Prayogik Rasayan

Quinone Monoacetals: Building Blocks for Regioselective Synthesis of Complex Aromatics

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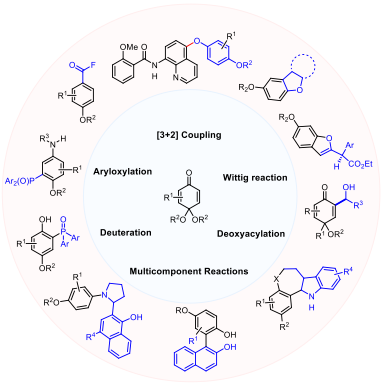
Abstract

Regioselective reactions on biologically significant quinones are challenging. Many techniques for the dearomatization processes that produce reactive intermediates like quinone monoacetals (QMAs) have been developed over the past 20 years. Recently, there has been an upsurge of interest in developing QMA chemistry because of their innate dual nature as nucleophiles and electrophiles. The existence of varied functionalities makes them significant scaffolds. Thus, these intermediates are intensively employed to develop methodologies for synthesizing the vastly functionalized and varied chemical structures. These synthons are also adaptable for asymmetric synthesis. This review summarizes the recent developments in using QMAs for allylic substitution, multicomponent reactions, deoxyacylation, Wittig reaction, deuteration, aryloxylation, and annulation reactions, including [3+2] annulation. Hopefully, this review will open doors to synthesizing complex frameworks using cheap and readily available QMAs as starting materials.

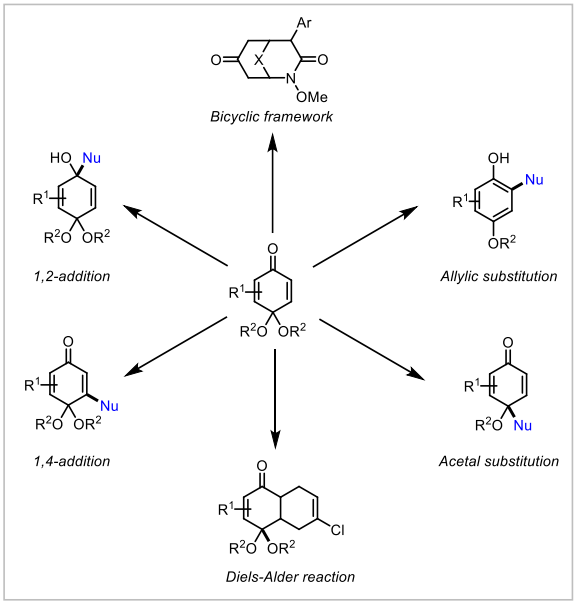


Keywords: Quinone Monoacetals, Scaffolds Synthesis, Mechanistic aspects.

Introduction

Quinones and their derivatives are essential in organic transformations because they are omnipresent in the skeleton of several pharmaceuticals, natural products, and functional materials and are also valuable as synthetic intermediates.[1] Due to the presence of unsaturated enone structures, they are used mainly as versatile electrophiles in organic synthesis. However, including an enone and two carbonyl functionalities in one molecule causes several chemo- and regioselectivity issues with the electrophilic ring carbons, limiting the use of quinones in organic synthesis.

Phenol dearomatization has drawn a lot of interest since the resultant product, which contains a cyclic enone framework, may be utilized for additional transformations to yield a variety of complex molecules and natural products. *p*-Quinone monoacetals (QMAs) or 4,4-dimethoxycyclohexa-2,5-dienone and its analogs are a significant class of chemical compounds that have attracted a lot of attention in organic synthesis due to their rich chemical reactivity and ease of availability.[2,3,4.] Conventionally, they are obtained by the dearomatization of suitable phenols in alcoholic solvents[5]. As desymmetrized *p*-benzoquinone derivatives, they can be ideal candidates for exploring regioselective reactions on quinone-type compounds. The bifunctionality arising from enones and allyl-ketal moieties renders them versatile for synthesizing key intermediates for natural product synthesis *via* acetal displacement,[6] 1,2-additions to carbonyls,[7] 1,4-nucleophilic addition,[8] allylic substitutions[9] with a variety of nucleophiles, Diels Alder reaction[10], tunable desymmetrization of cyclohexadienones,[11] constructing bridged cyclic framework[12], and the regioselective and less explored *α*-alkylation reaction[13] (**Scheme 1**). This review underscores the reactivity of QMAs as versatile synthons for regioselective synthesis of diverse organic molecules. Hopefully, the literature covered in this paper will provide newer routes to synthesizing complex and useful organic frameworks.

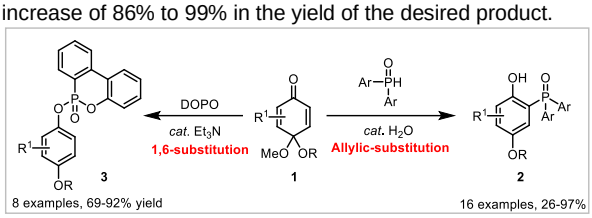


Scheme 1: Diverse reactivity of QMAs.

1. Allylic substitution

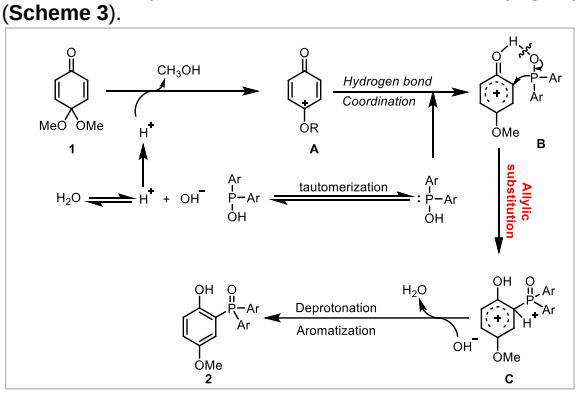
Developing efficient and simple techniques for creating C-P bonds has been a key task in synthetic organic chemistry

because of the significance of organophosphorus compounds in functional materials, medicines, and agrochemicals. In a recent report, Xiong and group[14] proposed an efficient allylic and 1,6-substitution reaction to form C- and O-phosphoryl substituted phenols **(2)** from QMAs **(1)** and diaryl H-phosphine oxides in the presence of water/Et_3N as a catalyst (**Scheme 2**). Toluene was the best solvent for the reaction among the organic solvents explored (e.g., DCE, CH_3CN, THF, toluene, EtOAc, 1,4-dioxane, and DMF). A study on the influence of various Brønsted acids (e.g., acetic acid, benzoic acid, H_2O, salicylic acid, and diphenyl phosphinic acid) in the model reaction indicated that water was the best solvent for the reaction since the use of 20 mol% of water caused an increase of 86% to 99% in the yield of the desired product.



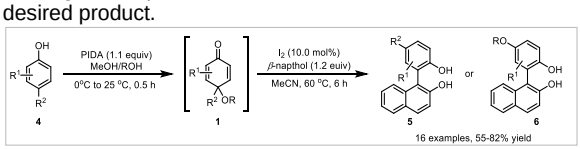
Scheme 2: Allylic substitution of QMAs with diaryl H-phosphine oxides

Reaction tolerated a variety of substituents on the QMA and phenyl ring of diaryl H-phosphine oxides. However, it was noticed that electron-withdrawing groups (EWG) on the QMA led to a drop in the desired product yields due to the deactivating effects of the EWG on the intermediate oxonium cation. In the unsymmetrical QMAs, the steric factor controlled the preferential elimination of the alkoxy group (**Scheme 3**).



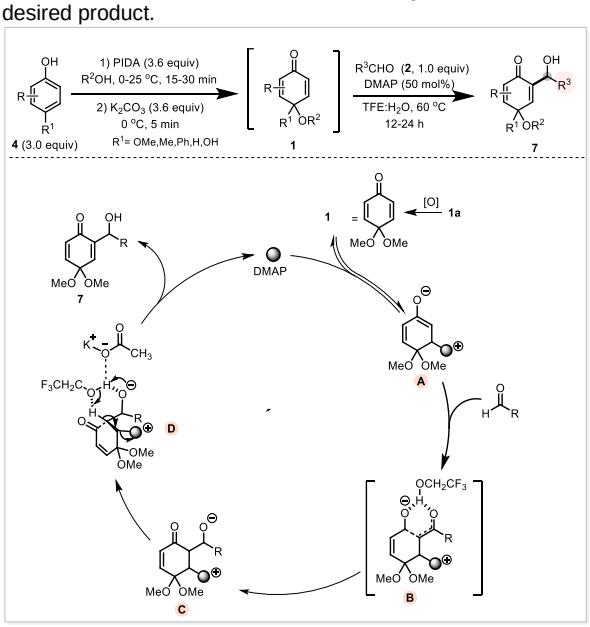
Scheme 3: Plausible Mechanism for allylic substitution reaction of QMAs.

The practical utility of the protocol was depicted by a 92% yield in the 10 mmol scale, allylic substitution under optimized conditions. Interestingly, the reaction of QMA **(1)** with 9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO) in 20 mol% triethylamine gave the 1,6-substitution product **(3)** in decent 69-90% yields (**Scheme 2**). In this case, the reaction formed a base-promoted zwitter ion, followed by aromatization and elimination of an alcohol unit. Finally, forming an ion-pair with DOPO and 1,6-substitution led to the desired product.



Scheme 4: Synthesis of *α*-arylated phenols from QMA.

In 2024, Tyagi et al.[15] used QMAs as electrophiles for synthesizing unsymmetrical *α*-arylated phenols **(5, 6)** through cost-efficient iodine-catalyzed coupling with *α*/*β*-naphthols (**Scheme 4**). The *ortho*-selective reaction involved quinone oxonium cation as an intermediate; nucleophilic attack of naphthol on quinone oxonium cation formed the mixed acetal, which finally underwent [3,3] sigmatropic rearrangement to form the desired products in good 55-82% yields. The reaction showed wide functional group acceptance since phenols having -*o*/*m*/*p*- substituents and those having naturally occurring sesamol and eugenol yielded good to excellent results for the desired product. Similarly, *β*-naphthols bearing EDG at 3/6/7-position were well tolerated under optimized conditions. Notable highlights of the protocol include metal-free catalysis, mild reaction conditions (I_2 as a catalyst, 60 °C), and scalability to the gram scale since a 10 mmol scale reaction gave 72% of the desired product.



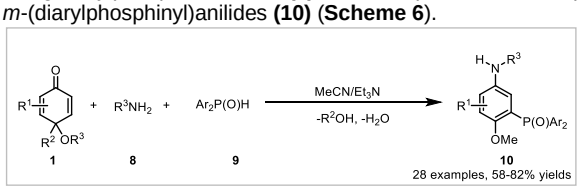
Scheme 5: *α*-alkylation of QMAs to form *α*-alkylated phenols.

In complete contrast to the report of Xiong et al.[14] and Tyagi et al.[15], Sharma and coworkers[13] have reported an unparalleled progression in QMA chemistry by constructing *α*-alkylated QMAs **(7)** *via* one-pot, phenyl iodonium diacetate (PIDA) mediated, dearomatization of phenols **(4)**, followed by Morita-Baylis-Hillman reaction with aryl/heteroaryl/aliphatic aldehydes and other electrophiles. Umpolung chemistry transformed the electrophilic QMAs into nucleophiles using DMAP as the base, followed by aldol-type condensation with numerous electrophiles to form the desired product (**Scheme 5**). The reaction displayed high functional group tolerance since diverse QMAs, including those bearing naturally occurring nerol and sesamol, an array of substituted benzaldehydes, heteroaromatic aldehydes, aliphatic aldehydes including those bearing cholesterol and L-menthol, gave excellent 43-95% yields. Mechanistic studies uncover that the solvent (TFE: water (1:1)) and potassium acetate, generated *in situ*, speed up the reaction. The MBH adducts were scalable to gram-scale and endured numerous late-stage functionalization and post-synthetic transformations. Interestingly, the QMA adducts could also be transformed into biologically significant *o*-hydroxy benzyl alcohols in 65% overall yield through aromatization of QMA adducts with $NaBH_4$.

2. Multicomponent Reactions

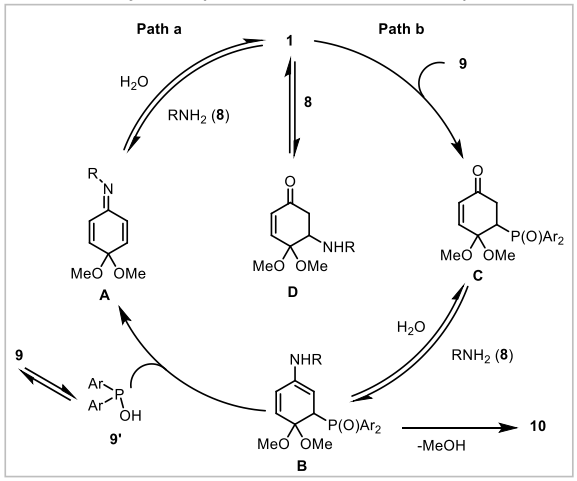
In contemporary organic synthesis, multicomponent reactions (MCRs) have developed into a very effective technique for obtaining highly functionalized compounds.[16,17] The protocol's

utilization of easily accessible building blocks, high atom efficiency, ease of usage, cost savings, and occasionally environmentally benign conditions are among its noteworthy advantages. QMA-related multicomponent reactions (MCRs) are still in infancy.[18] This could be explained by the fact that these molecules have numerous reactive sites, making it challenging to regulate the selectivity in such conversions. An account of highly regioselective MCRs involving QMAs is presented in this section. To construct two new C−heteroatom bonds (C−N/C−P) on an aromatic ring, Shen and group[19] have reported a highly regioselective, three-component reaction of QMAs **(1)**, with primary amines **(8)**, using diarylphosphine oxides **(9)** as nucleophiles, to develop *m*-(diarylphosphinyl)anilides **(10)** (**Scheme 6**).



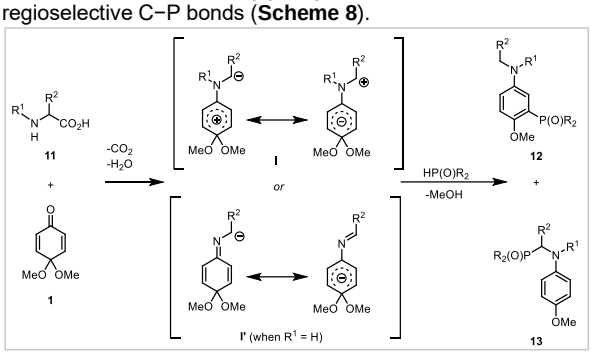
Scheme 6: MCR of QMA with primary amine and diaryl phosphine oxide.

Optimization studies revealed that the highest yields were obtained when Et_3N was used as a base and MeCN as cosolvent. This could be because Et_3N may tautomerize diaryl phosphine oxide to more nucleophilic hydroxyl phosphine (**Scheme 7**) and stabilize other intermediates in basic conditions. Other solvents, like ethanol, DMSO, toluene, etc., yielded poor results for the desired product.



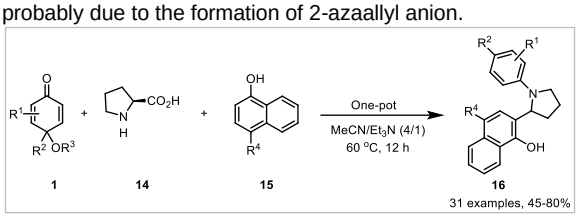
Scheme 7: Probable mechanism for the three-component reaction of QMA with primary amine and diaryl phosphene oxide.

Et_3N also proved to be the best base compared to other organic bases like DBU, K_2CO_3, and pyridine, all of which gave mixtures. QMAs with various substitution patterns reacted with widely substituted diarylphosphine oxides to afford the desired product in moderate to good 58-82% yields. However, *ortho*-substituted QMAs reduced yields, probably due to steric hindrance to forming imino-quinone acetal. No reaction was also seen with aniline, probably due to the lower nucleophilicity of the amine. The reaction was industrially suitable since it could be easily scaled up to a 3.25 mmol scale with an excellent 52% yield. Later, a three-component response of QMAs **(1)** with diarylphosphine oxides and *α*-amino acids **(11)** was developed by Wang and coworkers[20] to provide *N*-aryl-2-(diarylphosphinyl)-pyrrolidines **(12)** and 3-(diarylphosphinyl)-anilides **(13)** in 36-80% yield. The transformation involved a decarboxylation of *α*-amino acids with QMAs to form conjugated azomethine ylides or 2-aza-allyl anion species, followed by trapping of the intermediate with diarylphosphine oxides, to form regioselective C−P bonds (**Scheme 8**).



Scheme 8: Phosphorylation of azomethine ylides(I) or 2-azaallyl anion(I') species from QMA.

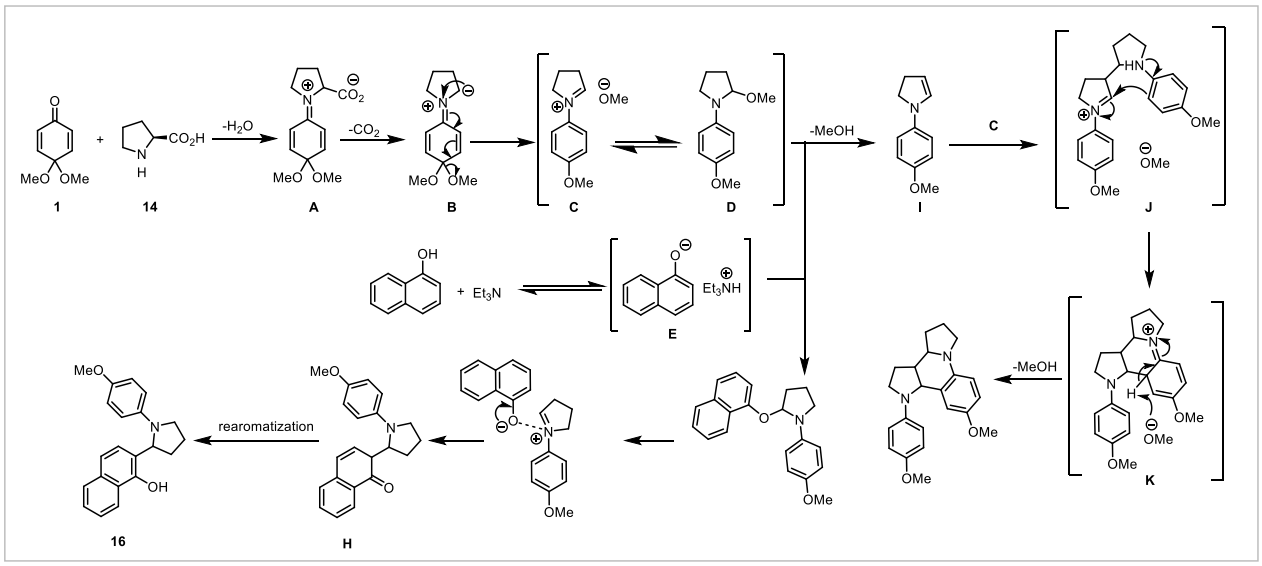
Optimization studies revealed that pyridine and other inorganic bases such as K_2CO_3, K_3PO_4, and KOH were ineffective, and Et_3N was the best base and co-solvent for the reaction. The combinations of Et_3N and other organic solvents like toluene, dioxane, DMF, DMSO, and EtOH resulted in poor yields for the desired product. *α*-amino acids and N-methyl α-amino acids reacted with various substitution patterns of QMAs to afford the desired 3-(diarylphosphinyl)anilides. EDG on QMA led to decreased yields, probably due to the reduced electrophilicity. Unlike other amino acids, L-proline underwent a different pathway to afford *N*-aryl-2-diarylphosphinylpyrrolidines in 72% yields and the expected 3-(diarylphosphinyl)anilides in poor 7% yield, probably due to the formation of 2-azaallyl anion.



Scheme 9: One-pot, three-component reaction of QMAs with L-proline and 1-/2-naphthols.

In another study, Wang and group[20] developed a highly chemo- and regioselective, one-pot, three-component reaction of QMAs **(1)** with L-proline **(14)** and 1-/2-naphthols **(15)** for synthesizing N-aryl-2-arylpyrrolidines **(16)** (**Scheme 9**). As in the previous report, Et_3N was the best among other bases. This is probably because it also increased the nucleophilicity of naphthols by acting as a Brønsted base, besides forming hydroxyphosphine oxide. Interestingly, the reaction could be scaled up to a 3.5 mmole scale with an excellent 72% yield of the desired product. Unlike the previous report[18], substitution patterns on QMA did not adversely affect the reaction. This could be because the nucleophile attacks the iminium ion species c (**Scheme 9**).

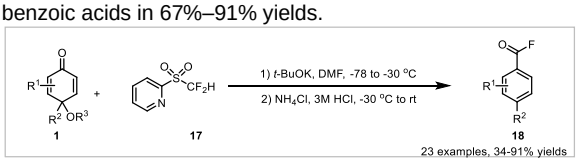
Loss of chirality in the product despite using L-proline confirms the presence of iminium ion species(c). As expected, *o*-substituted QMAs did not provide the desired product. The reaction proved *ortho-selective* and probably proceeded through the intermediate formation of tight ion-pair intermediates (**Scheme 10**) since both 1-/2- naphthol gave C-2 and C-1 substituted products, respectively. Additionally, proline was essential to the pathway since a similar reaction with pyrrolidine afforded 13% of the desired product. Notably, QMA is coupled with L-proline to form complex dipyrroloquinolines, in the absence of naphthol.



Scheme 10: Probable mechanism for reaction of QMAs with *L*-proline and 1-/2-naphthols.

3. Deoxyacylation of phenols

Benzoyl fluorides are useful synthons since a special balance between reactivity and stability, influenced by the C–F link enables their use as an equivalent of the acyl group, fluoride ions, and the aryl group. Therefore, developing methods for synthesizing benzoyl fluorides is crucial, especially from simple and easily accessible substrates.[21] A strong C sp^2–O linkage and the tremendously reactive acidic -OH group prevent the direct attack of any nucleophile on the phenolic carbon.[22] However, oxidative dearomatization of phenols to QMAs and other cyclohexadienones converts the phenolic OH group to the more electrophilic carbonyl group. Yang et al.[21] developed a metal-free, deoxyacylation reaction of 2,5-cyclohexadienones, including QMAs **(1)**, to produce benzoyl fluorides **(18)** and benzoic acids. Nucleophilic difluoro methyl-2-pyridyl sulfone **(17)**, upon reaction with 2,5-cyclohexadienones in the presence of *t*-BuOK as base and DMF as a solvent, produced gem-difluoro olefins, which were trapped *in situ* by nucleophiles like water and aromatized to benzoyl fluorides **(18) (Scheme 11**). The use of other gem-difluoro olefination agents, like $ClCF_2CO_2Na$, $BrCF_2CO_2Na$, CF_2Br_2, (triphenylphosphine) fluoroacetate (PDFA), did not give the desired product. Trace or poor yields were obtained by replacing t-BuOK with MeONa, KHMDS, and PPh_3.The hydrolysis of benzoyl fluorides in concentrated acid produced benzoic acids in 67%–91% yields.

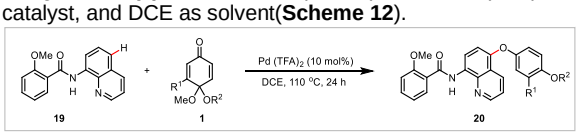


Scheme 11: Deoxyacylation of QMA

The broad-scoped reaction tolerated several substituted QMAs and 2,5-cyclohexadienones, yielding the desired product in 34-91%. However, *ortho*-substituents on QMA led to decreased yields, probably due to steric factors. Interestingly, the protocol worked better for benzoic acid synthesis than benzoyl fluoride in terms of yield and substrate scope, probably due to the reduced stability of the latter in acidic conditions.

4. Aryloxylation reaction

Aryl ether-bearing quinolines occur widely in fluorescent probes, natural products, pesticides, pharmaceuticals, etc. Nucleophilic aromatic substitution, or the Ullmann cross-coupling reaction employed for this purpose, has limited step economy. So, direct C−H functionalization methods are highly desirable for quinolines. There have been only a few examples of selective etherification of quinolines at C5.[23] This is because the etherification of 8-aminoquinoline generally requires a strong oxidant. Still, the phenols, which are necessary for forming aryl ethers, are prone to oxidation, making it difficult to find a suitable condition to achieve the desired transformation. Xun and coworkers[23] have recently developed a methodology for regioselective, coordination-induced C5 aryl etherification of 8-amido quinolines **(20)** by using QMA **(1)** as a nucleophilic partner, $Pd(TFA)_2$ as catalyst, and DCE as solvent(**Scheme 12**).



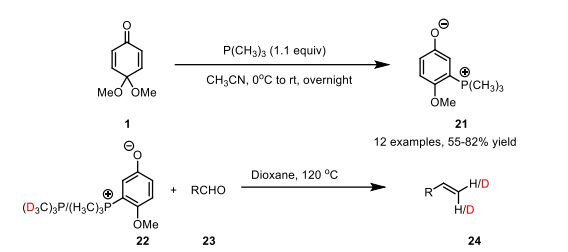
Scheme 12: C−H aryl etherification or amination of 8-amidoquinolines.

QMA acted as an aryl etherification agent, prevented the involvement of an exogenous oxidizing agent through oxidant behavior, and avoided the problem of phenol oxidation. Notably, using other organic solvents like toluene, HFIP, and DMSO gave poor or no yield. Similarly, other TM catalysts like $Cu(OAc)_2$ $Ni(ClO_4)_2$, $Co(OAc)_2$, $Co(NO_3)_2$, $Pd(OAc)_2$, etc., afforded the desired product in poor or no yields. The synthetic utility of the protocol was demonstrated by 76% yield in the gram-scale reaction. It was shown that the type of acyl group and the presence of a bidentate ligand greatly influenced the product yield since the replacement of quinoline with naphthalene or substrates with 4-fluorobenzyl, acetyl, *t*-butyryl, 2,6-difluorobenzoyl, *t*-butyloxy carbonyl groups did not give the desired product. Interestingly, the reaction completely contrasts with a regular directing-group mediated transition-metal-catalyzed and mediated C−H activation/functionalization reaction of *N*-(8-quinolinyl) benzamide, which proceeds at the ortho position to the phenyl ring of the amide group.

5. Wittig reaction

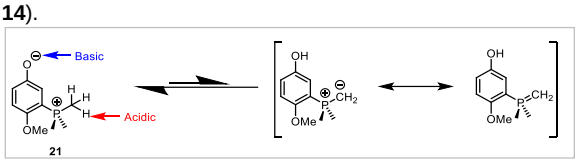
In an interesting application of QMAs, Xiao and coworkers[24] transformed *p*-quinone monoacetate to air and moisture-stable 4-Methoxy-3-(trimethyl phosphonium) phenolate **(21)**

in excellent 92% yield via regioselective *meta*-addition of PMe_3 followed by aromatization (**Scheme 13**). The resulting phosphonium phenolate was heat stable up to 100 ºC and exhibited reactivity like phosphonium ylides to fashion Wittig olefinations of aldehydes without adding an exogenous base. The broad-scoped reaction tolerated several aliphatic



Scheme 13: Wittig reaction of 4-Methoxy-3-(trimethylphosphonio) phenolate.

aldehydes and aromatic aldehydes bearing EWG, EDG, terminal alkynyl, and alkenyl groups to afford the desired product in good 55-82% yields. The basic phenolate ion probably abstracted a proton from the weakly acidic methyl groups of the trimethyl phosphonium moiety to form phosphonium phenolate zwitterion, which tautomerizes to phosphonium ylide to enable the transformation (**Scheme 14**).

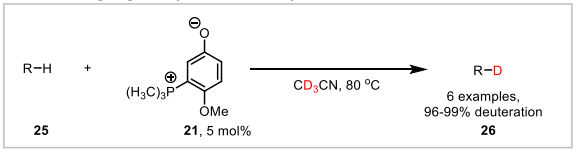


Scheme 14: Probable mechanism for the formation of phosphonium Ylide.

Interestingly, the reaction could also be exploited for synthesizing 1,1-dideuterio styrene in 61-83% yield(>92% deuteration) when deuterated trimethyl phosphonium phenolate **(22)** was used as the catalyst.

6. Deuteration reaction

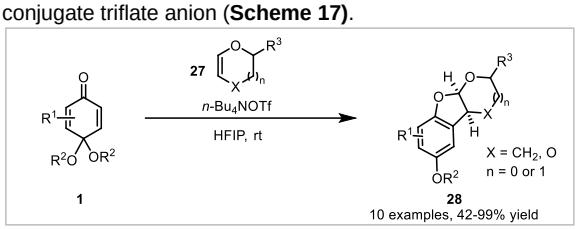
In an extension of their report[24], Xiao and group also used the QMA-derived 4-methoxy-3-(trimethylphosphonium) phenolate **(21)** for H/D isotope exchange of several compounds bearing weakly acidic hydrogens in CD_3CN as a solvent and deuterating agent (**Scheme 15**).



Scheme 15: Deuteration reaction with QMA-derived 4-methoxy-3-(trimethylphosphonium) phenolate.

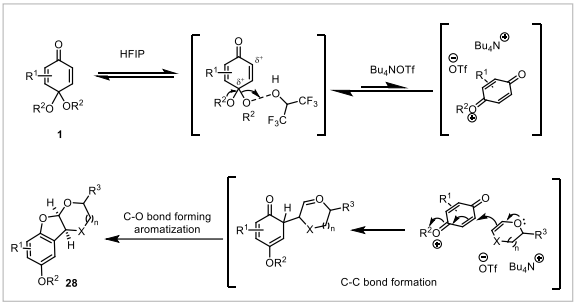
7. [3+2] Coupling reactions

The 2-oxygenated dihydrobenzofuran forms the core skeleton of several natural products, functional materials, and other biologically active compounds. [3+2] coupling reactions of QMAs with alkenes in the presence of mild acid catalyst have successfully prepared dihydrobenzofuran.[25] Therefore, [3+2] coupling of vinyl ethers with QMAs can be one strategy to form 2-oxygenated dihydrobenzofuran through simultaneous C−C and C−O bond formation. In 2021, Kamitanaka and coworkers[26] reported a regioselective and acid-free method for the [3+ 2] coupling reaction of diverse vinyl ethers **(27)** with QMAs **(1)** to form 2-oxygenated dihydrobenzofurans **(28)** (**Scheme 16**). HFIP was crucial for the response since it served as a solvent and proton donor to generate the intermediate quinone oxonium cation. Interestingly, metal salts improved the product yield, while acid catalysts did not give the desired product. Amongst salts tested for the reaction (NaOTf, KOTf, *n*-Bu_4NOTf), *n*-Bu_4NOTf gave the highest yield of the desired product. This could probably be due to the increased polarity of the reaction medium and stabilization of the intermediate cation by conjugate triflate anion (**Scheme 17)**.



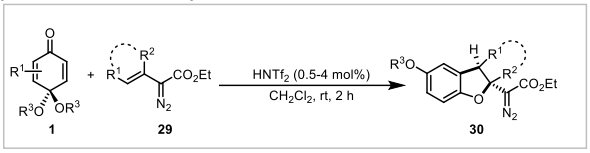
Scheme 16: Synthesis of 2-oxygenated dihydrobenzofurans from QMAs.

The reaction could be carried out under mild conditions (room temperature, acid-free) and tolerated a variety of vinyl ethers, including dihydropyran and dioxene and several *α* and *β* substituted QMAs. The *β*-substituted QMAs required equimolar amounts of *n*-Bu_4NOTf, probably due to steric hindrance.



Scheme 17: Probable route to synthesis 2-oxygenated dihydrobenzofurans from QMAs using tetrabutylammonium triflate as catalyst.

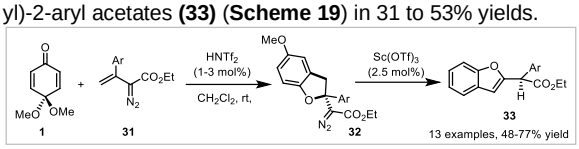
Further, acyclic vinyl ethers required TFE as a solvent instead of HFIP, perhaps because the higher acidity of HFIP led to the decomposition of the acyclic vinyl ethers. This method could be extended to other nucleophiles like alkoxy arenes, styrenes, and 2-naphthol to obtain the coupled products in 66-98% yields.



Scheme 18: [3 + 2] cyclization of QMAs with vinyl diazo compounds.

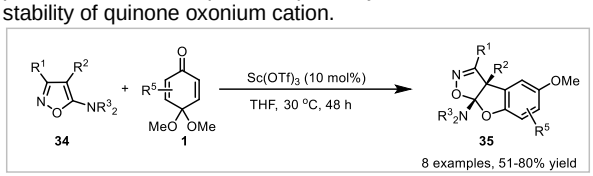
Vinyl diazo compounds are useful nucleophiles with potential complementary to metal carbenes[27]. The stability of vinyl diazonium ions falls in between their alkyl and aryl equivalents. Thus, using appropriate electrophiles controlled the loss of the diazo group, presenting unconventional approaches to synthesizing complex diazo compounds. Using this cue, Zheng and group[27] explored using QMAs as electrophiles to fashion a regioselective and metal-free [3 + 2] cyclization with vinyl diazo esters **(29)** to form *β*-benzohydrofurans **(30)** (**Scheme 18**).Diverse Lewis acid catalysts like $B(C_6F_5)_3$, $Et_2O{\bullet}BF_3$, $Sc(OTf)_3$, $Fe(OTf)_3$, $Zn(OTf)_2$, CF_3COOH, TfOH, $HNTf_2$ were screened for the reaction. It was found that the low nucleophilicity and poor coordinating ability of bistriflimide gave the best yields in the case of bistriflimidic acid($HNTf_2$). The reaction was broad-

scoped since it tolerated diverse *β*-alkylated vinyl diazo compounds, including those with azide (N_3) and *tert*-butyldimethylsilyl ether (OTBS) groups, *β*-cycloalkenes and those derived from natural products like estrone and epiandrosterone. However, inert *β*-aryl-substituted vinyl diazo esters **(31)** underwent [3+2]-cycloaddition followed by denitrogenation and aryl migration to form 2-(benzofuran-2-yl)-2-aryl acetates **(33)** (**Scheme 19**) in 31 to 53% yields.



Scheme 19: Synthesis of 2-(benzofuran-2-yl)-2-arylacetates from QMA.

Several substituents on the QMA skeleton, including those with 2-methyl- and 2-phenyl groups and naphthoquinone ketal, gave good to excellent 48-77% yield and excellent 19:1 dr of the desired product. However, QMAs with EWG did not provide the desired product, probably due to the reduced stability of quinone oxonium cation.

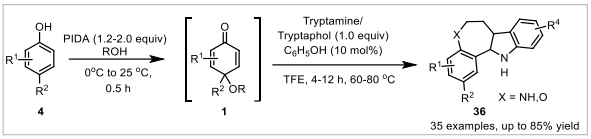


Scheme 20: Dearomative [3+2] annulation reaction of QMA with 5-amino isoxazoles.

One of the major changes in organic synthesis is the catalytic dearomatization of abundant aromatics, which makes it possible to quickly and easily assemble three-dimensional structures[28]. QMAs are excellent dearomatizing reagents for dearomative [3+2] annulation reactions.[29] Yan and group [29] reported scandium triflate(20 mol%) catalyzed dearomative [3+2] annulations of QMAs with 5-amino isoxazoles **(34)** (**Scheme 20**) to afford 2,3-dihydro benzofuran-fused isoxazolines **(35)** in moderate 51 to 80 % yields and excellent diastereoselectivities (all cases >20:1 dr). This approach showcased a broad substrate scope since an array of 5-amino-isoxazoles reacted with QMAs bearing EWG and EDG (Me, Cl, and Br) under mild conditions (30 °C, THF as solvent), affording the dearomatized 2,3-dihydro benzofuran-fused isoxazolines. Mechanistic studies revealed that scandium triflate behaved as a Lewis acid to form an intermediate quinone oxonium cation, which underwent nucleophilic addition with 5-amino isoxazoles followed by aromatization and subsequent intramolecular cyclization to afford the desired product.

8. Miscellaneous reaction

An easy and competent synthetic method has been developed by Mahato et al. to produce 5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-*b*]indole and 7,12-dihydro-6*H*-benzo[2,3]oxepino[4,5-*b*]indole derivatives **(36)** under mild conditions(**Scheme 21**).[30] The synthesis is achieved through a Brønsted acid-catalyzed cyclization reaction. The key intermediate in the process is a dihydrospiroquinoline, which is generated *in situ* and undergoes a cyclization reaction to form the desired azepinoindole or oxepinoindole structure. The paper proposes a mechanistic cyclization pathway involving the dihydrospiroquinoline intermediate's protonation, forming the azepinoindole or oxepinoindole ring system. The intermediates are highly reactive, but the reaction conditions are designed to selectively control the final product's formation. The reaction demonstrates a broad synthetic scope, allowing for preparing both azepinoindoles and oxepinoindoles from various substrates. This highlights the versatility of the method and its potential utility for the synthesis of diverse heterocyclic compounds. The method can be used to access these compounds with good yields and selectivity, potentially accelerating drug discovery or the development of new materials.



Scheme 21: Synthesis of Azepinoindoles and Oxepinoindoles via Brønsted-Acid-Catalyzed Cyclization.

In conclusion, this review has demonstrated the utility of QMAs as useful synthons in organic synthesis because of their special dual electrophilic and nucleophilic characteristics. Because of their vast functionalization potential, a variety of approaches to building intricate and biologically meaningful frameworks by QMAs in multicomponent reactions, allylic substitution, deoxyacylation, Wittig reactions, deuteration, aryloxylation, and annulation reactions like [3+2] annulation has been demonstrated. Heterocycles such as pyrrolidines, benzofurans, dihydrobenzofurans, azepinoindoles, and oxepinoindoles can now be synthesized efficiently thanks to these useful synthons. Notably, the production of C-C, C-X, C-P, and C-O bonds has significantly advanced with the invention of metal-free, regioselective techniques employing QMAs. These methods support the ideas of green chemistry by providing economic and ecologically favorable substitutes for conventional metal-catalyzed processes. The production of new materials with desirable qualities and the discovery of new synthetic pathways are both potential outcomes of the ongoing investigation of QMA chemistry. Future studies are anticipated to increase the usefulness of QMAs even more, especially in asymmetric synthesis and the construction of intricate molecular structures with possible medicinal uses.

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