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Review

Versatile Use of Para-Toluenesulfonic Acid in Organic Synthesis. A Review

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Abstract: *p*-Toluenesulfonic acid is commercially available, non-toxic, cheap organic compound with robust stability. *p*-Toluenesulfonic acid is solid, non-corrosive and a strong organic acid that can be handled easily. Due to this *p*-toluenesulfonic acid could be the better replacement of other conventional acids like nitric acid, sulfuric acid, perchloric acid and $AlCl_3$ in organic transformations. Moreover, *p*-toluenesulfonic acid could be used synergistically with other mode of catalysis like transition metal catalysis and photocatalysis. In recent years, the use of this solid organic acid in organic and polymer synthesis has grown tremendously. In this review, we present an overview of *p*-toluenesulfonic acid promoted various organic reactions with particular emphasis to the more recently reported methods. In some cases, we also detailed the understanding of the reactions by providing the reaction mechanism. Despite these advances, there are still many opportunities for the development of new reactions using PTSA. Industry and academia have become more conscious to adopt sustainable chemical processes using safer reagents and solvents and the use of PTSA in this context is highly significant. This review will inspire researchers for further reaction development employing *p*-toluenesulfonic acid.

Keywords: *p*-toluenesulfonic acid; tosic acid; catalytic; organic reactions; multicomponent reactions

1. Introduction

p-Toluenesulfonic acid has attracted much attention over the years as a catalyst for various organic transformations due to its superior stability, air and water compatibility, non-toxicity, ease of operation, ready availability, inexpensiveness, and strong organic acidic nature. *p*-Toluenesulfonic acid is an organic compound with molecular formula $CH_3C_6H_4SO_3H$, and it is abbreviated as PTSA, Tosh or *p*-TSA. It is a white solid that is soluble in water, alcohols, and other polar organic solvents. Generally, TsOH refers to the monohydrate, TsOH. H_2O. *p*-Toluenesulfonic acid is a strong organic acid, approximately a million times stronger than benzoic acid. It is one of the few strong acids that is solid and can be conveniently weighed. Unlike other strong mineral acids (especially nitric acid, sulfuric acid, and perchloric acid), TsOH is non-oxidizing. PTSA is an environmentally benign, non-volatile, recyclable solid acid catalyst. Solid acid catalysts have been widely used in different industrial purposes. Still a significant number of acid catalyzed reactions are carried out using conventional acids, such as H_2SO_4 and $AlCl_3$ and the processes are typically associated with problems of high toxicity, corrosion, and use of large amounts of catalyst. So, the replacement of liquid acids with environmentally friendly solid acids is highly desirable.

Herein we wish to demonstrate the application of this versatile and powerful acid in plethora of organic reactions leading to the formation of bioactive molecules and useful building blocks. To the best of our knowledge, so far only one review article is available in the literature, [1] date back to 2011. We believe that this is high time to summarize the application of *p*-toluenesulfonic acid in organic transformations. The review is divided into four section: 1. application of PTSA as a catalyst; 2. application of PTSA as a reagent; 3. application of PTSA in combination with metal salts and other reagents; 4. application of PTSA in ionic liquids

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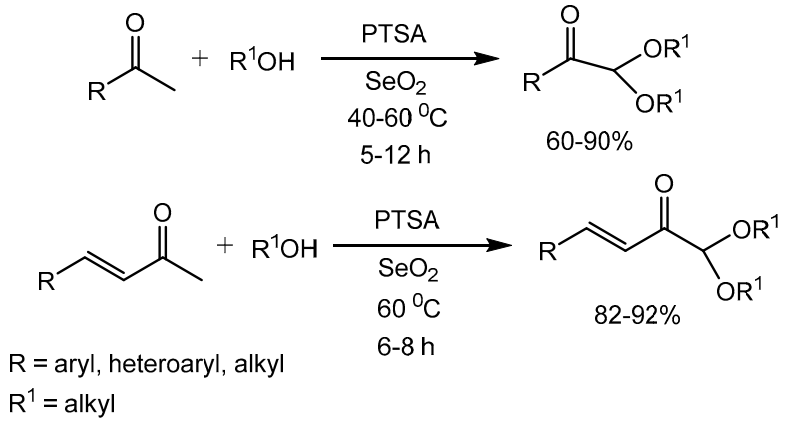
2. Advances of *p*-Toluenesulfonic Acid Promoted Reactions in Organic and Polymer Chemistry

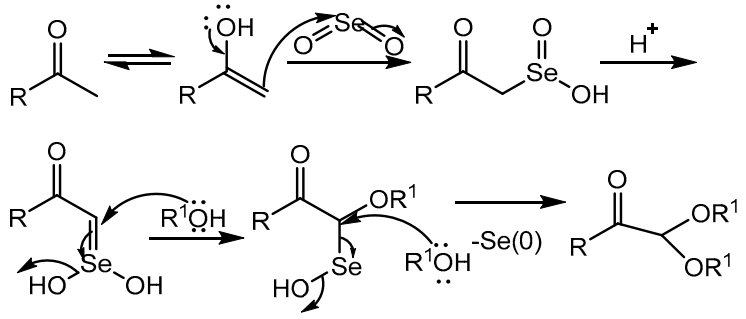
2.1. Application of p-Toluenesulfonic Acid as a Catalyst

Myrboh group [2] reported *p*-toluenesufonic acid (PTSA) catalysed reaction of aryl methyl ketones and alkyl methyl ketones with a variety of aliphatic alcohols in the presence of selenium dioxide leading to the generation of α-ketoacetals in 60-90% yields (Scheme 1). These compounds are considered as important building blocks in organic synthesis and many biologically active compounds are synthesized using α-ketoacetals as key intermediates. The methodology was further extended to the substituted benzylidine acetones to produce the corresponding acetals in 82-92% yields (Scheme 1).



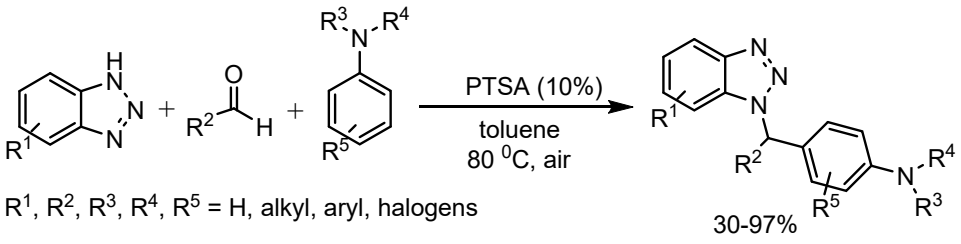
Scheme 1. PTSA catalyzed synthesis of α-ketoacetals using selenium dioxide.

The mechanism of the reaction is proposed (Scheme 2) based on their earlier works [3] on selenium dioxide. The precipitation of elemental selenium occurred in the reaction.



Scheme 2. Plausible mechanism for α-ketoacetal formation.

Xiuling Cui *et al.* [4] described an efficient synthesis of N-alkyl benzotriazoles in 30-97% yields (Scheme 3) via a condensation reaction involving benzotriazoles, aldehydes and tertiary anilines using catalytic amount of *p*-toluenesulfonic acid (PTSA). This methodology showed high atom economy, excellent regioselectivity and good functional group tolerance. Mechanistic investigations indicated that, presumably the reaction moved through an aza quinone methide intermediate.



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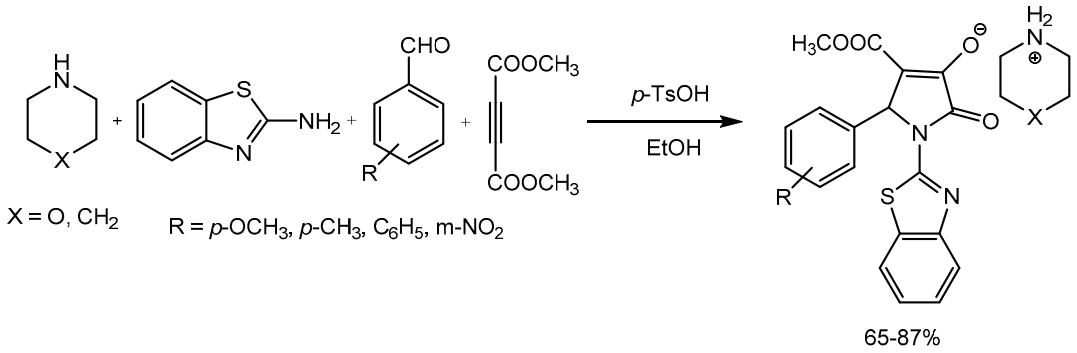
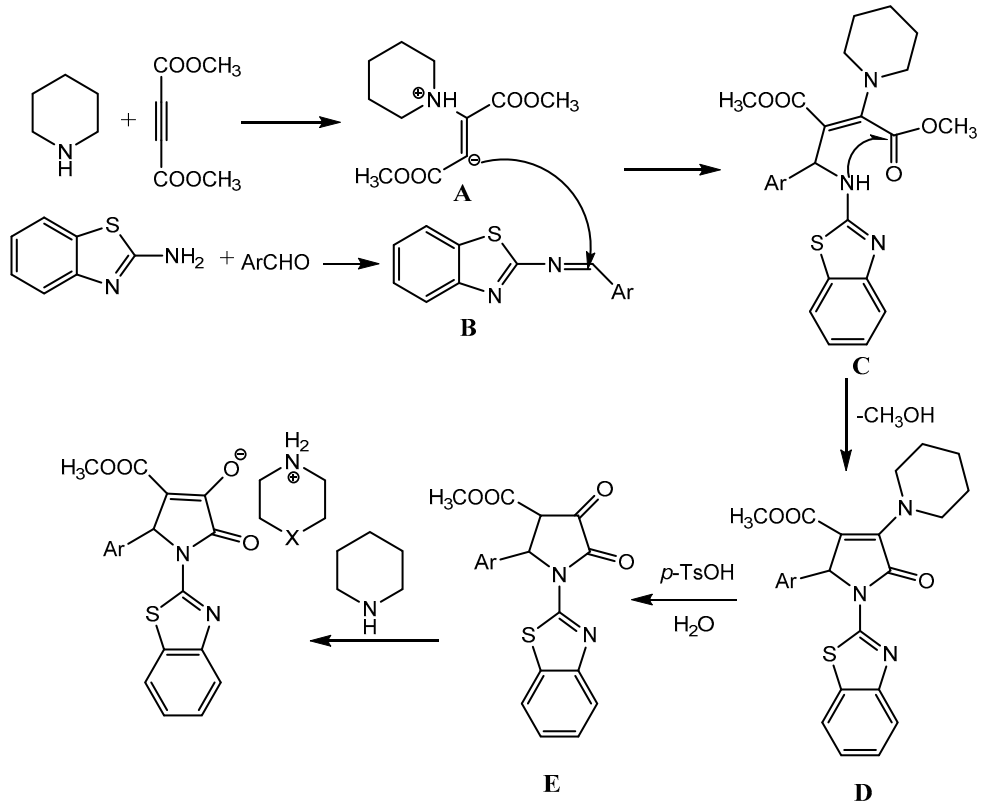
Scheme 3. PTSA catalyzed synthesis of N-alkyl benzotriazoles.

Yan group [5]reported a four-component reaction involving 2-aminobenzothiazole, aromatic aldehydes, acetylenedicarboxylate and piperidine or pyrrolidine in presence of catalytic amount of *p*-toluenesulfonic acid in ethanol resulted the formation of functionalized morpholinium or piperidinium 2-pyrrolidinon-3-olates in 65-87% yields (Scheme 4). This protocol could potentially be used for other complex heterocycles synthesis useful in medicinal chemistry.



Scheme 4. Synthesis of functionalized pyrrolidinones.

In the proposed mechanistic pathway, piperidine reacts with acetylenedicarboxylate to produce 1,3-dipolar intermediate A, which then react with aldimine B to generate intermediate C. Intramolecular cyclization of C to give intermediate D, which in presence of of *p*-toluenesulfonic acid form the product (Scheme 5).



Scheme 5. Proposed mechanism.

Gogoi *et al.* [6] described diastereoselective synthesis of chroman-fused tetralins as B-ring-modified analogues of (±)-brazilin in 75-96% yields. The key step of this transformation is *p*-

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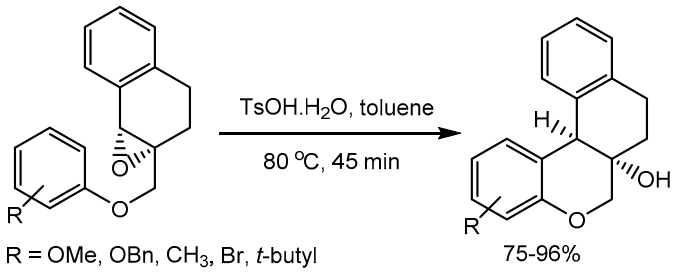
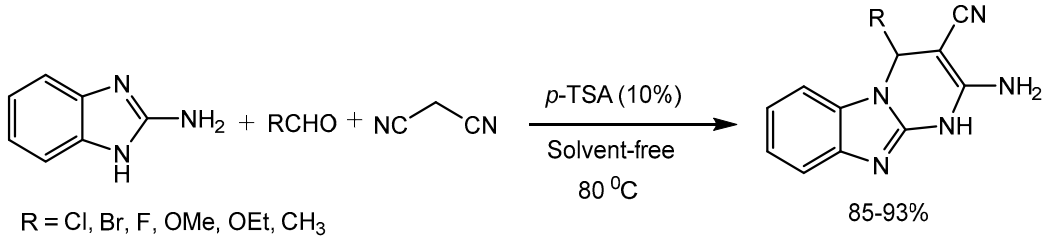
toluenesulfonic acid catalysed intramolecular Friedel–Crafts epoxy–arene cyclization of 1-tetralone-derived glycidyl ethers (Scheme 6). This work can be considered as a useful addition in the diversity-oriented synthesis of natural-product like molecules.



Scheme 6. Synthesis of chroman-fused tetralins.

Jeong research group [7] developed a simple, efficient, and green procedure for one-pot synthesis of 2-amino-4-substituted-1,4- dihydrobenzolo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitriles in 85-93% yields via multi-component condensation of 2-aminobenzimidazole, aldehydes and malononitrile in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 7). Multicomponent reactions (MCRs) have emerged as one of the most powerful tools in organic synthesis. The idea of involving three or more reagents in a one-pot transformation and generating the products with complexity and diversity while incorporating most of the atoms from the reagents in the final structure. MCRs are considered green and sustainable approach as it increases the atom and step economy, decreases the time and labor required in linear syntheses and reduces the waste. Pyrimidinobenzimidazoles motifs have broad range of biologically activities and are present in many pharmaceuticals and agrochemicals. [8]



Scheme 7. PTSA catalysed synthesis of 2-amino-4-substituted-1,4- dihydrobenzolo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitriles.

An interesting mechanism of the reaction was proposed to showcase the catalytic activity of PTSA (Scheme 8). Firstly, a Knoevenagel condensation between malononitrile and aldehyde occurs to form the intermediate **1** in the presence of p-TSA, which immediately reacts with 2-aminobenzimidazole via Michael addition to generate the intermediate **2**. Finally, intramolecular cyclisation of intermediate **2** produces the product.

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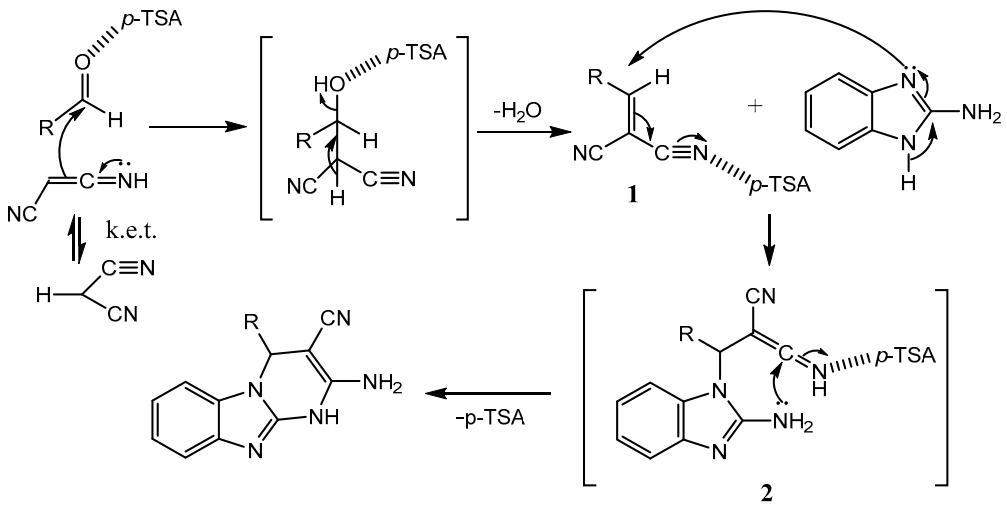
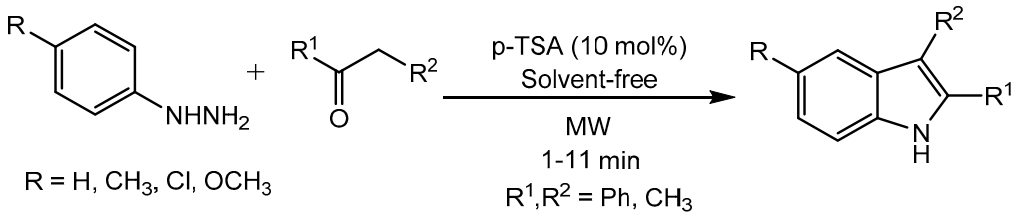


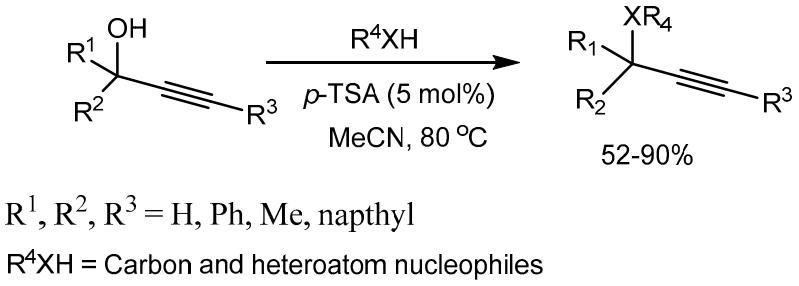
Scheme 8. Plausible mechanism for the catalytic activity of *p*-TSA.

Creencia *et al.* [9] reported *p*-toluenesulfonic acid (*p*-TSA) catalyzed microwave (MW) assisted one-pot synthesis of indole derivatives under green and solvent-free condition. The indole derivatives were prepared from the reaction between phenylhydrazines and enolizable ketones via Fischer-indole process (Scheme 13). Indole moiety is found in different classes of pharmaceutically active molecules.



Scheme 9. *P*-TSA catalysed indole synthesis under microwave irradiation.

Sanz *etal* [10] reported *p*-toluenesulfonic acid catalysed direct nucleophilic substitutions of the hydroxy groups of propargylic alcohols with a large variety of carbon- and heteroatom-centered nucleophiles to generate the products in 52-90% yields under mild conditions (Scheme 10).



Scheme 10. *P*-TSA catalysed propargylic substitution of alkynols with nucleophiles.

The group nicely applied this methodology for direct propargylic substitution of hydroxy groups with carbon-centered nucleophile, like allyltrimethylsilane to synthesize the corresponding 1,5-enynes in 78-80% yields (Scheme 11). This methodology provides an attractive alternative for the construction of sp3 –sp3 carbon–carbon bonds without using any metallic catalyst.

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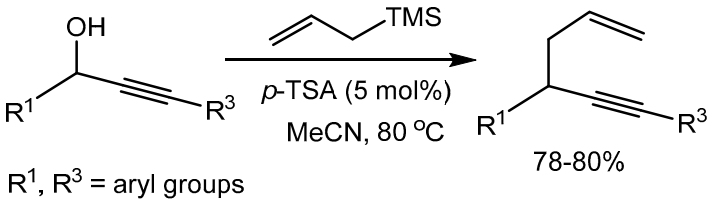
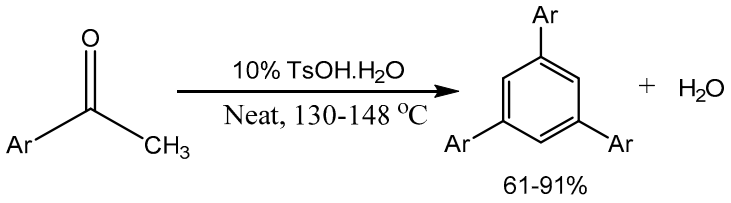


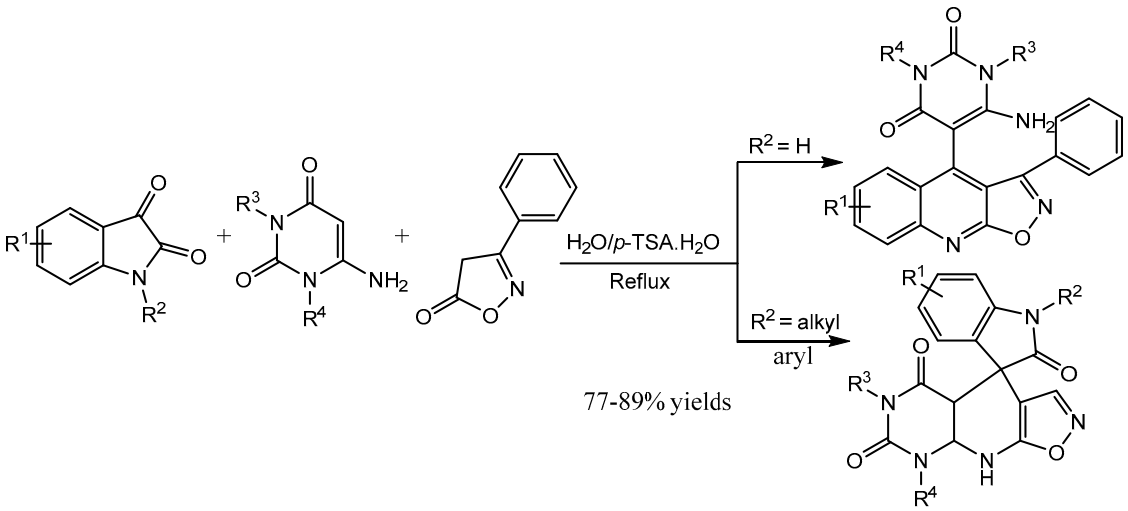
Scheme 11. Propargylic substitution of alkynols with allyltrimethylsilane.

Jia group [11] described a green and economical process of PTSA catalysed cyclotrimerization of aryl methyl ketones for sustainable production of 1,3,5-triarylbenzenes in 61-91% yields (Scheme 12).



Scheme 12. Cyclotrimerization of aryl methyl ketones.

Perumal and co-workers [12] reported a green and efficient one-pot method for the regioselective synthesis of novel 6-amino-5-(3-phenyl-isoxazolo[5,4-*b*]quinolin-4-yl)pyrimidine-2,4(*1H,3H*)-diones and 3-methyl-1-phenyl-4-(3-phenylisoxazolo-[5,4-*b*]quinolin-4-yl)-1*H*-pyrazol-5-amines via the cleavage of the isatin C–N bond followed by a ring expansion reaction using environmentally benign *p*-toluenesulfonic acid as a catalyst (Scheme 13). An exciting feature of this reaction is that the formation of product depends on the nature of the group attached to the isatin ring nitrogen atom. This method is attractive because of short reaction time, an excellent yield (77-89%), practical simplicity and high regioselectivity.



Scheme 13. Synthesis of isoxazoloquinolines and spiroxindoles.

Scott research group [13] developed a green and efficient approach for the synthesis of calix[4]resorcinarenes by the direct reaction of aldehyde and resorcinol in the presence of catalytic amount of *p*-toluenesulfonic acid (Scheme 14). Calix[4]resorcinarenes were prepared in high yield (80-92%) and purity at ambient temperature under solvent-free conditions. Calix[4]resorcinarenes have wide range of application such as supramolecular tectons, DNA recognition, as components in liquid crystals, metal ion extraction agents, selective membranes, gas adsorption, nanotubes, and catalysis.

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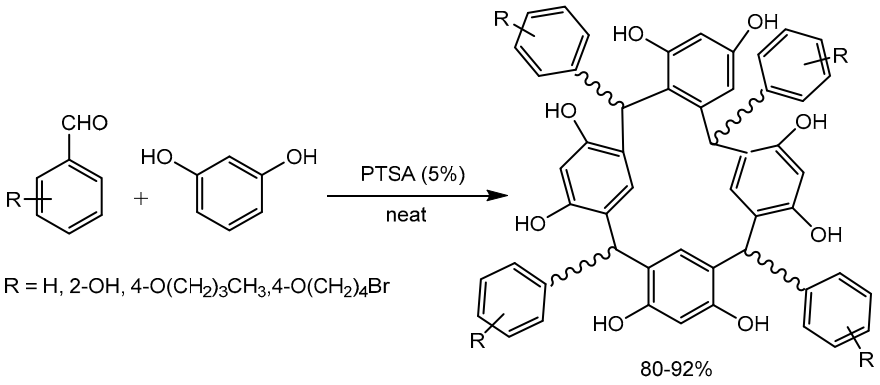
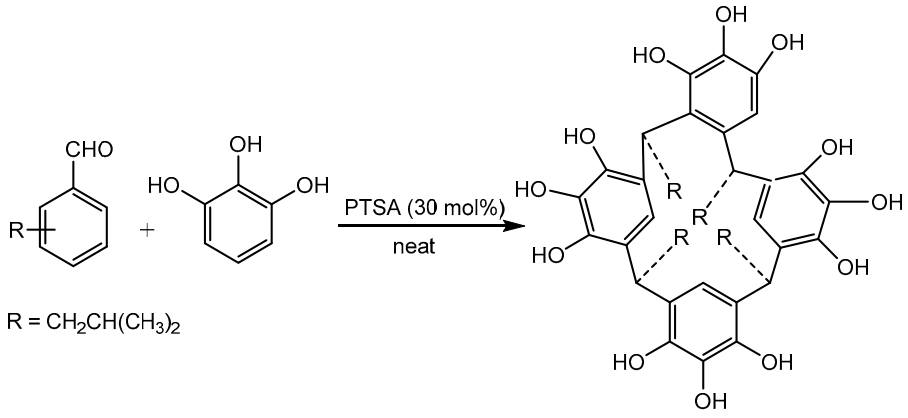


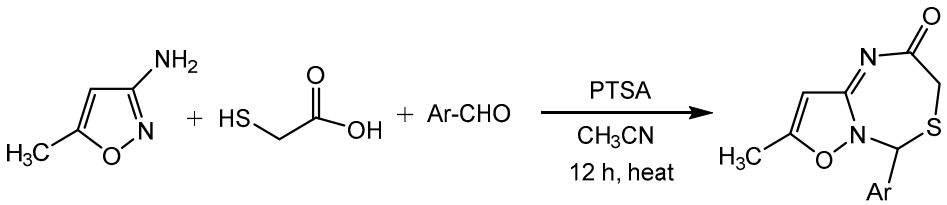
Scheme 14. Synthesis of calix[4]resorcinarenes.

Atwood and coworkers [14] reported a solvent free protocol for the single step direct synthesis of pyrogallol[4]arene from isovaleraldehyde and pyrogallol in the presence of catalytic amount of *p*-toluenesulfonic acid (Scheme 15). The spontaneous self-assembly of these supramolecular building blocks produce nano-sized molecular capsules in the absence of solvent.



Scheme 15. Synthesis of pyrogallol[4]arene.

Rajanarendar group [15] disclosed a green approach for the efficient synthesis of novel isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones by one-pot three-component Domino reaction using *p*-toluene sulfonic acid (PTSA) as a catalyst (Scheme 16). Based on the versatile bioactivities of thiadiazepines and isoxazoles, it is promising that the design of thiadiazepine implanted with isoxazole framework might result in the discovery of new drug candidates.



Scheme 16. PTSA catalysed multi-component synthesis of isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones.

Bras *et al.* [16] reported *p*-toluene sulfonic acid (PTSA) catalysed annulation of various functionalized diarylalkynes for the synthesis of variety of 3-aryl-substituted isocoumarins in 59-89% yields. This metal-free process operated under microwave irradiation (Scheme 17). Isocoumarins are prevalent motifs in many natural products that exhibit a broad range of biological activities.

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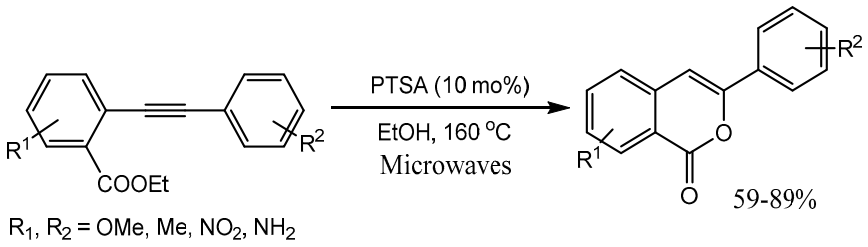
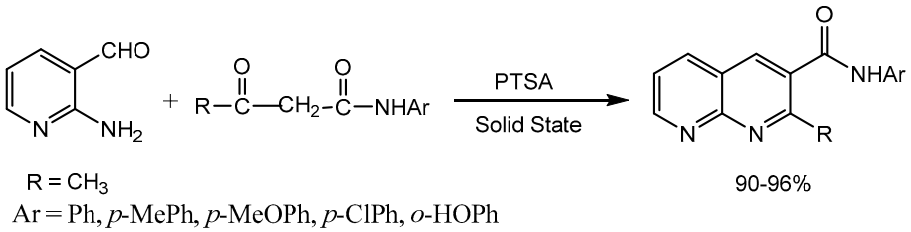


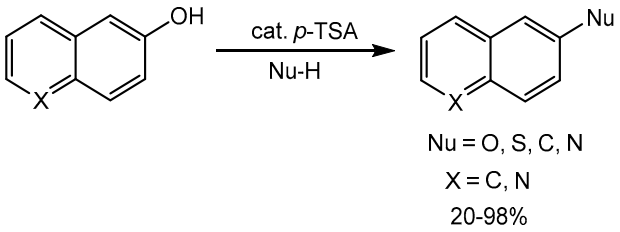
Scheme 17. PTSA catalysed one pot synthesis of 3-aryl-isocoumarins.

Mogilaiah group [17] developed *p*-toluene sulfonic acid (PTSA) catalysed Friedlander condensation of various active methylene compounds with 2-aminonicotinaldehyde in the solid state to produce corresponding 1,8-naphthyridines at room temperature in excellent yields (90-96%) with high purity (Scheme 18).



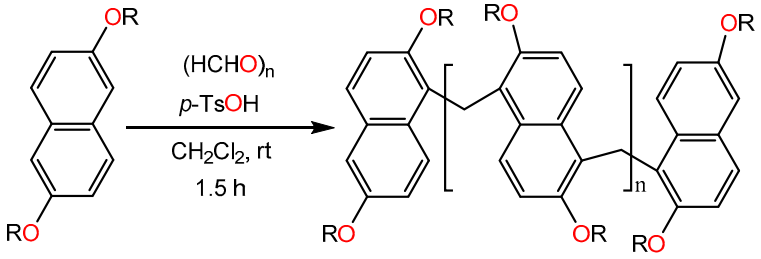
Scheme 18. PTSA catalysed synthesis of 1,8-naphthyridines.

Biswas group [18] reported *p*-toluene sulfonic acid (*P*-TSA) catalysed nucleophilic substitution of hydroxyl groups of naphthol and tautomerizable phenol derivatives by O-, S-, N-, and C-centered nucleophiles under solvent-free reaction conditions to produce the products in 20-98% yields (Scheme 19).



Scheme 19. *P*-TSA catalysed nucleophilic substitution of naphthyl C–OH bonds.

Pan *et al.* [19] described a regioselective route for the synthesis of methylene-bridged naphthalene oligomers from 2,6- dialkoxyl naphthanene and paraformaldehyde using catalytic amount of *p*-toluene sulfonic acid (*P*-TsOH) (Scheme 20). Methylene-bridged aromatic macrocycles are considered as versatile supramolecular hosts in host–guest chemistry.



Scheme 20. *P*-TsOH catalysed synthesis of methylene-bridged naphthalene oligomers.

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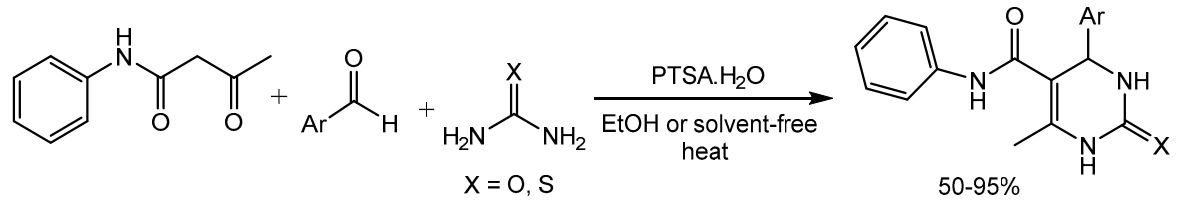
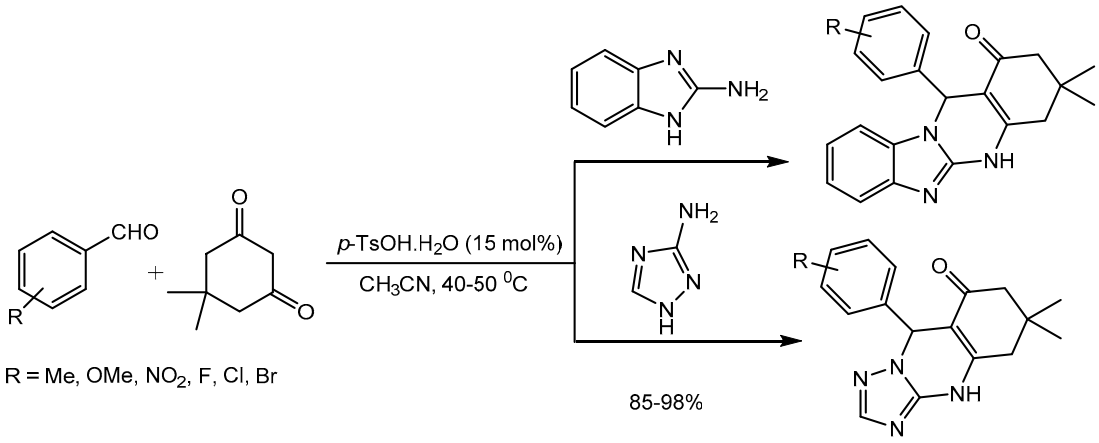
Gündoğan group [20] disclosed a fast and efficient method for the synthesis of a variety of 1,2,3,4-tetrahydro 2-pyrimidinone/thione derivatives (Scheme 21) bearing a phenylcarbamoyl group at C-5 position via one-pot three-component Biginelli condensation reaction using acetoacetanilide, aromatic aldehydes and urea/thiourea in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) in 50-95% yields. Since pyrimidines have different biological properties, the synthesized compounds have potential applications in medicinal chemistry.



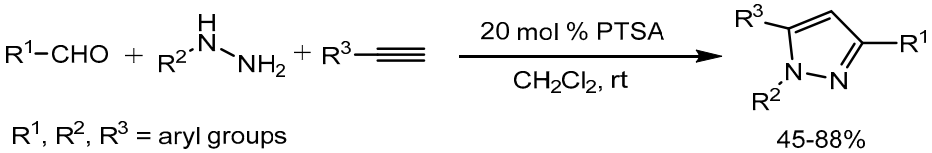
Scheme 21. PTSA·H_2O catalysed synthesis of 1,2,3,4-tetrahydro 2-pyrimidinone/thione derivatives.

Mousavi and Maghsoodlou [21] reported a one-pot three-component reaction of dimedone, aldehydes and 2-aminobenzimidazole or 3-amino-1,2,4-triazole for the synthesis of biologically important benzimidazoquinazolinone and triazoloquinazolinone derivatives under mild conditions using *p*-toluenesulfonic acid monohydrate as catalyst (Scheme 22). This metal-free environmentally friendly protocol has high yields (85-98%), shorter reaction times and no column chromatographic separation. Multicomponent reactions (MCRs), leading to interesting heterocyclic scaffolds, are particularly useful for combinatorial chemistry and medicinal chemistry.



Scheme 22. *P*-TsOH·H_2O catalysed synthesis of benzimidazoquinazolinone and triazoloquinazolinone derivatives.

Wang and co-workers [22] developed a convenient one pot three component reaction of aldehydes, hydrazines and alkynes for the synthesis of 1,3,5- trisubstituted pyrazoles derivatives in 45-88% yields using *p*-toluenesulfonic acid monohydrate (PTSA) as catalyst (Scheme 23).



Scheme 23. PTSA catalysed synthesis of 1,3,5- trisubstituted pyrazoles.

PTSA acts as a multifunctional catalyst and promotes three transformations in tandem, Mannich-type reaction, *5-end-dig* cyclization and oxidation in a single reaction vessel to produce pyrazole derivatives (Scheme 24).

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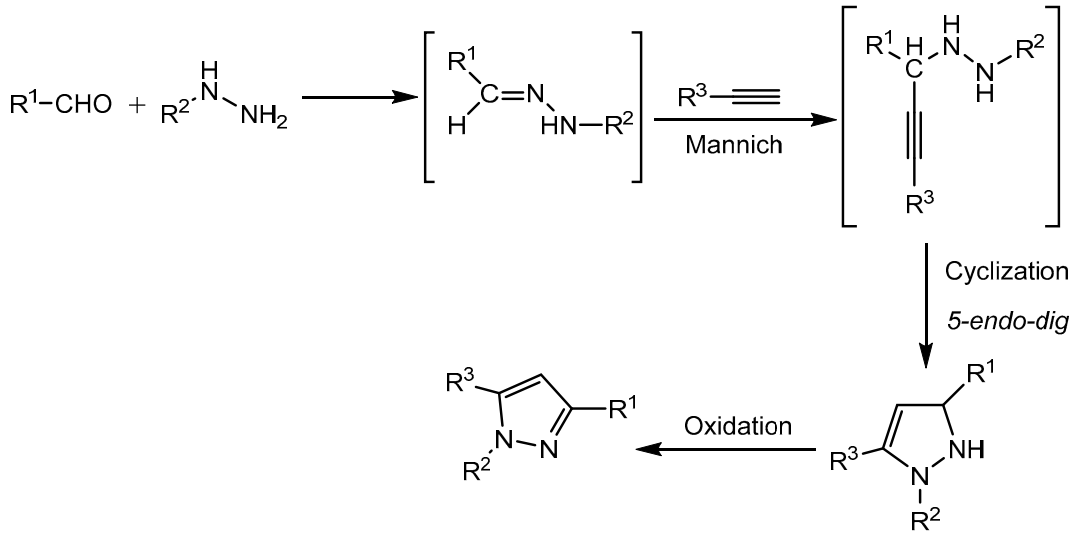
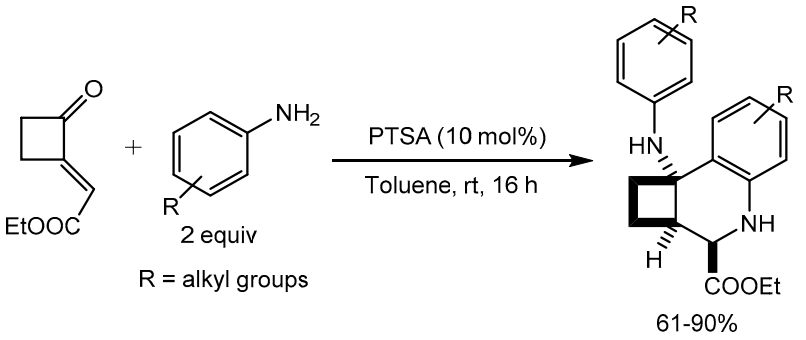


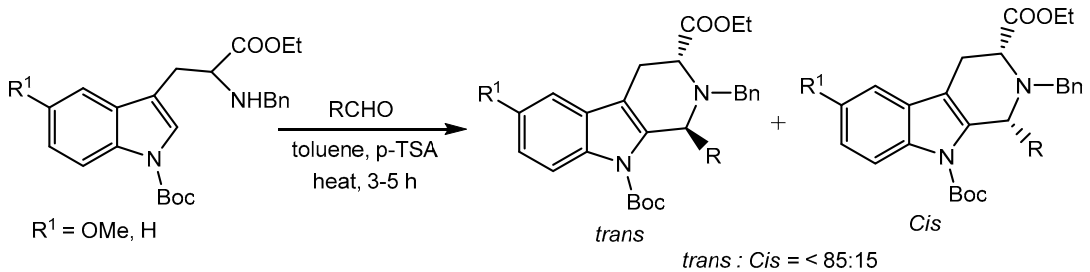
Scheme 24. PTSA catalysed tandem process involving Mannich-type–cyclization–oxidation.

Marras *etal* [23] disclosed *p*-toluenesulfonic acid monohydrate (PTSA) catalyzed novel tandem aza-Michael addition-aza-Friedel–Crafts cyclization process, for the synthesis of highly functionalized cyclobuta-fused tetrahydroquinoline carboxylic esters in 61-90% yields from anilines and 2-alkylenecyclobutanones at room temperature. The cyclization is highly stereoselective resulting in the formation of three contiguous stereocenters (Scheme 25).



Scheme 25. PTSA catalysed synthesis of cyclobuta-fused tetrahydroquinoline carboxylic esters.

Hennkens *et al* [24] reported *p*-toluenesulfonic acid (*p*-TSA) catalysed Pictet-Spengler (P-S) reaction between N_{α}-Boc protected tryptophans and a series of aldehydes for the synthesis of biologically important tetrahydro-β-carbolines (THBCs) with the desired *trans* diastereoselectivity (Scheme 26).



Scheme 26. PTSA catalysed synthesis of tetrahydro-β-carbolines (THBCs).

Elwahy group [25] described a *p*-toluenesulfonic acid (*p*-TSA) catalysed facile Multicomponent reaction (MCR) of dimedone or pyrazolone with bis-aldehydes and ammonium acetate in ethanol

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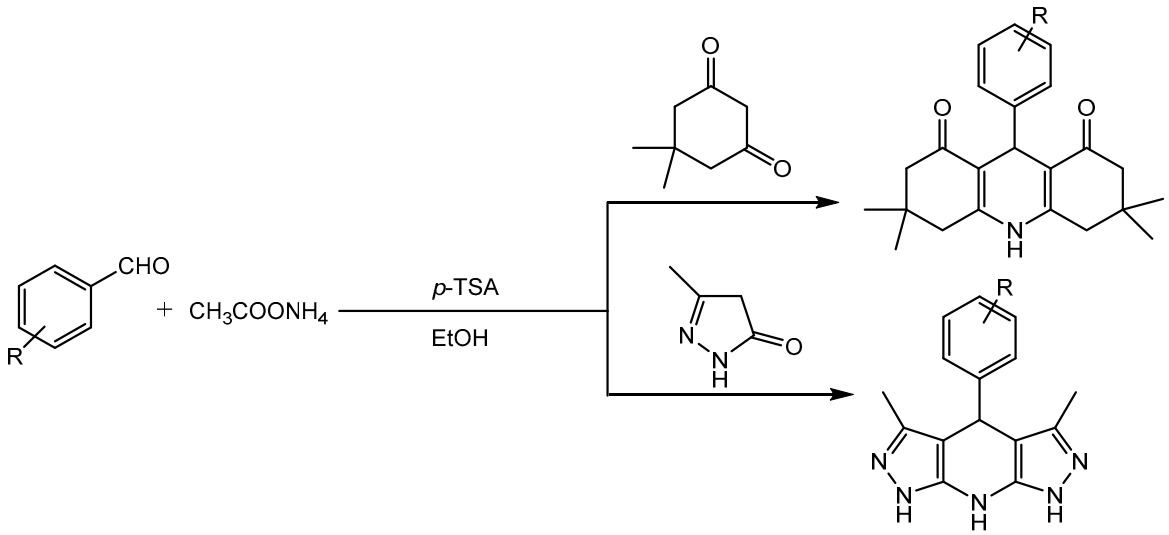
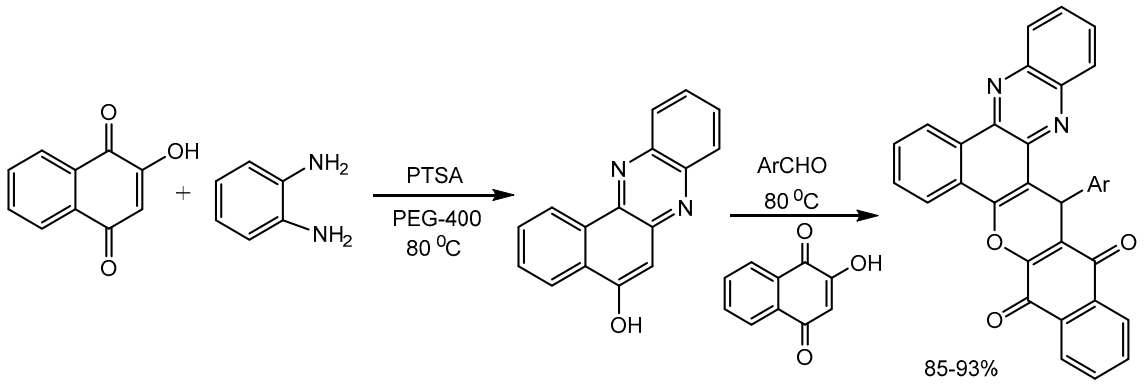
under conventional heating as well as under microwave irradiation for the synthesis of bis(hexahydroacridine-1,8-diones) and bis(tetrahydrodipyrazolo[3,4-b:4′,3′-e]pyridines) derivatives (Scheme 27). This protocol is attractive because of operational simplicity, mild and green conditions, good yields, and easy purification of the products. Acridine derivatives and pyrazolopyridines attracted considerable attentions due to their wide range of biological activities.



Scheme 27. PTSA catalysed synthesis of hexahydroacridines and tetrahydrodipyrazolopyridines via three component reaction.

Mohebat *et al.* [26] developed an efficient *p*-toluenesulfonic acid catalysed one-pot four-component domino reactions of 2-hydroxynaphthalene-1,4- dione, o-phenylenediamine, aromatic aldehydes using polyethylene glycol as solvent for the synthesis of 11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione derivatives in 85-93% yields (Scheme 28). This domino protocol produces biologically important heterocycles with the formation of C–C, C=C, C–N, C=N, C–O bonds in a single operation.



Scheme 28. Synthesis of 11H-benzo[a]benzo[6,7]chromeno[2,3-c]phenazine-11,16(17H)-dione derivatives in the presence of catalytic PTSA.

Khosropour and Khodaei [27] reported an efficient and straightforward approach for the synthesis of 14-alkyl or aryl-14-H-dibenzo[a,j]xanthenes in 80-96% yields via *p*-toluenesulfonic acid (*p*-TSA) catalysed one-pot condensation of β-naphthol with alkyl or aryl aldehydes in solution and solvent-free Conditions (Scheme 29).

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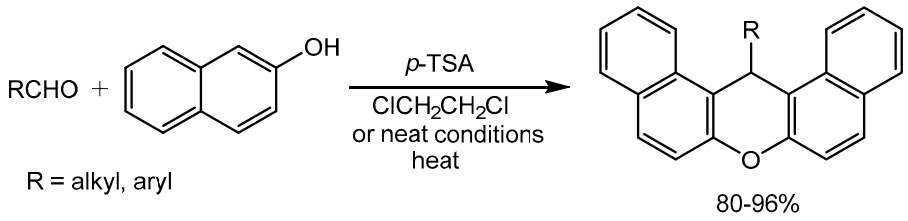
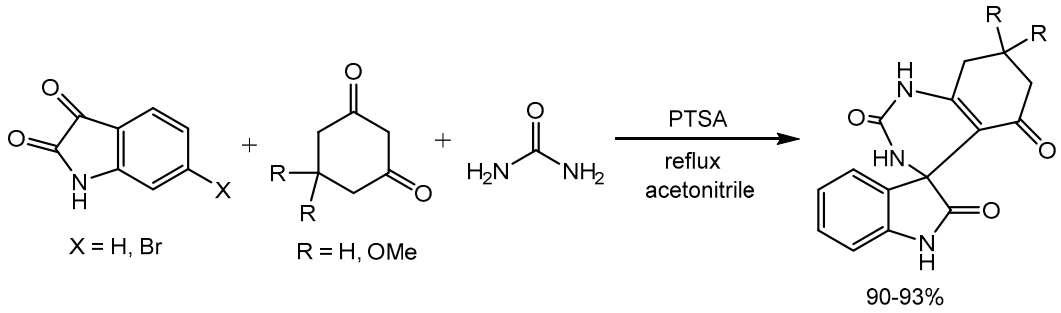


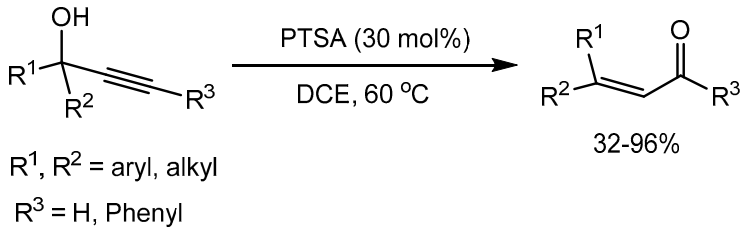
Scheme 29. Synthesis of 14-alkyl- or aryl-14-H-dibenzo[a,j]xanthenes using catalytic amount of *p*-TSA.

Baghernejad group [28] elaborated *p*-toluenesulfonic acid (PTSA) catalysed one-pot synthesis of spirooxindoles in 90-93% yields via three-component reaction of urea, isatin, and 1,3-dicarbonyl compounds in acetonitrile (Scheme 30). Spirooxindole skeleton are present in many natural products and biologically active compounds.



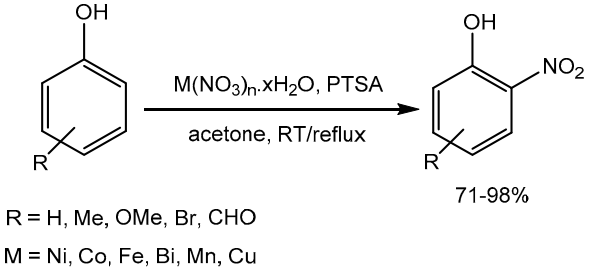
Scheme 30. Synthesis of spirooxindoles catalyzed by PTSA.

Park *etal* [29] described an efficient and simple protocol of *p*-toluenesulfonic acid (PTSA) catalysed Meyer–Schuster rearrangement of propargyl alcohols into α,β-unsaturated carbonyl compounds in 32-96% yields in 1,2-dichloroethane (Scheme 31).



Scheme 31. PTSA–catalyzed Meyer–Schuster rearrangement.

V. Anuradha *et al.* [30] disclosed a *p*-toluenesulfonic acid (PTSA) catalysed highly regiospecific mononitration of phenols using a variety of metal nitrates to obtain *o*-nitrophenols in 71-98% yields. Nitro phenols are intermediates for fine chemicals, pharmaceuticals, and agrochemicals (Scheme 32).



Scheme 32. PTSA–catalysed nitration of phenols.

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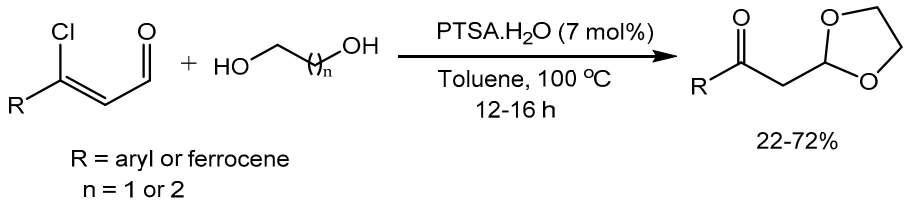
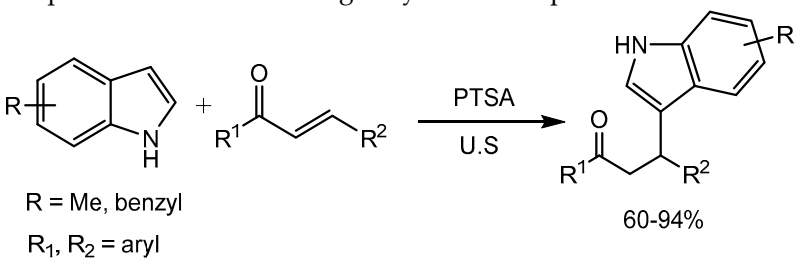
Joshi research group [31] developed a metal-free, *p*-toluenesulfonic acid (PTSA) catalyzed facile synthesis of β-ketoacetal from β-chlorocinnamaldehyde and dihydroxy alcohols in 22-72% yields (Scheme 33). PTSA catalysed selective protection of the aldehydic group to form the β-chloroacetal and the subsequent dechlorination by H_2O resulted the formation of β-ketoacetal. In this transformation multitasking nature of PTSA is observed.



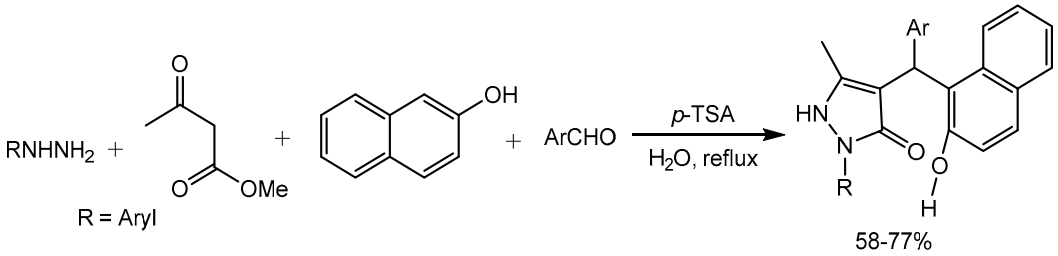
Scheme 33. Synthesis of β-ketoacetal using catalytic PTSA.

Ji and Wang [32] reported *p*-toluenesulfonic acid (PTSA) catalyzed Michael addition of indole to α,β-unsaturated ketones for the expeditious synthesis of β-indolylketones in 60-94% yields under ultrasonic irradiation (Scheme 34). β-indolylketones are considered important building blocks for the synthesis of natural products and other biologically active compounds.



Scheme 34. PTSA–catalysed synthesis of β-indolylketones under ultrasonic irradiation.

Perumal research group [33] reported expedient synthesis of a series of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones via one-pot, four-component sequential reactions of phenylhydrazine, methyl acetoacetate, aromatic aldehydes and β-naphthol in the presence of *p*-toluenesulfonic acid in water. The products were obtained in 58-77% yields and the compounds were screened for *in-vitro* antimycobacterial activity against Mycobacterium tuberculosis H37Rv (MTB). One of the compound 4-[(2,4-dichlorophenyl)(2- hydroxy-1-naphthyl)methyl]-2-(4-fluorophenyl)-5-methyl-2,3-dihydro-1H-3-pyrazolone displays the maximum potency in the series with a minimum inhibitory concentration (MIC) of 1.6 μM against MTB, being 2.94 and 4.75 times more active than antibiotic ciprofloxacin and ethambutol respectively (Scheme 35).



Scheme 35. Synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones in the presence of *p*-TSA.

Naidu *et al.* [34] developed a simple and efficient one pot three components protocol for the synthesis of highly functionalized indoles in 70-88% yield in an easy workup procedure. In presence of PTSA, the reaction occurred via reductive alkylation of α-keto imines, followed by a cyclization process (Scheme 36). Indole moiety is present in diverse biologically active natural products and pharmaceuticals.

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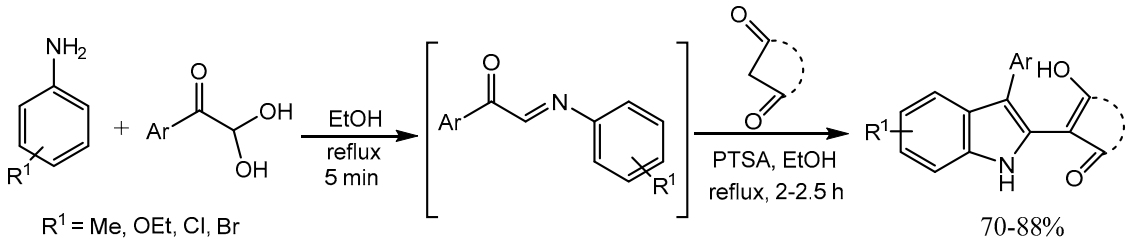
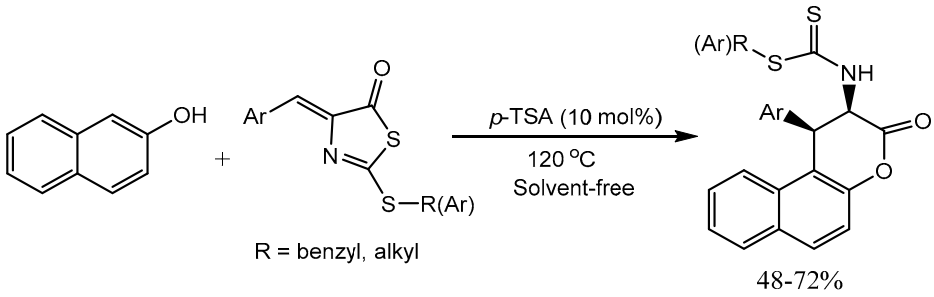


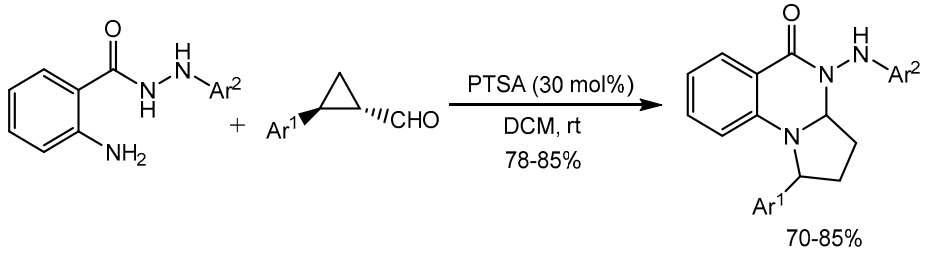
Scheme 36. Synthesis of highly functionalized indoles using PTSA.

Halimehjani and Khoshdoun [35] disclosed an efficient PTSA catalysed synthesis of functionalized 1,2-dihydrobenzo[f]chromen-3-ones and 3,4- dihydrochromen-2-ones via tandem esterification/ intramolecular 1,4-addition-type Friedel–Crafts alkylation reaction of phenols or naphthols with Olefinic Thioazlactones. The reaction proceeds with high yields (48-72%) and diastereoselectivity (Scheme 37). Due to the widespread occurrence and broad range of biological activities chromenes, chromanes and their benzo-fused derivatives are highly attractive synthetic targets.



Scheme 37. *P*-TSA catalysed Synthesis of 1,2-Dihydrobenzo[f]chromen-3-one.

Singh *et al.* [36] described *p*-toluene sulfonic acid (PTSA) catalysed regioselective annulation of cyclopropane aldehydes with N′-aryl anthranil hydrazides for the synthesis of tetrahydropyrrolo[1,2-a]quinazolin-5(1H)ones (Scheme 38). The reaction involves domino imine formation followed by intramolecular cyclization and nucleophilic ring opening of the cyclopropyl ring to form the desired products in good to excellent yield (70-85%) with complete regioselectivity. This methodology provides a simple and step-efficient synthesis of pyrroloquinazolinone derivatives which is an important core of a variety of natural products and biologically active molecules.



Scheme 38. PTSA catalysed synthesis of pyrroloquinazolinone derivatives.

Jaratjaroonphong and co-workers [37] reported a novel strategy of PTSA-catalyzed transindolylation of the readily synthesized 3,3′-bis(indolyl)ethylamines (3,3′-BIEAs) with tryptamine derivatives in 46-62% yields. The group has nicely applied this strategy for the first and short total synthesis of the marine sponge 2,3′-bis(indolyl)ethylamine (2,3′-BIEA) alkaloid (±)-gelliusine E in 58% yield. This modular approach allows the rapid synthesis of other members of the 2,3′-BIEA family. Additionally, cytotoxicity of these alkaloids in breast cancer cells was investigated (Scheme 39).

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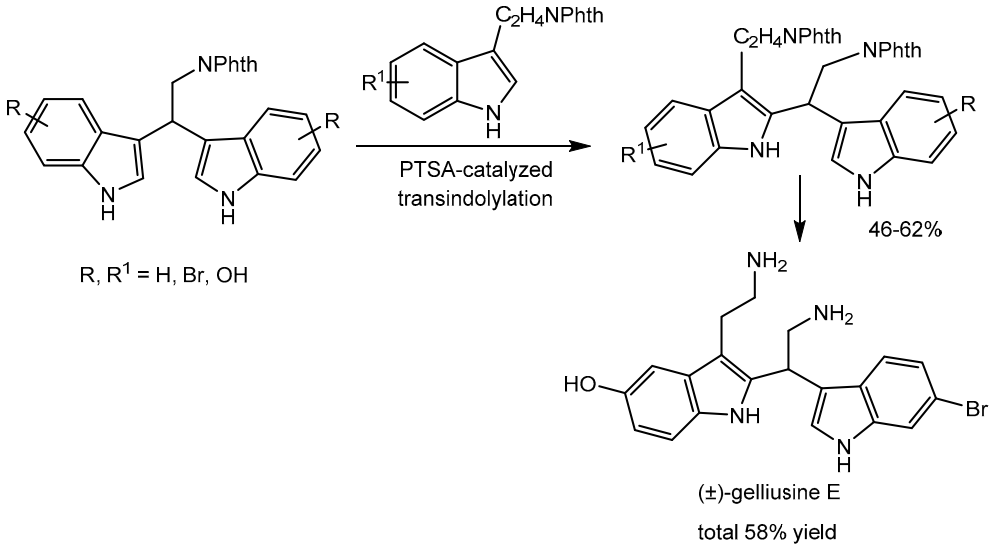
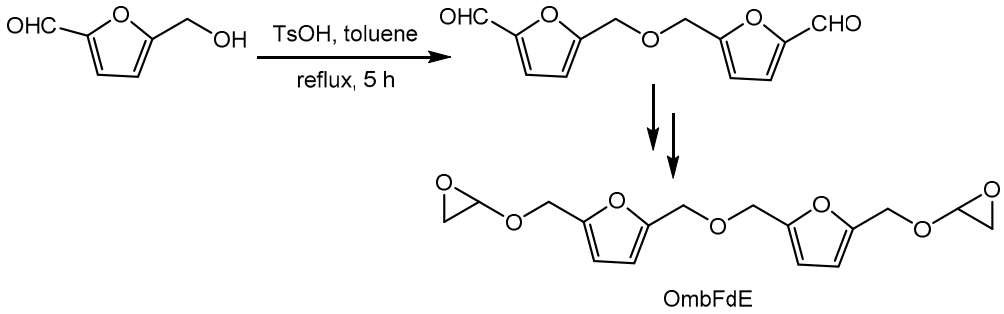


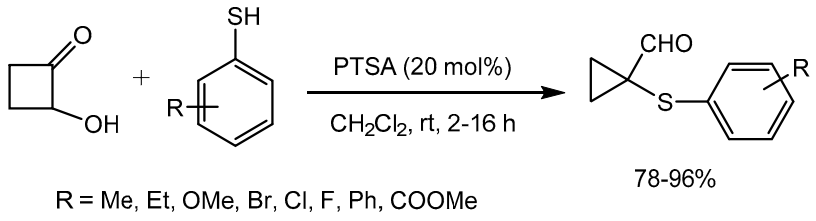
Scheme 39. PTSA catalysed transindolylation for the synthesis of (±)-gelliusine E.

Meng *etal* [38] disclosed the method for the synthesis of novel bis-furan diepoxide (OmbFdE) via a mild and scalable route, and applied in epoxy resins in an eco-friendly manner, with the resulting materials showing good thermal stability. Difuranic dialdehyde, the precursor the difuranic diepoxide monomer (OmbFdE) was synthesized from HMF in the presence of catalytic *p*-toluenesulfonic acid. Further reduction and etherification yielded the bis-furan diepoxide product on a large scale (Scheme 40).



Scheme 40. Synthesis of bis-furan diepoxide (OmbFdE) in the presence of catalytic PTSA.

Secci group [39] described a general strategy for the synthesis of arylthio cyclopropyl carbaldehydes and ketones via *p*-toluene sulfonic acid (PTSA) catalyzed arylthiol addition followed by ring contraction reaction. The methodology produced a variety of cyclopropyl carbaldehydes in 78-96% yields (Scheme 41).



Scheme 41. PTSA catalysed synthesis of arylthio cyclopropyl carbaldehydes.

Baire and Tharra [40] reported *p*-toluene sulfonic acid (PTSA) catalysed nucleophilation of propargylic alcohols via Meyer–Schuster rearrangement (M–S) for the synthesis of α-arylenone esters

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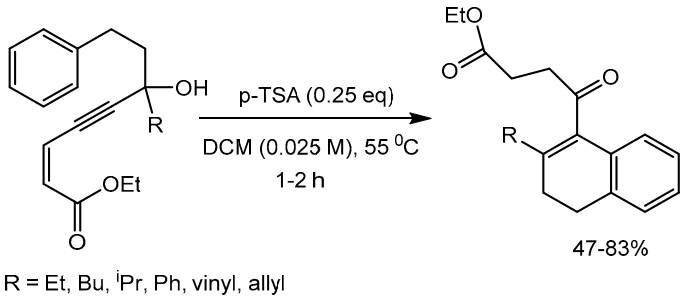
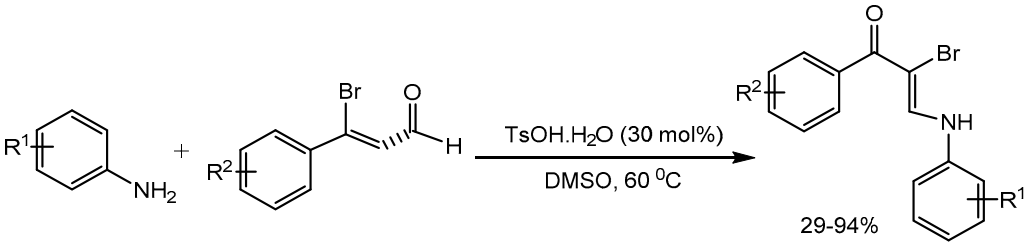
in 47-83% yields (Scheme 42). This protocol involves cis-enoate assisted reverse polarization of the M–S intermediate allenyl cation. To showcase the application of this method, the α-arylenone esters was successfully converted to the biologically important molecules such as pyrazoles and 4,5-seco-abietane.



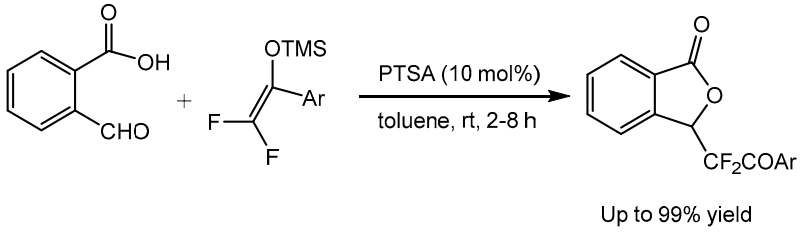
Scheme 42. Z-enoate assisted, nucleophilic intercepted M–S rearrangement.

Enaminone chemistry has attracted enormous attention in recent years because enaminones are a versatile intermediate used for the synthesis of various heterocyclic compounds and the enaminone framework is also found in many bioactive molecules. Yao group [41] developed a one-pot strategy for the synthesis of α-bromo enaminones in 29-94% yields via reactions of 3-bromopropenals with anilines in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate (TsOH·H_2O) without using an external brominating agent (Scheme 43).



Scheme 43. One-pot synthesis of α-bromo enaminones using catalytic *p*-toluenesulfonic acid monohydrate.

Ren and co-workers [42] described a convenient approach for the synthesis of 3-difluoroalkyl phthalides from phthalaldehydic acids and difluoroenoxysilanes using catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA). The reaction provided a variety of 3- difluoroalkyl phthalides and cyclic difluoroalkyl ethers up to 99% yield (Scheme 44).



Scheme 44. Synthesis of 3-difluoroalkyl phthalides using catalytic PTSA.

Ma and his group [43] disclosed *p*-toluenesulfonic acid monohydrate (TsOH·H_2O) catalysed unprecedented cascade reaction involving C(sp^2)–H addition to carbonyl and the C(sp^2)–CN/C(sp^2)–H coupling of 2-(2-oxo-2-arylethyl)benzonitriles with indoles. The metal-free cascade approach is operationally simple and represent a new route for the synthesis of benzo[a]carbazole derivatives with a broad substrate scope and 38-97% yields (Scheme 45).

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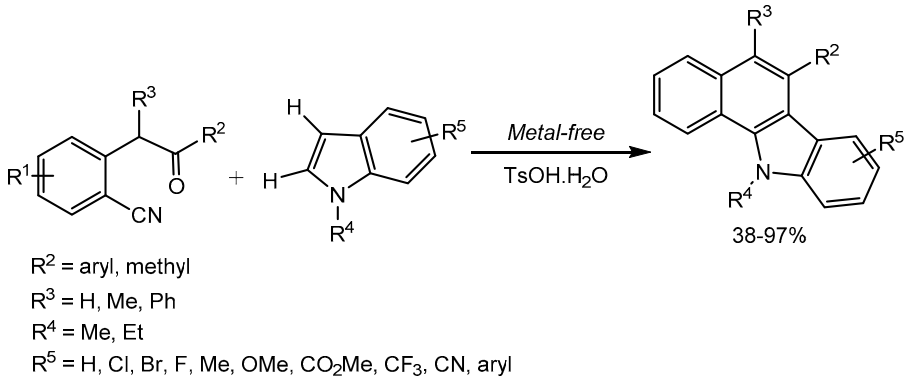
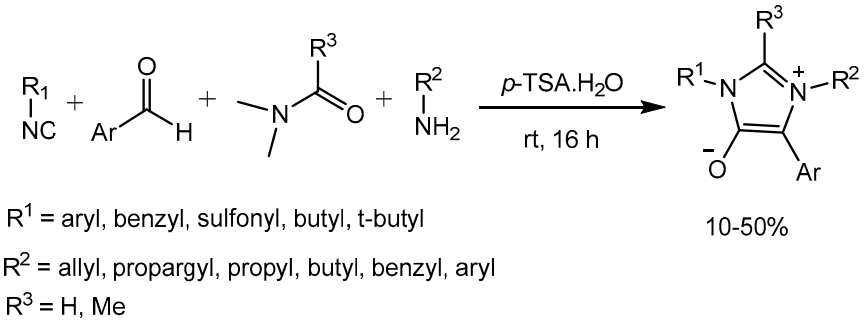


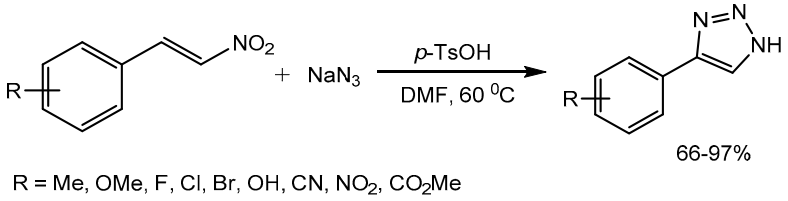
Scheme 45. TsOH·H_2O catalysed cascade reaction of 2-(2-oxo-2-arylethyl)benzonitriles with indoles.

Cankařová and co-workers [44] reported a *p*-toluenesulfonic acid (*p*-TSA) catalysed four-component condensation of an isocyanide, amine, aldehyde, and amide leading to the generation of diversely substituted mesoionic 1*H*-imidazol-3-ium-4-olates in one step in 10-50% yields. The mesoionic compounds formed are structurally related to sydnones and münchnones and direct precursors for anionic N-heterocyclic carbenes. Mild reaction conditions, atom economy and time efficiency make this protocol attractive (Scheme 46).



Scheme 46. *p*-TSA catalysed four-component condensation of an isocyanide, amine, aldehyde, and amide.

Guan group [45] described a *p*-toluenesulfonic acid (*p*-TsOH) promoted 1,3-dipolar cycloaddition of nitroolefins and sodium azide for the rapid synthesis of valuable 4-aryl-*NH*-1,2,3-triazoles in high yields (66-97%). 1,2,3-Triazoles have been widely applied in medicinal chemistry, agrochemistry, and materials chemistry (Scheme 47).



Scheme 47. *p*-TsOH promoted 1,3-dipolar cycloaddition of nitroolefins and sodium azide.

Wang group [46] developed an efficient methodology for the synthesis of substituted 2, 2-aminobenzophenone derivatives and aromatic β-ketosulfones. The reactions were carried out using *p*-toluenesulfonic acid monohydrate under microwave irradiation. The synthetic route is atom-economical and a series of pharmaceutically active 3-arylsulfonylquinolines were prepared in 72-94% yields (Scheme 48).

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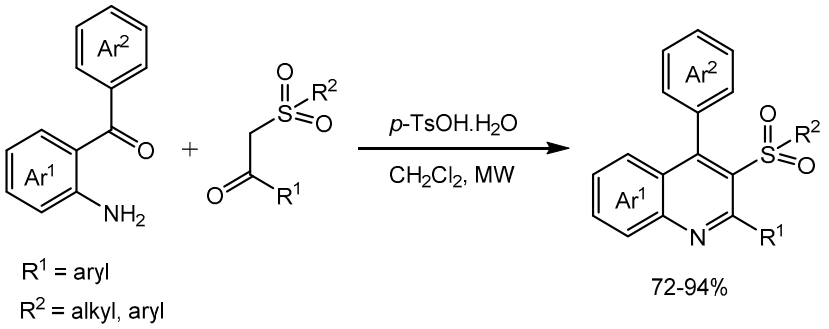
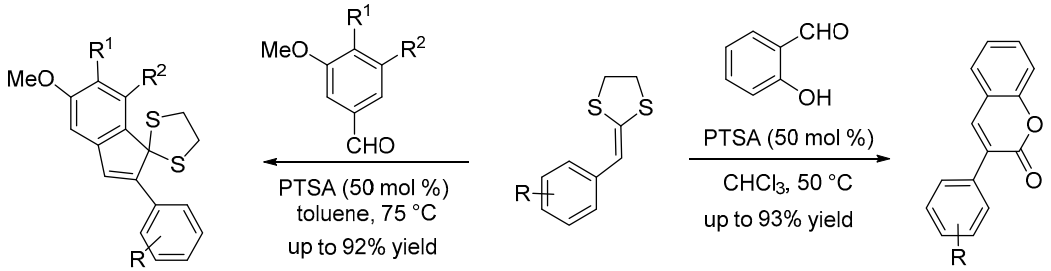


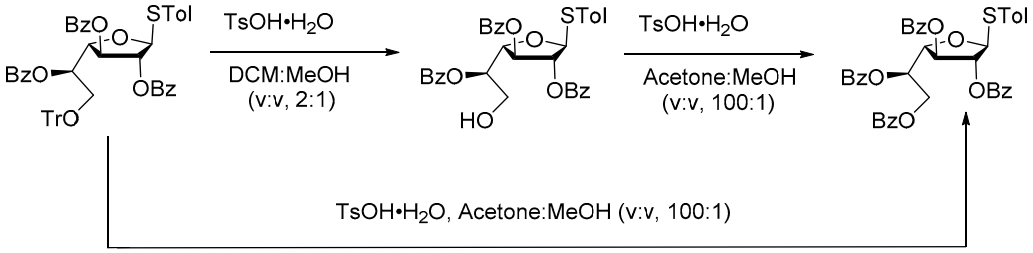
Scheme 48. Synthesis of substituted 2,4-diaryl-3-sulfonylquinolines using *p*-TsOH.H2O..

Singh and co-workers [47] reported the *p*-toluenesulfonic acid catalyzed divergent synthetic routes toward 3-aryl coumarins and indenes via annulations of ketene dithioacetals. The process is transition-metal and oxidant free and these important moieties were obtained in more than 90% yield under mild conditions (Scheme 49).



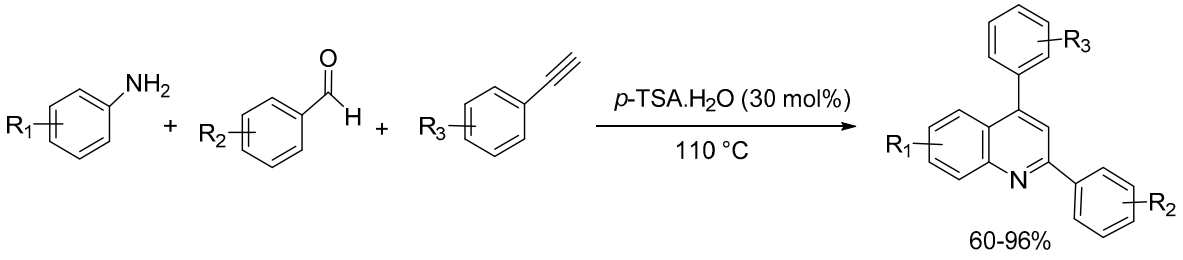
Scheme 49. PTSA catalyzed synthesis of 3-aryl coumarins and indenes.

Huang group [48] developed an efficient method for regioselective acyl migration of benzoyl ester catalyzed by *p*-toluenesulfonic acid monohydrate (TsOH.H2O) for accessing wide range of orthogonally protected monosaccharides, which are useful intermediates for the synthesis of natural oligosaccharides (Scheme 50).



Scheme 50. TsOH.H2O catalyzed synthesis of diverse orthogonally protected monosaccharides.

Khan and co-workers [49] disclosed metal- and solvent-free environmentally benign synthesis of 2,4-diarylquinolines via a one-pot three component reaction of arylamine, aryl aldehyde, and aryl acetylene using 30mol% *p*-toluenesulfonic acid monohydrate (*p*-TSA·H2O). The substrate scope of the reaction is wide and the products were obtained in 60-96% yields (Scheme 51).



Scheme 51. *p*-TSA·H2O catalyzed synthesis of 2,4-diarylquinolines.

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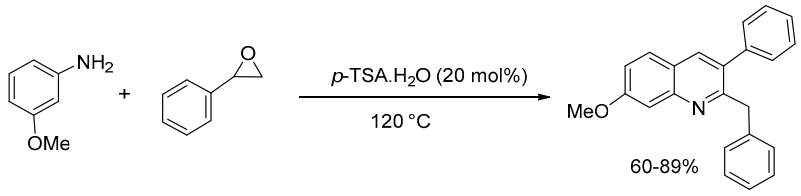
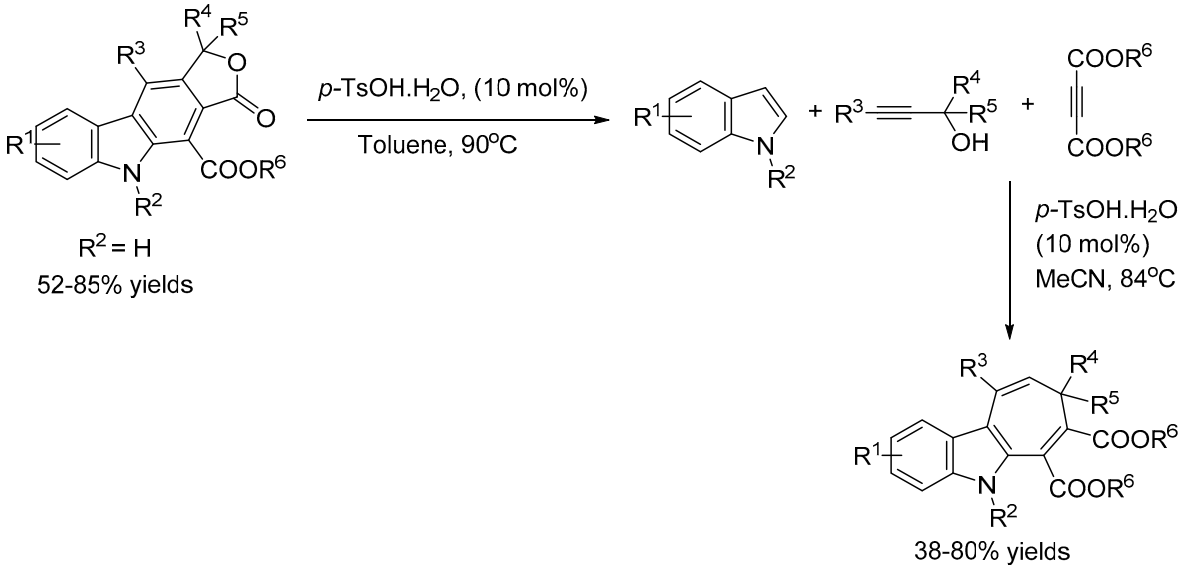
Khan group [50] also developed a metal- and solvent-free highly efficient and straightforward synthetic route for the synthesis of 2-benzyl-3-arylquinoline derivatives from aryl amines and styrene oxides in the presence of 20 mol% *p*-toluenesulfonic acids (Scheme 52). The reaction also can produce 2,3-dialkylquinoline derivative using aliphatic epoxide. The metal- and solvent-free reaction conditions, operational simplicity, broad substrate scope, good to excellent yields (60-89%) of the products, and the formation of one C-N and two C-C bonds in a single step make this protocol attractive.



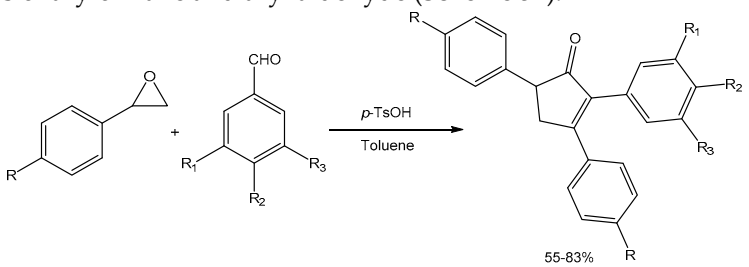
Scheme 52. *p*-TSA·H2O catalyzed synthesis of 2-benzyl-3-arylquinoline derivatives.

Wang and co-workers [51] reported a metal-free environmentally friendly approach for the synthesis of biologically important cyclohepta[b]indole in 38-80% and furo[3,4-b]carbazole frameworks in 52-85% yields respectively via a three-component reaction of indoles, tertiary propargylic alcohols, and activated alkynes using catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH.H2O) (Scheme 53). A gram-scale reaction and further synthetic transformations of the products were also performed to demonstrate the practicality of the methodology.



Scheme 53. Synthesis of cyclohepta[b]indoles and furo[3,4-b]carbazoles using *p*-TsOH.H2O.

Baskaran group [52] developed a facile domino strategy involving a sequence of semipinacol rearrangement, iterative aldol condensation, and iso-Nazarov cyclization reactions for the synthesis of biologically active cyclopent-2-enones in 55-83% yields via *p*-toluene sulfonic acid (*p*-TSOH) promoted reactions of aryloxirane and aryl aldehyde (Scheme 54).



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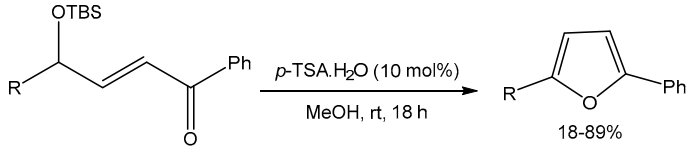
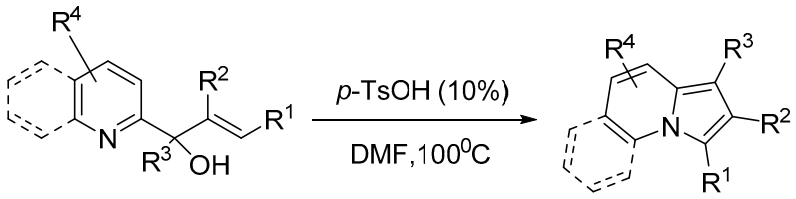
Scheme 54. *P*-TSOH promoted synthesis of biologically important cyclopent-2-enones.

Taylor and co-workers [53] reported *para*-toluenesulfonic acid (*p*-TSA) catalyzed desilylative heterocyclisation of *tert*-butyldimethylsilyl (TBS) protected γ-hydroxy-α,β-unsaturated ketones for the synthesis of substituted furans in 18-89% yields. The reaction proceeds at room temperature under mild conditions (Scheme 55).



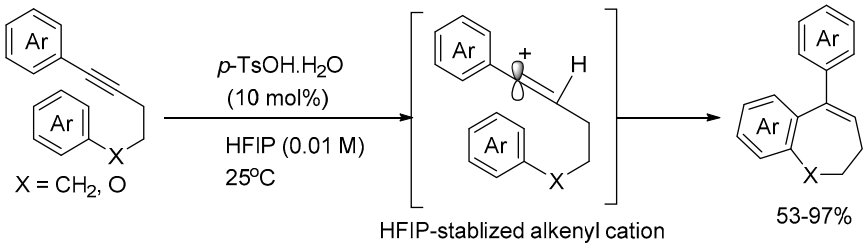
Scheme 55. Synthesis of substituted furans catalyzed by p-TSA.

Xinxin *etal* [54] described an approach of *p*-toluenesulfonic acid catalyzed intramolecular amination of allylic alcohols for efficient access to biologically important multisubstituted indolizines. This metal-free process enabled the divergent synthesis of these important frameworks in high yields (Scheme 56).



Scheme 56. *P*-TSOH catalyzed synthesis of biologically important multisubstituted indolizines.

Anada group [55] reported *p*-toluenesulfonic acid (*p*-TsOH.H2O) catalyzed transition metal-free intramolecular 7-endo hydroarylation reaction of 1,5-diaryl-1-pentynes using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent in 53-97% yields (Scheme 57). To demonstrate the potential of this methodology, KGP-18, an analogue of the anticancer natural product combretastatin A4 was synthesized.



Scheme 57. *p*-TsOH.H2O catalyzed intramolecular 7-endo hydroarylation reaction.

Maiti and co-workers [56] described an unprecedented *p*-toluenesulfonic acid (*p*-TsOH) catalyzed [5+1] and [4+1] annulation of cyclic anhydrides or *o*-formylbenzoates with *o*-alkynylanilines for the construction of valuable fused-*N*-heterocycles, isoindolo/pyrido/pyrrolo-quinolinediones and isoindolo-indolones (Scheme 58). The process is metal-free, operationally simple, highly regioselective, atom economical, high yielding. All these features make this protocol sustainable.

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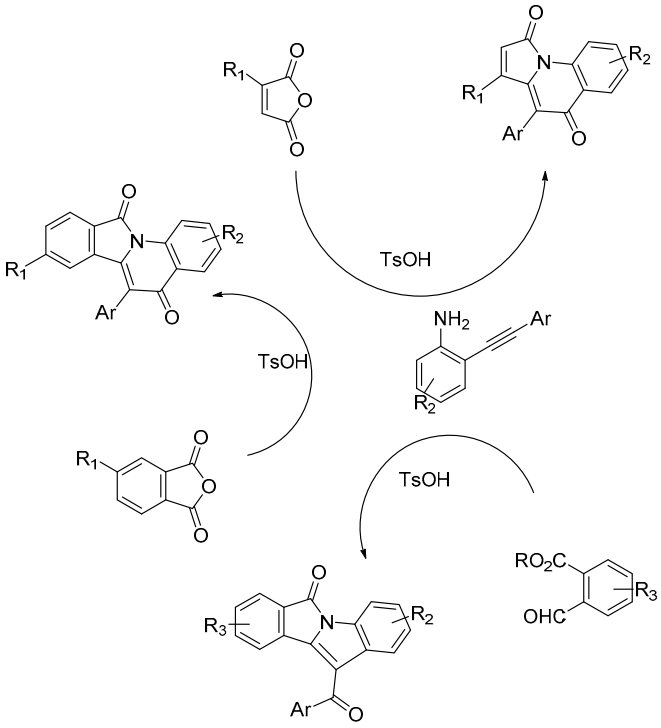
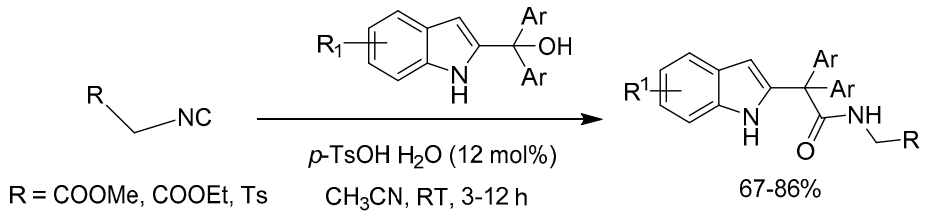


Scheme 58. *p*-TsOH catalyzed synthesis of valuable fused-*N*-heterocycles.

Tandon group [57] developed a *p*-toluenesulfonic acid (*p*-TsOH) catalyzed regioselective direct carboxamidation reaction of 2-indolylmethanols with readily available isocyanoesters/isocyanides. The reaction produced benzylic regioselective amides in 67–86% yield under mild conditions (Scheme 59). This methodology provides alternative access to traditional metal-free carboxamidation approach *via* C–C and C–O bond formation with high atom economy.



Scheme 59. Regioselective direct carboxamidation reaction of 2-indolylmethanols catalyzed by *p*-TsOH.

Zhan *etal* [58] reported a [3 + 2] cycloaddition reaction of various 3-vinylindoles and (indol-2-yl)diphenylmethanols catalyzed by *p*-TsOH to synthesize functionalized cyclopenta[*b*]indoles in good yields (58-88%) and with high diastereoselectivity (Scheme 60).

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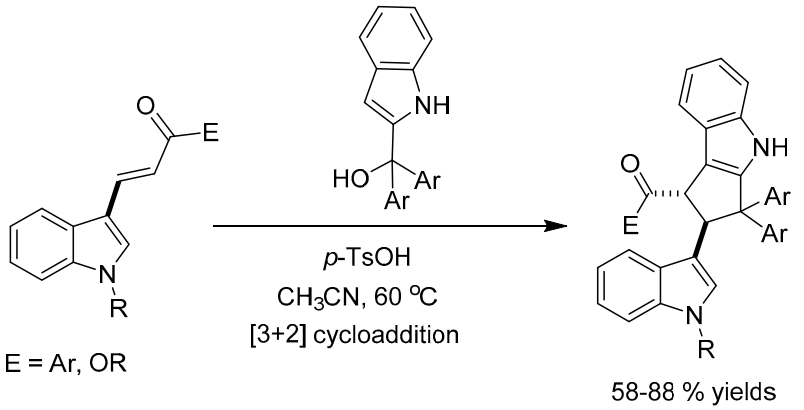
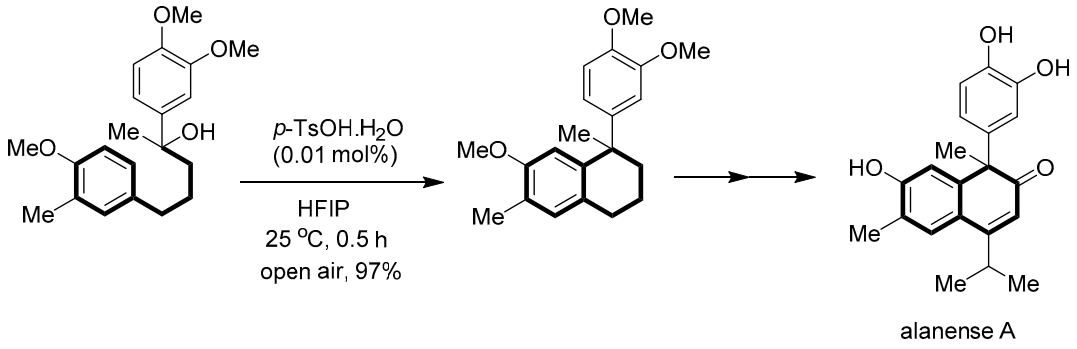


Scheme 60. Synthesis of cyclopenta[b]indoles catalyzed by *p*-TsOH.H_2O.

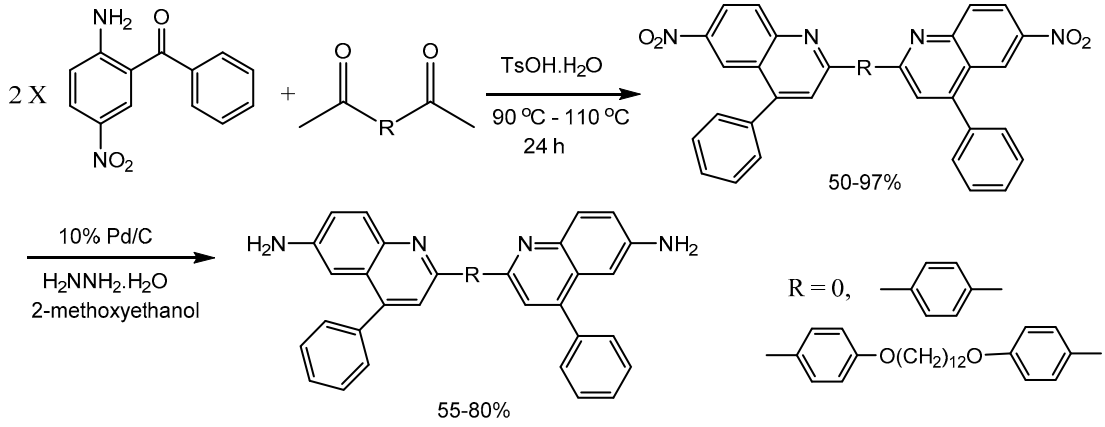
Makino group [59] reported the first total synthesis of cadinane sesquiterpenoid alanense A *via* an intramolecular dehydrative Friedel–Crafts alkylation of 2,5-diaryl-2-pentanol. The combination of *p*-toluenesulfonic acid (*p*-TsOH.H_2O) as a catalyst and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent provides 1,1-disubstituted tetrahydronaphthalene in 97% yield (Scheme 61).



Scheme 61. Total synthesis of sesquiterpenoid alanense A via *p*-TsOH.H_2O catalyzed Friedel–Crafts alkylation reaction.

2.2. Application of p-Toluenesulfonic Acid as a Reagent

Bhowmik research group [60] developed a new class of bisquinoline diamines photoactive amorphous molecular materials with high glass transition temperatures and high thermal stabilities. The intermediate bisquinoline dinitro compounds was synthesized by *p*-toluenesulfonic acid (PTSA) mediated Friedländer condensation reaction in 50-97% yields. Finally the dinitro compounds was reduced to bisquinoline diamines in 55-80% yields (Scheme 62).



Scheme 62. Synthesis of bisquinoline diamines.

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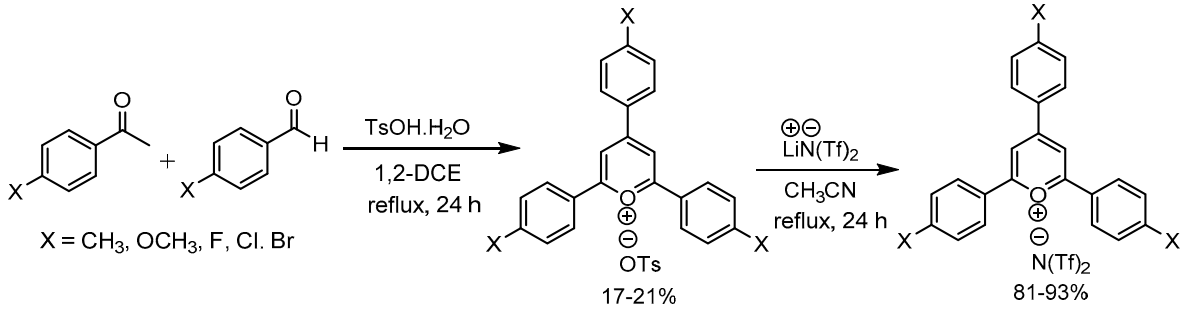
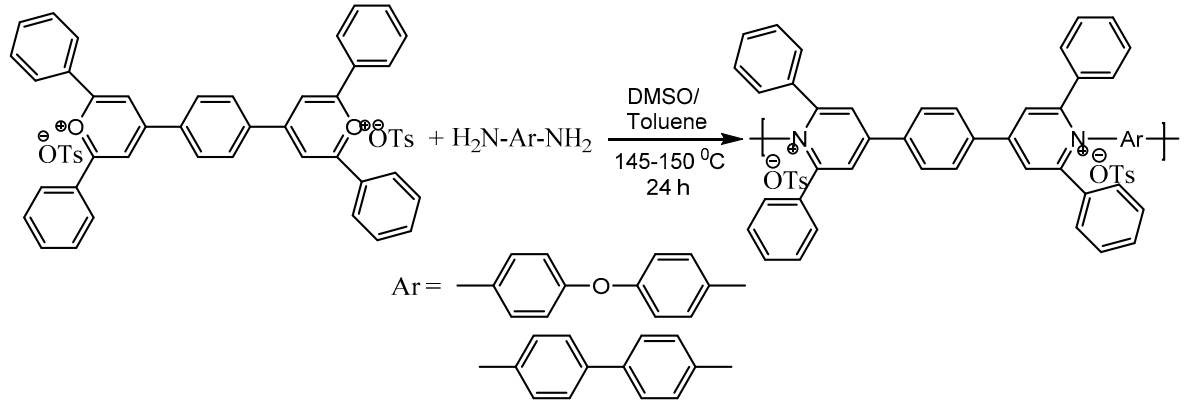
Bhowmik *et al.* [61] elaborated a nice application of tosic acid for the synthesis of 2,4,6-tris(4-substituted phenyl)pyrylium tosylates from para-substituted benzaldehydes and para-substituted acetophenones in 17-21% yields in one pot. Further these pyrylium tosylate salts were converted to the corresponding triflimide salts in 81-93% yields. Study of the optical and thermal properties of these salts indicated that some of these pyrylium salts emitted strong blue and green light and showed excellent thermal stability (Scheme 63).



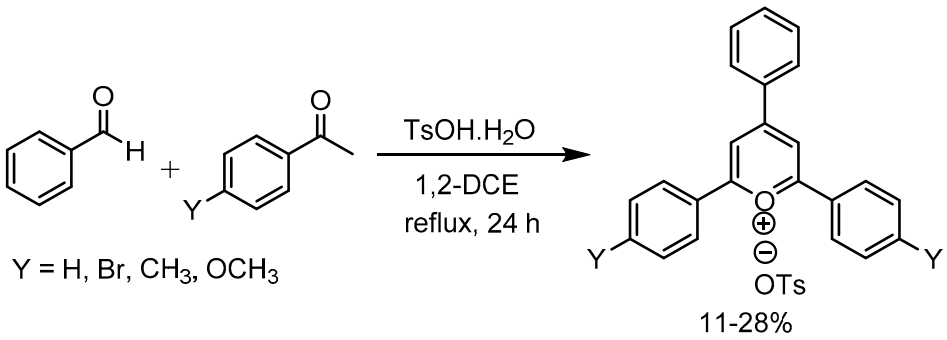
Scheme 63. Synthesis of pyrylium tosylates and triflimides.

The group [62] also showed the application of pyrylium tosylates to prepare a new series of poly(pyridinium salt)s with tosylate counterion that exhibited both lyotropic liquid-crystalline and light-emitting properties (Scheme 64).



Scheme 64. Synthesis of poly(pyridinium salt)s.

Bhowmik research group [63] disclosed a safe and inexpensive method for the synthesis of a series of four substituted 2,4,6-triphenylpyrylium tosylate salts in 11-28% yields using *p*-toluenesulfonic acid monohydrate and studied their optical spectroscopy and laser potential (Scheme 65).



Scheme 65. Synthesis of four substituted 2,4,6-triphenylpyrylium tosylate salts.

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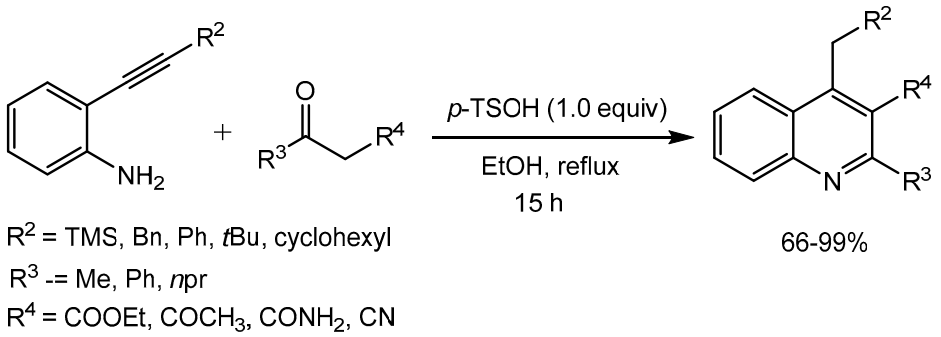
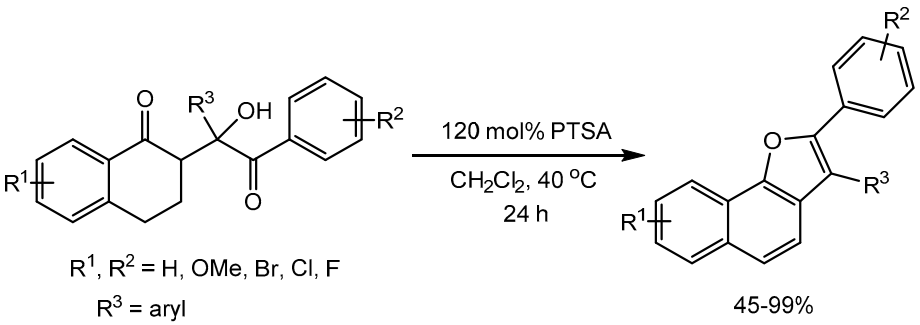
Zhu group [64] disclosed *p*-toluenesulfonic acid promoted annulation of 2-alkynylanilines with activated ketones for efficient synthesis of 4-alkyl-2,3-disubstituted quinolines in 66-99% yields (Scheme 66). The substituents at the other end of the triple bond of 2-alkynylanilines makes this method valuable to access diversified 4-alkylquinolines, which are difficult to obtain by classical methods like Friedländer reaction.



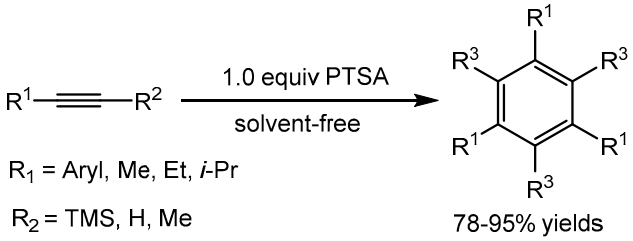
Scheme 66. *p*-Toluenesulfonic acid promoted annulation of 2-alkynylanilines with activated ketones.

Yan and co-workers [65] reported an unprecedented PTSA-promoted sequential furan annulation and aromatization in one pot for the construction of various highly substituted benzo[b]furan derivatives in 45-99% yields. Benzo[b]furans are privileged structures found in numerous natural products and biologically active compounds and this motif is also used in organic semiconductor and organic light-emitting devices (Scheme 67).



Scheme 67. PTSA–catalyzed one pot construction of benzo[b]furan derivatives.

Li and co-workers [66] described an efficient and environmentally friendly approach for cyclotrimerisation of alkynes leading to the synthesis of 1,3,5-trisubstituted benzenes in 78-95% yields using *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) under solvent-free conditions. This method provides good to excellent yields and overcomes the shortcomings of previous methods for the synthesis of substituted benzenes (Scheme 68).



Scheme 68. Solvent-free synthesis of substituted benzenes using *p*-TsOH·H_2O.

Babu *et al.* [67] disclosed a high-speed deprotection of Boc group from Boc amino acids and protected peptide esters using *p*-toluenesulfonic acid. The reaction was carried out in toluene under microwave irradiation and found to be complete in 30 s with 8-96% yields. The strategy can be

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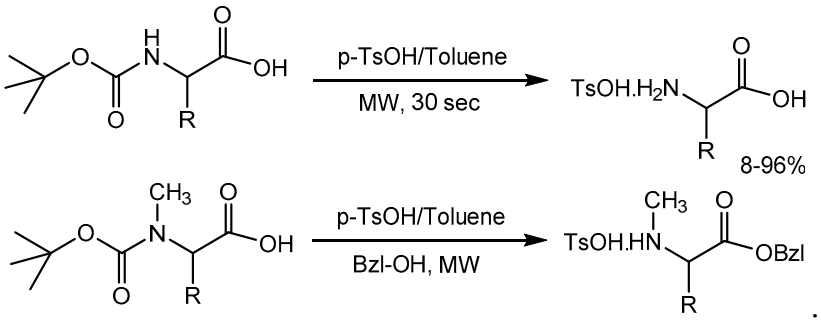
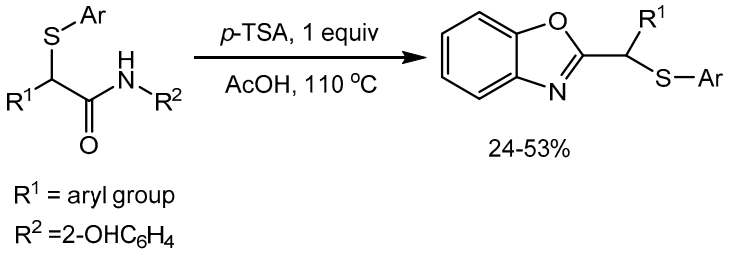
extended for the concomitant removal of the Boc group and the formation of C-benzyl amino acid esters in single step (Scheme 69).



Scheme 69. Deprotection of Boc group and formation of N-Me amino acid benzylester TsOH salt under MW irradiation.

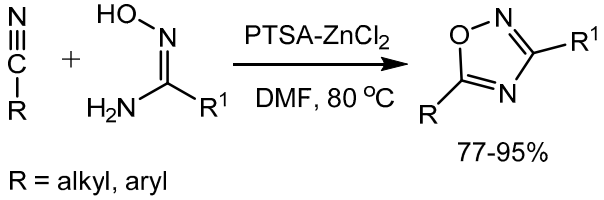
Tian *et al.* [68] reported transition metal-free C(*sp3*)-H sulfenylation of arylacetamides with thiophenols and the corresponding sulfenylated products have been successfully converted to 2-thiomethyl benzoxazoles in 24-53% yields via *p*-toluenesulfonic acid (*p*-TSA) promoted annulation (Scheme 70).



Scheme 70. *p*-TSA promoted Synthesis of 2-thiomethyl benzoxazoles.

2.3. Application of p-Toluenesulfonic Acid in Combination with Metal Salts and Other Reagents

Augustine and co-workers [69] discovered that PTSA-$ZnCl_2$ is an efficient and mild catalyst for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from amidoximes and organic nitriles in 77-95% yields. The 1,2,4-oxadiazole moiety has been proved to be a stable ester or amide bioisostere and is found in several drug molecules [70] (Scheme 71).



Scheme 71. PTSA-$ZnCl_2$ catalysed synthesis of 3,5-disubstituted-1,2,4-oxadiazoles.

Ghorai and co-workers [71] developed an interesting PTSA promoted efficient cyclization for the synthesis of biologically important 3,4-dihydropyrazino[1,2-a]indoles in 57-70% yields via an unprecedented Pictet-Spengler-detosylation cascade. This method would find tremendous utility of accessing medicinally important polycyclic indole-fused heterocycles (Scheme 72).

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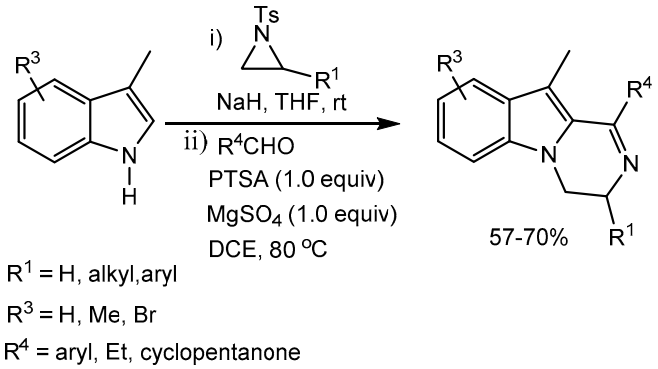
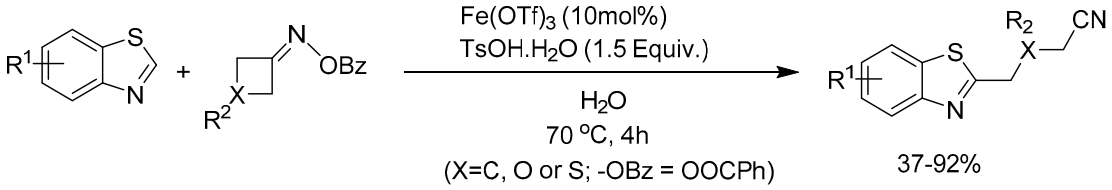


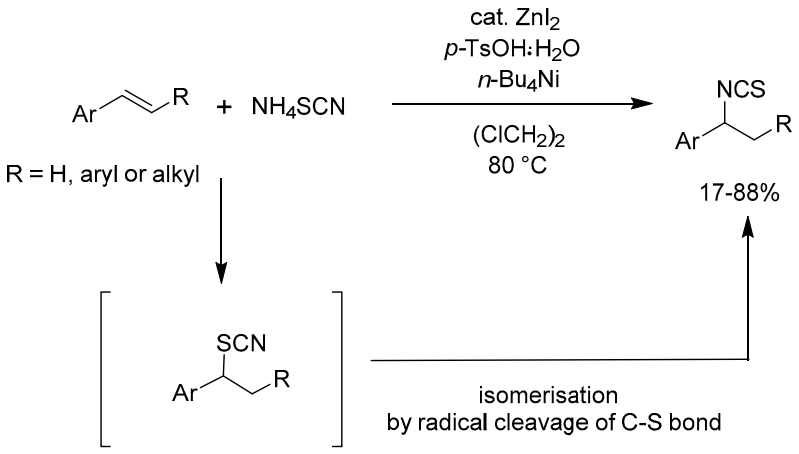
Scheme 72. PTSA promoted synthesis of 3,4-dihydropyrazino[1,2-a]indoles.

Zhou and co-workers [72] described a *p*-toluenesulfonic acid (*p*-TsOH.H2O) promotrd Fe-catalyzed coupling reaction between oxime ester and benzothiazole involving C–C bond cleavage of oxime ester via a single-electron transfer process. The coupling worked efficiently in water under mild conditions to produce alkyl nitrile substituted benzothiazole derivatives in 37-92% yields (Scheme 73).



Scheme 73. *p*-TsOH.H2O promoted Fe-catalyzed synthesis of alkyl nitrile substituted benzothiazole derivatives.

Taniguchi [73] reported a ZnI2-catalyzed addition of ammonium thiocyanate to olefins in the presence of *p*-toluenesulfonic acid (*p*-TsOH.H2O) and tetrabutylammonium iodide. The reaction proceeds by a Markovnikov-type hydroisothiocyanation of alkenes followed by a radical isomerization, and gives the corresponding isothiocyanates selectively in good yields (17-88%) (Scheme 74).



Scheme 74. Hydroisothiocyanation of alkenes in the presence of *p*-TsOH.H2O.

Ghorai and co-workers [74] developed a mild and efficient method for the one-pot stereospecific synthesis of highly functionalized imidazolidines and oxazolidines via SN2-type ring-opening of the aziridines and epoxides with amines and subsequent intramolecular cyclization with aldehydes catalysed by *p*-toluenesulfonic acid (PTSA). The methodology tolerates wide range of functional

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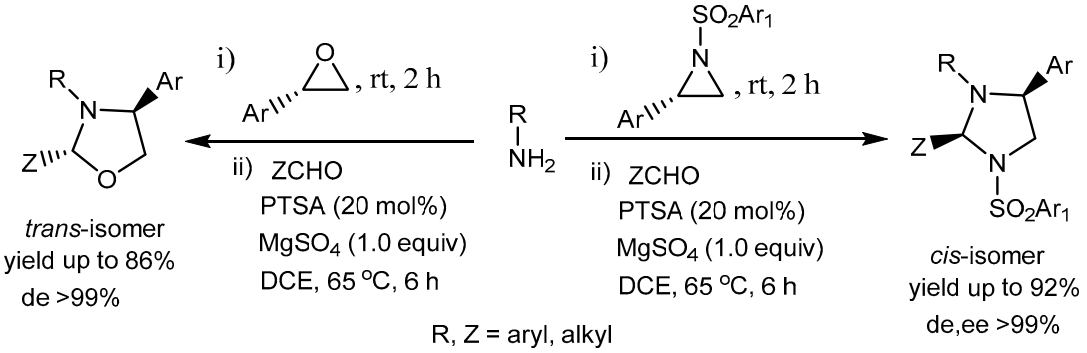
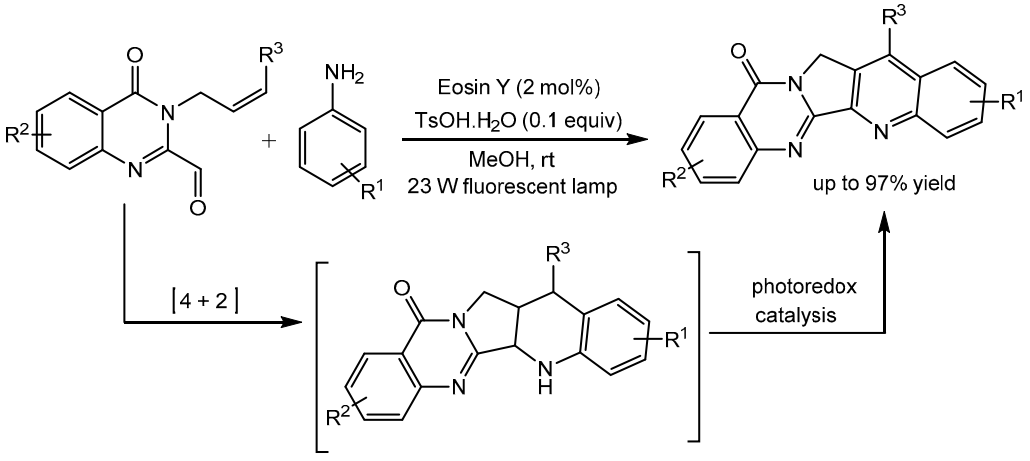
groups and provide the desired products in high yields (up to 92%) with excellent stereoselectivities (de, ee > 99%) (Scheme 75). Interestingly, imidazolidines were formed as the cis-isomers, under the reaction conditions whereas oxazolidines were produced as trans-isomers exclusively. Imidazolidine and oxazolidine moieties are prevalent in bioactive natural products and pharmaceuticals.



Scheme 75. One-pot synthesis of imidazolidines and oxazolidines using catalytic PTSA.

Wu *et al.* [75] disclosed the rapid synthesis of Luotonin A derivatives with up to 97% yield by merging visible-light photoredox and acid catalysis using eosin Y as the photocatalyst and *p*-toluenesulfonic acid monohydrate (TSOH.H2O) as the co-catalyst. The reaction proceeds through Povarov cycloaddition followed by visible-light mediated dehydrogenation. Luotonin A is a cytotoxic alkaloid reported to inhibit topoisomerase I and the compound has anticancer activity (Scheme 76).



Scheme 76. Synthesis of Luotonin A derivatives via synergestic visible-light photoredox and acid catalysis.

Substituted xanthene moiety exhibits a wide range of activity in biological and material sciences. Deore and De [76] described a visible light-mediated approach for Cross-Dehydrogenative Coupling (CDC) of Xanthene with β-keto moieties using MoS_2 Quantum Dot (QD) as a photoredox catalyst. This methodology is attractive as it does not require pre-functionalized starting material and the reaction conditions are mild and water is used as solvent , substrate scope is broad, yields of the products are good (42-94%) and recyclability of catalyst up to six cycles without loss of yield and selectivity (Scheme 77).

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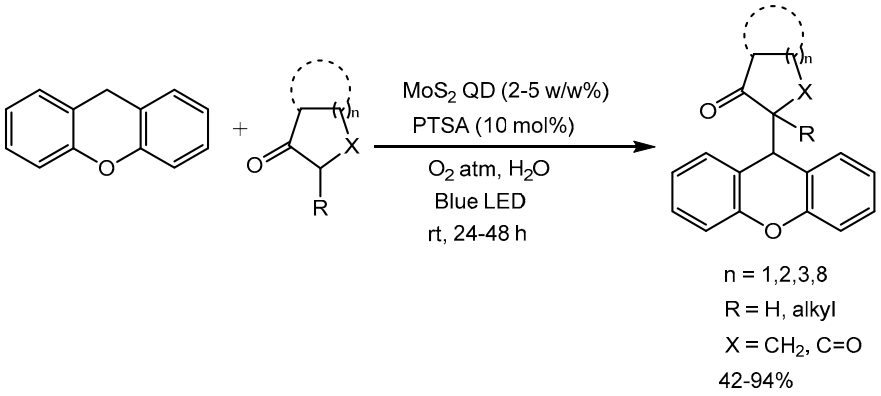
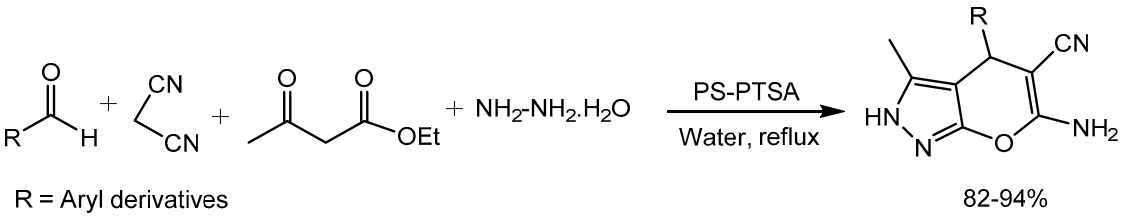


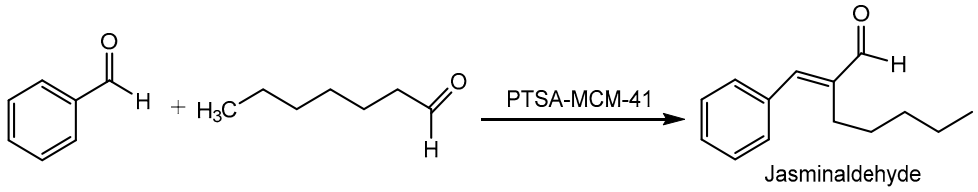
Scheme 77. PTSA promoted Cross-Dehydrogenative Coupling (CDC) of Xanthene with β-keto moieties.

Shingare group [77] developed a highly efficient and sustainable protocol for the synthesis of dihydropyrano[2,3-c]pyrazolesin in 82-94% yields in water using polystyrene-supported *p*-toluenesulfonic acid as reusable catalyst (Scheme 78). Dihydropyrano[2,3-c]pyrazoles exhibit diverse biological activities. [78]



Scheme 78. Polystyrene-supported *P*-TSA catalysed dihydropyrano[2,3-c]pyrazoles synthesis.

Ganga *etal* [79] disclosed synthesis of perfumery chemical-jasminaldehyde under solvent-free condition using *p*-toluene sulfonic acid (PTSA)-MCM-41 as a green, efficient, and reusable heterogeneous catalyst *via* cross-aldol condensation of active methylene bearing aliphatic aldehydes with aromatic aldehydes under solvent and metal-free condition. The PTSA-MCM-41 catalyst displayed high efficiency and selectivity in cross-aldol condensation reaction and was reusable (5 cycles) with no apparent loss in activity (Scheme 79).



Scheme 79. PTSA catalysed synthesis of Jasminaldehyde.

Jeong research group [80] described polystyrene supported *p*-toluenesulfonic acid (PS-PTSA) promoted one-pot multicomponent reaction of aldehydes, nitroalkane, amine and active methylene compound for the synthesis of diversified pyrrole derivatives via cross-coupling-cyclization–oxidation under microwave irradiation. This solvent-free and metal-free environmentally benign protocol provides remarkable advantages such as good to excellent yields (78-93%), shorter reaction time and easy work-up procedure (Scheme 80).

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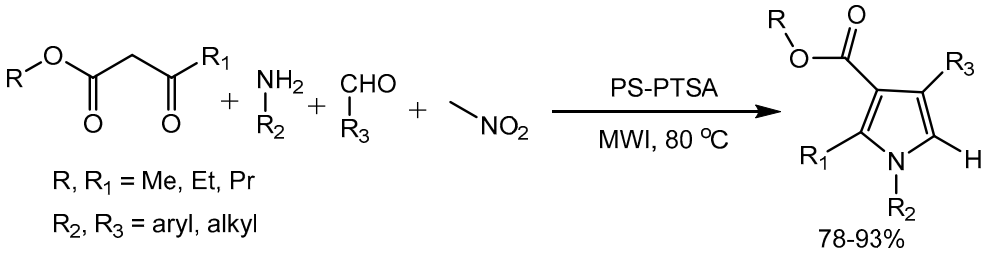
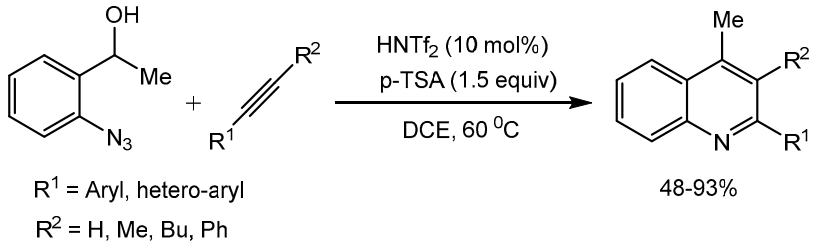


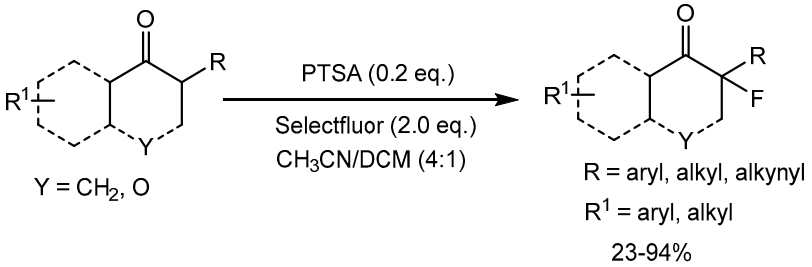
Scheme 80. Synthesis of tetrasubstituted pyrrole derivative catalyzed by PS-PTSA.

Substituted quinoline motifs are present in numerous biologically active natural products and pharmaceuticals. Hence synthesis of these compounds is of much importance. Niggemann and Stopka [81] reported a metal free carboamination of unactivated alkynes for the synthesis of highly substituted quinolones in 48-93% yields in the presence of PTSA and $HNTf_2$. Mechanistic studies indicated that the reaction proceeds via a highly reactive vinyl cation in a C–C bond formation – Schmidt reaction sequence. These findings indicate that PTSA could be used in combination with other Brønsted acid catalyst in a synergistic mode (Scheme 81).



Scheme 81. Synthesis of quinolines via synergistic catalysis using PTSA and $HNTf_2$.

Tang *et al.* [82] developed a *p*-toluenesulfonic acid catalyzed fluorination of α-branched ketones for the construction of fluorinated quaternary carbon centers in 23-94% yields. This method is environmentally benign, operationally simple and has a broad substrate scope. The structural motif bearing a quaternary C–F center is widely present in pharmaceuticals, agrochemicals, and functional materials (Scheme 82).



Scheme 82. PTSA catalysed construction of the quaternary C–F bond from ketone derivatives.

The radionuclide labelled molecules and nuclear imaging techniques has become important for the study of dynamic biochemical processes at the cellular levels useful in drug discovery process. In this context, Sloan group [83] reported a mild and efficient one-pot tandem protocol for incorporation of radioactive iodine into aryl amines via stable diazonium salts synthesized using *p*-toluenesulfonic acid monohydrate. The method is operationally simple and tolerate broad range of functional groups, allowing late-stage, rapid access to a variety of ^{125}I-labelled aryl compounds in 61-97% yields and SPECT radiotracers (Scheme 58).

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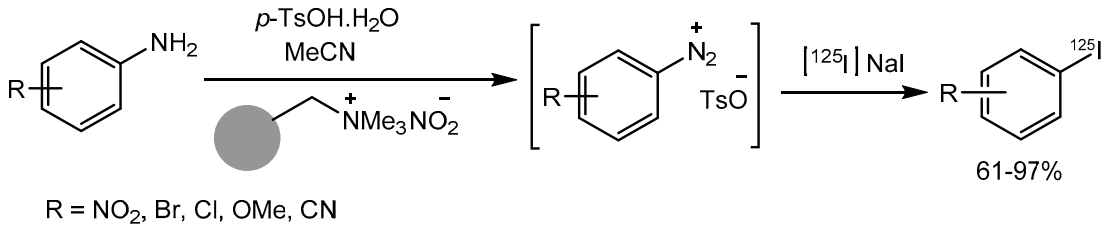
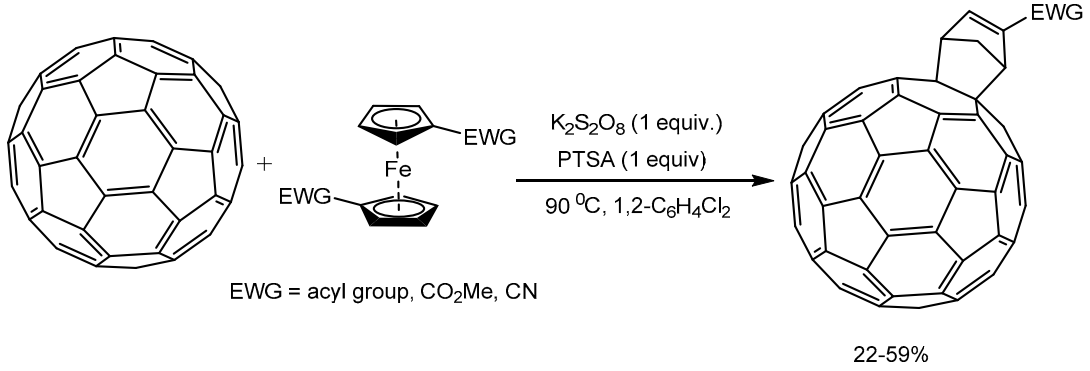


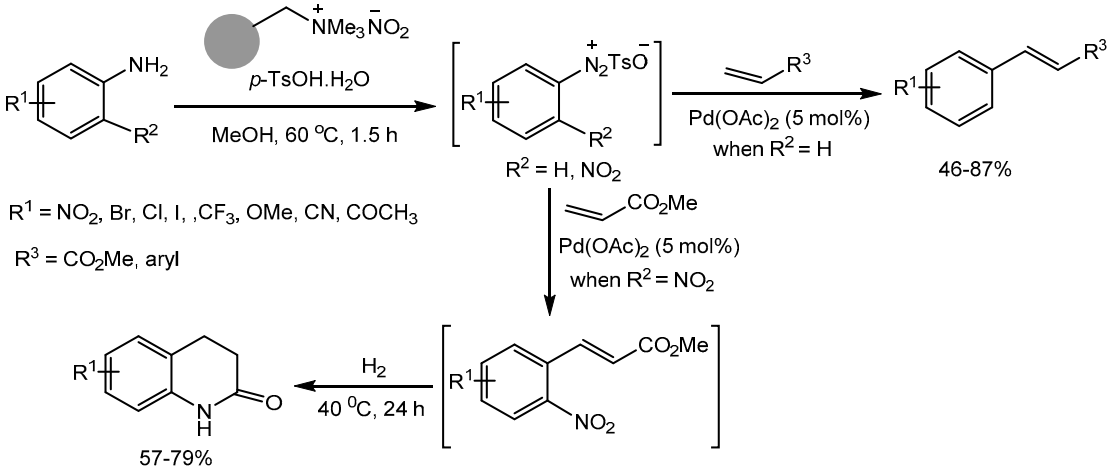
Scheme 83. One-pot radioiodination of anilines using *p*-TsOH.H2O.

Liu *et al.* [84] reported the Diels–Alder reaction of [60]fullerene (C_{60}) with ferrocenes bearing electron-withdrawing groups to afford single isomers of [2 + 4] cycloadducts of C_{60} in 22-59% yields (Scheme 84). Mechanistic studies indicate that in the presence of oxidant $K_2S_2O_8$ and *p*-toluenesulfonic acid cyclopentadienes are in situ generated from electron-deficient ferrocenes which then undergoes [2 + 4] cycloadditions with dienophiles.



Scheme 84. PTSA promoted reaction of [60]fullerene with electron-deficient ferrocenes.

Sutherland and co-workers [85] also showed that multibond forming tandem reactions of anilines could be possible via stable aryl diazonium salts generated in situ using a polymer-supported nitrite reagent and *p*-toluenesulfonic acid. This stable aryl diazonium tosylate salts effectively converted to Heck coupled products in 46-87% yields via one-pot tandem process. This one-pot tandem process was extended for the direct synthesis of 3,4-dihydroquinolin-2-ones using 2-nitroanilines as substrates in 57-79% yields (Scheme 85). The synthetic utility of this method was demonstrated by the synthesis of quinolinone-based sodium ion channel modulator.



Scheme 85. PTSA promoted one-pot tandem processes using stable aryl diazonium tosylate salts.

Chakrabarty group [86] described the efficient preparation of 2-Substituted and 1,2-disubstited benzimidazoles in 26-87% and 35-84% yields respectively from o-phenylenediamines and various

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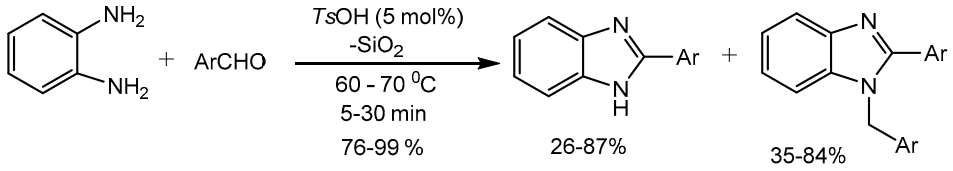
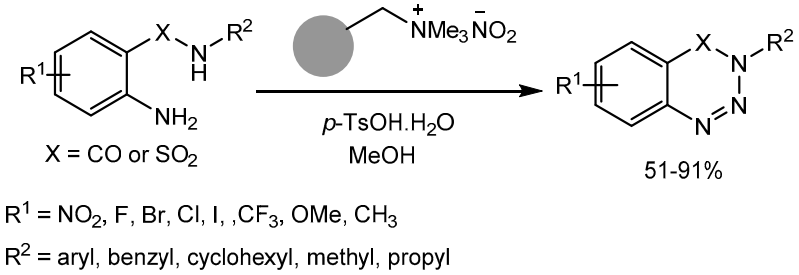
aryl aldehydes using *p*-toluenesulphonic acid (5 mol%)-on-silica gel as a cheap and environmentally benign catalyst (Scheme 86). Benzimidazoles are useful compounds having wide range of biological activities.



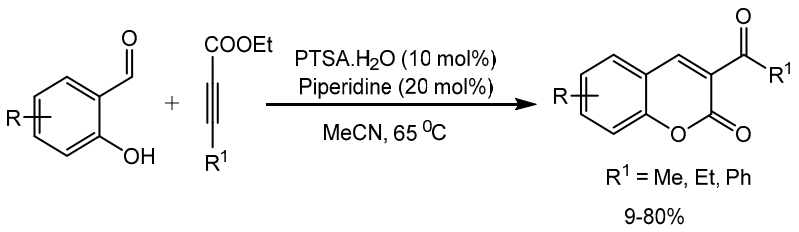
Scheme 86. Synthesis of substited benzimidazoles using tosic acid-on-silica gel.

Sutherland group [87] also reported a mild and efficient one-pot synthesis of N-substituted 1,2,3-benzotriazin-4(3H)-ones and benzothiatriazine-1,1(2H)- dioxides in 51-91% yields (Scheme 87). The method involves the diazotisation of 2-aminobenzamides and 2-aminobenzenesulfonamides using a polymer-supported nitrite reagent and *p*-tosic acid to form stable aryl diazonium tosylate salts, followed by intramolecular cyclisation to produce the desired products. The reaction was compatible with a broad range of aryl functional groups and amide/sulfonamide-substituents and application of this protocol was demonstrated with the preparation of an α-amino acid containing 1,2,3-benzotriazin-4(3H)-one. Benzotriazin-4(3H)-ones and benzothiatriazine-1,1(2H)-dioxides are privileged structures present in a wide range of pharmaceutically relevant compounds.



Scheme 87. Synthesis of N-substituted 1,2,3-benzotriazin-4(3H)-ones and benzothiatriazine-1,1(2H)-dioxides using *p*-tosic acid.

Saejong *et al.* [88] developed an efficient dual organocatalytic strategy for the synthesis of coumarin derivatives. A combination of *p*-toluenesulfonic acid monohydrate (PTSA.H_2O) and piperidine effectively catalyzed the cyclization between salicylaldehydes and alkynoic esters to afford various coumarin derivatives in 9-80% yields and high regioselectivity. Mechanistic studies indicated that the conjugate addition between piperidine and alkynoic esters played a crucial role in the reaction (Scheme 88).



Scheme 88. Dual organocatalytic synthesis of coumarin derivatives.

Jadhav and co-workers [89] developed a metal-free approach the synthesis of 2,5-furandicarboxylic acid (FDCA) from 5-hydroxymethylfurfural (HMF), fructose and glucose using a *p*-toluene sulfonic acid (*p*-TSA)-derived heterogeneous solid acid catalyst (*p*-TSA–POM). The synthesis proceeds via the conversion of HMF, fructose and glucose to 2,5-diformylfuran (DFF) using the *p*-TSA–POM catalyst and subsequent oxidation of DFF to FDCA using oxone (Scheme 89).

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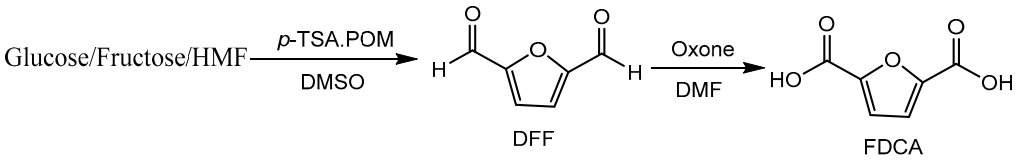
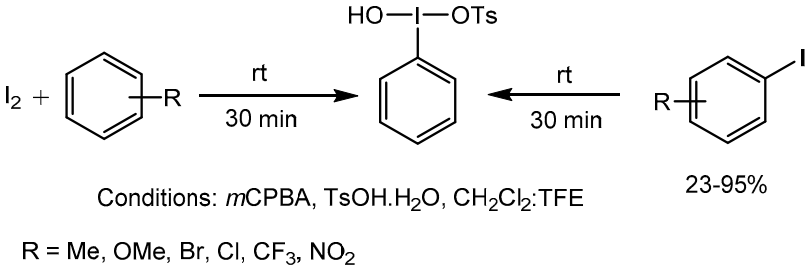


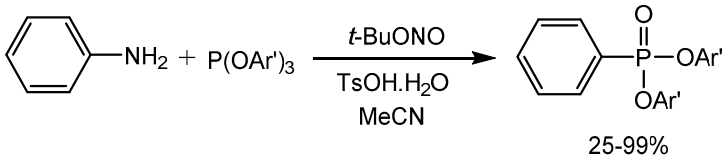
Scheme 89. Synthesis of 2,5-furandicarboxylic acid (FDCA) using the *p*-TSA–POM catalyst and oxone.

Olofsson group [90] reported one-pot facile synthesis of neutral and electron-rich [hydroxy(tosyloxy)iodo]arenes, (HTIBs), also known as Koser's Reagent from iodine or aryl iodides using *p*-toluenesulfonic acid monohydrate (TsOH.H$_2$O) in 23-95% yields. The reaction conditions are mild and avoid the use of expensive iodine(III) precursors and generate variety of HTIBs which are useful reagents for wide range of synthetic transformations (Scheme 90).



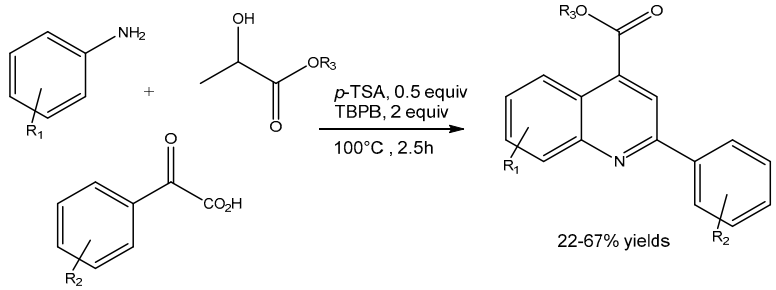
Scheme 90. Synthesis of Substituted HTIBs using TsOH·H$_2$O.

Wang *et al. [91]* described a metal-free efficient phosphorylation process via a Sandmeyer-type reaction from aryl amines employing *p*-toluenesulfonic acid monohydrate (TsOH.H$_2$O). The reaction proceeds smoothly at room temperature and tolerates a wide range of functional groups. The phosphorylation products were obtained in 25-99% yields. This method is thus considered to be valuable for the formation of aromatic carbon−phosphorus bonds (Scheme 91).



Scheme 91. TsOH.H$_2$O promoted metal-free carbon−phosphorus bond formation. .

Huang *etal* [92] disclosed a new and metal-free method for the synthesis of diverse 2,4-disubstituted quinolines in 22-67% yields *via* the reactions of anilines, *α*-keto acids and alkyl lactates in the presence of *p*-toluene sulfonic acid (*p*-TSA) and *tert*-butyl peroxybenzoate (TBPB) (Scheme 92). This method resulted the construction of new C=C double, C–C single and C=N double bonds without producing any organic mass-based side product. The anti-inflammatory activity of the quinolines has also been investigated.



Scheme 92. *P*-TSA catalyzed synthesis of 2,4-disubstituted quinolines.

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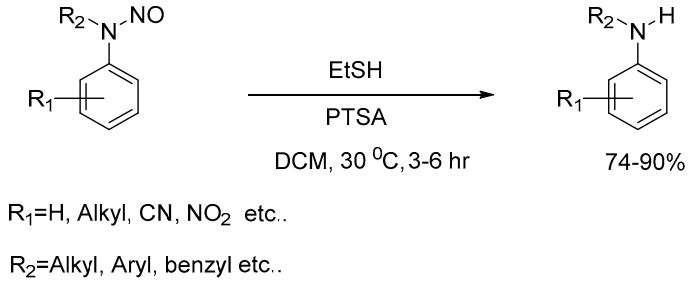
Kandasamy group [93] disclosed a convenient route for the denitrosation of aryl-*N*-nitrosamines by a transnitrosation strategy using ethanethiol and *p*-toluene sulfonic acid (PTSA) under mild conditions to access various amines in good to excellent yields (74-90%) (Scheme 93).

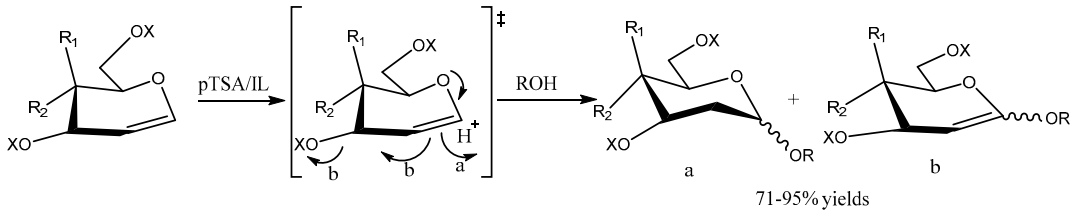


Scheme 93. *P*-TSA catalyzed synthesis of amines via denitrosation of aryl-*N*-nitrosamines.

2.4. Application of p-Toluenesulfonic Acid in Ionic Liquids

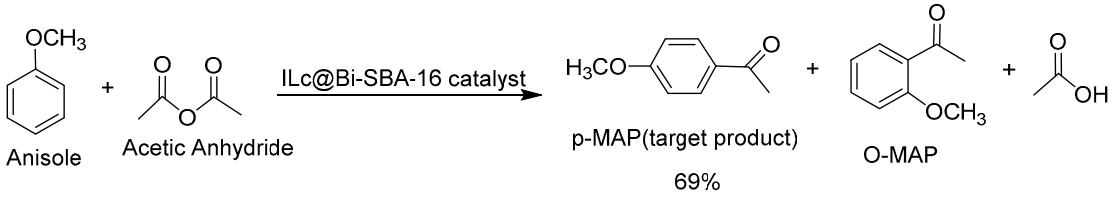
Ionic liquids are generally organic salts which comprise of organic cation and suitable inorganic or organic anion. In recent years, ionic liquids have emerged as one of the most promising green solvents for organic reactions, due to their high thermal stability, non-volatility, non-flammability and recyclability. Because of negligible vapour pressure, ionic liquids are considered an environmentally benign alternative to traditional volatile and flammable organic solvents. Ionic liquids are found to be an efficient reaction media for different catalytic avenues, like transition metal-based catalysts, Lewis acid catalysts, and enzyme catalysts. *p*-Toluenesulfonic acid (*p*TSA) have also been used to catalyze reactions in ionic liquids which would be discussed in this section. Due to their high polarity, reactions in ionic liquids have different kinetic and thermodynamic behavior than classical solvents, which often leads to improved efficiency of the reactions.

Ponzinibbio group [94] described the synthesis of α-2-deoxyglycosides in ionic liquid ([bmim]BF_4) by stereoselective glycosylation of endo-glycals with various o-nucleophiles in the presence of catalytic amount of *p*-Toluenesulfonic acid (*p*TSA) in 71–95 % yield (Scheme 94). High yields of the products and reusable reaction medium (*p*TSA/[bmim][BF_4] ionic liquid) with consistent activity makes this protocol green and sustainable.



Scheme 94. *p*TSA catalyzed synthesis of α-2-deoxyglycosides in ionic liquid.

Jiang and co-workers [95] developed *p*-toluenesulfonic acid (*p*-TSA) functionalized imidazole ionic liquids encapsulated into bismuth SBA-16 as high-efficiency catalysts for Friedel–Crafts acylation reaction of anisole with acetic anhydride in 69% yield (Scheme 95).



Scheme 95. Friedel–Crafts acylation reaction catalyzed by *p*-TSA functionalized imidazole ionic liquids encapsulated into bismuth SBA-16.

Nguyen group [96] disclosed "PTSA/1-alkyl-3-methylimidazolium ionic liquids" as reusable couple for efficient halogenation of fatty diols (Scheme 96). The kinetics of halogenation of fatty

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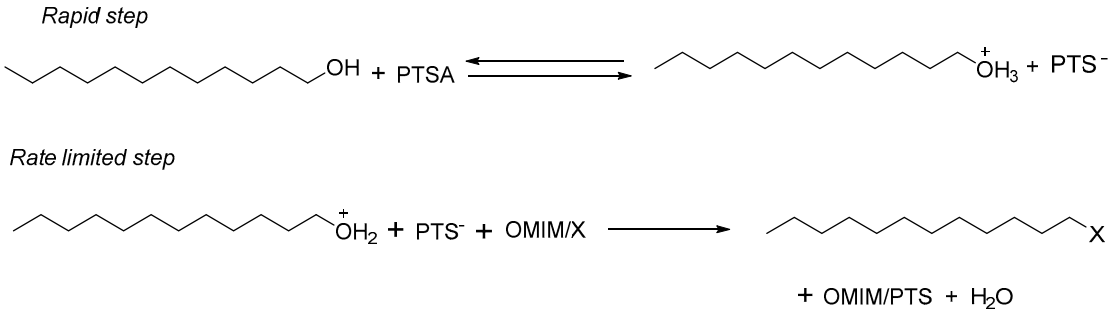
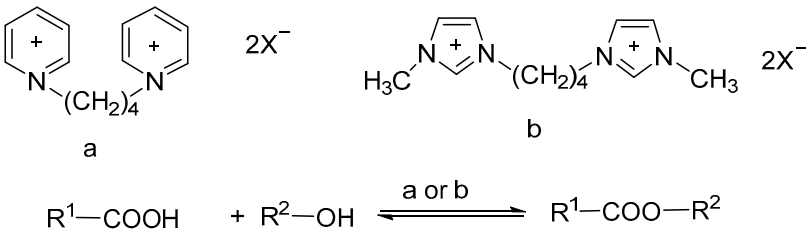
dialcohols proved the A2 (or SN2c) mechanism in which monohalogenation was four-fold faster than dihalogenation.



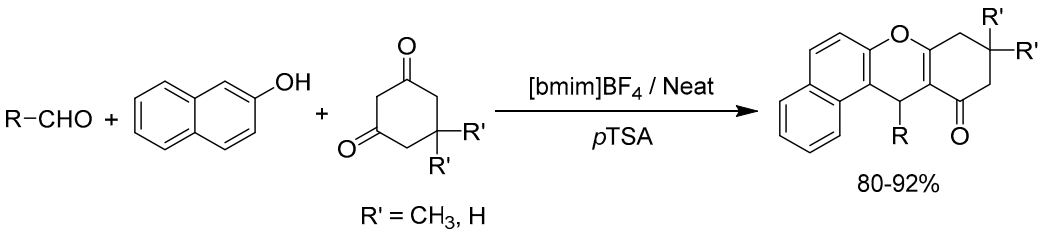
Scheme 96. Halogenation of fatty diols by "PTSA/1-alkyl-3-methylimidazolium ionic liquids".

Zhao *etal* [97] described the synthesis of functional binuclear ionic liquids based on bis-(3-methyl-l-imidazole)butylidene double *p*-toluene sulfonic acid salt (Im-PTSA) and bis-(1-pyridine)butylidene double *p*-toluene sulfonic acid salt (Py-PTSA) and studied the catalytic activity of the binuclear ionic liquids for the esterification of succinic acid with ethanol (Scheme 97). The results show that under the optimized conditions, diethyl succinate was obtained in 93.6% and the selectivity was near up to 100%. Im-PTSA was recycled and reused at least 8 times without significant decrease in activity after drying under vacuum.



Scheme 97. Esterification of acid using bis-(3-methyl-l-imidazole)butylidene double *p*-toluene sulfonic acid salt (Im-PTSA).

Khurana group [98] developed *p*-toluenesulfonic acid (pTSA) catalyzed multi-component reaction of β-naphthol, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds in ionic liquid([bmim]BF_4) for the one pot synthesis of a series of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones (Scheme 98). High yields of the products (80-92%) and reusable reaction medium makes this protocol efficient and environmentally benign.



Scheme 98. pTSA catalyzed multi-component synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones in ionic liquid.

A plausible mechanism for the pTSA catalyzed formation of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives is proposed in Scheme 99.

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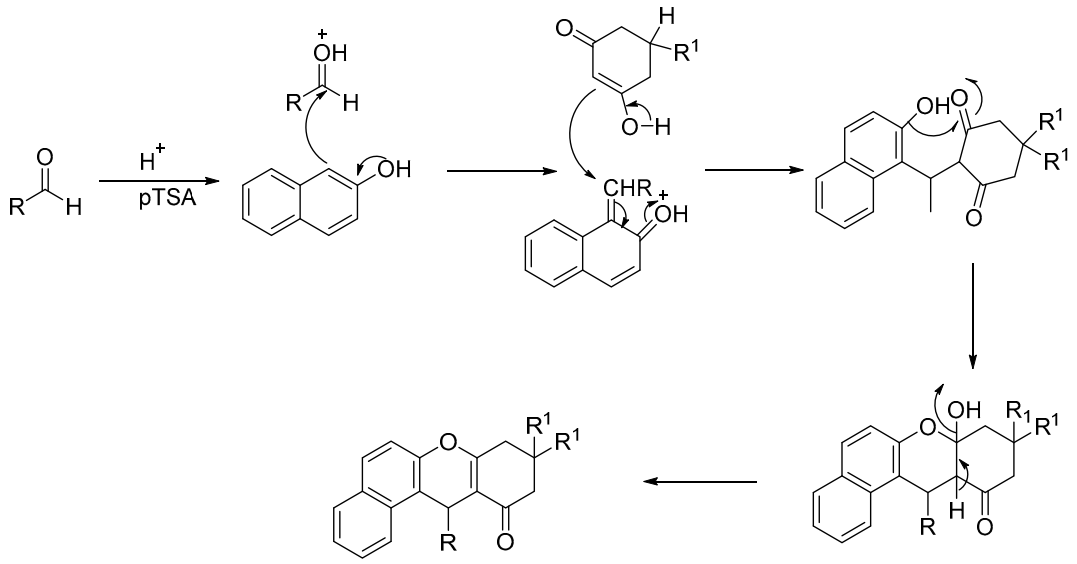

Scheme 99. Plausible mechanism of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones formation.

3. Conclusions

In this review, versatile applications of *p*-toluenesulfonic acid in various organic reactions for synthesizing useful building blocks, heterocyclic compounds, polymers and supra molecules have been depicted. Several new synthetic approaches have been discussed for functional group transformations, photoactive materials synthesis, multicomponent reactions (MCRs) for bioactive molecule synthesis, liquid-crystalline and light-emitting materials synthesis, cyclization reaction, substitution and condensation reaction, Michael type addition reaction, tandem reaction, rearrangement reaction, transition metal catalysed reaction, privileged heterocycles and radio-labelled compound synthesis, photochemical reaction, cycloaddition reaction and Cross-Dehydrogenative Coupling (CDC). This review also demonstrates the potential of polystyrene, zeolite and silica supported *p*-toluenesulfonic acid in different organic reactions. We have also described the use of PTSA in environmentally benign ionic liquids for different organic transformations. PTSA promoted synthesis has produced structures with interesting properties. The summary of the synthesis and useful features will be helpful to researchers working in the fields of chemical, biological and materials sciences. We present several reactions here exemplifying the multiple roles of PTSA. Since the discovery, great progress has been made regarding the use of PTSA in synthetic organic transformations. In conclusion, the advances in synthetic methodology using PTSA and a better understanding of the reaction mechanisms have been very significant. Therefore, we expect that this review will encourage more organic chemists to continue investing their creative strength in the discovery of new reactions using this environmentally benign solid organic acid with novel mechanisms.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1.

Author Contributions: Conceptualization, Pradip Bhowmik; Software, Pradip Bhowmik; Supervision, Pradip Bhowmik; Writing – original draft, Biplab Banerjee and Haesook Han; Writing – review & editing, Biplab Banerjee, Haesook Han and Pradip Bhowmik.

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Conflicts of Interest: The authors declare no conflict of interest.

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