

Recent Advances in Quinone Imine Ketal Chemistry: Regioselective Functionalization and Synthetic Applications

Vaishnavi Murlidhar Chopde^a and Amardeep Ramprasad Jadhao^{*a}

^aDepartment of Chemistry, Late Pushpadevi Patil Arts & Science College, Risod, Dist-Washim, MS India-444506.

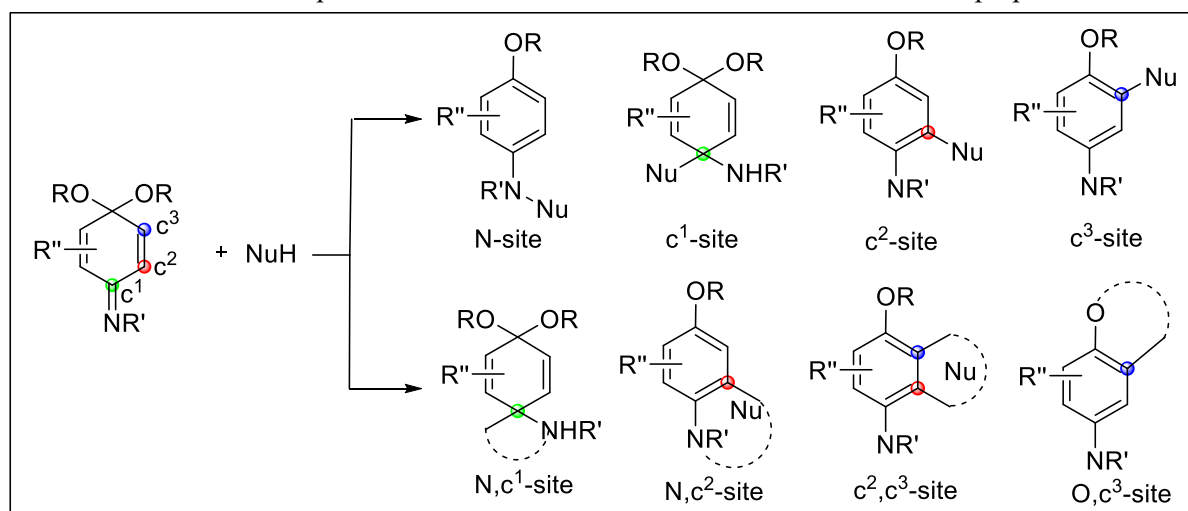
* Corresponding author amardeepjadhao@gmail.com

Introduction

In recent years, quinone imine ketals (QIKs) have been used as outstanding organic synthons for the construction of complex organic molecules as they were equipped with varied functional groups (C=N, C=C and ketal etc.). Unravelling the site selectivity (chemo-, regio- and stereo-selectivity) of QIKs is not only a very noteworthy, but also a thought-provoking research topic. The preparation methods of QIKs and its applications in organic synthesis needs to be explored as very fewer reports were available in the literature.¹ Since the quinone imine ketals (QIKs) contains conjugated carbon-nitrogen double bonds in the molecular structure (C=N) and carbon-carbon double bond (C=C) along with ketal functional group, there may be competition among all these functional group sites for the reaction. During participation of these sites in the reaction, there are great challenges associated in realizing their high-selectivity reactions (chemo-selectivity, regioselectivity, and stereo-selectivity) (Scheme 1). In recent years, many research groups worldwide have successively established diverse effective synthetic strategies towards construction of novel and complex organic molecules using quinone imine ketals (QIKs). Furthermore, unravelling new reactions to accomplish site-selective reactions of QIKs, and their application in constructing the novel and complex organic molecules will still be a very highly attractive research topic of academic significance. The synthetic methods for quinone imine ketals (QIKs) and their synthetic applications are summarized in this section.

1. Synthesis of quinone imine ketals (QIKs)

Swenton and coworkers reported the electrochemical anodic oxidation method for preparati-



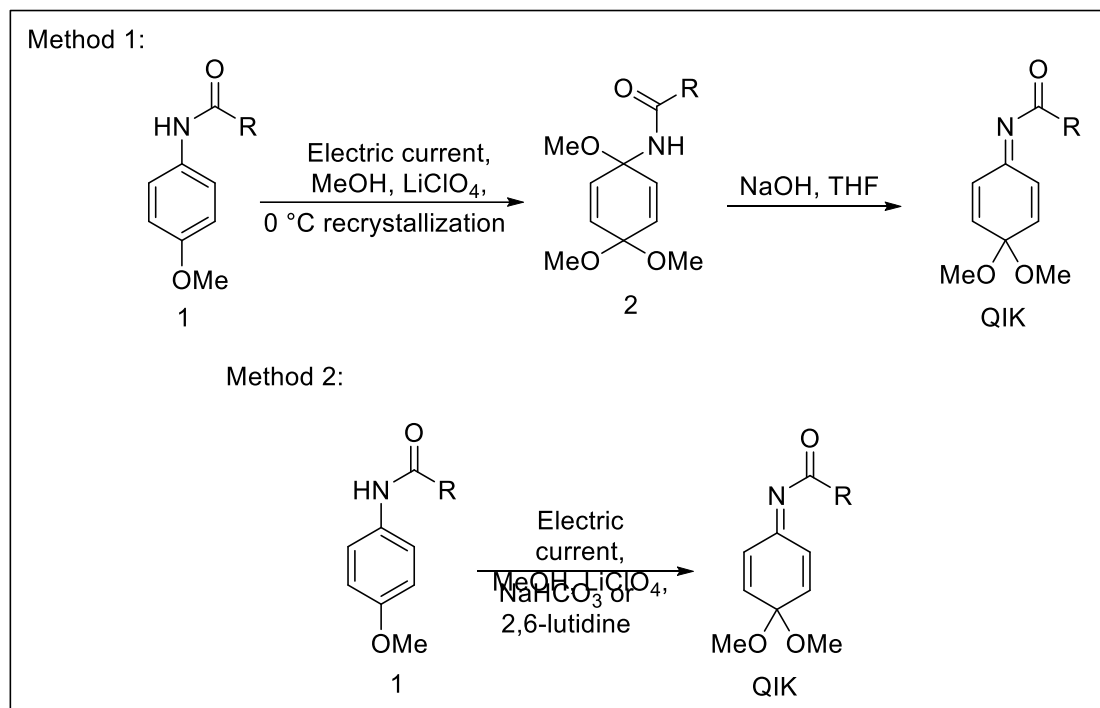
Scheme 1. Selectivity and reactive sites of QIKs

on of N-acyl quinone imine ketal (QIKs) and fused ring quinone imine ketal.² Kerr et al reported the method of N-sulfonyl quinone imine ketal (QIKs) preparation using iodobenzenediacetic acid (PIDA) by oxidation of *p*-methoxyaniline derivatives.³ Reisman research group developed a classic two-step synthesis of phthalic acid by oxidation of *p*-methoxyphenol derivatives, and tetraethyl titanate condensation via N-tert-butylsulfinimide ketal (QIKs).⁴

1.1. Swenton's route

In 1987, Swenton research group^{2a} reported synthesis of intermediates **2** from N-acyl *p*-Methoxyaniline in presence of methanol and lithium perchlorate (w = 2%) under galvanolytic dielectric conditions. The yield of **2** was obtained in 80%. The intermediate **2** further transformed to quinone imine ketal (QIK) in yield 86% yield. (Scheme 2, Method 1). Subsequently, the group^{2b} further established a one-pot naive approach to efficiently synthesis quinone imine ketals

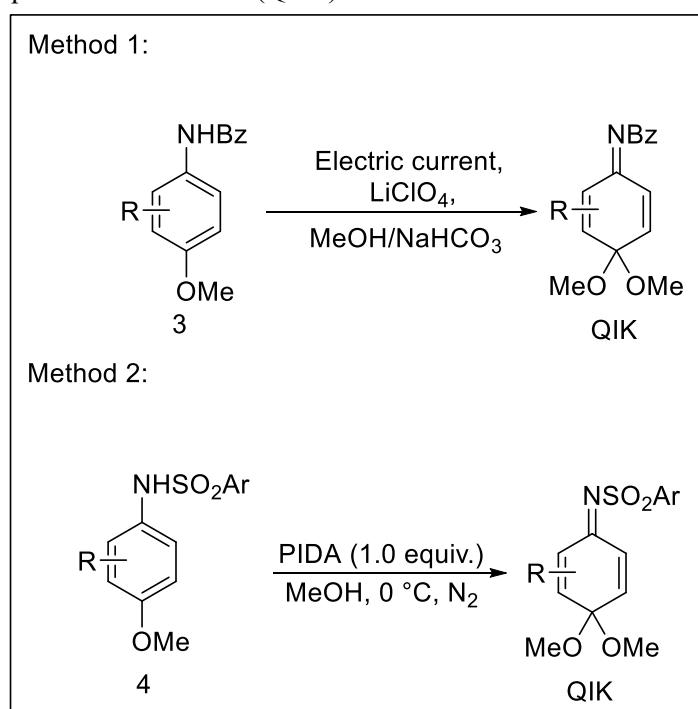
(QIKs), in the presence of sodium bicarbonate or 2,6-Dihydropyridine in an anodic oxidation of N-substituted *p*-anisidines under alkaline conditions in 80%-95% yields (Scheme 2, Method 2). Out of these two methods it is noteworthy that in Method 2, sodium bicarbonate was reacted under alkaline conditions, and the product thus obtained has to be treated rapidly to avoid the de-acylation of quinone imine ketal (QIKs); while when the reaction performed using 2,6-lutidine as a base, not only avoids post-treatment de-acylation reaction, but also generally gives higher product yields (Scheme 2).



Scheme 2. Swenton's methods to synthesize QIKs

1.2. Kerr's route

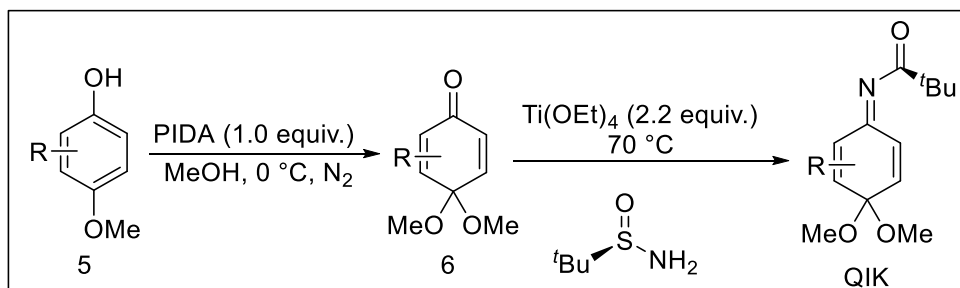
Kerr research group in 2004^{3c} reported the anodizing method for the synthesis of quinone imine ketals (QIKs). They also modified Swenton's methods and reported the new simple route to obtain quinone imine ketals (QIKs).^{3c} In this modified route they used oxidation method by using iodobenzenediacetic acid (PIDA) and MeOH in stoichiometric amounts to obtain 72%~89% yield of quinone imine ketals (Scheme 3). This route hereon been widely used to synthesize quinone imine ketals (QIKs).



Scheme 3. Kerr's routes for synthesizing QIKs

1.3. Reisman's route

Reisman and coworkers in 2011^{4d} during the total synthesis of (-)-3-demethoxyerythratidinone prepared the QIK. In this method the phenol derivative **5** was dissolved in ice cooled methanol, followed by dropwise addition of iodobenzenediacetic acid (PIDA), and stirred until the starting material (phenol derivative) **5** disappeared completely; Subsequently, the reaction was quenched with saturated solution of sodium bicarbonate and followed by extraction in EtOAc. The crude product was purified by column chromatography to obtain the compound **6** (*R*)-tert-butylsulfonamide which was further dissolved in dry THF, treated with Ti(OEt)₄ by slow addition, and heated until the starting material disappears; then, the reaction solution is diluted with ethyl acetate and washed with brine, stirred for a period of time, filtered through diatomaceous earth (Celite) and extracted, finally the crude product QIK was separated by column chromatography.



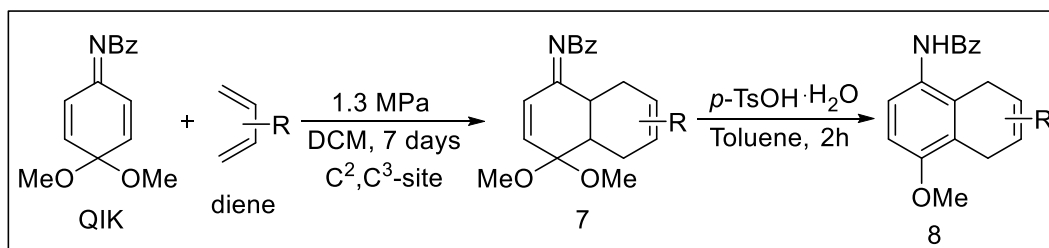
Scheme 4. Kerr's route to synthesize QIKs

2. Some examples of applications of QIKs in organic synthesis

After development of simple and efficient method to synthesize quinone imine ketals (QIKs) by Kerr et al in 2004, it is being widely used in organic synthesis. Some examples of these applications are discussed below.

2.1. Synthesis of dihydronaphthalene derivatives

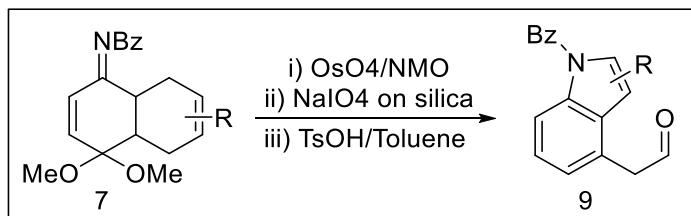
In 2001, Kerr research group from Canada,^{3b} depending on the previous reaction conditions of high-pressure endorsed the intermolecular interaction between quinone imine ketals and diene in a Diels-Alder reaction, to synthesize a series of dihydronaphthalene derivatives **7** as a cycloaddition product which under acidic conditions further aromatized to yield dihydronaphthalene benzamides **8** (Scheme 5).



Scheme 5. Synthesis of dihydronaphthalenes from QIKs

2.3. Synthesis of indole derivatives^{3a}

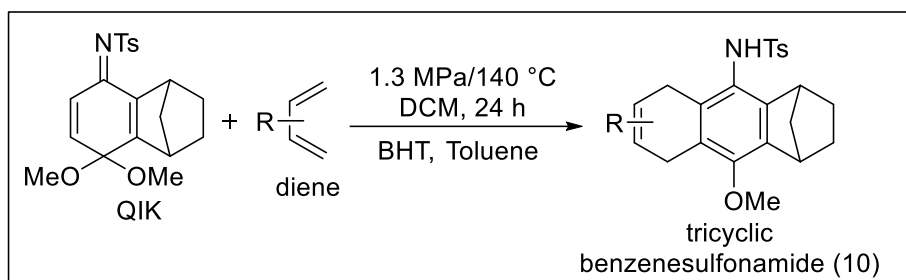
Kerr et al, further utilized intermediate **43** to form indole derivatives, in this study they treated QIK with Osmium tetroxide under acidic oxidative cyclization conditions to yield indoles **9** (Scheme 6)



Scheme 6. Synthesis of indoles from QIKs

2.4. Synthesis of tricyclic compounds

In 2004, Kerr et al^{24c} supplementarily improved the preparatory method of quinone imine ketals (QIKs), and studied its response with diene molecules a Diels-Alder reaction to transform in a tricyclic product **10** (Scheme 7).



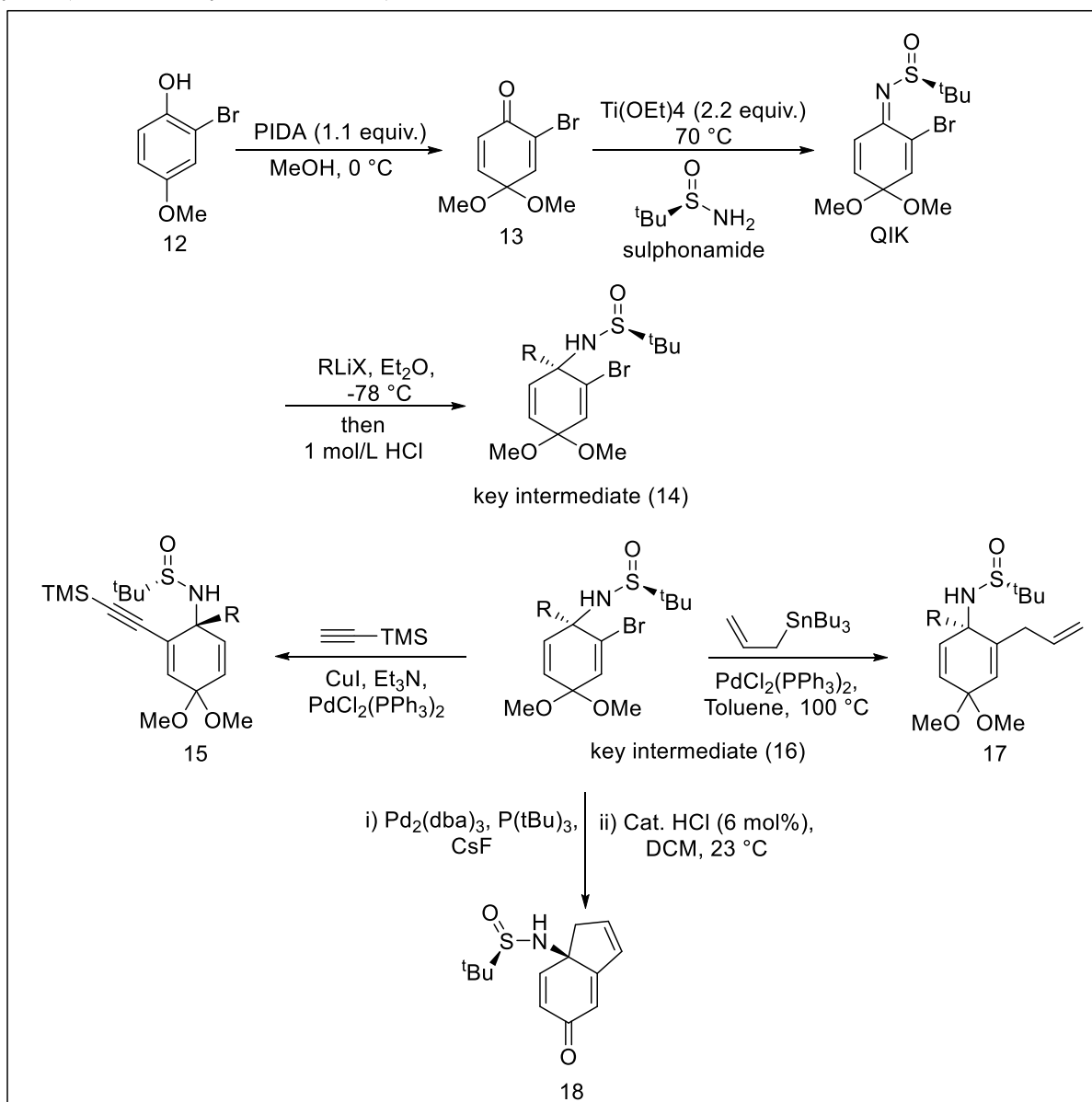
Scheme 7. Synthesis of tricyclic benzene sulphonamide from QIK

2.5. Synthesis of C-C cross coupling compounds

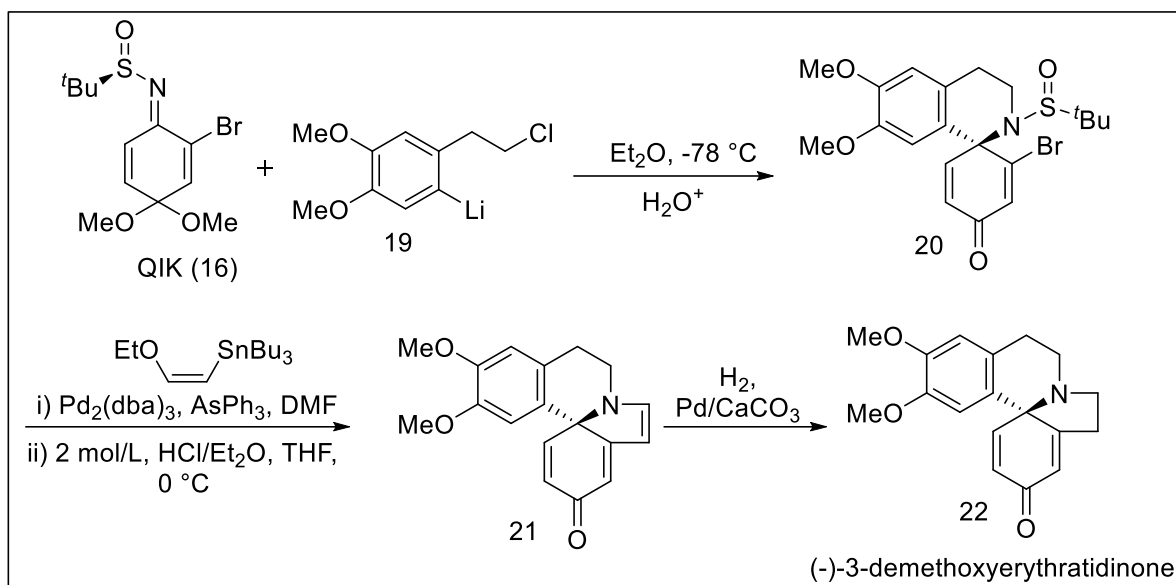
Reisman research group in 2011,^{4c} reported synthesis of a series of (R)-N-tert-butylsulfinimide ketal (QIK).

Subsequently, the quinone imine ketal

(QIK) reacts at C1-site with organolithium reagents (RLiX) to yields important intermediates **14** which after a cross-coupling reaction catalyzed by palladium (II) to yield the corresponding alkynyl and allyl coupling products **12** to **18** respectively (**Scheme 8**). Subsequently, substrate **13** was reacted with organolithium reagent to synthesis intermediate **14** is a key step. Intermediate **14** further in presence Pd₂(dba)₃ and AsPh₃ reacts with alkenyl stannane, to obtain the Stille-coupling product **17**. Compound **16** through catalytic reduction yields (-)-3-Demethoxyerythron **22** in 65% yield (36% overall yield, **Scheme 9**).



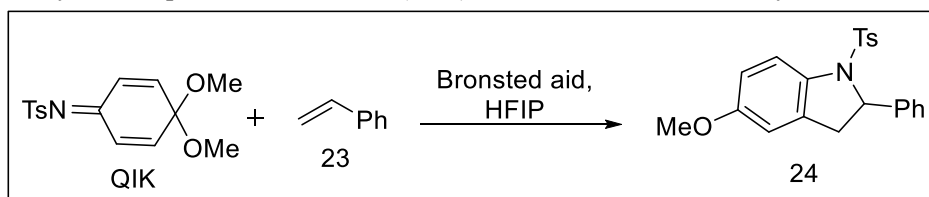
Scheme 8. Synthesis of C-C cross coupling compounds from QIK



Scheme 9. Synthesis of (-)-3-demethoxyerythratidinone

2.6. Synthesis of indolines

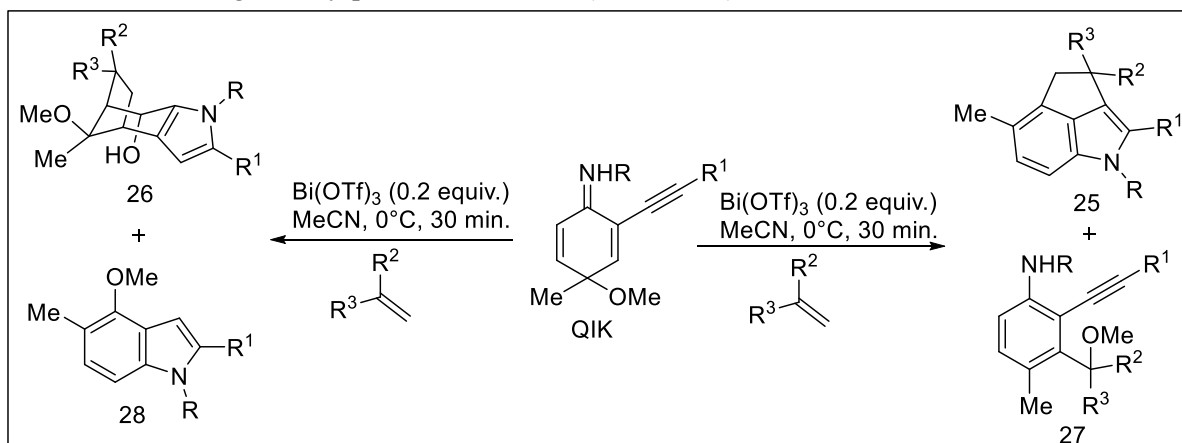
Kita research group in 2011⁵ reacted perfluorobenzoic acid as Brønsted acid and hydrogen bond donor hexafluoroisopropanol (HFIP), in situ generating a new type of composite acid catalyst. By treating this in situ generated catalyst with quinone imine ketal (QIK) and alkenes **23** in [3+2] cyclization reaction, to yield indoline derivatives **24**.



Scheme 10. Synthesis of indoline derivatives

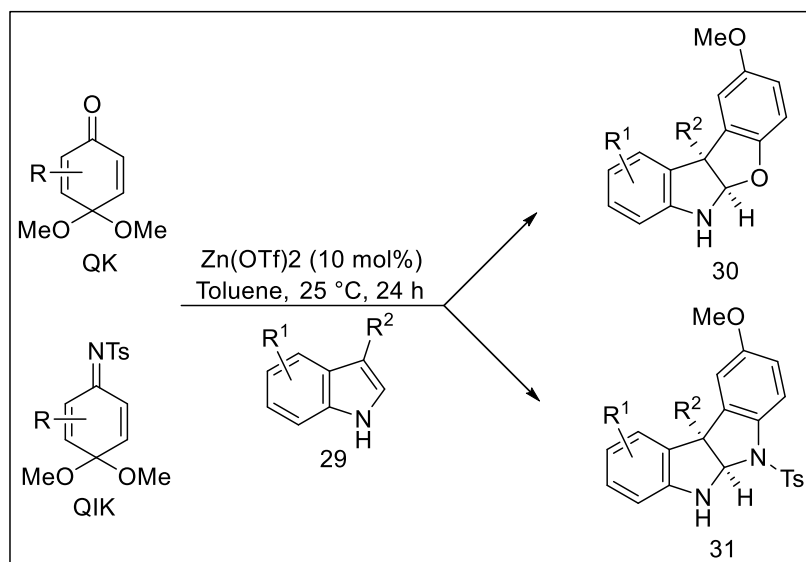
2.7. Transition metal catalyzed cascade reaction

In 2012, Fan Renhua's group⁶ developed a transition metal catalyzed controlled divergent cascade reaction of alkynyl quinone imine ketals (QIKs) with alkenes to synthesized a variety of nitrogen containing heterocycles. In this report, aniline derivatives were first oxidized with iodobenzenediacetic acid (PIDA) to 2-Alkynyl quinone imine ketal (QIKs) followed by Bi(OTf)₃-catalyzed cyclization reaction to synthesize the indole derivatives **25** and tricyclic pyrrole derivatives **26**, along with by-products **27** and **28** (Scheme 11).



Scheme 11. Synthesis of indole and pyrroles from QIKs

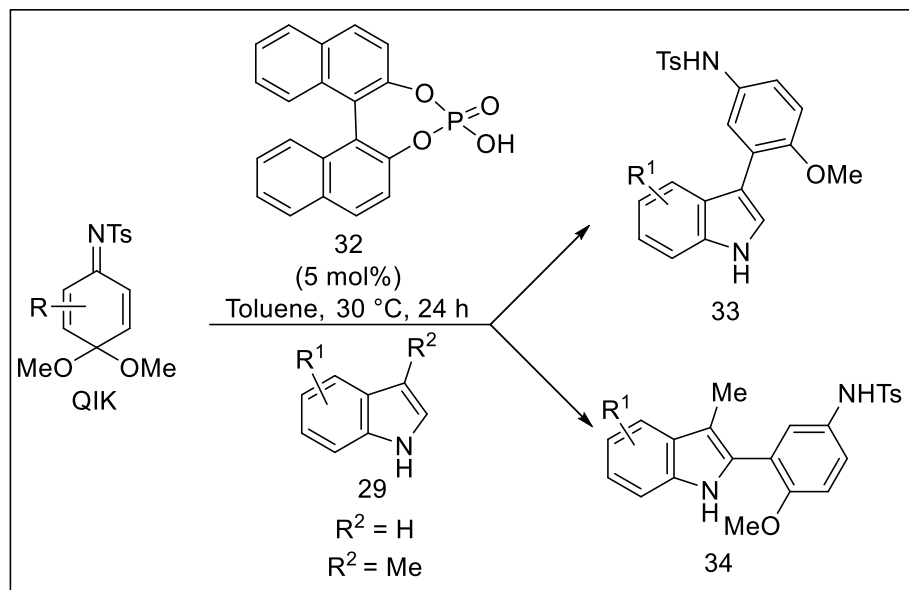
Recently, Zhang Xiaomei et al⁷ reported Zn(OTf)₂ catalyzed [3+2] cyclization reaction of 3-Substituted indole **29** with quinone ketal (QK/QIK). This route provides a series of racemic benzofuran indole derivatives **30**. At the same time, under the same reaction conditions, when quinone imine ketal (QIK) were used, a series of novel indoline derivatives **31** were formed with 42%-86% yields (Scheme 12).



Scheme 12. Synthesis of benzofuran indole and indoline derivatives

2.8. synthesis of 3-indole *m*-aniline and 2-indole *m*-aniline

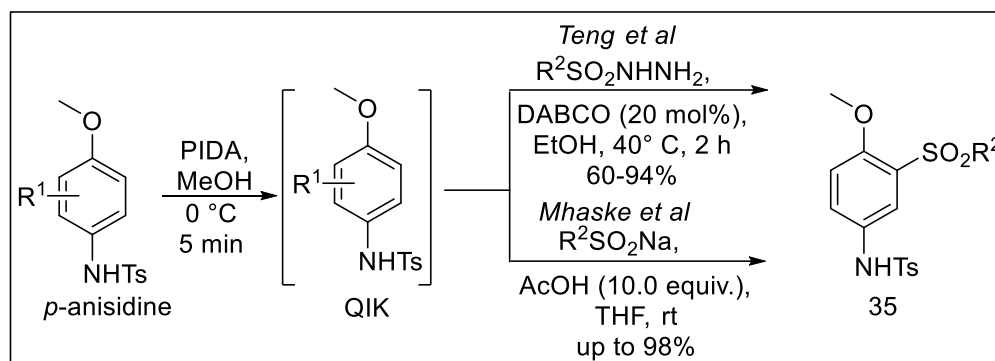
Shi Feng's research group in 2015⁸ reported 1,4-addition/alcohol elimination reaction. They reacted quinone imine monoketal (QIK) with indole/3-Substituted indole **29** in presence of racemic phosphonic acid **32** catalyst, to synthesize 3-indole *m*-aniline and 2-indole *m*-aniline derivatives **33** and **34**. It is noteworthy here that the double hydrogen bond between the phosphonic acid catalyst and the substrate plays a key role the activation of the reaction, to give the product (Scheme 13).



Scheme 13. synthesis of 3-indole *m*-aniline and 2-indole *m*-aniline derivatives from QIK

2.9. Synthesis of aryl sulfones

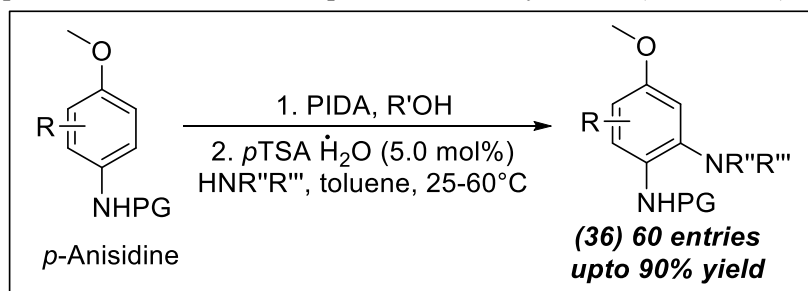
In 2019 Teng et al and Mhaske et al reported the synthesis of aryl sulfones **35** using QIK intermediates. Teng and coworkers⁹ synthesis involves 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed sulfonation of quinone imine ketals (QIKs) at C3-site with sulfonyl hydrazide via 1,4-addition reaction. Whereas, Mhaske and coworkers¹⁰ route involves sodium sulfonates as a sulfonating agent under an acidic condition to obtain same product. A series of arylalkyl sulfones, aryl-aryl sulfones, aryl-alkenyl sulfones and aryl-heteroaryl sulfones have been synthesized by these groups. (Scheme 14)



Scheme 14. synthesis of aryl sulfone derivatives from QIK

Hazra et al's approach

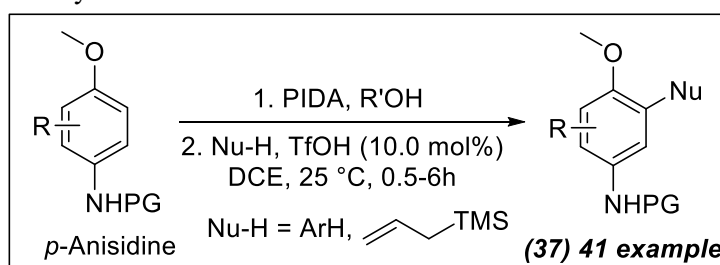
C. K. Hazra et al. reported a Brønsted acid-catalyzed method for the selective meta-amination of anisidines with aliphatic, heterocyclic, and aromatic amines.¹¹ The study demonstrated an unusual reversal of the conventional site-selectivity observed in C–H activation, providing a useful retrosynthetic approach to otherwise difficult-to-access meta-substituted anilines. The reaction was developed as a one-pot protocol and showed good scalability along with broad functional-group tolerance. Its synthetic utility was further demonstrated through the late-stage functionalization of pharmaceutical molecules and natural products. Control experiments and computational studies were carried out to investigate the reaction mechanism and to explain the origin of the observed meta-selectivity. The authors also extended the methodology to the synthesis of challenging tri-aminated arenes. Furthermore, the practical significance of the method was highlighted through its application in the synthesis of 5-HT6 receptor antagonists, including the antipsychotic compounds SB-214111, SB-258510, and the antischizophrenic drug SB-271046. Overall, this study provided a concise and versatile strategy for accessing meta-aminated aromatic compounds and demonstrated its potential for medicinal and pharmaceutical synthesis. (**Scheme 15**)



Scheme 15. Hazra et al approach to regioselective *ortho*-amination of anilines via QIK

Hazra and co-workers

The authors reported a metal-free, nondirected, site-selective, one-pot method for the meta-arylation of arylamines.¹² The study developed a Brønsted acid-catalyzed direct C–C bond-forming reaction that enabled the selective introduction of aryl groups at the meta position, thereby overcoming the conventional site-selectivity of arylamine functionalization. The methodology exhibited a broad substrate scope and good scalability, making it a useful approach for the synthesis of meta-substituted anilines. (**Scheme 16**) The authors further demonstrated that the protocol could be extended to the meta-allylation of anilines and applied to late-stage functionalization. Its synthetic utility was also highlighted through the preparation of medicinally important arylated diamines and densely functionalized anilines. Control experiments and density

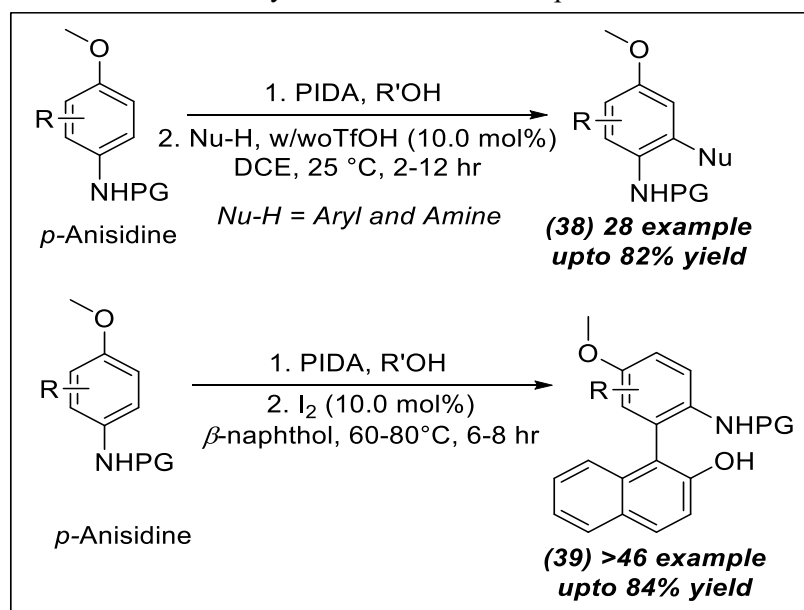


Scheme 16. Hazra's approach for *meta*-arylation of anilines via QIK

functional theory (DFT) calculations were performed to investigate the reaction mechanism and provide an understanding of the factors responsible for the observed site-selectivity. Overall, the study established a versatile metal-free strategy for selective meta-functionalization of arylamines with potential applications in synthetic and medicinal chemistry.

Hazra's other studies on QIK

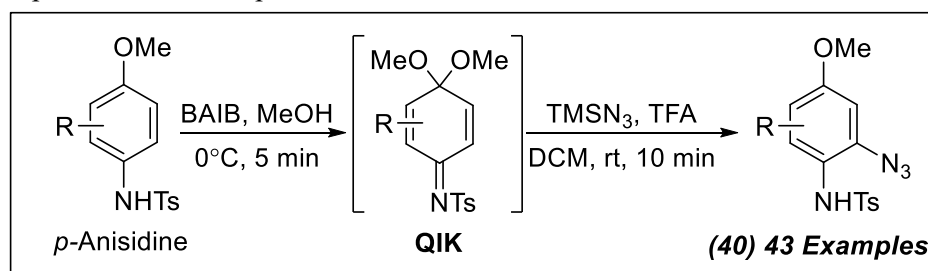
Recent studies have established efficient nondirected strategies for the selective ortho-functionalization of anilines under acid-catalyzed conditions.^{13,14} An acid-catalyzed one-pot approach was reported for the regioselective ortho-functionalization of anilines, providing a simplified route to otherwise challenging ortho-substituted anilines with excellent regioselectivity and good scalability. The methodology also allowed further derivatization of the products, while control experiments provided insights into the reaction mechanism and the origin of the observed ortho-selectivity. Building on this concept, an iodine-catalyzed coupling of quinone imine ketals (QIKs) or quinone monoacetals (QMAs) with β -naphthols was developed for the synthesis of aniline biaryls and unsymmetrical phenol biaryls. This method enabled the unusual and selective formation of ortho-substituted anilines and phenols without the involvement of transition-metal catalysts or external/internal directing templates. Mechanistically, the transformation was proposed to proceed through an in situ generated mixed acetal, followed by a key [3,3]-sigmatropic rearrangement that accounts for the high ortho-selectivity. The reaction demonstrated broad functional-group tolerance, scalability, and applicability to the late-stage derivatization of natural products. The use of an inexpensive, air-tolerant iodine catalyst further enhanced the practical utility of the methodology by avoiding hazardous metal-based catalytic systems. Collectively, these studies demonstrated the potential of nondirected acid- and iodine-catalyzed approaches for controlling ortho-selectivity in aniline functionalization and highlighted QIKs/QMAs as valuable intermediates for the construction of structurally diverse and medicinally relevant aromatic compounds.



Scheme 17. Hazra's recent work on regioselective nucleophilic addition on QIK

Jadhao and coworkers regioselective azidation of anilines

Recently, we demonstrated a metal-free, Brønsted acid-catalyzed, regioselective nondirected C–H activation reaction that efficiently achieves *ortho*-azidation of *p*-anisidines via quinone imine ketals.¹⁵ Besides streamlining the synthesis of *ortho*-azidated anilines, our method is scalable and exhibits a high tolerance to various functional groups. Control experiments and comprehensive 2D

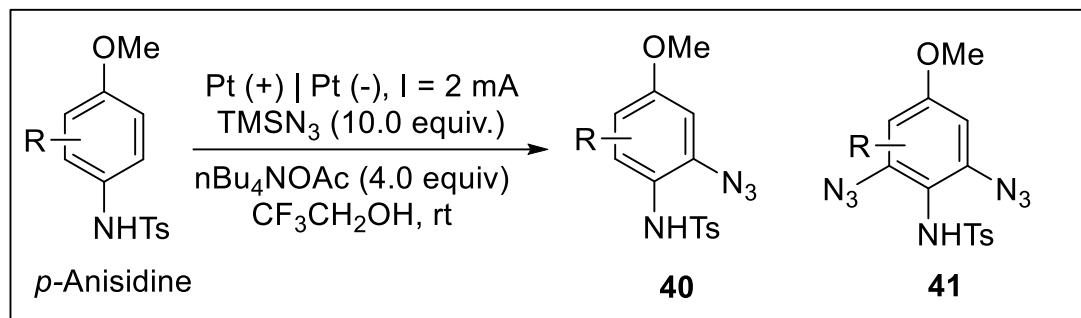


Scheme 18. Jadhao azidation method

NMR analysis confirmed the *ortho*-selectivity. The protocol was also adapted to synthesize difficult diaminated arenes and successfully used to produce marketed proton-pump inhibitors, Ufiprazole and Omeprazole.

Fan et al's electrochemical approach

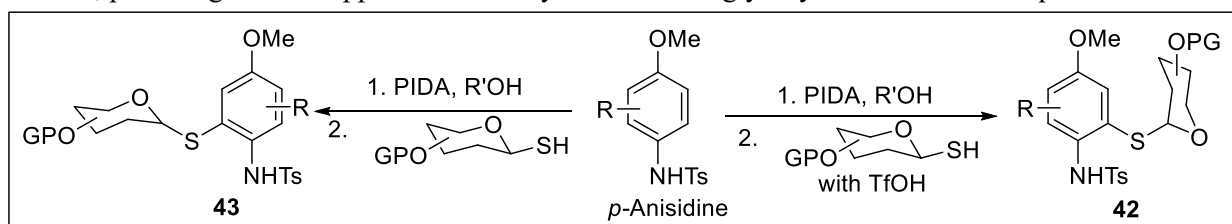
The growing significance of aryl azides in various areas of synthetic and medicinal chemistry has stimulated the development of efficient methods for their preparation. In this context, an electrochemical approach was reported for the C–H azidation and diazidation of anilines using trimethylsilyl azide (TMSN₃) as an azide source.¹⁶ The methodology provided a direct route to the corresponding aryl azides through C–H functionalization, avoiding the need for pre-functionalized substrates. Under the optimized electrochemical conditions, both azidation and diazidation of anilines could be achieved, and the reaction showed good tolerance toward a range of functional groups. This study therefore demonstrated the potential of electrochemical C–H functionalization as a convenient strategy for the synthesis of structurally diverse aryl azides from readily accessible aniline substrates.



Scheme 19. Fan et al's electrochemical azidation of anilines

Mandal's thioglycosylation approach

The site-selective construction of C–S bonds through thioglycosylation of aniline derivatives has attracted considerable interest because thioglycosylated aromatic compounds possess useful properties and potential applications in diverse fields. However, selective C–H thioglycosylation of anilines remains challenging because of their intrinsic electronic bias, which can lead to competing regioisomeric products. To address this challenge, a metal-free, nondirected, one-pot strategy was reported for the regiodivergent C(sp²)–H thioglycosylation of anilines through quinone imine ketal (QIK) intermediates.¹⁷ The methodology enabled site-selective C–S bond formation while overcoming the inherent electronic preference of aniline substrates. Mechanistic investigations involving control experiments, density functional theory (DFT) calculations, and single-crystal X-ray diffraction analysis provided evidence for the proposed reaction pathway and helped elucidate the origin of the observed regioselectivity. Overall, this study demonstrated the versatility of QIK intermediates as key intermediates for achieving metal-free, nondirected, and regioselective C–H functionalization of anilines, providing a useful approach for the synthesis of thioglycosylated aromatic compounds.



Scheme 20. Mandal regiodivergent thioglycosylation approach

3. Conclusion

The quinone imine ketal (QIK) has a multifunctional structure with C=N, C=C and ketals, etc. functional groups. In recent years, they have been used in the synthesis of novel, complex organic molecules under the catalytic conditions of achiral/chiral catalysts. Methodological research of QIK focuses on N, C1, C2, C3, ketal-site selective reaction, but there is very little research on the application of QIK to synthesize active drug molecules. The future research on QIK will further explore the site-selective reactions, their applications and photocatalytic approaches. It is potentially one of the hot and challenging research topics.

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