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Recent synthetic strategies for the construction of functionalized carbazoles and their heterocyclic motifs enabled by Lewis acids†

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This article demonstrates recent innovative cascade annulation methods for preparing functionalized carbazoles and their related polyaromatic heterocyclic compounds enabled by Lewis acid catalysts. Highly substituted carbazole scaffolds were synthesized *via* Lewis acid mediated Friedel–Crafts arylation, electrocyclization, intramolecular cyclization, cycloaddition, C–N bond-formations, aromatization and cascade domino reactions, metal-catalyzed, iodine catalyzed reactions and multi-component reactions. This review article mainly focuses on Lewis acid-mediated recent synthetic methods to access a variety of electron-rich and electron-poor functional groups substituted carbazole frameworks in one-pot reactions. Polyaromatic carbazole and their related nitrogen-based heterocyclic compounds were found in several synthetic applications in pharma industries, energy devices, and materials sciences. Moreover, the review paper briefly summarised new synthetic strategies of carbazole preparation approaches will assist academic and pharma industries in identifying innovative protocols for producing poly-functionalized carbazoles and related highly complex heterocyclic compounds and discovering active pharmaceutical drugs or carbazole-based alkaloids and natural products.

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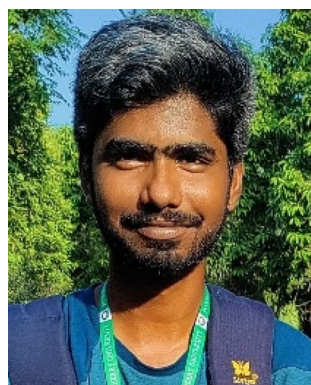
1. Introduction

Carbazoles are one of the most important nitrogen-based tricyclic aromatic heterocycles, as their aryl rings fused polycyclic carbazole scaffolds are present in many drugs and natural products (Fig. 1).^{1–19} In recent years, many research groups have

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Marappan Pradeep Kumar

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of Technology Karaikal, Puducherry, working under the supervision of Dr Vasudevan Dhayalan. His research interests encompass Organocatalysis and Green Chemistry, reflecting his commitment to sustainable and environmentally friendly chemical processes.



Mahantesh G.

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focused on the difficult synthesis of annulated carbazole scaffolds using Lewis acid-mediated methods which have applications in bio-medical and pharmaceutical fields.^{20–27} However several catalytic and non-catalytic methods have been

discovered for the formation of the annulated carbazoles.^{28–32} The first isolation of carbazole from coal tar was reported by Graebe and Glazer in 1872.³³ Later, in 1965 murrayanine, a carbazole derivative, was isolated from *Murraya koenigii* spreng by Bose and his groups.³⁴ The groups of Knölker and Reddy together extensively studied the preparation of biologically active carbazoles and their alkaloids.^{35,36} Carbazole and its derivatives have attracted unique attention in synthetic organic chemistry and material sciences because of their numerous applications.^{37–51} In recent years, various research groups have



P. Amaladass

Dr P. Amaladass was born in Tamil Nadu state, India, in 1978. He was completed his schooling in the year of 1996 from Don Bosco Higher Secondary School in Tamil Nadu state. He received his under-graduation (B.Sc.,-Chemistry) and post-graduation (M.Sc.,-Chemistry) degree from Loyola College in Chennai which affiliated to University of Madras. After completion of his post-graduation, he worked as Junior Research Fellow in Spic Science foundation during ten months period. He obtained his Ph.D., in Organic Chemistry (Year: 2007) from the University of Madras, Department of Organic Chemistry under the supervision of Dr A. K. Mohanakrishnan (Prof. & Head of Organic Chemistry Department, University of Madras). His area of research is in synthetic organic chemistry. He is mainly focused on the synthesis of organic molecules which is highly useful in the area of "Light emitting diodes, solar cells, field effect transistors and hole transport materials". Additionally, he did his post-doctoral research in Weizmann Institute of Science, Israel during the year of 2008–2009 under the supervision of Dr Michael Bendikov. In Israel, he did research on "Synthesis of oligoselenophenes (End free as well as End-capped Saxiselenophene analogues, End free fluorinated plus End capped fluorinated analogues) for organic field effect transistors (OFETs) applications". Then he moved to next post-doctoral research in Nanyang Technological University, Singapore under the supervision of Dr Liu Xue-Wei during the year of 2009–2011. During his tenure in NTU, he synthesized organic dyes (aryl/heteroaryl ethyne bridged and selenophene based dyes) and also he has done basic fabrication part. After post-doc work in Singapore, he moved to Seoul National University from South Korea during the year of 2011 to 2015 under the supervision of Prof. Tae-Lim Choi. He has done research on synthesis of highly region-regular and high molecular weight polymers for organic photovoltaic applications (OPVs). In addition, He also carried out research work on Nanostar and Nanonetwork crystals fabricated by in situ Nanoparticlizations of conjugated polymers. Additionally, he worked on synthesis of organic dyes based on boron analogues (BODPIY chemistry) for medicinal applications as sensors from South Korea in Dankook University during the period of 2015–2016. After completing his post-doctoral research, he moved as research professor at Korea University in South Korea (2017–2018). He has focused on "Synthesis of wide-bandgap conjugated copolymer and its application to non-fullerene polymer solar cells". Currently, he is working as Assistant professor in the department of Chemistry from Madanapalle Institute of Technology & Science (MITS). Now, he is focussing on the synthesis of organic functional materials.



Chitrrasu Manikandan

Dr Chitrrasu Manikandan was born in Thozuvanthangal, Sankarapuram, Tamil Nadu, India. He received his Bachelor of Science (BS) in chemistry from Thiruvalluvar University (2007–2010). At the University of Madras, he completed his MS and PhD in Chemistry. He's presently working on projects Assistant in National Institute of Technology (NITPY) Puducherry now working NHC with the OMC group of Dr Vasudevan Dhayalan and was an interest in synthetic organic chemistry.



Vasudevan Dhayalan

Dr Vasudevan Dhayalan obtained his MSc in Organic Chemistry (2005) and his Ph.D. in Organic Chemistry (2011) at the University of Madras, India. He then joined the group of Prof. Masahiko Hayashi at Kobe University (Kobe, Japan) as a postdoctoral researcher (2011–2012). Later, he worked with Prof. Paul Knochel at the Ludwig-Maximilians-University Munich (Munich, Germany) for three years (2013–2015). In 2016, he joined the group of Prof. Anat Milo at the Ben-Gurion University of the Negev (Beer Sheva, Israel) with PBC outstanding postdoctoral research fellowship (2016–2020). Currently, he works as DST-SERB-Ramanujan Faculty at the National Institute of Technology Puducherry (Karaikal, India), supported by the Ramanujan fellowship (2020–2025). He was recently awarded a prestigious Ramanujan fellowship and Core-Research Grant (CRG) from Science and Engineering Research Board (SERB), India. His OMC research group projects are focused on the design and synthesis of drugs and natural products via organocatalysis and Li, Mg, Zn-organometallics. He has published 79 research articles in reputed international journals till now (September 2023).





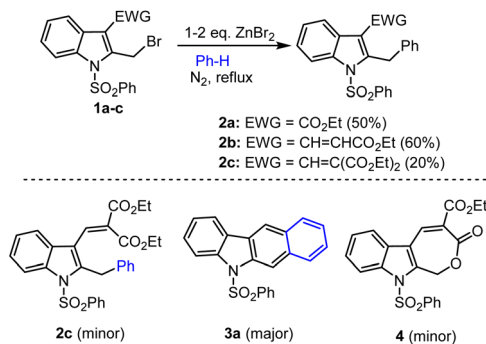
Fig. 1 Carbazole-based biologically active natural products and drugs.

remarkably found that carbazole derivative have divergent biological applications such as affinity to bind with estrogen receptors,⁵² anti-tumor activity,^{53–56} antiparasitic,⁵⁷ antimalarial,⁵⁸ antibiotic,⁵⁹ antifungal,^{60,61} *etc.* Besides their biological applications, they also have bioimaging properties, applications in developing OLEDs,^{46–49} OFETs,⁴¹ solar dyes,⁴³ conducting polymers,³⁷ photovoltaic devices,³⁹ optoelectric properties,^{38,40} and organic semiconductors. Several benzo- and naphthocarbazole analogs have been investigated as potential

anticancer drugs, according to a previous report.^{62,63} Recently, several groups explored Lewis acid-mediated Friedel–Crafts arylation of benzyl halides, benzyl alcohol/acetate, olefins *etc.*^{64–72} Dhayalan *et al.* recently discovered new synthetic strategies *via* a Lewis acid-mediated Friedel–Crafts types arylation and heteroarylation of benzylic indole system.⁷³ In 2008, Mohanakrishnan and co-workers demonstrated innovative cascade techniques for hetero-annulated carbazoles, enabled by Lewis acids using electron-rich arenes and hetero-arenes.^{74–81}

Over the past three decades, *N*-protected indole substrates have been widely used for the selective preparation of highly substituted carbazole derivatives used by various catalytic approaches. Due to their diverse applications, various synthetic methodologies have been developed for the synthesis of substituted carbazoles and annulated carbazole derivatives *via* cycloadditions,^{82–85} metal-catalyzed cross-coupling,^{86–89} metal-free cyclization,^{90–94} multi-component reactions,^{90,95} sigma-tropic reactions^{74–76} and thermal electrocyclic,^{96–99} base-mediated cyclizations.^{100–103} Among these divergent methods, Lewis acid catalyzed methods are highly effective and attractive in academic and pharmaceutical industries due to their non-toxic, atom economy, high-efficiency conversions, and increased reproducibility. Over the past decade, various Lewis acid catalysis methods have been developed, resulting in the production of carbazole analogs because of their simplicity compared to traditional methods.^{74–81} Hence, in this review, we have summarised the various synthetic methods for constructing functionalized carbazoles and their heterocyclic motifs enabled by Lewis acids.

Based on the previous literature reports, various research groups described sustainable processes for the preparation of carbazole and their analogs *via* the Lewis acid mediated Friedel–Crafts types arylation and C–C cross-coupling reactions. In the initial test reaction, Dhayalan *et al.* planned for the preparation of *N*-protected bromomethyl indole,^{73–75} from corresponding indole methyl compounds *via* NBS-mediated radical bromination. The authors decided to prepare a synthetic precursor of *N*-SO₂Ph, Ts, Boc groups protected-2-benzyl indoles **2a–c** starting from the respective ester functional group substituted bromo methyl indoles **1a–c** in the presence of 1–2 equivalent of ZnBr₂ *via* Friedel–Crafts arylation approaches (Scheme 1).



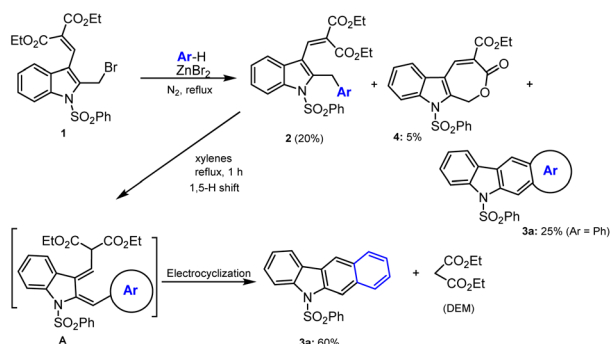
Scheme 1 Arylation of 3-substituted bromomethyl indole used by ZnBr₂.



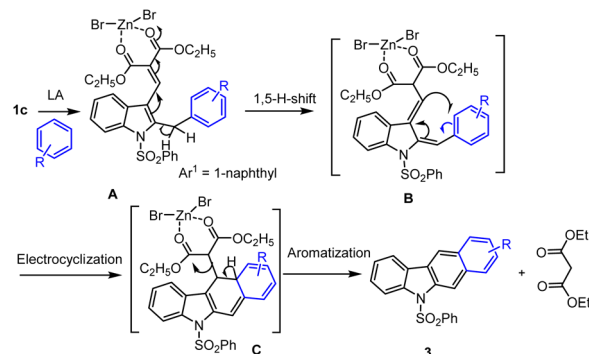
2. Lewis acid catalysed synthesis of polyfunctional groups substituted carbazoles and their related heterocyclic scaffolds

2.1. Lewis acid mediated synthesis of annulated carbazoles derivatives from bromomethyl indoles

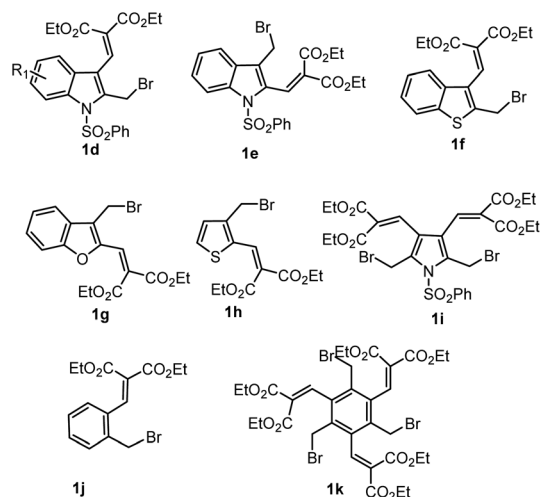
The direct arylation of respective indole-based benzylic bromo compound **1a/1b** using benzene as an arene substrate and solvent in the presence of 2 eq. of ZnBr_2 at reflux condition was found to be successful conversions and led to the formation of desired arylated indole products **2a** and **2b** in 50% and 60% yields respectively. However, under identical sustainable conditions, in the case of diethyl malonate containing benzylic bromo compound **1c**, a similar Friedel–Crafts arylation protocol was found to produce a mixture of product as shown in Scheme 1.⁷⁴ A careful column chromatographic separation of the crude reaction mixture led to the isolation of unexpected domino reaction product of benzo[*b*]carbazole **3a** (25%) and byproduct lactone **4** (5%), in addition to the expected cross-coupling 2-benzylindole **2c** (20%) as cited in Schemes 1 and 2. Authors observed the formation of stable cyclic lactone **4** that might be realized *via* the loss of ethyl bromide from the bromomethyl indole **1c** in the presence of Lewis acid, which was confirmed by the formation of **4** (50–60%) under refluxing **1c** with 2 equiv. of anhydrous ZnBr_2 in DCE. The formation of fused benzo[*b*]carbazole product **3a** might occur from arylmethylindole **2c**. Hence, the *N*-phenylsulfonyl-2-benzylindole **2c** was refluxed in a high boiling solvent, xylene for 1–2 h, which led to the formation of carbazole **3a** in good yield (60%) and diethyl malonate (DEM) as a byproduct (Scheme 2).⁷⁴ Obviously, the arylated compound **2** underwent ZnBr_2 facilitated a thermally facile 1,5-hydrogen shift to form a triene species **A**, which on electrocyclization followed by subsequent elimination of diethyl malonate unit afforded the expected carbazole **3a** in good yields. In addition, authors attempted several annulation reactions of benzyl indole **2b** under reflux in xylenes but were unsuccessful in producing the desired carbazole. Hence, in the case of vinyl ester containing bromo compound **2b**, the expected thermal 1,5-hydrogen shift is not as feasible as that of **2c**.



Scheme 2 ZnBr_2 mediated domino reaction of indole methyl bromides.



Scheme 3 Proposed mechanism for domino reaction of bromomethyl indole enabled by ZnBr_2 .



Scheme 4 Appropriate aryl and heteroaryl methyl bromides for domino reactions catalysed by LAs.

The domino reaction of bromomethyl indole **1c** with arenes or heteroarenes in the presence of ZnBr_2 under heating conditions in 1,2-DCE at 80 °C for 1–5 h produced the arylated indole **A** *via* Friedel–Crafts process. Next ZnBr_2 prompted thermal 1,5-hydrogen shift to form a triene intermediate **B**, which occurs at high-temperature electrocyclization permit. The desired non-aromatic compound **C** formation followed by subsequent aromatization and elimination of diethyl malonate unit afforded the expected carbazole **3a** in good yields as shown in the Scheme 3.^{74–76}

Due to the high simplicity of the present domino reaction protocol reported by Dhayalan *et al.*, they planned and tested this protocol by setting reaction between arenes/heteroarenes and bromomethyl heterocycles and benzylic bromides (**1d–k**) as cited in Scheme 4. Surprisingly, bromo compound **1d–k** on heating with arenes in the presence of 1–2 equiv. of ZnBr_2 or catalytic amounts of 10–20 mol% Lewis acid (InBr_3 , $\text{Yb}(\text{OTf})_3$, FeBr_3 , SnCl_4 , $\text{Sc}(\text{OTf})_3$) led to the formation of a variety of carbazole derivatives (Scheme 5) in the range of 25–65% yields.



Scheme 5 LA-mediated domino reaction of aryl/heteroaryl methyl bromides with various arenes and heteroarenes.



Scheme 6 ZnBr_2 mediated domino reaction of indole methyl bromides with various arenes.

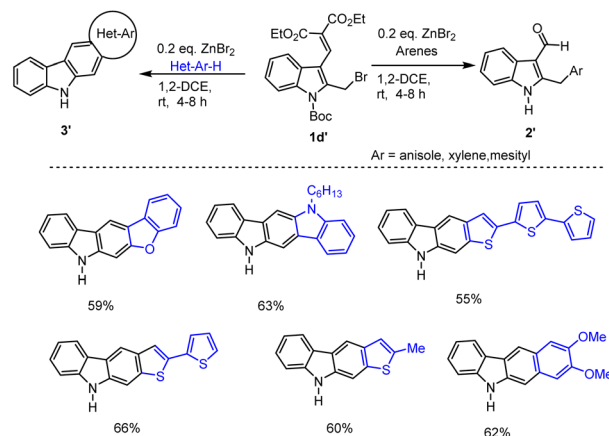
The bromo compounds substrate scope and product limitations of the domino reaction were further explored with 2-bromomethyl indole **1d**, 3-bromomethyl indole **1e**, benzo[*b*]



Scheme 7 ZnBr_2 mediated domino reaction of indole methyl bromides with various heteroarenes.

thienyl 2-methylbromide **1f**, 3-benzo[*b*]furan 3-methylbromide **1g**, 3-bromomethylthiophene **1h**, 2,5-di-bromo methyl pyrrole **1i**, as well as mono and tri-benzyl bromide **1j-k**, under optimized reaction conditions, obtained a broad range of results summarised in Schemes 5–7.^{74–76}

Furthermore, using optimized domino reaction approaches various highly functionalized arenes and heteroarenes were tested under identical conditions in the presence of 2 eq. ZnBr_2 or 10 mol% InBr_3 in 1,2-DCE under refluxing condition 1–5 h. Electron-donating arenes and heteroarenes produced expected



Scheme 8 ZnBr_2 mediated domino reaction of Boc-protected indole methyl bromides with various heteroarenes.



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complex heterocyclic compounds in moderate to good yield as mentioned in the Schemes 5 and 6. This domino system tolerates various heteroarenes such as furan, thiophene, indole, benzofuran, and benzothiophene and arenes such as benzene, toluene, xylene, anisole, veratrole, mesityl, fullerene, naphthalene, and the list of obtained carbazole products and their derivatives have been shown in Scheme 7.

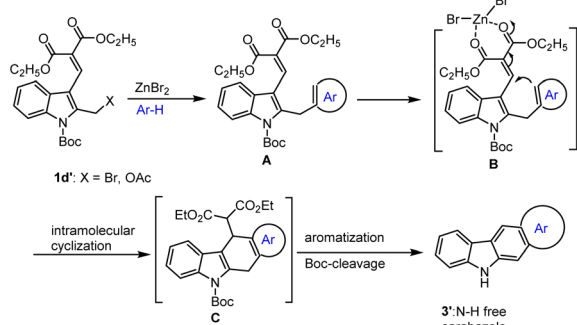
Finally, the challenging bis-annulation of pyrrole bromo compound **1f** was performed with bithiophene/*p*-xylene used by 4 equiv. of ZnBr_2 to afford dithienocarbazole and dibenzocarbazole in 54% and 58% yields, respectively (Scheme 7). Unfortunately, the tribromo compound **1k** failed to produce expected poly-aromatic products **3** under the same reaction conditions.

In 2009 Dhayalan and co-workers reported a direct and general method for the preparation of cyclo[*b*]-fused carbazoles scaffolds that have been established by starting from suitably *N*- SO_2Ph protected 2/3-(bromomethyl)indoles and various arenes and electron-rich heteroarenes under mild conditions *via* Lewis acid catalysis.⁷⁵ The attractive new feature of this efficient protocol is the fact that a broad variety of highly π -conjugated annulated carbazole derivatives can be readily accessed by the suitable choice of commercially available variety of electron-rich arenes and heteroarenes. The annulation method has been successfully extended to (bromomethyl)benzene as well as 1,3,5-tri(bromomethyl)benzene. The results of the Lewis acid-mediated cascade approach indicated that arenes were found to react less favourably with the indolyl-2-methylacetate substrate than with the comparable 2-(bromomethyl)indole. However, in the case of the simple benzylic acetate, the system was found to be more applicable compared to benzylic bromides.

Surprisingly, under identical conditions, in the presence of 20 mol%. ZnBr_2 in 1,2-DEC under refluxing condition 1–5 h the domino reaction of the *n*-Boc protected bromo compound **1d'** with electron-rich heteroarenes such as furan, thiophene, and indole led to the formation of annulated *N*-H free carbazole **3'** in 55–66% yield. Fortunately, the reaction between bromo compound **1d'** and veratrole produced the desired annulated carbazoles in 62% of yield (Scheme 8)⁷⁷ This system clearly indicates that in the case of 1,2-dimethoxybenzene or

heteroarenes, the electron density of the veratryl/heteroaryl unit induces the formation of carbazoles. But solvents like benzene, toluene, xylene, and anisole under the same conditions led to the formation of corresponding 2-arylated indole 3-aldehydes **2'**. The indole-2-arylated intermediate **A** upon intramolecular cyclization promoted by ZnBr_2 may lead to the formation of the desired cyclized product **C**. The later elimination of diethyl malonate and aromatization process followed by simple cleavage of labile Boc unit might have produced *N*-H carbazole derivatives **3'** in good yields as shown in Scheme 9.⁷⁷

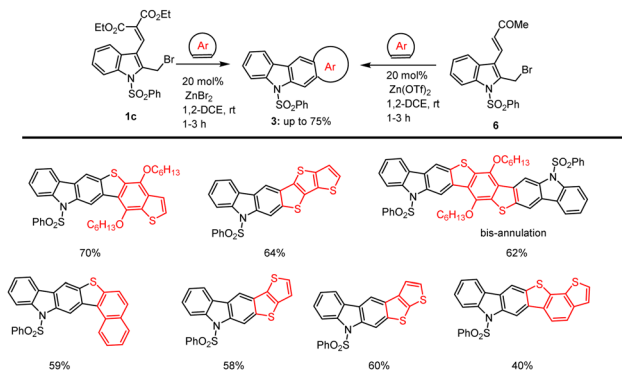
Later, Dhayalan and co-workers developed another new method for the FeCl_3 -Lewis acid-mediated simple and practical cascade annulation sequence that has been developed in this project which lead to new synthetic applications in the field of synthesizing polycyclic aromatic and heterocyclic products. An attractive industrial applicable domino reaction procedure was established using *N*- SO_2Ph -protected bromomethyl indole diacetate **5**. The interesting results were obtained which are summarised in Scheme 10.⁷⁶ The synthesized π -conjugated indole and thiophene-based annulated carbazoles derivatives can be readily be applied in various pharmaceutical and materials applications such as OLED, OFETS, organic semiconductor, organic photovoltaics, and conductive polymers.



Scheme 9 Proposed mechanism for domino reaction of *N*-Boc-bromomethyl indole enabled by ZnBr_2 .



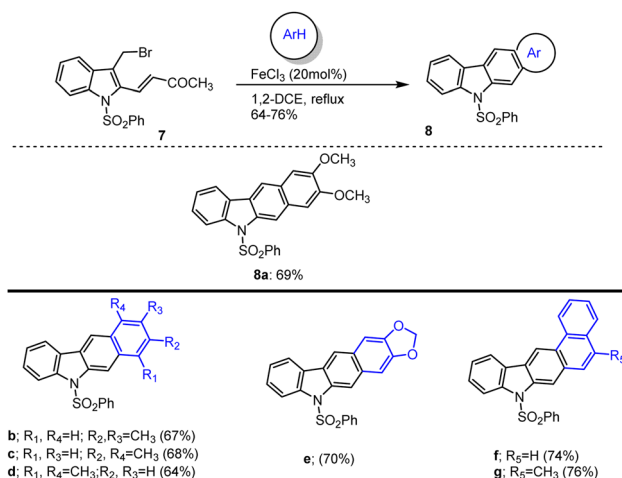
Scheme 10 FeCl_3 mediated cascade annulation of bromomethyl indole with various arenes and heteroarenes.



Scheme 11 Zn(II)-catalyzed annulation of vinyl ester substituted 2/3-bromomethylindole with heteroarenes.

Recently in 2022, the groups of Mohanakrishnan and co-workers reported the straightforward protocol for the annulation of 2-bromomethylindoles **1c** and **6** containing masked aldehyde with electron-rich heteroarenes in the presence of 20 mol% of $\text{Zn}(\text{OTf})_2$ in 1,2-DCE at room temperature for 1–3 h led to the formation of benzo[*b*]ring fused annulated carbazole derivatives in good yields in the range of 40–70%. This reaction condition led to the production of highly complex heterocyclic compounds, **3** in high yields as cited in Scheme 11.¹⁰⁴

In 2021 Mohanakrishnan and his group reported the synthesis of annulated carbazole **8a** 69% by reacting bromomethylindole with veratrole by using 20 mol% FeCl_3 as Lewis acid. They further studied substrate scope by having the best conditions in their hand. The desired annulated carbazoles were generated in **8b–e** 64–70% yields by the cascade annulation reaction of 3-bromomethylindole provided by 2-vinyl ester with xylenes and benzodioxole in the presence of 20 mol% FeCl_3 (Scheme 12).¹⁰⁵ In the same way, naphthocarbazole (**8f–g**) was prepared with yields of 74% and 76%. The proposed Lewis acid



Scheme 12 Preparation of annulated carbazoles.



Scheme 13 Plausible mechanism for FeCl_3 -catalyzed synthesis of carbazoles.

mediated annulation mechanism is cited in Schemes 12 and 13. Initially arylmethylindoles (**A**) is formed and undergo FeCl_3 -catalyzed intramolecular Friedel-Crafts alkylation at the beta position of methyl vinyl ketone (MVK) unit followed by aromatization to give adduct dihydrocarbazole (**C**) followed by aromatization through FeCl_3 influenced elimination of acetone affords carbazoles **8**.

The same group additionally prepared hetero-annulated carbazoles by utilizing SnCl_4 as a Lewis acid in 1,2-DCE at



Scheme 14 Synthesis of hetero-annulated carbazoles.

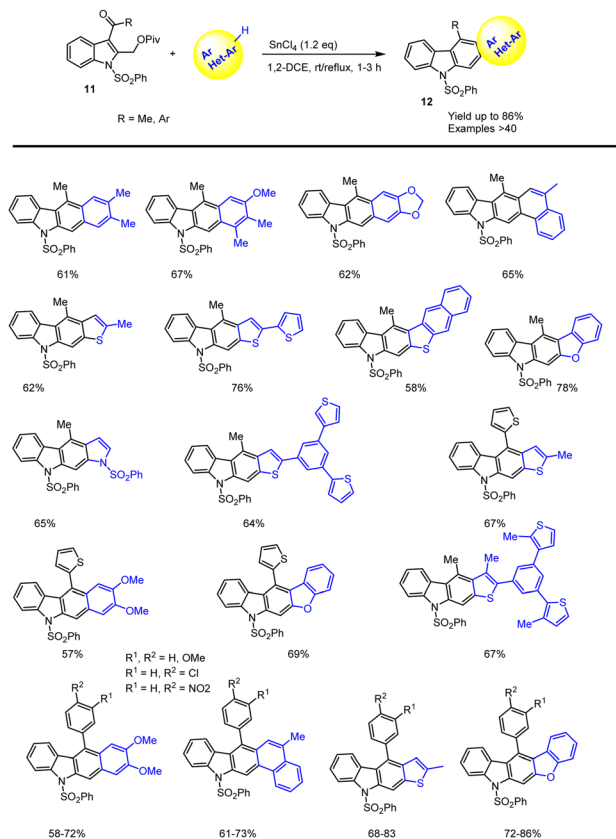
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room temperature. Different hetero-annulated carbazoles were prepared by using the best conditions. The reaction of 3-bromomethylindole **7** with methylthiophene afforded corresponding thienocarbazoles **8a–b** accordingly. An indivisible mixture of carbazole **8c** and **8c'** was formed (1 : 0.4 ratio) by the reaction of bromomethylindole with benzo(*b*)thiophene. **8d** was formed on reaction with 2-bromomethylindole with benzo[*b*]furan. The desired heteroannulated carbazoles **8e–j** were obtained by reaction of bromomethylindole with thiophene-, indole-, and pyrrole-based heteroarenes as mentioned in Scheme 14.¹⁰⁵

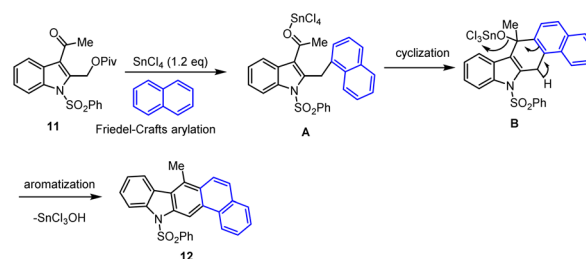
2.2. Synthesis of substituted carbazole analogs from acetoxyethyl-, pivaloyloxymethyl- and hydroxymethyl indoles enabled by Lewis acids

Mohanakrishnan and co-workers showed a new method for the preparation of 5-aryl substituted carbazole derivatives *via* BF₃·OEt₂ Lewis acid-mediated domino reaction of bis-diacetoxyethyl substituted aryl and heteroaryl compounds as shown in Scheme 15.¹⁰⁶ In the presence of 40 mol% BF₃·OEt₂ at rt, 4–6 h, they planned the annulation reactions of indole-derived tetra-acetate **9** with 2-hexylthiophene and bithiophene, which on cyclization followed by aromatization furnished the conjugated annulated heterocycles **10** in 49–58% yields. Similarly, under identical conditions, the annulation reaction with benzofuran afforded the anticipated carbazole product **10** in 53% yields.

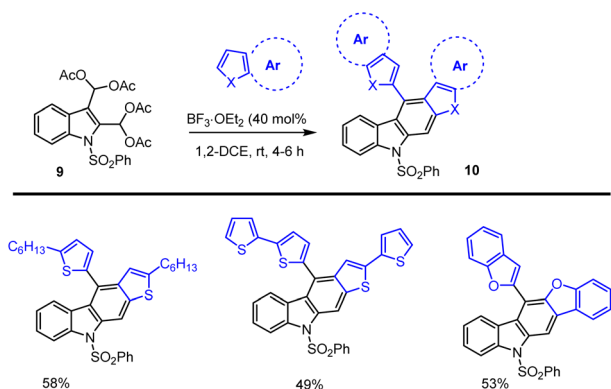
Later, in 2016, the same group developed a straightforward method for preparing aryl and hetero-aryl ring fused annulated carbazoles was developed using SnCl₄-mediated Friedel–Crafts arylation, cyclization, and aromatization reactions from readily accessible 3-acetyl or aryl groups substituted 2-pivaloyloxymethyl indoles **11** (Scheme 16).¹⁰⁷ The initial step involved SnCl₄ mediated Friedel–Crafts acylation giving the intermediate **A** followed by intramolecular cyclization led to the dihydrocarbazole **B**, and the final steps involved a simple aromatization process to offer the expected naphthocarbazole **12** as shown in Scheme 17. The required indole starting material is



Scheme 16 SnCl₄-catalyzed cascade reaction of 2-pivaloyloxymethyl indoles with various arenes and heteroarenes.



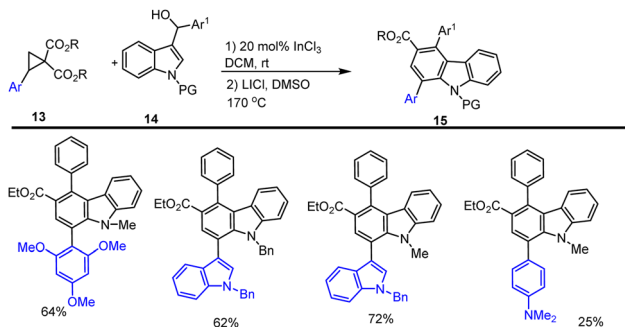
Scheme 17 Proposed mechanism of SnCl₄-catalyzed cascade reaction of 2-pivaloyloxymethyl indoles.



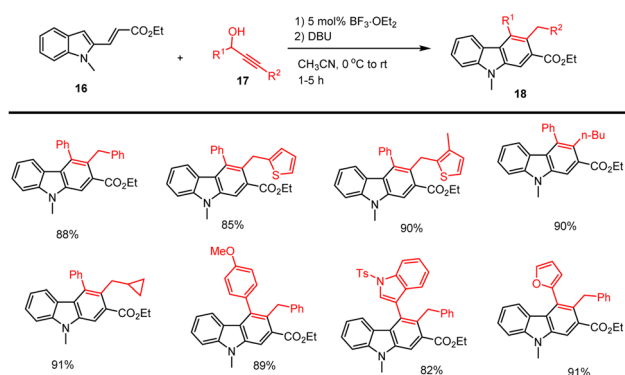
Scheme 15 BF₃·OEt₂ Lewis-catalyzed construction of carbazole motifs.

easily prepared from commercially available 2-methylindole *via* Friedel–Crafts acylation method, followed by NBS-bromination and pivaloylation steps. Remarkably, various electron-poor and electron-rich aryl units including indoles or different heterocyclic systems are well tolerated in the presence of stoichiometric amount of SnCl₄. Moreover, this protocol could be extended to the successful synthesis of poly-heterocyclic compounds *via* bis-cascade annulation of 2,5-bis-(2-pivaloyloxymethyl)pyrrole under optimized conditions, which can offer good yield of complex carbazole.

In order to synthesize highly substituted carbazole analogues **15**, Banerjee and his colleagues established an efficient cascade protocol in 2019 for annulating DACs and indonyl



Scheme 18 Lewis acid catalyzed [3 + 3] annulation with indole and DACs.



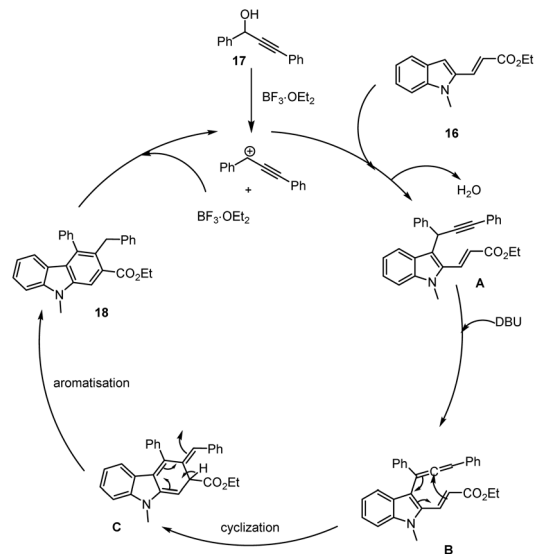
Scheme 19 $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed construction of carbazole.

methyl 3-alcohol using Lewis acids. The annulation of indole alcohol **14** was performed at room temperature, with cyclopropyl ester **13** using a 20 mol% InCl_3 catalysed [3 + 3] annulation in DCM, and the desired highly substituted carbazoles **15** was obtained with moderate to good yield, up to 72%, as illustrated in Scheme 18.¹⁰⁸

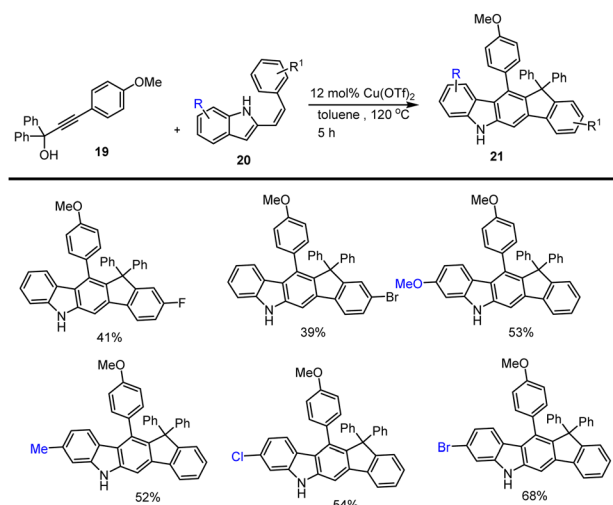
2.3. Synthesis of annulated carbazoles from propargylic alcohols and ester used by Lewis acids

Reddy *et al.* demonstrated the mild conditions for the synthesis of carbazole analogs **18** using a catalytic amount of Lewis acid ($\text{BF}_3 \cdot \text{OEt}_2$, 5 mol%) with the addition of propargylic alcohols **17** and indole ester **16** through Friedel–Crafts arylation and electrocyclization of allene **B** in DBU, CH_3CN at room temperature for 1–5 h. Applying this method allows various polycyclic aromatic compounds to be synthesized efficiently as shown in Schemes 19 and 20,¹⁰⁹ the reaction proceeds under sustainable conditions, yielding water as the byproduct.

In 2018 a new copper(II)-catalyzed intermolecular cascade annulation approach for the construction of a large variety of pentacyclic backbone having valuable carbazole derivatives **21** was developed from easily available propargylic alcohols as a substrate **19** reported by Liang and his group. This procedure,



Scheme 20 Proposed reaction mechanism for the construction of carbazoles.

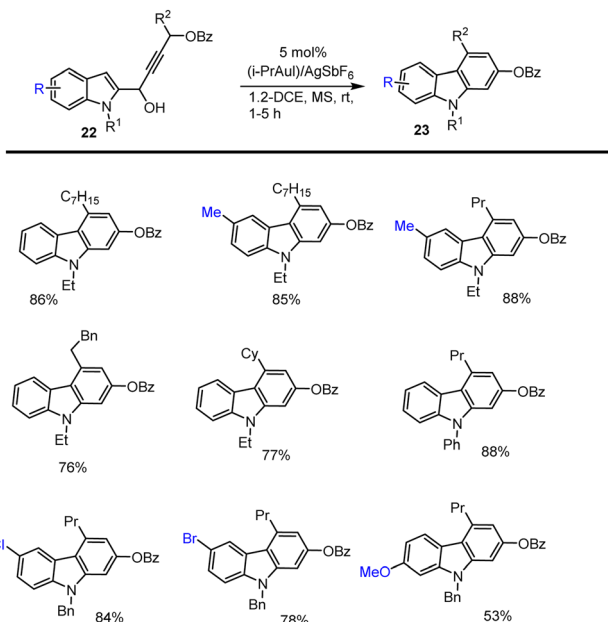


Scheme 21 Lewis acid-catalysed synthesis of highly substituted carbazole from propargylic alcohols.

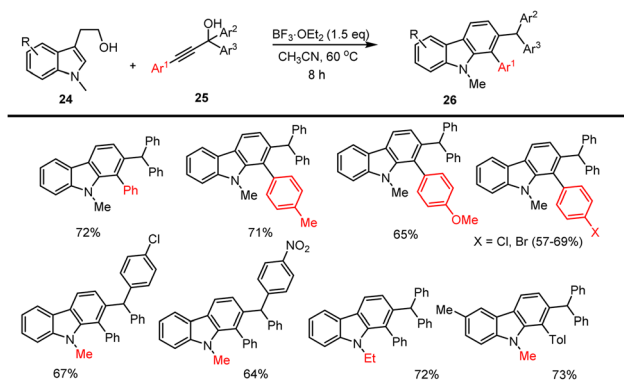
which involves a following sequences Meyer–Schuster rearrangement/-isomerization/cascade cyclization, permits facile and atom-economical access to various carbazole based heterocyclic compounds with wide-range of functional-group tolerance in good to moderate yields in toluene at 120 °C under mild conditions as shown in Scheme 21.¹¹⁰

In 2014 Ma and his groups developed a simple and more efficient $[\text{i-PrAuCl}]/\text{AgSbF}_6$ -catalyzed cascade reaction of indole alkynols **22**, for which starting materials are readily available and prepared from the 1,2-addition of indole-carbaldehydes with the related terminal alkynes in presence of 4 Å MS, offering various functional groups substituted carbazoles **23** with good yields under mild conditions. This cascade reaction





Scheme 22 Au-catalysed preparation of carbazoles.

Scheme 23 BF₃·OEt₂ Lewis acid catalyzed preparation of carbazole.

tolerated various functional groups including electron-rich and electron-poor substituents in the presence of 5 mol% Au catalyst in 1,2-DCE at 25 °C for 15 h and obtained results are summarised in Scheme 22.¹¹¹

BF₃ Lewis acid promoted annulated cascade reactions carried out between indole alcohol **24** and propargylic alcohols **25** furnished carbazoles with excellent selectivity and good yields of carbazoles **26** up to 72% based on the substrate structure reported by Huang *et al.* This cascade reaction tolerated various functional groups including electron-rich and poor substituents in the presence of 1.5 eq. of Lewis acid in CH₃CN at 60 °C for 1 h as cited in Scheme 23.¹¹²

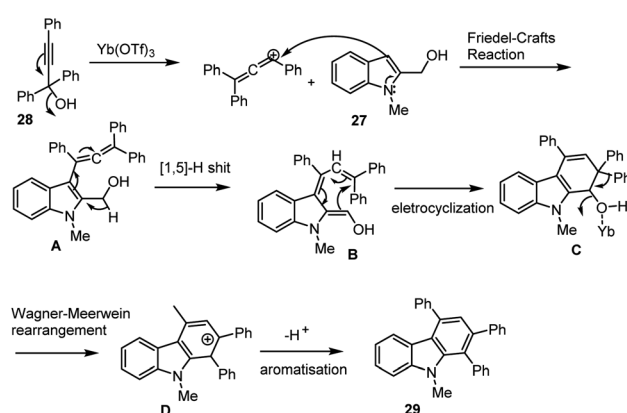
Through Lewis acid catalysed dehydrative [3 + 3]-annulation of easily available indole methyl alcohols **27** and substituted propargylic alcohols **28**, Wang *et al.* investigated a new technique for producing nitrogen-based heterocycles. It was



Scheme 24 Synthesis of carbazole via Lewis acid catalyzed cascade reaction.

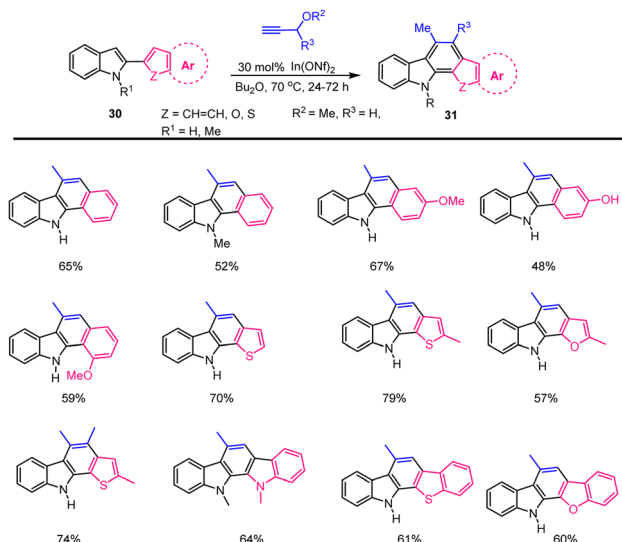
established to produce the required poly functional groups substituted carbazole derivatives **29** with moderate to good yields and under sustainable conditions, however it simply produced water as a green byproduct. The proposed cascade annulation reaction and the mechanism was described in the Schemes 24 and 25 involving the following sequences such as a cascade domino process involving Friedel–Crafts-type allenylation, 1,5-H shift, 6π-electrocyclization, and Wagner–Meerwein rearrangement, aromatisation process.¹¹³

Tsuchimoto, Shirakawa and their groups have established a new annulation method that sustainable system permits the assembly of readily available indole building blocks **30** convert into diverse aryl- and heteroaryl ring fused annulated[a]carbazoles **31** enabled by an In(ONF)₃ Lewis acid catalyst in 2005. The primary characteristics of this novel approach are the direct application of aromatic C–H bond activation and the evident absence of extra-directing functional groups on the aryl substrates. Various aryl and heteroaryl systems tolerate this annulation protocol in indole building blocks and the list of



Scheme 25 Proposed mechanism for Lewis acid catalyzed cascade reaction.



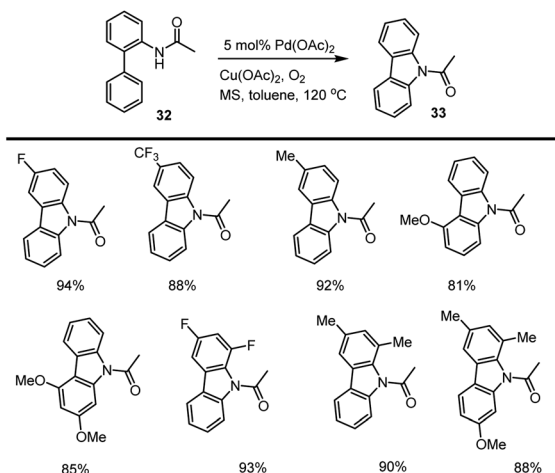


Scheme 26 In(ONf)₃-catalyzed annulation of 2-aryl and heteroaryl indoles with propargyl ethers.

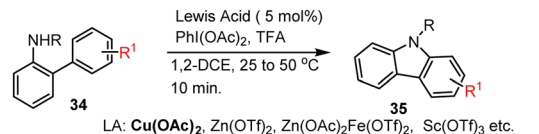
obtained conjugated carbazole products as summarised in Scheme 26 in high yield.¹¹⁴

2.4. Synthesis of annulated carbazoles *via* intramolecular C–H amination approaches

Jiang *et al.* in 2008 developed a novel method for the preparation of unsymmetrical carbazole derivatives **33** enabled by 5 mol% Pd(OAc)₂. The intramolecular cyclization approach involves the selective functionalization of an aromatic C–H bond and the construction of an intramolecular new aromatic C–N bond. This coupling method is well-suited to a variety of electron-rich and poor functional groups. The efficacy of the new method was established by the concise preparation of



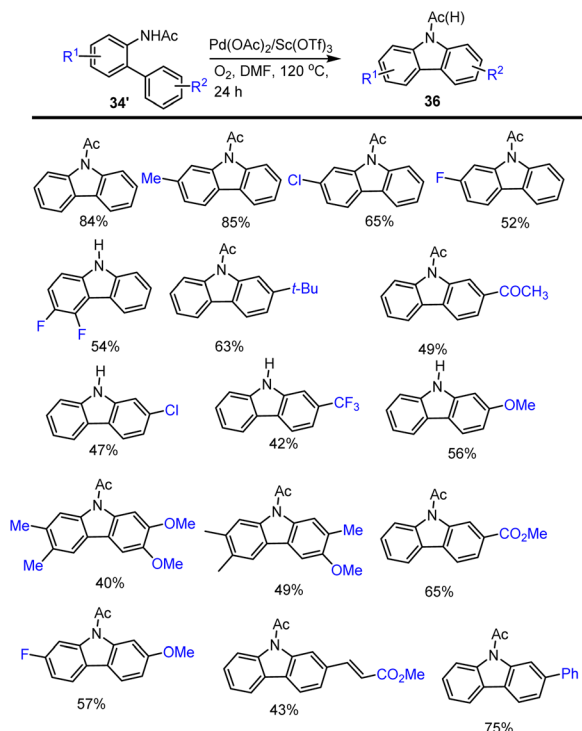
Scheme 27 Synthesis of carbazoles *via* C–H activation and C–N bond formation.



Scheme 28 Synthesis of carbazoles *via* intramolecular oxidative C–N bond formation reaction.

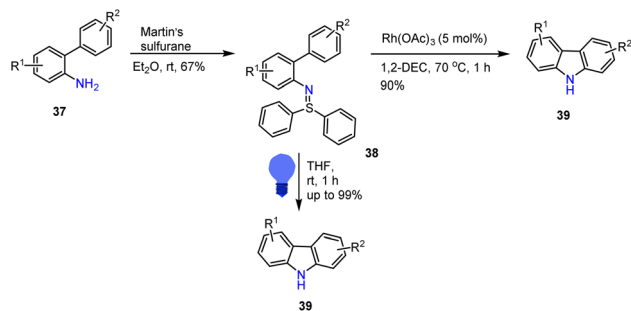
various carbazole-based natural products **33** from commercially available starting materials **32** in good yield as cited in Scheme 27.¹¹⁵

Chang and his groups demonstrated the synthesis of carbazoles under mild conditions through intramolecular oxidative C–N bond-forming reaction of *N*-protected 2-amido biphenyls **34**. As expected, the intramolecular cyclization took place in the presence Cu(OTf)₂ 5 mol%. Under optimized conditions, various substrates are afforded moderate to high yields of substituted carbazoles up to 91%. This intramolecular



Scheme 29 Pd(II)/Sc(III)-catalyzed intramolecular oxidative C–H amination.



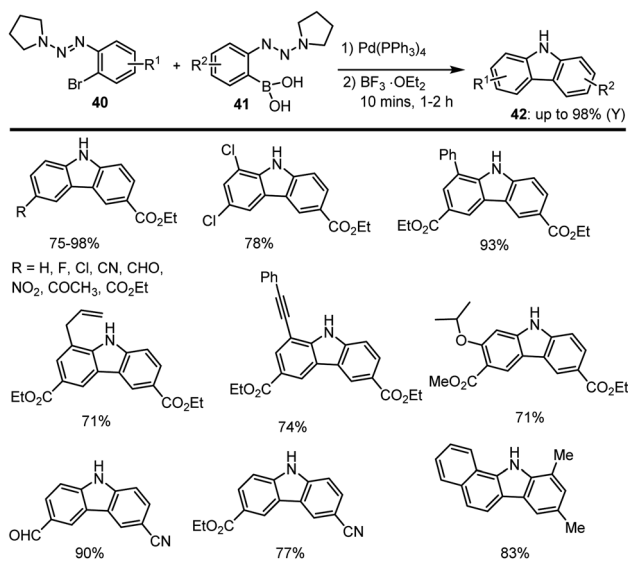


Scheme 30 Synthesis of carbazoles from sulfilimines by intramolecular C–H aminations.

oxidative C–N bond formation reaction works well with other Lewis acids such as $\text{Zn}(\text{OTf})_2$, $\text{Zn}(\text{OAc})_2$, $\text{Sc}(\text{OTf})_3$, $\text{Fe}(\text{OAc})_2$, $\text{BF}_3 \cdot \text{OEt}_2$ has a lower yield compared to copper catalyst as cited in Scheme 28.¹¹⁶

Yin and his group showed a $\text{Pd}(\text{II})/\text{Sc}(\text{OTf})_3$ catalyzed intramolecular C–H functionalization of biphenyl amide **34'** to formation of carbazole derivatives **36** in the use of O_2 as the sole oxidant under mild conditions. This C–H activation reaction tolerated various functional groups including electron-rich and electron-poor substituents in the presence of 40 mol% Lewis acid in DMF at 120 °C for 24 h and obtained results are summarised in Scheme 29.¹¹⁷

Hashmi and his groups reported a mild synthesis of carbazole derivatives and related building blocks **39** through an intramolecular C–H amination approach. A prominent advantage of this new protocol is highly reactive aryl sulfilimines scaffolds **38** working well under photo condition as well as Lewis acids. To find the best-optimized reaction conditions,



Scheme 31 Lewis acid-promoted synthesis of functionalized carbazoles.

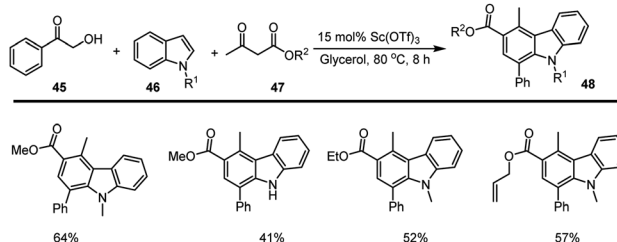


Scheme 32 ZnBr_2 -mediated synthesis of indolocarbazole.

authors tested different Lewis acid catalysts, and various light sources. In the presence of LEDs, light itself produced the best yield with a wide-ranging range of substrate scope and more significant numbers of functional group tolerances, as shown in Scheme 30.¹¹⁸

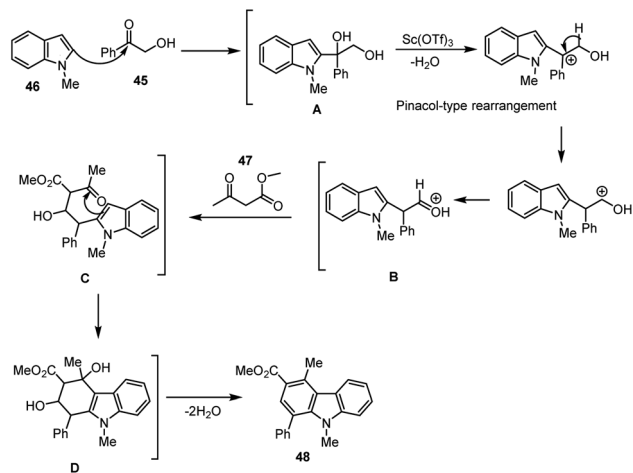
In 2011 Ren and co-workers examined a $\text{BF}_3 \cdot \text{OEt}_2$ Lewis acid-mediated nucleophilic aromatic substitution process for the regioselective preparation of highly functionalized carbazole scaffolds **42** in good yields. These amination reactions are carried out between Ar-Br **40** and $\text{Ar}(\text{OH})_2$ **41** in the presence of 5 mol% Pd cat. and 2 eq. of $\text{BF}_3 \cdot \text{OEt}_2$ under mild conditions. This C–C and C–N coupling system tolerates various classes of functional groups such as CHO, CO_2R , CN, NO_2 , F, Cl, *etc.* Furthermore, this novel procedure was effectively applied to prepare carbazole-based natural alkaloids, such as clausine A–C analogs. The obtained interesting results are summarised in Scheme 31.¹¹⁹

Mohanakrishnan and his groups developed a new method for the preparation of indolocarbazole *via* ZnBr_2 mediated intramolecular cyclization of nitro compound **43** in the presence of triethyl phosphite at 90–95 °C for 12–15 h led to the construction of the respective indolocarbazole derivatives **44** in excellent yields in the range of 85–91%. This system tolerates a wide range of electron-donating groups as shown in Scheme 32.¹²⁰

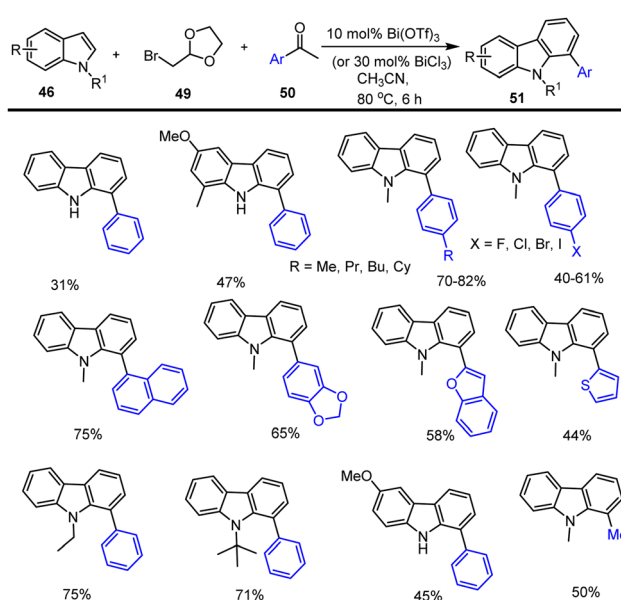


Scheme 33 $\text{Sc}(\text{OTf})_3$ -catalyzed preparation of carbazoles *via* [4 + 2] annulation reaction.





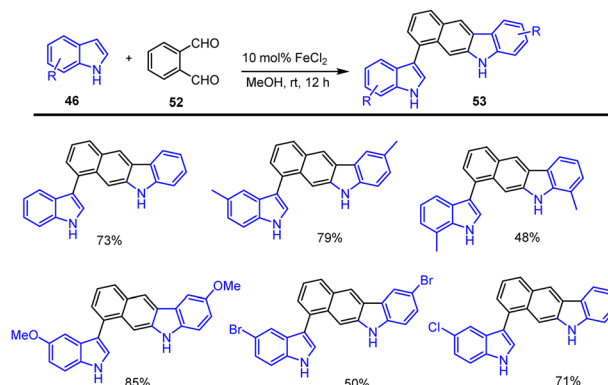
Scheme 34 Plausible mechanism for $\text{Sc}(\text{OTf})_3$ -catalyzed synthesis of carbazoles.



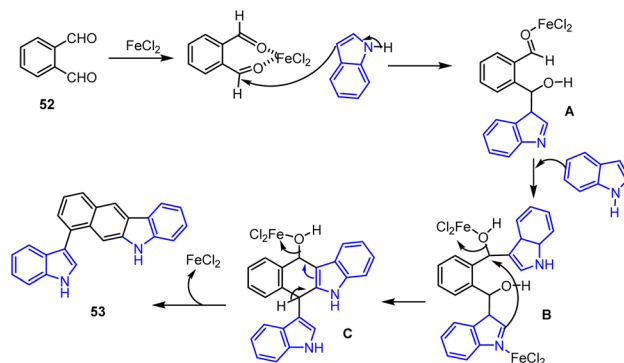
Scheme 35 $\text{Bi}(\text{OTf})_3$ -catalyzed three-component coupling reactions.

2.5. Synthesis of annulated carbazoles *via* multi component coupling reactions

A green synthetic method for producing carbazole and its derivatives **48** from basic chemical molecules such as hydroxy acetophenone **45** and α -keto-ester **47** was disclosed by Yanlong Gu and co-workers. The annulation reaction was performed in a bio-based green solvent, glycerol using 15 mol% $\text{Sc}(\text{OTf})_3$ as a Lewis acids catalyst. The important aspect of this cascade reaction is that solvent and catalyst can be recovered and reused. The reasonable mechanism of [4 + 2] annulation reaction was proposed *via* the nucleophilic attack of C2 carbon at the carbonyl carbon of α -hydroxy acetophenone generating the intermediate A. The activation of intermediate A with the use of $\text{Sc}(\text{OTf})_3$ enhances the formation of intermediate B by pinacol-type rearrangement reaction. The intermediate B reacts with



Scheme 36 Fe-catalyzed cycloaddition of indoles and *o*-phthalaldehyde.



Scheme 37 Proposed mechanism for Fe-catalyzed cycloaddition reaction.

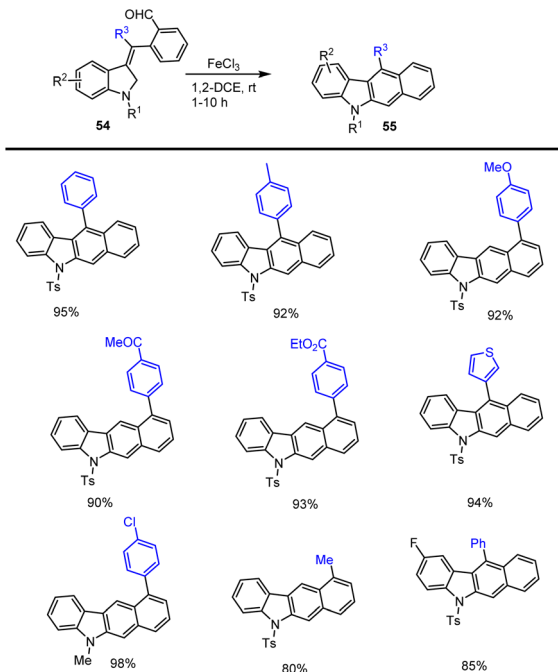
another molecule of β -keto-ester to form the intermediate C. Another nucleophilic addition of the C3 carbon of indole onto the keto group takes place, leading to the formation of species D which bears a six-membered ring system. Finally, the carbazole analogs **48** were generated by the dehydration of water molecules (Schemes 33 and 34).¹²¹

Gu *et al.* have discovered a unique three-component coupling process using the Lewis acid $\text{Bi}(\text{OTf})_3$ and indoles **46**, bromoacetaldehyde acetals **49**, and aryl ketones **50** to synthesise structurally varied carbazoles **51** in good yields. With the aid of 10 mol% bismuth(III) triflate, the multi-component indole reaction takes place with ketone and bromo compounds in CH_3CN for 16 h at 80 °C. Given the abundance of readily accessible simple indoles and the wide range of commercially available aryl ketones **50**, the suggested catalytic technique is a potential way for the synthesis of carbazole libraries with a high degree of diversity (Scheme 35).^{122,123}

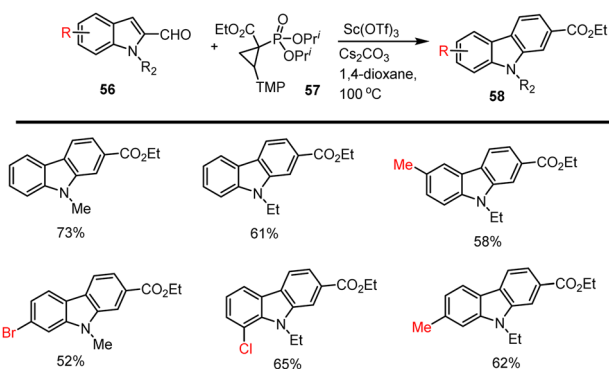
2.6. Synthesis of annulated carbazoles scaffolds from aromatic aldehydes or ketones enabled by Lewis acids

Indolyl ring-linked benzo[*b*]carbazoles **53** were synthesized by the efficient one-pot FeCl_2 -catalyzed cycloaddition of the indole





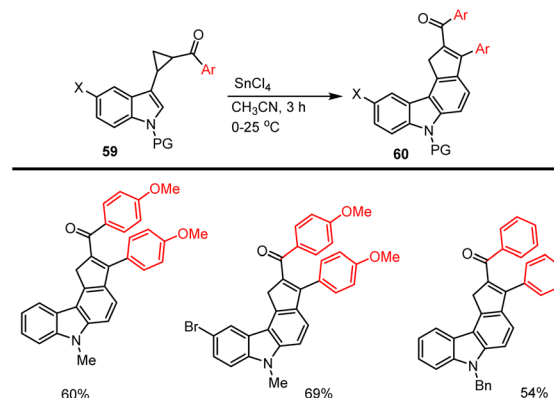
Scheme 38 Synthesis of substituted benzo[b]carbazoles enabled by Fe-catalysis.



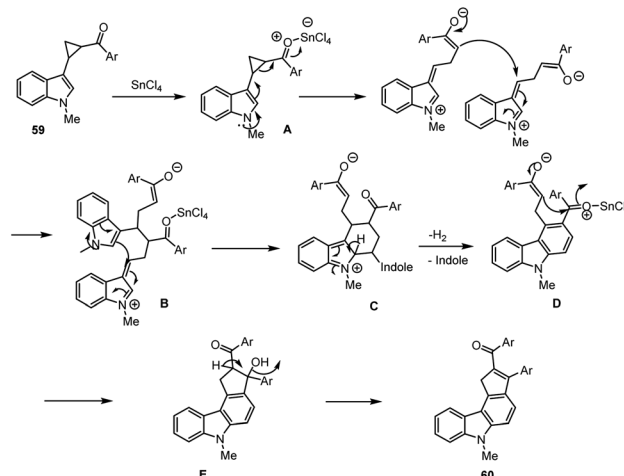
Scheme 39 Synthesis of carbazoles used by Sc(OTf)₃.

moiety **46** and simple phenyl dialdehyde (*o*-phthalaldehyde) **52**, as reported by Xu and his colleagues in 2014. This process involved sequential carbon–carbon bond-forming addition, intramolecular alkylation, and aromatization. The proposed Lewis acid-catalyzed cycloaddition reaction and mechanism were discussed in Schemes 36 and 37. The addition of indole **46** and dialdehyde **52** to generate species **A** and **B** after intramolecular cyclization and elimination of water to furnish the carbazoles **53** in good yields. This process tolerates various electron-rich and electron-poor functional groups in MeOH at rt for 12 h.¹²⁴

By using Fe-catalyzed domino reaction sequences from substituted indole methyl benzaldehyde derivatives **55**, Jana and groups established a unique and effective methodology for



Scheme 40 SnCl₄-induced rearrangement of the synthesis of carbazole.



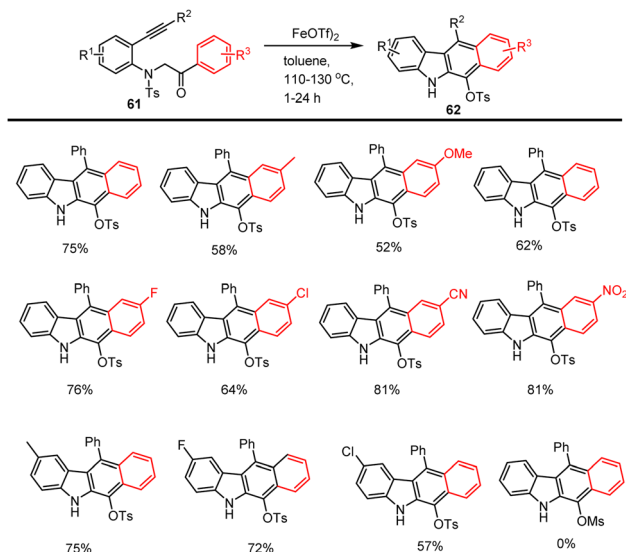
Scheme 41 Proposed mechanism of domino carbocationic rearrangement.

producing substituted benzo[b]carbazole derivatives **54**. Notably, this sustainable system produced substituted carbazole derivatives in good to high yields as mentioned in Scheme 38.¹²⁵

Recently Ruijter and co-workers reported a strategy for the synthesis of carbazole analogs **58** using a stoichiometric amount of Lewis acid Sc(OTf)₃ through condensation between indole aldehyde **56** and phosphonate ester **57** in Cs₂CO₃, 1,4-dioxane at 100 °C for 24 h. Using this applicable method, various functional group substituted carbazole compounds can also be synthesized efficiently under sustainable conditions. The obtained list of carbazole derivatives is cited in Scheme 39.¹²⁶

In 2002, Ila and co-workers developed SnCl₄-induced domino carbocationic rearrangement for the synthesis of carbazole analogs **60** from *N*-protected indolyl cyclopropyl ketones **59** leading to the formation of 2,3-substituted cyclopentyl ring fused carbazoles (Scheme 40).¹²⁷ This typical annulation system allows us to form synthetically useful carbazole products with good yields. Several unexpected interesting paths





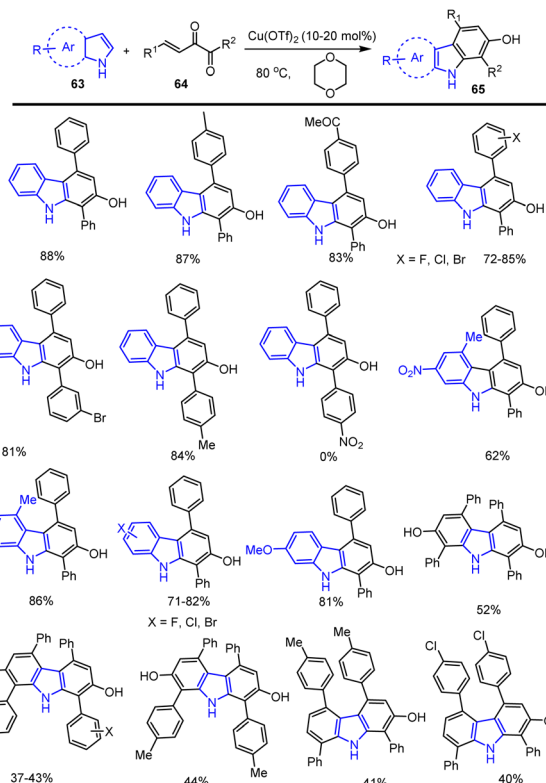
Scheme 42 Fe-catalyzed method to benzo[b]carbazoles.



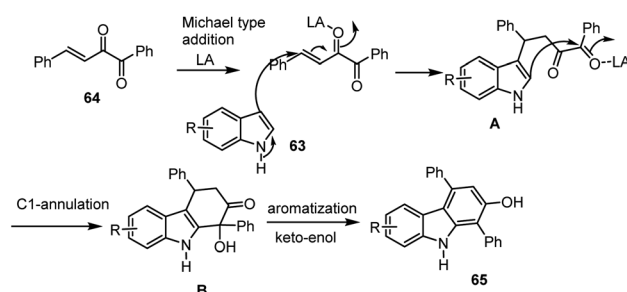
Scheme 43 Proposed pathway for preparation of benzo[b]carbazoles via Fe-catalysis.

are involved in the presence of Lewis acid-mediated intramolecular enolate cyclization, indole position-2 C–H carbon cyclization, and the elimination of indole moiety. This protocol tolerates various functional groups on aryl rings, and the proposed possible domino reaction mechanism has been discussed in Scheme 41.

Wang groups in 2015 significantly described a simple and direct protocol for the preparation of benzo[b] carbazole derivatives **62** enabled by Fe-catalysed 5-*exo*-dig intramolecular cyclization and a subsequent 6 π -electrocyclization and aromatization. With the help of the Fe-catalyst, the annulation reaction went through an unusual [1,4]-Ts group migration from nitrogen to oxygen. As illustrated in Scheme 42, this straightforward, environmentally friendly, non-toxic iron catalytic system has key advantages for the moderate to good yield



Scheme 44 Preparation of oxygenated carbazole scaffolds.

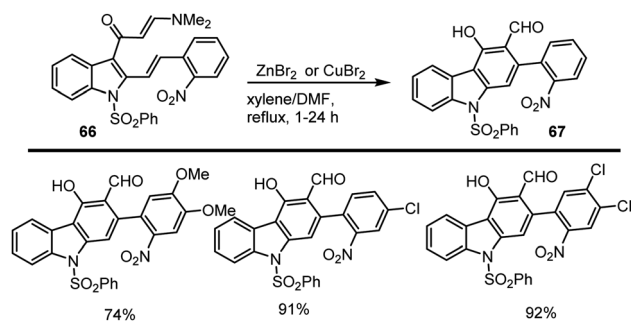


Scheme 45 Proposed strategy for the construction of carbazole.

synthesis of annulated carbazole derivatives, including tolerating functional groups like F, Cl, Me, CN, NO₂, *etc.* (Scheme 43) follows Iron assisted keto–enol tautomerization, cyclization, electrocyclization, aromatization, and tosyl group migration led to afford the unexpected fused carbazole motifs.¹²⁸

A unique technique for the synthesis of hydroxyl group substituted N–H free carbazoles **65** was published in 2018 by the team of Chen and co-workers. It involves the sequential cross-coupling of the C–C bond of electron-rich indoles and pyrrole with Cu. This report represents an atom economical procedure for the synthesis of both symmetric and unsymmetric functional groups substituted carbazoles achieved from easily accessible indole starting materials without the need for any expensive transition metal catalyst, ligands and harsh reaction





Scheme 46 Lewis acid mediated synthesis of tri-substituted carbazole.

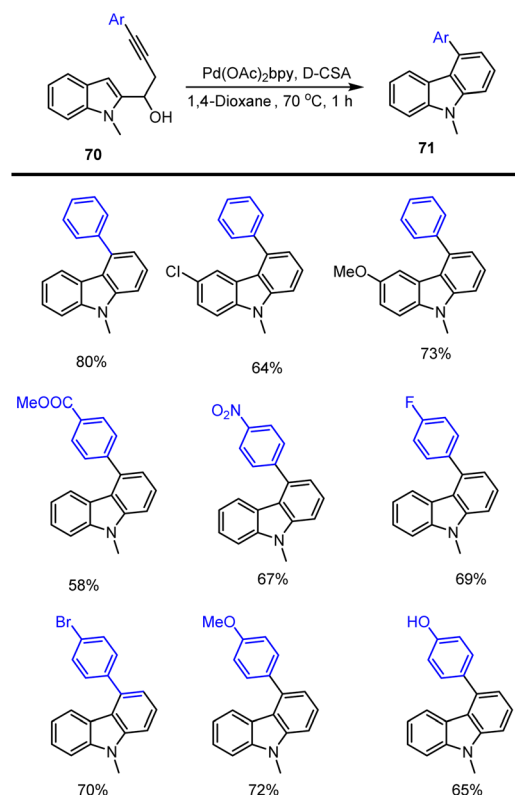


Scheme 47 InCl₃-Lewis acid mediated aminobenzannulation approach.

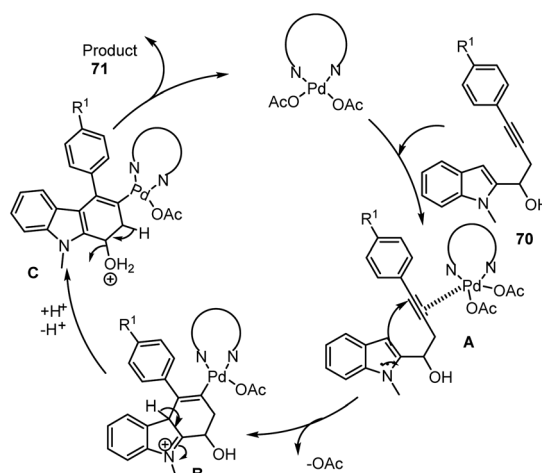
conditions (Scheme 44). Possible mechanism involves the following sequences Lewis acid mediated Michael addition to furnish species **A** followed by intramolecular cyclization produce intermediate **B** and them simple aromatization offer substituted carbazole **65** as mentioned in Scheme 45. This simple Lewis acid system provides important features for the synthesis of annulated carbazole derivatives in good to high yields, including toleration of functional groups such as F, Cl, Br, I, Me, OMe, COMe, NO₂, *etc.*, under sustainable conditions.¹²⁹

The group of Mohanakrishnan and colleagues in 2013 examined the Lewis acid-mediated thermal cyclization of the enamine **66** was then carried out using different Lewis acids, such as ZnBr₂, CuBr₂, InBr₃, CeCl₃, and FeCl₃, and the obtained results are cited in Scheme 46. In general, the preparation of carbazole **67** was found to be successful with various Lewis acids.¹³⁰

Rossi and co-workers reported the synthesis of highly substituted amino carbazole derivatives were obtained by using InCl₃ as a Lewis acid and another LAs such as GaCl₃ and TiCl₄ also work well; under optimized condition, the



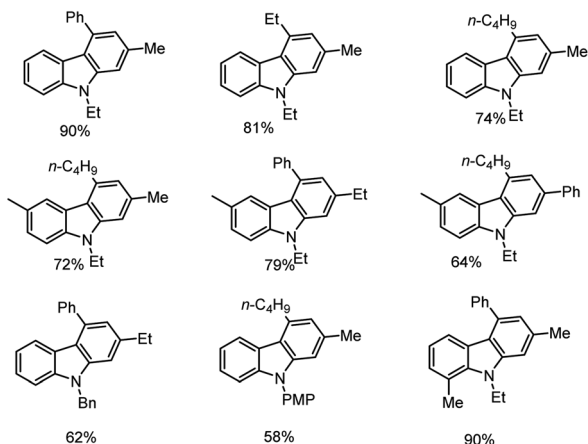
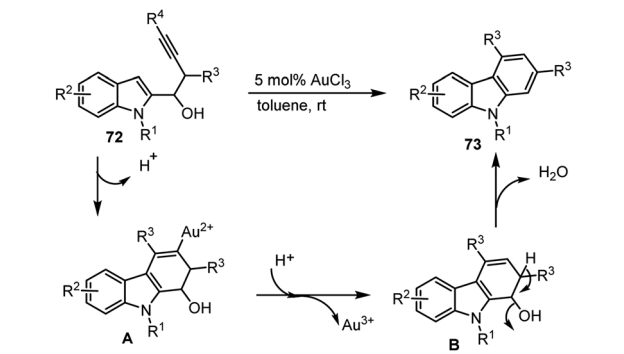
Scheme 48 Synthesis of carbazoles using Pd(OAc)₂bpy catalyst.



Scheme 49 Plausible mechanism for Pd(OAc)₂bpy-catalyzed synthesis of carbazoles.

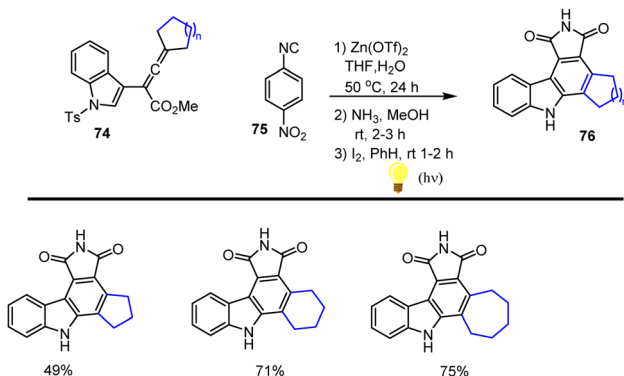
desired carbazole **69** was obtained in 71–83% yield. Next, the authors decided to evaluate the scope and limitations of the suitable indole substrates catalysed by InCl₃, which is an air-insensitive Lewis acid and is used as a carbon–carbon triple bond activator and can be used in catalytic amounts as LA even in producing the water from the first condensation



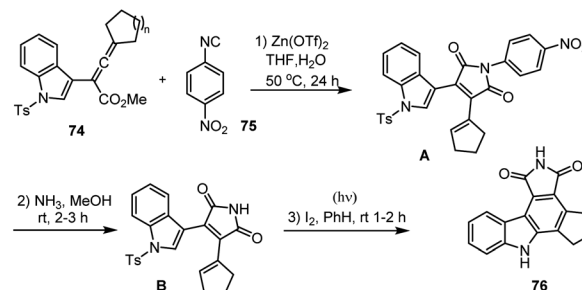
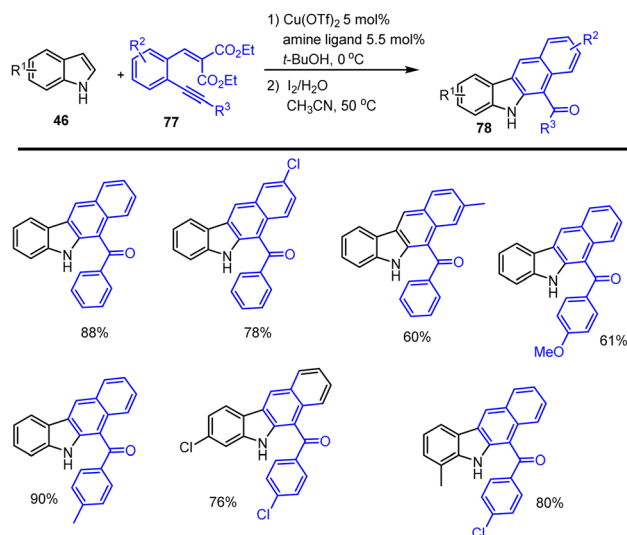
Scheme 50 AuCl₃-catalyzed synthesis of carbazole.

process. Under the optimized domino reaction conditions, 10 mol% of InCl₃, pyrrolidine (1.2 equiv.), dry CH₃CN at 75 °C led to the expected amino carbazoles **69** in good yields as shown in Scheme 47.¹³¹

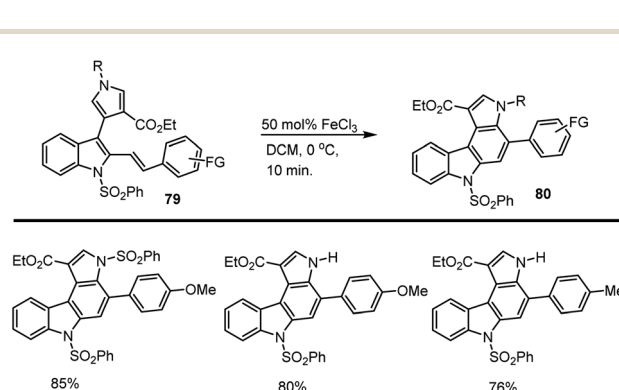
Chinmay Chowdhury and co-workers reported an atom-economical way of preparing carbazoles containing diverse functional groups **71** through Pd(II) catalyzed cascade reaction using 1-(indol-2-yl)but-3-yn-1-ols as starting material **70**. The catalyst Pd(OAc)₂bpy acting as Lewis acid activates the triple

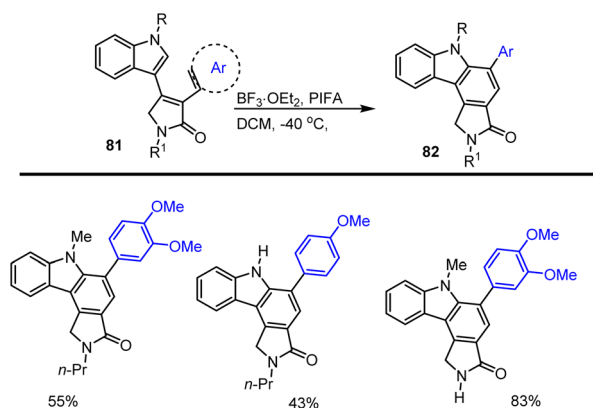


Scheme 51 Lewis acid-catalyzed tandem annulation reaction.

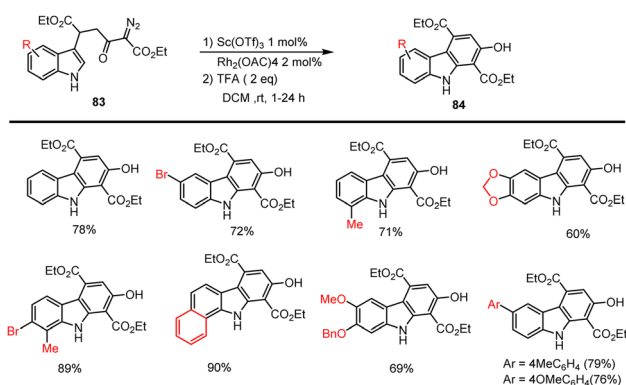
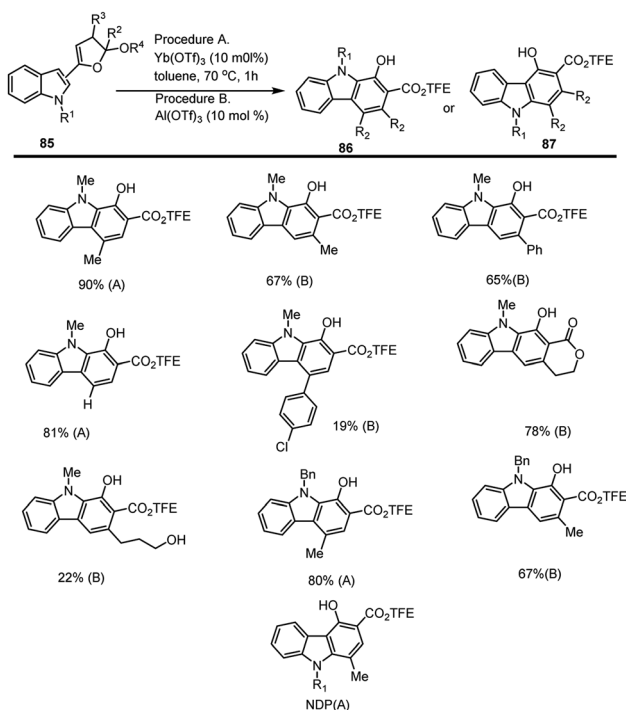
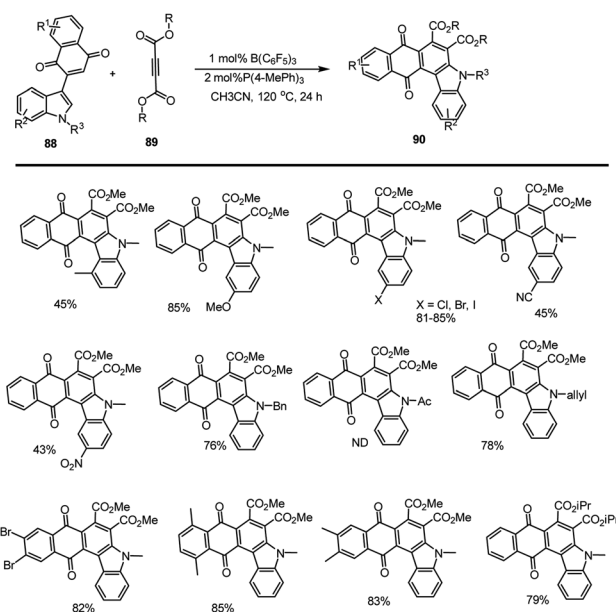
Scheme 52 Zn(OTf)₂-catalyzed cascade annulations for synthesis of carbazole.Scheme 53 Cu-catalyzed alkylation and I₂-promoted cyclization of indoles.

bond of the substrate to generate intermediate **A**. The triple bond of the intermediate may undergo intramolecular nucleophilic attack (6-endo-dig) to form palladated intermediate **B**. Subsequent deprotonation at the indole ring followed by reprotonation of the hydroxyl group followed by dehydration and protonolysis leads to the formation of carbazole **71** and the

Scheme 54 Synthesis of pyrrolo[2,3-c]carbazoles catalysed by FeCl₃.



Scheme 55 Synthesis of benzo[a]carbazoles enabled by LA.

Scheme 56 LA catalysed annulation of indolyl α -diazo acetate.Scheme 57 Synthesis of carbazoles *via* acetal ring opening benzanulations by using lewis acid.Scheme 58 [4 + 2] Cyclization strategy catalysed by $B(C_6F_5)_3$.

catalyst is regenerated as mentioned in the Schemes 48 and 49.¹³²

2.7. Synthesis of annulated carbazoles *via* cascade domino reactions

Ma and co-workers in 2011 reported $AuCl_3$ -catalyzed cyclization of 1-(indol-2-yl)-3-alkyn-1-ols **72** in toluene at room temperature for 3–15 h to form a fused benzene ring leading to a series of carbazole analogs **73** in good yields up to 90%. A possible intramolecular cyclization mechanism has been examined for the formation of expected carbazole derivatives **73** as shown in Scheme 50.¹³³

In 2007 Yang and his groups demonstrated $Zn(OTf)_2$ -Lewis acid catalyzed tandem annulation of aryl isonitriles **75** and indole-based allenic esters **74** which is an efficient and simple route for synthesising a broad range of structurally essential and biologically active carbazoles analogs **76**. This reaction substrate scope is employed with the use of readily available



Scheme 59 Synthesis of functionalized benzo[b]carbazoles enabled by Lewis acids.

Table 1 Application of biologically active carbazole scaffolds

S. no.	Compound structure	Activity/properties	Ref.
1		Antitumor	142
2		Antitumor	143
3		Antitumor	144
4		Antitumor	144
5		Antitumor	144
6		Antitumor	145
7	 $R = \text{Me}, \text{CO}_2\text{Me},$ $R^1 = \text{H}, \text{OH}$ $R^2 = \text{H}, \text{CON}(\text{NO})\text{Me}$	Antitumor	146
8		Antitumor	142
9		Antitumor	147
10	 $R = \text{Cl}, \text{Me}$	Antitumor	148
11	 $R = \text{H}, \text{OH}$	Anticancer	149



Table 1 (Contd.)

S. no.	Compound structure	Activity/properties	Ref.
12		Anticancer	150
13		Anticancer	149
14		Anticancer	149
15		Anticancer	151
16	 R = 4(2-dimethylaminoethyl)piperazin-1-yl	Anticancer	152
17	 R = H, OH	Anticancer	153
18		Anticancer	153
19		Anticancer	153
20		Anticancer	154
21		Anticancer	154



Table 1 (Contd.)

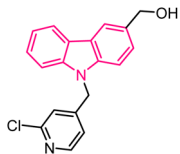
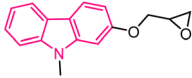
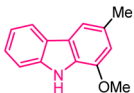
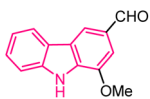
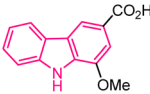
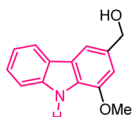
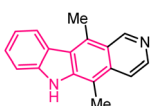
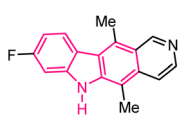
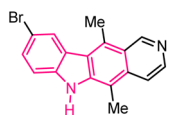
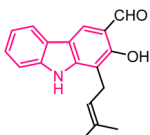
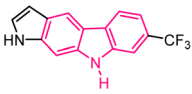
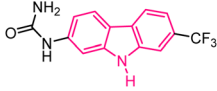
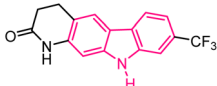
S. no.	Compound structure	Activity/properties	Ref.
22		Anticancer	149
23		Anticancer	149
24		Anticancer	155
25		Anticancer	155
26		Breast cancer	155
27		Anticancer	155
28		Antibacterial	156
29		Antibacterial	156
30		Antibacterial	156
31		Antibacterial	157
32		Kinesin spindle protein inhibitors	158
33		Kinesin spindle protein inhibitors	158
34		Kinesin spindle protein inhibitors	158



Table 1 (Contd.)

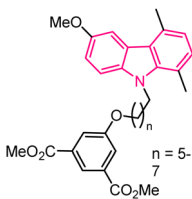
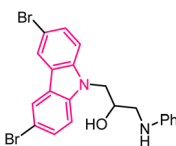
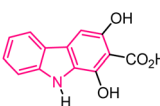
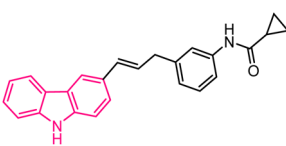
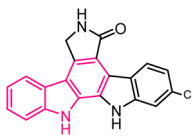
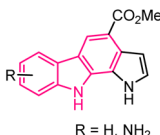
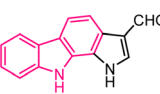
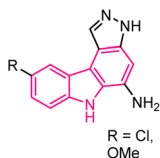
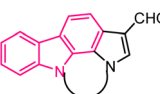
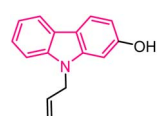
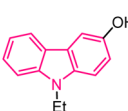
S. no.	Compound structure	Activity/properties	Ref.
35		STAT3 inhibitors	159
36		Neuroprotective agents	160
37		Neuroprotective agents	161
38		XO inhibitors	162
39		CDK5/p25 kinase inhibition	163
40		Pim kinase inhibitors	164
41		Pim kinase inhibitors	164
42		Pim kinase inhibitors	165
43		Pim kinase inhibitors	166
44		Antiplasmodial	167
45		Antiplasmodial	167

Table 1 (Contd.)

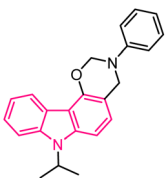
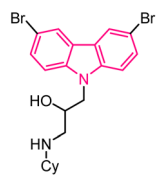
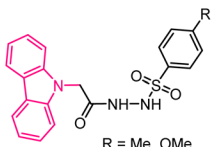
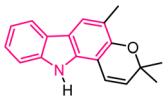
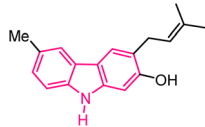
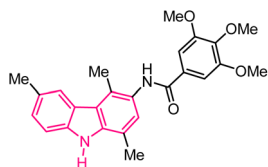
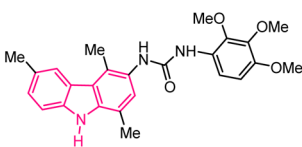
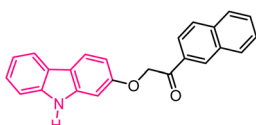
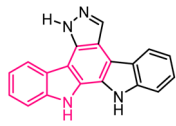
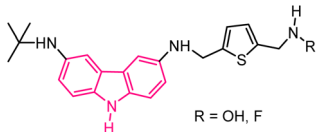
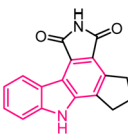
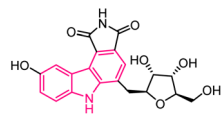
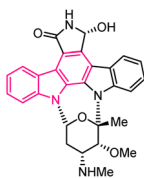
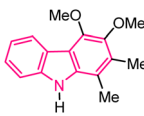
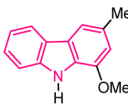
S. no.	Compound structure	Activity/properties	Ref.
46		Antiplasmodial	167
47		Antimalarial	168
48		Antioxidant	169
49		Antioxidant	170
50		Anti-HIV	171
51		Antiproliferative agents	172
52		Antiproliferative agents	172
53		Antiproliferative agents	173
54		Antiproliferative agents	174
55		Telomerase inhibitors	175



Table 1 (Contd.)

S. no.	Compound structure	Activity/properties	Ref.
56		PARP-1 inhibitor	176
57		Chk-1 inhibitor	177
58		Chk-1 inhibitor	177
59		Anti-yeast	178
60		Antifungal	179

starting materials under mild reaction conditions. Selectively generated heterocyclic compounds are found to have considerable value in drug discovery and natural product synthesis. In Schemes 51 and 52, the proposed reaction path is explored, and a number of carbazole derivatives **76** is cited.¹³⁴

In 2014 Wan and his groups showed a convenient procedure to access benzo[*b*]carbazole motifs **78** via a successive Cu-catalyzed arylation of electron-rich indole derivatives with Michael acceptor **77** and I₂-promoted electrophilic cyclization followed by nucleophilic substitution and aromatization. The scope of the reaction is shown in Scheme 53.¹³⁵

In 2016, Mohanakrishnan and his teams established a straightforward, easy-to-follow approach for the one-pot electrocyclization and aromatization reaction procedure utilised to create heteroaryl ring fused annulated carbazoles **80**. The annulation reaction was carried out with 3-indolylpyrroles **79** and 50 mol% of FeCl₃ Lewis acid in DCM at 0 °C for 10 min. Which led to the formation of the respective pyrrolocarbazoles **80** in excellent yields up to 85% (Scheme 54).¹³⁶

Pelkey and his groups reported a simple and flexible method to access 3-pyrrolin-2-one fused carbazoles. The critical essential step involves the BF₃-mediated cyclization in DCM at −40 °C, providing access to aryl group-substituted carbazole derivatives **82** in good yields. This method represents the first example of the preparation of the benzo[*a*]pyrrolo[*c*]carbazole core system. In the literature, it was found that indolo[*a*]pyrrolo[*c*]carbazol-5-one is a significant biologically active compound (Scheme 55).¹³⁷

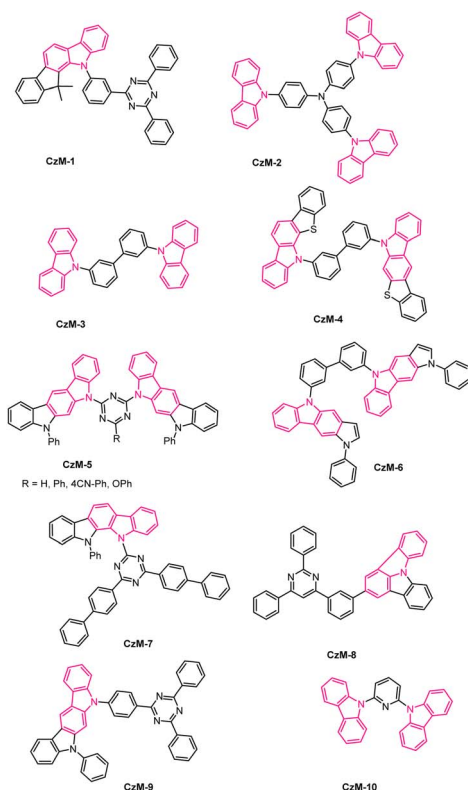
Recently Balamurugan and his groups developed an efficient method for preparation highly functionalized hydroxy carbazole building blocks **84**. The mild synthesis involves domino catalysis by 1 mol% of Sc(OTf)₃ and 2 mol% of Rh₂(OAc)₄. The critical role of Sc(OTf)₃ is to facilitate both the initial intermolecular Michael reaction of the indole derivatives **83** and the subsequent Rh(II)-catalyzed intramolecular annulation in DCM at rt with the addition of TFA. This protocol offers good yields of annulated carbazoles with various functional groups, as shown in Scheme 56.¹³⁸

France and co-workers reported a new method of synthesizing 1-hydroxy carbazoles **86** and **87** via acetal ring opening benzannulations of compound **85** by using Lewis acid as a catalyst. During the Lewis acid screening for ring-opening benzannulation, researchers found that Yb(OTf)₃ acts as an excellent catalyst leading to maximum yield compared to other Lewis acids. When they explored benzannulation reactions with synthesized substrates of substituted dihydrofuran acetals, it was found that *trans*-dihydrofuran isomers react faster than the corresponding *cis*-dihydrofuran. The contradiction is illustrated by the fact that the *trans*-3-phenyl modified dihydrofuran substrate generated an epimer of the same substrate rather than a hydroxy carbazole. It is reasonable that the phenyl substituent provides anchimeric assistance resulting in the stabilization of the dihydrofuran and reversible ring opening. It is also found that when one drop of water is added to Al(OTf)₃, the desired carbazole derivatives are formed with a high yield. This rapid shift in the reactivity with added water is due to the



formation of TfOH which enables the formation of dihydrofuran hemiacetal intermediate that undergoes ring opening. When the effects of changing *N*-methyl substituent to a *N*-benzyl was explored, it was found that procedure A gives maximum yield for *N*-benzyl substituents. It is noteworthy, that the reaction did not work when 3-indolyl dihydrofuran was explored (Scheme 57).¹³⁹

Wang and his groups showed a series of new carbazolequinones **90** prepared by a $B(C_6F_5)_3$ -catalyzed [4 + 2] cyclization reaction. This method involved a simple operation, a broad range of substrate variety, and high atomic economy, 1 mol% Lewis acid catalyst loading and avoided using toxic metal catalysts. The carbazole-fused derivatives was found a significant impact on the fluorescence properties (Scheme 58).¹⁴⁰



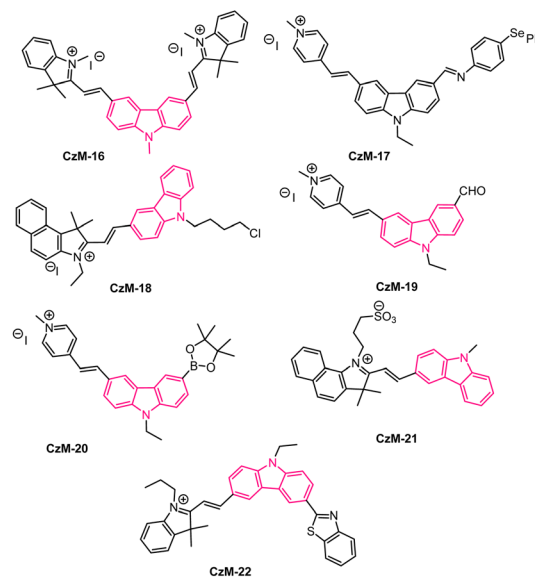
S. No	Carbazole number	Activity/properties	Year	Ref.
1	CzM-1	OLEDs	2017	180
2	CzM-2	OLEDs	2017	180
3	CzM-3	OLEDs	2021	181
4	CzM-4	OLEDs	2021	181
5	CzM-5	OLEDs	2014	182
6	CzM-6	OLEDs	2017	183
7	CzM-7	OLEDs	2018	184
8	CzM-8	OLEDs	2021	185
9	CzM-9	OLEDs	2018	186
10	CzM-10	OLEDs	2020	187

Fig. 2 Organic light-emitting diodes (OLEDs) of carbazole analogs.



S. No	Compound no	Activity/properties	Year	Ref.
1	CzM-11	TADF	2014	188
2	CzM-12	TADF	2015	189
3	CzM-13	TADF	2017	190
4	CzM-14	TADF	2019	191
5	CzM-15	TADF	2018	192

Fig. 3 Thermally activated delayed fluorescence (TADF) of carbazole derivatives.



S. No	Compound no	Activity/properties	Year	Ref.
1	CzM-16	MTFP	2016	193
2	CzM-17	MTFP	2017	194
3	CzM-18	MTFP	2016	195
4	CzM-19	MTFP	2016	196
5	CzM-20	MTFP	2022	197
6	CzM-21	MTFP	2016	198
7	CzM-22	MTFP	2019	199

Fig. 4 Mitochondria-targeted fluorescent probe (MTFP) of carbazole scaffolds.



Given the expected carbazole **92** in lower yields ranging from 6% to 39% at 50 °C for after stirring for 1–10 h as shown in Scheme 59, Liu and groups investigated the annulation reaction of ynamide **91** bearing two aryl groups at the alkyne terminus using various Lewis acids such as $\text{Zn}(\text{OTf})_2$, ZnCl_2 , FeCl_3 , and AgSbF_6 as the catalyst. Gratifyingly, $\text{JohnphosAu}(\text{MeCN})\text{SbF}_6$ was one of the best catalysts for this protocol, leading to the production of 1-aryl substituted carbazole **92** in 93% yield. The resulting high-yield formation of carbazole indicates that the nature of the phosphine ligands played a significant role in increasing catalytic activity.¹⁴¹

3. Selective examples of biologically active carbazole derivatives and their applications

Carbazoles and their analogs are one of the most essential heteroaromatic compounds, where many of them are isolated

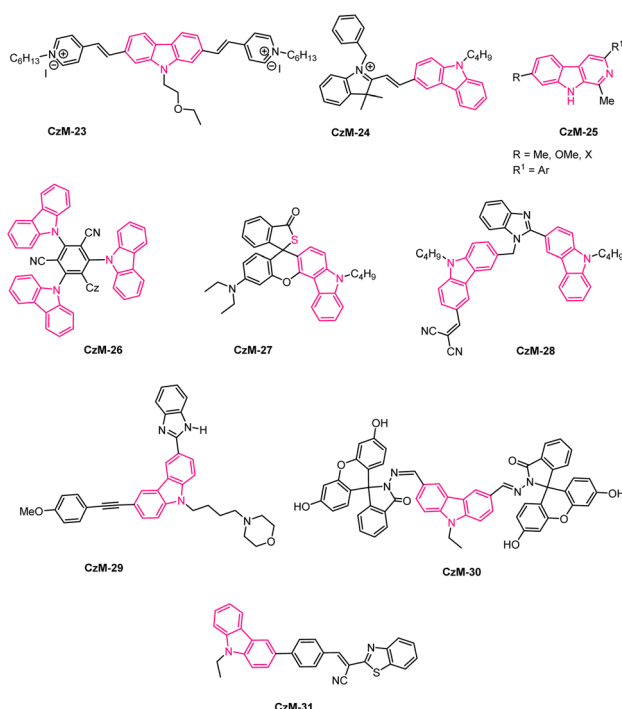
from various natural sources. Over the last two decades, several research groups and pharma companies have focused on the design and synthesis of annulated carbazoles and related polycyclic aromatic heterocycles *via* catalytic and non-catalytic methods. In recent years, many research reports shows that carbazole scaffolds have found to have significant applications in medicinal and pharmaceutical fields such as antitumor, anti-cancer, antiviral, antibacterial, Kinesin Spindle Protein Inhibitors, neuroprotective agents, XO inhibitors, CDK5/p25 kinase inhibition, Pim kinase inhibitors, antiplasmodial, antimalarial, antioxidant, antiproliferative agents, telomerase inhibitors *etc.* Moreover, carbazole backbone is present in many pharma drugs and natural products. The selectively collected list of carbazoles and annulated carbazoles as well as their bio-applications are detailed and summarised in the Table 1.^{142–179}

4. Selective examples for carbazole-based material applications

In recent days, many material science research groups have been very much interested in the design and preparation of highly π -conjugated sulfur and nitrogen-based annulated carbazoles derivatives that could be readily applied in various materials applications such as organic light-emitting diodes (OLEDs), thermally activated delayed fluorescence (TADF), Mitochondria-targeted fluorescent (MTF), fluorescent properties, conductive polymers, *etc.* The selectively collected list of carbazoles and annulated carbazoles and their materials applications or properties are detailed and summarised in the Fig. 2–5.^{180–208}

5. Conclusions

Over the past two decades, Lewis acid-mediated synthetic methods are remarkably considered as one of the significant approaches and an appropriate tool in modern organic synthesis which plays a vital role in discovering carbazole-based pharmaceutical drugs or carbazole-alkaloids and natural products. This review article mainly proves that the recent innovative cascade annulation strategy for synthesizing polyfunctionalized carbazoles and their related nitrogen-based complex heterocyclic compounds with poly aromatic compounds enabled by Lewis acid. Highly conjugated carbazole-based oligothiophenes and poly aromatic nitrogen heterocycles were synthesized *via* Lewis acid-mediated organic synthesis, including Friedel–Crafts arylation, electrocyclization, intramolecular cyclization, intramolecular oxidative C–N bond-formations, aromatization and cascade domino reactions under sustainable conditions. The highly substituted carbazole and their related heterocyclic carbazole compounds were found in several synthetic applications in medicinal chemistry, chemical biology, energy storage devices, and materials applications. Moreover, the review paper briefly summarised new synthetic strategies for producing carbazole derivatives which will assist academics and industries in identifying innovative, sustainable protocols for constructing poly-functionalized carbazoles and related highly complex



S. No	Compound no	Activity/properties	Year	Ref.
1	CzM-23	Fluorescent prob	2016	200
2	CzM-24	Fluorescent prob	2016	201
3	CzM-25	Fluorescent prob	2020	202
4	CzM-26	Fluorescent prob	2016	203
5	CzM-27	Fluorescent prob	2017	204
6	CzM-28	Fluorescent prob	2018	205
7	CzM-29	Fluorescent prob	2019	206
8	CzM-30	Fluorescent prob	2020	207
9	CzM-31	Fluorescent prob	2020	208

Fig. 5 Fluorescent properties of carbazole scaffolds.

heterocyclic compounds and discovering active pharmaceutical drugs or carbazole-based alkaloids and natural products.

Author contributions

VD wrote the major part of the paper. MPK is responsible for a list of reference paper collections; a few schemes and applications are described. GM, PA and CM partially wrote a few sections and supported manuscript corrections.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- J. M. Pedersen, W. R. Bowman, M. R. Elsegood, A. J. Fletcher and P. J. Lovell, *J. Org. Chem.*, 2005, **70**, 10615–10618.
- M. W. Saif and R. B. Diasio, *Clin. Colorectal Cancer*, 2005, **5**, 27–36.
- M. R. Naffziger, B. O. Ashburn, J. R. Perkins and R. G. Carter, *J. Org. Chem.*, 2007, **72**, 9857–9865.
- A. Ueno, T. Kitawaki and N. Chida, *Org. Lett.*, 2008, **10**, 1999–2002.
- K. E. Knott, S. Auschill, A. Jäger and H.-J. Knölker, *Chem. Commun.*, 2009, 1467–1469.
- G. G. Rajeshwaran and A. K. Mohanakrishnan, *Org. Lett.*, 2011, **13**, 1418–1421.
- A. Caron, A. C. Hernandez-Perez and S. K. Collins, *Org. Process Res. Dev.*, 2014, **18**, 1571–1574.
- A. E. Goetz, A. L. Silberstein, M. A. Corsello and N. K. Garg, *J. Am. Chem. Soc.*, 2014, **136**, 3036–3039.
- P. Raju, G. Gobi Rajeshwaran and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2015, **2015**, 7131–7145.
- S. Wu, S. Harada, T. Morikawa and A. Nishida, *Chem. Pharm. Bull.*, 2018, **66**, 178–183.
- H. Li, Q. Chen, Z. Lu and A. Li, *J. Am. Chem. Soc.*, 2016, **138**, 15555–15558.
- O. m. Dilek, S. I. Patir, T. Tilki and E. Ertürk, *J. Org. Chem.*, 2019, **84**, 7901–7916.
- V. Y. Shuvalov, V. A. Elisheva, A. S. Belousova, E. V. Arshinov, L. V. Glyzdinskaya, M. A. Vorontsova, S. A. Chernenko, A. S. Fisyuk and G. P. Sagitullina, *Chem. Heterocycl. Compd.*, 2020, **56**, 73–83.
- O. Dilek, S. I. Patir, T. Tilki and E. Ertürk, *J. Org. Chem.*, 2019, **84**, 7901–7916.
- T. Nishiyama, A. Matsuoka, R. Honda, T. Kitamura, N. Hatae and T. Choshi, *Tetrahedron*, 2020, **76**, 131110.
- J. Matsuoka, S. Inuki, Y. Matsuda, Y. Miyamoto, M. Otani, M. Oka, S. Oishi and H. Ohno, *Chem.-Eur. J.*, 2020, **26**, 11150–11157.
- C. Alayrac, D. Schollmeyer and B. Witulski, *Chem. Commun.*, 2009, 1464–1466.
- B. R. Rosen, E. W. Werner, A. G. O'Brien and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5571–5574.
- S. B. Markad and N. P. Argade, *Org. Lett.*, 2014, **16**, 5470–5473.
- W. M. O'Brien and G. F. Bagby, *Pharmacotherapy*, 1987, **7**, 16–24.
- C. Ito, M. Itoigawa, A. Sato, C. M. Hasan, M. A. Rashid, H. Tokuda, T. Mukainaka, H. Nishino and H. Furukawa, *J. Nat. Prod.*, 2004, **67**, 1488–1491.
- B. Vehar, M. Hrast, A. Kovač, J. Konc, K. Mariner, I. Chopra, A. O'Neill, D. Janežič and S. Gobec, *Bioorg. Med. Chem.*, 2011, **19**, 5137–5146.
- T. Takeuchi, S. Oishi, T. Watanabe, H. Ohno, J.-i. Sawada, K. Matsuno, A. Asai, N. Asada, K. Kitaura and N. Fujii, *J. Med. Chem.*, 2011, **54**, 4839–4846.
- A. A. Pieper, S. L. McKnight and J. M. Ready, *Chem. Soc. Rev.*, 2014, **43**, 6716–6726.
- Y. Feng, D. Li, Q. Wang, S. Wang, X. Meng, Z. Shao, M. Zhu and X. Wang, *Sens. Actuators, B*, 2016, **225**, 572–578.
- Z. Meng, H. Yu, L. Li, W. Tao, H. Chen, M. Wan, P. Yang, D. J. Edmonds, J. Zhong and A. Li, *Nat. Commun.*, 2015, **6**, 6096.
- X. Wu, J. Kosaraju, W. Zhou and K. Y. Tam, *ACS Chem. Neurosci.*, 2017, **8**, 676–685.
- T. Janosik, A. Rannug, U. Rannug, N. Wahlström, J. Slätt and J. Bergman, *Chem. Rev.*, 2018, **118**, 9058–9128.
- F. Giraud, E. Pereira, F. Anizon and P. Moreau, *Eur. J. Org. Chem.*, 2019, **2019**, 5025–5042.
- T. Aggarwal and A. K. Verma, *Org. Biomol. Chem.*, 2019, **17**, 8330–8342.
- A. Banerjee, S. Kundu, A. Bhattacharyya, S. Sahu and M. S. Maji, *Org. Chem. Front.*, 2021, **8**, 2710–2771.
- J. Roy, A. K. Jana and D. Mal, *Tetrahedron*, 2012, **68**, 6099–6121.
- C. Graebe and C. Glaser, *Adv. Cycloaddit.*, 1872, **163**, 343–360.
- D. Chakraborty, B. Barman and P. Bose, *Tetrahedron*, 1965, **21**, 681–685.
- H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303–4428.
- A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193–3328.
- G. Zotti, G. Schiavon, S. Zecchin, J.-F. Morin and M. Leclerc, *Macromolecules*, 2002, **35**, 2122–2128.
- P. Gao, D. Cho, X. Yang, V. Enkelmann, M. Baumgarten and K. Müllen, *Chem.-Eur. J.*, 2010, **16**, 5119–5128.
- J. Li and A. C. Grimsdale, *Chem. Soc. Rev.*, 2010, **39**, 2399–2410.
- N. Blouin and M. Leclerc, *Acc. Chem. Res.*, 2008, **41**, 1110–1119.
- C. Wang, H. Dong, W. Hu, Y. Liu and D. Zhu, *Chem. Rev.*, 2012, **112**, 2208–2267.



- 42 X. Liu, Y. Xu and D. Jiang, *J. Am. Chem. Soc.*, 2012, **134**, 8738–8741.
- 43 J.-Y. Su, C.-Y. Lo, C.-H. Tsai, C.-H. Chen, S.-H. Chou, S.-H. Liu, P.-T. Chou and K.-T. Wong, *Org. Lett.*, 2014, **16**, 3176–3179.
- 44 F. Chen, Y. S. Hong, S. Shimizu, D. Kim, T. Tanaka and A. Osuka, *Angew. Chem., Int. Ed.*, 2023, **62**, e202302761.
- 45 J. Zhang, W. Chen, S. Kalytchuk, K. F. Li, R. Chen, C. Adachi, Z. Chen, A. L. Rogach, G. Zhu and P. K. Yu, *ACS Appl. Mater. Interfaces*, 2016, **8**, 11355–11365.
- 46 K. Ivaniuk, V. Cherpak, P. Stakhira, Z. Hotra, B. Minaev, G. Baryshnikov, E. Stromylo, D. Volyniuk, J. V. Grazulevicius and A. Lazauskas, *J. Phys. Chem. C*, 2016, **120**, 6206–6217.
- 47 K. Albrecht, K. Matsuoka, D. Yokoyama, Y. Sakai, A. Nakayama, K. Fujita and K. Yamamoto, *Chem. Commun.*, 2017, **53**, 2439–2442.
- 48 G. Li, J. Zheng, K. Klimes, Z.-Q. Zhu, J. Wu, H. Zhu and J. Li, *ACS Appl. Mater. Interfaces*, 2019, **11**, 40320–40331.
- 49 Z.-J. Gao, T.-H. Yeh, J.-J. Xu, C.-C. Lee, A. Chowdhury, B.-C. Wang, S.-W. Liu and C.-H. Chen, *ACS Omega*, 2020, **5**, 10553–10561.
- 50 P. Xu, X. Liu, L. Liu, W. Zhu, C. Li and M. Fang, *J. Chin. Chem. Soc.*, 2021, **68**, 106–113.
- 51 C. M. Hendrich, L. M. Bongartz, M. T. Hoffmann, U. Zschieschang, J. W. Borchert, D. Sauter, P. Krämer, F. Rominger, F. F. Mulks and M. Rudolph, *Adv. Synth. Catal.*, 2021, **363**, 549–557.
- 52 E. Von Angerer and J. Prekajac, *J. Med. Chem.*, 1986, **29**, 380–386.
- 53 F. Song, D. Liu, X. Huo and D. Qiu, *Arch. Pharm.*, 2022, **355**, 2100277.
- 54 Y.-Q. Wang, X.-H. Li, Q. He, Y. Chen, Y.-Y. Xie, J. Ding, Z.-H. Miao and C.-H. Yang, *Eur. J. Med. Chem.*, 2011, **46**, 5878–5884.
- 55 D. Nettleton, T. Doyle, B. Krishnan, G. Matsumoto and J. Clardy, *Tetrahedron Lett.*, 1985, **26**, 4011–4014.
- 56 K. F. Kinzer and J. H. Cardellina, *Tetrahedron Lett.*, 1987, **28**, 925–926.
- 57 G. Lin and A. Zhang, *Tetrahedron*, 2000, **56**, 7163–7171.
- 58 L. B. Kardono, C. K. Angerhofer, S. Tsauri, K. Padmawinata, J. M. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.*, 1991, **54**, 1360–1367.
- 59 H. Cardellina II, M. P. Kirkup, R. E. Moore, J. S. Mynderse, K. Seff and C. J. Simmons, *Tetrahedron Lett.*, 1979, **20**, 4915–4916.
- 60 L. M. Browne, K. L. Conn, W. Ayer and J. P. Tewari, *Tetrahedron*, 1991, **47**, 3909–3914.
- 61 W. A. Ayer, P. A. Craw, Y.-t. Ma and S. Miao, *Tetrahedron*, 1992, **48**, 2919–2924.
- 62 S. Routier, P. Peixoto, J.-Y. Mérour, G. Coudert, N. Dias, C. Bailly, A. Pierré, S. Léonce and D.-H. Caignard, *J. Med. Chem.*, 2005, **48**, 1401–1413.
- 63 S. Routier, J.-Y. Mérour, N. Dias, A. Lansiaux, C. Bailly, O. Lozach and L. Meijer, *J. Med. Chem.*, 2006, **49**, 789–799.
- 64 I. Iovel, K. Mertins, J. Kischel, A. Zapf and M. Beller, *Angew. Chem., Int. Ed.*, 2005, **44**, 3913–3917.
- 65 M. Angeli, M. Bandini, A. Garelli, F. Piccinelli, S. Tommasi and A. Umani-Ronchi, *Org. Biomol. Chem.*, 2006, **4**, 3291–3296.
- 66 J. Kischel, I. Jovel, K. Mertins, A. Zapf and M. Beller, *Org. Lett.*, 2006, **8**, 19–22.
- 67 M. Sonntag and P. Strohriegel, *Tetrahedron*, 2006, **62**, 8103–8108.
- 68 M. Rueping, B. J. Nachtsheim and W. Ieawsuwan, *Adv. Synth. Catal.*, 2006, **348**, 1033–1037.
- 69 J. Yadav, B. S. Reddy, S. Aravind, G. N. Kumar and A. S. Reddy, *Tetrahedron Lett.*, 2007, **48**, 6117–6120.
- 70 C. Unaleroglu and A. Yazici, *Tetrahedron*, 2007, **63**, 5608–5613.
- 71 S.-J. Hong, S.-D. Jeong, J. Yoo, J. S. Kim, J. Yoon and C.-H. Lee, *Tetrahedron Lett.*, 2008, **49**, 4138–4141.
- 72 Z. Tu, B. R. Raju, T.-R. Liou, V. Kavala, C.-W. Kuo, Y. Jang, Y.-H. Shih, C.-C. Wang and C.-F. Yao, *Tetrahedron*, 2009, **65**, 2436–2442.
- 73 V. Dhayalan, N. Ramesh and A. K. Mohanakrishnan, *Synth. Commun.*, 2009, **39**, 1241–1256.
- 74 A. K. Mohanakrishnan, V. Dhayalan, J. A. Clement, R. B. R. Sureshbabu and N. S. Kumar, *Tetrahedron Lett.*, 2008, **49**, 5850–5854.
- 75 V. Dhayalan, J. A. Clement, R. Jagan and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2009, **2009**, 531–546.
- 76 R. Sureshbabu, V. Saravanan, V. Dhayalan and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2011, **2011**, 922–935.
- 77 V. Dhayalan, R. Sureshbabu and A. K. Mohanakrishnan, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2011, **50**, 843.
- 78 V. Dhayalan and A. K. Mohanakrishnan, *Synth. Commun.*, 2012, **42**, 2149–2160.
- 79 V. Saravanan, T. Mageshwaran and A. K. Mohanakrishnan, *J. Org. Chem.*, 2016, **81**, 8633–8646.
- 80 P. Raju, T. Mageshwaran, B. M. Ramalingam and A. K. Mohanakrishnan, *SynOpen*, 2018, **02**, 0246–0250.
- 81 B. Muthu Ramalingam, A. K. Mohanakrishnan, *et al.*, *J. Med. Chem.*, 2018, **61**, 1285–1315.
- 82 C.-B. Chen, X.-F. Wang, Y.-J. Cao, H.-G. Cheng and W.-J. Xiao, *J. Org. Chem.*, 2009, **74**, 3532–3535.
- 83 M. Tian and P. Belmont, *J. Org. Chem.*, 2008, **73**, 4101–4109.
- 84 T. G. Back, A. Pandya and J. E. Wulff, *J. Org. Chem.*, 2003, **68**, 3299–3302.
- 85 D. Alonso, E. Caballero, M. Medarde and F. Tomé, *Tetrahedron Lett.*, 2005, **46**, 4839–4841.
- 86 J. Y. Lee, H. Ha, S. Bae, I. Han and J. M. Joo, *Adv. Synth. Catal.*, 2016, **358**, 3458–3470.
- 87 J.-Q. Wu, Z. Yang, S.-S. Zhang, C.-Y. Jiang, Q. Li, Z.-S. Huang and H. Wang, *ACS Catal.*, 2015, **5**, 6453–6457.
- 88 Y. Zhou and J. G. Verkade, *Adv. Synth. Catal.*, 2010, **352**, 616–620.
- 89 F. Jafarpour and H. Hazrati, *Adv. Synth. Catal.*, 2010, **352**, 363–367.



- 90 S. Chen, Y. Li, P. Ni, H. Huang and G.-J. Deng, *Org. Lett.*, 2016, **18**, 5384–5387.
- 91 J. Wang, H.-T. Zhu, Y.-F. Qiu, Y. Niu, S. Chen, Y.-X. Li, X.-Y. Liu and Y.-M. Liang, *Org. Lett.*, 2015, **17**, 3186–3189.
- 92 R. Gu, A. Hameurlaine and W. Dehaen, *J. Org. Chem.*, 2007, **72**, 7207–7213.
- 93 R. Gu, S. Van Snick, K. Robeyns, L. Van Meervelt and W. Dehaen, *Org. Biomol. Chem.*, 2009, **7**, 380–385.
- 94 C. Ding, S. Tu, Q. Yao, F. Li, Y. Wang, W. Hu and A. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 847–853.
- 95 M. L. Deb, S. Mazumder, B. Baruah and P. J. Bhuyan, *Synthesis*, 2010, **2010**, 929–932.
- 96 S. Tohyama, T. Choshi, K. Matsumoto, A. Yamabuki, K. Ikegata, J. Nobuhiro and S. Hibino, *Tetrahedron Lett.*, 2005, **46**, 5263–5264.
- 97 M. F. Martínez-Espéron, D. Rodríguez, L. Castedo and C. Saá, *Org. Lett.*, 2005, **7**, 2213–2216.
- 98 A. R. Katritzky and L. Xie, *J. Org. Chem.*, 1995, **60**, 3707–3710.
- 99 A. K. Mohanakrishnan and P. C. Srinivasan, *J. Org. Chem.*, 1995, **60**, 1939–1946.
- 100 K. Liu and S. Zhang, *ACS Med. Chem. Lett.*, 2015, **6**, 894–897.
- 101 A. R. Katritzky, G. Zhang, L. Xie and I. Ghiviriga, *J. Org. Chem.*, 1996, **61**, 7558–7563.
- 102 Y. Miki, Y. Aoki, H. Miyatake, T. Minematsu and H. Hibino, *Tetrahedron Lett.*, 2006, **47**, 5215–5218.
- 103 C. O. Salas, F. J. Reboredo, J. C. Estévez, R. A. Tapia and R. J. Estévez, *Synlett*, 2009, **2009**, 3107–3110.
- 104 P. Manikandan, E. Sankar and A. K. Mohanakrishnan, *Synth. Commun.*, 2022, **52**, 1389–1396.
- 105 V. Saravanan and A. K. Mohanakrishnan, *Synthesis*, 2021, **53**, 2304–2318.
- 106 J. A. Clement, R. Sivasakthikumar, A. K. Mohanakrishnan, S. Sundaramoorthy and D. Velmurugan, *Eur. J. Org. Chem.*, 2011, **2011**, 569–577.
- 107 V. Saravanan, T. Mageshwaran and A. K. Mohanakrishnan, *J. Org. Chem.*, 2016, **81**, 8633–8646.
- 108 R. K. Varshnaya and P. Banerjee, *J. Org. Chem.*, 2019, **84**, 1614–1623.
- 109 C. Raji Reddy, R. Rani Valleti and U. Dilipkumar, *Chem.–Eur. J.*, 2016, **22**, 2501–2506.
- 110 X.-S. Li, Y.-P. Han, X.-Y. Zhu, Y. Xia, W.-X. Wei, M. Li and Y.-M. Liang, *Adv. Synth. Catal.*, 2018, **360**, 4441–4445.
- 111 Y. Qiu, J. Zhou, C. Fu and S. Ma, *Chem.–Eur. J.*, 2014, **20**, 14589–14593.
- 112 K. Huang, G. Sheng, P. Lu and Y. Wang, *Org. Lett.*, 2017, **19**, 4114–4117.
- 113 S. Wang, Z. Chai, Y. Wei, X. Zhu, S. Zhou and S. Wang, *Org. Lett.*, 2014, **16**, 3592–3595.
- 114 T. Tsuchimoto, H. Matsubayashi, M. Kaneko, E. Shirakawa and Y. Kawakami, *Angew. Chem., Int. Ed.*, 2005, **44**, 1336–1340.
- 115 H. Jiang, K. Li, S. Dong, Z. Chen and G. Yin, *Eur. J. Org. Chem.*, 2023, e202300598.
- 116 S. H. Cho, J. Yoon and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 5996–6005.
- 117 H. Jiang, K. Li, S. Dong, Z. Chen and G. Yin, *Eur. J. Org. Chem.*, 2023, **26**, e202300598.
- 118 X. Tian, L. Song and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2020, **59**, 12342–12346.
- 119 W. Yang, J. Zhou, B. Wang and H. Ren, *Chem.–Eur. J.*, 2011, **17**, 13665–13669.
- 120 G. G. Rajeshwaran and A. K. Mohanakrishnan, *Org. Lett.*, 2011, **13**, 1418–1421.
- 121 Z. Chen, W. Huang, L. Yi, X. Dong, K. Sheng, M. Li, R. Bai, A. Y. Sidorenko, J. Huang and Y. Gu, *Green Chem.*, 2022, **24**, 2919–2926.
- 122 F. Wu, W. Huang, Yiliqi, J. Yang and Y. Gu, *Adv. Synth. Catal.*, 2018, **360**, 3318–3330.
- 123 Y. Gu, W. Huang, S. Chen and X. Wang, *Org. Lett.*, 2018, **20**, 4285–4289.
- 124 J.-F. Zou, H. Wang, L. Li, Z. Xu, K.-F. Yang and L.-W. Xu, *RSC Adv.*, 2014, **4**, 47272–47277.
- 125 K. Paul, K. Bera, S. Jalal, S. Sarkar and U. Jana, *Org. Lett.*, 2014, **16**, 2166–2169.
- 126 M. Faltracco, M. Damian and E. Ruijter, *Org. Lett.*, 2021, **23**, 7592–7596.
- 127 C. Venkatesh, H. Ila, H. Junjappa, S. Mathur and V. Huch, *J. Org. Chem.*, 2002, **67**, 9477–9480.
- 128 S. S. K. Boominathan, G. C. Senadi, J. K. Vandavasi, J. Y.-F. Chen and J.-J. Wang, *Chem.–Eur. J.*, 2015, **21**, 3193–3197.
- 129 Y. Qiao, X. X. Wu, Y. Zhao, Y. Sun, B. Li and S. Chen, *Adv. Synth. Catal.*, 2018, **360**, 2138–2143.
- 130 B. M. Ramalingam, V. Saravanan and A. K. Mohanakrishnan, *Org. Lett.*, 2013, **15**, 3726–3729.
- 131 D. Facoetti, G. Abbiati and E. Rossi, *Eur. J. Org. Chem.*, 2009, **2009**, 2872–2882.
- 132 S. Pramanik, S. Chatterjee, R. Banerjee and C. Chowdhury, *Org. Lett.*, 2022, **24**, 1895–1900.
- 133 Y. Qiu, W. Kong, C. Fu and S. Ma, *Org. Lett.*, 2012, **14**, 6198–6201.
- 134 Y. Li, H. Zou, J. Gong, J. Xiang, T. Luo, J. Quan, G. Wang and Z. Yang, *Org. Lett.*, 2007, **9**, 4057–4060.
- 135 J. Wu, D. Wang, H. Wang, F. Wu, X. Li and B. Wan, *Org. Biomol. Chem.*, 2014, **12**, 6806–6811.
- 136 P. Raju and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2016, **2016**, 4361–4371.
- 137 N. J. Truax, F. Banales Mejia, D. O. Kwansare, M. M. Lafferty, M. H. Kean and E. T. Pelkey, *J. Org. Chem.*, 2016, **81**, 6808–6815.
- 138 S. Sakthivel and R. Balamurugan, *J. Org. Chem.*, 2018, **83**, 12171–12183.
- 139 S. Yuan, G. Guerra Faura, H. E. Areheart, N. E. Peulen and S. France, *Molecules*, 2022, **27**, 8344.
- 140 H. Xu, B. Wang, F.-Y. Li and J.-Y. Wang, *J. Org. Chem.*, 2023, **88**, 2703–2713.
- 141 W. Xu, G. Wang, X. Xie and Y. Liu, *Org. Lett.*, 2018, **20**, 3273–3277.
- 142 (a) C. Paoletti, J. B. Le Pecq, N. Dat-Xuong, P. Juret, H. Garnier, J. L. Amiel and J. Rouesse, *Cancer Chemo- and Immunopharmacology*, 1980, pp. 107–123; (b)



- T. Indumathi, A. Muthusankar, P. Shanmughavel and K. J. R. Prasad, *MedChemComm*, 2013, **4**, 450–455.
- 143 A. Rozovsky, E. Regozin, M. Oron-Herman, A. Albeck and G. Gellerman, *Eur. J. Org. Chem.*, 2015, **2015**, 1811–1818.
- 144 C. Ito, M. Itoigawa, A. Sato, C. M. Hasan, M. A. Rashid, H. Tokuda, T. Mukainaka, H. Nishino and H. Furukawa, *J. Nat. Prod.*, 2004, **67**, 1488–1491.
- 145 W. Lin, Y. Wang, S. Lin, C. Li, C. Zhou, S. Wang, H. Huang, P. Liu, G. Ye and X. Shen, *Eur. J. Med. Chem.*, 2012, **47**, 214–220.
- 146 R. Mori, A. Kato, K. Komenoi, H. Kurasaki, T. Iijima, M. Kawagoshi, Y. B. Kiran, S. Takeda, N. Sakai and T. Konakahara, *Eur. J. Med. Chem.*, 2014, **82**, 16–35.
- 147 C. S. Francisco, L. R. Rodrigues, N. M. F. S. A. Cerqueira, A. M. F. Oliveira-Campos and A. P. Esteves, *Eur. J. Med. Chem.*, 2014, **87**, 298–305.
- 148 L. Vairavelu, M. Zeller and K. J. Rajendra Prasad, *Bioorg. Chem.*, 2014, **54**, 12–20.
- 149 Y. Liu, Y. Wu, I. Sun, Y. Gu and L. Hu, *Eur. J. Med. Chem.*, 2020, **191**, 112181.
- 150 B. Tylińska and B. Wiatrak, *Biology*, 2021, **10**, 564.
- 151 C. Ito, M. Itoigawa, K. Nakao, T. Murata, N. Kaneda and H. Furukawa, *J. Nat. Med.*, 2012, **66**, 357–361.
- 152 G. A. Çiftçi, H. E. Temel, Ş. U. Yıldırım, Z. A. Kaplancıklı, M. D. Altıntop and L. Genç, *Med. Chem. Res.*, 2013, **22**, 3751–3759.
- 153 (a) S. Routier, P. Peixoto, J.-Y. Mérour, G. Coudert, N. Dias, C. Bailly, A. Pierré, S. Léonce and D.-H. Caignard, *J. Med. Chem.*, 2005, **48**, 1401–1413; (b) S. Routier, J.-Y. Mérour, N. Dias, A. Lansiaux, C. Bailly, O. Lozach and L. Meijer, *J. Med. Chem.*, 2006, **49**, 789–799.
- 154 W. Maneerat, T. Ritthiwigrom, S. Cheenpracha and S. Laphookhieo, *Phytochem. Lett.*, 2012, **5**, 26–28.
- 155 C. Ito, M. Itoigawa, K. Nakao, T. Murata, N. Kaneda and H. Furukawa, *J. Nat. Med.*, 2012, **66**, 357–361.
- 156 B. Vehar, M. Hrast, A. Kovač, J. Konc, K. Mariner, I. Chopra, A. O'Neill, D. Janežič and S. Gobec, *Bioorg. Med. Chem.*, 2011, **19**, 5137–5146.
- 157 R. Eswaramoorthy, H. Hailekiros, F. Kedir and M. Endale, *Adv. Appl. Bioinf. Chem.*, 2021, **14**, 13–24.
- 158 T. Takeuchi, S. Oishi, T. Watanabe, H. Ohno, J.-i. Sawada, K. Matsuno, A. Asai, N. Asada, K. Kitaura and N. Fujii, *J. Med. Chem.*, 2011, **54**, 4839–4846.
- 159 C. Saturnino, C. Palladino, M. Napoli, M. S. Sinicropi, A. Botta, M. Sala, A. Carcereri de Prati, E. Novellino and H. Suzuki, *Eur. J. Med. Chem.*, 2013, **60**, 112–119.
- 160 A. A. Pieper, S. L. McKnight and J. M. Ready, *Chem. Soc. Rev.*, 2014, **43**, 6716–6726.
- 161 K. Liu and S. Zhang, *ACS Med. Chem. Lett.*, 2015, **6**, 894–897.
- 162 B. P. Bandgar, L. K. Adsul, H. V. Chavan, S. N. Shringare, B. L. Korbad, S. S. Jalde, S. V. Lonikar, S. H. Nile and A. L. Shirfule, *Bioorg. Med. Chem.*, 2012, **20**, 5649–5657.
- 163 P. Raju, G. Gobi Rajeshwaran and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2015, **2015**, 7131–7145.
- 164 F. Giraud, R. Akué-Gédu, L. Nauton, N. Candelon, E. Debiton, V. Théry, F. Anizon and P. Moreau, *Eur. J. Med. Chem.*, 2012, **56**, 225–236.
- 165 V. Suchaud, L. Gavara, E. Saugues, L. Nauton, V. Théry, F. Anizon and P. Moreau, *Bioorg. Med. Chem.*, 2013, **21**, 4102–4111.
- 166 F. Giraud, M. Bourhis, L. Nauton, V. Théry, L. Herfindal, S. O. Døskeland, F. Anizon and P. Moreau, *Bioorg. Chem.*, 2014, **57**, 108–115.
- 167 Z. Bouaziz, S. Issa, J. Gentili, A. Gratz, A. Bollacke, M. Kassack, J. Jose, L. Herfindal, G. Gausdal, S. O. Døskeland, C. Mullié, P. Sonnet, C. Desgrouas, N. Taudon, G. Valdameri, A. Di Pietro, M. Baitiche and M. Le Borgne, *J. Enzyme Inhib. Med. Chem.*, 2015, **30**, 180–188.
- 168 J. Molette, J. Routier, N. Abila, D. Besson, A. Bombrun, R. Brun, H. Burt, K. Georgi, M. Kaiser, S. Nwaka, M. Muzerelle and A. Scheer, *ACS Med. Chem. Lett.*, 2013, **4**, 1037–1041.
- 169 İ. Çapan, M. Hawash, N. Jaradat, Y. Sert, R. Servi and İ. Koca, *BMC Chem.*, 2023, **17**, 60.
- 170 Y. Y. Kok, L. Y. Mooi, K. Ahmad, M. A. Sukari, N. Mat, M. Rahmani and A. M. Ali, *Molecules*, 2012, **17**, 4651–4660.
- 171 K. M. Meragelman, T. C. McKee and M. R. Boyd, *J. Nat. Prod.*, 2000, **63**, 427–428.
- 172 A. Panno, M. S. Sinicropi, A. Caruso, H. El-Kashef, J.-C. Lancelot, G. Aubert, A. Lesnard, T. Cresteil and S. Rault, *J. Heterocycl. Chem.*, 2014, **51**, E294–E302.
- 173 L.-C. Chen, S.-H. Juang, K.-M. Chang, C.-C. Tzeng, J.-J. Chen, I.-L. Chen and T.-C. Wang, *Chem. Pharm. Bull.*, 2014, **62**, 106–111.
- 174 B. Douara, Y. J. Esvan, E. Pereira, F. Giraud, Y. L. Volodina, D. N. Kaluzhny, A. A. Shtil, F. Anizon and P. Moreau, *Tetrahedron*, 2018, **74**, 892–901.
- 175 C. Uvarani, N. Jaivel, M. Sankaran, K. Chandraprakash, A. Ata and P. S. Mohan, *Fitoterapia*, 2014, **94**, 10–20.
- 176 D. Dunn, J. Husten, M. A. Ator and S. Chatterjee, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 542–545.
- 177 S. Ichikawa, N. Tatebayashi and A. Matsuda, *J. Org. Chem.*, 2013, **78**, 12065–12075.
- 178 K. Sakano, K. Ishimaru and S. Nakamura, *J. Antibiot.*, 1980, **33**, 683–689.
- 179 N. M. Cuong, H. Wilhelm, A. Porzel, N. Arnold and L. Wessjohann, *Nat. Prod. Res.*, 2008, **22**, 950–954.
- 180 K. Guo, H. Wang, Z. Wang, C. Si, C. Peng, G. Chen, J. Zhang, G. Wang and B. Wei, *Chem. Sci.*, 2017, **8**, 1259–1268.
- 181 A. Arai, H. Sasabe, K. Nakao, Y. Masuda and J. Kido, *Chem.–Eur. J.*, 2021, **27**, 4971–4976.
- 182 D. Zhang, L. Duan, Y. Li, H. Li, Z. Bin, D. Zhang, J. Qiao, G. Dong, L. Wang and Y. Qiu, *Adv. Funct. Mater.*, 2014, **24**, 3551–3561.
- 183 J. M. Choi, J. H. Kim, Y. J. Kang and J. Y. Lee, *Org. Electron.*, 2017, **49**, 393–399.
- 184 Y. Li, D. Zhang and L. Duan, *Org. Electron.*, 2018, **57**, 53–59.
- 185 Y. Hiraga, R. Kuwahara and T. Hata, *Tetrahedron*, 2021, **94**, 132317.
- 186 D. Zhang, X. Song, M. Cai, H. Kaji and L. Duan, *Adv. Mater.*, 2018, **30**, 1705406.



- 187 X. Zheng, F. Cao, C. Wang, T. Tsuboi, Y. Zhu, Q. Ai, C. Deng, D. Wang, L. Su, Z. Liu and Q. Zhang, *J. Mater. Chem. C*, 2020, **8**, 10021–10030.
- 188 Q. Zhang, H. Kuwabara, W. J. Potscavage Jr, S. Huang, Y. Hatae, T. Shibata and C. Adachi, *J. Am. Chem. Soc.*, 2014, **136**, 18070–18081.
- 189 D. R. Lee, S.-H. Hwang, S. K. Jeon, C. W. Lee and J. Y. Lee, *Chem. Commun.*, 2015, **51**, 8105–8107.
- 190 J. H. Kim, M. Eum, T. H. Kim and J. Y. Lee, *Dyes Pigm.*, 2017, **136**, 529–534.
- 191 C. S. Oh, H. L. Lee, S. H. Han and J. Y. Lee, *Chem.-Eur. J.*, 2019, **25**, 642–648.
- 192 Y. H. Lee, S. Park, J. Oh, S.-J. Woo, A. Kumar, J.-J. Kim, J. Jung, S. Yoo and M. H. Lee, *Adv. Opt. Mater.*, 2018, **6**, 1800385.
- 193 G. Wang, H. Chen, X. Chen and Y. Xie, *RSC Adv.*, 2016, **6**, 18662–18666.
- 194 C. Sun, W. Du, P. Wang, Y. Wu, B. Wang, J. Wang and W. Xie, *Biochem. Biophys. Res. Commun.*, 2017, **494**, 518–525.
- 195 J. Xu, J. Pan, X. Jiang, C. Qin, L. Zeng, H. Zhang and J. F. Zhang, *Biosens. Bioelectron.*, 2016, **77**, 725–732.
- 196 Y. Feng, D. Li, Q. Wang, S. Wang, X. Meng, Z. Shao, M. Zhu and X. Wang, *Sens. Actuators, B*, 2016, **225**, 572–578.
- 197 L. Xu, J. Yu, Y. Wang, Y. Chen, X. Zhang, R. Han, J. Jing, R. Zhang and X. Zhang, *Dyes Pigm.*, 2022, **207**, 110622.
- 198 Y. Liu, K. Li, K.-X. Xie, L.-L. Li, K.-K. Yu, X. Wang and X.-Q. Yu, *Chem. Commun.*, 2016, **52**, 3430–3433.
- 199 W. Gao, Y. Ma and W. Lin, *Analyst*, 2019, **144**, 4972–4977.
- 200 Y. Liu, F. Meng, L. He, X. Yu and W. Lin, *Chem. Commun.*, 2016, **52**, 8838–8841.
- 201 J.-Y. Wang, Z.-R. Liu, M. Ren, X. Kong, K. Liu, B. Deng and W. Lin, *Sens. Actuators, B*, 2016, **236**, 60–66.
- 202 V. Y. Shuvalov, V. A. Elisheva, A. S. Belousova, E. V. Arshinov, L. V. Glyzdinskaya, M. A. Vorontsova, S. A. Chernenko, A. S. Fisyyuk and G. P. Sagitullina, *Chem. Heterocycl. Compd.*, 2020, **56**, 73–83.
- 203 J. Zhang, W. Chen, S. Kalytchuk, K. F. Li, R. Chen, C. Adachi, Z. Chen, A. L. Rogach, G. Zhu, P. K. N. Yu, W. Zhang, K. W. Cheah, X. Zhang and C.-S. Lee, *ACS Appl. Mater. Interfaces*, 2016, **8**, 11355–11365.
- 204 R. Guo, Q. Wang and W. Lin, *J. Fluoresc.*, 2017, **27**, 1969–1974.
- 205 L. Kong, L. Yang, G.-b. Zhang, Q.-y. Chen, H. Wang, X.-p. Gan, H. Li, H.-p. Zhou, J.-x. Yang and Y.-p. Tian, *J. Mater. Sci.*, 2018, **53**, 921–936.
- 206 P. Ning, L. Hou, Y. Feng, G. Xu, Y. Bai, H. Yu and X. Meng, *Chem. Commun.*, 2019, **55**, 1782–1785.
- 207 N. Wang, W. Xu, D. Song and P. Ma, *Spectrochim. Acta, Part A*, 2020, **227**, 117692.
- 208 M. Peng, J. Yin and W. Lin, *Spectrochim. Acta, Part A*, 2020, **224**, 117310.

