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Ionic liquids in the synthesis of indole derivatives

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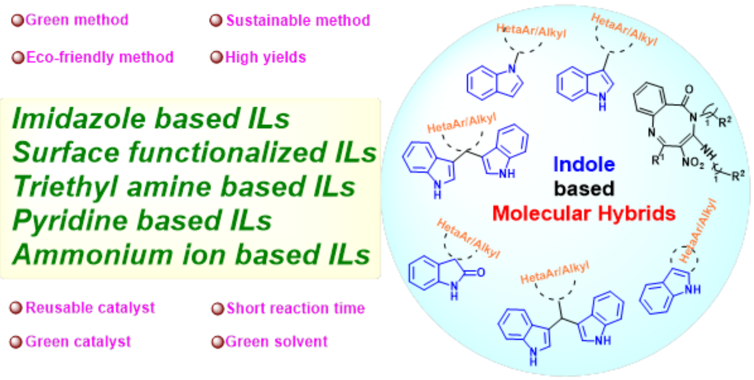
Abstract

There is now more demand for sustainable and environmentally friendly methods in organic synthesis. Green synthesis or chemistry accentuates the use of recyclable or renewable resources while lowering harmful side effects and supporting eco-friendly construction of privileged organic building blocks. Green synthesis of organic heterocycles, which have grown well-known for their unique characteristics and uses in organic synthesis, is a major topic of attention. Among organic heterocycles, indoles are recognized for their beneficial pharmacological properties and synthetic utilization in organic chemistry. Moreover, indoles form basic structures in many biologically useful compounds, including prospects for medications including pindolol, selisistat, oxypertine, arbidol, indomethacin, and sumatriptan. Owing to their adaptability and possibility for functionalizing, indoles are extensively sought in the synthesis of new medical drugs. This manuscript examines the sustainable features of ILs in the synthesis of indole derivatives. This is the first report that emphasized on current progress in the formation of pharmaceutically active indole frameworks using ILs.



Keywords: Green methods; sustainable methods; reusable; solvent; catalyst; indole derivatives

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1. Introduction

Adhering to the values of green chemistry, scientists are endeavouring to create environmentally sustainable methods for the synthesis of significant motifs.[1-2] A green catalyst and solvent should be economical, stable, selective, non-toxic, and reusable.[3] Consequently, creating a multifaceted catalyst and solvent for diverse reactions is a challenging endeavour. Ionic liquids (ILs) are considered innovative, environmentally benign solvents and catalysts owing to their distinctive physicochemical characteristics, including non-flammability, low volatility, high conductivity, robust solvation capabilities, effective recyclability, and remarkable thermal stability.[4] Furthermore, scientists are intrigued by ILs because of its diverse intermolecular interactions, including ionic, hydrogen bonding, and π-π interactions, as well as their adjustable features.[5] They have profoundly altered the research community and have been examined across various scientific disciplines, including Chemistry and Biochemistry, functioning as electrolytes in solar cells and serving as co-solvents in protein folding.[6-8] Imidazole-based ILs have garnered significant scientific interest due to the crucial role of the imidazole ring in the histidine amino acid in various biological processes.[9] The scientific community has focused considerable attention on imidazole-based ILs due to their unique characteristics. For several years, IL has served as a notable catalysts and solvents system for the synthesis of various organic heterocycles, including pyrazole,[10] pyrrole,[11-12] carbazole,[13] isatin,[14] and imidazole.[15] ILs, due to their unique composition, remarkable properties, and wide-ranging uses, serve as an outstanding catalyst and solvent system for the synthesis of various organic heterocycles, garnering significant interest among organic chemists in the realm of green synthesis.[16] Although

ILs are frequently claimed to be environmentally friendly because they possess a low vapor pressure and may be adjusted to release fewer volatile organic compounds but a lot of research indicates that they may not be as environmentally friendly as they appear due to their manufacture, long-term consequences, and potential harm to animals both on land and in water. Ionic liquids may be environmentally beneficial, but further research is needed to determine their effects and whether they decompose naturally.[17]

On the other hand, indole is a privileged scaffold among aza-heterocycles and studied widely in synthetic organic chemistry.[18-21] Moreover, indole has gained significant attention due to its novel pharmaceutical properties and utilization in various fields of science.[22] Specifically, in drug development, indole is a fundamental structural motif with great versatility for building different receptor ligands.[23] Indole derivatives exhibit distinctive properties, including the capacity to emulate peptide structures and reversibly interact with enzymes, so offering significant promise for the identification of innovative medications with specific modes of action.[24] Derivatives of indole are used extensively in the pharmaceutical, agrochemical, dyestuff, and other industries.[25] Pindolol,[26] oxypertine,[27] selisistat,[28] indomethacin,[29] arbidol,[30] and sumatriptan[31] are the few indoles based bioactive frameworks (Figure 1). Apart from their anti-inflammatory, anticancer, antibacterial, anti-HIV, antiviral, antitumor and antirheumatic, action, indole derivatives also find use as copolymers, corrosion inhibitors and sanitizers.

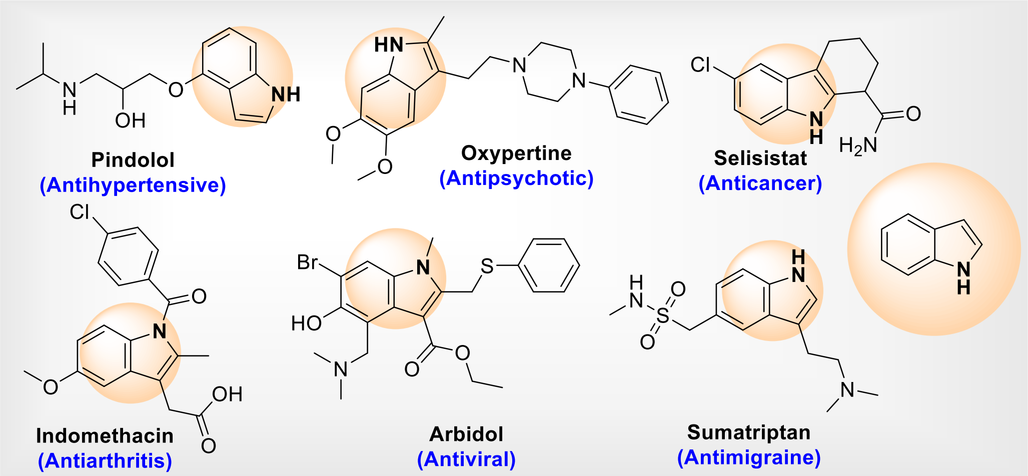


Figure 1. Selected examples of indole based bioactive molecular hybrids.

Despite the substantial importance and distinctive reactivity of indole derivatives and ILs, the synthetic potential of indole derivatives employing ILs has not been before summarized. Exploring ILs as a catalyst or solvent for the production of indole derivatives may yield much more advantageous and remarkable outcomes. As a result, novel synthetic methodologies for indole derivatives have garnered the attention of synthetic organic and medicinal chemists, evidenced by the rising number of publications in this field. In recent years, several research groups[32-34] have compiled green studies on the synthesis of indole derivatives; nonetheless, issues such as a lack of specificity in green methodologies, incomplete compilation of reports, and an extensive substrate scope persist. Nevertheless, the published reports are on green methodology but none have concentrated on the role of ILs. We have recently published several studies[35-39] detailing the synthesis of heterocycles utilizing environmentally friendly and sustainable methodologies. Consequently, through our efforts to address the research gap, we want to develop a report that specifically examines the dual role of ILs in the synthesis of extremely valuable indole scaffolds. This review assesses recently developed synthetic approaches aiming at sustainability in the synthesis of indole and its derivatives. This work presents the useful synthetic techniques applied using ILs to produce indole-based fused and tethered scaffolds. This review offers first summarized data (from 2002 to 2024) on the synthesis of indole derivatives using ILs.

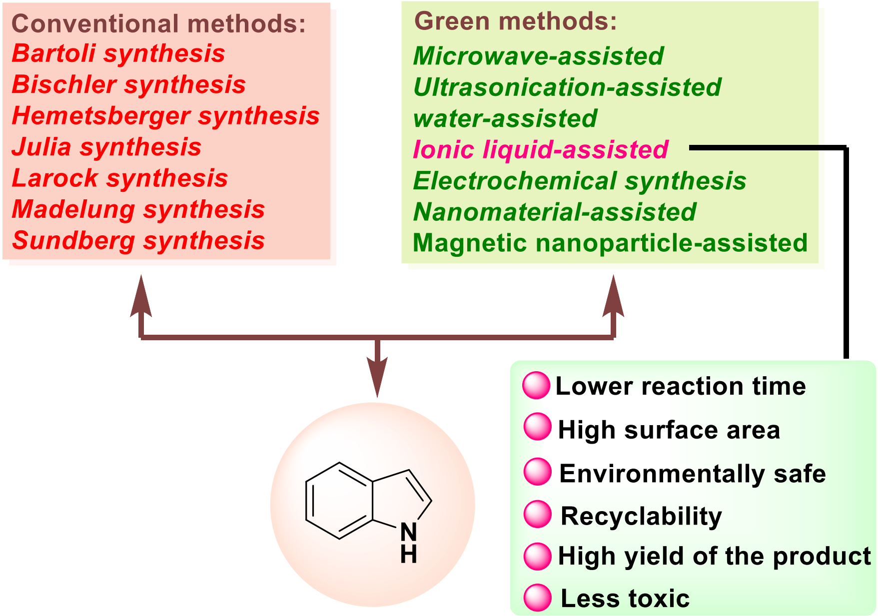
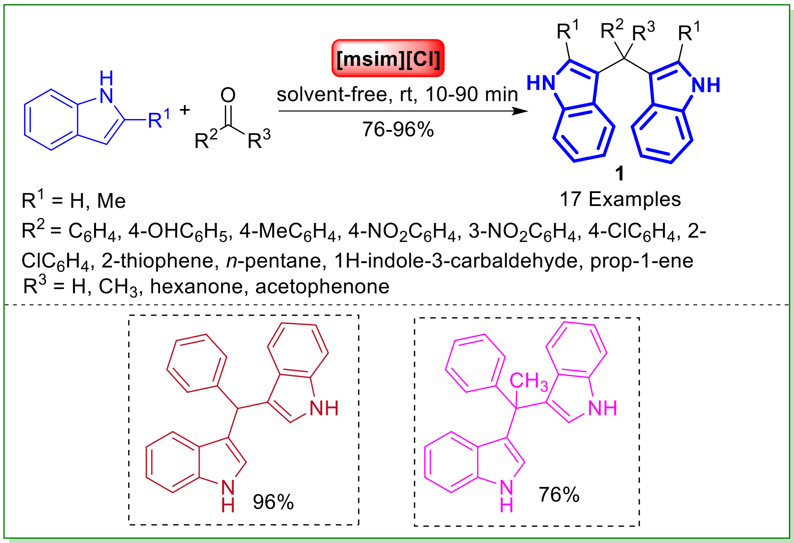


Figure 2. Comparison of traditional versus eco-friendly methods for the synthesis of indole derivatives.

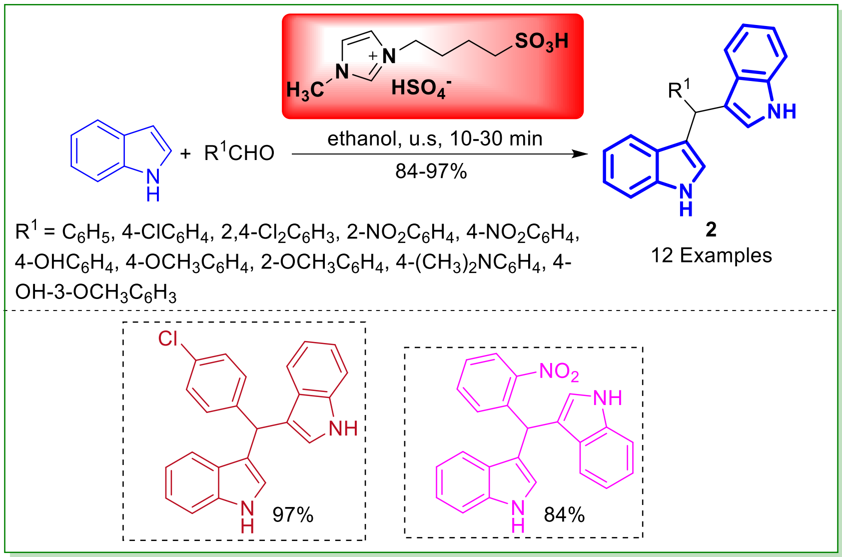
2.0 Methods assisted by imidazole-based ILs

In 2010, Zare *et al.*[40] introduced an IL (3-methyl-1-sulfonic acid imidazolium chloride) as a novel cost-effective catalyst for the preparation of bis(indolyl)methanes **1** (Scheme 1). This acidic IL proved effective in catalyzing the rapid condensation of aldehydes and ketones with indoles under solvent-free conditions at room temperature. The resulting bis(indolyl)methanes **16** were obtained in excellent yields ranging from 76% to 96% within 10 to 90 minutes of reaction time. Notably, the reaction time was reduced up to 10 min in the presence of the IL as compared to conventional methods.



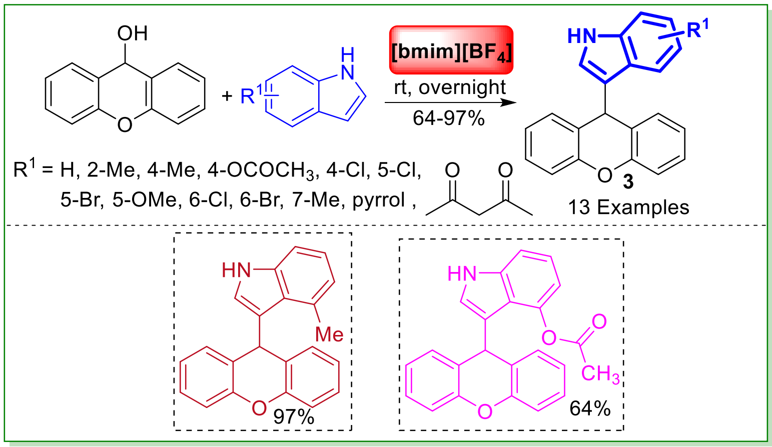
Scheme 1. Formation of bis-indole derivatives

Zang and colleagues[41] employed an IL ($[(CH_2)_4SO_4][HSO_4]$) as a proficient catalyst for the electrophilic substitution of carbonyl compounds with indole, yielding bis(indolyl)methanes **2** in substantial yields (84-97%) under ultrasonic irradiation (Scheme 2). The authors developed a collection of 12 examples to illustrate the method's versatility. The combination of ultrasonication and IL significantly reduced reaction times (10-30 min). It is noteworthy that 4-chlorobenzaldehyde achieved a remarkable yield of 97% for the products **17** under mild reaction conditions.



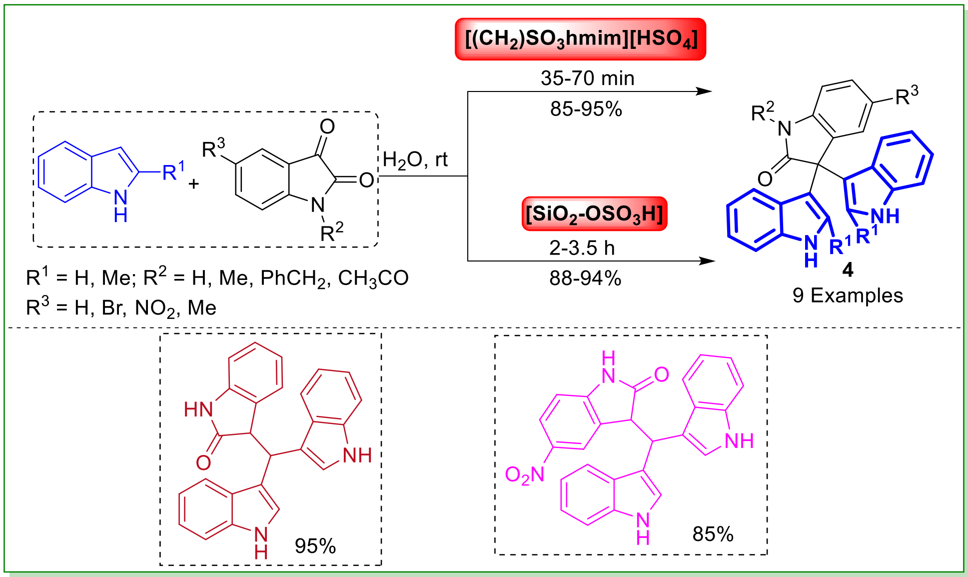
Scheme 2. IL-promoted synthesis of bis-indole derivatives

In 2011, IL-assisted protocol with great efficiency, atom economy, and environmental sustainability was established by the research group of Li[42] for the S_N1-type replacements of 9*H*-xanthen-9-ol with indoles or other nucleophiles (Scheme 15). The indole-substituted xanthene **3** was synthesized with yields ranging from 64% to 97% through the treatment of the initial substrates. This approach yielded a variety of products **3**, achieving high or exceptional yields in $[bmim][BF_4]$ at ambient temperature. The requirement for overnight heating may prove to be more energy-demanding in contrast to microwave or solvent-free methodologies.



Scheme 3. $[Bmim][BF_4]$-promoted reaction of indoles and 9*H*-xanthen-9-ol.

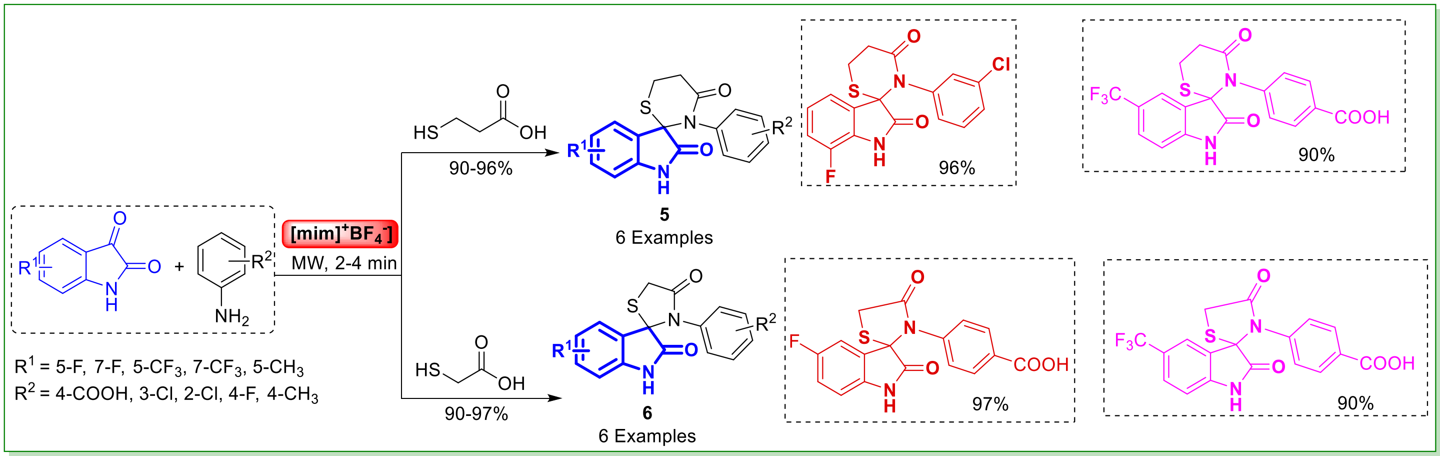
Herein, Majid's research team[43] developed an oxindole derivatives **4** through the condensation of indoles with isatins in the presence of a green and recyclable catalyst $[(CH_2)_4SO_3HMIM][HSO_4]$ or SiO_2-OSO_3H in aqueous solution at ambient temperature. Both the ILs delivered final products (**4**) successfully as illustrated in Scheme 4. In comparison, the SiO_2–OSO_3H system observed for slower reaction time (2.5–5 h), nonetheless delivers commendable yields (80–91%). The methodology encompasses a range of electron-donating and withdrawing groups (e.g., Me, Cl, Br, NO_2), demonstrating extensive substrate scope and adaptability.



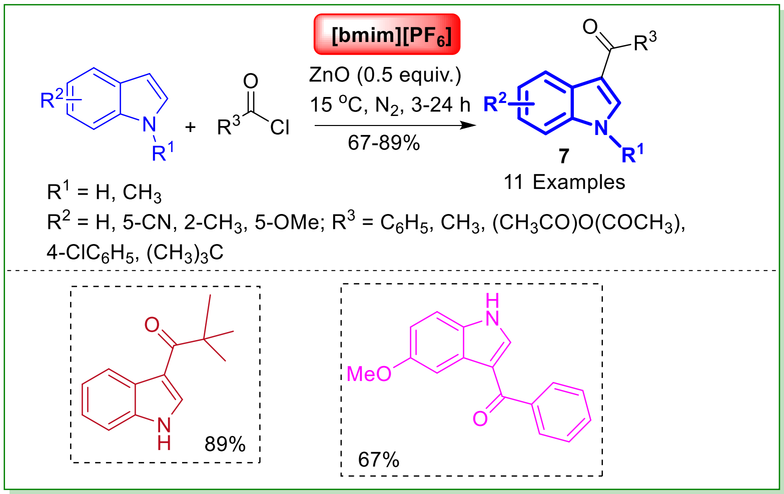
Scheme 4. Reaction of indoles and isatins.

Furthermore, in 2012, Brønsted acidic ILs comprising nitrogen-based organic cations, specifically 1-methylimidazolium and 1-butyl-3-methylimidazolium, alongside inorganic anions such as BF_4, PF_6, and *p*-toluenesulfonic acid (PTSA), examined as catalysts and reaction media by Arya *et al.*[44] (Scheme 5). Among the ILs, $[MIM][BF_4]$ gave excellent results for the manufacture of fluorinated spiro[3*H*-indole-3,2-tetrahydro-1,3-thiazine]-2,4(1*H*)-diones **5**, fluorinated spiro[3*H*-indole-3,2'-thiazolidine]-2,4(1*H*)-diones **6** in 90-96% and 90-97% yields, respectively. The present approach uses a microwave-assisted, one-pot, environmentally friendly technology. Notably, electron-withdrawing groups performed better on both the phenyl ring and the indole moieties.

Here, Yi *et al.*[45] established a Friedel-Crafts acylation of indoles utilizing acyl chlorides, catalyzed by zinc oxide in an IL medium (Scheme 6). The 3-acylindoles **7** were obtained in good to excellent yields (67-89%). For the acylation of indoles, zinc oxide and $[bmim][PF_6]$ were used as a green system. The authors developed a library of 11 examples to verify the wide applicability of the protocol. ZnO acts as a mild Lewis acid catalyst, enhancing the condensation and cyclization steps efficiently without generating toxic by-products. However, the relatively long reaction times (2-24 h) may limit its practical throughput in high-volume applications.

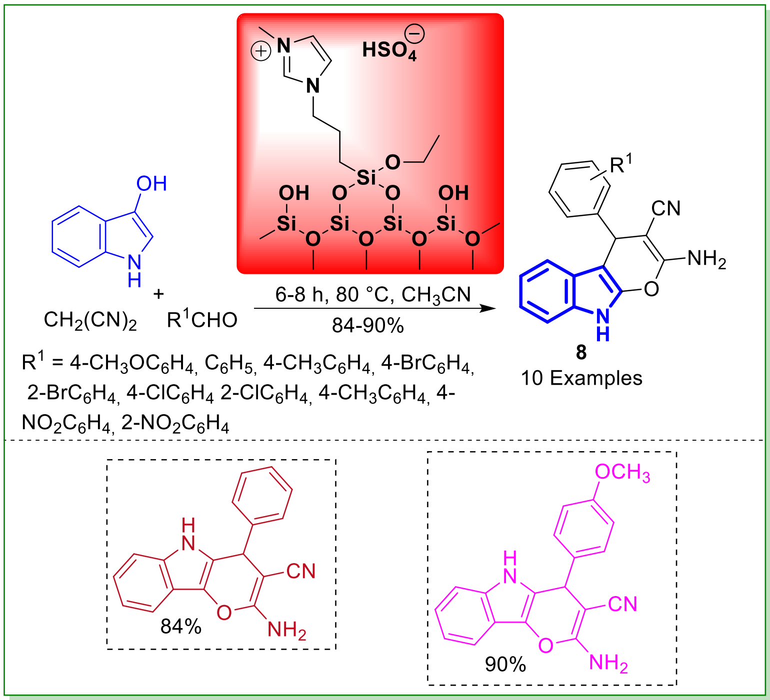


Scheme 5. Reaction of isatins and substituted aniline for the synthesis of spiro indole-thiazinones/ thiazolidinones.



Scheme 6. One-pot synthesis of substituted indoles.

Damavandi's research team[46] described the IL-catalyzed synthesis of pyrano[3,2-*b*]indole-3-carbonitriles **8** *via* a novel three-component condensation involving 3-hydroxyindole, malononitrile and aromatic aldehydes, utilizing silica-supported IL [pmim]HSO_4SiO_2 (silica-supported 1-methyl-3-(triethoxysilylpropyl)imidazolium hydrogensulfate) as an effective catalyst. The synthesized compounds **8** were obtained in 84-90% yields in the presence of IL as described in Scheme 7. The catalyst was reusable up to five cycles.



Scheme 7. One-pot synthesis of pyrano[3,2-*b*]indoles.

Figure 3 shows the reaction pathway for the synthesis for indole based pyrano[3,2-*b*]derivatives. 3-Hydroxyindole, malononitrile and arylaldehyde may condense by Knoevenagel condensation, intramolecular cyclization, Michael addition, and isomerization approaches. Initially, intermediate is generated with the help of [pmim]HSO_4 by the condensation of 3-hydroxyindole and aromatic aldehyde. Malononitrile reacts with intermediate to produce another intermediate. Next, the analogous pyrano[3,2-*b*]indole product **8** is produced by heterocyclization and isomerization following the theft of the proton of intermediate by the counter anion HSO_4.

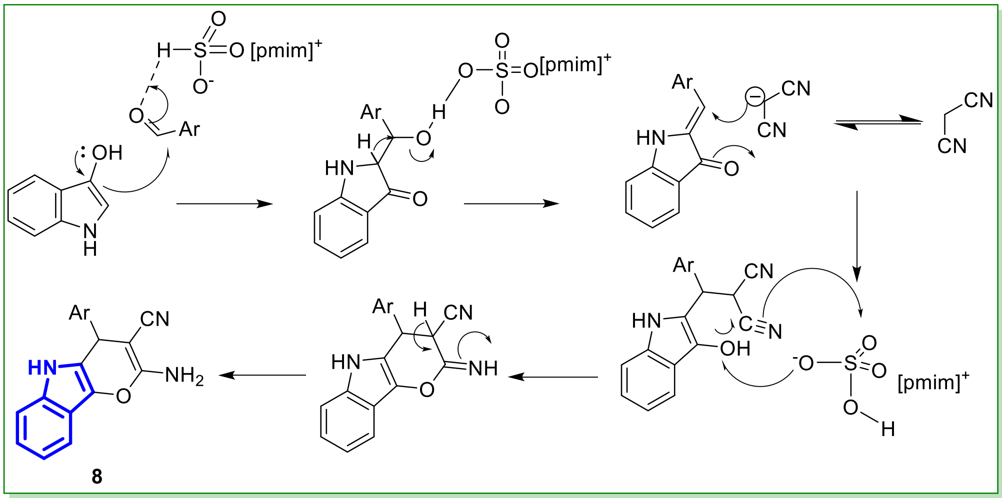
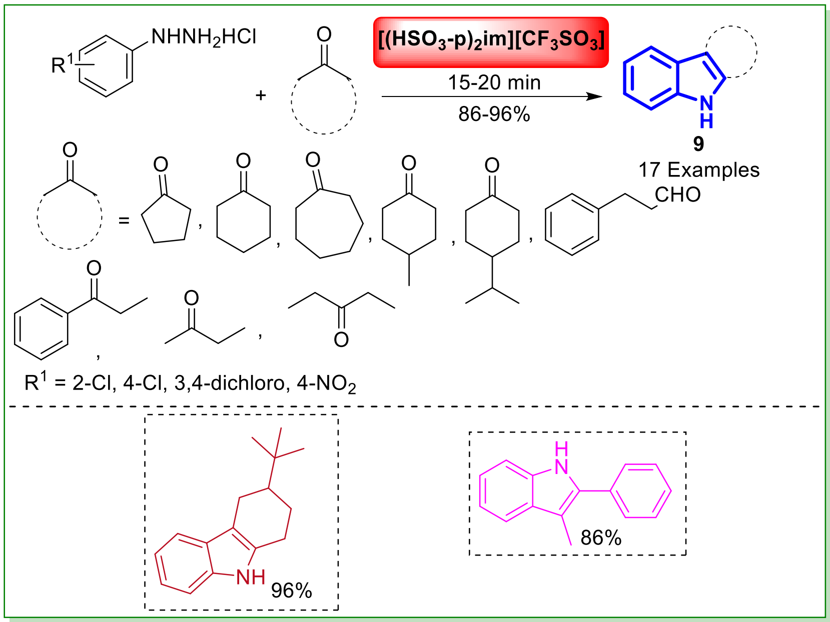


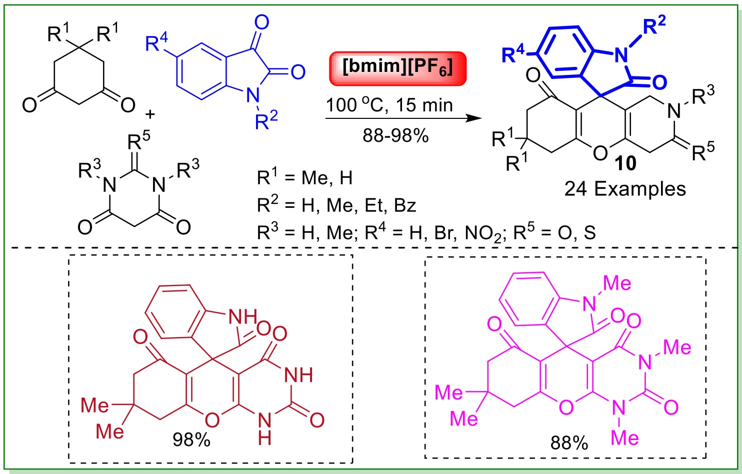
Figure 3. Plausible reaction mechanism.

The use of SO_3H-functionalized ILs as catalysts for one-pot Fischer indole synthesis in an aqueous media under microwave irradiation was examined by Li *et al.*[47] in 2012 (Scheme 8). Using aliphatic and aromatic, cyclic and acyclic aldehydes and ketones in combination with arylhydrazine hydrochlorides, a variety of indole derivatives were synthesized. The indole products **9** were effectively separated and the catalytic system of [(HSO$_3$-*p*)$_2$im][CF$_3$SO$_3$] could be directly employed without any processing. The reaction accommodates a broad spectrum of functionalized substrates, featuring both electron-donating and electron-withdrawing groups on the aromatic aldehyde, resulting in a varied collection of indole analogues (17 examples illustrated).



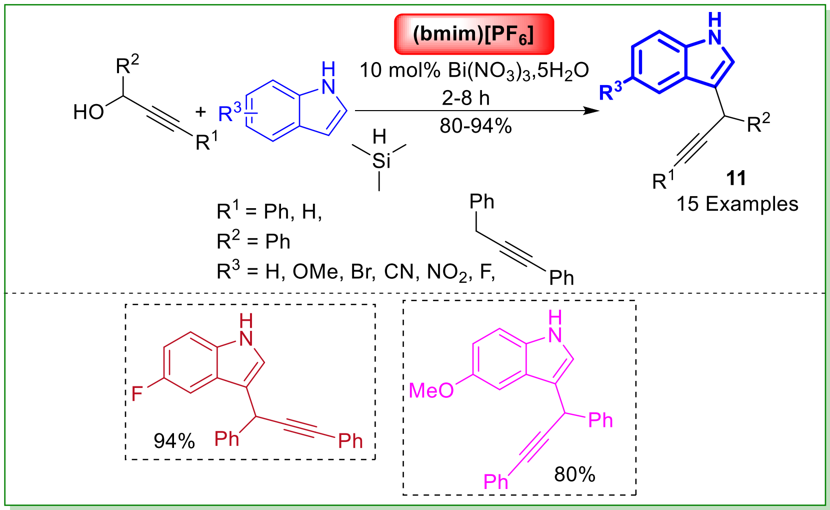
Scheme 8. Reaction of phenylhydrazine hydrochloride and carbonyl compound.

Ramin *et al.*[48] developed amalgamation of isatin, barbituric acid, and cyclohexane-1,3-dione derivatives, utilizing alum (KAl(SO$_4$)$_2$·12H$_2$O) as a catalyst. The IL [BMIM][BF$_4$] performed exceptionally well towards the formation of spiro compounds (chromeno[2,3-*d*]pyrimidine-5,3'-indoline-tetraones) **10** in 88-98% yields shown in Scheme 9. They also examined the catalyst's reusability and discovered that it could be reused multiple times without experiencing a discernible loss of activity. The catalyst could be reused multiple times without experiencing a discernible loss of activity.



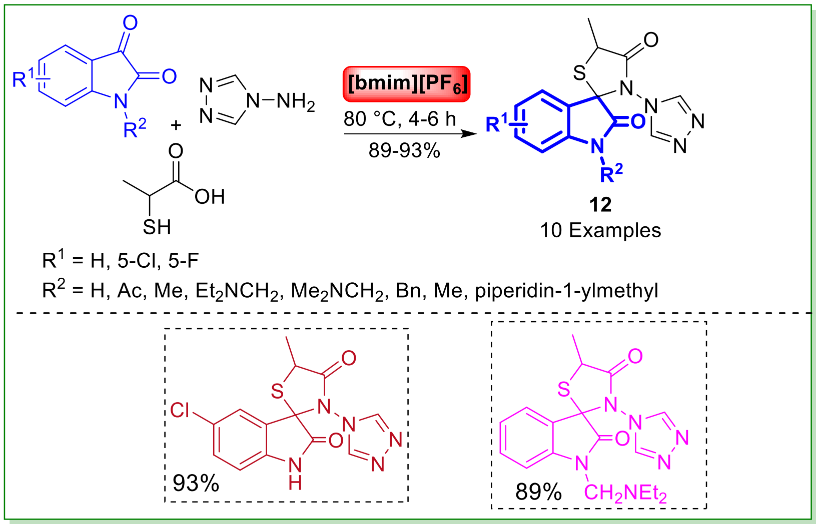
Scheme 9. Multi-component reaction towards the synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-tetraones.

Laali's research team[49] devised propargylation of various substituted indoles **11** as presented in Scheme 10. The catalytic levels (10 mol%) of easily accessible $Bi(NO_3)_3.5H_2O$ in the IL [bmim][PF_6] were used to achieve the current methodology, which made it easier to recycle and reuse the IL repeatedly. The author synthesized a total of 15 samples to assess the methodology's generality. Functional groups like –OMe, –CN, –Br, –NO_2, and –F exhibit a commendable level of tolerance, indicating a notable degree of electronic flexibility.



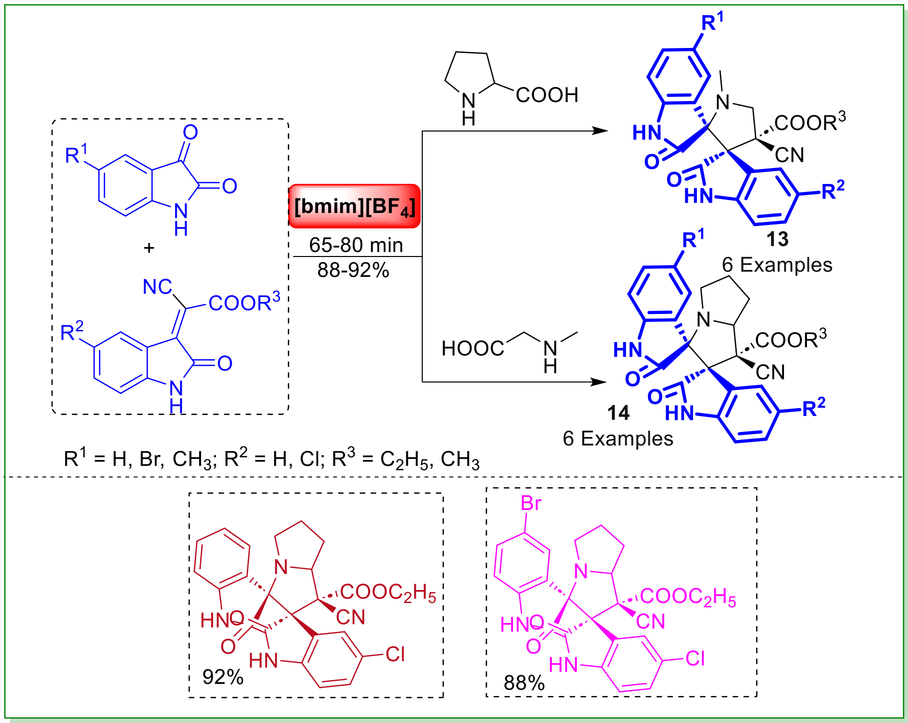
Scheme 10. Synthesis of substituted indole derivatives.

In another study, a one-pot, three-component method for the formation of new spiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-diones **12** were synthesized by the research group of Jain.[50] Good to excellent yields (89–93%) of the products **12** without any catalyst were obtained by condensing 1*H*-indole-2,3-diones, 2-sulfanylpropanoic acid and 4*H*-1,2,4-triazol-4-amine in [bmim]PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate) (Scheme 11). Among other benefits over conventional techniques, this one provided easy reaction conditions, shortened reaction times (4-6 h) and high product yields (89-93%).



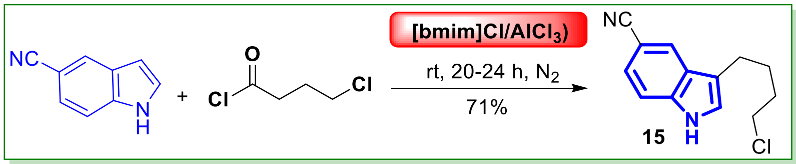
Scheme 11. Three-component strategy for the synthesis of indole-3,2'-thiazolidine]-2,4'(1*H*)-diones.

In 2013, Dandia *et al.*[51] evaluated the reactivity profile of *E/Z* isomerized alkyl 2-oxoindolin-3-ylidene)acetate **13-14**(Scheme 12). The first substrates in the reaction which took place in the presence of an IL ([Bmim][BF4), isatin and either proline or sarcosine. Reacting as a dipolarophile with the *E*-isomer of (2-oxoindolin-3-ylidene)acetate, sarcosine-derived azomethine ylide generates dispiropyrrolidine-bisoxinoles **13**. Conversely, the azomethine ylide from proline engaged the *Z*-isomer of(2-oxoindolin-3-ylidene)acetate to produce dispiropyrrolizidine-bisoxindoles**14** as the sole product. Four or more reuses of the IL were accomplished without any apparent decline in yield.



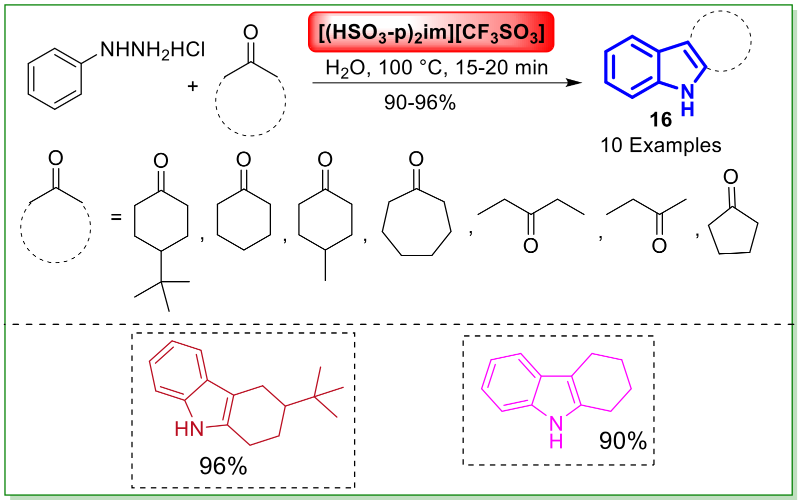
Scheme 12. Cycloaddition reaction for the formation of dispirobisoxindoles.

In the same year, Fengping's research team[52] described the Friedel-Crafts acylation of 5-cyanoindole with 4-chlorobutyryl chloride was performed in the IL 1-butyl-3-methylimidazolium chloroaluminate ([bmim]Cl/AlCl₃), yielding 5-cyano-3-(4-chlorobuty)indole **15** as the main product. The single product **15** was obtained in 71% yield at room temperature under nitrogen atmosphere as depicted in Scheme 13. The application of [bmim]Cl/AlCl₃ is especially significant, serving dual roles as both solvent and catalyst, thereby augmenting the electrophilicity of the carbonyl group and promoting cyclization.



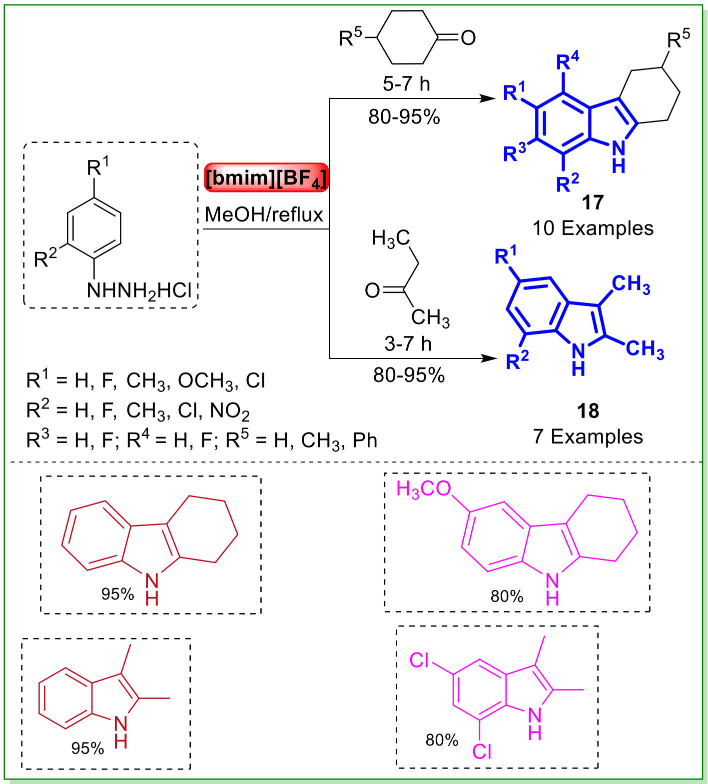
Scheme 13. Synthesis of 5-cyano-3-(4-chlorobutanoyl)indole.

An efficient and straightforward synthesis of indole **16** established by the research group of Tao[53] utilizing ketones/cyclohexanediones with arylhydrazine hydrochlorides. The high yields of the compounds were received in water under ultrasonic irradiation with a novel SO₃H-functionalized ILs catalyst. Sulfonic acid-functionalized ionic liquid significantly improves proton availability and facilitates effective cyclization. The elevated yields and brief reaction duration render this approach particularly suitable for the swift synthesis of libraries comprising biologically relevant indole scaffolds. The authors synthesized total 10 examples to investigate the generality of the protocol (Scheme 14).



Scheme 14. One-step synthesis of fused indole derivatives.

Mahadevan's research team[54] used an IL [bmim][BF_4] as a catalyst for the synthesis of tetrahydrocarbazoles **17** and 2,3-dimethylindoles **18**. The products were obtained in high yields (80-95%) with a decreased reaction time (5-7 and 3-7 hr) (Scheme 15). The results show that the [bmim(BF_4)] IL is quite effective in the Fischer indole synthesis because of its operational simplicity, high yields, dual catalyst-solvent properties and capacity to be reused for five consecutive reactions. The flexibility of the method for large-scale reactions emphasizes its potential for industrial-scale synthesis.



Scheme 15. Synthesis of indole tether and fused derivatives.

The reaction mechanism is illustrated in Figure 4. Initially, the reaction of hydrazine and keto compound generates imine intermediate through the interaction of IL ([bmim][BF$_4$]). Further, the aromatization and cyclization of imine intermediate affords the cyclized intermediate by the removal of the IL. Finally, the removal of ammonium molecule led to the formation of indole derivatives.

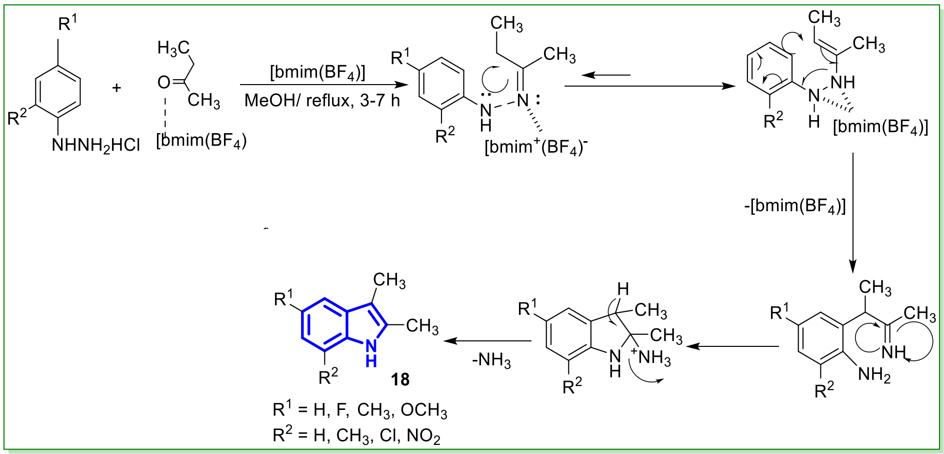
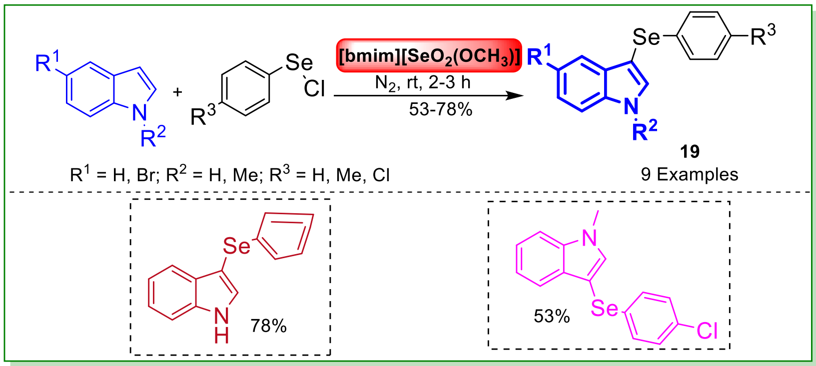


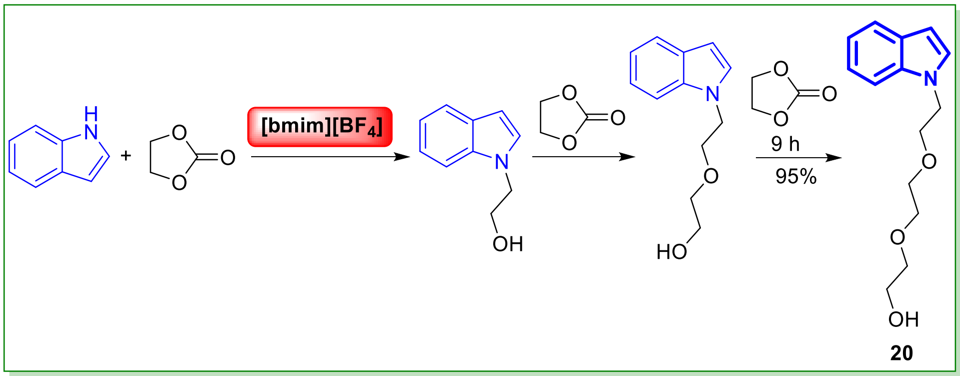
Figure 4. Mechanistic pathway for the formation of substituted indole derivatives.

In another work, Perin *et al.*[55] efficiently used ([bmim][SeO$_2$(OCH$_3$)]) IL as a solvent in the catalyst-free synthesis of 3-arylselenylindoles **19**. The solvent was easily reused for several cycles with good results (Scheme 16), and the products **19** were selectively generated in high yields (62–78%) free of any additives. The use of selenium-containing ionic liquid is notably inventive, functioning simultaneously as a solvent and a source of selenium, thereby obviating the necessity for external oxidants or metal catalysts. The tolerance of functional groups, such as halogens, methyl, and methoxy substituents, illustrates the versatility of the method.



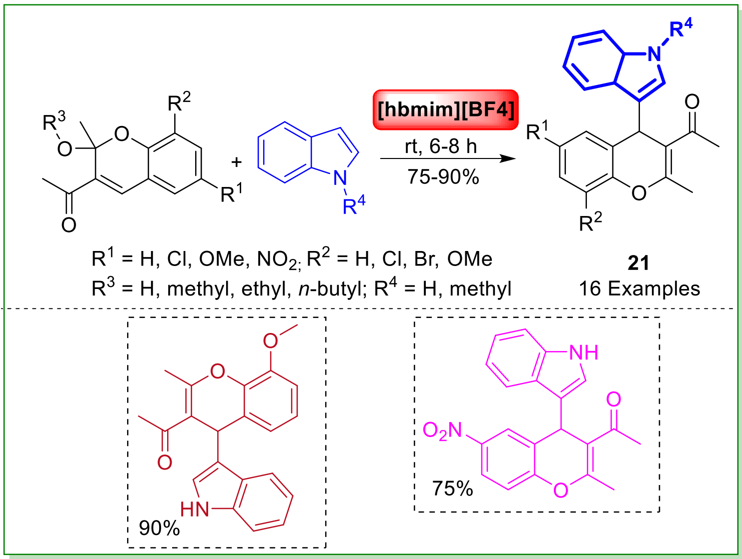
Scheme 16. Synthesis of 3-selenylindoles.

Guohua *et al.*[56] have developed an ecologically friendly technique based on catalytic amount of imidazolium-based ILs under solvent-free conditions for the synthesis of hydroxyalkyl indoles **20** (Scheme 17). Indole coupled with ethylene carbonate/propylene carbonate under optimal reaction conditions produced 1-(2-hydroxyethyl)indole or 1-(2-hydroxypropyl)indole **20** in high yields (95%).



Scheme 17. Multi-step synthesis of indole substituted derivatives.

Kumar *et al*.[57] in 2014 designed a regioselective catalyst-free method for synthesizing a novel class of 4*H*-chromene scaffolds **21** at room temperature in an IL ([Hbmim])[BF$_4$]) in 6-8 hours with a 75-90% yields. [hbmim][BF$_4$], an ionic liquid that donates hydrogen bonds, presumably serves a dual function as both solvent and catalyst, thereby augmenting reactivity and selectivity without necessitating supplementary acids or bases. The method works well for a variety of 2*H*-chromenes and indole derivatives **21** (Scheme 18).



Scheme 18. Reaction of indole with 2*H*-chromenes in the catalysis of [Hbmim])[BF$_4$].

The process starts with the generation of the more stable benzopyrryolium cation with two reactive sites by the IL. Among these, carbocation is most beneficial and can participate in the process more actively. Moreover, intermediate sterically prevents from participating in the reaction. These elements might cause the indole nucleophile to interact at the C-4 position and produce the needed regioselective product **21** (Figure 5). In this process the IL serves as an acid catalyst.

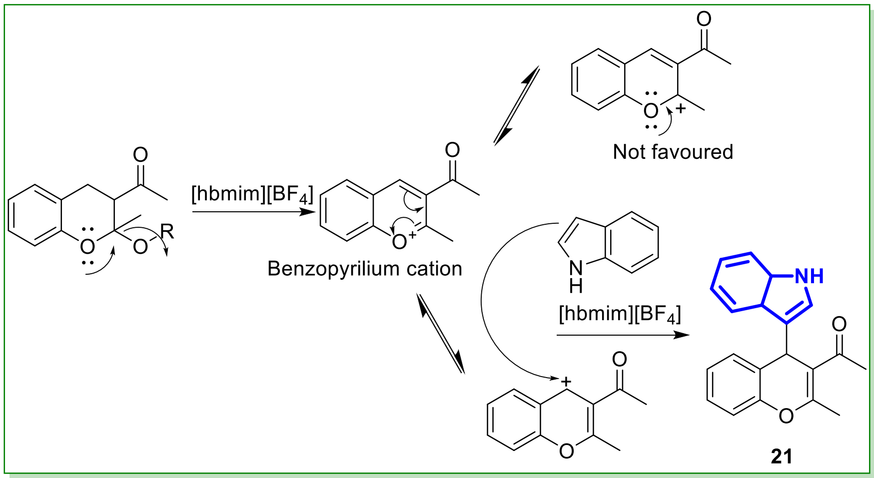
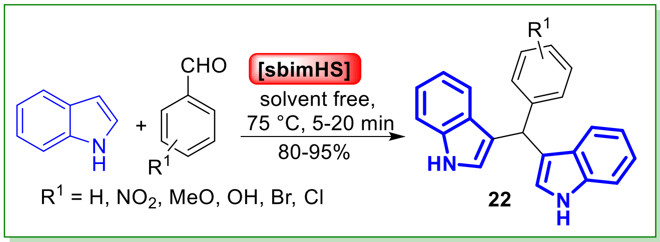


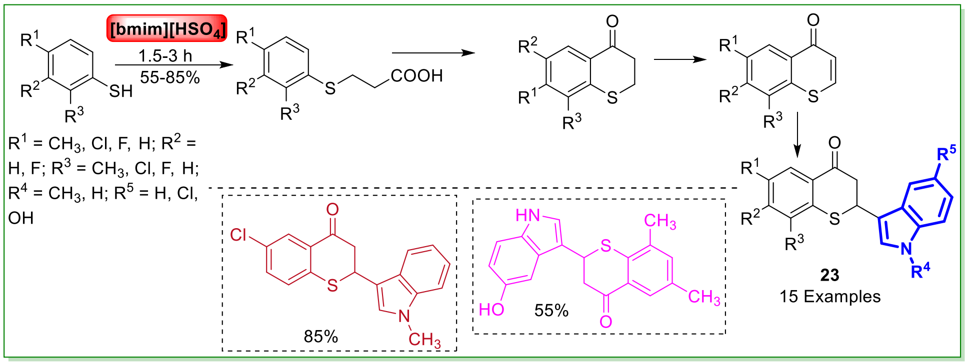
Figure 5. Putative reaction mechanism for the formation of indole tethered 4*H*-chromenes.

In the same year, Shirini's research team[58] developed a novel approach for the formation of bis-indole derivatives **22** in the presence of [Sbim][HS] as described in Scheme 19. The reaction of substituted benzaldehydes and indole at 75 °C delivered a class of bis-indole derivatives **22.** The IL effectively played in the current reaction and reduced reaction time up to 5-50 min. The synthesized products **22** were obtained in 80-95% yields.



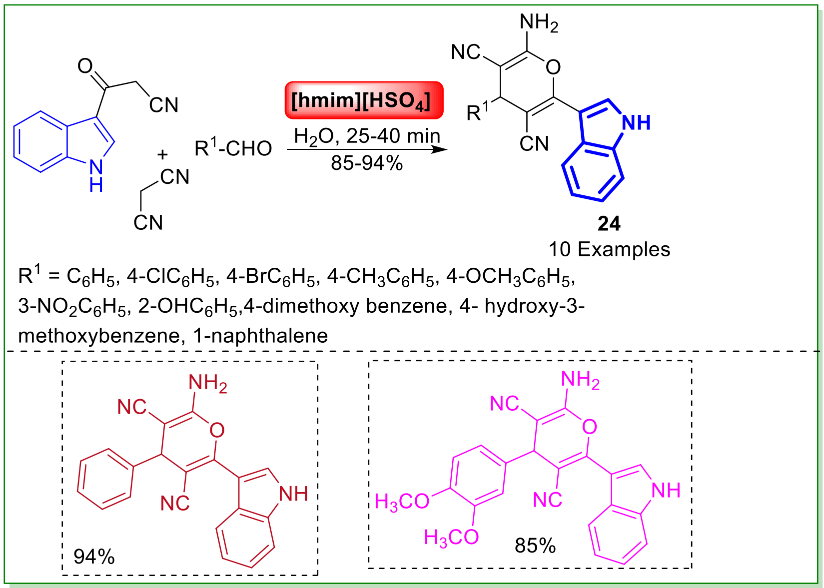
Scheme 19. [Sbim][HS]-assisted formation of bis-indole derivatives.

In 2015, Song and their co-workers[59] synthesized 2-(indole-3-yl)-thiochroman-4-ones **23** using IL and evaluated for *in vitro* antifungal activity. In this work, the IL [bmim]HSO_4 played a significant part in the Michael addition process. The compounds **23** were produced in 1.5–3 hours of reaction time with yields ranging from 55-85%. When thiochroman-4-one's phenyl ring contains an electron-withdrawing group, like fluoro or chloro, the activity is higher than when it contains an electron-donating group (methyl). With a yield of 22–81%, the reusable study was carried out six times. The most of these compounds **23** exhibited superior antifungal efficacy compared to fluconazole (standard). The findings indicate that 2-(indole-3-yl)-thiochroman-4-ones **23** may serve as effective antifungal agents for the future perspectives (Scheme 20).



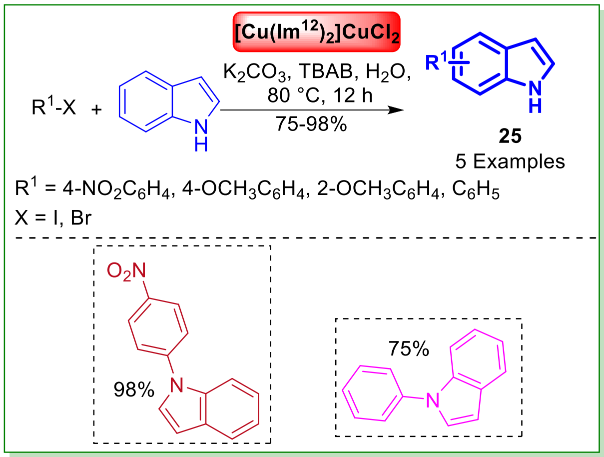
Scheme 20. Multi-step synthesis of 2-(indole-3-yl)-thiochroman-4-ones.

Herein, a sustainable approach was delineated by the research group of Munde.[60] A one-pot synthesis of 3-pyranyl indole derivatives **24** was achieved by the reaction of 3-cyano acetyl indole, malononitrile and aromatic aldehydes utilizing [Hmim]HSO$_4$ as a green catalyst. In total 10 examples were synthesized by the authors in 85-94% yields to examine the generality of the current strategy (Scheme 21). Both electron donating and electron withdrawing substituents cause the reaction to proceed very smoothly. This approach offered a straightforward work process, utilization of a green catalyst and solvent, short reaction time (25-40 min), and high product **24** yields. Reusability is a key component; the catalyst can be used four times without seeing a discernible drop-in catalytic activity.



Scheme 21. Multi-component reaction for the synthesis of 3-pyranyl indole derivatives.

An effective copper-based IL promoter was evaluated by Heidarizadeh's research team[61] as a reusable system for the *N*-arylation of indole using various aryl halides. The compounds **25** were acquired in good to excellent yields (75-98%) by a straightforward one-pot Ullmann type coupling method as shown in Scheme 22. The reaction was conducted in water and did not necessitate arylboronic acids as the active aryl source, palladium as the catalyst, or a strong base. Aryl iodides with electron-withdrawing groups showed more reactivity than those with electron-donating groups.



Scheme 22. Synthesis of substituted indoles.

A mechanistic reaction pathway for the formation of indole derivative is depicted in Figure 6. The indole derivative initially interacts with the IL to generates an intermediate. After that the addition of iodo benzene on *N*-H indole followed by the removal of IL generates the indole derivatives **25**.

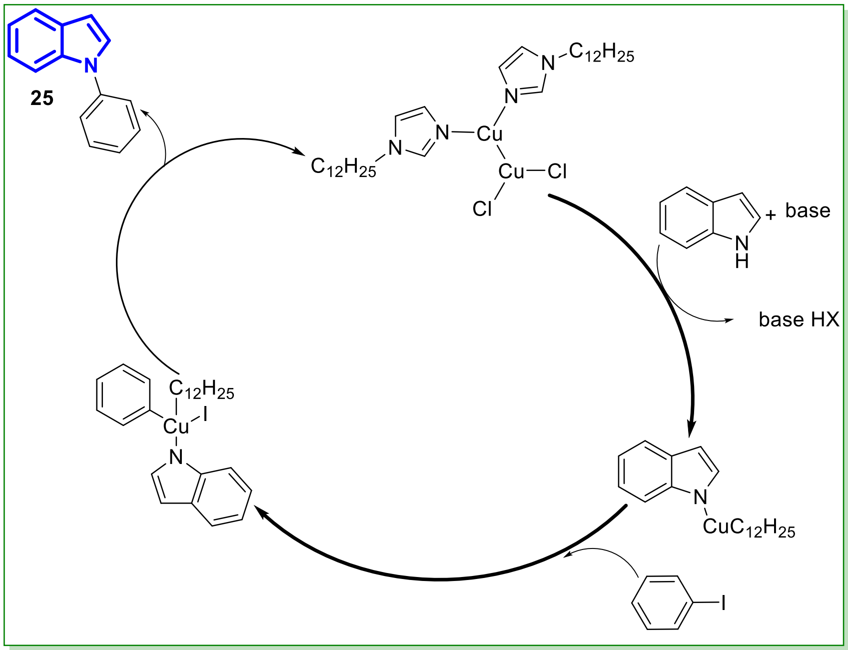
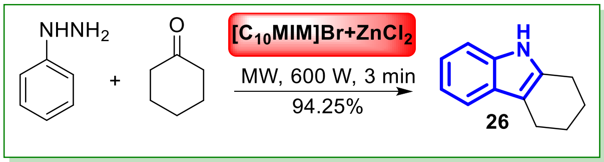


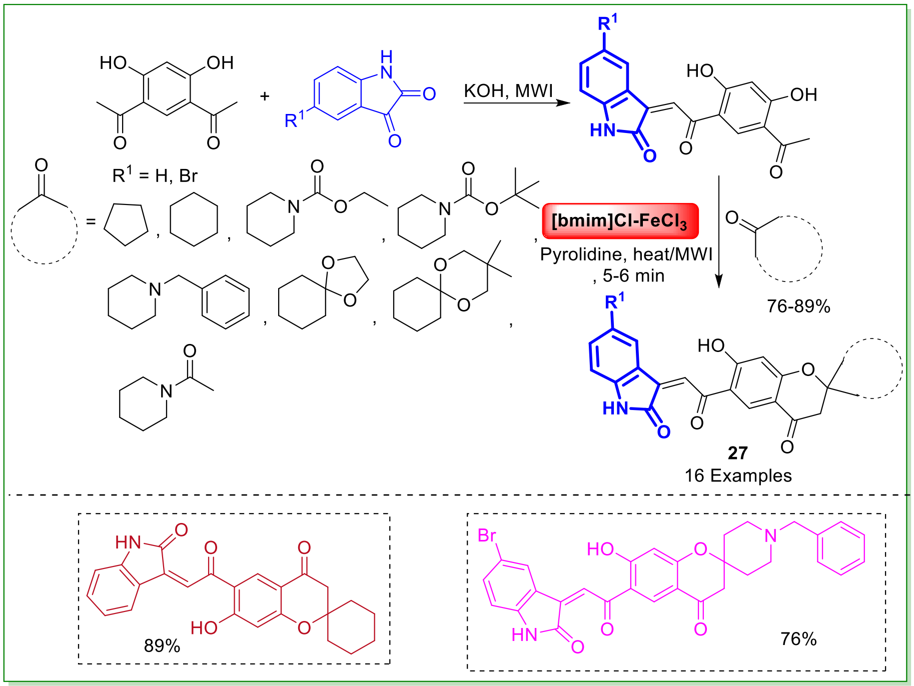
Figure 6. Reaction mechanism for the synthesis of substituted indole derivatives(check by paper same fig).

In the same year, the research group of Librando[62] developed 1,3-dialkylimidazolium bromide based ILs. Furthermore, the use of ILs was investigated as eco-friendly catalysts for the one-pot MW-assisted Fischer indole synthesis of 1,2,3,4-tetracarbazole **26** (Scheme 23). Other catalysts, including ILs mixed with $ZnCl_2$ (IL+$ZnCl_2$) and $ZnCl_2$ alone, were compared to the Fischer indole synthesis of 1,2,3,4-tetracarbazole catalyst employing ILs. The results revealed notable catalytic activity obtained by the use of ILs and $ZnCl_2$ (IL+$ZnCl_2$).



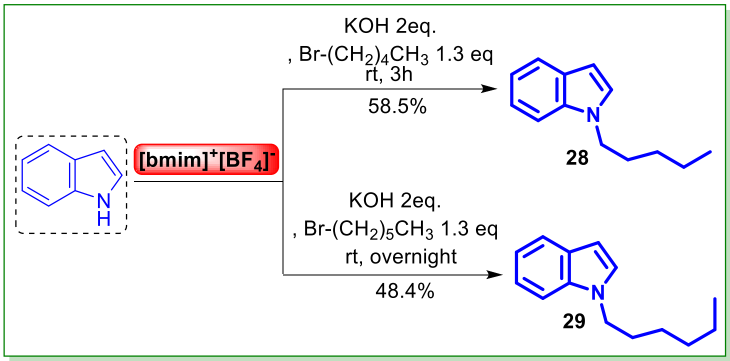
Scheme 23. Reaction of phenylhydrazine and cyclohexanone.

A convenient synthetic technique for the IL, 1-*n*-butyl-3-methylimidazolium tetrachloroferrate, [bmim][FeCl$_4$], enabled by Reddy's research team[63] for the construction of novel indolin-2-one annulated spirochromanone conjugates **27** (Scheme 24). The spirochromanone scaffolds **27** were synthesized efficiently *via* Kabbe condensation of substituted 3-[2-(5-acetyl-2,4-dihydroxyphenyl)-2-oxoethylidene]indolin-2-ones with diverse cycloalkanones, catalyzed by pyrrolidine in IL [bmim][Cl]/FeCl$_3$ subjected to microwave irradiation. This method has several benefits such as short reaction time (5-6 min), high yields (77-89%), mild conditions, ease of operation, and the ability to recycle the IL.



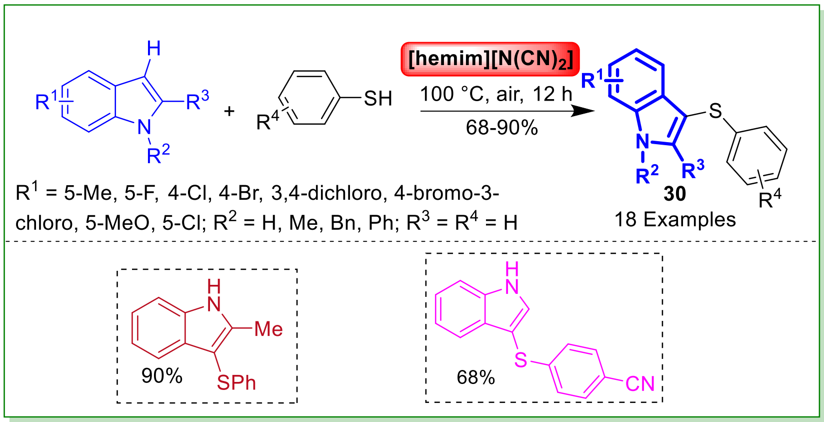
Scheme 24. Formation of indolin-2-one annulated spirochromanone.

Moreover, in 2016, Krstenansky and colleagues[64] presented a comparison of two synthetic approaches employing an IL-based solvent for the *N*-alkylation of indole **28-29** (Scheme 25). The green approach used [bmim]$^+$[BF$_4$]$^-$and worked effectively. Although the reaction yield was smaller than that of the conventional procedure, the use of a less reactive base, a non-volatile solvent, and the possibility of solvent recycling have prospective advantages.



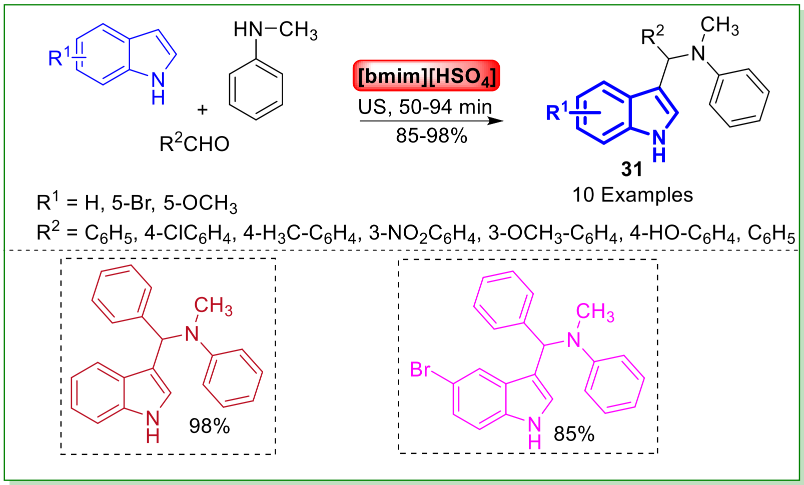
Scheme 25. Alkylation of indole.

Next, in 2017, Shaorong *et al*.[65] unfolded a convenient transition metal-free procedure for the synthesis of 3-sulfenylindole derivatives **30** in a basic IL (Scheme 26). This sulfenylation process provided a novel route for directly accessing 3-sulfenylindoles **30** in good to excellent yields (68-89%) and good functional group tolerance with high atom efficiency. For a broad range of starting substrates embellished with electron-donating and withdrawing groups, the technique was well tolerated. To assess the protocol's generality and adaptability, a total of eighteen derivatives were synthesized by the authors.



Scheme 26. Reaction of indoles with thiols.

A methodical and environmentally friendly approach to the synthesis of 3-substituted indoles **31** has been documented by the research group of Shirini,[66] utilizing ultrasound irradiation at ambient temperature. As illustrated in Scheme 27, the synthesized products **31** were obtained with yields ranging from 85% to 98% within a reaction time of 50 to 94 minutes, facilitated by the presence of the acidic IL ([bmim]HSO_4). Moreover, [bmim]HSO_4 demonstrates the capacity for recycling up to four times while maintaining its activity without significant decline.



Scheme 27. Reaction of indole, amine and benzaldehyde.

Figure 7 shows the suggested mechanism of reaction for the synthesis of 3-substituted indole derivatives. Initially, [bmim]HSO$_4$ protonates aryl aldehyde to enable a Mannich condensation with *N*-methylaniline to generate an intermediary iminium ion. Then, an electron-rich indole attacks the iminium ion to produce the desired 3-substituted indoles **31**.

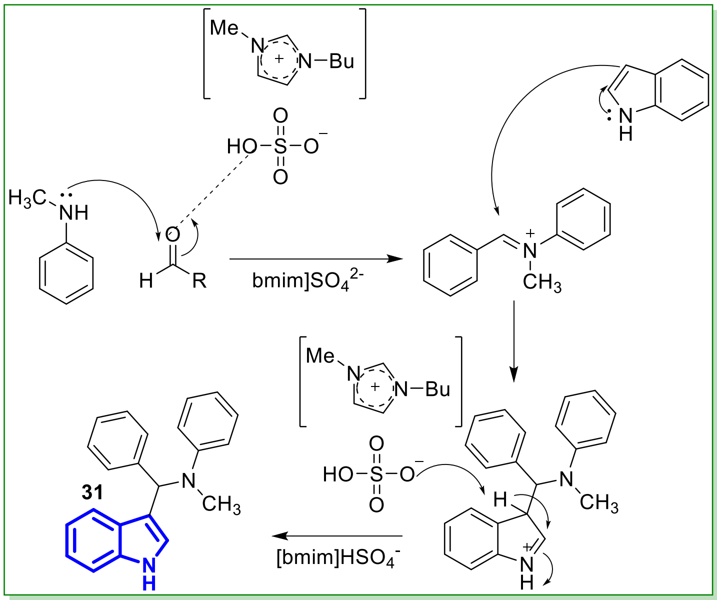
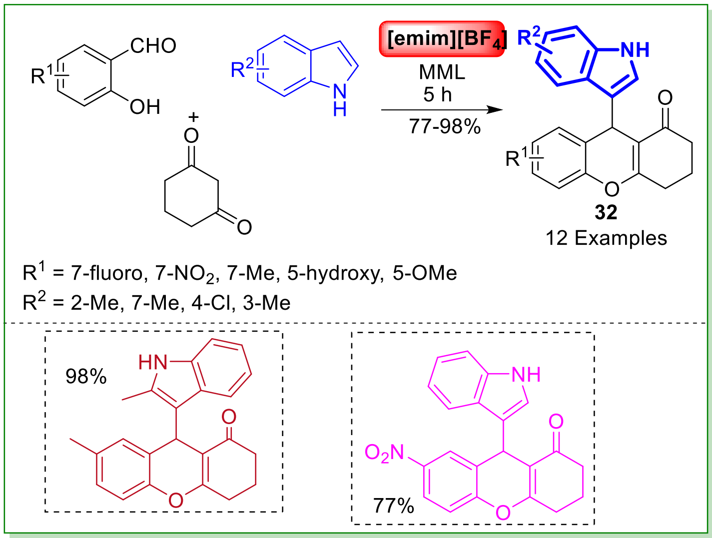


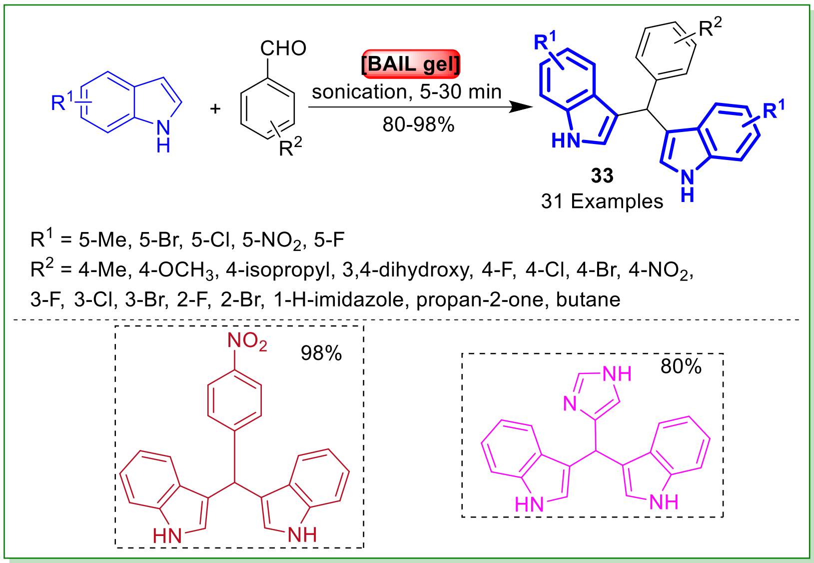
Figure 7. Possible reaction mechanism.

A synthetic approach to indolyl 4*H*-chromene **32** *via* a three-component reaction catalyzed by lipase in IL, revealed by the Wang research team.[67] ILs ([emim][BF$_4$]) successfully catalysed the synthesis of nitro-substituted chromene and indole in high yields (77–98%) (Scheme 28). Moreover, [emim][BF$_4$] showed good reusability in this reaction. The methyl substituted (electron-donating) starting substrates delivered high yield (99%) of derivative **32**; however, the low yield (77%) was obtained in case of nitro-substituted chromene and indole.



Scheme 28. Three-component reaction for the synthesis of substituted indoles.

Under Scheme 29, Tran's research group[68] developed a Brønsted-acidic IL gel by combining 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate with tetraethoxysilane. This gel efficiently catalyzed the synthesis of bis(indolyl)methanes **33**, delivering products in high yields (83–98%) within a short reaction time of 5 to 30 minutes. Additionally, this method offers a convenient and scalable route for the direct synthesis of bis(indolyl)methanes **33** and demonstrates a broad substrate scope, as shown by 11 representative examples (Scheme 29).



Scheme 29. Synthesis of bis-indole derivatives.

The Brønsted acid-catalyzed alkylation of indoles with aromatic aldehydes is described in Figure 8. The presence of BAIL gel increases the electrophilicity of the carbonyl carbon, so facilitating its reaction with indole to yield the intermediate. The equivalent 3-arylidene-3*H*-indole was subsequently synthesized by means of the dehydration of intermediate. The intermediate interacted with another indole to obtain the expected product **33**.

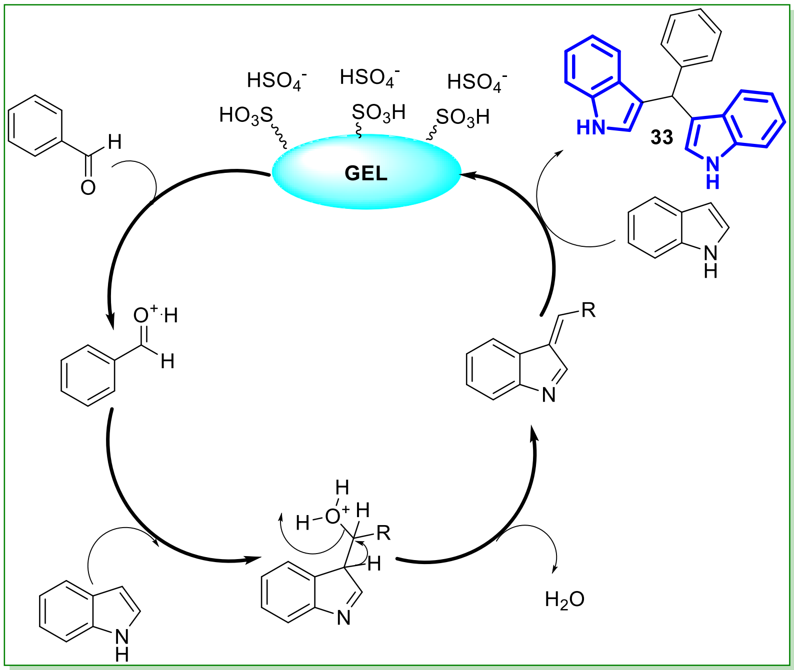
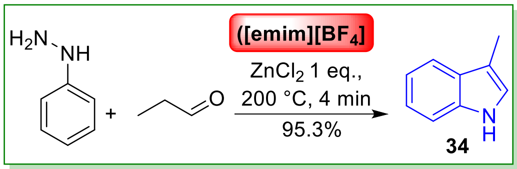


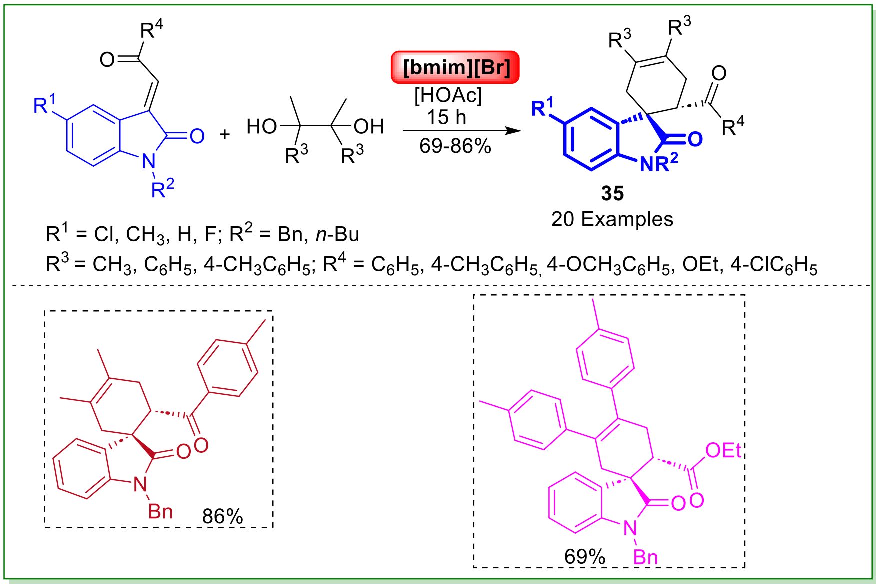
Figure 8. Putative reaction mechanism for the formation of bis-indoles.

Xu *et al.*[69] introduced [emim][BF_4] IL for Fischer indole synthesis of 3-methylindole **34** by the reaction between propylaldehyde and phenyl hydrazines (Scheme 30). This method used removal of NH_3 produced during the synthesis of indole ring **34** as well as stoichiometric Lewis acid ($ZnCl_2$) as catalyst. Based on its high-temperature tolerance and good product distribution, the IL ([emim][BF_4]) was used as reaction solvent. Under optimized conditions, 3-methylindole **34** was produced in a 95.3% yield.



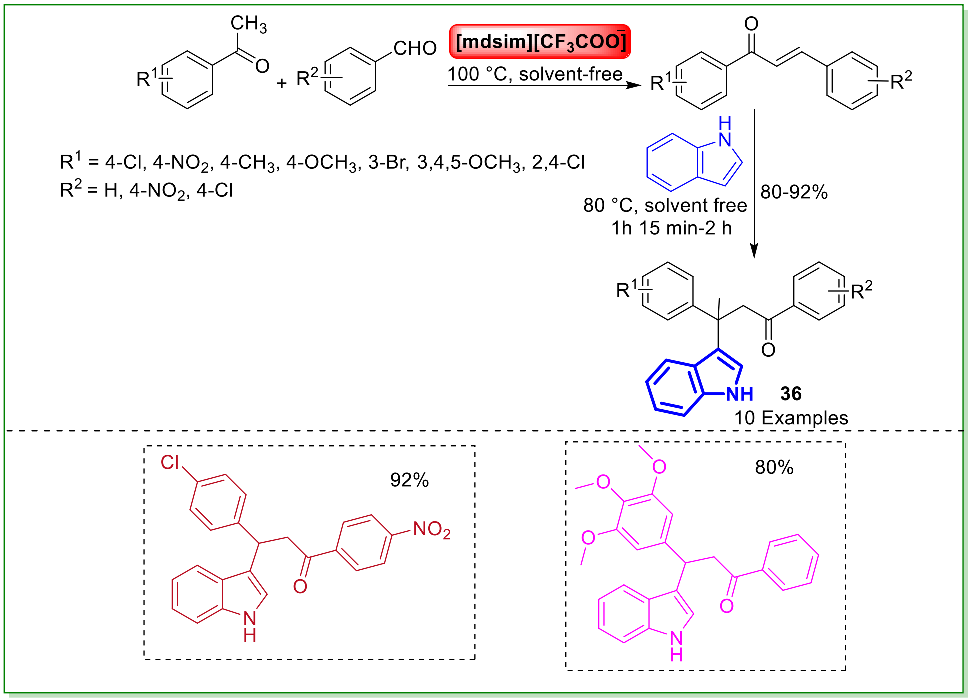
Scheme 30. [EMIM][BF_4]-promoted synthesis of substituted indoles.

Next, in 2018, a diastereoselective synthetic protocol for the construction of spiro[cyclohexane-1,3'-indolin]-3-en-2'-ones **35** was established by Yan *et al.*[70] The HOAc-mediated domino reaction of pinacols with dienophiles (3-methyleneoxindolines and 2-arylideneindane-1,3-diones) in the IL [Bmim]Br led to the formation of 7 examples of final indole based spiro compounds **35**. This domino reaction involved the *in-situ* generation of 1,3-dienes from acid-mediated dehydration of various pinacols and the sequential Diels-Alder reaction as depicted in Scheme 31.



Scheme 31. Formation of indole based spiro derivative.

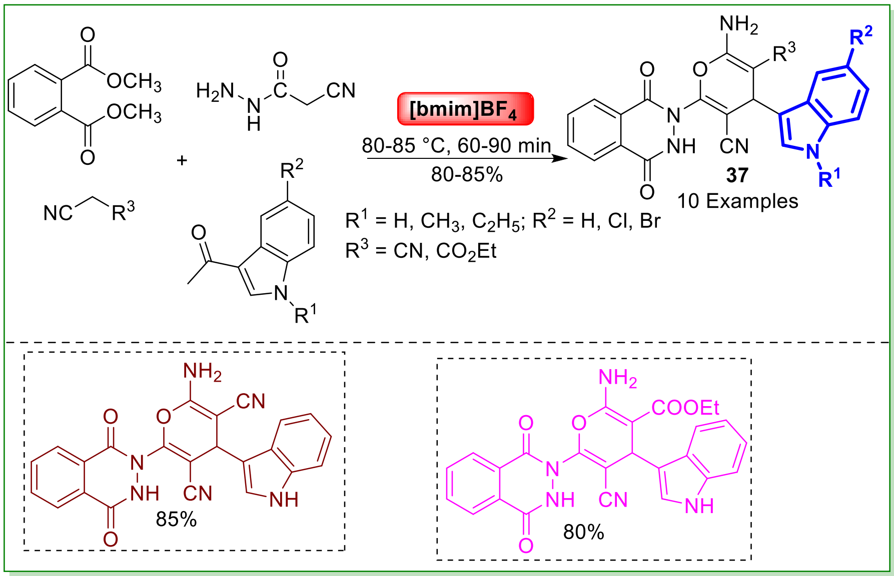
In 2019, Borah's team[71] used an acidic IL-catalyzed one-pot technique to synthesis 3-substituted indoles **36** from *in situ* produced chalcones (Scheme 32). Using a Claisen-Schmidt condensation of acetophenone with aromatic aldehydes, the chalcones were produced; then a Michael-like addition of indoles formed them. Effective IL catalysts for the two-step one-pot synthesis of 3-substituted indoles **36** were found to be ([EDSIM][CF₃COO]) and ([MDSIM][CF₃COO]). Up to four cycles of use for the IL ([MDSim][CF₃COO]) does not reduce its catalytic activity.



Scheme 32. Two-step reaction for the synthesis of indole tethered keto compounds.

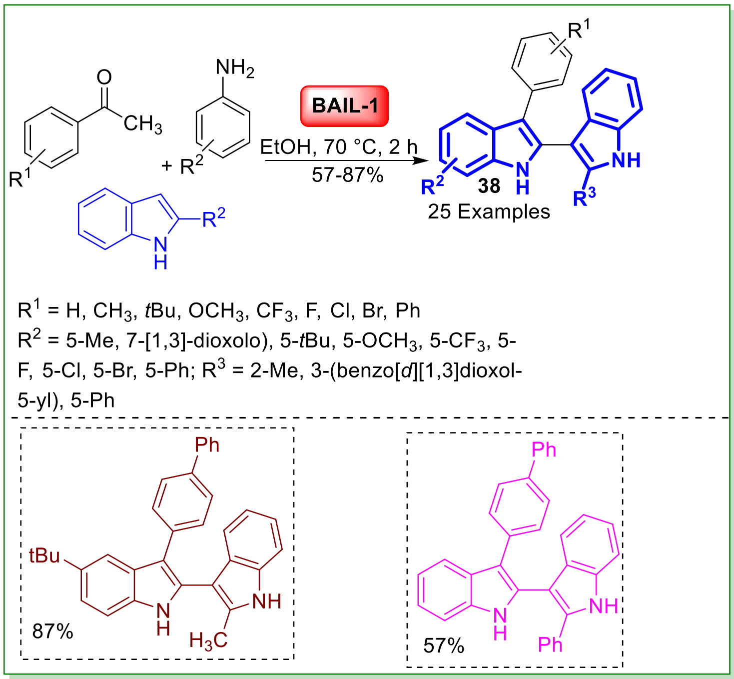
In 2021, Ahmed *et al.*[72] presented a synthetic method in the presence of [BMIM]BF₄. A one-pot four-component reaction resulted in the formation of novel phthalazinone-based indole-pyran hybrids **37** (Scheme

33). The final products **37** were obtained in 80-85% yields within 60-90 min of reaction time. The notable features of this methodology were short reaction times, green approach, diversity in the formation of library of compounds.



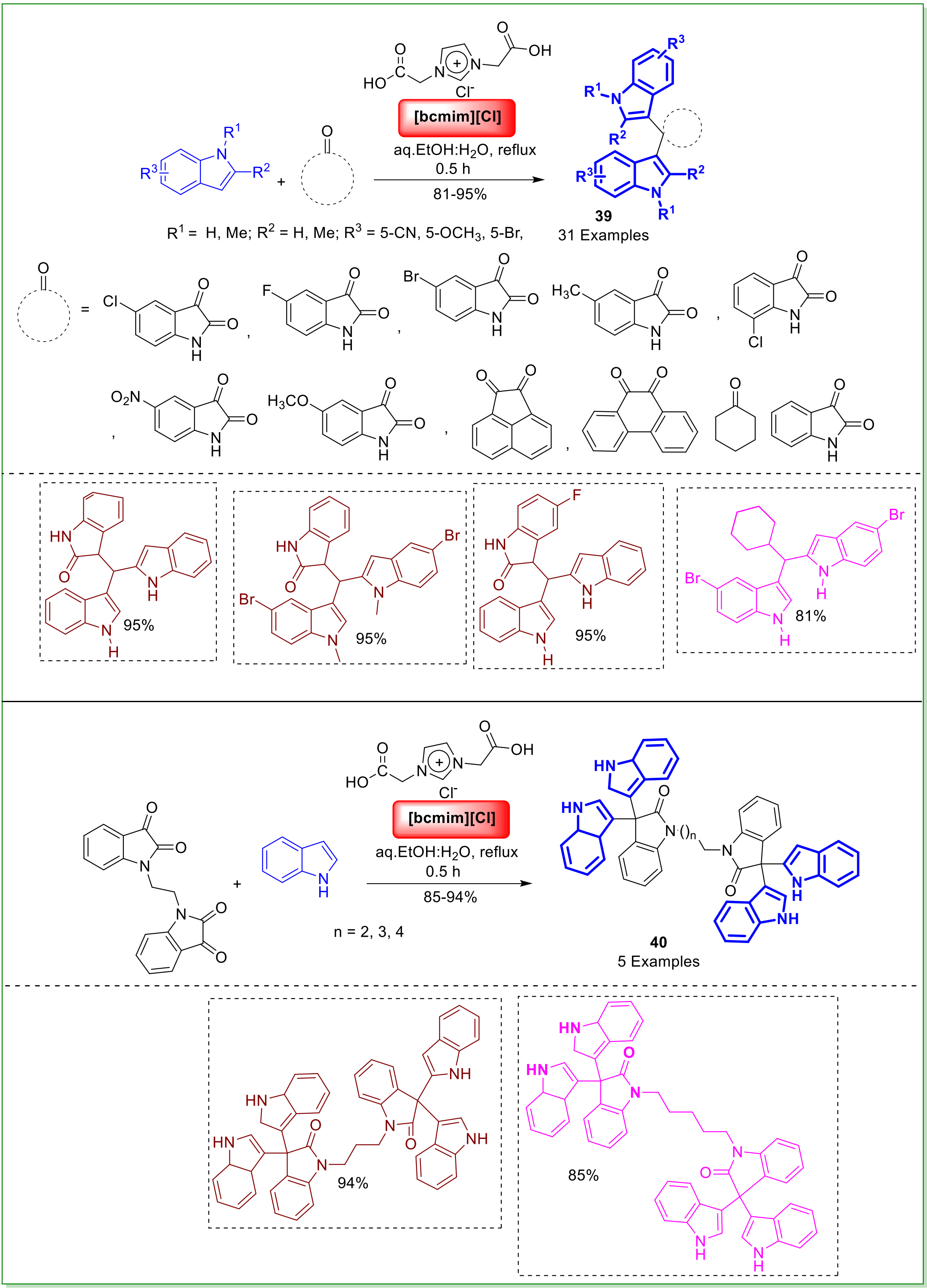
Scheme 33. four-component synthesis of novel phthalazinone based indole-pyran hybrids.

Recently (in 2024), Sarkar and co-workers[73] developed another protocol by using Brønsted acidic ionic liquid for the formation of 2,3′-bi-indole derivatives **38** (Scheme 34). This process entailed imine formation, nucleophilic addition, and cyclisation, producing water as the sole by-product. The final products **38** were obtained in high yields (57-87%) with the preparation of 25 examples. This protocol offers several advantages such as metal-free, mild reaction conditions, simple purification technique, broad substrate scope, and results in lower E-factors.



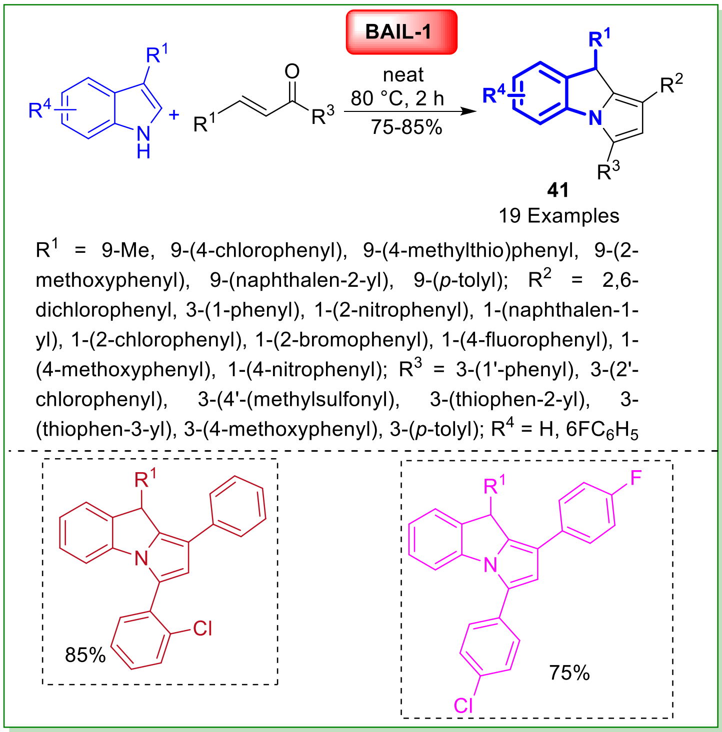
Scheme 34. one-pot synthesis of 2,3′-bi-indole derivatives.

In the same year, Maiti *et al.*[74] highlighted pseudo-three-component synthetic method by using [BCMIM][Cl] (Scheme 35). A total of 35 derivatives **39-40** were produced with yields reaching up to 95% within a time frame of 0.5 to 1.5 hours. The reaction of substituted indole and diverse ketone delivered a wide range of 31 examples of dimeric indoles **39**. In the extension of this study, the reaction of indole with dimer of isatin as a ketone substrate provided another dimer product **40** in 85-94% yields. [BCMIM][Cl] effectively catalysed both the reaction and delivered products smoothly.



Scheme 35. Synthesis of dimeric indoles from Friedel Crafts reaction.

Herein, the research team of Majee[75] devised a synthetic methodology by utilizing BAIL (1-methyl-3-(4-sulfobutyl)-1*H*-imidazol-3-ium tosylate) as catalyst (Scheme 36). The established protocol facilitates the synthesis of biologically significant pyrrolo[1,2-*a*]indole derivatives **41** from readily available chalcones with diverse substituents. The process begins with the Michael addition of indoles to chalcones, followed by annulations that occur through the elimination of a water molecule, resulting in the formation of the 9*H*-pyrrolo[1,2-*a*]indoles **41**. This procedure offers notable advantages, including a clean reaction, easily accessible reactants, and environmentally friendly conditions that are free from metals and solvents.



41
19 Examples

R^1 = 9-Me, 9-(4-chlorophenyl), 9-(4-methylthio)phenyl, 9-(2-methoxyphenyl), 9-(naphthalen-2-yl), 9-(*p*-tolyl); R^2 = 2,6-dichlorophenyl, 3-(1-phenyl), 1-(2-nitrophenyl), 1-(naphthalen-1-yl), 1-(2-chlorophenyl), 1-(2-bromophenyl), 1-(4-fluorophenyl), 1-(4-methoxyphenyl), 1-(4-nitrophenyl); R^3 = 3-(1'-phenyl), 3-(2'-chlorophenyl), 3-(4'-(methylsulfonyl), 3-(thiophen-2-yl), 3-(thiophen-3-yl), 3-(4-methoxyphenyl), 3-(*p*-tolyl); R^4 = H, 6FC$_6$H$_5$

Scheme 36. Synthesis of pyrrolo[1,2-*a*]indoles.

2.1 Comparative study

This comparative data highlights the essential importance of ionic liquid structure (cation & anion), reaction design (metal co-catalysts, support), and reaction conditions (time/temperature) in attaining optimal synthetic efficiency. Sulfonic acid-functionalized and Brønsted acidic ionic liquids typically demonstrate superior performance compared to conventional ionic liquids, excelling in both yield and efficiency over time. Nonetheless, [bmim]-based ILs continue to be favoured owing to their extensive adaptability. The systems identified as entries 2, 5, 14, and 27 exhibit considerable promise for both practical and environmentally sustainable synthesis, characterised by their swift reaction times, outstanding yields, and reduced ecological impact (Table 1).

Table 1. Comparison of ILs with respect to time and yield of reaction

Scheme	ILs	Time	Yield
1.	[msim][Cl] (3-Methyl-1-sulfonic acid imidazolium chloride)	10-90 min	76-96%
2.	[(CH$_2$)$_4$SO$_4$hmim][HSO$_4$] (1-Methyl-3-(4-sulfobutyl)-1*H*-imidazolium bisulfate)	10-30 min	84-97%

Table 1. Continued

Scheme	ILs	Time	Yield
3.	[bmim][BF_4] (1-Butyl-3-methylimidazolium tetrafluoroborate)	12 h	64-97%
4.	[$(CH_2)_4SO_3$hmim][HSO_4] (1-(4-Sulfobutyl)-3-methylimidazolium hydrogen sulfate) [SiO_2-OSO_3H] (Silica Sulfuric Acid)	35-70 min 2-3.5 h	85-95% 88-94%
5.	[mim]$^+$[BF_4]$^-$ (Methylimidazolium tetrafluoroborate)	2-4 min	90-97%
6.	[bmin][PF_6] (1-Butyl-3-methylimidazolium hexafluorophosphate)	3-24 h	67-89%
7.	[pmim]HSO_4SiO_2 (Silica supported 1-methyl-3-(trimethoxysilylpropyl) imidazolium hydrogensulfate)	6-8 h	84-90%
8.	[$(HSO_3$-p$)_2$im][CF_3SO_3] (1,3-Bis(3-sulfonic acid)propyl imidazolium trifluoromethanesulfonate)	15-20 min	86-96%
9.	[bmin][PF_6]	15 min	88-98%
10.	[bmin][PF_6]	2-8 h	80-94%
11.	[bmin][PF_6]	4-6 h	89-93%
12.	[bmin][BF_4]	65-80 min	88-92%
13.	[bmim]Cl/$AlCl_3$ (1-Butyl-3-methylimidazolium chloride / aluminum chloride)	20-24 h	71%
14.	[$(HSO_3$-p$)_2$im][CF_3SO_3] (1,3-Bis(3-sulfonic acid)propyl imidazolium triflate)	15-20 min	90-96%
15.	[bmim (BF_4)]	3-7 h	80-95%
16.	[bmim][$SeO_2(OCH_3)$)] (1-Butyl-3-methylimidazolium methylselenite)	2-3 h	53-78%
17.	[bmin][BF_4] 1-Butyl-3-methylimidazolium tetrafluoroborate	9 h	95%
18.	[hbmin][BF_4]	6-8 h	75-90%
19.	[sbimHS] (Imidazolium based Brönsted acidic ionic liquid)	5-20 min	80-95%
20.	[bmim][HSO_4] (1-Butyl-3-methylimidazolium hydrogen sulfate)	1.5-3 h	55-85%
21.	[hmim][HSO_4] (1-Methylimidazolium hydrogen sulfate)	25-40 min	85-94%
22.	[Cu(Im^{12})$_2$]$CuCl_2$ (hydrated bis(1-dodecylimidazole)copper(I) copper(II) tetrachloride)	12 h	75-98%
23.	[C_{10}MIM]Br+$ZnCl_2$ (1-Decyl-3-methylimidazolium bromide)	3 min	94.25%
24.	[bmim]Cl-$FeCl_3$ (1-Butyl-3-methylimidazolium chloride-Iron(III) chloride)	5-6 min	76-89%
25.	[bmin]$^+$[BF_4]$^-$	3 h-overnight	48.4-58.5%
26.	[hemim][$N(CN)_2$] (1-(2-Hydroxyethyl)-3-methylimidazolium dicyanamide)	12 h	68-90%
27.	[bmim][HSO_4] (1-Butyl-3-methylimidazolium hydrogen sulfate)	50-94 min	85-98%
28.	[emim][BF_4] (1-Ethyl-3-methylimidazolium tetrafluoroborate)	5 h	77-98%
29.	[BAIL gel] (Brønsted Acidic Ionic Liquid)	5-30 min	80-98%
30.	[emim][BF_4]	4 min	95.3%
31.	[bmim][Br] (1-Butyl-3-methylimidazolium Bromide)	15 h	69-86%
32.	[mdsim][CF3COO] (2-Methyl-1,3-disulfoimidazolium trifluoroacetate)	1-2 h	80-92%
33.	[bmim][BF4]	60-90 min	80-85%

Table 1. Continued

Scheme	ILs	Time	Yield
34.	BAIL-1	2 h	57-87%
35.	[bcmim][Cl] (1-Butyl-3-Methylimidazolium Chloride)	0.5 h	81-95%
	[bcmim][Cl]	0.5 h	85-94%
36.	BAIL-1	2 h	75-85%

2.2 Reusability study

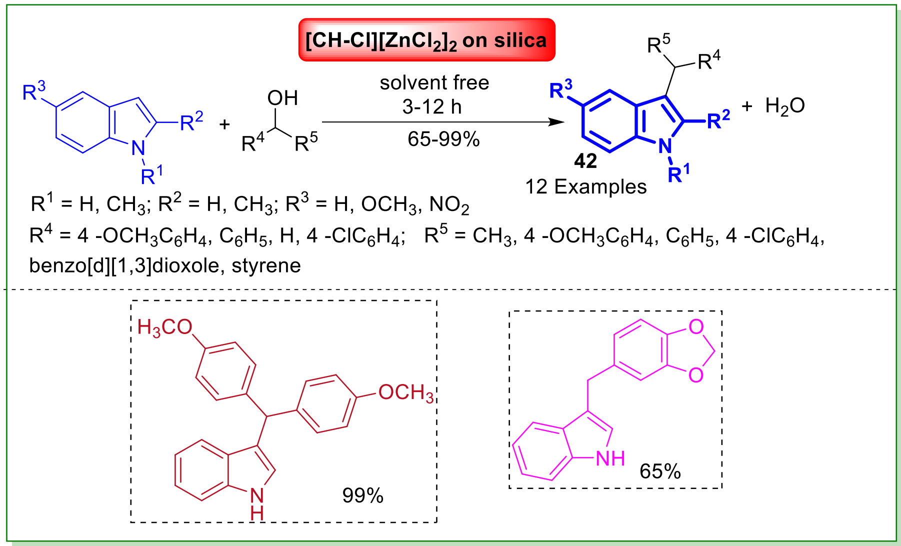
Table 2 elucidates the recyclability of diverse ionic liquids (ILs) by examining yield retention across multiple cycles. Ionic liquids such as [$(HSO_3$-*p*$)_2$im][CF_3SO_3], [emim][BF_4], and [bmim][HSO_4] (entry 27), along with bail-1, exhibit remarkable stability, achieving high yields (88–98%) across 5–12 cycles, which underscores their significant reusability and environmentally friendly potential. Conversely, [bmim][$SeO_2(OCH_3)$] and [bmim][HSO_4] (entry 20) exhibit a notable decline in activity, indicating a lack of stability. Gel-supported ionic liquids, such as [BAIL gel], provide reliable yields alongside straightforward recovery processes. In summary, the architecture of ionic liquids, particularly the acidic and supported forms, is fundamental in influencing both the durability of catalysts and their appropriateness for sustainable synthesis.

Table 2. Recyclability data of ILs

Scheme	ILs	No of cycles	Yield
5.	[mim]$^+$[BF_4]$^-$	5	94-96%
7.	[pmim]HSO_4SiO_2	5	82-90%
8.	[$(HSO_3$-p$)_2$im][CF_3SO_3]	12	88-96%
11.	[bmin][PF_6]	3	87-92%
12.	[bmin][BF_4]	4	89-92%
16.	[bmim][$SeO_2(OCH_3)$]	6	trace-77%
17.	[bmin][BF_4]	4	91-94%
20.	[bmim][HSO_4]	6	22-81%
21.	[hmim][HSO_4]	4	81-94%
22.	[$Cu(Im^{12})_2$]$CuCl_2$	4	80-92%
26.	[hemim][$N(CN)_2$]	11	48-94%
27.	[bmim][HSO_4]	5	93-98%
28.	[emim][BF_4]	10	91-92%
29.	[BAIL gel]	5	91-92%
30.	[emim][BF_4]	4	90.4-91.5%
32.	[mdsim][CF_3COO]	4	80-90%
35.	[bcmim][Cl]	4	91-95%
36.	BAIL-1	5	91-95%

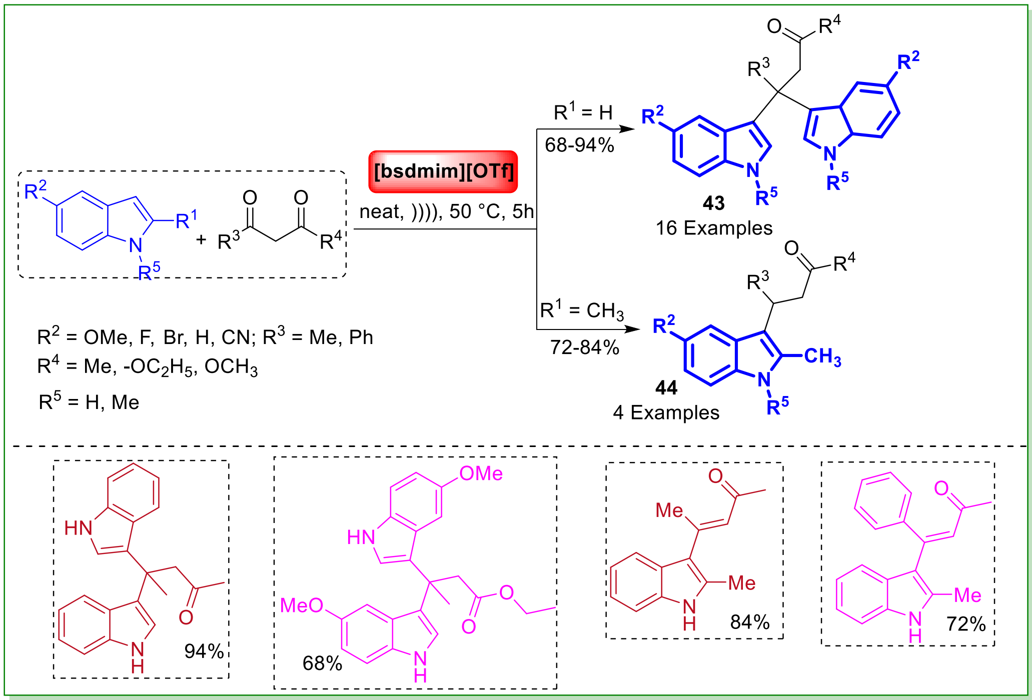
3.0 Methods assisted by surface functionalized-based ILs

In 2016, Wang and colleagues[76] developed a hydroxyl functionalized Lewis acid IL based on silica. For the Friedel-Crafts benzylation reaction of iodole at C-3, IL was showed to be effective (Scheme 37). Under solvent-free reaction conditions, the indole derivatives **42** were produced in 65–99% yields. The authors synthesized a total of 12 examples to test the broad applicability of the approach. With no discernible loss in activity or selectivity, the catalyst could be readily recycled and used again for at least six cycles.



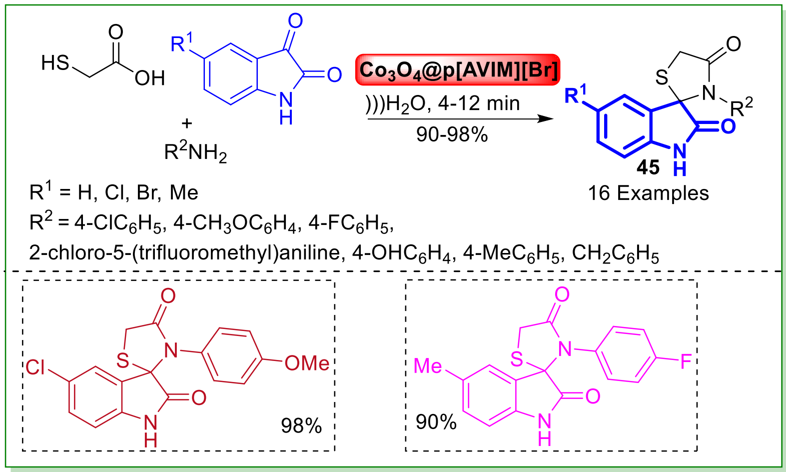
Scheme 37. Construction of tetra-substituted indole derivatives.

A method developed by Kumar's research team[77] for the synthesis of 3-alkenylated indoles **43** and bis(indol-3-yl) derivatives **44** using a sulfonic acid functionalized IL (SFIL). The reaction of 1,3-diketones/3-ketoesters with indole catalyzed under solvent-free ultrasonic irradiation. Products **43-44** of the reaction depends on the substituent at the C-2 position of indole (Scheme 38). For up to four cycles, the catalyst is recyclable and reusable without appreciable loss of its catalytic efficiency. In comparison to traditional heating, sound wave activation offers significant advantages, including reduced reaction times, simplified work-up, enhanced yields, and milder conditions.



Scheme 38. Synthesis of bis-indoles and substituted indole derivative.

Figure 9 shows a mechanism for the reaction. Indole first forms intermediate by reacting with the active carbonyl group of the 1,3-dicarbonyl molecule. Depending on the substituent, intermediate either removes water to generate a 3-alkenylated indole derivative **44** or performs acid-catalyzed substitution with another indole molecule to make bis(indol-3-yl) derivatives **43**.



R^1 = H, Cl, Br, Me

R^2 = 4-ClC_6H_5, 4-$CH_3OC_6H_4$, 4-FC_6H_5, 2-chloro-5-(trifluoromethyl)aniline, 4-OHC_6H_4, 4-MeC_6H_5, $CH_2C_6H_5$

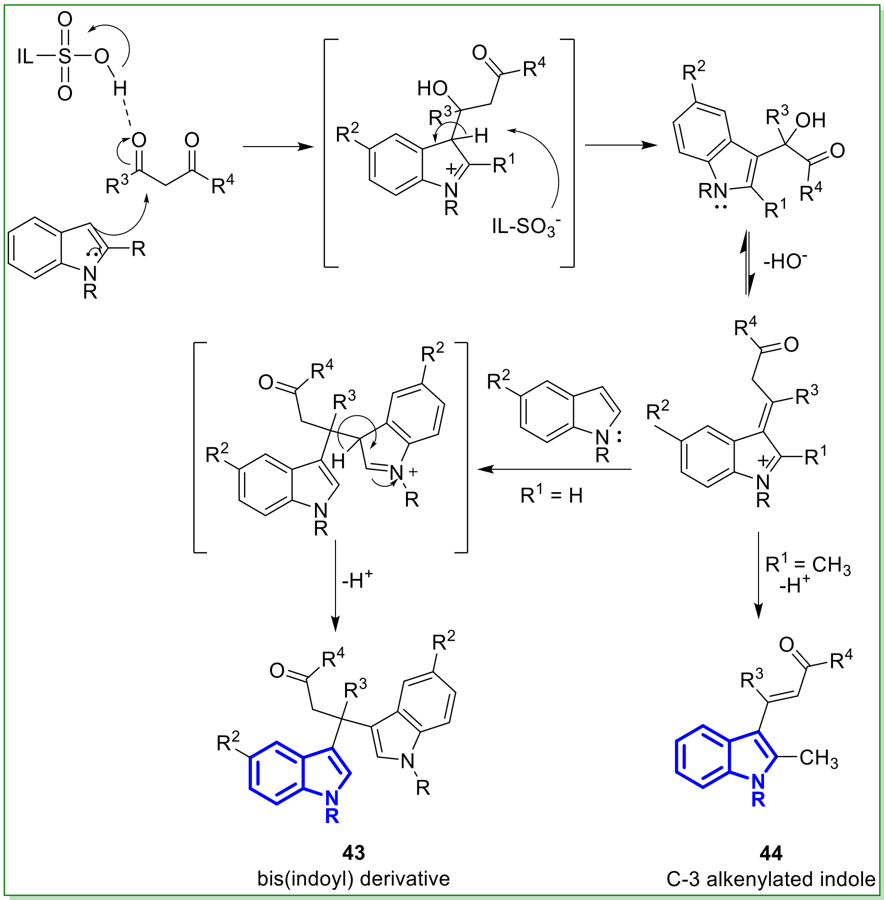
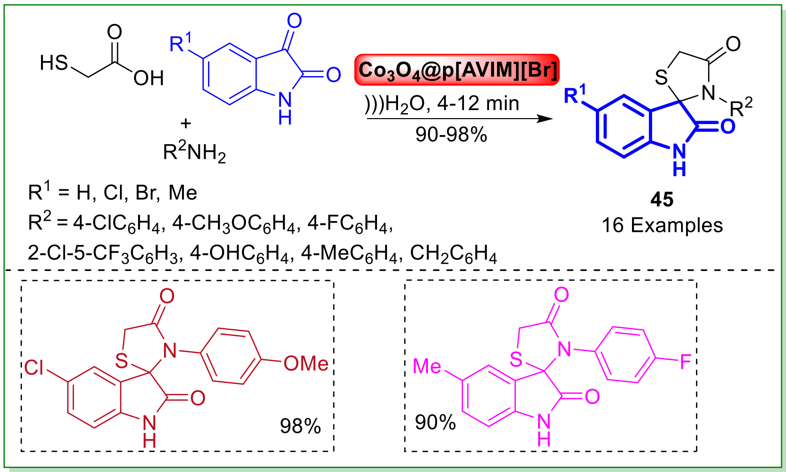


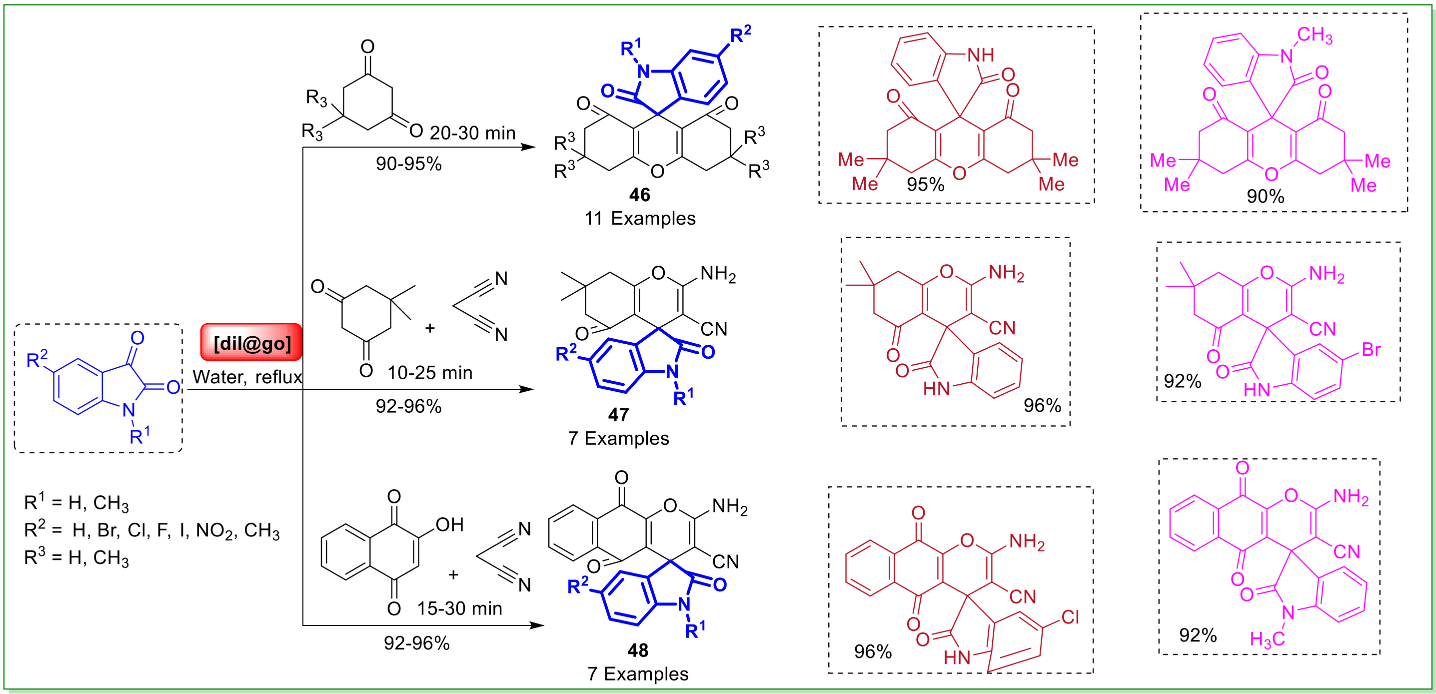
Figure 9. Tentative reaction mechanism for the synthesis of bis-indole derivative.

In 2020, the study by Ghomi and their co-workers[78] presented fabrication of a micro–mesoporous polymeric IL (PIL) including acid-base bifunctional active sites. A comparative investigation identified the preferred nanoporous PIL, which was employed as the sonocatalyst in a reaction including isatins, thioglycolic acid and primary amines (Scheme 39). A range of novel spiro-4-thiazolidinone derivatives **45** were synthesized at room temperature, achieving high yields (90-98%) within brief reaction times (4-12 mins). Amines with electron-donating substituents produced the desired spiro products in excellent yields while the amines bearing electron-withdrawing substituents takes longer time.



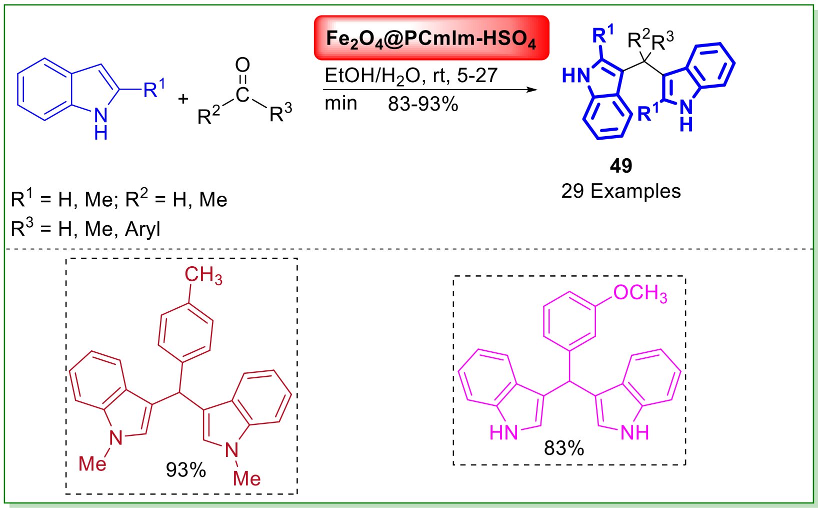
Scheme 39. Synthesis of spiro based indole compounds.

Thereafter, in 2021, the report by Dadhania and their co-workers[79] presented a mild and highly effective synthetic method for the preparation of spiro[indoline-3,9′-xanthene]trione **46** spiro[chromene-4,3′-indoline]-3-carbonitrile derivatives **47** utilizing graphene oxide-supported dicationic ILs (DIL@GO) as a heterogeneous catalyst in aqueous conditions. While spiro[chromene-4,3′-indoline]-3-carbonitrile derivatives **48** were produced by a one-pot reaction involving substituted isatins and malononitrile. The DIL@ GO catalyst showed remarkable catalytic efficacy, generating high yields (91-96%) of the end products **46-48** in a short reaction time (10-30 min) (Scheme 40).



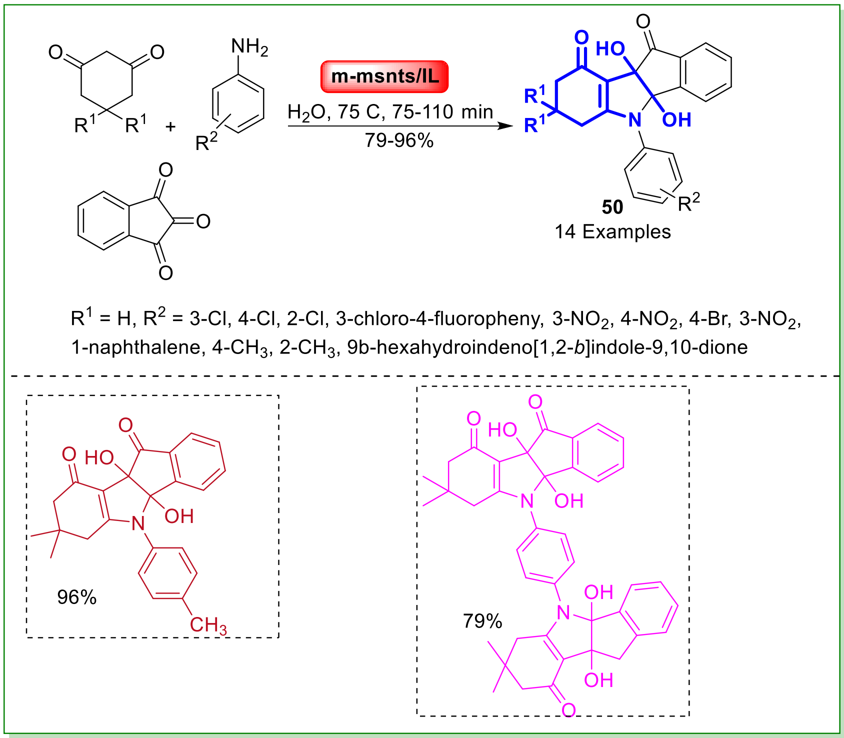
Scheme 40. One-pot synthesis of a series of indole based spiro compounds.

In 2022, the work group of Nongkhlaw[80] effectively synthesized bis(indolyl)methane derivatives **49** from indole/2-methyl indole and aldehydes utilizing acidic IL adsorbed on magnetic Fe_3O_4 NPs. Using electron-donating and withdrawing groups on starting substrates as outlined in Scheme 41, total 29 examples were synthesised easily in the presence of IL. The catalyst, used up to five runs without any appreciable loss of its catalytic activity, can be easily extracted using an external magnet.



Scheme 41. Synthesis of bis-indole derivatives.

Recently (in 2024), Moradi *et al.*[81] unfolded acidic IL supported on magnetic mesoporous silica nanotubes (M-MSNTs/IL) in organic heterocyclic formation (Scheme 42). The synthesized catalyst was effectively utilised as a novel reusable heterogeneous catalyst for the one-pot three-component indeno[1,2-*b*]indole-9,10-dione derivatives **50** in a green solvent. All desired products **50** were obtained with yields ranging from 79% to 96% after relatively short reaction times. The applied nanocatalyst was recovered using an external magnet and reused six times, exhibiting minimal reduction in catalytic activity.



Scheme 42. one-pot three-component indeno[1,2-b]indole-9,10-dione derivatives.

3.1 Comparative study

Table 3 presents a comparative analysis of diverse catalytic systems supported by ionic liquids, focusing on reaction time and yield. Co_3O_4@p[AVIM][Br] (entry 39) and dil@go (entry 41) are distinguished by their remarkably rapid reactions (4–30 min) and outstanding yields (90–98%), underscoring their exceptional catalytic performance. Fe_2O_4@PCmim-HSO_4 and M-msnts/IL demonstrate commendable efficacy within reasonable durations, achieving substantial yields. Conversely, systems such as [bsdmim][OTf] necessitate extended durations (5–12 h) and present yields that are more inconsistent. [CH-Cl] The use of $[ZnCl_2]_2$ on silica demonstrates considerable versatility, achieving impressive yields ranging from 65% to 99%, albeit accompanied by extended reaction durations. In summary, the enhancement of reactivity in supported IL systems is evident; however, the efficiency in terms of time is contingent upon the specific design of the catalyst.

Table 3. Comparison of ILs with respect to time and yield of reaction

Scheme	ILs	Time	Yields
37.	[CH-Cl]$[ZnCl_2]_2$ on silica (Choline chloride-zinc chloride ionic liquid)	3-12 h	65-99%
38.	[bsdmim][OTf] (1-Butyl-3-methylimidazolium trifluoromethanesulfonate)	5 h	68-94%
39.	Co_3O_4@p[AVIM][Br] (Poly(1-aminopropyl-3-vinylimidazolium bromide)	4-12 min	90-98%
41.	dil@go (Dicationic Ionic Liquid Graphene Oxide)	10-30 min	90-96%
42.	Fe_2O_4@PCmim-HSO_4 (1-(3-Carboxylic acid)propyl-3-methylimidazolium hydrogen sulfate)	5-27 min	83-93%
43.	M-msnts/IL (Magnetic Mesoporous Silica Nanotubes functionalized with an Ionic Liquid)	75-110 min	79-96%

3.2 Reusability study

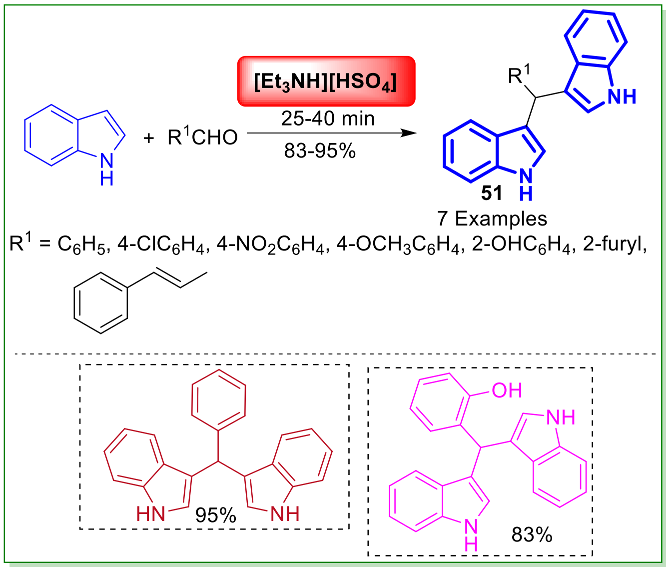
Table 4 presents a comparative analysis of the recyclability of ionic liquid-supported catalysts, focusing on yield retention across several cycles. dil@go, [bsdmim][OTf], and M-msnts/IL demonstrate remarkable reusability, sustaining high yields (91–96%) across 5–6 cycles, which reflects their robust catalytic stability. Fe_2O_4@PCmim-HSO_4 demonstrate commendable recyclability, achieving yields exceeding 82%. Conversely, [CH-Cl]$[ZnCl_2]_2$ on silica and Co_3O_4@p[AVIM][Br] exhibit diminishing activity, with yields decreasing to 22% and 45% respectively, indicating restricted long-term applicability. In summary, the efficacy of supported ionic liquid systems in improving catalyst recovery and promoting sustainability is contingent upon the specific structure of the ionic liquid, the characteristics of the support material, and the prevailing reaction conditions.

Table 4. Recyclability data of ILs

Scheme	ILs	No of cycles	Yields
37	[CH-Cl]$[ZnCl_2]_2$ on silica	6	22-81%
38	[bsdmim][OTf]	5	91-94%
39	Co_3O_4@p[AVIM][Br]	8	45-90%
540	dil@go	5	93-96%
41	Fe_2O_4@PCmim-HSO_4	6	82-88%
42.	M-msnts/IL	6	87-96%

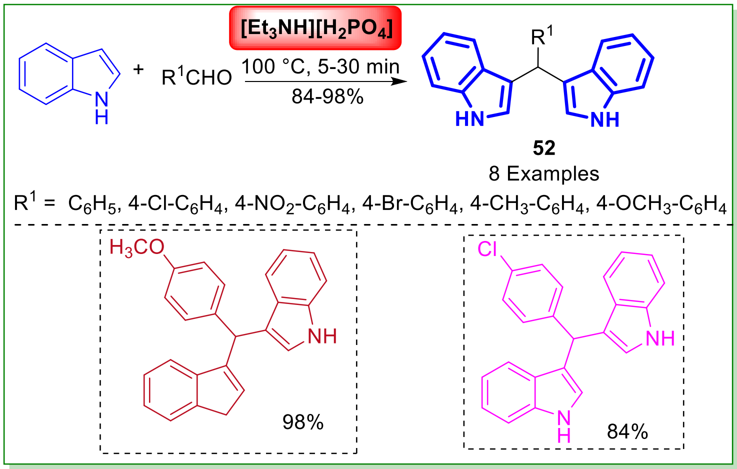
4.0 Methods assisted by triethyl amine-based ILs

In 2011, the study by Rajendran and their co-workers[82] conducted many electrophilic substitution reactions of indoles with different aldehydes, employing a cost-effective and recyclable ILs $[Et_3NH][HSO_4]$ as a catalyst, resulting in the formation of bis(indolyl)methanes **51** with high yields (83-95%) (Scheme 43). The catalytic performance of ILs$[Et_3NH][HSO_4]$ in comparison to that of traditional catalysts. The reaction was specifically chemo-selective and only worked with aldehydes and not ketones. A library of 7 examples was synthesized by using various substituted starting substrates. The ILs was recovered and reused over five times without any significant reduction in its efficacy.



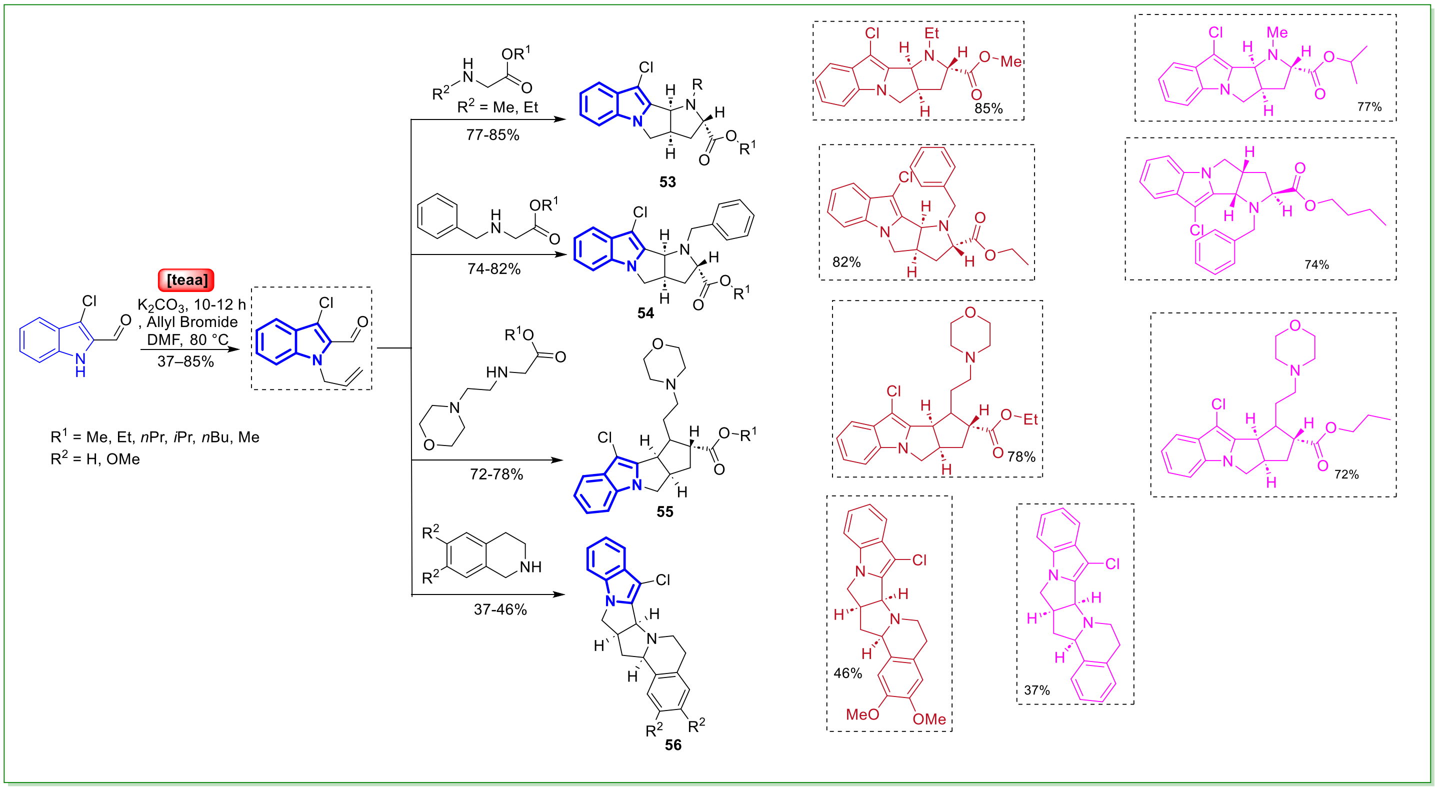
Scheme 43. $[Et_3NH][HSO_4]$-Assisted reaction of indole and benzaldehyde.

In 2012, Kalantari's research team[83] developed mild acidic IL catalyst for the manufacture of bis(indolyl)methanes **52** from triethyl ammonium dihydrogen phosphate. Within 5-30 min of reaction time only, the bis-indole derivatives **52** were obtained in 84-98% yields (Scheme 44). 8 Synthetic examples were synthesized to test the general applicability of the protocol. Both aromatic aldehydes with electron-withdrawing groups as well as electron-donating groups acquired in good yields.



Scheme 44. One-pot synthesis of bis-indole derivatives.

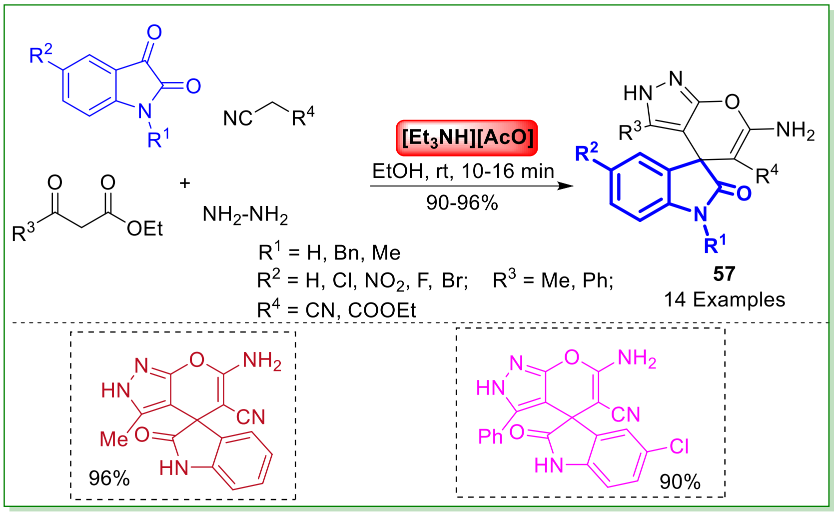
Next, in 2015, the synthesis of novel pyrrolo-fused pyrrolo[1,2-*a*]indole derivatives **53-56** has been accomplished by Sutariya *et al.*[84] The reaction of *N*-allyl-indole-2-carbaldehyde with various *N*-alkyl-glycine esters and tetrahydroisoquinolines in ILs (triethylammonium acetate; TEAA) delivered a series of indole derivatives **53-56** as described in Scheme 45. The reaction was accomplished through an intramolecular [3+2] cycloaddition reaction. This novel process was exceptionally efficient, and the utilized ILs was recyclable.



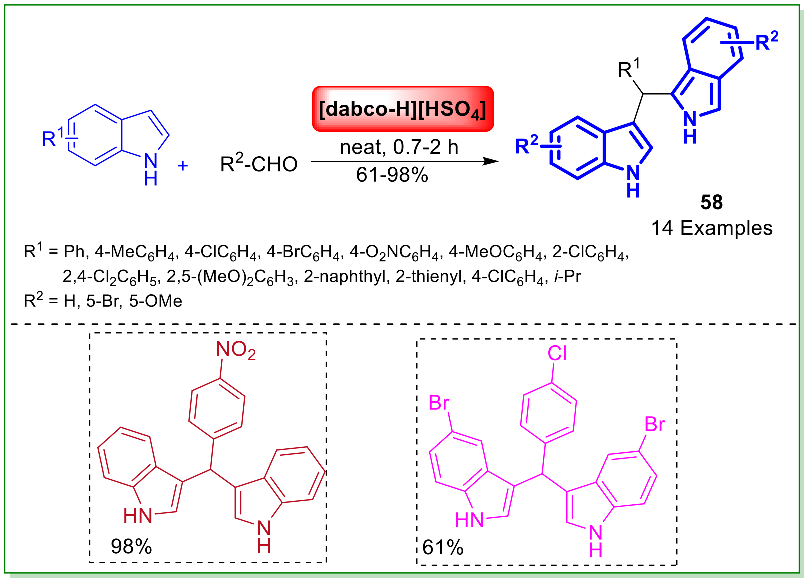
Scheme 45. TEAA-catalysed formation of a series of indole based fused molecular hybrids.

In 2016, Raouf *et al.*[85] developed a new and highly efficient method for one-pot four-component preparation of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] **57** (Scheme 46). The reaction delivered products **57**in high yields (90-96%) using ammonium acetate as an inexpensive, non-toxic, efficient, re-usable and readily prepared catalyst in very short times. The authors prepared 14 total examples to test the broad applicability and adaptability of the technique. The catalyst is affordable, effective, benign, and easily prepared and reusable for five consecutive runs with negligible activity loss.

In the same year, Xu and colleagues[86] revealed a straightforward method for synthesizing bis(indolyl)methane (BIM) derivatives **58**. Under solvent-free reaction conditions, the reaction yielded final products **58** in good to excellent yields (61–98%), in the presence of DABCO-based IL catalysts. The catalysts are conveniently recovered and utilized several times without a significant drop-in activity (Scheme 47).

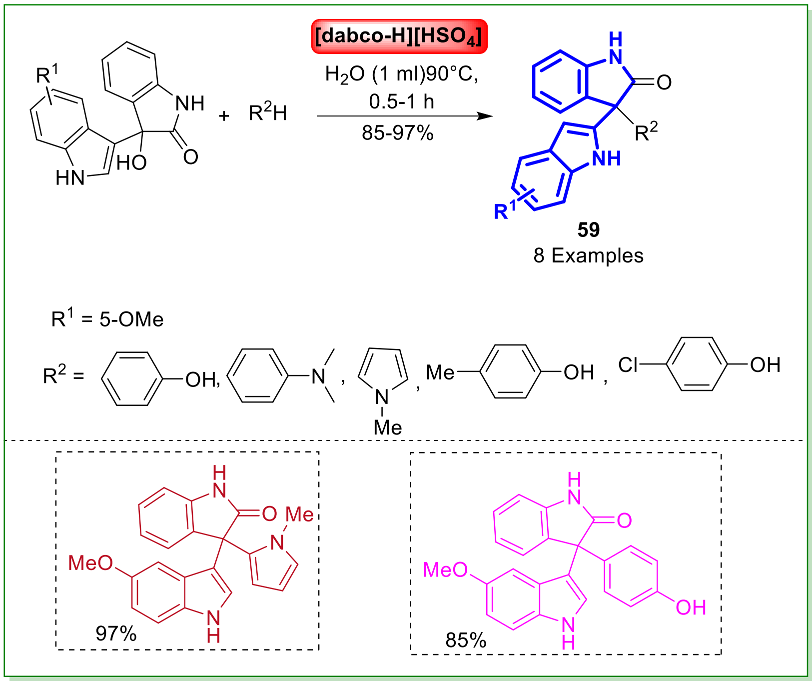


Scheme 46. Multi-component reaction for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazoles].



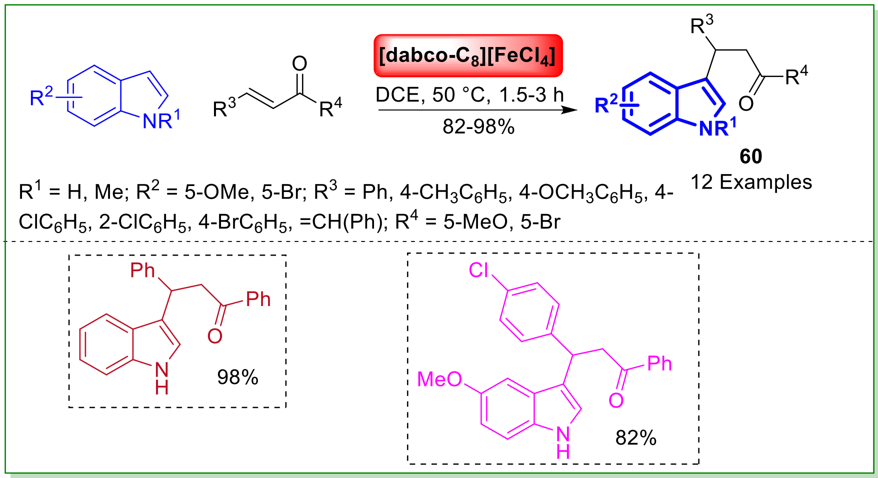
Scheme 47. Synthesis of bis-indole derivatives.

Under this work, in 2017, a convenient method for the syntheses of 3-indolyl-3-hydroxy oxindoles **59** has been developed by the research group of Xu.[87] [DABCO-*H*][HSO_4] was used as the catalyst in water at 55 °C to afford 3-indolyl-3-hydroxy oxindoles **59**. The catalyst [DABCO-*H*][HSO_4] could accelerate the reaction further and provide symmetric 3,3-diindolyl oxindoles **59** even increasing the reaction temperature to 90 °C. The reaction accommodates a range of substituted aryl aldehydes and β-diketones, demonstrating excellent compatibility with functional groups. The implementation of a recyclable and metal-free catalyst in an aqueous medium highlights the sustainability of the protocol. Five times of recycling the catalysts yields five times of activity loss free (Scheme 48).



Scheme 48. Formation of 3-indolyl-3-hydroxy oxindoles.

Herein, Xu's research team[88] unfolded Michael-type addition of indoles to electron-deficient olefins. The current reaction was run using the novel magnetic IL catalyst ([DABCO-C₈][FeCl₄]) which produced indole derivatives **60** in 83-98% yields (Scheme 49). Chalcones, nitro-olefins and enones are among the electron-deficient olefins for which this catalyst system is suitable; it provides the corresponding 3-alkylindole derivatives **60** in good to excellent yields (83-98%) under mild conditions within short durations (1.5-3 h).



Scheme 49. Reaction of substituted indole and active methylene compounds.

Figure 10 shows possible mechanism involve direct C3 alkylation of indoles with electron-deficient olefins. Originally obtained from the reversible reaction of $FeCl_4^-$, the Lewis acid $FeCl_3$ coordinates the carbonyl oxygen, hence activating the carbonyl group in enone and producing adduct. An addition process transpired between and indole, yielding an intermediate enolate, which can then be protonated to give the adduct. The latter subsequently yields the desired product **60** and restores the catalyst.

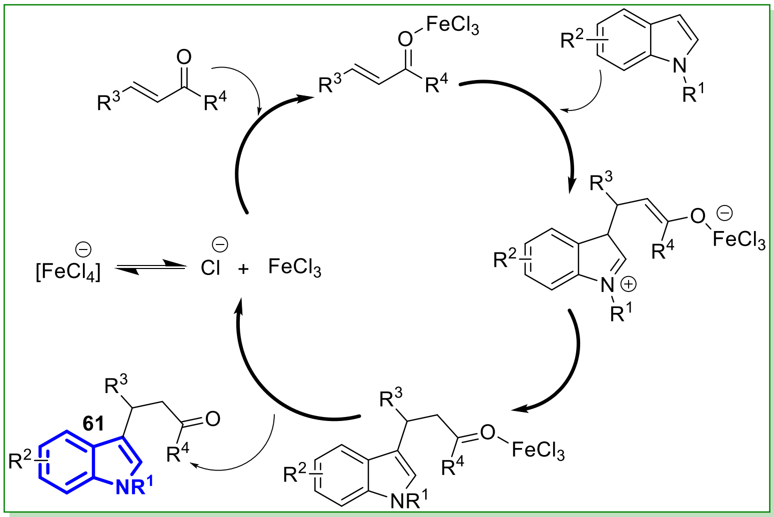
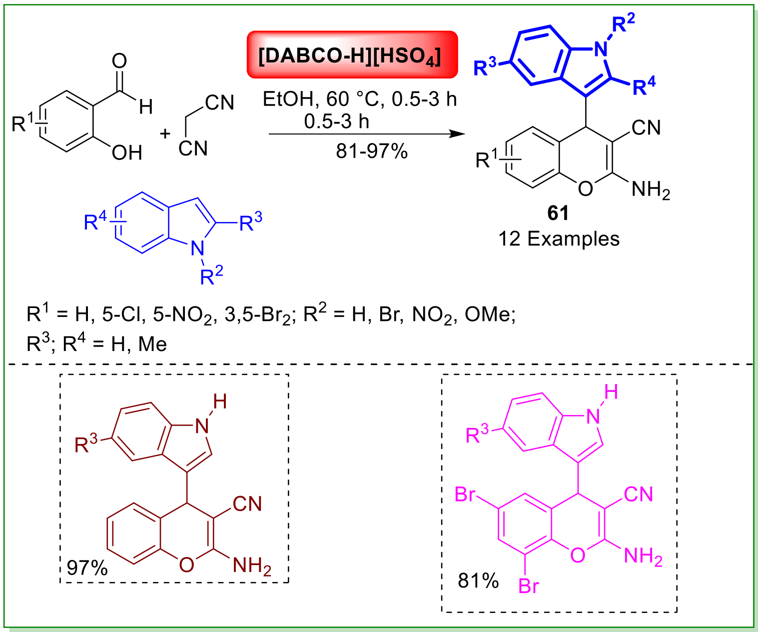


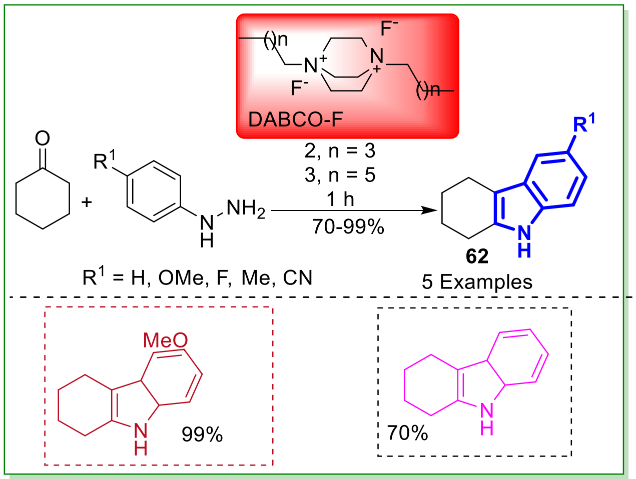
Figure 10. Putative reaction mechanism.

Furthermore, in 2018, a strategy for the construction of biologically relevant 2-amino-4*H*-chromene scaffolds by using a DABCO-based IL has been established by Xu *et al*[89] (Scheme 50). The current methodology successfully completed and delivered diversified library of 2-amino-4*H*-chromene derivatives **61** in 81-97% yield. All products **61** underwent purification through simple crystallisation. The catalyst is capable of being recycled a minimum of five times.



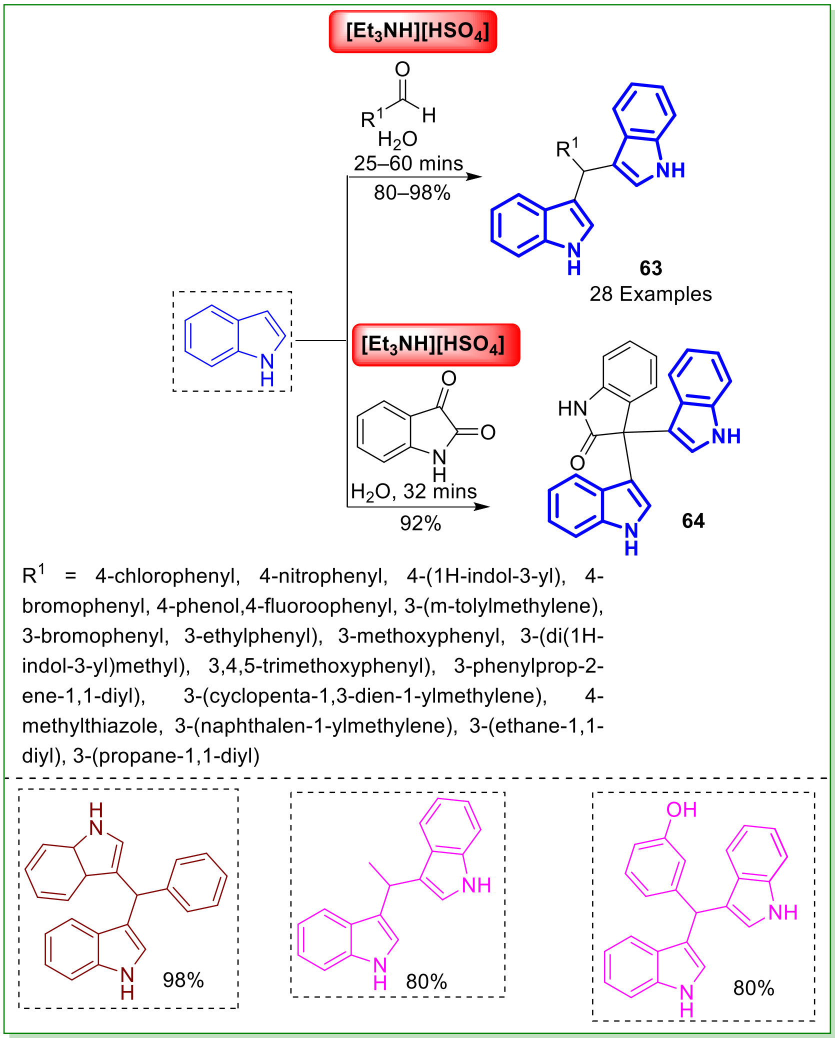
Scheme 50. Three-Component Reaction for the Rapid Synthesis of 2-Amino-4*H*-chromenes.

In 2022, Hameed and co-workers[90] synthesized indole based 1,4-dihydropyridines by using DABCO-based IL-mediated reaction (Scheme 51). The efficiency of DABCO ionic liquids for the synthesis of various indoles based 1,4-dihydropyridines **62** was examined and gave the corresponding products in 70-99% yield. Quantum mechanical calculations were conducted to determine the optimised geometric configuration of ionic liquids, and their stability was assessed through binding energy calculations derived from the MP2 method applied to the optimized structures.



Scheme 51. Synthesis of substituted indoles.

In 2023, Agarwal *et al.*[91] disclosed an eco-friendly method for synthesising a library of 34 bis(indoyl)methane derivatives **63-64** (Scheme 52). The current reaction was facilitated by utilising triethylammonium hydrogen sulphate IL as a green catalyst. The reaction was straightforward, involving the mixing of two equivalents of indole with one equivalent of various aldehydes (aromatic, heterocyclic, and aliphatic) and isatin in the presence of an IL catalyst and water as a green solvent. The existing methodology presents multiple advantages, including operational simplicity, a brief duration of 25–60 minutes, cost efficiency, environmental sustainability, high yields (**63**; 80-98% and **64**; 92%), a readily recoverable catalyst, and high reusability for up to five cycles.



R^1 = 4-chlorophenyl, 4-nitrophenyl, 4-(1H-indol-3-yl), 4-bromophenyl, 4-phenol,4-fluoroophenyl, 3-(m-tolylmethylene), 3-bromophenyl, 3-ethylphenyl), 3-methoxyphenyl, 3-(di(1H-indol-3-yl)methyl), 3,4,5-trimethoxyphenyl), 3-phenylprop-2-ene-1,1-diyl), 3-(cyclopenta-1,3-dien-1-ylmethylene), 4-methylthiazole, 3-(naphthalen-1-ylmethylene), 3-(ethane-1,1-diyl), 3-(propane-1,1-diyl)

Scheme 52. Synthesis of Bis(indoyl)methanes.

4.1 Comparative study

Table 5 depicts a comparative study of Brønsted acidic ionic liquids, focusing on their reaction times and yields. The compounds [Et$_3$NH][H$_2$PO$_4$], [Et$_3$NH][AcO], and [DABCO-F] exhibit remarkable yields ranging from 84% to 99% within brief reaction periods of 5 to 30 minutes up to 1 hour, thereby demonstrating significant catalytic efficacy. [DABCO-H] The variants of [HSO$_4$] presented in entries 47, 48, and 50 demonstrate commendable performance, achieving yields ranging from 61% to 98% within reasonable timeframes. Conversely, teaa triethylammonium acetate (entry 45) exhibits the most prolonged reaction time (10–12 h) and fluctuating yields (37–85%), indicating a diminished level of efficiency. In summary, triethylammonium and DABCO-based ionic liquids demonstrate exceptional efficacy, particularly those incorporating HSO$_4^-$ or H$_2$PO$_4^-$ anions, facilitating rapid, high-yield, and environmentally friendly transformations.

Table 5. Comparison of ILs with respect to time and yield of reaction

Scheme	ILs	Time	Yields
43.	$[Et_3NH][HSO_4]$ (Triethylammonium hydrogen sulfate)	25-40 min	83-95%
44.	$[Et_3NH][H_2PO_4]$	5-30 min	84-98%
45.	teaa (Triethylammonium acetate)	10-12 h	37-85%
46.	$[Et_3NH][AcO]$ (triethylammonium acetate)	10-16 min	90-96%
47.	[dabco-H]$[HSO_4]$ (1,4-diazabicyclooctane-based ionic liquid with a hydrogen sulfate anion)	0.7-2 h	61-98%
48.	[DABCO-H]$[HSO_4]$	0.5-1 h	85-97%
49.	$[DABCO\text{-}C_8][FeCl_4]$ ([1,4-Diazabicyclooctane-N-octyl] tetrachloroferrate ($[FeCl_4]^-$))	1.5-3 h	82-98%
50.	[DABCO-H]$[HSO_4]$	0.5-3 h	81-97%
51.	[DABCO-F] (1,4-diazabicyclooctane-based ionic liquid with a fluoride anion)	1 h	70-99%
52.	$[Et_3NH][HSO_4]$ (triethylammonium hydrogen sulfate) $[Et_3NH][HSO_4]$	25-60 min 32 min	80-98% 92%

4.2 Reusability study

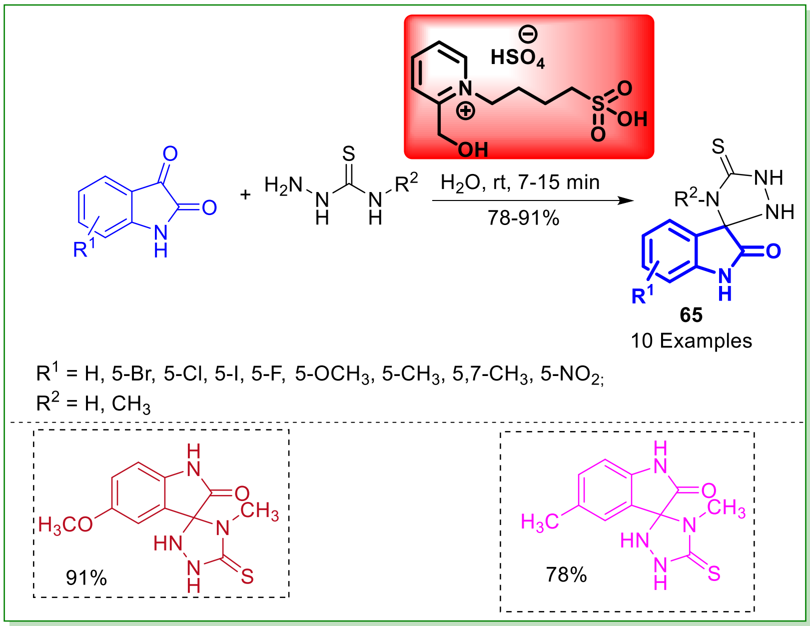
Table 6 contrasts the recyclability of Brønsted acidic ionic liquids according to their efficacy across several cycles. [DABCO-H]$[HSO_4]$ (entry 47 and 48) has exceptional stability, sustaining high yields (90–98%) across six cycles, signifying robust catalytic efficiency and reusability. Likewise, $[Et_3NH][HSO_4]$ and $[Et_3NH][AcO]$ maintain high yields (81–98% and 82–95%) across five cycles, indicating sustained efficacy. Nonetheless, entry 50, which also employs [DABCO-H]$[HSO_4]$, has a substantial yield reduction (10–64%), indicating potential catalyst degradation or susceptibility to particular circumstances. These ionic liquids demonstrate notable recyclability, with DABCO- and Et_3NH-based systems proving effective for sustainable catalysis when well optimised.

Table 6. Recyclability data of ILs

Scheme	ILs	No of cycles	Yields
43.	$[Et_3NH][HSO_4]$	5	83-94%
46.	$[Et_3NH][AcO]$	5	82-95%
47.	[dabco-H]$[HSO_4]$	6	90-97%
48.	[dabco-H]$[HSO_4]$	6	90-98%
50.	[dabco-H]$[HSO_4]$	5	10-64%
52.	$[Et_3NH][HSO_4]$	5	81-98%

5.0 Methods assisted by pyridine-based ILs

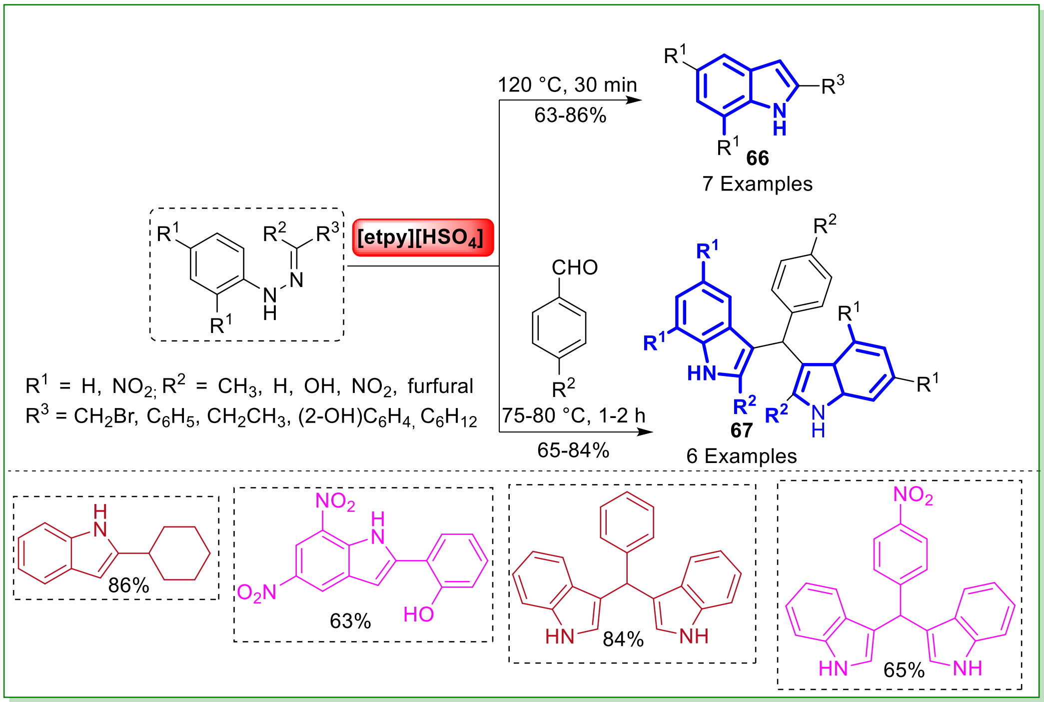
Further (in 2016), Korade's research team[92] has developed an effective task-specific IL, [2-hydroxymethylpyridinium butanesulfonic acid], for the quick synthesis of spiro-1,2,4-triazolidine-3-thiones **6**5from isatins and thiosemicarbazides in water (Scheme 53). Under aqueous conditions, the hydroxymethyl group joined to the pyridinium nucleus accelerates the process. The method's originality resides in the synthesis of a new task-specific IL distinguished by energy efficiency, a wide substrate scope, short reaction times, atom economy, high product yields (78-91%), all of which help to explain its environmentally friendly properties.



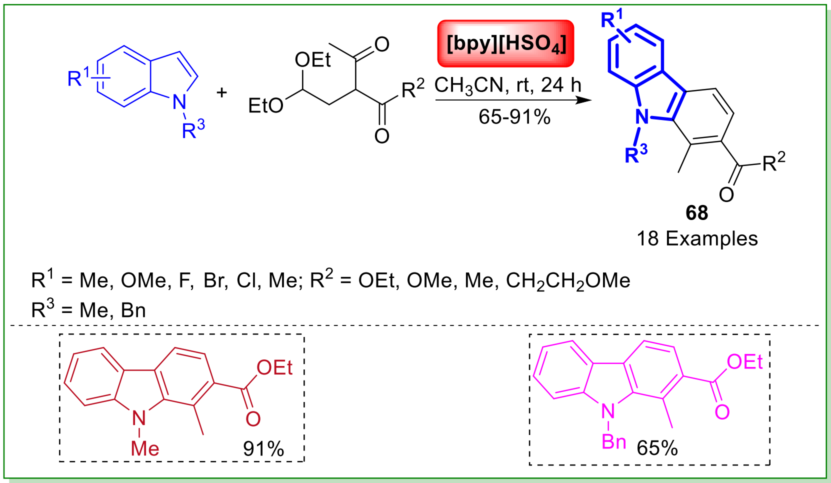
Scheme 53. One-pot engineering of spiro-1,2,4-triazolidine-3-thiones.

Gupta *et al.*[93] synthesized ILs *N*-ethylpyridinium hydrogen sulfate ([etpy][HSO_4]) in 2017 using it as a recyclable catalyst for the construction of a series of substituted indoles **66** and bis(indolyl)methanes **6**7 (Scheme 54). With 63–86% yields respectively, the substituted indole **66** and bis-indole derivatives **6**7 were obtained. The synthesized compounds **66-67** were then investigated much more for their possible antibacterial action against *Bacillus* and *E. coli*. Using water helped in terms of eliminating organic solvents, offering easy product recovery, and enabling catalyst recycling.

Under [4+2] annulation of 3-(2,2-diethoxyethyl)-1,3-dicarbonyl compounds with indoles, the research group of Han[94] synthesized a series of carbazoles **68** in 2018 (Scheme 55). Furthermore, the reaction was catalysed in the presence of a novel Brønsted acid IL([BPy] HSO_4) at room temperature. Within 24 hours of reaction time, the products **68** obtained yields of 65-91%. The ability to accommodate a variety of substituents, whether electron-donating or withdrawing, underscores the protocol's reliability, rendering it appropriate for the synthesis of pharmacologically significant acridine scaffolds.

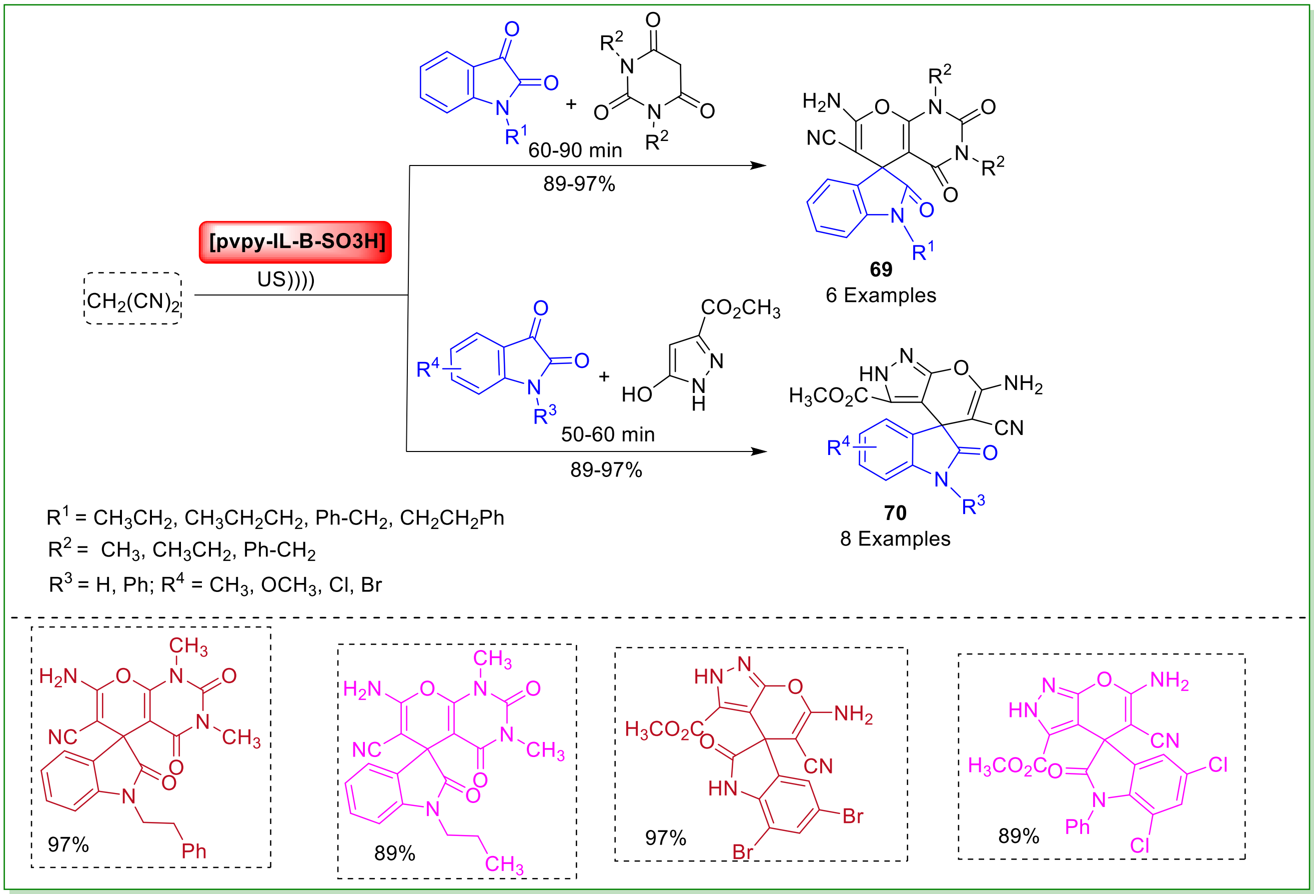


Scheme 54. Synthesis of substituted and bis-indoles.



Scheme 55. [4+2]-Annulation of 3-(2,2-diethoxyethyl)-1,3-dicarbonyl compounds with indoles.

In 2023, Klein *et al.*[95] synthesized and employed a sulfonated poly-4-vinyl pyridinium (PVPy-IL-B-SO$_3$H) including an acidic pyridinium/HSO$_3$ IL. Under ultrasonic irradiation conditions, this catalyst proved its potential for three-component reaction of malononitrile with 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and 1-alkylindoline-2,3-diones to produce indole based carbonitrile derivatives **69-70**. As reported in Scheme 56, the indole-based derivatives **69-70** were obtained in 89-97% yields within short reaction durations (50-90 min). The protocol provided additional advantges such as good yields under mild circumstances, makes separation simple, and eliminates the need for column chromatography for product isolation and purification.



Scheme 56. Synthesis of spiro-indoline-3,5-pyrano[2,3-*d*]-pyrimidines and-pyrazines.

5.1 Comparative study

Table 7 indicates that [pvpy-IL-B-SO_3H] demonstrates superior performance, achieving high yields (89–97%) within a moderate timeframe. [2-Hydroxymethylpyridinium][HSO_4] delivers favourable results rapidly. Conversely, [BPy][HSO_4] necessitates 24 hours of reaction time, rendering it the slowest option although yielding satisfactory results. [etpy][HSO_4] demonstrates moderate efficacy and temporal equilibrium.

Table 7. Comparison of ILs with respect to time and yield of reaction

Scheme	ILs	Time	Yields
53.	[2-Hydroxymethylpyridinium butanesulfonicacid]HSO_4	7-15 min	78-91%
54.	[etpy][HSO_4] (N-Ethylpyridinium hydrogen sulfate)	0.5-2 h	63-86%
55.	[BPy]HSO_4 (1-Butylpyridinium hydrogen sulfate)	24 h	65-91%
56.	[pvpy-IL-B-SO_3H] (Sulfonated poly-4-vinyl pyridinium ionic liquid)	50-90 min	89-97%

5.2 Reusability study

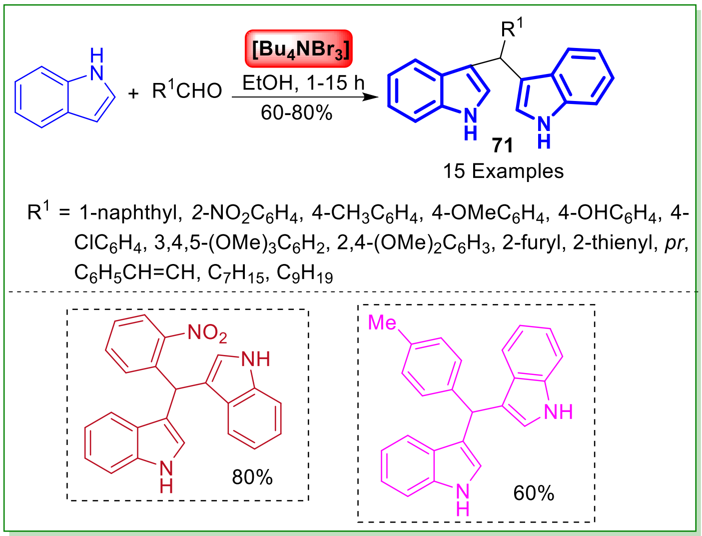
Table 8 indicates that both ILs demonstrate commendable recyclability, with [pvpy-IL-B-SO_3H] sustaining consistently high yields (91–92%) across 10 cycles, signifying exceptional stability. 2-Hydroxymethylpyridinium butanesulfonic acid [HSO_4] has commendable performance, attaining yields of 82–95% across 6 cycles, rendering both substances appropriate for sustainable and reusable catalytic applications.

Table 8. Recyclability data of ILs

Scheme	ILs	No of cycles	Yields
53.	[2-Hydroxymethylpyridinium butanesulfonicacid][HSO_4]	6	82-95%
56.	[pvpy-IL-B-SO_3H]	10	91-92%

6.0 Methods assisted by ammonium ion-based ILs

In 2010, a proficient method has been established by Majee and their co-workers[96] by using a novel ammonium IL for the synthesis of bis(indolyl)methane derivatives **71**through the condensation of aldehydes with indole, utilized tetrabutylammonium tribromide as a catalyst to afford the bis(indolyl)methane derivatives (Scheme 57). The products **71** were achieved in 60-80% yields in the presence of IL and ethanol as a solvent. Using substrates with electron-donating and withdrawing substituents produced a total of 15 examples.



Scheme 57. Synthesis of bis(indolyl)methanes.

Figure 11 shows a tentative reaction mechanism. Anhydrous HBr freed in the reaction between TBATB with ethanol catalyses addition of indole to carbonyl compounds **71**. The acidity of the medium can be adjusted with the choice of suitable solvent.

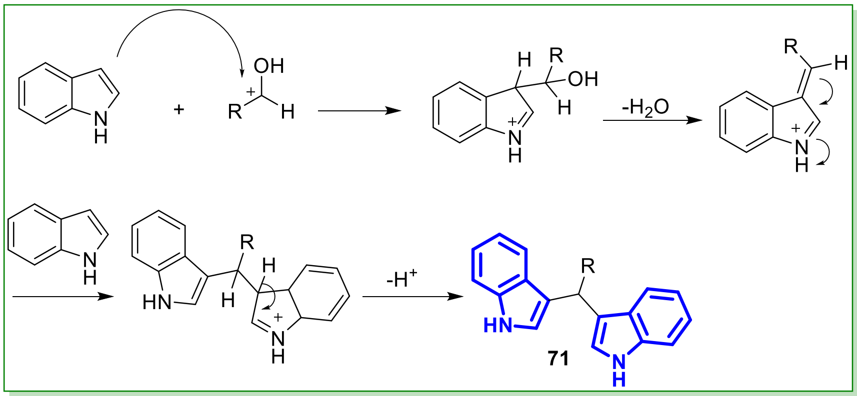
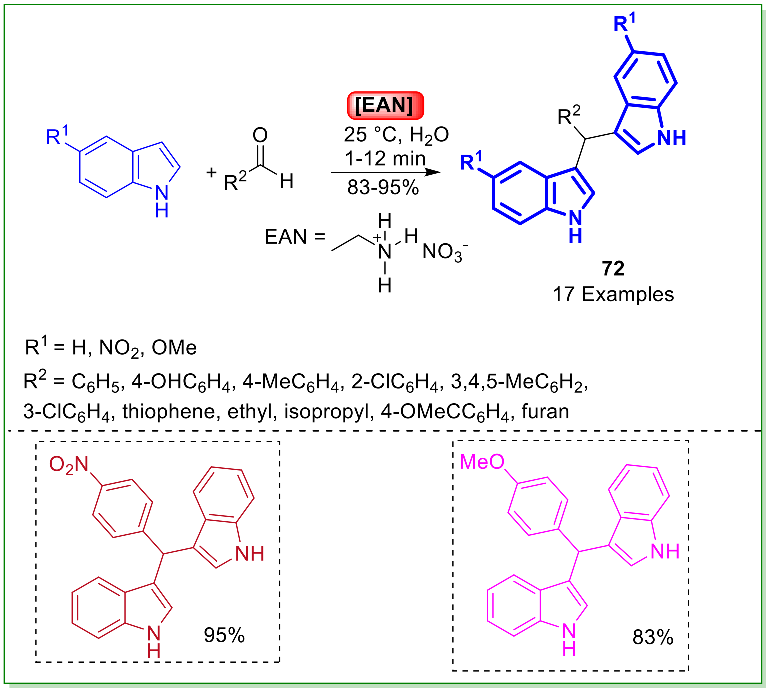


Figure 11. Plausible reaction mechanism.

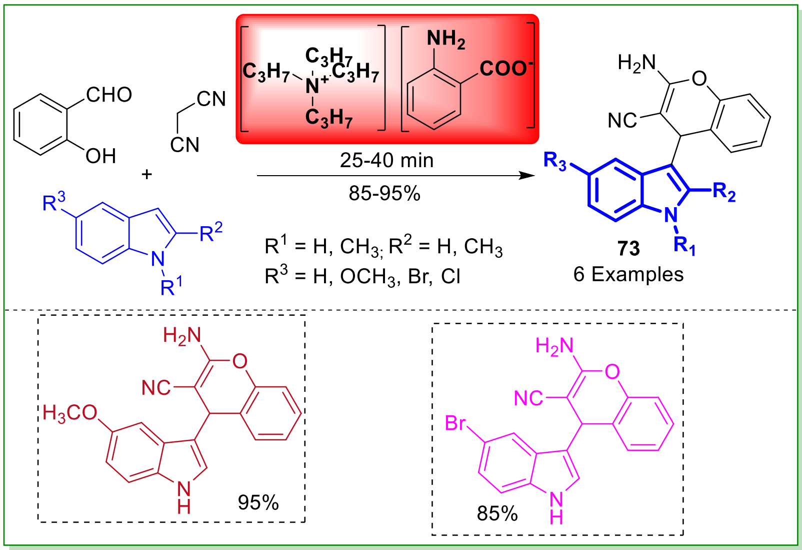
Next, in 2012, a straightforward and expedited technique has been established by the research group of Mulla[97] for the effective synthesis of bis(indolyl)methane **72** in high yields (83-95%), utilizing ethyl ammonium nitrate (EAN) as a recyclable IL. This catalyst also played well for synthesizing the final products in 83-95% yield. In the presence of EAN, the reaction time was reduced significantly up to 1-12 min. as presented in Scheme 58. The technique entailed an electrophilic substitution reaction between indoles and various aldehydes.



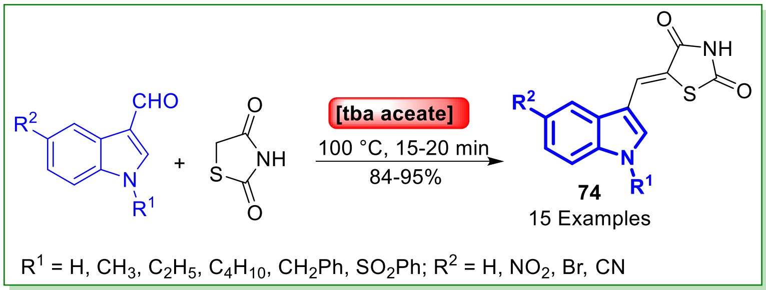
Scheme 58. One-pot engineering to synthesis of bis(indolyl)methane.

Rajendran's research team[98] focused on the synthesis of TSIL employing salicylate and tricaprylmethyl ammonium chloride (TCMA). After that, a synthetic method for the synthesis of indolyl chromenes **73** has been successfully developed, yielding 85-95% through a one-pot three-component reaction that incorporates malononitrile, salicylaldehyde, and indole (Scheme 59). TSIL was obtained and employed on six cycles, exhibiting no noticeable decline in efficacy. A significant number of compounds assessed to demonstrate the generality of the protocol.

Subsequently, in 2013, Dubey *et al.*[99] presented a straightforward synthesis of indolylidine-thiazolidine-diones **74**. The interaction of indole-3-aldehyde with thiazolidinedione/cyclic-1,3-diketones was facilitated by tetrabutylammonium acetate (TBAA), which serves as an economical, and reusable IL. This process occurs under solvent-free green conditions at a temperature of 100 °C for a duration of 15-20 minutes, eliminating the need for any supplementary catalyst. The indolylidine-thiazolidne-diones **74** were obtained in 84-95% yield by synthesizing 15 examples as described in Scheme 60.

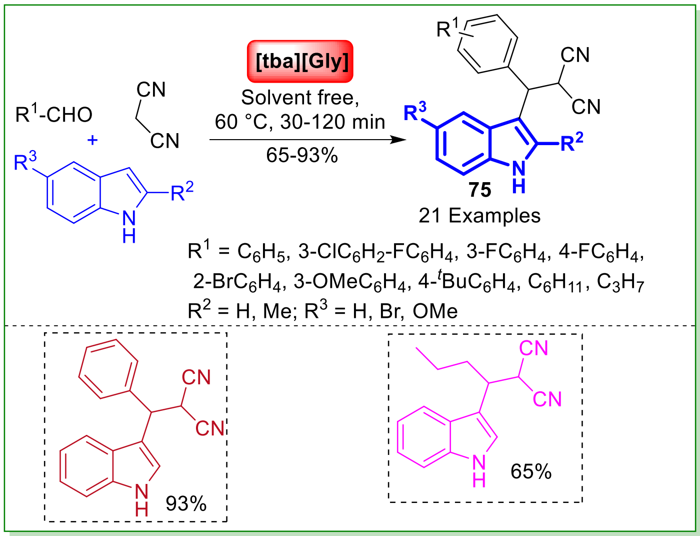


Scheme 59. Synthesis of indole with fused chromenes by using MCR approach.



Scheme 60. Synthesis of indole-based thiazole derivatives.

In 2015, tetrabutylammonium glycinate [TBA][Gly] IL unfolded by Rawat *et al.*[100] as recyclable, and biodegradable organocatalyst for the selective synthesis of 3-substituted indoles **75** (Scheme 61). The interaction of substituted aliphatic or aromatic aldehydes, indoles and malononitrile enabled by [TBA][Gly] IL, resulted in the formation of 3-substituted indoles **75** with high yields (65-93%). Indolyl-4*H*-chromenes were synthesized with remarkable efficiency through the substitution of benzaldehydes with salicylaldehyde, achieved under standardized reaction conditions.



Scheme 61. Synthesis of substituted indoles.

A proposed mechanism for the formation of 3-substituted indole and indol-3-yl-4*H*-chromene, facilitated by the IL [TBA][Gly], is illustrated in Figure 12. The ammonium ion activates the carbonyl group of the aldehyde, while the carboxylate anion deprotonates malononitrile, forming a reactive carbanion. This carbanion then reacts with the activated aldehyde *via* Knoevenagel condensation to yield olefinated intermediates. In path I, [TBA][Gly] promotes the Michael addition of indole to this intermediate, leading to a rearranged 3-substituted indole **75**. In Path II, [TBA][Gly] facilitates a cyclization of the Knoevenagel product to form an iminochromene intermediate, which then undergoes Friedel–Crafts alkylation with indole to afford indol-3-yl-4*H*-chromene.

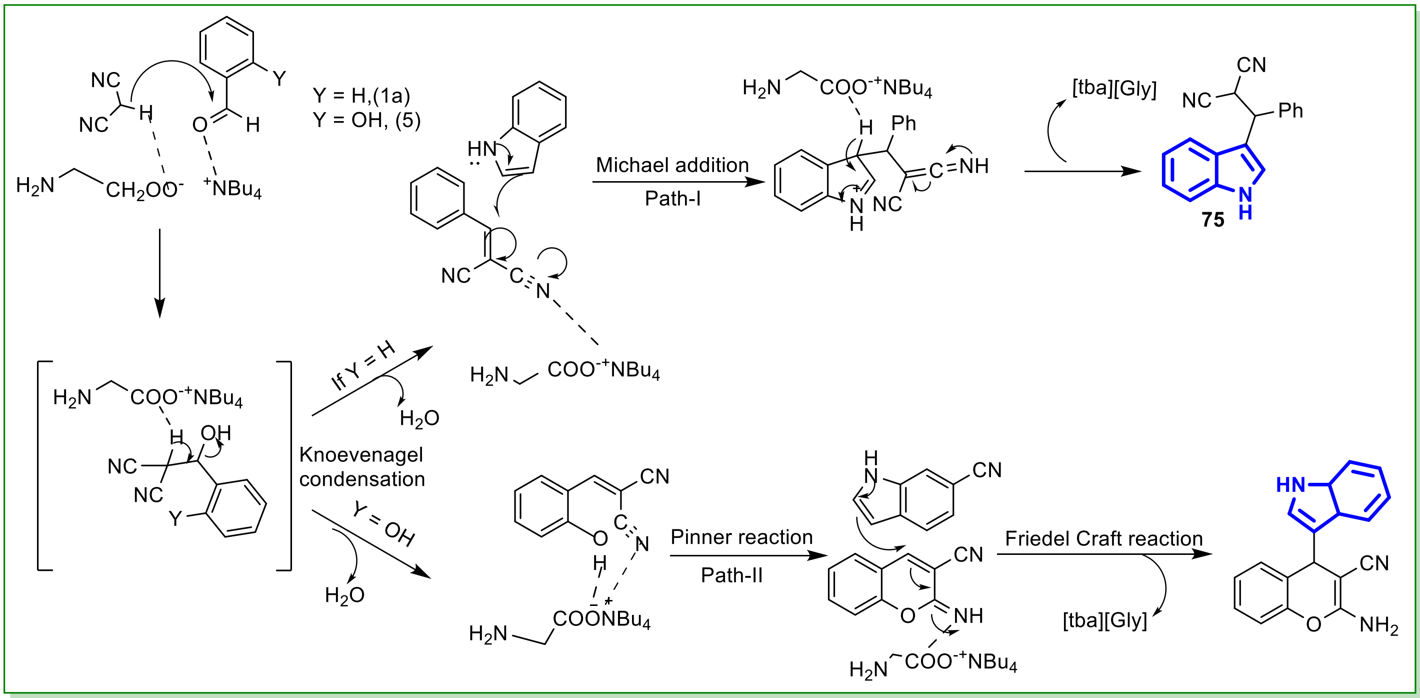
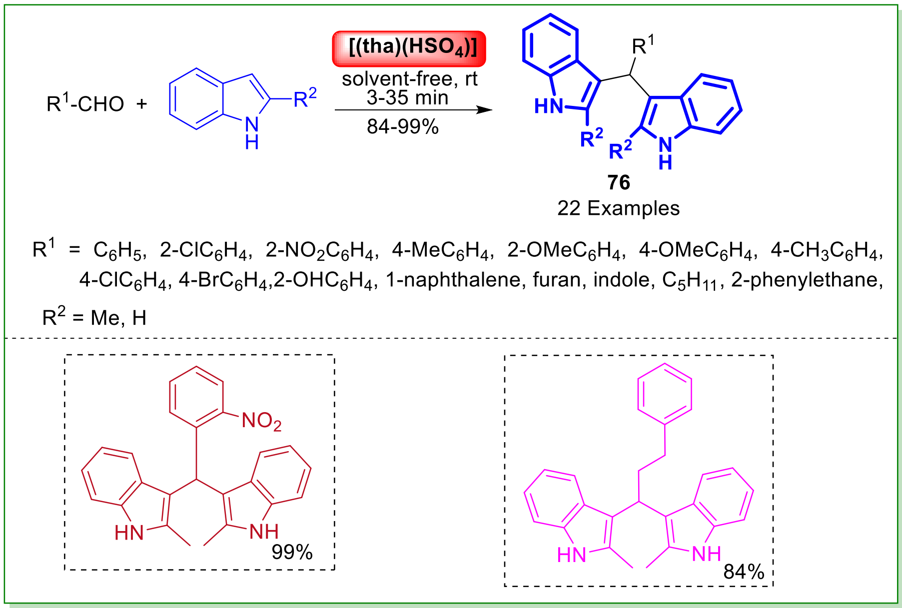


Figure 12. Possible reaction mechanism for the formation of indolyl-4*H*-chromenes.

In 2016, the study by the research group of Honarmand[101] generated [(THA)(HSO_4)] tetrahexylammonium hydrogensulfate as novel nano aliphatic ammonium-based IL (Scheme 63). The [(THA)(HSO_4)] IL was effectively utilized for the synthesis of bis(indolyl)methane derivatives **76** at room temperature under solvent-free conditions. The bis-indole derivatives **76** were achieved in 84-99% yields at room temperature. Total 22 examples were synthesized by the author to check the generality of the protocol. This approach was environmentally friendly, and eliminates the need for organic solvents and costly catalysts.



Scheme 62. Synthesis of bis(indolyl)methanes.

6.1 Comparative study

Table 9 presents a comparison of the performance of different ionic liquids, focusing on reaction time and yield. [EAN] and [(tha)(HSO_4)] demonstrate remarkable efficiency, achieving high yields (83–99%) in mere minutes, underscoring their exceptional catalytic activity. Methyl-tricapryl-ammonium thiosalicylate and [tba acetate] provide impressive yields (84–95%) in less than 40 minutes. [tba][Gly] necessitates extended durations (up to 2 hours) while achieving moderate to good yields. Conversely, [Bu_4NBr_3] demonstrates the lowest efficiency, requiring as much as 15 hours and achieving yields of only 60–80%, which suggests slower kinetics. In summary, acidic and hydrogen bond-donating ILs demonstrate superior performance in terms of reactivity and efficiency compared to other types.

Table 9. Comparison of ILs with respect to time and yield of reaction

Scheme	ILs	Time	Yields
57.	[Bu_4NBr_3] (Tetrabutylammonium tribromide)	1-15 h	60-80%
58.	[EAN] (Ethylammonium Nitrate)	1-12 min	83-95%
59.	Methyl-tricapryl-ammoniumthio-salicylate	25-40 min	85-95%
60.	[tba acetate] Tetrabutylammonium acetate)	15-20 min	84-95%
61.	[tba][Gly] (Tetrabutylammonium glycinate)	30-120 min	65-93%
62.	[(tha)(HSO_4)] (Tris(hydroxymethyl)methane ammonium hydrogensulphate)	3-35 min	84-99%

6.2 Reusability study

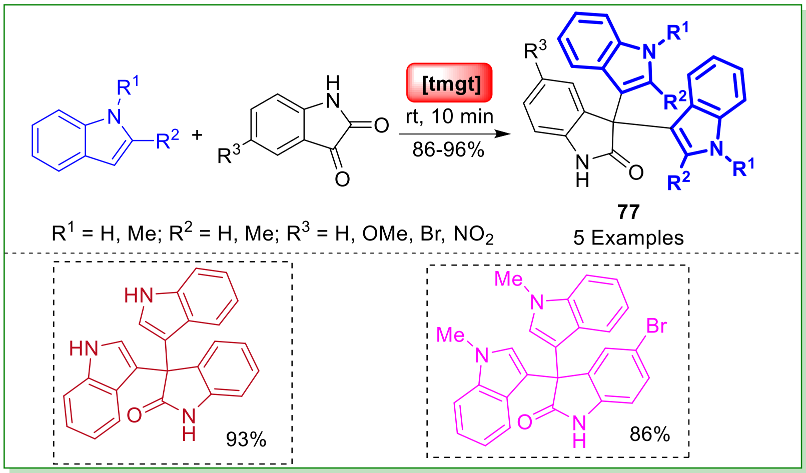
The table (Table 10) demonstrates outstanding recyclability for all ILs, with [(tha)(HSO_4)] attaining the highest yields (96–98%) across five cycles. [EAN], [tba acetate], and [tba][Gly] continue to demonstrate robust performance, achieving results between 92% and 95%. Methyl-tricapryl-ammonium thiosalicylate demonstrates slightly reduced yields while maintaining effectiveness across six cycles, suggesting commendable catalytic stability.

Table 10. Recyclability data of ILs

Scheme	ILs	No of cycles	Yields
58.	[EAN]	5	93-95%
59.	Methyltricaprylammonium thiosalicylate	6	85-90%
60.	[tba acetate]	4	92-95%
61.	[tba][Gly]	6	92-93%
62.	[(tha)(HSO_4)]	5	96-98%

7.0 Methods assisted by miscellaneous-based ILs

In 2010, Rad-Moghadam *et al.*[102] investigated three ILs such as [BMIM][BF_4], (TMGT), and TMGTf in the synthesis of 3-indolyl-3-hydroxyindolin-2-ones **77**. These ILs were evaluated for their efficacy as solvents in the 3-indolylation of isatins. From the investigated ILs, TMGT promotes additional reactions through Friedel-Crafts substitution, leading to the formation of symmetrical 3,3-di(indol-3-yl)indolin-2-ones **77** (Scheme 63). A total of five examples of indole polymers **77** were obtained with yields ranging from 86% to 96%.



Scheme 63. Synthesis of symmetrical and unsymmetrical 3,3-di(indolyl)indolin-2-ones.

The reaction mechanism process by which 3,3-di(indol-3-yl)indolin-2-ones are synthesized is depicted in Figure 13. The condensation of isatin with indole derivatives begins with the nucleophilic addition of indole to the ketonic carbonyl group of isatin, forming the intermediate 3-(indol-3-yl)-3-hydroxyindolin-2-one. Subsequent dehydration of this intermediate generates a reactive species, which then undergoes a second nucleophilic addition by another indole molecule, ultimately yielding the final products as 3,3-di(indol-3-yl)indolin-2-ones **77** (Figure 13).

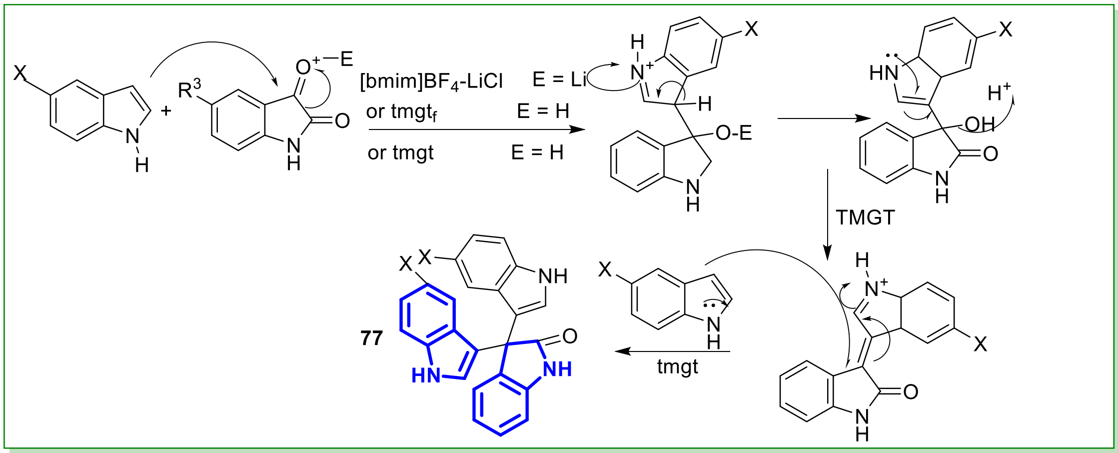
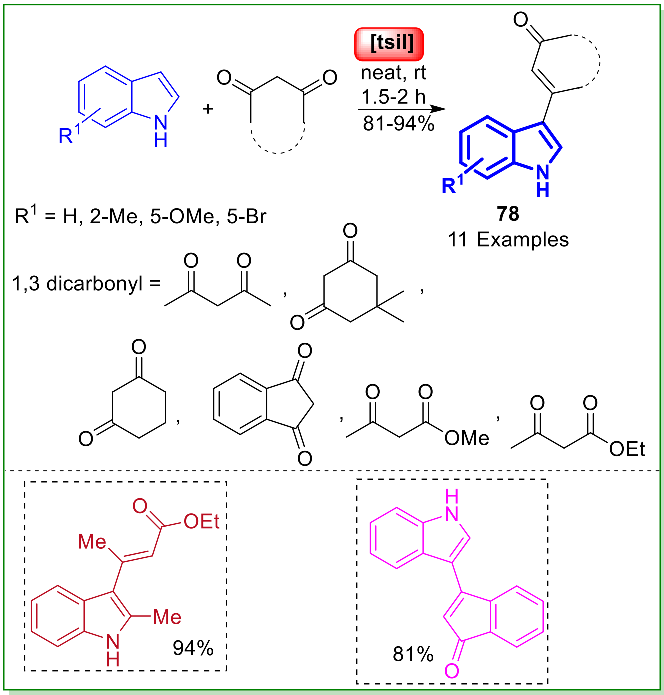


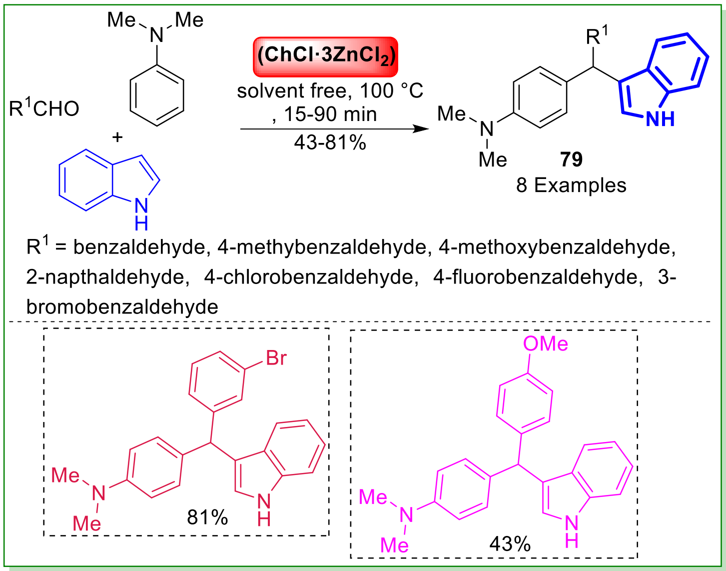
Figure 13. Synthesis of indole based spiro derivatives.

In 2011, the direct alkenylation of indoles at the 3-position using 1,3-dicarbonyl compounds established by Majee's research team[103] under the catalysis of Brønsted acidic ILs. The reaction of substituted indole and carbonyl compounds led to the formation of substituted indole derivatives **78** in 81-94% yield as displayed in Scheme 64. The yields were exceptional; the catalyst can be utilized minimum six times without degrading its catalytic activity.



Scheme 64. Couplings of indoles with 1,3-dicarbonyl compounds.

In 2013, Mousavizadeh and colleagues[104] presented a sustainable approach the synthesis of (indolyl)(aryl)methyl)-*N*,*N*-dimethylanilines **79**, employing choline chloride·3ZnCl$_2$ as an IL. The reaction was executed at a temperature of 100 °C and under conditions devoid of solvent (Scheme 65). The indoles **79** were synthesized with yields ranging from 43% to 81% over a reaction period of 15 to 90 minutes. The catalyst went through four instances of recycling without any obvious change in its activity.



Scheme 65. Construction of (indolyl)(aryl)methyl)-*N,N*-dimethylanilines.

Figure 14 suggests a reasonable synthesis of (indolyl)(aryl)methyl)-*N*,*N*-dimethylaniline. The reaction between aromatic aldehyde and dimethylaniline generates an intermediary by means of the activation of the carbonyl group *via* Lewis acidity of zinc chloride clusters and the development of hydrogen bonding with the hydroxyl group in the choline cation. The resulting chemical (indolyl)(aryl)methyl)-*N*,*N*-dimethylaniline **79** is generated then by adding indole.

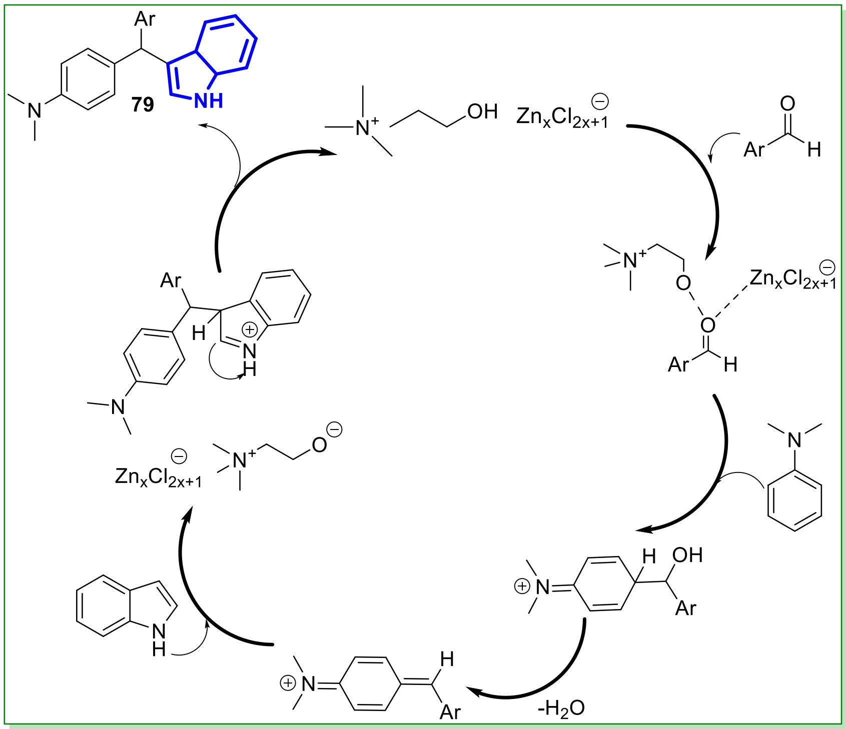
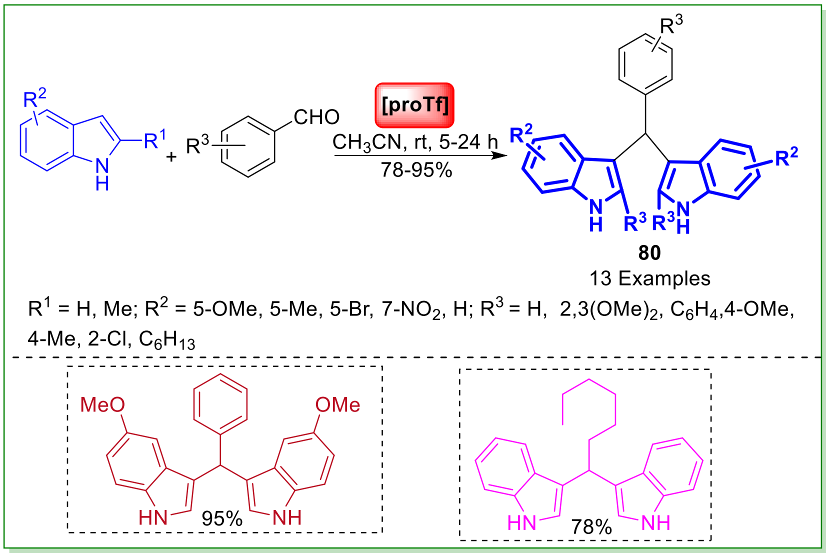


Figure 14. Mechanistic route.

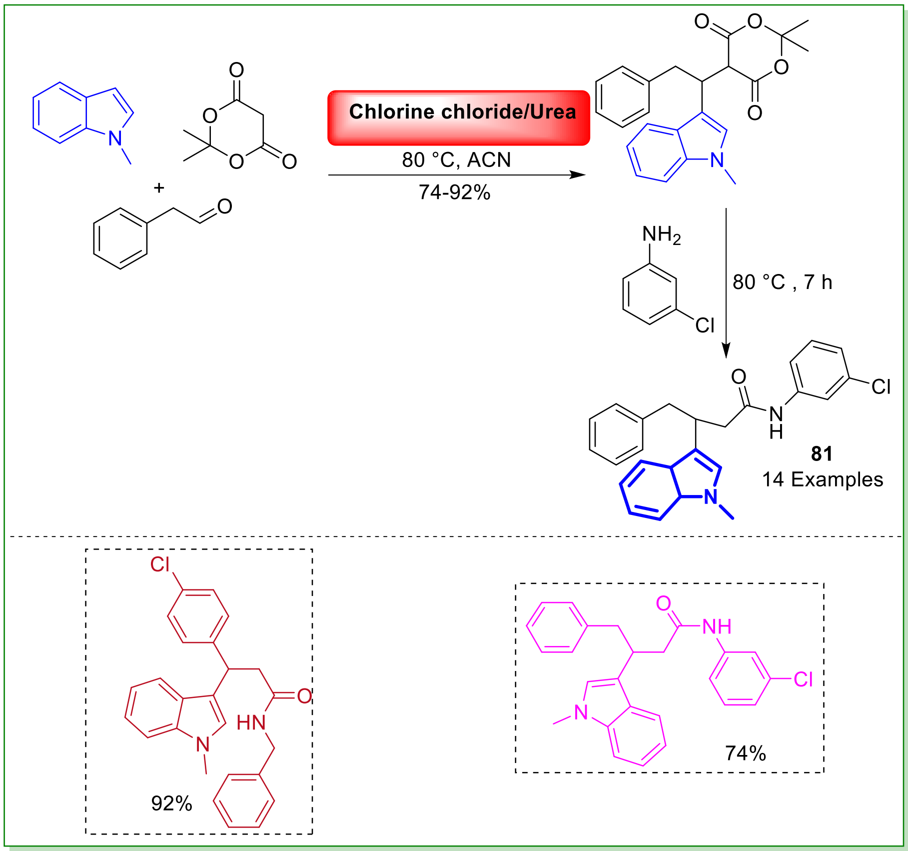
In the following year, Shiri and coworkers[105] synthesized prolinium triflate (ProTf) through the addition of triflic acid to an aqueous solution of L-proline, as depicted in Scheme 66. The reaction enabled the synthesis of bis-indole derivatives **80**, achieving yields between 78% and 95% over a period of 5 to 24 hours. The ILs served as a catalyst, facilitating the condensation of indoles with aldehydes or ketones in an aqueous medium, resulting in the efficient synthesis of a series of bisindolylmethanes **80** with high yields. The method demonstrates tolerance for a range of electron-donating and -withdrawing groups, highlighting its versatility.



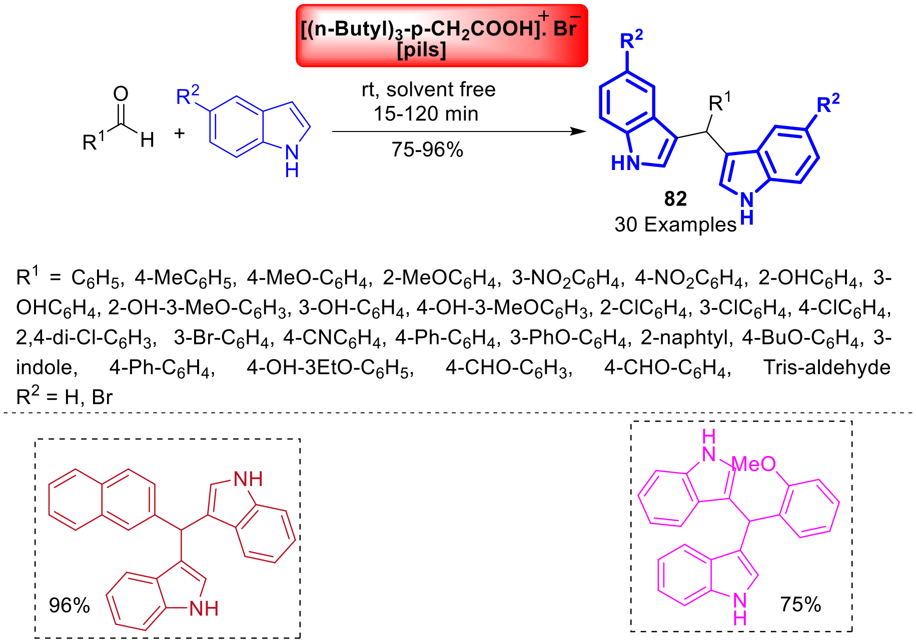
Scheme 66. Synthesis of bis-indoles.

A sequential three-component reaction involving aromatic aldehydes, Meldrum's acid, and *N*-methyl indole, utilizing choline chloride/urea ILs as a green catalyst, was reported by the research group of Kumar.[106] A number of indole-3-propanamide derivatives **81** were synthesized with good to excellent yields (74-92%) in this one-pot multicomponent process (Scheme 67). This technology presents multiple advantages, including rapid response, straightforward isolation, and operational simplicity, rendering it a valuable and appealing choice for the library development of indole-3-propanamides in drug discovery.

Khazaei's research team[107] developed a straightforward green synthesis of bis(indolyl)methanes **82** entailed the interaction of aldehydes with indole utilizing a phosphonium salt IL as the catalyst (Scheme 68). The synthesized compounds 94 were acquired with high yields (75%-96%) at room temperature. A varied collection of compounds was acquired within a reaction time of 15-20 minutes. This methodology presents several benefits, including facile experimental protocols, short reaction durations (15-120 minutes), elevated product yields of 95%, a non-toxic catalyst, and the elimination of classical solvents.



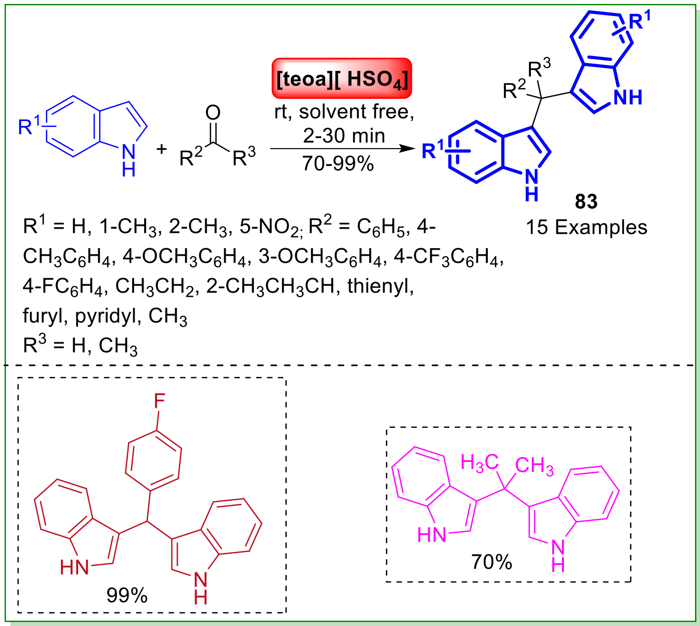
Scheme 67. One-pot synthesis of indole-3-propanamide derivatives.



R^1 = C_6H_5, 4-MeC_6H_5, 4-MeO-C_6H_4, 2-MeOC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-OHC_6H_4, 3-OHC_6H_4, 2-OH-3-MeO-C_6H_3, 3-OH-C_6H_4, 4-OH-3-MeOC_6H_3, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-di-Cl-C_6H_3, 3-Br-C_6H_4, 4-CNC_6H_4, 4-Ph-C_6H_4, 3-PhO-C_6H_4, 2-naphtyl, 4-BuO-C_6H_4, 3-indole, 4-Ph-C_6H_4, 4-OH-3EtO-C_6H_5, 4-CHO-C_6H_3, 4-CHO-C_6H_4, Tris-aldehyde
R^2 = H, Br

Scheme 68. Synthesis of bis(indolyl)methanes.

In 2014, Ying and colleagues[108] developed novel acidic ILs derived from triethanolamine (TEA), which serves as an effective catalyst for the synthesis of bis-indolylmethanes **83** at ambient temperature under solvent-free conditions. From the investigated ILs, [TEOA][HSO_4] exhibited the most superior catalytic performance. The methodology asserts its eco-friendliness and is relevant to a wide array of aldehydes and ketones that engage in reactions with indole and its substituted derivatives. Aldehydes equipped with electron withdrawing groups undergo faster reaction and yields highest. Hetero aromatic aldehydes took relatively longer time with lower yields (Scheme 69).



Scheme 69. Solvent-free synthesis of bis-indolylmethanes.

The role of [TEOA][HSO_4] in accelerating the formation of BIMs can be elucidated by the tentative mechanism (Figure 15). Initially, the quadruple hydrogen-bonding interactions may activate the carbonyl group and enhance the electrophilicity of the carbon atom within the carbonyl group. Conversely, following the production of intermediate, the quadruple hydrogen-bonding interactions may expedite the release of water molecules to generate intermediate followed by the formation of bs-indole derivatives **83**.

In 2016, Hu and colleagues[109] documented the synthesis of a 4-methylbenzenesulfonic acid supported on silica gel (IL-SO_3H-SiO_2). The efficacy of IL was tested for the Fischer synthesis of indoles **84**, utilizing phenylhydrazines with ketones/aldehydes. This diverse catalyst demonstrated remarkable efficiency and could be readily recovered through straightforward filtration, allowing for multiple reuses without any notable decline in catalytic performance. A series of 12 derivatives of indoles were synthesised in high yields (84-96%) (Scheme 70).

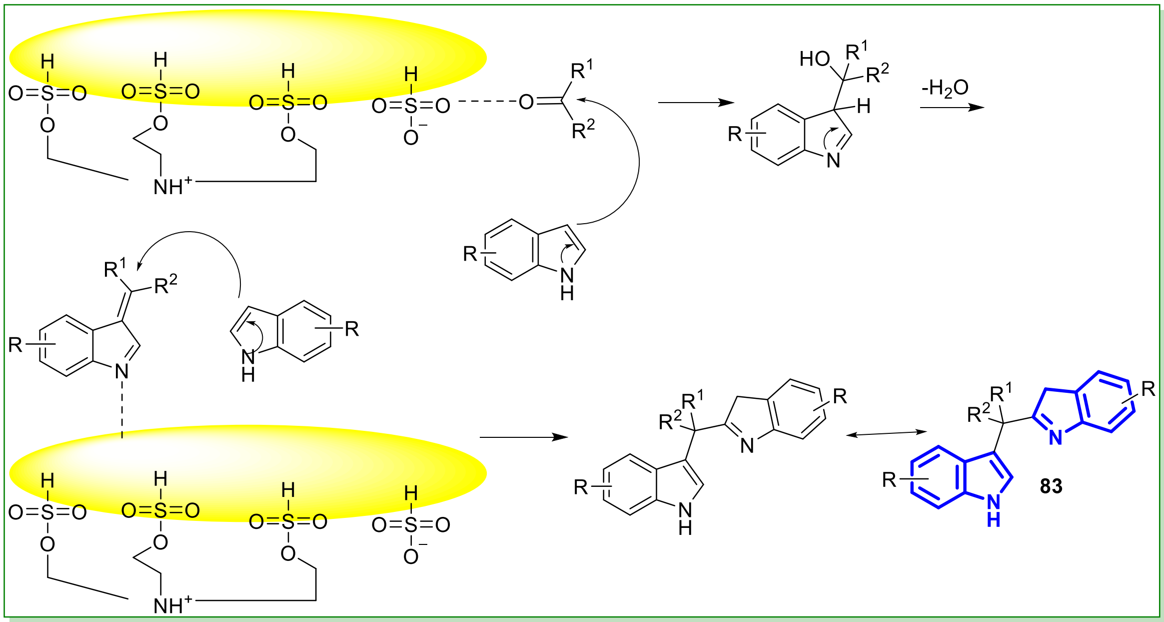
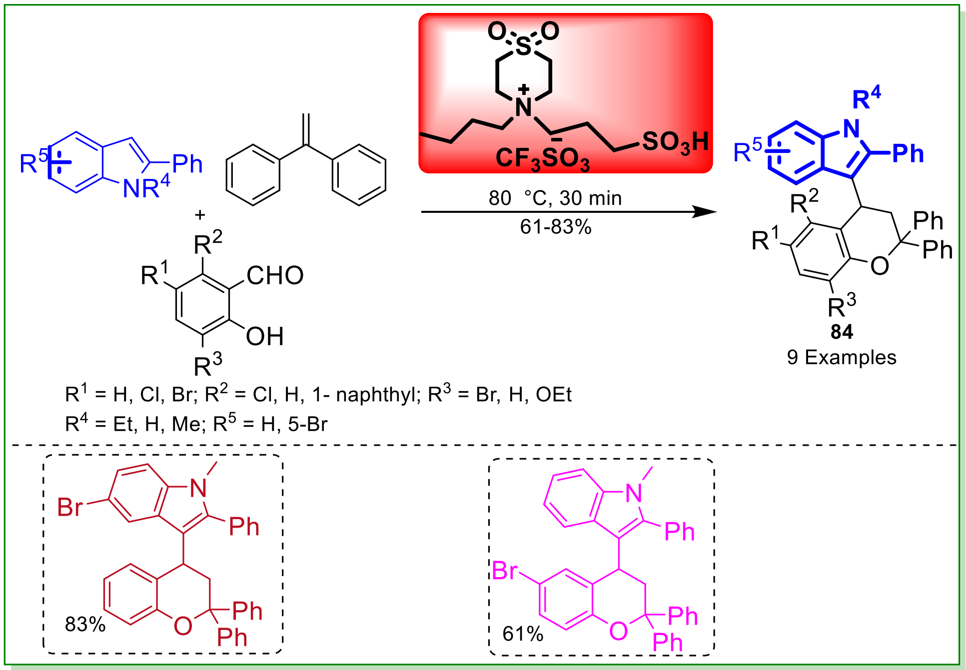
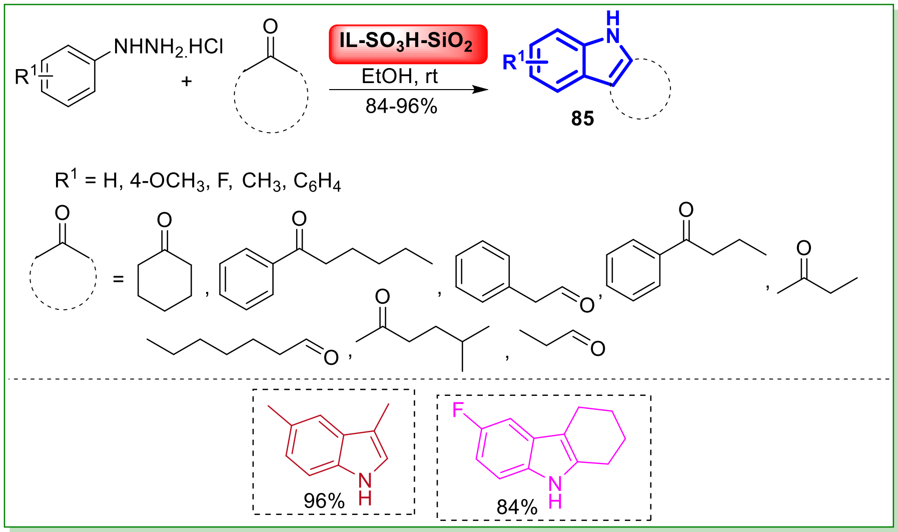


Figure 15. Reaction mechanism for the synthesis of bis-indolylmethanes.



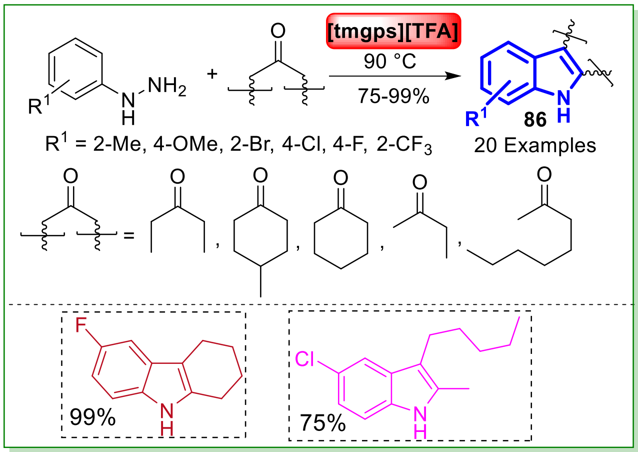
Scheme 70. Three-component reactions of aromatic aldehydes, 1,1-diarylethylenes and indoles.

In the following year, IL on silica gel (IL-SO$_3$H-SiO$_2$) was developed by the research group of Hu.[110] Subsequently, IL-SO$_3$H-SiO$_2$ was employed as a heterogeneous catalyst for the synthesis of indoles **85** through the one-pot Fischer reaction involving ketones/aldehydes and phenyl hydrazines as delineated in Scheme 71. The heterogeneous catalyst can be conveniently recovered through filtration and can be employed repeatedly with minimal degradation of its catalytic efficacy.



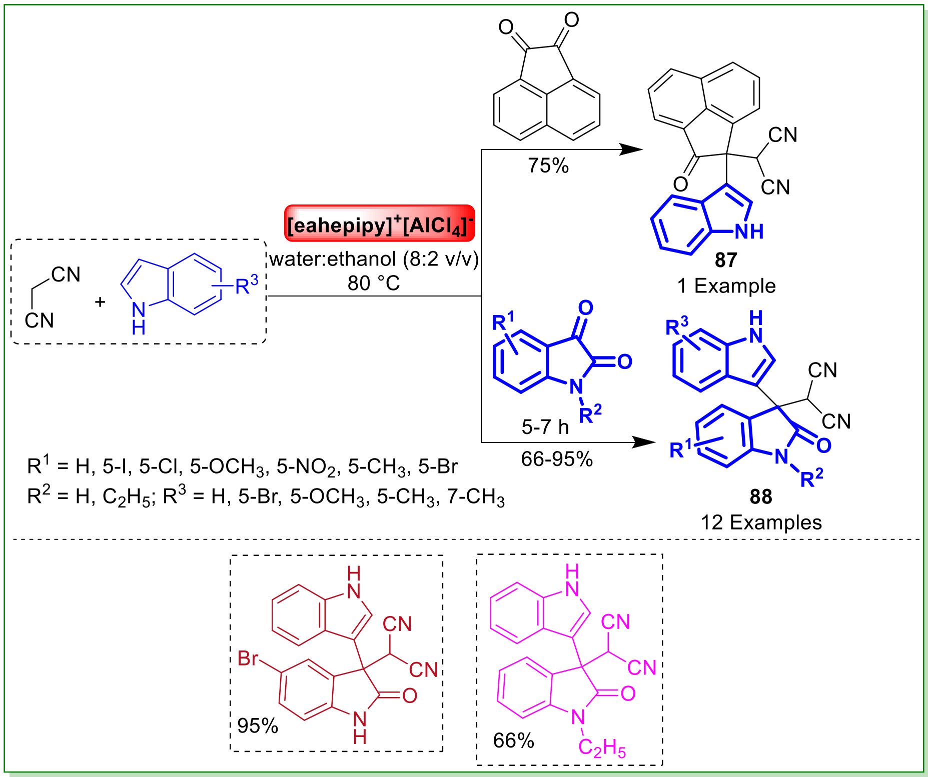
Scheme 71. Synthesis of fused indole derivatives.

Neuhaus and team[111] developed sustainable [TMGHPS][TFA] IL, employing it as both a catalyst and medium for the synthesis of indole products **86** through the Fischer indole synthesis involving a diverse array of ketones and hydrazines. High yields (75-99%) of indole compounds **86** were achieved with minimal use of organic solvent. A total of 20 indole products **86** were prepared. Mostly all the substituted reactants provide satisfactory yields except for highly deactivated hydrazines, which provided mostly complex mixtures (Scheme 72).



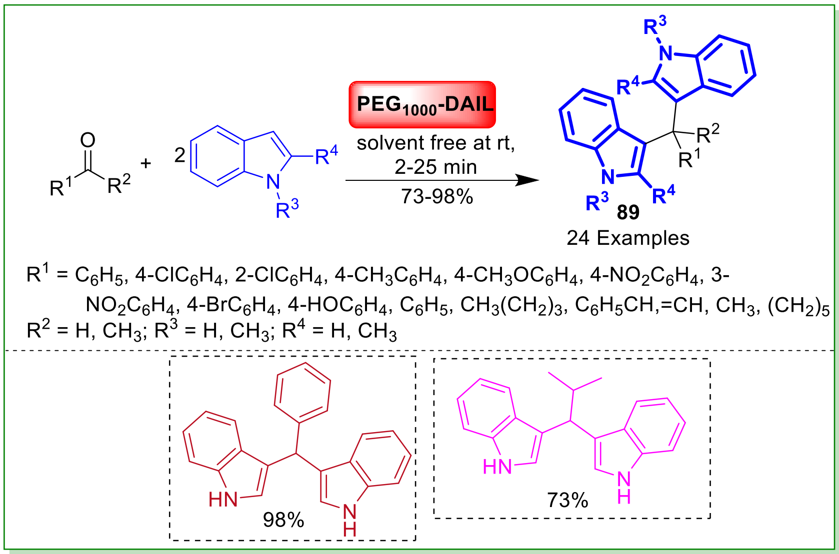
Scheme 72. Synthesis of fused and tethered indole derivatives.

In 2017, Dige and co-workers[112] developed a TSIL, [EAHEPiPY]$^+$[AlCl$_4$]$^-$), tailored for catalytic applications. They evaluated its performance in a multicomponent reaction involving isatin, malononitrile and indole which proceeded *via* a tandem Knoevenagel/Michael addition pathway to produce 3,3-disubstituted oxindoles **87-88.** The reaction, conducted at 80 °C in a water–ethanol mixture (80:20), delivered excellent yields ranging from 66% to 95% (Scheme 73).



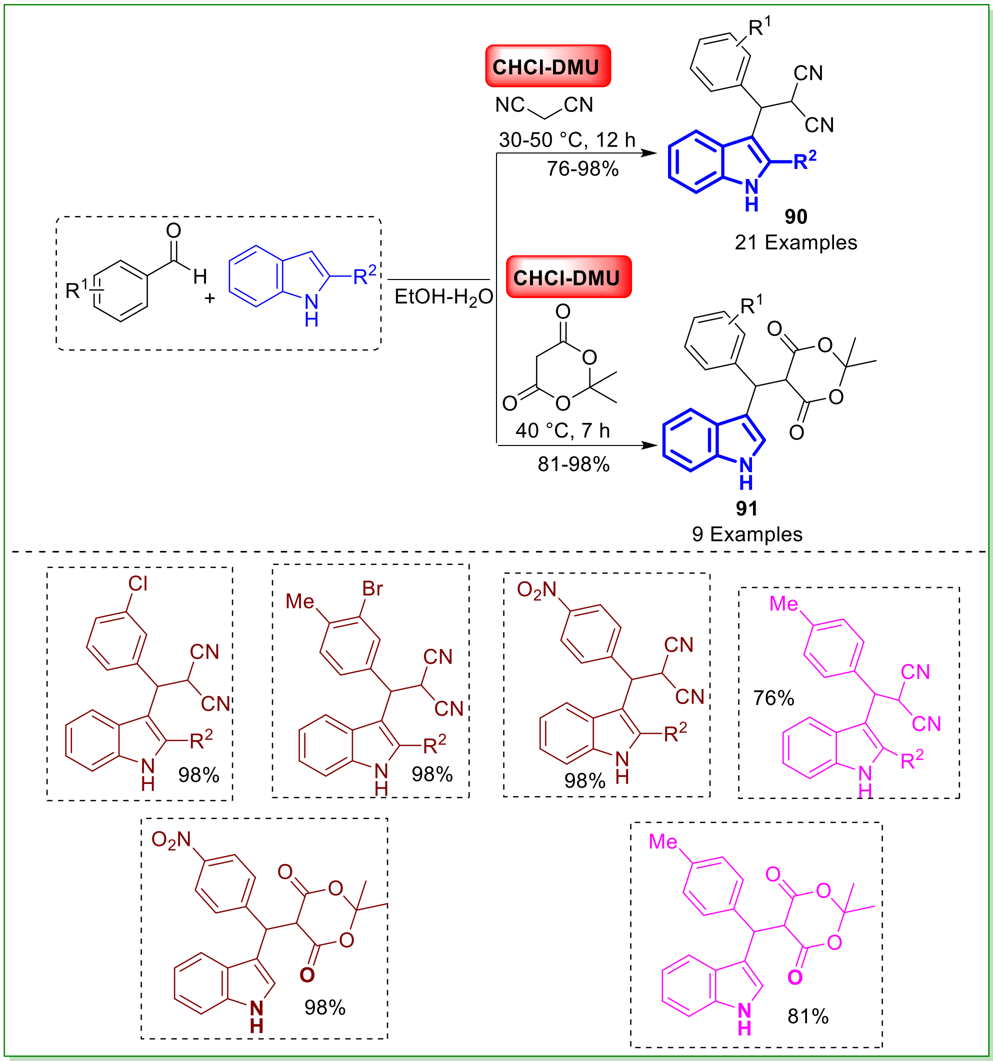
Scheme 73. Synthesis of 3,3-disubstituted oxindoles.

In 2017, Ren and colleagues[113] showcased a solvent-free formation of bis(indolyl)methanes **89** through the treatment of aldehydes/ketones with indoles facilitated by PEG_{1000}-based IL (PEG_{1000}-DAIL). The adaptability of the methodology was demonstrated through the reaction of diverse aromatic aldehydes with multiple types of indoles, resulting in the desired products **89** with improved yields ranging from 73% to 98%. The benzaldehydes featuring electron-donating groups exhibited a prolonged duration compared to their counterparts with electron-withdrawing groups (Scheme 74).



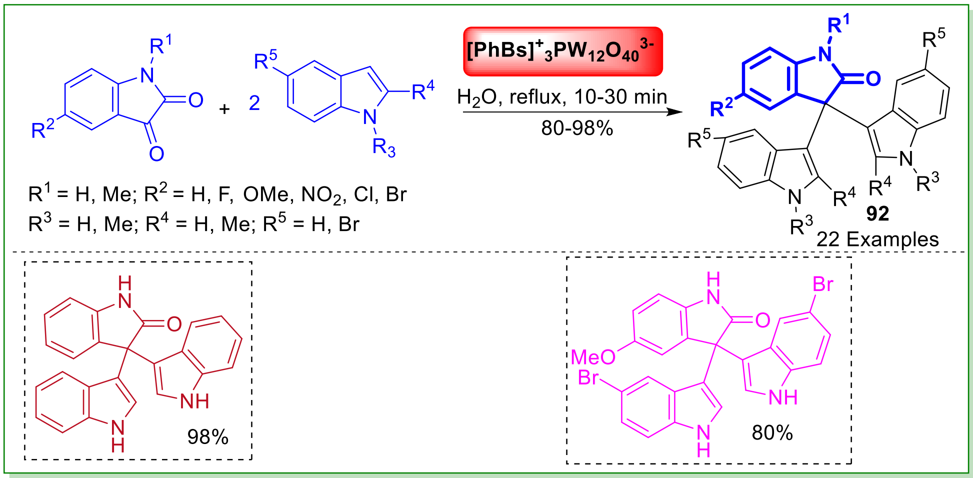
Scheme 74. Synthesis of bis(indolyl)methanes.

In 2018, Chengwei Lv *et al.*[114] developed a green methodology consisting condensation of indole, benzaldehyde, and malononitrile/substituted dimedone (Scheme 75). A strategy utilising catalytic amounts of choline chloride-dimethylurea deep eutectic salts as a cost-effective and safe catalyst was used. The introduction of an appropriate amount of water into the reaction system was found to be critical. This method accommodates variations in all three components to achieve satisfactory yields of 3-substituted indoles **90-91**. In case of malononitrile, the products **90** was obtained in 76-98% yields whereas in case of substituted dimedone, the products **91** were obtained in 81-98% yields.



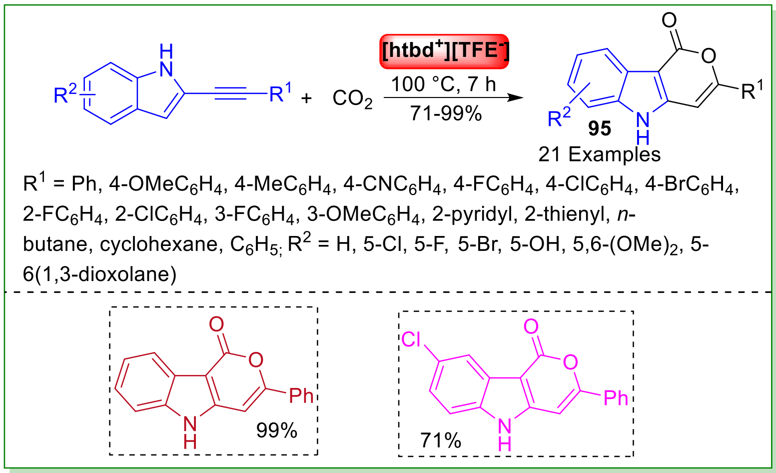
Scheme 75. Synthesis of 3-substituted indoles.

In 2019, a novel $[PhBs]_3^+PW_{12}O_{40}^-$ IL was synthesized and checked by Yazdankisha *et al.*[115] The novel acidic catalyst was tested for its catalytic efficiency and reusability for making 3,3'-diaryloxindole derivatives **92** in water under optimal conditions. A total series of 22 examples (**92**) were developed in higher yields (80-98%). The catalyst shown outstanding activity and was easily separated and reused for up to 8 runs, with minimal drop in efficiency (Scheme 76).



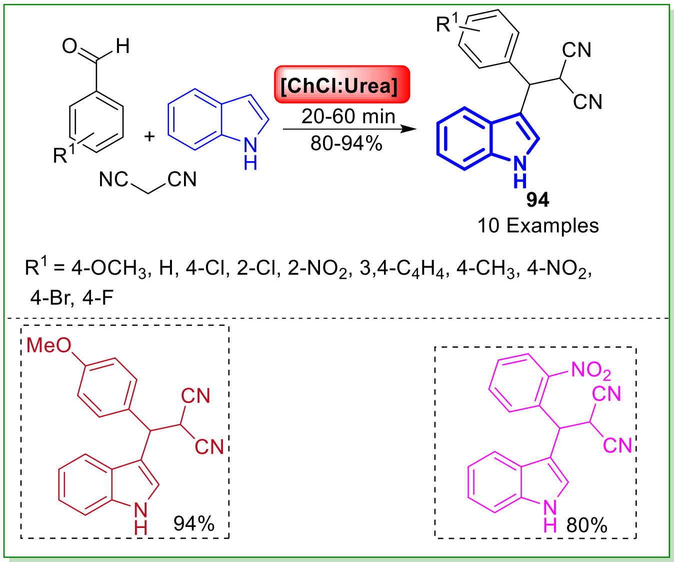
Scheme 76. Efficient synthesis of 3,3-diaryloxindoles.

In that same year, a method was developed by Zhang's research team[116] for the synthesis of pyrano[4,3-*b*]indol-1(5*H*)-ones **93**, employing a protic IL [HTBD$^+$][TFE$^-$] as both the solvent and reaction facilitator. The reactions were carried out under atmospheric pressures of CO$_2$, resulting in the formation of various pyrano[4,3-*b*]indol-1(5*H*)-ones **93** with a range of functionalities, achieving moderate to high yields (71-99%) as illustrated in Scheme 77.



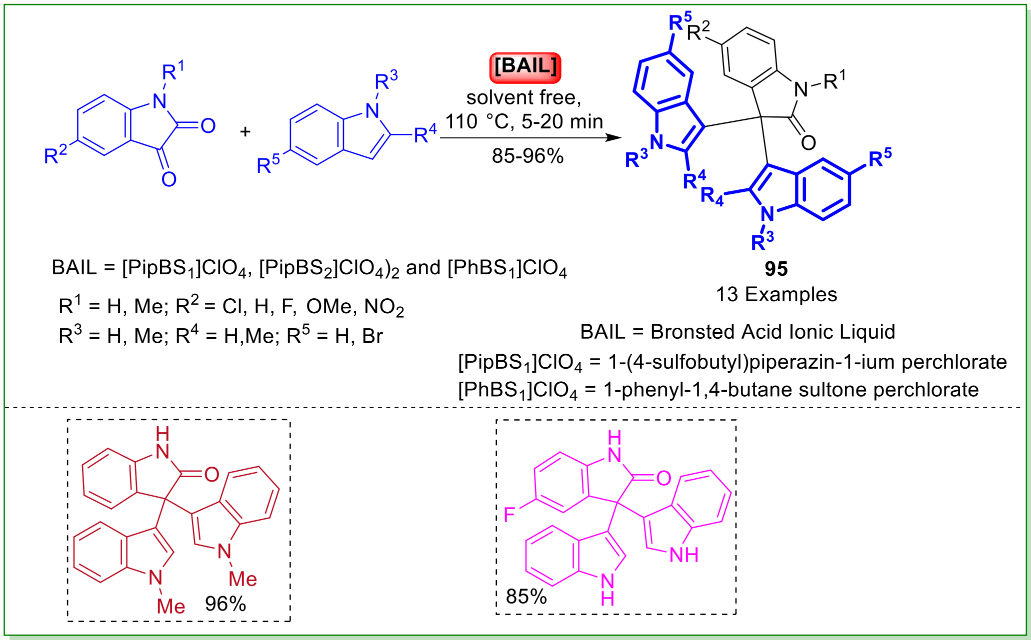
Scheme 77. Efficient synthesis of pyrano[4,3-*b*]indol-1(5*H*)-ones.

In 2021, a method for the formation of indole based molecular hybrids **94** developed by Agrawal *et al.*[116] The reaction of substituted benzaldehydes, malononitrile and indole delivered products **94** in 80-94% yields within 20-60 mins. The utilisation of ChCl:Urea, a biodegradable and cost-effective green solvent, effectively eliminates the need for hazardous organic solvents while also enhancing reusability and supporting sustainable synthesis. Total 10 examples were synthesized by employing electron-donating and -withdrawing groups decorated starting substrates as illustrated in Scheme 78.



Scheme 78. Synthesis of 3-substituted indoles.

The research group of Keshavarz synthesized three novel Brønsted acidic ILs based on 1,4-butane sulfone, utilizing perchlorate as the counter-anion.[117] The reaction involved the ring opening of 1,4-butane sulfone through the utilization of 1,4-dimethylpiperazine/1,10-phenanthroline as sources of nitrogen nucleophiles. Their catalytic efficiency was examined in the context of synthesizing symmetric 3,3′-diaryloxindole compounds **95** (Scheme 79). The introduced acidic ILs have been determined to be entirely eco-friendly, specifically tailored for tasks, and exhibit remarkable catalytic stability. This process yields the target products **95** in brief reaction times (85-96%) with impressive yields ranging from 85% to 96%.



Scheme 79. Synthesis of symmetric 3,3′-diaryloxindoles.

Initially, the carbonyl group of isatin is activated through *o*-protonation by the sulfonic acid functional group of BAIL, resulting in the formation of intermediate. Thereafter, the sulfonate group generated from *o*-protonation facilitates the activation of the nitrogen within indole, leading to the creation of the intermediate indolyl anion. Subsequently, the nucleophilic addition of the indolyl anion to the activated carbonyl group of the intermediate results in the formation of a another intermediate. Ultimately, the Michael addition of an additional indole reactant to the intermediate, accompanied by subsequent protonation and deprotonation, is enabled by both sulfonic and sulfonate forms of BAIL, resulting in the formation of the end product **96** (Figure 16).

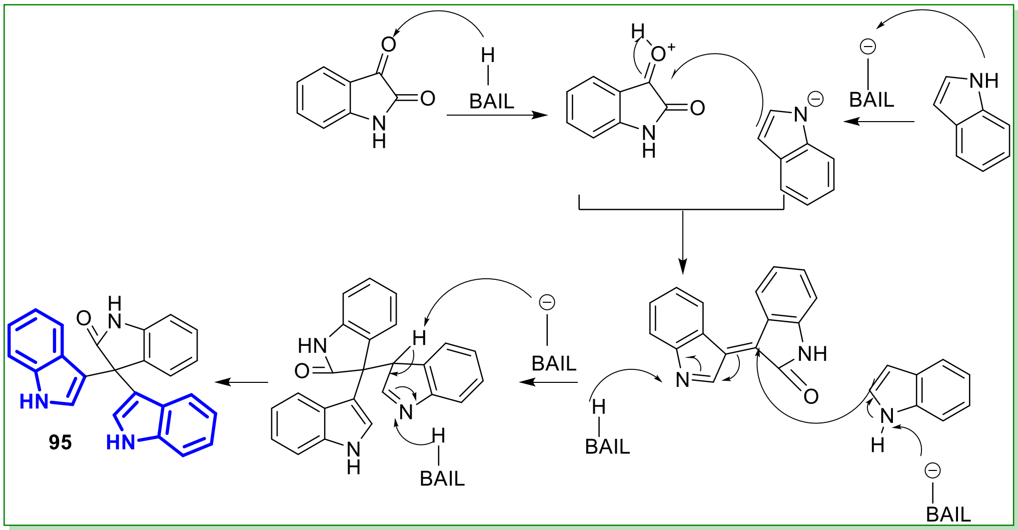
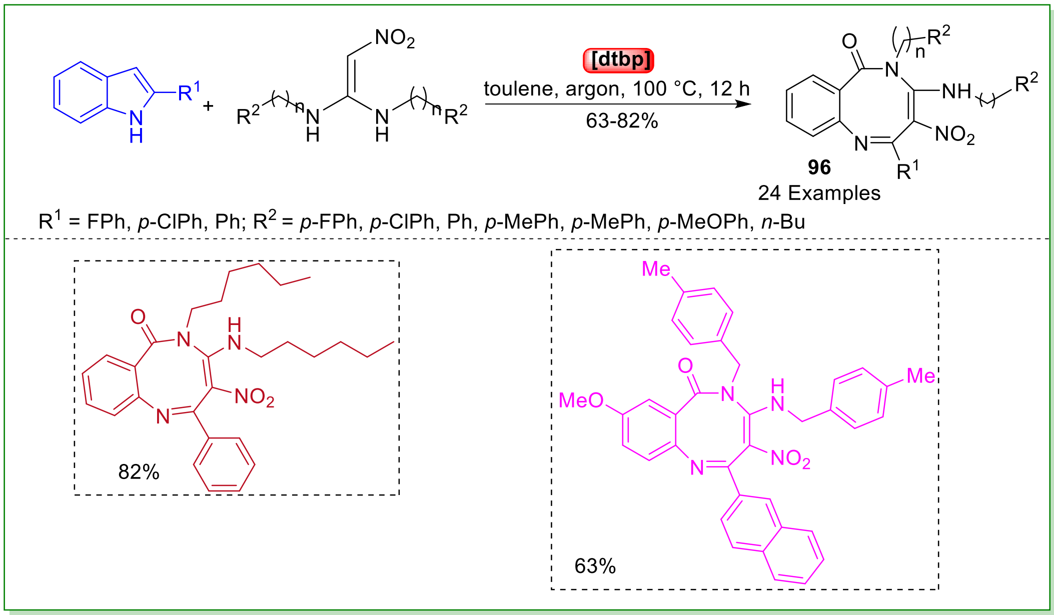


Figure 16. Putative reaction mechanism for the synthesis of bis-indole based spiro derivative.



Scheme 80. Synthesis of benzo[*b*][1,5]diazocin-6(5*H*)-one.

In 2023, Yan *et al.*[118] reported a method for synthesizing highly functionalized benzo[*b*][1,5]diazocin-6(5*H*)-one derivatives (BDCOs) **96**using 2-aryl-1*H*-indoles and 1,1-enediamines. The reaction sequence involved a regioselective free radical oxidation, followed by 1,2-imine addition, imine–enamine tautomerization, intramolecular cyclization, and ring expansion, as illustrated in Scheme 80. This cascade transformation was efficiently promoted by di-tert-butyl peroxide (DTBP) as the oxidant and anhydrous CuI as the catalyst in a toluene medium, yielding BDCOs **96** with high regioselectivity and good overall yields ranging from 63% to 82%.

7.1 Comparative study

Table 11 provides a comparative analysis of several ionic liquids (ILs) and deep eutectic solvents (DESs) regarding reaction time and yield. Rapid and high-yielding systems encompass [tmgtf], [teoa][HSO_4], PEG1000-DAIL and [BAIL], all achieving yields of 85–99% within minutes, demonstrating exceptional catalytic efficiency. Likewise, [tmghps][TFA] and $ILSO_3H$-SiO_2 give high results (84–99%), albeit without designated durations. Conversely, systems such as [proTf], [$htbd^+$][tfe^-], and [dtbp] di-*tert*-butyl peroxide necessitate extended durations (5–12 hours) with more moderate yields. ChCl-based deep eutectic solvents, such as ChCl/Urea, exhibit intermediate efficiency (74–94%) over extended periods. In general, ionic liquids containing acidic or functionalized groups have superior performance in terms of both reaction rate and yield.

Table 11. Comparison of ILs with respect to time and yield of reaction

Scheme	ILs	Time	Yields
63.	[tmgtf] (N,N,N,N-Tetramethylguanidinium triflate)	10 min	86-96%
64.	[tsil] (Task-specific ionic liquid)	1.5-2 h	81-94%
65.	($ChCl\cdot 3ZnCl_2$) (Choline chloride and zinc chloride)	15-90 min	43-81%
66.	[proTf] (Protic ionic liquid trifluoromethanesulfonate anion	5-24 h	78-95%
67.	Choline chloride/Urea	7 h	74-92%
68.	[(*n*-Butyl)$_3$-*p*-CH_2COOH]$^+$.Br^-[pils] (Tributyl(carboxymethyl)phosphonium) Protic Ionic Liquids	15-120 min	75-96%
69.	[teoa][HSO_4] (Triethylammonium hydrogen sulfate)	2-30 min	70-99%
70.	Sulfonyl-containing BAIL	30 min	61-83%
71.	$ILSO_3H$-SiO_2 (Silica-immobilized sulfonic acid-functionalized ionic liquid)		84-96%
72.	[tmghps][TFA] (Ttetramethylguanidinium propanesulfonic acid trifluoromethylacetate)		75-99%
73.	[eahepipy]$^+$[$AlCl_4$]$^-$ (1-(Ethylacetoacetate)-1-(2-hydroxyethyl) piperidinium tetrachloroaluminate)	5-7 h	66-95%
74.	PEG_{1000}-DAIL (Poly(ethylene glycol)-linked 1000-based dicationic acidic ionic liquid)	2-25 min	73-98%
75.	CHCl-DMU (Choline chloride *N,N'*-dimethylurea) CHCl-DMU	12 h 7 h	76-98% 81-98%
76.	[PhBs]$^+{}_3PW_{12}O_{40}{}^{3-}$ (Butane mono-sulfoacid-functionalized phenanthrolinum salt of phosphortungstate)	10-30 min	80-98%
77.	[$htbd^+$][tfe^-] (1,5,7-Triazabicyclodec-5-en-5-ium 2,2,2-trifluoroethanolate)	7 h	71-99%
78.	[ChCl:Urea]	20-60 min	80-94%

Table 11. Continued

Scheme	ILs	Time	Yields
79.	[BAIL]	5-20 min	85-96%
80.	[dtbp] (Di-tert-butyl peroxide)	12 h	63-82%

7.2 Reusability study

Table 12 provides a comparative analysis of several ionic liquids (ILs) and deep eutectic solvents (DESs) regarding reaction time and yield. Rapid and high-yielding systems encompass [tmgtf], [teoa][HSO_4], PEG1000-DAIL, and [bail], all achieving yields of 85–99% within minutes, demonstrating exceptional catalytic efficiency. Likewise, [tmghps][TFA] and $ILSO_3H$-SiO_2 give high results (84–99%), albeit without designated durations. Conversely, systems such as [proTf], [htbd$^+$][tfe$^-$], and [dtbp] necessitate extended durations (5–12 hours) with more moderate yields. ChCl-based deep eutectic solvents, such as ChCl/Urea, exhibit intermediate efficiency (74–94%) over extended periods. In general, ionic liquids containing acidic or functionalized groups have superior performance in terms of both reaction rate and yield.

Table 12. Recyclability data of ILs

Scheme	ILs	No of cycles	Yields
65.	($ChCl_3.ZnCl_2$)	4	71-77%
69.	[teoa][HSO_4]	5	89-92%
71.	$ILSO_3H$-SiO_2	6	91-94%
72.	[tmghps][TFA]	10	20-98%
75.	CHCl-DMU	3	81-97%
76.	$[PhBs]^{+}{}_3PW_{12}O_{40}{}^{3-}$	8	93-98%
79.	[BAIL]	6	88-95%

8.0. Conclusions

In recent years, ILs have emerged as a pivotal element in organic chemistry and synthesis, attributed to their exceptional extensive surface area, catalytic activity, minimal toxicity, and the convenience of retrieval and reuse. IL has shown considerable significance in the synthesis of indole derivatives, with a wide range of applications. Indole derivatives have demonstrated significant applicability in biological and materials research due to their diverse functional properties. Utilizing IL as a catalyst and solvent, the following compounds have been synthesized: Substituted indoles, bis(1*H*-indol-3-yl)methanes, Indoles with isatins, spiro[3*H*-indoles], pyrano[3,2-*b*]indole-3-carbonitriles, chromeno[2,3-*d*]pyrimidine-indoline, 2*H*-indazolo[2,1-*b*]phthalazinetriones, dispirobisoxindole, 5-cyano-3-(4-chlorobuty)indole, 2,3-dimethylindoles, 3-arylselenylindoles, tetrahydrocarbazoles, 2-(indol-3-yl)-thiochroman-4-ones, indeno[1,2-*b*]indole, spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles], indole with fused chromenes, pyrano[4,3-*b*]indol-1(5*H*)-ones, benzo[*b*][1,5]diazocin-6(5*H*)-one derivatives. This review's findings underscore the promise of IL as environmentally benign catalysts for the synthesis of innovative indole-based heterocyclic molecules.

9.0 Future scope

Prior research has suggested that the capability of IL in developing indole-based chemical structures has yet to be investigated. This work offers a thorough examination of the utilization of IL in multicomponent processes and other modern techniques for synthesizing indole scaffolds. The application of IL in the synthesis of indole derivatives is anticipated to produce more favourable and effective results. Our research indicates that IL could possess wide applicability in the development of indole-based frameworks. This study seeks to assist researchers in organic, physical chemistry and nanotechnology in promoting sustainable advancements in both disciplines.

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