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Recent advancements of carbazoles synthesis: Towards the green synthesis approach

Shafrizal Rasyid Atriardi[1,*]
[1] *Chemistry Institute for Functional Material, Pusan National University, Busan, Korea, Republic of.*
*Correspondence: shafrizalrasyid@pusan.ac.kr

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ABSTRACT

Background: The importance of carbazoles synthesis had been a motive to study deeper about the synthesis of carbazoles. For the development of carbazoles synthesis, a green synthesis approach became an important aspect that needed to be improved. The sustainable synthesis of carbazoles also plays a role in the reducing the hazardous impact to the environment. **Methods**: This carbazoles synthesis review was based on the generation of A or B ring in the carbazole molecules that analyzed by retrosynthetic analysis, updating several works from the past 10 years and highlighting the green synthesis approaches of carbazoles. **Findings:** Some of the green synthesis approaches were reported by the utilization of a green energy sources, mild solvents, and low catalysts loading that were used in the reaction. Non-toxic and non-hazardous material were also preferable to maintain the sustainability of this reaction. These currently developed approaches were inevitably encountered by several limitations, including lower yields and reactivities. **Conclusion**: Some of the reviews provides an improvement of the results, providing a broad substrate scopes with the moderate-to-good yield using a green synthesis approach. **Novelty/Originality of this article:** This review were focusing on the development of a green synthesis approach of carbazoles, which never reported in any review before.

KEYWORDS: carbazoles; environment; green synthesis; natural products.

1. Introduction

Carbazole is a tricyclic compound consisting of a five-membered nitrogen-containing pyrrole ring fused with two six-membered benzene rings. These aromatic compounds can stabilizes the compound via electron delocalization, making most of the carbazoles stable under room temperature conditions (Fig. 1 (a)). Carbazole has a good planarity and rigidity, act as a hydrogen donor, has unique photophysical properties, and excellent biocompatibility (Yin et al., 2020; Mitra, 2022; Carioscia et al., 2025). There are many types of carbazole alkaloids that were found in the nature, most of the carbazole alkaloids usually found in some plants from the genus *Murraya, Glycosmis,* and *Clausena* in the Ruteceae family (Knölker & Reddy, 2002; Schmidt et al., 2012). Carbazoles known as versatile compounds, hence a lot of studies reported the bioactivity of carbazoles that were used as a drug, antioxidant, and antiviral material (Fig. 1 (b)) (Knölker & Reddy, 2002). Some of the carbazole alkaloids example were Antiostatin A_4 for antioxidant (Alayrac et al., 2009), Furostifoline and Midostaturine as an anthelmintic and myeloid leukimia drug, respectively (Soos et al., 1999; Weisberg et al., 2002). On the other hand, carbazoles were used as a thermally-activated delayed fluorescence (TADF) materials due to its unique photophysical properties (Ledwon, 2019). The utilization of carbazoles as a TADF emitter were firstly reported by Uoyama et al. (2012). They reported a carbazolyl dicyanobenzene (CDCB) -

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based organic material that consist of four carbazoles as the electron donor that were linked to the dicyanobenzenes as the electron acceptor. One of the most famous CDCB-based organic material was 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) (Fig. 1 (b)). To date, the utilization of this materials are exponentially increased by years in the TADF as well as photoredox catalysis-based research (Allen & Natho, 2023). Therefore, the isolation and synthesis of carbazoles were essential to be studied.

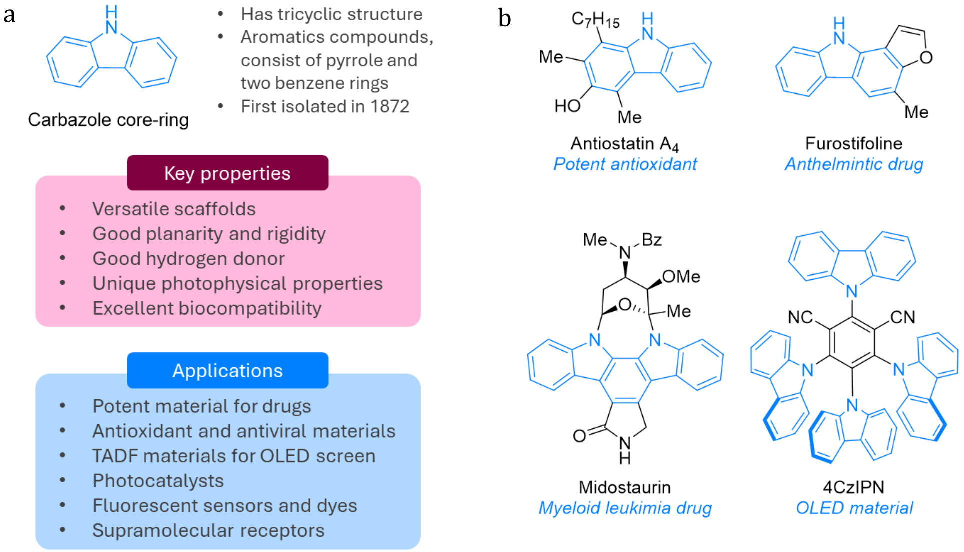

Fig. 1 (a) Carbazoles and its features; (b) Representative of carbazoles derivatives

The first isolation of carbazole alkaloids were reported from several natural resources such as coal tar (Graebe & Glazer, 1872) and *Murraya koenigii* plant. Years after this invention, some of researchers reported the isolation of carbazole alkaloids from different plants and studied the diversity of carbazole alkaloids, including their biological activities. Despite the isolation procedure were deployed, the drawbacks in the isolation of carbazoles were still unhindered. Most of the cases were the efficiency or low yield observed, which led researcher to solve this problem. To overcome this issues, aside from the isolation process, researcher are tend to synthesis carbazoles from the small starting material. Aiming the synthesis process resulting better efficiency and yield compared with the isolation process. The first synthesis of carbazoles were developed by Borsche & Meyer (1921) and was known as Fischer-Borsche synthesis, followed by the invention of Graebe-Ullmann synthesis (Knölker & Reddy, 2002). Afterwards, the synthesis of carbazoles were quickly gained many interest from the researcher and a lot of carbazoles natural products were synthesized. In the past 10 years, some review articles of carbazoles synthesis were reported based on the starting material used (Berkowitz & McCombie, 2017; Aggarwal et al., 2019; Banerjee et al., 2021), and the disconnection approach (Georgiades et al., 2019; Allen & Natho, 2023; Munawar et al., 2024). Nevertheless, the development of carbazoles synthesis is important for the future applications.

Over the past two decades, the green synthesis approach have garnered significant attention that allows milder reaction conditions, easier handling, and greater sustainibility for the environment. However, most of the synthesis approaches were still using harsh conditions, including elevated temperature, and used either hazardous material or problematic solvents (Allen & Natho, 2023). To solve the environmental issues, the green synthesis approach of carbazoles became one of the alternatives carbazoles synthesis that is necessary to study. To date, several green synthesis approaches of carbazoles were reported. Given that the yields are lower than the classical synthesis, the continuation in the development of green synthesis approaches is a desirable. This review contains the synthesis of carbazoles using green synthesis approaches by classifying based on the retrosynthetic analysis and the starting material that are used. This review covers both the fundamental approach of synthesis and its recent progress under mild conditions. Therefore, this review will aid researchers comprehend the development of green synthesis approaches of carbazoles.

2. Methods

The synthesis of carbazoles were already reported through many retrosynthetic analysis. In this review, the carbazole synthesis strategies were analyzed by the retrosynthetic disconnection of several bonds that form the A ring (benzene) and the B ring (pyrrole) (Fig. 2). Based on the retrosynthetic approach, several representative carbazoles synthesis were provided including the classical approach and the development of green synthesis approaches.

In the Fig. 2, carbazoles were synthesized from three major starting materials, such as indoles, *N,N′*-biphenyls and biphenyls. The A ring (benzene) and B ring (pyrrole) formation were reported by several strategies including the C-C bond formation, cyclization, and the pericyclic reaction. Disconnection of the C–C bond in the A ring (benzene) leads to indoles as starting materials, while disconnection of C–C or C–N bonds in the B ring (pyrrole) gives *N,N′*-biphenyls and biphenyls as starting materials. In addition, some of the interesting synthesis strategies, such as one-pot and three component reaction strategies were also included. The synthesis of carbazoles from these starting materials were described in the next section.

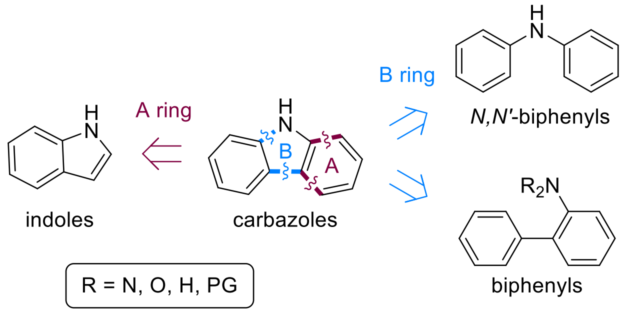

Fig. 2. The retrosynthetic analysis of carbazoles, PG = protecting group

3. Results and Discussion

3.1 Synthesis of A ring from indoles

Indoles 1 are aromatic compound that consist of one arene and pyrrole ring linked each other. Indoles 1 are versatile compounds that are readily available and an inexpensive starting material, making this synthesis approach as one of the best option to synthesis carbazoles (Aggarwal et al., 2019; Banerjee et al., 2021). The synthesis of carbazoles using unmodified indoles 1 were somehow difficult to access, and only a few studies had been reported. Rathore et al. (2014) designed an synergistic Rh(II)- and Brønsted acid-catalyst to construct carbazole-4-carboxylates in a single operation. Although this method encountered issues related to reactivity and selectivity, an elegant synthesis of disubstituted carbazoles (3) was later reported using unmodified indoles 1 and alkenes 2 via triple Heck reactions (Fig. 3) (Verma et al., 2015). The reactions goes smoothly by the presence of 15 mol% palladium(II) chloride ($PdCl_2$) and 40 mol% phosphine ligand as catalysts, with the support of copper(II) acetate ($Cu(OAc)_2$) in a mixture of DMF:DMSO. Although they were still using elevated temperature, this elegant strategy provides good yields with diverse amount of substrate scopes. The mechanism of this reaction were based on the Heck reaction, while palladium(0) will goes for oxidative addition at the C3 position of indoles 1, followed by the insertion of the alkenes, then 1,2-migratory insertion will push the palladium(II) to the terminal position of the alkene and loss the π-bond to generate alkylated palladium(II) intermediate. Then, palladium(II) released through β-hydride elimination and generates alkenenyl indoles as the intermediate products. This process continued with the second and third Heck reaction, completed by the cyclization of the last step to yield carbazoles 3 as products. This method provides a variety of scopes with different functional groups. The addition of electron-withdrawing groups in olefin such as methyl ester and ketones furnished carbazoles 3a and 3b with the yield of 63% and 68%, respectively. The installation of methoxy group on the C6 position of indoles also gave good yields (3c-d). However, the replacement of methoxy group in the C6 position with methyl ester gave lower yield (38% for 3e and 3f). Another similar work also reported in 2018 by employing the cascade synthesis of dihydrocarbazoles in the presence of scandium(III) triflate ($Sc(OTf)_3$) and rhodium(II) acetate ($Rh_2(OAc)_4$) as catalysts for the efficient construction of densely substituted carbazoles 3 (Sakthivel et al., 2018).

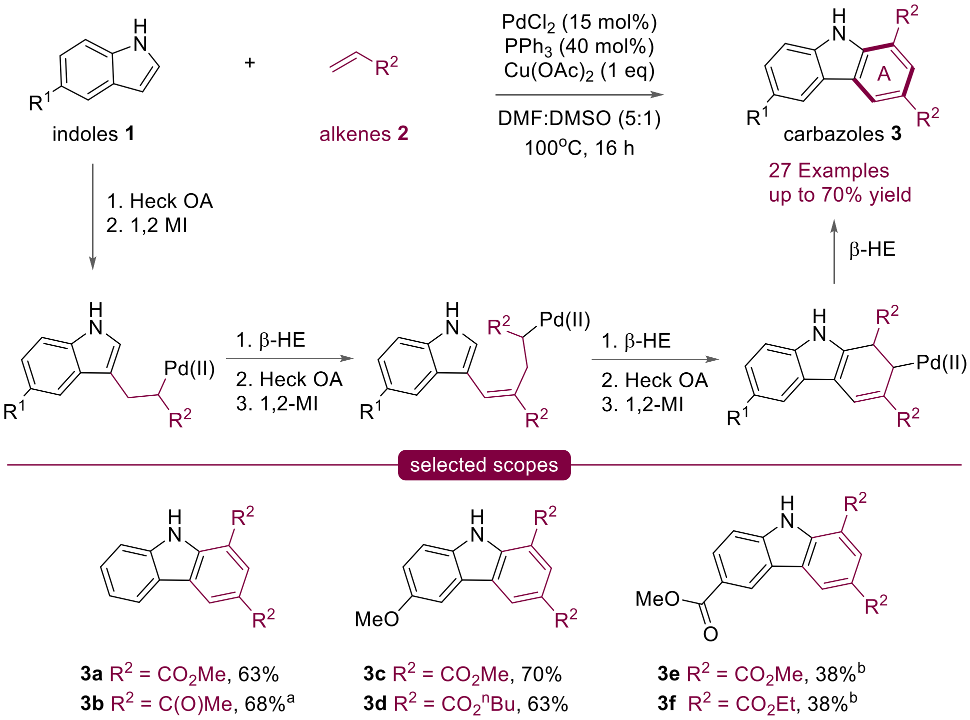

Fig. 3. The Heck approach to synthesis carbazoles 3 from indoles 1, OA = oxidative addition, 1,2-MI = 1,2-migratory insersion, β-HE = β-hydride elimination, [a]12 h, [b]18h

To reduce the cost of the reaction and applying the green synthesis approach, some of acid-base strategies were also reported. Zhao et al. (2015) reported the mild and facile synthesis of trisubstituted carbazoles 3 by acid-catalyzed ring-opening annulation of dihydrofurans 4 with unmodified indoles 1 (Fig. 4). A 40 mol% of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a lewis acid used to activate dihydrofurans 4 and generated iminium cation. Then, the nucleophilic addition reaction with indoles 1 led to the C-C bond formation, followed by the elimination of acetamide. This ene-intermediate then undergo intramolecular cyclization and condensation gives a spiro intermediate and finally the carbazoles 3 products were obtained in good yields. Some of substrate scopes have been reported such as unattached indoles 1 furnished carbazoles 3g with 55% of yield. The installation of several functional group in the C6 position of indoles, such as methoxy and bromine gave a contrast effect. The effect of the electron-donating groups will increase the yield (3h, 77%) while the electron-withdrawing groups gave lower yield (3i, 30%). Noteworthy, a variety of dihydrofurans 4 screening gave good yields (3J-k). This concept was then expanded by Cao et al. (2018). By utilizing triethylamine as a weak base and electron-deficient alkene, the [4 + 2] annulation of 3-nitroindoles with electron-deficient alkene yields carbazol-4-amine derivatives as a product. Another strategy to synthesize carbazole 3 from unmodified indoles 1 was using the radical strategy (Debnath et al., 2020). The introduction of phenacyl bromide can solely act as α-carbonyl radical source which then attack the indoles 1 to generate radical cationic species. With several radical transformation and cyclization, the 3,5-diarylcarbazoles 3 were synthesized with a good regioselectivity.

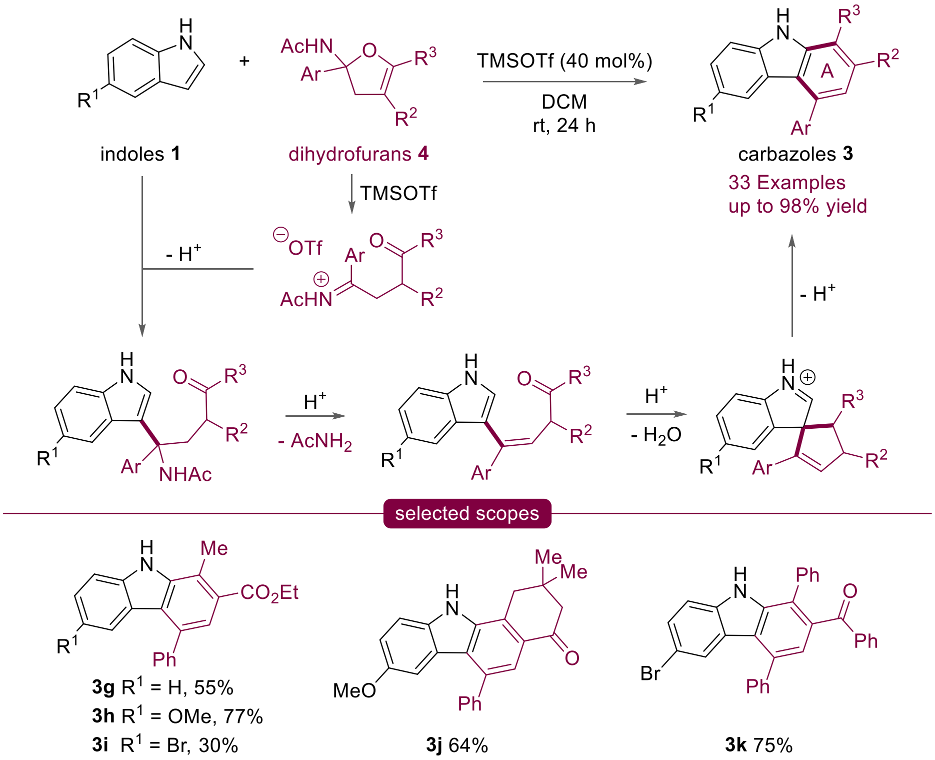

Fig. 4. Synthesis of carbazoles 3 catalyzed by lewis acid

Due to the lack of reactivity of the unmodified indoles 1, many researchers were modified indoles by attaching some functional groups at the C2 or C3 position of indoles 1. By modifying the indoles 1, this approach need some extra steps to synthesize starting material. This strategy was commonly developed due to the good reactivity of the modified indoles by employing a various type of reactions, such as metal-based reaction, and acid-based reaction (Aggarwal et al., 2019; Banerjee et al., 2021).

The synthesis of carbazoles using metal precursor were widely developed using several types of transition metals, such as silver (Ag), gold (Au), copper (Cu), and ruthenium (Ru) as the catalysts. One of a good examples to described this approach was reported by Qiu et al. in 2012 (Fig. 5). They were using an alkyne-substituted indoles at C2 position (1) and combining with 5 mol% of gold(III) chloride ($AuCl_3$) as a metal catalyst. Having a good affinity with alkyne functional group, gold(III) coordinated with alkyne to promote the intramolecular cyclization. This methods conducted in room temperatures and works well with several functional groups such as phenyl (3l), long aliphatic chain (3m) and *N*-benzyl protecting group (3n). However, this reaction were still have limitations in several functional groups, only 12 examples were reported in this study.

The development of modified indoles 1 using metal catalyst also reported using photoredox catalysis approach (Fig. 6) (Yuan et al., 2016). They developed the photoredox catalyzed carbazoles [4+2] cyclization of modified indoles 1 with α-bromo malonate at C3 position. The combination of 2 mol% of *fac*-tris(2-phenylpyridine)iridium (*fac*-Ir(ppy)$_3$) as a metal catalyst with the presence of a visible-light enabling the specific reaction through a radical redox mechanism. By applying a blue LEDs as a light source, this approach utilized the excited iridium(III) species as a single-electron reductor.

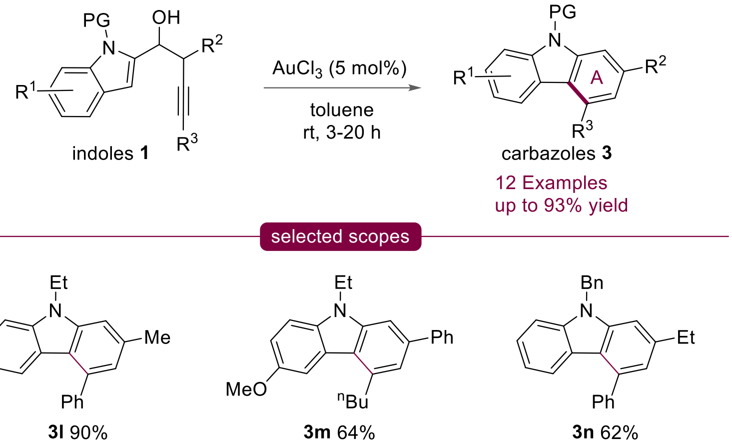

Fig. 5. Gold-mediated cyclization of indoles 1, PG = protecting group

This excited species will act as electron donor to malonate and redox reaction will produces an α-dicarbonyl radical as an intermediate. Then, the radical addition to the alkynes 5 following by the radical cyclization and keto-enol tautomerization furnished the radical intermediate. Finally, the oxidative aromatization by iridium(IV) yielded highly functionalized carbazoles 3 as a products. This reaction providing an environmentally friendly method which has good tolerance in several functional groups. A series of alkyne including the phenylacetylene, 1-hexyne, and cyclohexylacetylene gave the desired products with the yield of 84%, 67% and 73% for 3o-q respectively. The installation of both electron-donating and withdrawing groups in the C6 position of indoles 1 gave moderate-to-good yields (3r-t). Additionally, the replacement of malonates with β-ketoamides and β-ketoaldehydes gave 61% and 89% of yields (3u-v).

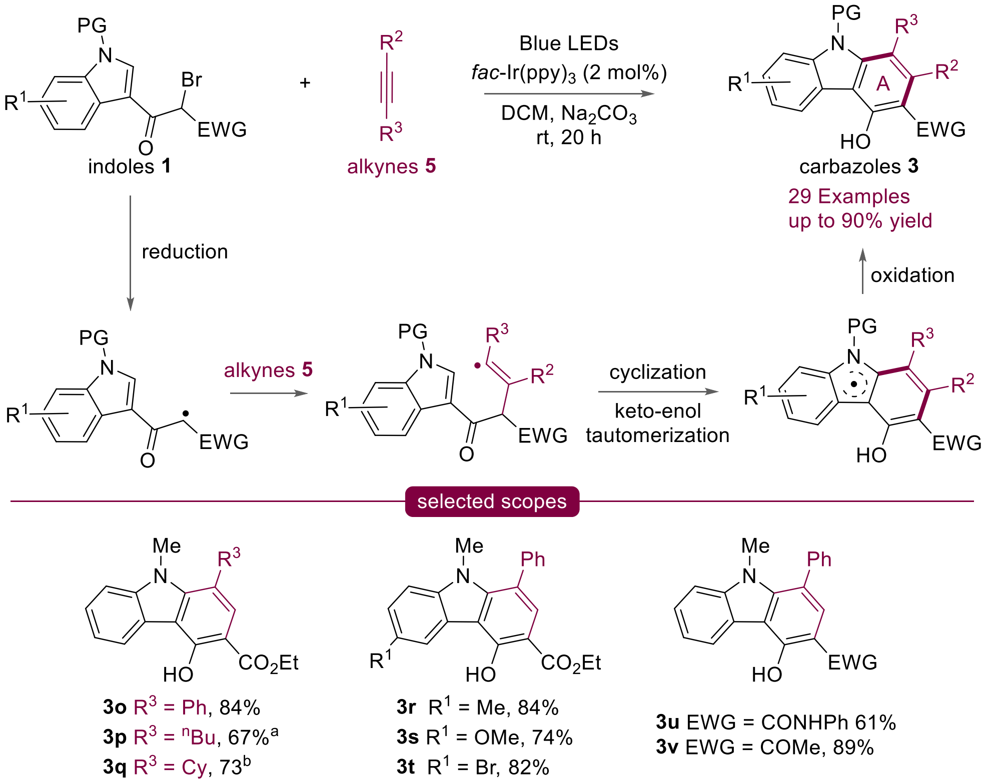

Fig. 6. Photoredox-catalyzed synthesis of carbazoles 3, PG = protecting group, EWG = electron-withdrawing group, ^{a}5 equivalent of alkyne, ^{b}36 h

Another alternatives to synthesize carbazoles 3 by using modified indoles 1 were using halides (Wang et al., 2015). This halides promoted the cyclization reaction by the formation of hypervalent iodine. The utilization of acid-base as a co-reactant in cyclization reaction of carbazoles 3 was also reported. One of the interesting approach was reported by Liu et al. (2019). They used a simple enolate chemistry concept by specifically designed the indoles 1 with methyl and aldehyde in the C2 and C3 position. With the help of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as a weak base under aerobic condition, this indoles proton in the α-methyl position will be deprotonated and generate enolate as shown in Fig. 7. This enolate then attacked the acrylaldehydes 2 to generate the 1,4-addition product via Michael reaction, following by the cyclization and protonation using LiCl as a lewis acid to furnished highly functionalized carbazoles 3 in good yields. Similar approaches was also reported by Biswas et al. in 2015. Instead of using methyl attached at the C2 position of indoles 1, they were using methylester to enhance the statbility of the enolates (Fig. 7). By using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a weak base and aqueous HCl as an acid, this mild reaction will also produced highly functionalized carbazoles 3 with good results. They were using nitroalkene 2 instead of acrylaldehydes 2, resulting in the elimination of nitrous acid in the last step. Both of these approaches provided a mild and an environmentally friendly methods with a diverse substrate scopes. Another examples to synthesis carbazoles 3 were reported by using some specialized reagent and unique approaches such as 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (Liu & Zhang, 2015), *N*-heterocyclic carbene (NHC) (Liu et al., 2018), and also using the montmorillonite as a heterogenous catalyst (Lim et al., 2015).

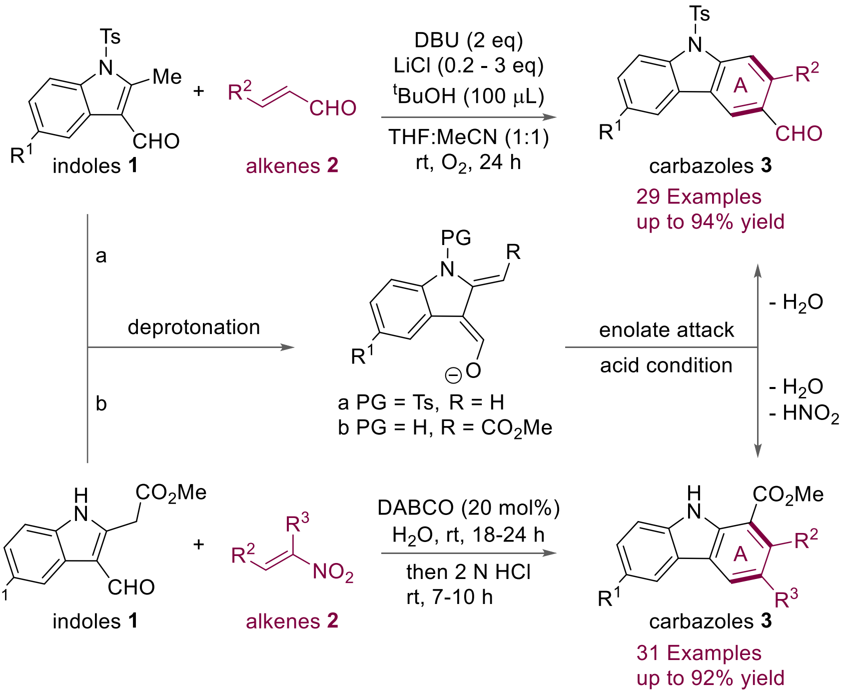

Fig. 7. The addition of acrylaldehydes and nitroethenes to activated indoles to synthesize carbazoles 3, PG = protecting group

3.2 Synthesis of B ring from N,N'-biphenyls

In a classical synthesis of carbazoles, the initial approach involved the construction of the B ring (pyrrole) from *N,N'*-biphenyls (Fig. 8). The *N,N'*-biphenyls are consist of two phenyls that are connected with amine as a bridge. This compound can be found in a various fields of study, mostly used as a catalyst and photoemitting material (Chagas et al., 2009). The first synthesis approach was reported by Borsche & Meyer in 1921, which was known as Fischer-Borsche reaction. Although they were not exactly used *N,N'*-biphenyls as their starting material, they used *N,N'*-biphenyls analogues in a similar way to construct the B ring. They utilized phenyl hydrazines 6 and cyclohexenones 7 as starting materials. The addition of acetic acid with reflux condition led to the formation of phenyl hydrazone intermediate (an analogue of *N,N'*-biphenyls) and subsequently converted to tetrahydrocarbazoles 8. The aromatization then took place using chloroaniline or palladium/carbon hydrogenation reaction to furnished carbazoles. Recently, a milder reaction condition was developed to synthesize carbazoles 3 from tetrahydrocarbazoles 8 (Sato et al., 2023). This work utilized an electrochemical method to assist the aromatization reaction that led to the desired carbazole 3. The second commonly known reaction was Greabe-Ullman reaction (Knölker & Reddy, 2002). They used *N,N'*-biphenyls 9 as a starting material followed by formation of triazole ring 10 using nitrous acid. The final step to synthesize carbazole 3 was conducted using elevated temperatue in neat condition by the elimination of nitrogen gas.

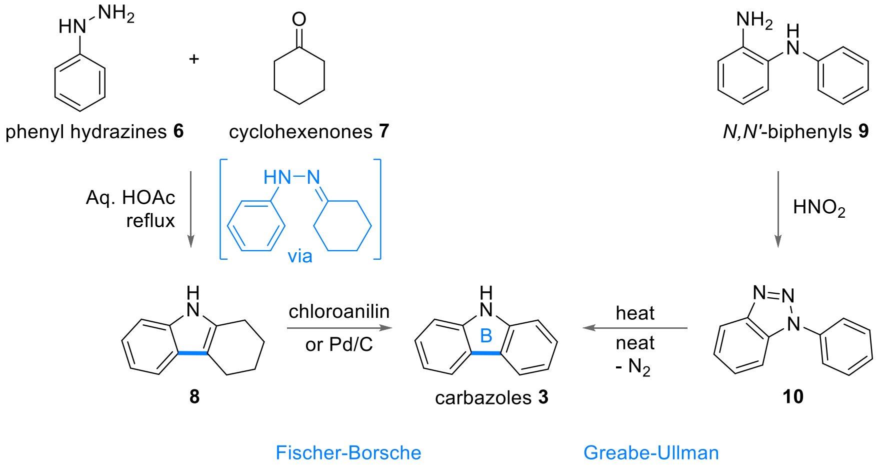

Fig. 8. The classical approach of carbazoles 3

The development of carbazole 3 synthesis using this approach were actually eluded by some researcher due to the inadequate availability of *N,N'*-biphenyls 9 as starting material, making extra step to prepare the starting material. Generally, some metal catalysts were frequently used in this approach with thermal condition. Melnika et al. (2013) reported a milder cyclization approach using radical strategy by installing iodides in the ortho position of *N,N'*-biphenyls 9 (Fig. 9). The generation of radical was initated by potassium *tert*-butoxides and 20 mol% of iron(II) bromides ($FeBr_2$). The resulting radical took place in the iodide position, generating phenyl radical and followed by the radical cyclization will furnished carbazoles 3 as products. Some of examples were reported up to 94% of yield by the installment of several electron-donating or withdrawing groups in the aromatic position (3w-aa).

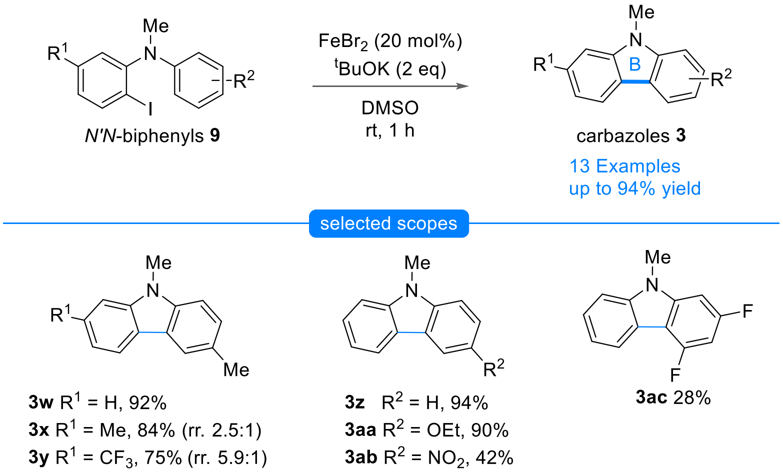

Fig. 9. Iron mediated cyclization of *N,N'*-biphenyls to synthesize carbazoles 3

The selectivity of several scopes were also obtained in good regioselectivity (up to 5.9:1 for 3y). However, the installment of electron-withdrawing group in the R^2 position gave slighly lower yield (42% for nitro 3ab and 28% for difluoro 3ac). To achieve a green synthesis route via this approach, an elegant strategy to synthesis carbazoles 3 was developed by Chakrabarty et al. (2013) (Fig. 10). They were using phenyl silanes 11 and nitrosobenzenes 12 as starting materials. First, phenyl silanes 11 was converted to benzynes by deprotection of silanes using CsF as fluorine sources and release triflates as a leaving group. Benzynes then reacted with nitrosobenzenes 12 and undergo [2+2] cycloaddition to provide the strained heterocycles intermediates. The cycloreversion then proceeds to form more stable *N*-phenyl benzimine, as an analogue of *N,N'*-biphenyls 9. Finally, the electrophillic aromatic substitution (EAS) furnished carbazoles 3 as products. This green synthesis method provides good yields with a fast reaction, mild solvent system and gave a lot of substrate scopes. A series of nitrosobenzenes 12 were screened and gave moderate-to-good results in several ortho derivatives (3ad-af, up to 65%). Another modification in the 2,3-position of nitrosobenzenes 12 led to the formation of diisopropanol 3ag (44%), diethoxy 3ah (58%), and dibromo 3ai (80%) products with good regioselectivity (up to 10:1 regioselectivity in diisopropanol 3ag). The installment of cyclic aliphatic chain in phenyl silanes 11 gave carbazoles 3aj in 50% of yield.

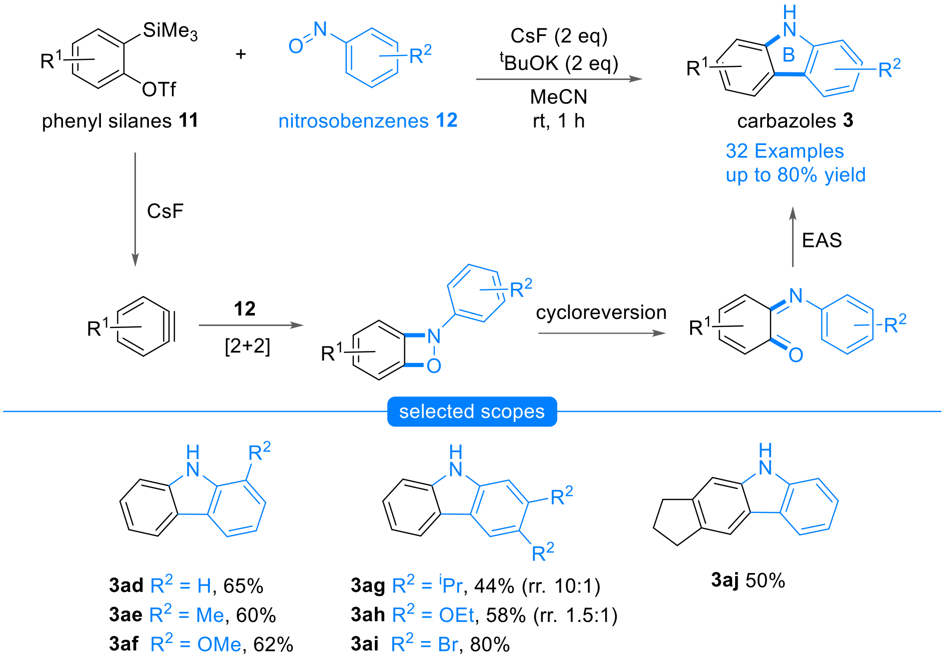

Fig. 10. Carbazoles 3 synthesis via [2+2] cycloaddition of benzynes with nitrosobenzenes 12, EAS = electrophilic aromatic substitution

3.3 Synthesis of B ring from biphenyls

Biphenyls 13 are aromatic compounds which are widely used in many industrial fields especially in catalysts and ligands (Ali et al., 2023). These advantages considered biphenyls 13 as a good starting material for synthesis of carbazoles 3 via cyclization reaction. One nitrogen atom usually attached in the ortho position of the benzene. The common reagent that used to generate carbazoles 3 were azidobiphenyl 13a, aminobiphenyl 13c and nitrobiphenyl 13d (Berkowitz & McCombie, 2017). These starting material usually generate nitrene as an intermediate that lead the cyclization reaction to produce carbazoles 3. In the case of azidobiphenyls 13a, several works were reported using thermal condition (May & Wilson, 2006), metal catalyzed reaction (Stokes et al., 2009) and photochemical reaction (Sundberg et al., 1970) to synthesis carbazoles 3. However, these classical approaches required harsh reaction condition, which were problematic for the environmental issues. Yang et al. (2018) reported a milder photochemical reaction of carbazoles 3 from azidobiphenyls 13a (Fig. 11 (a)). They used a fluorescence lamp as a light source with an aqueous acetone as a solvent. Although this approach need longer reaction time (48 hours) due to the slow generation of nitrene as intermediate, they reported various type of scopes with good yields. To overcome the reactivity issues, an interesting approach reported by Tian et al. (2020). Instead of using azido group in the biphenyls 13, they used the amine and modified using martin sulfurane to generate biphenyl sulfilimines 13b, that increase its reactivity to generate nitrene. The carbazoles 3 products proceeds faster in the presence of Blue LEDs as a light souce. Compared with previous work, this approach only need 1 hour to produced carbazoles 3 with satisfactory results. They also studied the reaction rates of each biphenyls 13 using deuterated THF as a solvent. The reaction time was set for 1 hour and the reaction rates of biphenyl sulfimines 13b were faster compared with the azidobiphenyls 13a as seen in Fig. 11 (b). This experiment also gave another insight into the development of carbazoles 3 synthesis using extraordinary approaches.

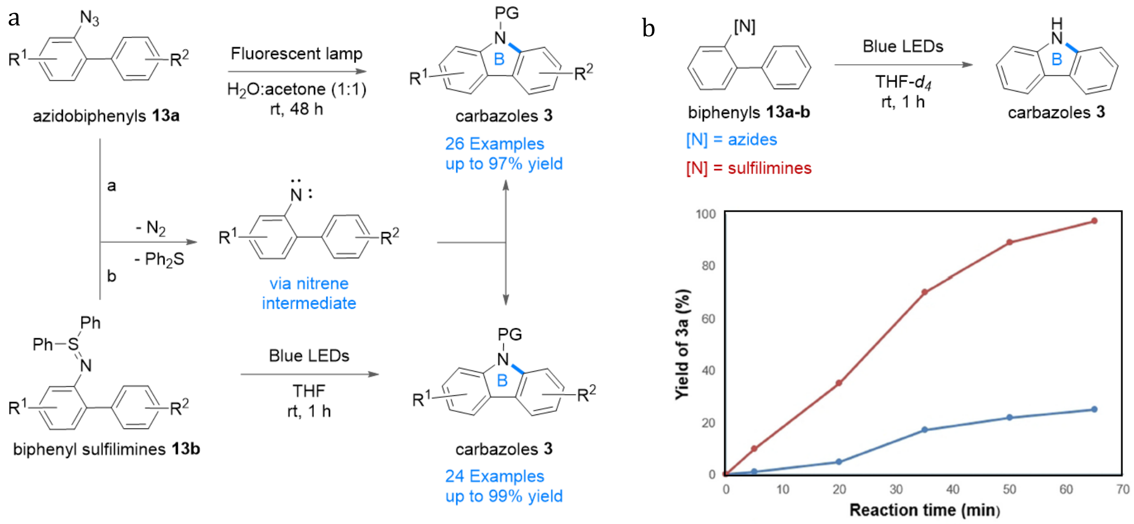

Fig. 11 (a) Two different approaches; (b) The reaction rate using photoreaction to synthesize carbazoles 3

On the other hand, the synthesis of carbazoles 3 using amino biphenyls 13c had been extensively studied. The common reagent that were used including metal catalyst (Hegedus et al., 1978) and iodine catalyst (Antonchick et al., 2011). By using metal catalyst such as palladium, the reaction proceed faster hence the installation of amine protecting group was necessary. Application of such dehydrogenative amination reaction to the total synthesis of Clausine C as naturally occurring carbazoles 3 were also reported using photochemical and electrochemical methods. Choi et al. (2015) developed a merged visible-light photoredox and palladium-catalyzed reaction to synthesis carbazoles 3. Further reaction of carbazoles 3 afforded the natural products. In another work, the requirement for the metal catalysts was removed under electrochemical conditions. The *N*-sulfonylated carbazoles 3 could be obtained from *N*-sulfonamidobiaryls under electrolysis with constant current and the applicability to total synthesis was conducted with several steps to afford the natural products (Zhang et al., 2020).

A green synthesis approach using one-pot reaction of carbazoles 3 was developed by Maiti et al. (2017) using 2.5 equivalent of (diacetoxyiodo)benzene ($PhI(OAc)_2$) as an iodine catalyst (Fig. 12). This reaction finished in 1 hour using trifluoroethanol (TFE) as a solvent. They used unusual *N*-protected anilines 14 and arenes 15 as starting materials, began with the nucleophilic attack to the electrophilic iodine followed by the removal of iodine to form cationic species of anilines. This cationic species resonances to generate imine and the addition of arenes 15 allows the formation of *N*-protected aminobiphenyls 13c. Finally, the cyclization step furnished carbazoles 3 in good yields. A variety of scopes were reported, including the installation of alkyl, alkoxy, halide, and heteroaromatics on the anilines and arenes (44-78% of yield for 3ak-ao). Different types of the amine protecting groups were also screened, such as tosyl and acetyl protecting groups were obtained in 61% and 52% of yield, respectively.

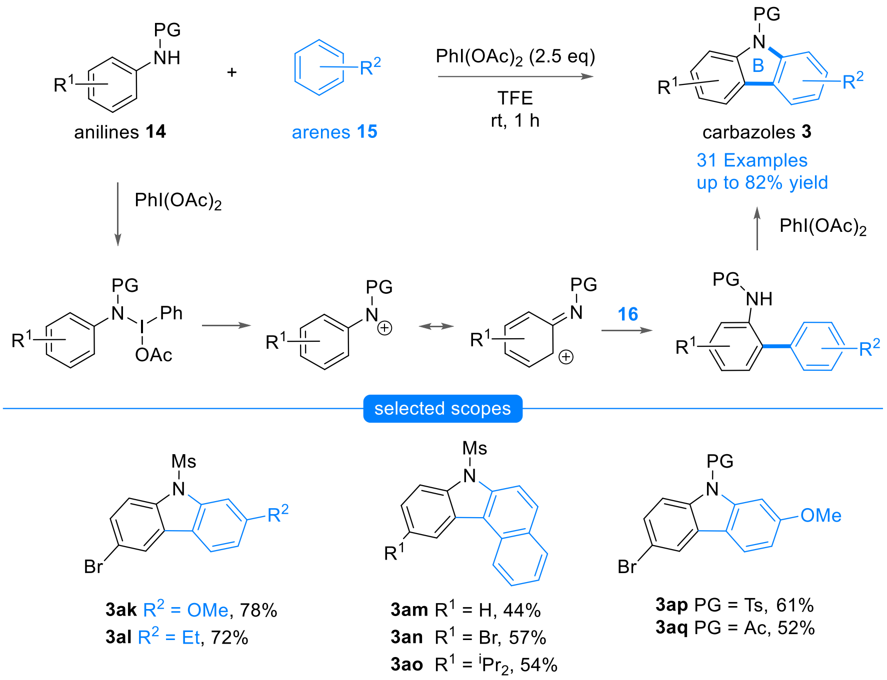

Fig. 12. The hypervalent iodine approach to synthesize carbazoles 3, PG = protecting group

Another reagent that were studied to generate carbazoles 3 are using nitrobiphenyls 13d as starting materials. In this reaction, the classical methods still required an elevated temperature, using a well known reductive amination protocol that invented by Cadogan et al. (1965). The original conditions involved heating the nitro compound in neat trialkyl phosphite at the reflux temperature (typically 150–160ºC), affording moderate to high yields for many substrates. Goo et al. (2016) reported a one-pot synthesis of carbazoles 3 followed by Kim et al. (2017). They conducted this strategies from bromonitrobenzenes and aryl boronic acid without any additional steps. The reaction includes a combination of the formation of nitrobiphenyls 13d by C-C bond coupling and reductive amination from nitrene to afford carbazoles 3 as products. However, they were also need elevated temperatures. Recently, the milder reductive amination approach also studied in one-pot fashion (Yang et al., 2025). The utilization of purple LEDs were sufficient to replace the thermal energy for this reaction. The addition of nitrobenzene and the phenyl Grignard as starting materials will furnished carbazoles 3 with good yields.

3.4 Miscellaneous reactions

The synthesis of carbazoles using different types of starting materials were currently developed to overcome its previous limitations. Instead of the green synthesis approach that has been describes in the previous chapter, another approaches that were using different types of materials are reported. Chutia et al. (2024) used diphenylacetylenes 16 as their starting materials (Fig. 13). The different substituents, including amine and aldehyde in the ortho position were used to conduct the reaction. With the presence of boron trifluoride-diethyl etherate ($BF_3{\cdot}OEt_2$) as a lewis acid, the formal [3+2] tandem cyclization proceeds between these two diphenylacetylenes 16 and furnished hetero-annulated carbazoles 3 within 3 hours. Initially, the imine was generated and activated by lewis acid. The first cyclization proceeds by the imine addition mechanism to form indole-like intermediate. Then, the second cyclization furnished the new 6-membered ring intermediate. Finally, a Friedel-Crafts reaction with several transformations will completed the synthesis to form hetero-annulated carbazoles 3.This reaction works with a variety of substrate scopes, giving about 40 examples with good yields.

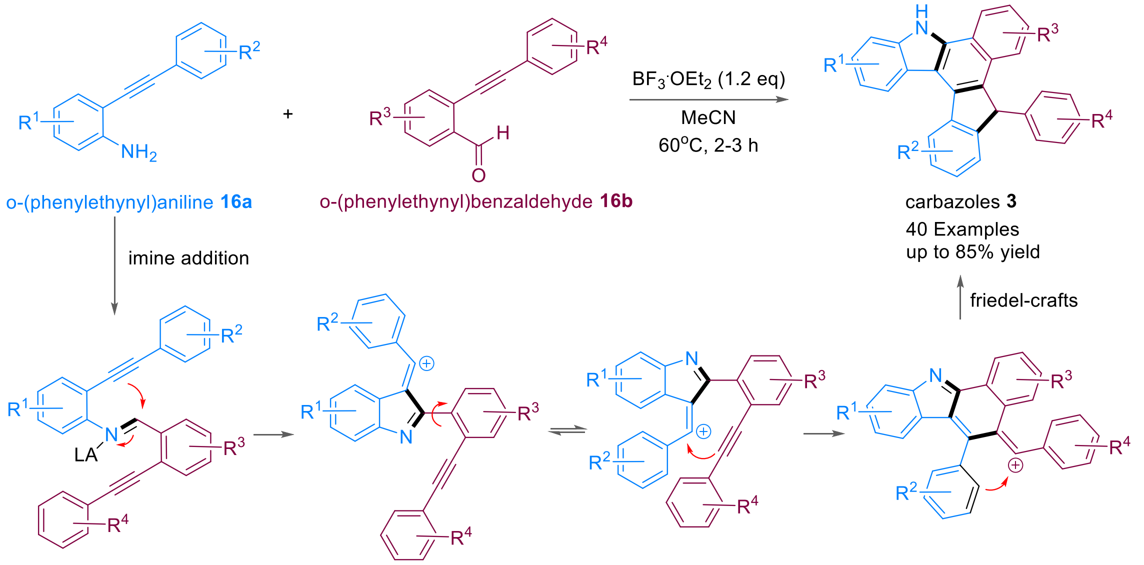

Fig. 13. Lewis acid promoted synthesis of hetero-annulated carbazoles 3

Another elegant approach were reported by Zhang et al. (2023). Using *N*-phenyl-2-naphthylamines 17 and quinones 18, they successfully synthesized the hetero-annulated carbazoles 3 using 20 mol% of chiral phosphoric acid (CPA) as a catalyst (Fig. 14). This approach offered milder reaction in room temperature condition, despite of the longer reaction time needed and used chlorinated solvent. This unique strategy started with the coordination of these two starting material with CPA, and C-C bond forming reaction was proceed. Then, the formation of pyrrole ring were obtained with the carbonyl attack, and rearomatization yielded hetero-annulated carbazoles 3. Notably, the presence of chiral catalyst led to the formation of atroposelective reaction. They also reported various type of scopes with excellent yields.

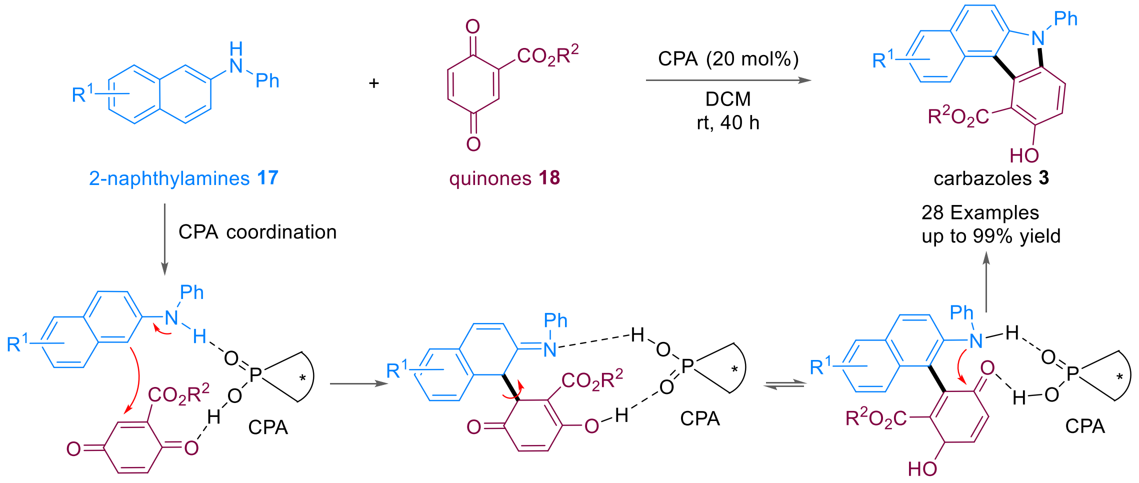

Fig. 14. Chiral phosphoric acid (CPA) promoted synthesis of hetero-annulated carbazoles 3

Although many researcher has been reported the unique design of the carbazole synthesis approach, the green synthesis approach remains its current challenges and requires additional improvement. Furthermore, key green chemistry metrics, including Atom Economy (AE), Atom Efficiency (AEf), Reaction Mass Efficiency (RME), E-factor, and Process Mass Intensity (PMI) were important aspects in the evaluation of green chemistry approaches that were necessary to be calculated (Fantozzi et al., 2023).

4. Conclusions

The development of carbazoles towards a green synthesis approaches have been reported by several researchers. This review provides the updated literature that performed the carbazoles synthesis using a green chemistry approach. Most of the reported works employed metal-based catalyst, acid-base catalysts, and some specialized reagents, regardless of which starting material was used. The development of green energy sources such as photochemical and electrochemical method also included in the synthesis of carbazoles. Nevertheless, these developed syntheses are still far from ideal in the term of green synthesis approach. There are many aspects such as the materials used, process, and system that can be improved to build a sustainable future. The measurement of green chemistry metrics was strongly encouraged. By this review, hopefully the researcher can gain knowledges, learn the current synthesis approaches and contribute in the future development of carbazoles synthesis.

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Author Contribution

The author conceived the study, designed the methodology, conducted the experiments, analyzed the data, and wrote the manuscript.

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Biographies of Author

Shafrizal Rasyid Atriardi, Chemistry Institute for Functional Material, Pusan National University, Busan, Korea, Republic of.

- Email: shafrizalrasyid@pusan.ac.kr
- ORCID: 0000-0001-5797-3741
- Web of Science ResearcherID: N/A
- Scopus Author ID: 57209224198
- Homepage: https://scholar.google.com/citations?user=snaoO-0AAAAJ&hl=en