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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 polyfunctionalized carbazoles and related highly complex heterocyclic compounds and discovering active pharmaceutical drugs or carbazole-based alkaloids and natural products.

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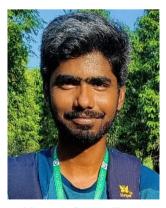
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1. Introduction

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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[†] Dedicated to Prof. A. K. Mohanakrishnan.

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



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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



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Dr Chitrarasu 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, Znorganometallics. He has published 79 research articles in reputed international journals till now (September 2023).

Quinofblcarbazo Benzofblcarbazole Carprofen

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} antiplasmodial, 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 solardyes, 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 metalfree cyclization, 90-94 multi-component reactions, 90,95 sigmatropic reactions⁷⁴⁻⁷⁶ and thermal electrocyclization, ⁹⁶⁻⁹⁹ basemediated cyclizations. 100-103 Among these divergent methods, Lewis acid catalyzed methods are highly effective and attractive in academic and pharmaceutical industries due to their nontoxic, 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 radial 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 ${\sf ZnBr}_2$.

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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 ZnBr₂ 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 2benzylindole 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 ZnBr₂ 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 ZnBr2 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 ZnBr₂ mediated domino reaction of indole methyl bromides.

$$\begin{array}{c} \text{Br-Zn} \overset{\text{Br}}{\sim} \text{Dr} \\ \text{OC}_2 \text{H}_5 \\ \text{C}_2 \text{H}_5 \\ \text{OC}_2 \text{H$$

Scheme 3 Proposed mechanism for domino reaction of bromomethyl indole enabled by ${\sf ZnBr}_2$.

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 $\rm ZnBr_2$ under heating conditions in 1.2-DCE at 80 °C for 1–5 h produced the arylated indole $\rm A$ via Friedel–Crafts process. Next $\rm ZnBr_2$ prompted thermal 1,5-hydrogen shift to form a triene intermediate $\rm B$, which occurs at high-temperature electrocyclization permit. The desired non-aromatic compound $\rm C$ formation followed by subsequent aromatization and elimination of diethyl malonate unit afforded the expected carbazole $\rm 3a$ in good yields as shown in the Scheme $\rm 3.^{74-76}$

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 ZnBr₂ or catalytic amounts of 10–20 mol% Lewis acid (InBr₃, Yb(OTf)₃, FeBr₃, SnCl₄, Sc(OTf)₃) led to the formation of a variety of carbazole derivatives (Scheme 5) in the range of 25–65% yields.

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

Scheme 6 ZnBr₂ 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 $1\mathbf{d}$, 3-bromomethyl indole $1\mathbf{e}$, benzo[b]

Scheme 7 ZnBr₂ mediated domino reaction of indole methyl bromides with various hetero-arenes.

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. ZnBr₂ or 10 mol% InBr₃ in 1,2-DCE under refluxing condition 1–5 h. Electron-donating arenes and heteroarenes produced expected

Scheme 8 ZnBr₂ 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 ZnBr2 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-SO₂Ph 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 1,3,5tri(bromomethyl)benzene. The results of the Lewis acidmediated 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.

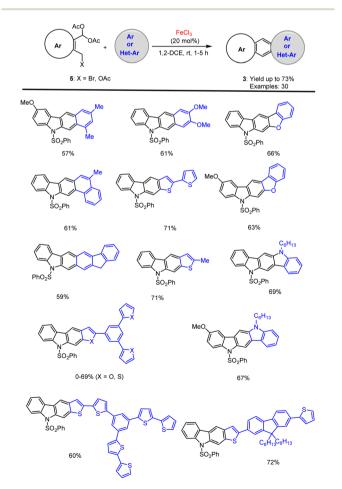
Surprisingly, under identical conditions, in the presence of 20 mol%. ZnBr₂ in 1,2-DEC under refluxing condition 1-5 h the domino reaction of the *n*-Boc protected bromo compound 1d' with electron-rich heteroarenes such as furan, thiophene, and indole led to the formation of annulated N-H free carbazole 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

1d': X = Br, OAc intramolecula 3':N-H free

Scheme 9 Proposed mechanism for domino reaction of N-Bocbromomethyl indole enabled by ZnBr₂

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 ZnBr₂ 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 FeCl₃-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-SO₂Ph-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.

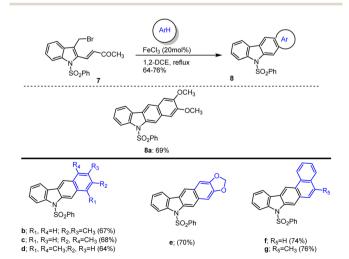


Scheme 10 FeCl₃ mediated cascade annulation of bromomethyl indole with various arenes and heteroarenes.

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

Recently in 2022, the groups of Mohanakrishnan and coworkers 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 Zn(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% FeCl₃ 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% FeCl₃ (Scheme 12).105 In the same way, napthocarbazole (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 FeCl3-catalyzed synthesis of carbazoles

mediated annulation mechanism is cited in Schemes 12 and 13. Initially arylmethylindoles (A) is formed and undergo FeCl₃catalyzed 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 FeCl3 influenced elimination of acetone affords carbazoles 8.

The same group additionally prepared hetero-annulated carbazoles by utilizing SnCl4 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-i were obtained by reaction of bromomethylindole with thiophene-, indole-, and

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

pyrrole-based heteroarenes as mentioned in Scheme 14.105

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 bisdiacetoxymethyl substituted aryl and heteroaryl compounds as shown in Scheme 15.106 In the presence of 40 mol% BF₃OEt₂ at rt, 4-6 h, they planned the annulation reactions of indolederived 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 napthocarbazole 12 as shown in Scheme 17. The required indole starting material is

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

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.

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 aroyl 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 BF₃·OEt₂-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% $\rm InCl_3$ 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 $(BF_3 \cdot OEt_2, 5 \text{ mol}\%)$ with the addition of propargylic alcohols **17** and indole ester **16** through Friedel–Crafts arylation and electrocyclization of allene **B** in DBU, CH₃CN 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(π)-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 [i-PrAuCl]/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

 BF_3 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 CH_3CN 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 -eletrocyclization, 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.

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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 \emph{via} C-H activation and C-N bond formation.

Scheme 28 Synthesis of carbazoles \emph{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.

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Scheme 30 Synthesis of carbazoles from sulfilimines by intra-molecular C–H aminations.

oxidative C–N bond formation reaction works well with other Lewis acids such as $Zn(OTf)_2$, $Zn(OAc)_2$, $Sc(OTf)_3$, $Fe(OAc)_2$, $BF_3 \cdot OEt_2$ has a lower yield compared to copper catalyst as cited in Scheme 28.¹¹⁶

Yin and his group showed a $Pd(n)/Sc(OTf)_3$ 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 ZnBr₂-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 BF₃·OEt₂ 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 Ar-(OH)₂ 41 in the presence of 5 mol% Pd cat. and 2 eq. of BF₃·OEt₂ under mild conditions. This C–C and C–N coupling system tolerates various classes of functional groups such as CHO, CO₂R, CN, NO₂, 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 $C(OTf)_3$ -catalyzed preparation of carbazoles *via* [4 + 2] annulation reaction.

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Scheme 34 Plausible mechanism for Sc(OTf)₃-catalyzed synthesis of carbazoles.

Scheme 35 $Bi(OTf)_3$ -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 -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% Sc(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 Sc(OTf)₃ enhances the formation of intermediate B by pinacoltype rearrangement reaction. The intermediate B reacts with

Scheme 36 Fe-catalyzed cycloaddition of indoles and ophthalaldehyde.

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 Bi(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 CH₃CN 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 FeCl₂-catalyzed cycloaddition of the indole

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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 $SnCl_4$ -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 6π -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

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

91%

InCl₃-Lewis acid mediated aminobenzannulation Scheme 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.

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 airinsensitive 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

$$R^{2} \xrightarrow{\text{II}} R^{3} \xrightarrow{\text{OH}} R^{3} \xrightarrow{\text{In}} R^{3$$

Scheme 50 AuCl₃-catalyzed synthesis of carbazole.

process. Under the optimized domino reaction conditions, 10 mol% of $InCl_3$, pyrrolidine (1.2 equiv.), dry CH_3CN 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 $Pd(OAc)_2$ bpy acting as lewis acid activates the triple

NC 1) Zn(OTf)₂
THF,H₂O
50 °C, 24 h
75 NO₂ rt, 2-3 h
3) I₂, PhH, rt 1-2 h
(hv)

1 Zn(OTf)₂
THF,H₂O
50 °C, 24 h
76 (hv)

Scheme 51 Lewis acid-catalyzed tandem annulation reaction.

Scheme 52 Zn(OTf)₂-catalyzed cascade annulations for synthesis of carbazole.

Scheme 53 $\,$ Cu-catalysed 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.

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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 benzan-nulations 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 AuCl₃-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

(Ts N Ph	Lewis acids 1,2-DCE, 50 °C, 7-10 h	Ts N Ph
	Entry	LA	yield(%)
	1 2 3 4 5	Zn(OTf) ₂ ZnCl2 FeCl ₃ Cu(OTf) ₃ AgSbF ₆ JohnphosAu(MeCN)	13 15 11 39 6 SbF ₆ 93

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	Me N N Me	Antitumor	142
2	N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-	Antitumor	143
3	MeO CH ₃	Antitumor	144
4	CH ₃	Antitumor	144
5	MeO Me OMe	Antitumor	144
6	MeO H	Antitumor	145
7	R_1 R_2 R_3 R_4 R_5	Antitumor	146
8	Aco N Me H	Antitumor	142
9	OH CO ₂ Et	Antitumor	147
10	OEt N N N R = CI, Me	Antitumor	148
11	OMe N OMe N OMe	Anticancer	149

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

158

158

33

34

Table 1 (Contd.) Compound structure Activity/properties S. no. Ref. 22 Anticancer 149 23 Anticancer 149 Anticancer 155 24 Anticancer 155 25 26 Breast cancer 155 27 Anticancer 155 Antibacterial 156 Antibacterial 156 30 Antibacterial 156 31 Antibacterial 157 32 Kinesin spindle protein inhibitors 158

Kinesin spindle protein inhibitors

Kinesin spindle protein inhibitors

S. no.	Compound structure	Activity/properties	Ref.
35	MeO ₂ C $\stackrel{\frown}{\longrightarrow}$ $\stackrel{\frown}{\bigcap}$ $\stackrel{\frown}{\bigcap$	STAT3 inhibitors	159
36	Br HO H-Ph	Neuroprotective agents	160
37	OH CO₂H H OH	Neuroprotective agents	161
38		XO inhibitors	162
39	H N C C I	CDK5/p25 kinase inhibition	163
40	R = H, NH ₂	Pim kinase inhibitors	164
41	н н сно	Pim kinase inhibitors	164
42	NH NH ₂ R = Cl, OMe	Pim kinase inhibitors	165
43	сно	Pim kinase inhibitors	166
44	ОН	Antiplasmodial	167
45	OH Et	Antiplasmodial	167

Table 1 (Contd.)

S. no.	Compound structure	Activity/properties	Ref.
46		Antiplasmodial	167
47	Br. Br	Antimalarial	168
48	N NH-NH R = Me, OMe	Antioxidant	169
49	H	Antioxidant	170
50	Me OH	Anti-HIV	171
51	Me O OMe OMe	Antiproliferative agents	172
52	Me O OMe OMe OMe	Antiproliferative agents	172
53	H H	Antiproliferative agents	173
54	H-N,N	Antiproliferative agents	174
55	HN NH S N R	Telomerase inhibitors	175

Table 1 (Contd.)

S. no.	Compound structure	Activity/properties	Ref.
56		PARP-1 inhibitor	176
57	HO HO OH	Chk-1 inhibitor	177
58	HOH Me NHMe	Chk-1 inhibitor	177
59	MeO OMe Me Me	Anti-yeast	178
60	Me N- Me Me	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 Cucatalyzed arylation of electron-rich indole derivatives with Michael acceptor 77 and I_2 -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

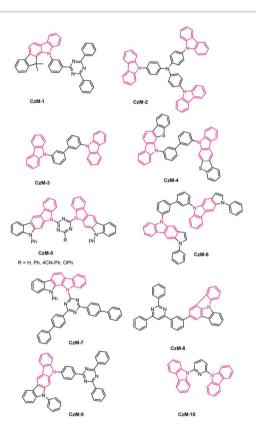
Pelkey and his groups reported a simple and flexible method to access 3-pyrrolin-2-one fused carbazoles. The critical essential step involves the BF₃-mediated cyclization in DCM at -40° C, providing access to aryl group-substituted carbazole derivatives 82 in good yields. This method represents the first 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 $Rh_2(OAc)_4$. The critical role of $Sc(OTf)_3$ is to facilitate both the initial intermolecular Michael reaction of the indole derivatives 83 and the subsequent $Rh(\pi)$ -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 ad 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 RSC Advances Review

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

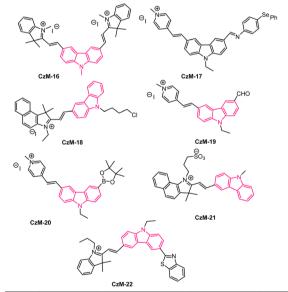


S. No	Carbazole number	Activity/ properties	Year	Ref.
1	CzM-1	OLEDs	2017	180
_				
2	CzM-2	OLEDs	2017	180
3	CzM-3	OLEDs	2021	181
4	CzM-4	OLEDs	2021	181
5	CzM-5	OLEDs	2014	182
6	CzM-6	OLEDs	2017	183
7	CzM-7	OLEDs	2018	184
8	CzM-8	OLEDs	2021	185
9	CzM-9	OLEDs	2018	186
10	CzM-10	OLEDs	2020	187

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

S.	Compound	Activity/	Year	Ref.
No	no	properties		
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

 $\begin{tabular}{ll} Fig. 3 & Thermally activated delayed fluorescence (TADF) of carbazole derivatives. \end{tabular}$



S.	Compound	Activity/	Year	Ref.
No	no	properties		
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.

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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 Zn(OTf)2, ZnCl2, FeCl3, and AgSbF₆ as the catalyst. Gratifyingly, JohnphosAu(MeCN)SbF₆ 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

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

S.	Compound	Activity/	Year	Ref.
No	no	properties		
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

Fluorescent properties of carbazole scaffolds.

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 polyaromatic 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, anticancer, 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

Selective examples for carbazolebased 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

Conclusions 5.

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 **RSC Advances** Review

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.

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