazole without toxicity to human embryonic lung cells [14].

Mono- and disubstituted synthetic analogues of *isocryptolepine* (Fig. 2) were found to be responsible for antiparasitic effect as they were evaluated for *in vitro* antimalarial and antiproliferative activity against CQS (3D7) and CQR (K1) strains [15,16].

☆ Dedication to Prof. Lixin Dai on the Occasion of His Centenary Birthday.

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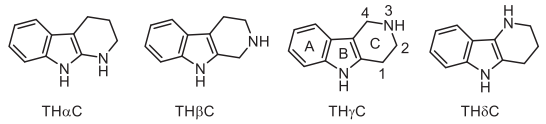


Fig. 1. Classification of tetrahydrocarbolines.

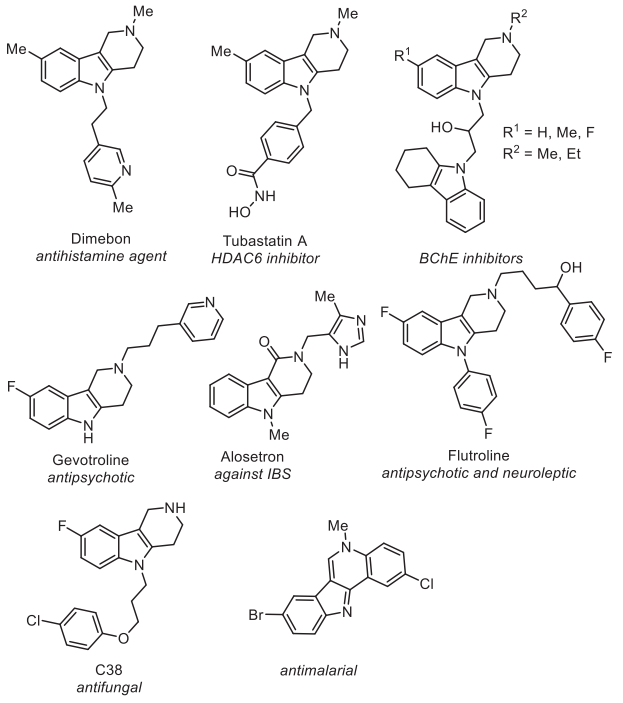


Fig. 2. Pharmaceuticals and bioactive compounds having THγC scaffold.

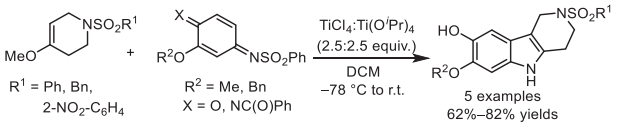
2. Strategies for the synthesis of tetrahydro-γ-carbolines

In the last few decades, several approaches have been developed for the construction of THγC scaffolds, concerning syntheses mostly starting from 2- or 3-substituted indole or aniline derivatives. Furthermore, according to the applied synthetic methods towards the desired THγC heterocyclic system, transition-metal-catalyzed, acid-catalyzed, and photoredox-catalyzed reactions were reported.

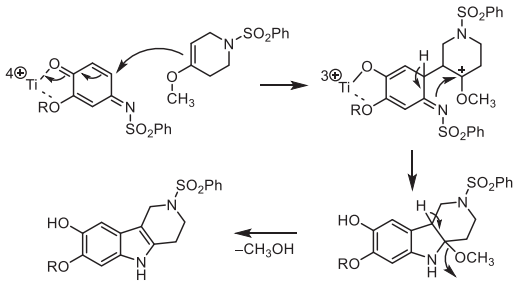
2.1. Transition-metal-catalyzed reactions

Many methodologies were realized with the utilization of several transition metals. The first attempts were accomplished by employing Ti, Pd or Au as metals; however, in the last decade Cu, Rh, Ag, Sc, and Ir were also proved to be suitable transition metals in these kinds of transformations.

With the application of Ti, two reports have been made by Engler. In 1997, the Lewis acid-directed reactions of piperidone enol ethers with quinone monoimines were investigated and it was found that the regioselectivity of the transformation can be controlled by the nature of the Lewis acid [17]. Hence, applying 5 equiv. of $TiCl_4$:Ti(O^iPr)$_4$ in the reaction, tetrahydrocarbolines were formed; however, the utilization of 1 equiv. $BF_3{\cdot}Et_2O$ afforded the corresponding benzofuran adducts. Starting from benzoquinone bisimines, using both catalysts only the formation of tetrahydrocarbolines was observed. The applicability of the developed procedure for the construction of THγCs was demonstrated over 3 examples. Three years later, the same methodology with a slightly extended substrate scope regarding the sulfonyl group of



Scheme 1. Lewis acid-catalyzed synthesis of tetrahydro-γ-carbolines from piperidone enol ethers and benzoquinone monoimines.

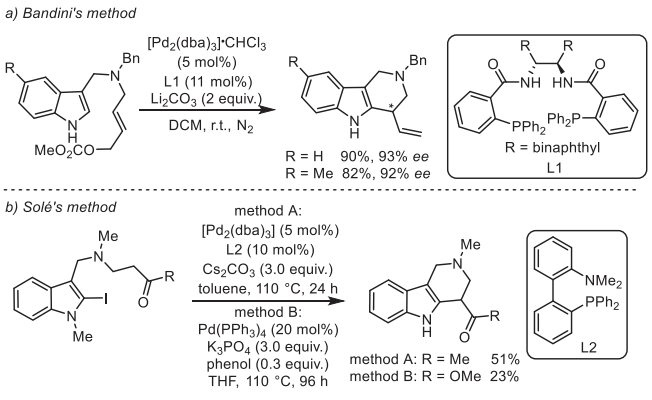


Scheme 2. Reaction mechanism of the cyclocondensation of enol ethers with quinone monimines.

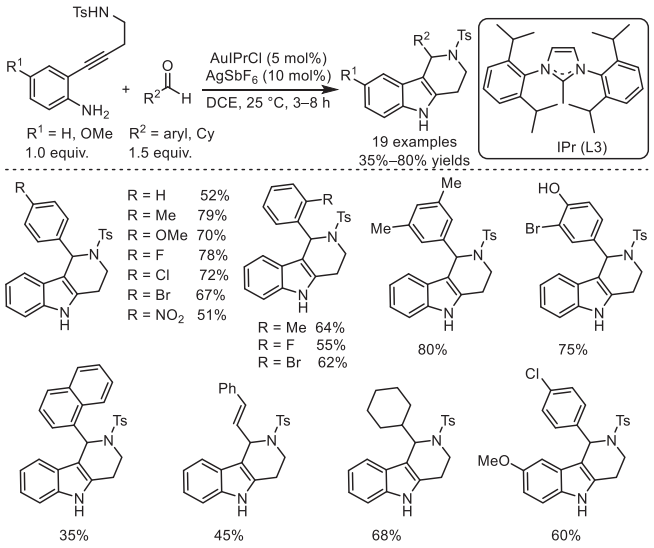
the piperidone enol ethers led to the desired products in 62%–82% yields (Scheme 1) [18].

Concerning the reaction mechanism, the bidentate Ti(IV) binds to the C-1 carbonyl and C-2 alkoxy oxygens of the quinone imine activating C-5 to nucleophilic addition of the enol ether followed by cyclization and elimination of methanol (Scheme 2).

Two methodologies were developed by Bandini and Solé for the preparation of THγCs applying palladium catalysis. In 2006, Bandini and co-workers reported the enantioselective synthesis of 1-vinyl-tetrahydro-γ-carbolines *via* palladium-catalyzed intramolecular allylic alkylation of 3-indolyl carbonates (Scheme 3a) [19]. [$Pd_2(dba)_3$]·$CHCl_3$, chiral ligand diphenylphosphinobenzoic acid (DPPBA, L1), and Li_2CO_3 as base were applied in the transformation furnishing the desired products in 82% and 90% yields. Additionally, the synthesis of 4-vinyl-tetrahydro-β-carbolines was also presented from 2-indolyl carbonates in moderate to excellent yields with high enantioselectivities. In 2011, the synthesis of THγCs was described by Solé *et al. via* the intramolecular palladium-catalyzed α-arylation of carbonyl compounds with amino-tethered 2-iodoindoles (Scheme 3b) [20]. Reactions were carried out employing $Pd_2(dba)_3$ with Buchwald's monodentate ligand (L2) or $Pd(PPh_3)_4$ as the catalyst, in either toluene or THF with Cs_2CO_3 or K_3PO_4 as the base, leading to the corresponding products in 51% and 23% yields, respectively. The developed methodology enables the construction of THβCs and pyrrolo[3,4-*b*]indoles as well from 2- or 3-iodoindole derivatives in moderate to good yields.

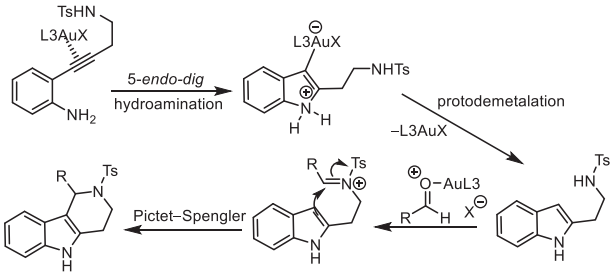


Scheme 3. Palladium-catalyzed syntheses of THγCs from indole derivatives.



Scheme 4. Gold-catalyzed synthesis of THγCs in the reaction of substituted anilines and aldehydes.

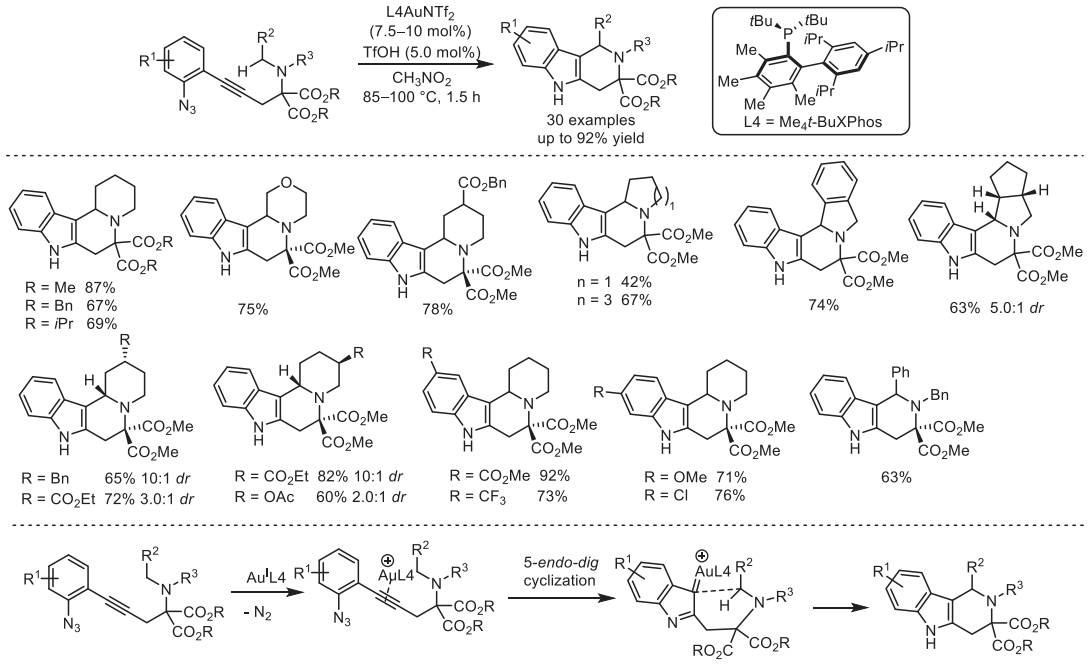
Utilizing Au as the transition metal catalyst, two attempts were made by Yadav and Gagosz for the construction of THγCs. A wide substrate scope was demonstrated in both transformations, in contrast to the previous palladium-catalyzed methods. In 2012, the gold-catalyzed domino cycloisomerization/Pictet–Spengler reaction of 2–(4-aminobut-1-yn-1-yl)anilines with aldehydes was achieved by Yadav and co-workers using *N*-heterocyclic carbene (NHC)-gold complex (AuIPrCl) in combination with $AgSbF_6$ to produce the appropriate 1-aryl-*N*-tosyl-2,3,4,5-tetrahydropyrido[4,3-*b*]indole derivatives in 35%–80% yields (Scheme 4) [21]. According to the plausible mechanism, the desired scaffolds are formed through a tandem 5-*endo-dig* cyclization (hydroamination and protodemetalation) in which *N*-tosylisotriptamine is formed *in situ* followed by a Pictet–Spengler reaction (Scheme 5).



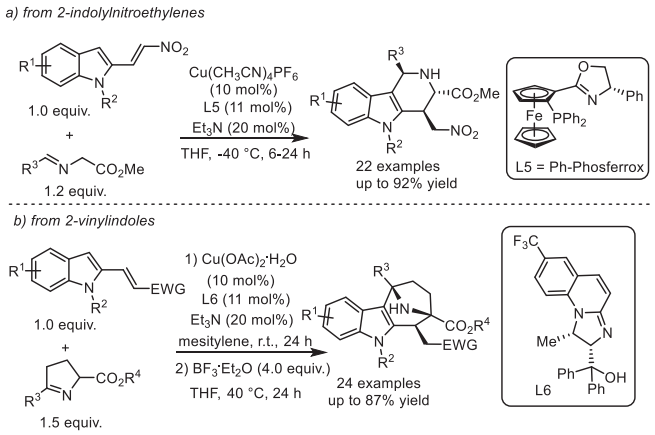
Scheme 5. Plausible mechanism for the gold-catalyzed cycloisomerization/Pictet–Spengler reaction.

Recently, the electrophilic gold-catalyzed α-C–H bond functionalization of tertiary amines for the synthesis of tetrahydro-γ-carbolines has been published by Gagosz *et al.* [22] in the presence of Me_4t-BuXPhos ligand (L4) and trifluoromethanesulfonic acid (TfOH). The malonate unit of the substrate plays a crucial role in this transformation with its electronic, steric, and conformational synergistic effects. The applicability of the developed procedure was presented over numerous examples leading to the desired products in good to high yields (Scheme 6). Furthermore, product derivatization to two compounds possessing the core structure of the alkaloid natural products Vernavosine and Mitragynine pseudoindoxyl was also accomplished. Mechanistic investigations revealed that similar to Yadav's proposal, a 5-*endo-dig* cyclization of the initially formed gold–alkyne complex occurs, then subsequent loss of N_2 generates the gold–carbene, from which the desired product is provided *via* 1,6-hydride shift.

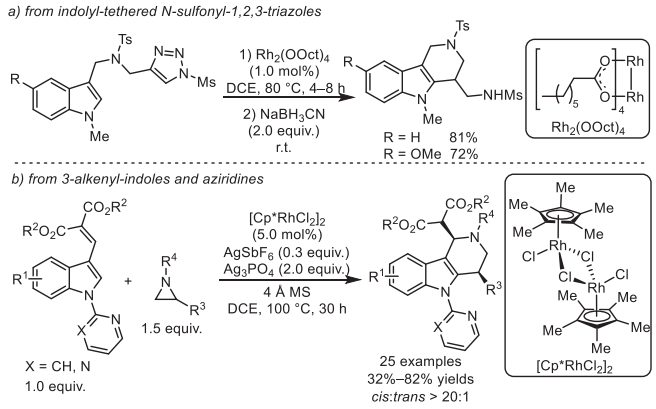
With the application of Cu, two approaches have been realized by Deng from the reaction of 2-substituted indole derivatives and azomethine ylides. In 2016, the copper-catalyzed chemo- and stereoselective [3 + 3] cycloaddition of azomethine ylides with 2–indolylnitroethylenes was described for the construction of highly substituted THγCs employing $Cu(CH_3CN)_4PF_6$, ferrocene *P,N*-ligand (Ph-Phosferrox, L5), and Et_3N base (Scheme 7a) [23]. The corresponding azaheterocycles were obtained in moderate to high yields.



Scheme 6. Gold-catalyzed intramolecular C–H bond functionalization of amines accessing THγCs.



Scheme 7. Copper-catalyzed syntheses of THγCs from 2-substituted indole derivatives and azomethine ylides (R^1 = H, alkyl; R^2 = alkyl, arylalkyl; R^3 = alkyl, (hetero)aryl, arylalkyl; R^4 = alkyl, arylalkyl).



Scheme 9. Rhodium-catalyzed syntheses of THγCs from 3-substituted indole derivatives (R^1 = H, alkyl; R^2 = alkyl, arylalkyl; R^3 = aryl; R^4 = SO_2Ar).

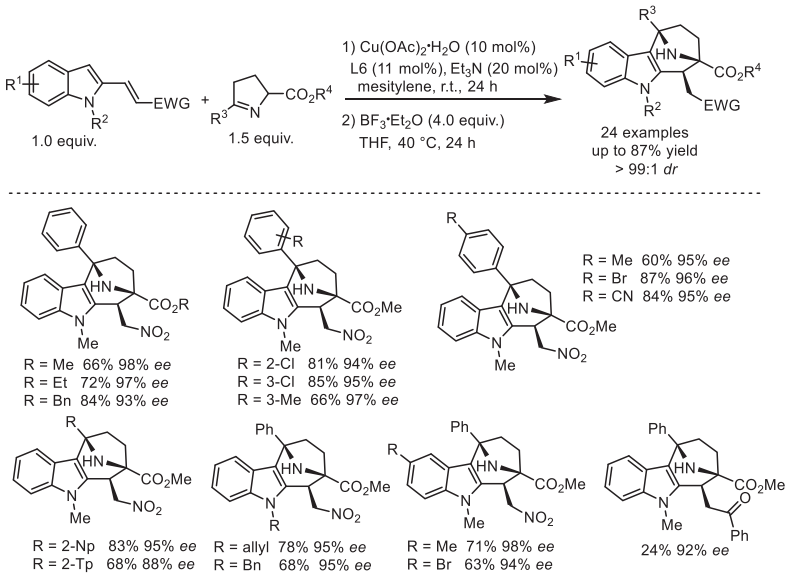
Two years later, the [3 + 3] annulation of cyclic azomethine ylides with substituted 2-vinylindoles constructing tropanes in the presence of Cu(II)/*N*,*O*-ligand complex and Lewis acid $BF_3{\cdot}Et_2O$ was also developed (Scheme 7b) [24]. The synthesis of the desired products was achieved *via* a tandem Michael addition/intramolecular aza-Friedel–Crafts reaction affording a wide range of highly substituted tropane derivatives in good to high yields (Scheme 8).

The synthesis of the THγC core was also accomplished by Davies and Zhu utilizing Rh as the catalyst. In 2017, the rhodium(II)-catalyzed intramolecular annulation (formal C–H functionalization) of indolyl-tethered *N*-sulfonyl-1,2,3-triazoles in the presence of dirhodium carboxylate catalyst ($Rh_2(OOct)_4$) and $NaBH_3CN$ as reducing agent was reported by Davies and Fu [25]. In addition to the synthesis of two THγC representatives in 72% and 81% yields (Scheme 9a), the developed method was suitable for the preparation of THβCs and azepino[4,5-*b*]indoles as well in moderate to good yields. Additionally, by tuning electronic and structural factors of the indole substrate, intramolecular [3 + 2] cycloadditions were also observed leading to polycyclic spiroindoles. Very recently, the diastereoselective access to 1,4-disubstituted THγCs *via* a $[Cp^*RhCl_2]_2$-catalyzed formal [3 + 3] cycloaddition involving sequential ring opening of aziridines initiated by C–H activation and Michael addition has been developed by Zhu and co-workers (Scheme 9b) [26].

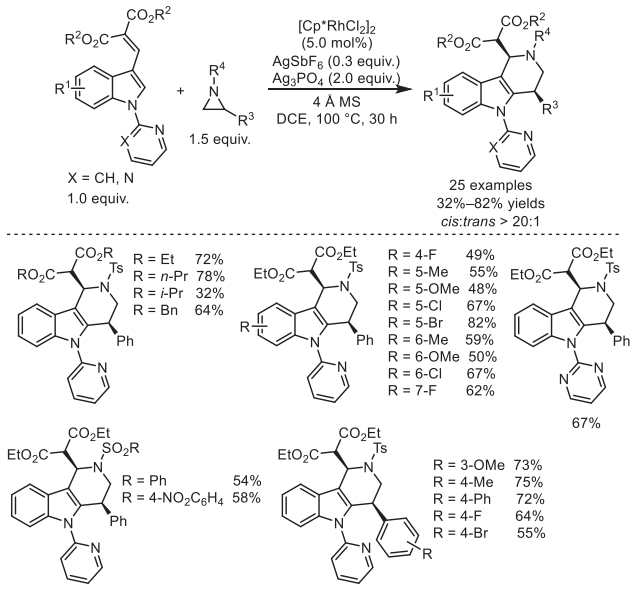
In the presence of $AgSbF_6$ and Ag_3PO_4 additives, a wide substrate scope was demonstrated furnishing the appropriate products in 32%–82% yields with excellent *cis*-diastereoselectivities (Scheme 10).

According to a possible mechanism, the reaction proceeds *via* the formation of a Rh(III) intermediate, generated from the C–H activation reaction of indole to the highly electrophilic Rh(III) species (Scheme 11). Next, coordination with aziridine followed by sequential opening and insertion reaction of the aziridine ring, an eight-membered rhodacycle is generated. Then, ring-opening reaction of the rhodacyle followed by Michael addition provides THγC with *cis*-diastereoselectivity.

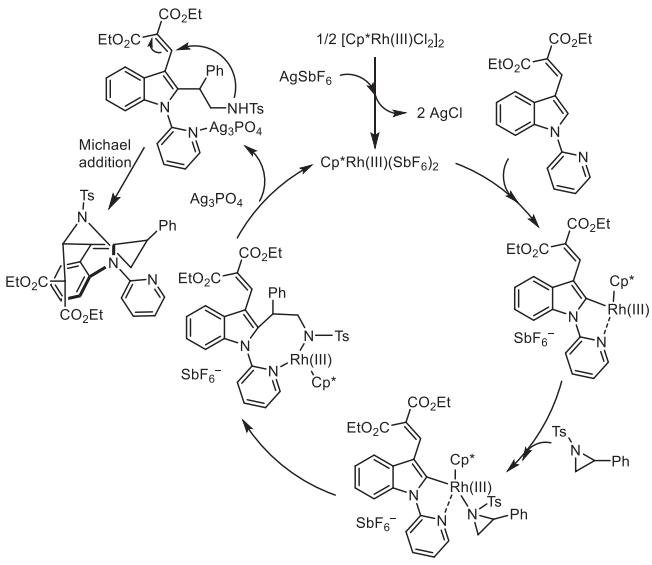
With the participation of Ag transition metal, an approach was realized by Deng in 2018 for the synthesis of highly substituted THγCs from azomethine ylides derived from ketones and 2-indolylethylenes [27]. In this report, the copper-catalyzed [3 + 3] cycloaddition strategy, developed previously by the authors, was implemented applying Ag(I)/Ph-Phosferrox complex in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as base



Scheme 8. Construction of THγCs from copper-catalyzed reaction of 2-vinylindoles and cyclic azomethine ylides.



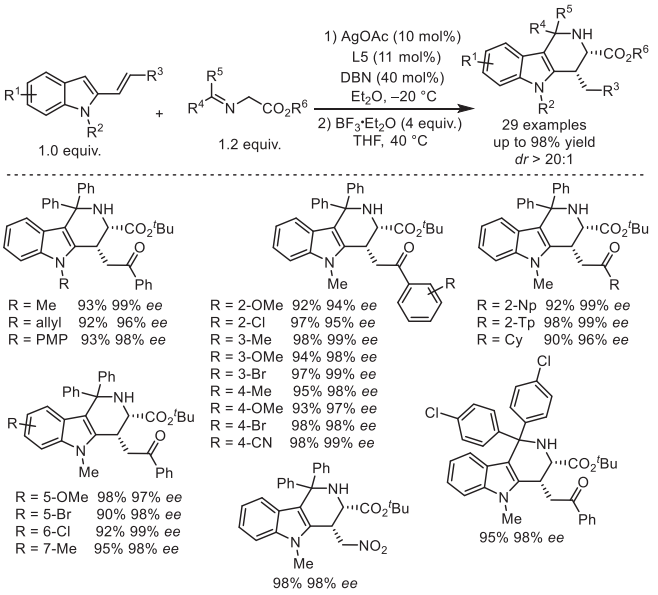
Scheme 10. Rhodium-catalyzed reaction of aziridines with indole derivatives leading to *cis*-1,4-disubstituted-THγCs.



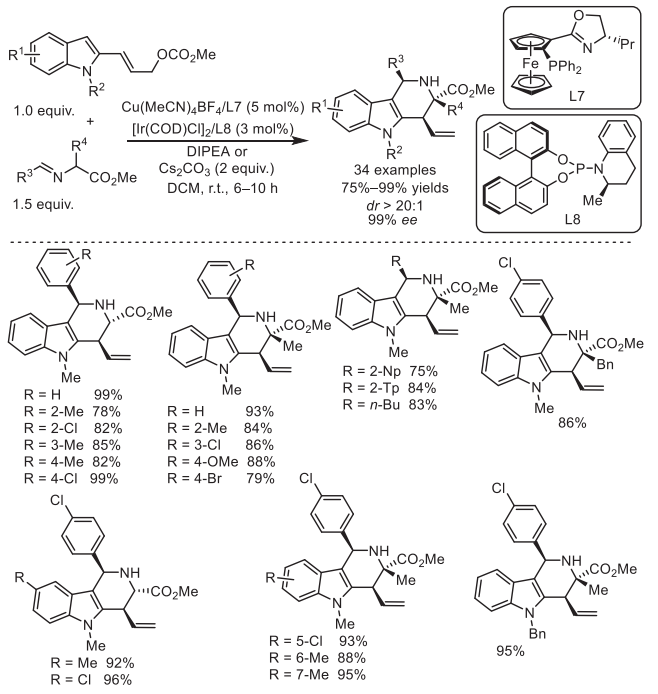
Scheme 11. Proposed mechanism for the rhodium-catalyzed formal [3 + 3] cycloaddition.

(Scheme 12). Notably, the competitive [3 + 2] cycloaddition could completely be avoided by utilizing sterically encumbered azomethine ylides. The regio- and stereoselective one-pot synthesis provided the corresponding products with wide substrate scope in high yields *via* tandem Michael addition and Friedel–Crafts reaction promoted by $BF_3{\cdot}Et_2O$.

A synergistic Cu/Ir catalyst system was also successfully applied for the construction of THγCs. The stereodivergent assembly of the desired skeletons was achieved by Wang and co-workers in 2019 in an efficient cascade process from aldimine esters and indolyl allylic carbonates. *N*,*N*-Diisopropylethylamine (DIPEA) or Cs_2CO_3 was used as the base of the transformation, in which a great number of products were obtained in 75%–99% yields (Scheme 13) [28]. Mechanistic investigations revealed, that a stereodivergent allylation reaction and a subsequent highly stereoselective iso-Pictet–Spengler cyclization are the key elements of the developed transformation.

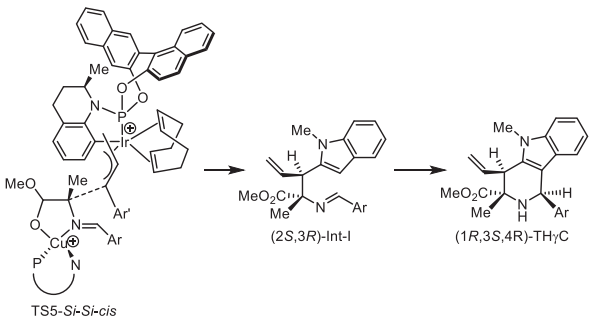


Scheme 12. Silver-catalyzed [3 + 3] annulation of azomethine ylides and 2-indolylethylenes accessing THγCs.

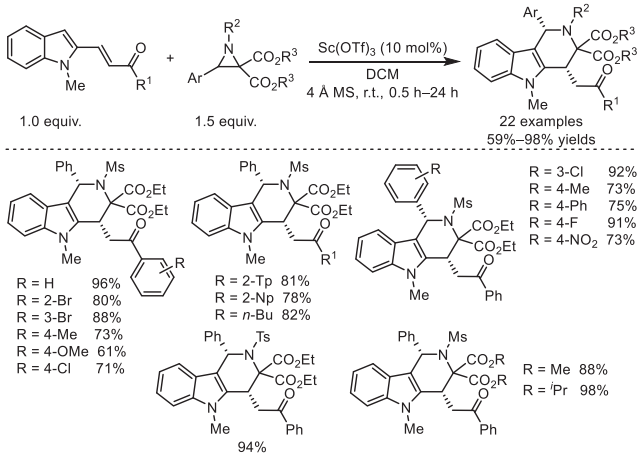


Scheme 13. Synthesis of THγCs with synergistic Cu/Ir catalyst from aldimine esters and indolyl allylic carbonates.

Additional density functional theory (DFT) calculations by the Dang group [29] indicated that the two catalytic cycles merge *via* a preferential nucleophilic addition of the *Si*-face of the Cu(I)-ylide species to the *Re*-face of the Ir(III)-π-allyl species (*Si*-*Re*), in which the two distinct metal catalysts control the absolute stereoselectivity (TS5-*Si*-*Si*-*cis*) leading to intermediate (2*S*,3*R*)-Int-I. TS5-*Si*-*Si*-*cis* was also stabilized though $\pi-\pi$ dispersion interactions between the aryl group of azomethine and the 2-indolyl allyl moiety (Scheme 14). The final THγC product with (1*R*,3*S*,4*R*) configuration is produced *via* the intramolecular nucleophilic attack of the indole C-3 position to the *Si*-face of the protonated imine moiety followed by acid-mediated iso-Pictet–Spengler cyclization.



Scheme 14. Structures of TS5-*Si*-*Si*-*cis*, (2*S*,3*R*)-Int-I and the final (1*R*,3*S*,4*R*)-THγC product.



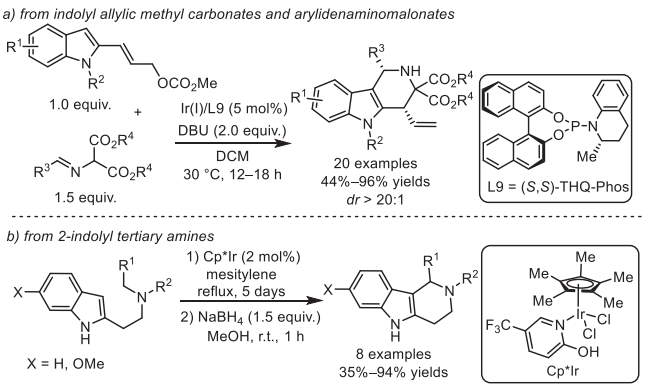
Scheme 15. Sc(OTf)$_3$-catalyzed synthesis of THγCs from aziridine diesters and β-(indol-2-yl)-α,β-unsaturated ketones.

After successfully employing Cu and Ag for the construction of the tetrahydro-γ-carboline core, the applicability of Sc for the diastereoselective synthesis of the same skeleton was also demonstrated by Deng in 2020 [30]. The mild synthetic strategy they developed proceeds *via* the [3 + 3] cycloaddition of 2,2′-diester aziridines with β-(indol-2-yl)-α,β-unsaturated ketones in the presence of Sc(OTf)$_3$ leading to the corresponding products as single diastereoisomers in 59%–98% yields (Scheme 15).

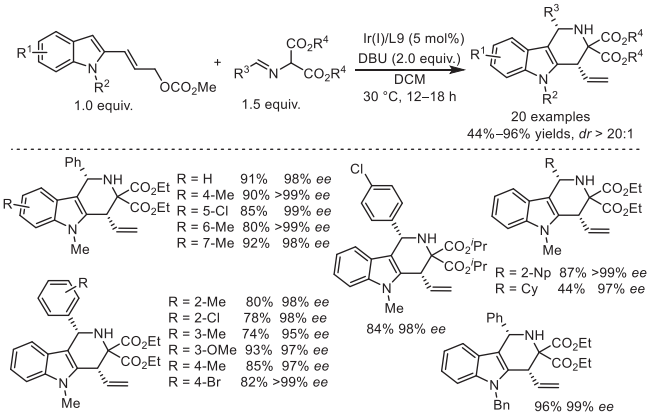
Applying Ir as the transition metal catalyst, two approaches have been realized for the synthesis of tetrahydro-γ-carbolines by Wang and Mardsen in 2021. After the development of a synergistic dual metal (Cu/Ir) catalytic system and its successful utilization in the asymmetric tandem allylation/iso-Pictet–Spengler cyclization accessing highly substituted chiral THγCs, Wang and co-workers also achieved the iridium-catalyzed version of this reaction (Scheme 16a) [31]. Arylidenaminomalonates and indolyl allylic methyl carbonates were used in this transformation in the presence of the Ir(I)/(*S*,*S*)-THQ-Phos complex and 1,8-diazabicyclo[5.4.0]undec–7-ene (DBU) as base providing the desired cycloaddition products in moderate to high yields with excellent enantioselectivities (Scheme 17). The method of the Mardsen group [32] was accomplished starting from 2-indolyl tertiary amines using Cp*Ir catalyst, mesitylene, and NaBH$_4$ furnishing the appropriate products *via* dehydrogenative iso-Pictet–Spengler cyclization in moderate to good yields (Scheme 16b).

2.2. Acid-mediated reactions

Several methodologies have been developed for the construction of THγCs in the presence of various acids such as AcOH, trifluoroacetic acid (TFA), benzoic acid (BzOH) or different phosphoric acid derivatives.



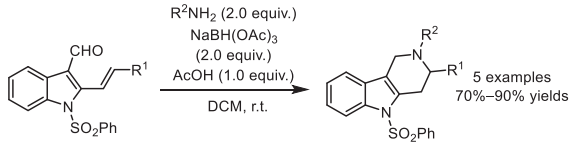
Scheme 16. Iridium-catalyzed syntheses of THγCs from 2-substituted indole derivatives (R^1 = H, alkyl; R^2 = alkyl, aryl, arylalkyl; R^3 = alkyl, (hetero)aryl; R^4 = Et, *i*Pr).



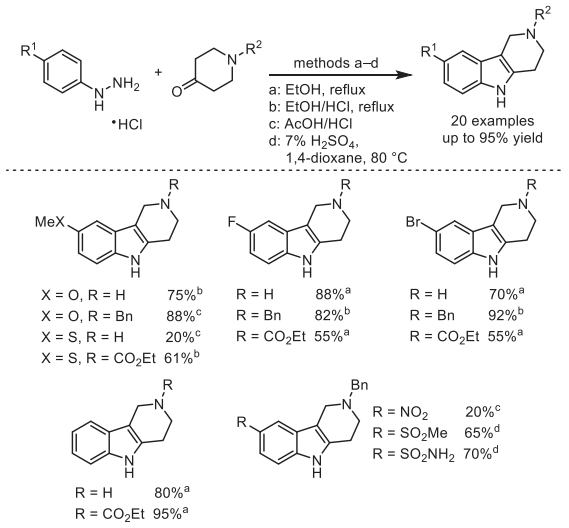
Scheme 17. Iridium-catalyzed synthesis of THγCs from indolyl allylic methyl carbonates and arylidenaminomalonates.

In 2005, the reaction of 2-vinyl-3-indolecarbaldehydes with primary amines for the formation of THγCs under mild reductive amination conditions applying NaBH(OAc)$_3$ and AcOH was reported by Bennasar and co-workers [33]. The desired products were obtained in 70%–90% yields; however, in some cases, the mixture of THγC and the secondary amine by-product was formed in the reaction (Scheme 18). According to the two assumed mechanistic pathways of the transformation, the reaction either starts with the formation of the imine (in the reaction of the primary amine and the carbonyl group of the aldehyde), or the initial conjugate addition of the primary amine to the γ,δ-unsaturated aldehyde. Both intermediates provided the final THγC product *via* intramolecular cyclization.

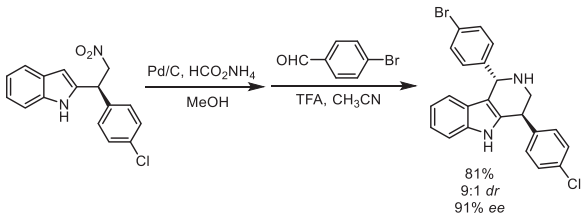
One year later, the Fischer reaction of arylhydrazines with *N*-protected-4-piperidones accessing 8-substituted tetrahydro-γ-carbolines under soft acidic conditions was accomplished by the



Scheme 18. Acetic acid-induced synthesis of THγCs from 2-vinyl-3-indolecarbaldehydes and primary amines (R^1 = H, Me; R^2 = alkyl, arylalkyl, aryl).



Scheme 19. Synthesis of 8-substituted THγCs from arylhydrazines and *N*-protected-4-piperidones.



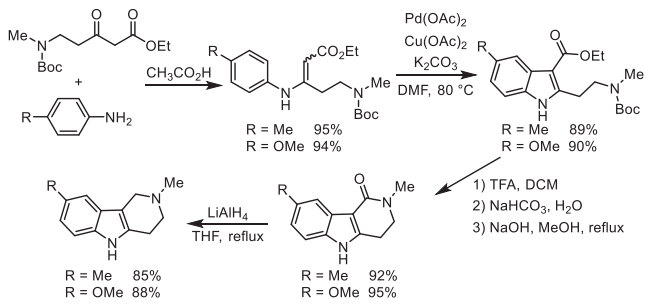
Scheme 20. TFA-mediated synthesis of *trans*-1,4-disubstituted-THγCs.

Hénichart group [34]. Four different acidic conditions (methods a–d) were proved to be suitable medium of the developed protocol leading to the appropriate products in moderate to high yields (Scheme 19). The transformation proceeds through a [3,3] sigmatropic rearrangement followed by cyclization and the elimination of ammonia.

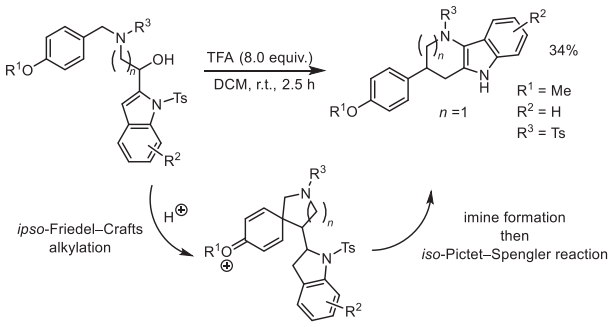
The first enantioselective acid-mediated synthesis of *trans*-1,4-disubstituted-THγC derivative was achieved by You *et al.* in 2009 from a 2-indolyl compound [35]. In the first step, the nitro group was reduced to amino function, then a reaction with 4-bromobenzaldehyde in the presence of TFA was carried out furnishing the desired product in 81% yield with high enantioselectivity (Scheme 20).

In the following years, three other attempts were made with the utilization of TFA in the acid-catalyzed synthesis of THγCs. In 2013, a new approach to construct 4-methyl and 4–methoxy tetrahydro-γ-carboline compounds from readily available 5-amino-3-oxopentanoate derivatives and substituted anilines was described by Zhao and co-workers [36]. In the first step of the sequence, an enamine intermediate was generated, then oxidative cyclization was performed leading to the corresponding indole derivative. Next, intramolecular lactamization was realized in the presence of TFA, $NaHCO_3$ as base, using NaOH in MeOH. Finally, carbonyl reduction with $LiAlH_4$ gave the corresponding THγC products in 85% and 88% respectively (Scheme 21).

One year later, the TFA-promoted skeletal rearrangement of 2-substituted indole derivatives was developed by Hamada *et al.* for the synthesis of six-, seven-, and eight-membered ring-fused tricyclic indoles in 31%–99% isolated yields [37]. The synthesis of a tetrahydro-γ-carboline derivative was realized in 34% yield (Scheme 22). The transformation was assumed to undergo a reaction cascade involving *ipso*-Friedel–Crafts alkylation of phenols,



Scheme 21. Construction of 4-substituted THγCs from 5-amino-3-oxopentanoate derivatives and substituted anilines.

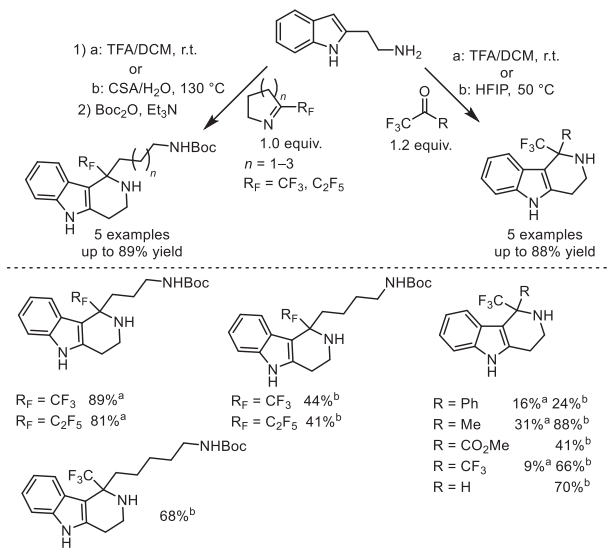


Scheme 22. TFA-promoted skeletal rearrangement of 2-substituted indole derivatives accessing fused tricyclic indoles.

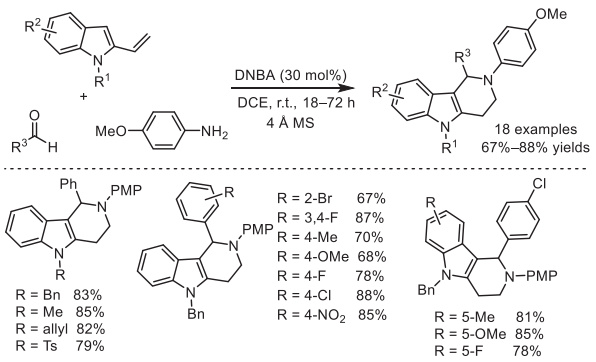
rearomatization of the spirocyclohexadienone unit, and an iso-Pictet–Spengler reaction.

In 2020, the iso-Pictet–Spengler synthesis of perfluoroalkylated THγCs from isotryptamines with trifluoromethylated carbonyls and 2-perfluoroalkyl-substituted five-, six-, and seven-membered cyclic imines was realized by Nenajdenko and co-workers [38]. TFA with either hexafluoropropan-2-ol (HFIP) or camphorsulfonic acid (CSA) was employed in the transformation leading to the corresponding products in moderate to good yields (Scheme 23).

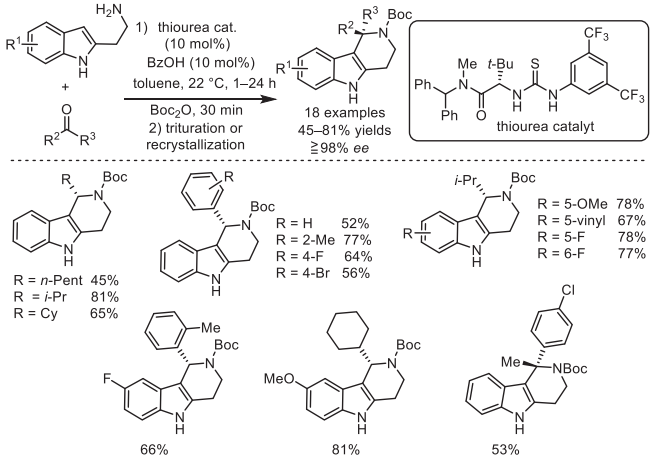
With the employment of 3,5-dinitrobenzoic acid (DNBA), a convenient synthesis of tetrahydro-γ-carbolines was accomplished by



Scheme 23. Acid-mediated synthesis of perfluoroalkylated THγCs from isotryptamines with trifluoromethylated carbonyls and 2-perfluoroalkyl-substituted cyclic imines.



Scheme 24. DNBA-induced multicomponent reaction of aldehydes, anilines, and 2-vinylindoles producing THγCs.



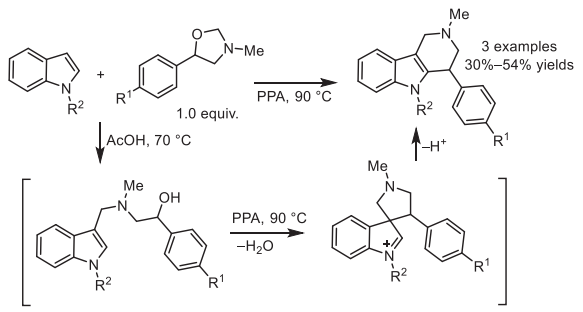
Scheme 25. Synthesis of THγCs from isotryptamines and aldehydes cocatalyzed by chiral thiourea/BzOH system.

Chen *et al.* in 2010 *via* the one-pot, multicomponent reaction of aldehydes, *p*-methoxyaniline, and 2-vinylindoles [39]. The chemo- and regioselectivity of the reaction was fully controlled by the protective group of the indole moiety. Namely, if *N*-protected indole derivatives were used in the reaction, the desired THγC products were afforded in 67%–88% yields (Scheme 24). However, in the presence of unprotected indole derivatives, tetrahydroquinolines were formed as a result of a formal inverse-electron-demand aza-Diels–Alder process.

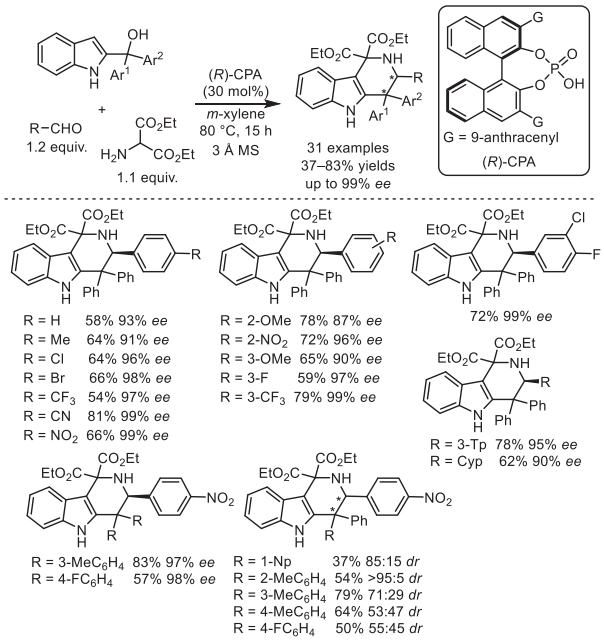
One year later, the one-pot condensation of isotryptamines and aldehydes affording enantiomerically enriched 4-substituted tetrahydro-γ-carbolines induced by a chiral thiourea/BzOH dual catalyst system was reported by Jacobsen [40]. The enantioselective iso-Pictet–Spengler reaction provided the appropriate *N*-Boc-protected products after trituration or recrystallization in moderate to high yields (Scheme 25).

Another one-pot approach for the preparation of 4-aryl-2-methyltetrahydro-γ-carbolines from 5-aryloxazolidines and indoles *via* a Mannich/Friedel–Crafts sequence was developed by Moshkin in 2014 [41]. According to the mechanism of the developed transformation, the first step is the ring opening of 5-aryloxazolidines in the presence of indoles in AcOH leading to amino alcohols. Then a subsequent cyclization with the participation of polyphosphoric acid (PPA) provides the appropriate THγC products in moderate yields (Scheme 26). The desired products can also be obtained directly from 5-aryloxazolidines and indoles in PPA.

Two attempts have been accomplished by Shi and Zhou for the construction of the tetrahydro-γ-carboline core utilizing chi-



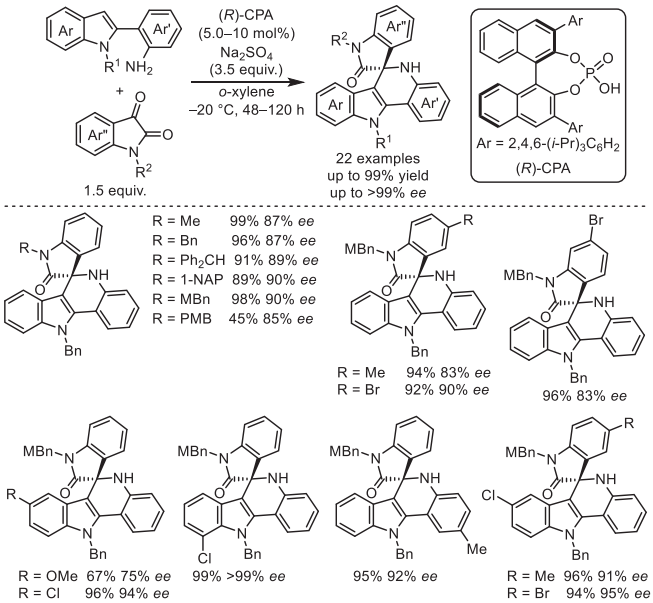
Scheme 26. PPA-mediated one-pot synthesis of 4-aryl-2-methyl-THγCs from 5-aryloxazolidines and indoles (R^1 = H, Br; R^2 = H, Me).



Scheme 27. CPA-catalyzed [3 + 3] cycloaddition of 2-indolylmethanols with azomethine ylides.

ral phosphoric acid (CPA) in the developed transformations. In 2016, they reported the first CPA-catalyzed enantio– and regioselective [3 + 3] cycloaddition of 2-indolylmethanols with azomethine ylides (generated *in situ* from aldehydes and amino ester) leading to a wide range of THγCs in 37%–83% yields with excellent enantioselectivities (Scheme 27) [42]. Concerning the mechanism of the reaction, the CPA anion as a chiral catalyst plays a crucial role in the transformation as it could simultaneously activate both the delocalized cation and azomethine ylide intermediates by dual hydrogen-bonding interaction. However, in contrast to previous reports, an abnormal regioselectivity was observed in the [3 + 3] cycloaddition.

In 2021, the CPA-catalyzed Pictet–Spengler reactions of 2-(1*H*-indolyl)aniline derivatives and isatins by condensation/cyclization was realized by Zhou and co-workers [43]. The developed protocol enabled the synthesis of a series of 5′,11′-dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-ones bearing quaternary stereogenic centers in good to high yields (Scheme 28). According to the plausible transition-state model, the 2-(1-benzyl-1*H*-indol-2-yl)aniline, in the presence of (*R*)-CPA, reacts with isatin to form ketimine *via* dehydration. Then CPA activates the C=N bond *via* hydrogen bonding followed by cyclization. The triisopropylphenyl groups of the catalyst shield the *Si*-face of ketimines; therefore, the nucle-



Scheme 28. CPA-catalyzed Pictet–Spengler reactions of 2-(1*H*-indolyl)aniline derivatives and isatins.

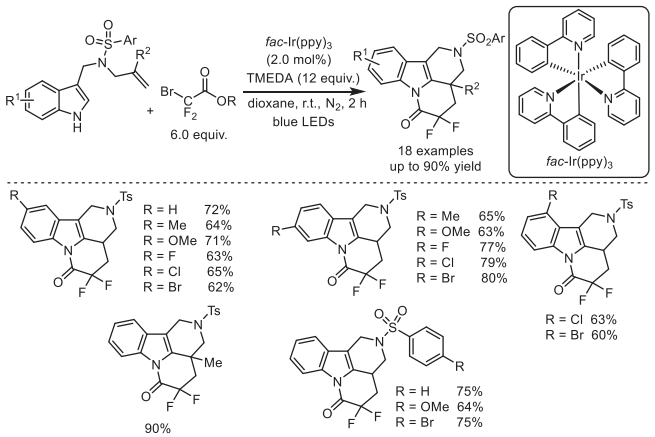
ophilic attack preferentially occurs at the *Re*-face leading to the *R*-configured product.

2.3. Photoredox-catalyzed reactions

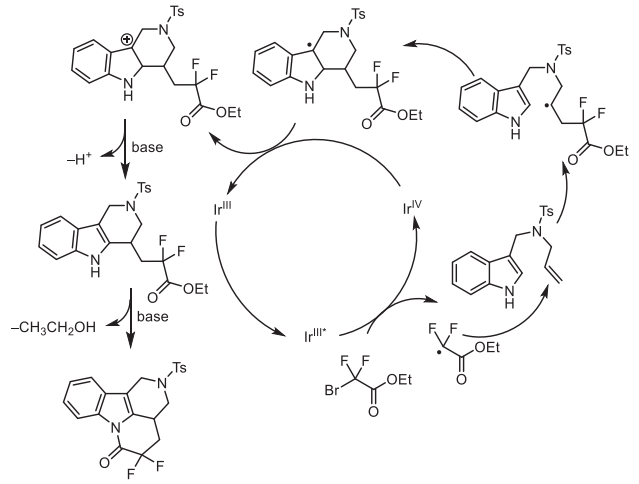
Recently, two approaches have been realized by the Han group for the construction of THγCs *via* photoredox-catalyzed cyclization reactions.

In the first report, the visible-light-irradiated cascade reaction of indole-tethered alkenes with bromodifluoroacetate esters was described accessing tetracyclic THγCs [44]. The developed method utilizing *fac*-Ir(ppy)$_3$ and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), tolerates a diverse pool of substrates affording the desired products in good to high yields under the irradiation of blue LEDs (Scheme 29).

Concerning the proposed mechanism of the visible-light-promoted cross-coupling reaction, initially, the Ir^{III*} excited state of the photocatalyst is formed. Then, a difluoroacetate radical is generated, which attacks the alkenyl bond furnishing a radical intermediate possessing the first new C–C bond. Next, intramolecular cyclization at the α-position of the indole moiety occurs affording a radical γ-carboline intermediate (bearing the second C–C bond



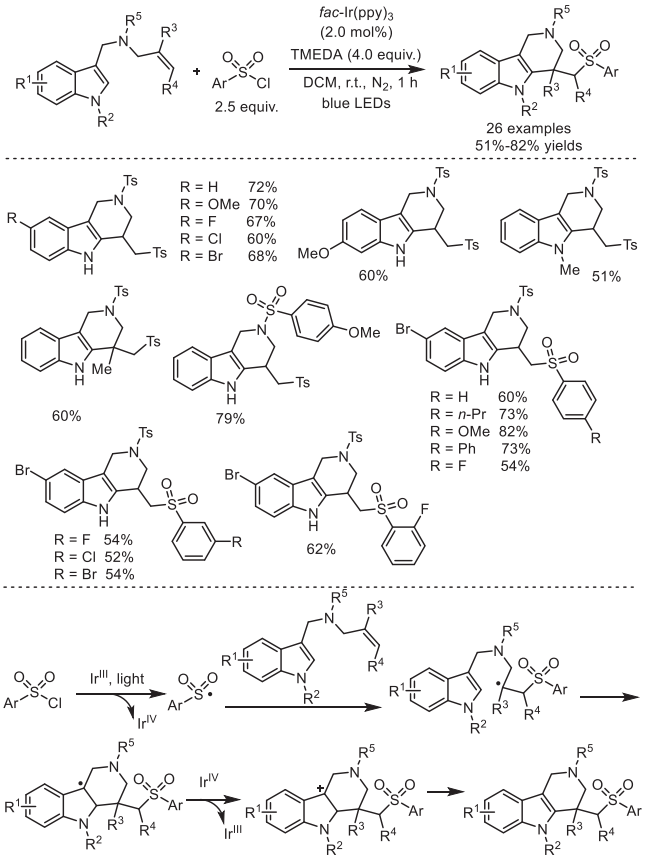
Scheme 29. Visible-light-mediated cascade reaction of indole-tethered alkenes with bromodifluoroacetate esters providing tetracyclic THγCs.



Scheme 30. Suggested mechanism of the visible-light-promoted cross-coupling reaction.

formed), followed by oxidation leading to a carbocationic intermediate along with the regeneration of the Ir^{III} photocatalyst. Subsequently, deprotonation and C–N cross-coupling provide the appropriate THγC product (Scheme 30).

In Han's second protocol, the visible-light-induced cyclization reaction of 3-alkenyl indole derivatives with arylsulfonyl chlorides leading to functionalized THγCs was achieved [45]. Similar to the previous method, *fac*-Ir(ppy)$_3$ and TMEDA were utilized in the transformation in the presence of blue LEDs furnishing a wide range of the corresponding products in 51%–82% yields (Scheme 31). Regarding the possible mechanism of the transfor-



Scheme 31. Visible-light-induced cyclization reaction of 3-alkenyl indole derivatives with arylsulfonyl chlorides giving THγCs.

mation, the key step of the reaction sequence is the generation of the radical intermediate, resulted from the capture of sulfonyl radical by the indole alkenyl moiety. Then, intramolecular cyclization, followed by oxidation and deprotonation affords the appropriate THγC product.

3. Synthesis of bioactive compounds with tetrahydro-γ-carboline core

Tetrahydro-γ-carboline skeleton has demonstrated as a key pharmacore in many bioactive molecules with a diversity of biological activities [1]. In the past years, a great number of bioactive compounds featuring THγC unit have been documented. According to the functionalization site on tetrahydro-γ-carboline heterocyclic system, piperidyl *N*-functionalized and indolyl *N*-functionalized tetrahydro-γ-carbolines were described.

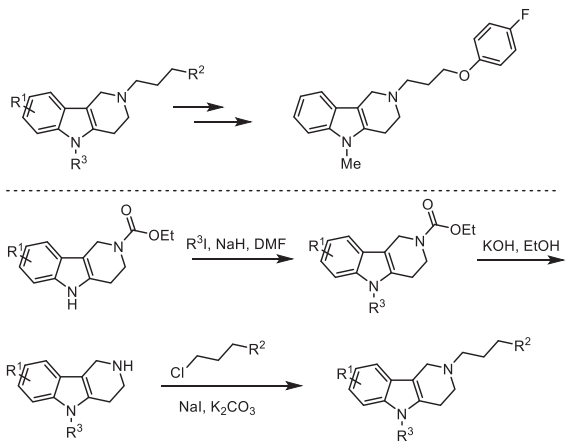
3.1. Piperidyl N-substituted tetrahydro-γ-carbolines

In 2003, Glennon and co-workers developed a series of piperidyl *N*-alkylated tetrahydro-γ-carbolines with affinity activity for 5-HT_{5A} [46]. As shown in Scheme 32, several tetrahydro-γ-carboline derivatives with different substituents on phenyl ring, indolyl nitrogen atom and piperidyl nitrogen atom were screened. The structure activity relationship (SAR) results showed that 5-methyl-2-[3-(4-fluorophenoxy)propyl]-1,2,3,4-tetrahydro-γ-carboline was demonstrated the most efficient one with a modest affinity for 5-HT_{5A} receptors with K_i value of 13 nmol/L.

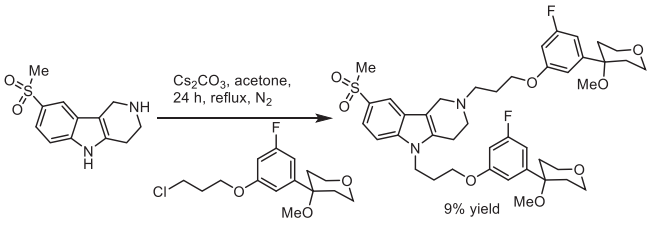
The synthesis of these *N*-alkylated tetrahydro-γ-carbolines was shown in Scheme 32 with tetrahydro-γ-carboline 2-carboxylate as the starting material [47]. First, alkylation on the nitrogen atom with the use of NaI in DMF, and the alkylated intermediate then underwent hydrolysis in the presence of KOH. Finally, the second alkylation with alkyl chloride gave the desired compounds.

The Glennon group also developed several tetrahydrocarboline derivatives for the binding at human 5-HT_{5A} receptors [48]. They designed a series of tetrahydro-γ-carboline compounds based on the leading compound 5-methyl-1,2,3,4-tetrahydro-γ-carboline. The alkyl substitution on nitrogen atom was carefully screened, and the compound featuring N^2-(3-(substituted-phenoxy)propyl) structural unit showed a high affinity.

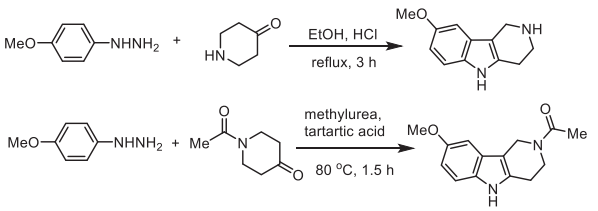
As the previous report on the compound 5-methyl-2-[3-(4-fluorophenoxy)propyl]−1,2,3,4-tetrahydro-γ-carboline [48], Bridoux and co-workers developed a series of THγC bearing a similar 3-(fluorophenoxy)propyl substituent as inhibitors of both 5-lipoxygenase (5-LOX) and cyclooxygenase (COXs)



Scheme 32. Synthesis of piperidyl *N*-alkylated THγCs with affinity activity for 5-HT_{5A}.



Scheme 33. Synthesis of THγCs bearing a 3-(fluorophenoxy)propyl substituent as 5-LOX and COXs inhibitor.



Scheme 34. Synthesis of 6–methoxy-THγCs.

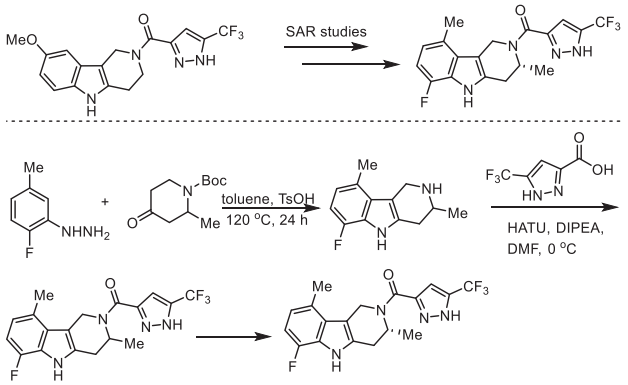
[49]. Interestingly, a substituted group, 4-methoxytetrahydro-2*H*-pyran-4-yl, was introduced to the phenyl ring, and the resulted 8-methylsulfonyl tetrahydro-γ-carboline bearing two methoxytetrahydro-pyran groups at nitrogen atoms of both indole and piperidyl rings showed the best performance (IC_{50} (PC-3) = 6.0 μmol/L, IC_{50} (L-1210) = 3.0 μmol/L).

The synthesis of the targeted compound was shown in Scheme 33, which used 8-methylsulfonyl tetrahydro-γ-carboline as the starting material. Refluxing 8-methylsulfonyl tetrahydro-γ-carboline and 4-(3-(3-chloropropoxy)-5-fluorophenyl)-4-methoxytetrahydro-2*H*-pyran in acetone with Cs_2CO_3 as a base under nitrogen atmosphere afforded the desired product in 9% yield.

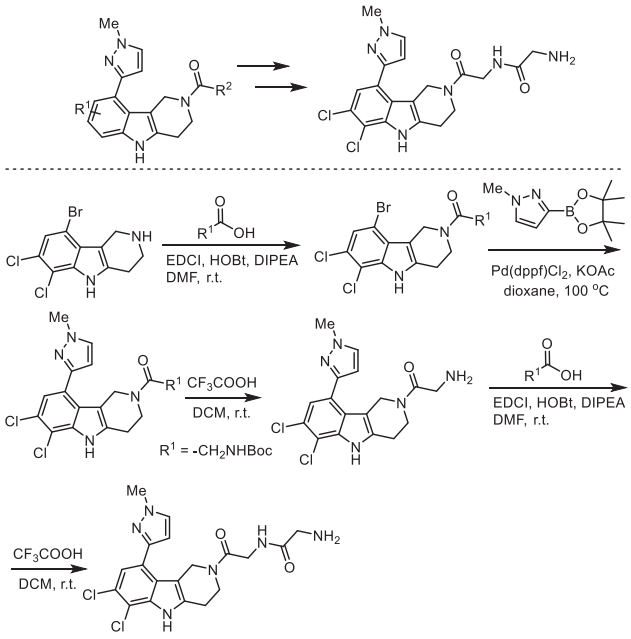
In 2015, Rodríguez-Franco and co-workers designed a series of tetrahydrocarboline derivatives based on the structural fragments of 6–methoxy-1,2,3,4-tetrahydro-β-carboline (pinoline) and *N*-acetyl-5-methoxytryptamine (melatonin) [50]. Among them, two examples containing tetrahydrocarboline unit were shown in Scheme 34. These two compounds were prepared *via* Fischer indole method with (4-methoxyphenyl)-hydrazine and the corresponding 4-piperidone as the starting materials. They were also subjected to pharmacological evaluation, and only the compound bearing a free amino group disclosed affinity for 5-hydroxytriptamine receptor (5-HTR).

In 2020, Pedemonte, Bertozzi, and co-workers discovered a series of THγC derivatives as a novel class of cystic fibrosis transmembrane conductance regulator (CFTR) potentiators [51]. The leading compound featured a key tetrahydro-γ-carboline and 5-(trifluoromethyl)-1*H*-pyrazole scaffolds and was used as a reliable molecule for the SAR study. Careful screening led to the chiral compound with 6-fluoro and 3,9-dimethyl groups as a CFTR potentiator with EC_{50} value of 1.7 nmol/L in F508del-CFTR FRT cells.

This chiral compound was prepared *via* Fischer-indole synthesis with phenyl hydrazine and *tert*–butyl 2-methyl-4-oxopiperidine-1-carboxylate as the starting materials in the presence of TsOH (Scheme 35). Then, condensation reaction of the tetrahydro-γ-carboline intermediate with 5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid by using 2-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU) in the presence of DIPEA resulted in the racemic compound, which was separated *via* semipreparative chiral separation to provide the desired chiral compound.



Scheme 35. Synthesis of 6-fluoro-3,9-dimethyl THγC.

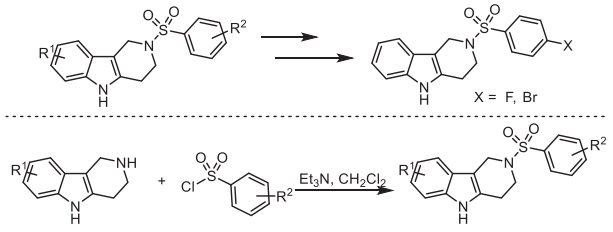


Scheme 36. Synthesis of *N*-glycylglycinoyl THγCs.

In 2021, Tang, Zhang, and co-workers developed a series of THγC derivatives as potent anti-inflammatory agents [52]. These compounds contained heterocyclic substituent on the phenyl ring, and acyl group on the piperidyl nitrogen atom. SAR studies showed that the compound bearing chloro and 1-methyl-pyrazoyl on phenyl moiety, and an *N*-glycylglycinoyl side chain on piperidyl ring was the most potential one with cellular IC_{50} values of 1.38 μmol/L for h-cGAS and 11.4 μmol/L for m-cGAS.

The preparation of these compounds was shown in Scheme 36. Condensation reaction between 9–bromo-6,7-dichloro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole and *N*-Boc amino acids with the use of *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) in the presence of DIPEA gave the *N*-acyl tetrahydro-γ-carboline intermediates. Then, these intermediates underwent a Pd-catalyzed Suzuki reaction with 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole affording the C9-(1-methylpyrazol-3-yl)tetrahydro-γ-carboline intermediate. After the removal of Boc group with the use trifluoroacetic acid, the condensation/deprotection steps were repeated to give the corresponding compound.

Recently, *N*-sulfonyl tetrahydro-γ-carbolines also have been developed as a new type of antischistosomal chemotypes by the Vennerstrom group [53]. SAR studies disclosed that both the *N*-aryl



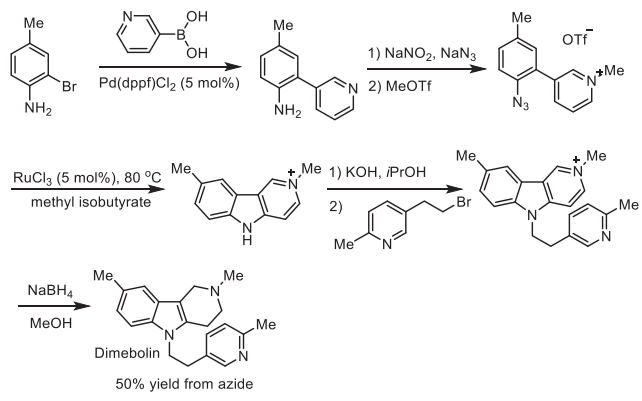
Scheme 37. Synthesis of compound arylsulfonyl THγCs.

sulfonyl and THγC units were essential for the antischistosomal activity, and the results led to the discovery of the most promising 2-((4-fluorophenyl)sulfonyl)- and 2-((4-bromophenyl)sulfonyl)-tetrahydro-γ-carbolines with less than 5 μmol/L IC_{50} values against ex *vivo* schistosoma mansoni. These *N*-aryl sulfonyl tetrahydro-γ-carbolines could be easily obtained from THγC and the corresponding arylsulfonyl chloride in the presence of trimethylamine (Scheme 37).

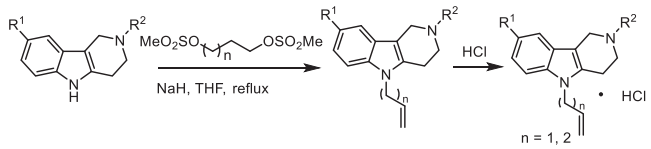
3.2. Indolyl N-substituted tetrahydro-γ-carbolines

Dimebolin is a marketed drug with the trade name of Dimebon™, which originally was used as a non-selective antihistamine for the treatment of allergy. In the past decade, Dimebolin also was developed as a 5-HT6 antagonist with acute cognition enhancing activities [54]. In 2011, Driver and co-workers developed a Ru(III)-catalyzed intramolecular cyclization reaction of 3-pyridyl substituted aryl azides, affording varieties of γ-carbolinium ion as products. The obtained γ-carbolinium ion products were further converted into tetrahydro-γ-carboline derivatives *via* reduction by $NaBH_4$ in methanol [55]. The utility of this protocol was demonstrated by the synthesis of the drug dimebolin with easily accessible 2–bromo-4-methylaniline as the starting material (Scheme 38). Pd-catalyzed Suzuki coupling reaction of 2–bromo-4-methylaniline with 3-pyridine boronic acid gave 4-methyl-2-(pyridin-3-yl)aniline, which was subjected to azidation and methylation reaction with methyl triflate to afford the azide intermediate. Then, Ru-catalyzed cyclization reaction of the azide intermediate successfully provided the γ-carbolinium ion. Subsequently, *N*-alkylation in the presence of KOH with 5-(2-bromoethyl)-2-methylpyridine as an alkyl source, which was followed by a reduction in methanol to give the desired dimebolin with 50% yield from the azide intermediate.

As reported, THγCs bearing various substituted groups at the nitrogen atom of indole moiety showed broad-spectrum activities, and several drugs have been developed based on this structural fragment [56,57].



Scheme 38. Synthesis of dimebolin.



Scheme 39. Synthesis of allyl and vinyl THγCs.

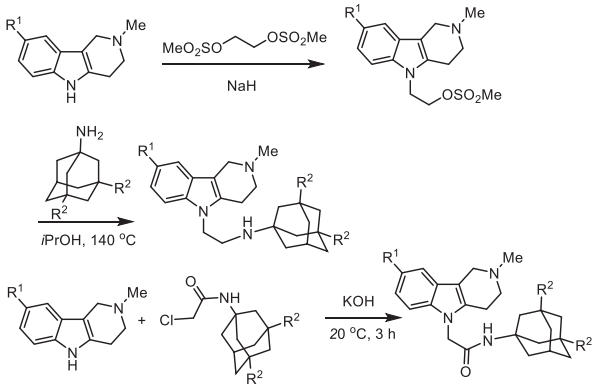
In 2018, Aksinenko and co-workers reported an excellent expansion of such type of compounds, and a series of 5-vinyl- and 5-allyl-tetrahydro-γ-carbolines were developed as potential neuroprotectors [58]. These compounds were synthesized *via* substitution/elimination reaction of alkane dimethyl sulfonates with THγCs in the presence of sodium hydride (Scheme 39). The bioactivity test disclosed that these *N*-vinyl- and *N*-allyl-tetrahydro-γ-carbolines showed moderate inhibitory activity against BChE. In particular, 2-ethyl-8-methyl-5-vinyl-tetrahydro-γ-carboline has been demonstrated to be the most promising one as a potential antioxidant and a selective BChE inhibitor.

Recently, Bachurin and co-workers developed two types of THγC derivatives containing aminoadamantane species based on the key fragments of the known neuroactive agents, memantine and dimebon [59]. All of these THγC-containing compounds showed inhibitory activity against AChE and BChE, in particular, stronger inhibitory activity against BChE.

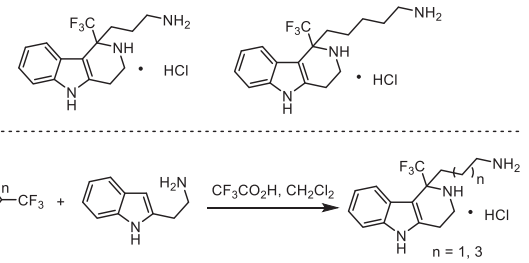
The synthesis of the first type of compounds with ethylene as a linker was presented in Scheme 40, which started from the substitution reaction with ethane-1,2-diyl dimethanesulfonate by using NaH as a base. The generated methanesulfonate intermediate underwent the second substitution reaction *via* heating with 1-aminoadamantanes at 140 °C for three days, and the desired aminoadamantane–γ-carboline compounds were obtained. The second type of tetrahydro-γ-carboline derivatives with an oxoethylene linker was directly synthesized *via* the reaction of THγC with acyl chloride in the presence of KOH in DMF.

In 2019, Bhadra and co-workers documented a series of trifluoromethylated carbolines bearing an aminoalkyl chain on the piperidyl ring, which have been demonstrated to feature antiproliferative effects on human cancer cell lines [60]. Careful SAR studies disclosed that the 1-trifluoromethylated tetrahydro-γ-carboline with a propanyl amine substituent showed the best binding activity and maximum cytotoxicity against colon cancer (HCT-116).

The designed trifluoromethylated tetrahydro-γ-carboline compounds could be easily prepared by Pictet-Spengler cyclization with tryptamine and cyclic trifluoromethylated imines as the starting materials. Mixing tryptamine and cyclic trifluoromethylated



Scheme 40. Synthesis of THγCs featuring aminoadamantane species.



Scheme 41. Synthesis of trifluoromethylated THγCs.

imine in dichloromethane in the presence of trifluoroacetic acid afforded the desired THγC compounds (Scheme 41).

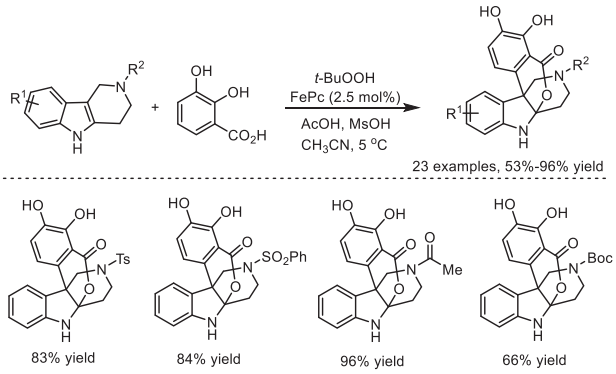
4. Derivatization of tetrahydro-γ-carbolines

THγCs represent an important class of indole-fused heterocyclic organic synthetic intermediates, and have been widely used in the synthesis of natural products, fused polycycles, and spirocyclic compounds. According to the reaction site occurring on the THγC, derivatization of THγCs *via* functionalization on carbon and nitrogen position was described.

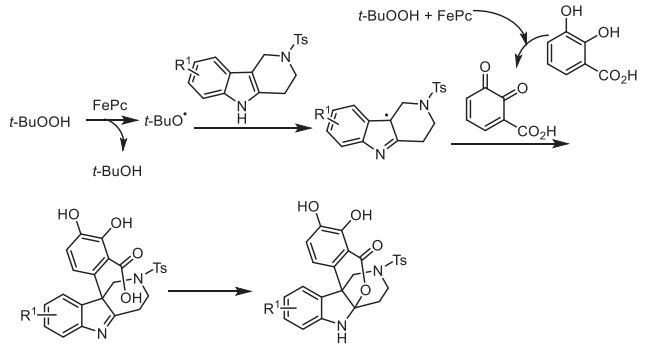
4.1. C-Functionalization

A practical and efficient strategy for the functionalization of THγCs with a low catalyst loading *via* biomimetic catalytic oxidation cyclization reaction was reported by the Chen group in 2018, which achieved the rapid synthesis of isochromanoindolenine derivatives (Scheme 42) [61]. The reaction of THγCs and 2,3-dihydroxybenzoic acid used 2.5 mol% iron(II) phthalocyanine (FePc) as a catalyst with *tert*–butyl hydroperoxide as an oxidant in the presence of acetic acid and methanesulfonic acid. The reaction completed rapidly, usually within about 10 min affording the desired isochromanoindolenines in 53%–96% yields. On the other hand, a broad substrate scope with regard to THγCs was shown in this work. The protecting group on the nitrogen atom could be arylsulfonyl and acetyl, and the same level yields were obtained. However, Boc protecting group provided a decreased yield of 66%. It should be mentioned that this reaction could also be conducted in gram-scale in good yield.

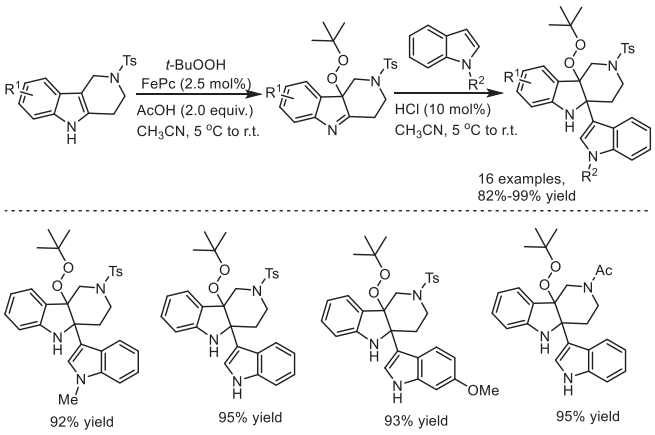
On the basis of the experimental results, the authors also proposed a possible mechanism for this oxidation cyclization reaction (Scheme 43). The reaction starts from the generation of *tert*–butyloxy radical from the reaction of *tert*–butyl hydroperoxide with the aid of FePc, which reacts with THγC at the C3 position of the indole ring to form the tetrahydro-γ-carboline radical. On the



Scheme 42. Oxidative coupling cyclization reaction THγCs.



Scheme 43. Possible mechanism for the oxidative coupling cyclization reaction THγCs.



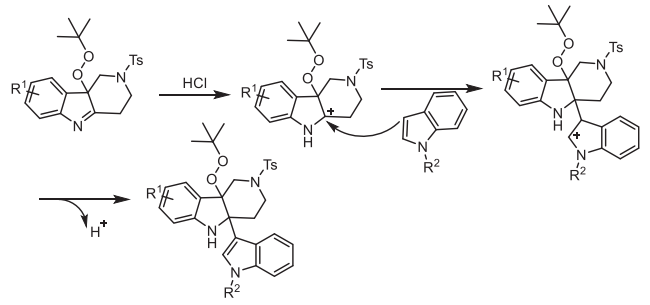
Scheme 44. Two-step oxidative difunctionalization of THγCs.

other hand, the starting substrate 2,3-dihydroxybenzoic acid undergoes oxidation by *tert*–butyl hydroperoxide providing the *ortho*-quinone intermediate. Then, coupling of tetrahydro-γ-carboline radical and *ortho*-quinone intermediate generates the intermediate, which finally affords the isochromanoindolenine derivative in the presence of acid.

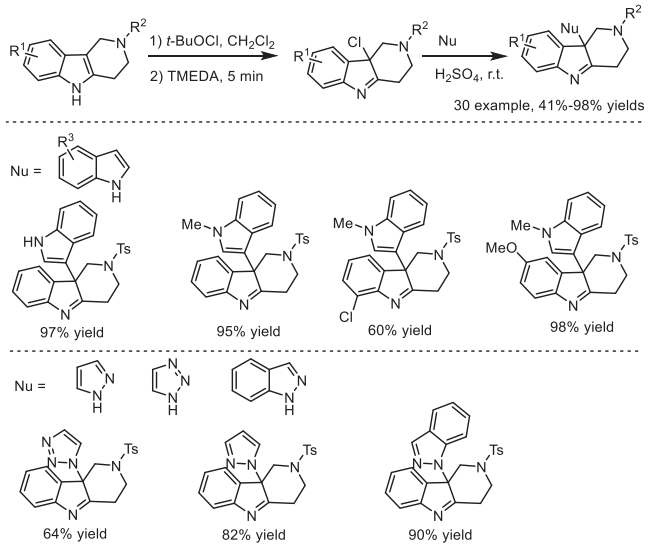
According to the idea on peroxidation of 2-oxindoles with hydroperoxides [62], the same group extended such THγC functionalization strategy in 2021, and developed a two-step oxidative difunctionalization of THγC at the C2 and C3 position of indole ring (Scheme 44) [63]. Under similar conditions with FePc as a catalyst in the presence of acetic acid, they observed the peroxidation of THγC at C3 position of the indole ring without the use of strong acid methanesulfonic acid. The obtained 3-peroxyindolenine intermediates could be further functionalized *via* HCl-catalyzed indolation to form 2-indolyl-3-peroxyindolenines in good to excellent yields. The reaction showed a great tolerance with regard to the structural, electronic and position of substituent on THγC and indole rings. Also, the free N–H of indole substrates worked even better to give the desired products. Furthermore, the authors tried the reaction of the obtained 2-indolyl-3-peroxyindolenines *via* treatment with methanesulfonic acid affording a series of spiroindolenines in excellent yields.

A possible mechanism was provided for the indolation step (Scheme 45). First step is the electrophilic addition of a proton to C–N double bond, affording the THγC cation intermediate. Then, coupling of the cation with the indole happens at C3 position of indole ring to give the indole cation intermediate, which undergoes deprotonation to afford the desired difunctionalized product.

Besides peroxidation of THγC at C3 position of the indole ring by the use of *tert*–butyl hydroperoxide, the Chen group also de-



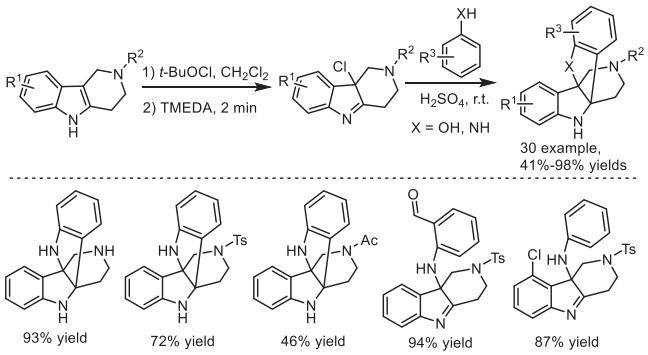
Scheme 45. Proposed mechanism for the two-step oxidative difunctionalization of THγCs.



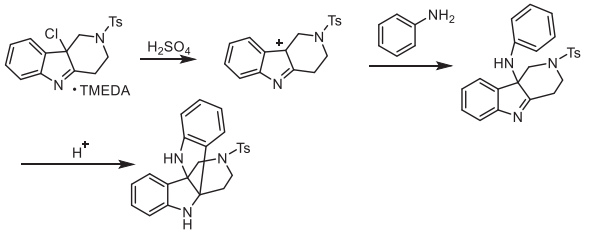
Scheme 46. Oxidative chlorination reaction of THγCs.

veloped an efficient chlorination reaction of THγC by the use of *tert*–butyl hypochlorite in 2019 (Scheme 46) [64]. In this protocol, a series of substituted THγCs were examined, which could be easily converted into the stable 3–chloroindolenine intermediates in the presence of TMEDA within a short reaction time (5 min). The generated 3–chloroindolenine intermediates were further subjected to substitution reaction with varieties of commercially available nucleophiles, including indoles, 1,2,3-triazoles, pyrazoles, indazoles, and 1*H*-pyrazol-5-ols, enabling the synthesis of diversely functionalized heterocycles. The substituent on the nucleophilic indole substrates showed few effect on the reaction outcome. However, the electron-donating substituent on the indole ring of THγC substrates was found to be more efficient to afford the corresponding with excellent yields. The reaction featured mild reaction conditions, easy scalability, and wide substrate scope (55 examples), which provided an excellent strategy for the construction of 3–functionalized indolenine derivatives.

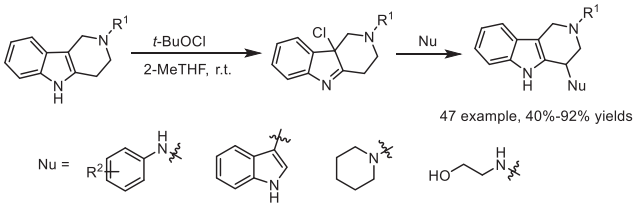
As an excellent extension of the C3 oxidation strategy, Chen and co-workers continued their oxidative functionalization strategy to accomplish a *tert*–butyl hypochlorite promoted one-pot oxidative coupling cyclization reaction of THγCs with various easily accessible anilines and phenols as coupling partners (Scheme 47) [65]. This reaction tolerated a wide range of THγC, aniline, and phenol substrate scope affording the three-dimensional bisindolines in up to 98% yield. Interestingly, THγC with free N–H was well tolerated in this oxidative coupling cyclization reaction affording better yield compared with Ts-protected THγC. Gram-scale reaction was also successful with the generation of desired bisindolines product in



Scheme 47. *t*-BuOCl-promoted one-pot oxidative coupling cyclization reaction of THγCs.



Scheme 48. Proposed mechanism for the one-pot oxidative coupling cyclization reaction of THγCs.



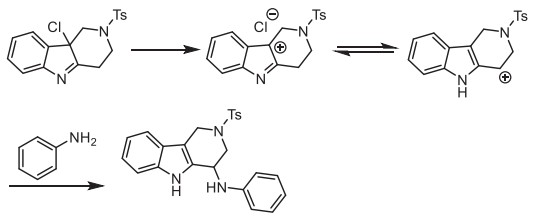
Scheme 49. C–H chlorination/nucleophilic substituent reaction of THγCs.

good yield (82%). In some cases, only the oxidative coupling products were observed. In particular, there existed a substituted group at the adjacent position of the reaction center on both THγCs and anilines. The author mentioned that this might be due to steric hindrance, electronic or other unclear factors.

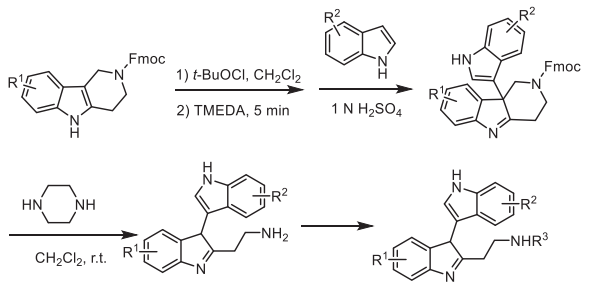
Based on their previous works [64], the reaction also starts from the generation of TMEDA stabilized 3-chloroindolenines, which is converted into indolenine cation *via* the treatment with acid. Then, coupling reaction between the cation intermediate with aniline gave the coupling product, which undergoes the acid-promoted intramolecular cyclization to furnish the desired bisindolines product (Scheme 48).

Later, the same group further extended the oxidative reaction by *tert*–butyl hypochlorite, and developed a substituent reaction of the obtained 3–chloroindolenine by using several kinds of nucleophiles (Scheme 49) [66]. Interestingly, in the absence of acid, the C–H functionalization occurred at the C4 position of THγCs, and several functionalized group, such as aniline, indole and aliphatic amine were introduced with 40%–92% chemical yields. Furthermore, this reaction has been applied in the synthesis of γ-eudistomin U with good chemical yield.

The reaction was proposed to proceed *via* the mechanism in Scheme 50. The 3–chloroindolenine intermediate undergoes heterolytic bond cleavage to give the indolenine cation intermediate, which is converted into its stable tautomerism allylic cation. Finally, coupling reaction of allylic cation with aniline nucleophile furnishes the desired product (Scheme 50).



Scheme 50. Possible mechanism for the nucleophilic substituent reaction of THγCs.



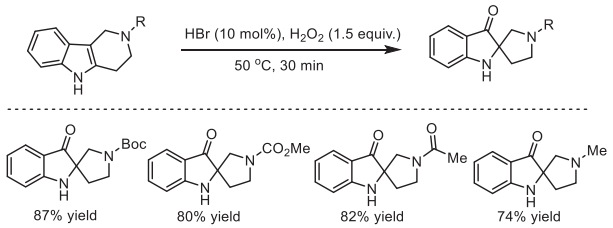
Scheme 51. Synthesis of 3,3′-bisindole *via* reaction of THγCs.

Very recently, the same group further expanded this oxidative coupling reaction of THγC (Scheme 51) [67]. They used Fmoc-protected THγCs as substrates, and the reaction provided an efficient method for the assembly of the 3,3′-bisindole products with moderate yields. The multi-steps reaction proceeded *via* a similar sequence of oxidative coupling reaction with *tert*–butyl hypochlorite and coupling with indole. During the removal of Fmoc protecting group, an unexpected pathway involving piperdine ring opening was observed, instead of the generation of free NH_2 group. It should be mentioned that the utility of the obtained bisindole product was demonstrated by the derivatization reaction with biotin. Investigation of the reaction mechanism was carried out and some key intermediates, including dibenzofulvene and 1-methylpiperazine were detected by HRMS, which discloses that the reaction involves the removal of Fmoc group and demethylenation.

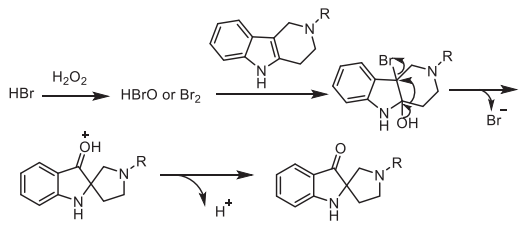
4.2. Oxidative rearrangement

Despite great progress in difunctionalization of aromatic C(sp^2)−H of indole moiety of THγCs has been achieved, direct construction of spirooxindoles *via* oxidative rearrangement represents another important synthetic application of THγCs.

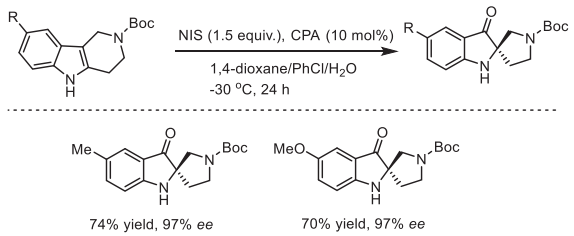
In 2017, Wang, Shao, and co-workers described an effective HBr-promoted oxidative rearrangement of tetrahydro-γ-carbolines by using hydrogen peroxide as an oxidant, leading to the corresponding spiropyrrolidinyl-oxindoles in good to excellent yields (74%–87%) (Scheme 52) [68]. The substituent on the nitrogen atom of piperidine moiety was screened, and the THγCs containing electron-withdrawing groups, such as Boc, ester and acyl, pro-



Scheme 52. HBr-promoted oxidative rearrangement of THγCs.



Scheme 53. Possible mechanism for HBr-promoted oxidative rearrangement of THγCs.



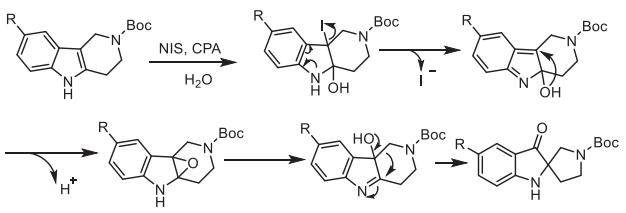
Scheme 54. NIS-promoted oxidative rearrangement of THγCs.

vided better yields. Additionally, this oxidative rearrangement reaction was applied in the synthesis of the natural products (±)-coerulescine and (±)-horsfiline.

The proposed mechanism was presented for this oxidative rearrangement reaction (Scheme 53), which proceeds with hydrobromination product as the key intermediate. The reaction starts from the generation of reactive brominating species *via* oxidation of HBr by hydrogen peroxide, which reacts with THγCs to give the 3–bromo-2–hydroxy indoline intermediate. Then, semi-pinacol rearrangement of the 3–bromo-2–hydroxy indoline intermediate happens to form the spirointermediate with the release of bromide anion. Finally, deprotonation happens to furnish the desired spiropyrrolidinyl-oxindoles.

Later in 2021, Sun and co-workers developed an asymmetric reaction of indoles to oxindoles by using chiral phosphoric acids (CPAs) as organocatalysts and *N*-iodosuccinimide (NIS) as an oxidant (Scheme 54) [69]. The authors screened a series of organocatalysts, which catalyzed the oxidative rearrangement in up to 99% enantioselectivity. Also, several types of indole-based heterocyclic compounds were examined in this organocatalytic reaction, including THβCs, tetrahydropyrano[3,4-*b*]indole, and THγC. Two examples of tetrahydro-γ-carbolines worked very well in this reaction, affording the corresponding spiropyrrolidinyl-oxindole products in moderate yields (70% and 74%) and high enantioselectivities (97% *ee*).

The authors provided a possible mechanism for this oxidative rearrangement of THγC with the formation of epoxide as the key step based on the idea of low migration ability of 2-substituent (Scheme 55). The first step is the electrophilic addition of indole by NIS and water in the presence of CPA, and the resulted intermediate undergoes C-I bond cleavage to give the alcohol intermediate. Then, cyclization reaction happens to form epoxide, which is converted into 3–hydroxy indolenine *via* epoxide ring-opening. Finally, rearrangement happens to give the spiropyrrolidinyl-oxindole product.



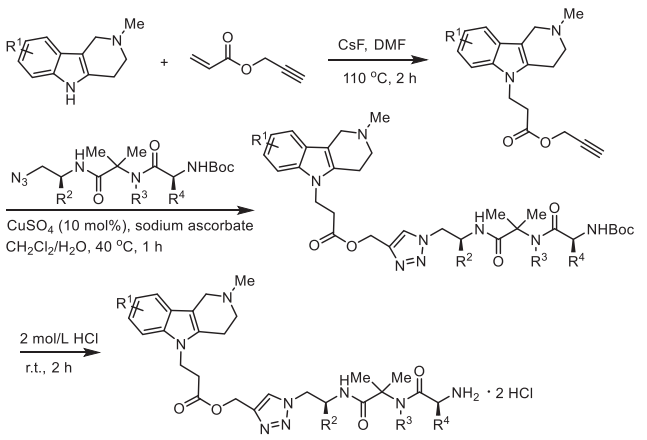
Scheme 55. Possible mechanism for NIS-promoted oxidative rearrangement of THγCs.

4.3. N-Functionalization

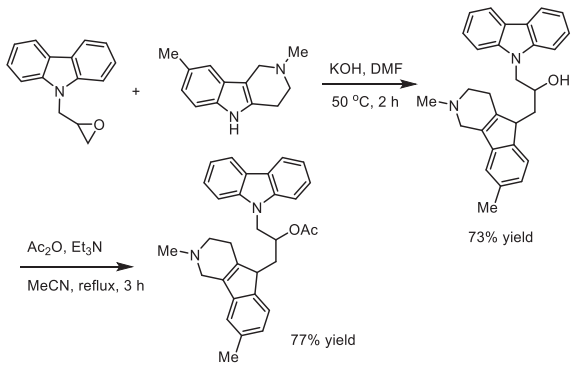
N-Substituted THγCs also represent an important class of bioactive heterocyclic compounds, as they have been documented as neuroprotectors, cognitive stimulants, and antidepressant [70]. On the other hand, free amino unit (NH) on the heterocyclic compounds has always been used as one of the most appealing groups, which can be used for functionalization. Thus, in addition to several examples of indolyl C–H bond functionalization, the funcationlization of N–H of THγCs has also been developed for the synthesis of bioactive *N*-substituted-tetrahydro-γ-carbolines.

Nenajdenko, Bachurin, and co-workers established a divergent functionalization of THγCs *via* a sequence of the Ugi multicomponent reaction and Cu-catalyzed click reaction, which enabled the synthesis of a series of peptide conjugates of *N*-substituted-tetrahydro-γ-carbolines (Scheme 56) [71]. They used THγCs as the starting reagents, which were subjected to an alkylation reaction with propargyl acrylate in the presence of 33 mol% CsF affording THγCs tethered terminal alkynes as products. On the other hand, the azidopeptides were prepared by an Ugi multicomponent reaction of the corresponding isocyanoazides, carbonyl compounds, amines and *N*-protected amino acids. Finally, the peptide was introduced to THγCs *via* a Cu-catalyzed click reaction in the presence of a catalytic amount of sodium ascorbate with a mixture of CH_2Cl_2/H_2O as solvent. Seven *N*-substituted tetrahydro-γ-carbolines containing peptide structural unit were obtained with 60%–70% yields. Interestingly, variation of the amino acid structures has almost no effect on this click reaction. Also, these obtained *N*-substituted tetrahydro-γ-carbolines showed good autooxidation and *t*-BHP-induced lipid peroxidation inhibitory activities.

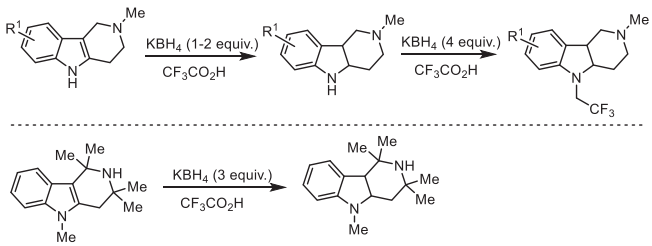
In 2016, Aksinenko and co-workers documented an *N*-alkylation of tetrahydro-γ-carbolines with 9-oxiranylmethylcarbazole as the alkylating reagent (Scheme 57) [72]. The *N*-alkylation reaction of 9-oxiranylmethylcarbazole was conducted in DMF with KOH as a base *via* a nucleophilic ring-opening, which afforded the corresponding alcohol in 73% yield. Additionally, a follow-up chemistry on the alcohol product was conducted, which reacted with acetic anhydride by using triethylamine as a base.



Scheme 56. Synthesis of THγCs tethered peptide.



Scheme 57. *N*-alkylation of THγCs.

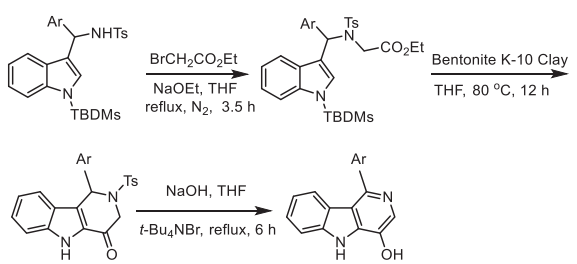


Scheme 58. Reduction of THγCs.

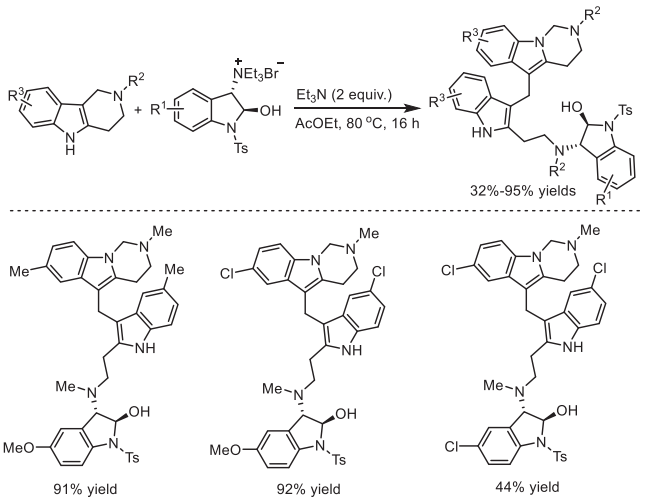
4.4. Miscellaneous

Reduction of alkylated THγC was another transformation strategy, which could provide an efficient method for the synthesis of 1,2,3,4,4a,9a-hexahydro-γ-carbolines. In 1980, A combination of KBH_4/CF_3CO_2H was developed as an efficient system for the reduction of THγC (Scheme 58) [73]. Tetrahydro-γ-carbolines with alkylated piperidine ring and unprotected indole ring were reduced to hexahydro-γ-carbolines by using 1–2 equiv. of KBH_4. The obtained products were further treated with 4 equiv. of KBH_4 in trifluoroacetic acid resulting in the *N*-trifluoroethyl hexahydro-γ-carbolines. When THγC with alkylated indole ring and unprotected piperidine ring was treated with 3 equiv. of KBH_4 in trifluoroacetic acid, only reduction product was obtained without *N*-alkylation reaction.

In addition, THγC derivatives have been applied in the synthesis of 1,4-disubstituted γ-carbolines in 2003 (Scheme 59) [74]. The synthetic route started from the generation of 3-aminomethyl indoles *via* an addition reaction of indoles to *N*-tosylaldimines. Then, *N*-alkylation of 3-aminomethyl indoles happened with ethyl bromoacetate as an alkyl reagent in the presence of sodium ethoxide. The subsequent intramolecular cyclization reaction of alkylated intermediate afforded γ-carbolones with the use of bentonite K-10 clay at 80 °C, which finally underwent aromatization reaction *via* reflux with NaOH for 6 h.



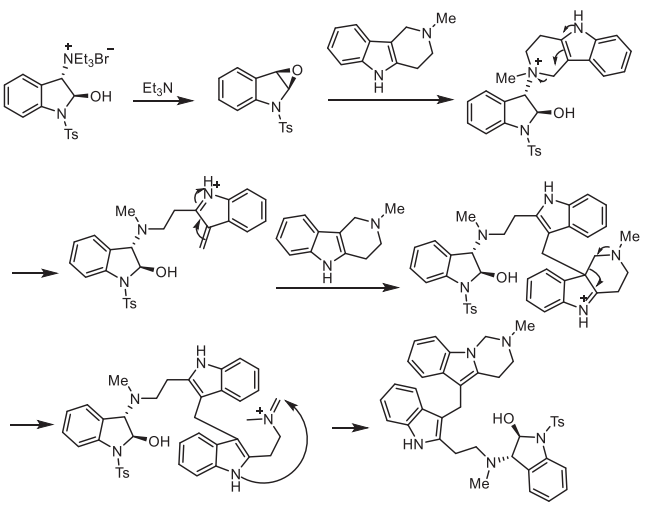
Scheme 59. Synthesis of 1,4-disubstituted γ-carbolines.



Scheme 60. "Open and shut" process of THγCs.

Abe, Yamada, and co-workers developed a stable compound, 2-hydroxyindoline-3-triethylammonium bromide, and used it as an efficient reagent for the formal C3-electrophilic reactions of indoles with several types of nucleophiles [75]. In continuation, they expanded to apply this stable reagent for the synthesis of multi-heterocyclic compounds featuring indoline, isotryptamines, and pyrimido[1,6-*a*]indole structural units *via* a double "open and shut" process of THγCs involving the sequence of Hofmann elimination, vinylogous Mannich, retro-Mannich, cyclization cascade sequences (Scheme 60) [76]. Twelve examples with diverse substituents were presented and up to 95% yield was obtained. Electron-donating group substituted 2-hydroxyindoline-3-triethylammonium bromide provided excellent yields.

A possible mechanism for this multi-step reaction was provided by the authors, which uses indole 2,3-epoxide as the key intermediate (Scheme 61). In the presence of trimethylamine, indole ammonium is converted into epoxide, which reacts with THγC to give the ammonium intermediate. Hofmann elimination of ammonium intermediate generates the indolenium intermediate with the ring opening of piperdine ring. Then, another THγC attacks the benzylic C=C bond of indolenium intermediate resulting in the indolenium cation intermediate. Subsequently, ring opening of piperdine ring of the cation intermediate generates the imine cation intermediate,



Scheme 61. Possible mechanism for multi-step reaction of THγCs.

which undergoes a cyclization reaction to give the corresponding product.

Additionally, THγCs can be looked as cyclic analogs of gramines, and the reaction of their ammonium could also undergo a similar nucleophilic attack with C–N bond cleavage. Tetrahydro-γ-carbolinium salt has been developed as a useful organic intermediate, which could be used in the nucleophilic ring-opening under mild conditions. Many functionalized indole derivatives were able to be prepared with the use of tetrahydro-γ-carbolinium salts [77,78].

5. Conclusions and outlook

THγCs belong to a special type of indole fused heterocyclic compounds, which have been successfully applied in the development of bioactive compounds, even some commercial drugs, such as Dimebon. Thus, the research in the area of THγCs is rapidly growing in the past decade. In this review, the recent chemistry of THγCs was discussed, including the synthetic methods for their preparation, synthesis of bioactive molecules featuring THγC unit and their application in organic synthesis. Although great achievements have been made on this heterocyclic compound, there still exists growing demand to develop efficient approaches for construction of such heterocyclic scaffold. For example, green tools, such as electrosynthesis, will be a new strategy for their synthesis which is environment-friendly and full of potential and innovations. On the other hand, there still exists ample room for their further application in organic synthesis, including difunctionalization of indolyl moiety, ring expansion of piperdinyl ring and spirocyclization. All in all, the application of THγCs in medicinal chemistry and material science is a promising and fast-growing multidisciplinary area, and we expect that this review will inspire new research on this fascinating heterocyclic compound.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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