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Doctoral Thesis

Studies on Controlled Coupling Cyclization of Unsymmetric Quinones

Doctoral Program in

Integrated Science and Engineering

Graduate School of Science and Engineering

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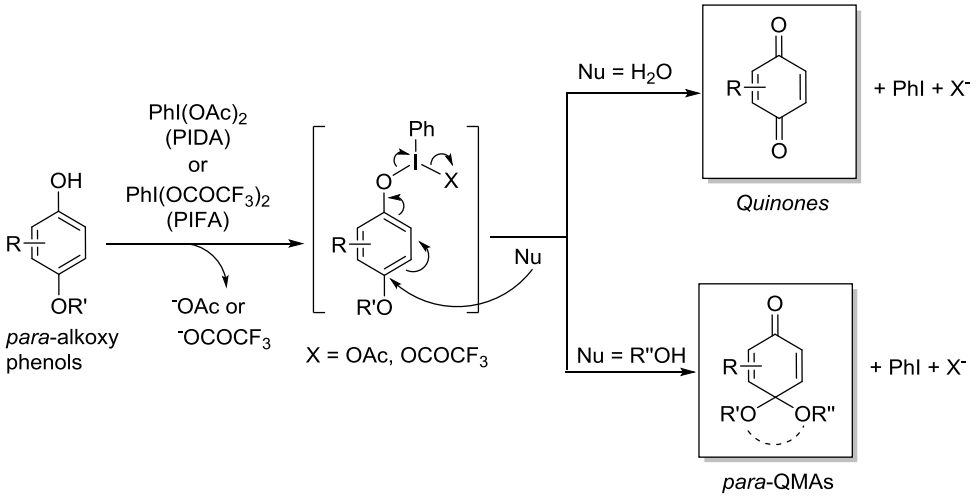
Overview

Phenolic compounds commonly referred as polyphenols or phenols are secondary metabolites occurring widely in food plants, and indispensible quantity is consumed in our daily dietary. Structurally, phenolics can be defined as bioactive substances which include an aromatic ring, bearing one or more hydroxyl substituents, possessing functional derivatives such as esters, methyl ethers, and glycosides, etc.[1)] Over the past few decades, our lab has been looking into the development of the synthesis and utilization of dearomatized phenols as well as their applications toward natural products synthesis from phenols,[2)] whereby, a wide array of quinone-type compounds have been reported *via* chemical oxidations by treatment with organic oxidants, specifically phenyliodine(III) diacetate ($PhI(OAc)_2$, PIDA) and phenyliodine(III) bis(trifluoroacetate) ($PhI(OCOCF_3)_2$, PIFA) in suitable alcohol solvents from corresponding phenols, which have emerged as a straightforward and attractive strategy in recent years (Scheme 1).[3)]



Scheme 1

Quinone-type compounds ubiquitously exist in nature and are frequently included in commercial and industrial chemicals of many broad and attractive applications. As a result, these quinone-type compounds are of importance in organic chemistry as synthetic intermediates and building blocks.[4,5)] Regarding the reactivity, many types of reactions based on the unsaturated enone structure as versatile electrophiles, especially, for various nucleophiles and dienophiles in cycloadditions, have been developed. At the same time, some chemo- and regio-selective issues toward all the ring carbon arise due to the presence of the two carbonyl functionalities and enone units, sometimes limiting the utility of quinones themselves in organic synthesis.

Issues for realization toward high levels of chemo- and regio-selectivity have always been the Achilles' heel of synthetic organic chemistry.[6] The achievements of regio-specific strategy for partitioning between the accessible reaction pathways mainly involve the controlling strategies *via* efficient reagents or modification of the substrates. Therefore, as one of the promising solutions to the selectivity issues, *quinone monoacetals* (Figure 1, QMAs **1**), the mono-protected quinone compounds, bearing not only α,β-unsaturated carbonyl but also allylacetal moieties in one skeleton, have already appeared for differentiating the reactivity of the two same carbonyl functional groups.[7] The desymmetrized quinones would serve as a useful alternative for selective chemical transformations in controlling the reactivity of quinones, and thus are frequently called ‘‘masked’’ quinones where only one carbonyl moiety of the enone unit is protected from the additions by nucleophiles and dienophiles, which could be severed as a potentially regio-specific quinone equivalents in synthetic utilities and naturally occurring compounds, for instance, pterocarpan type compound, such as maackiain, physostigmine, defucogilvocarcin M, and aranorosin (Figure 1).[8]

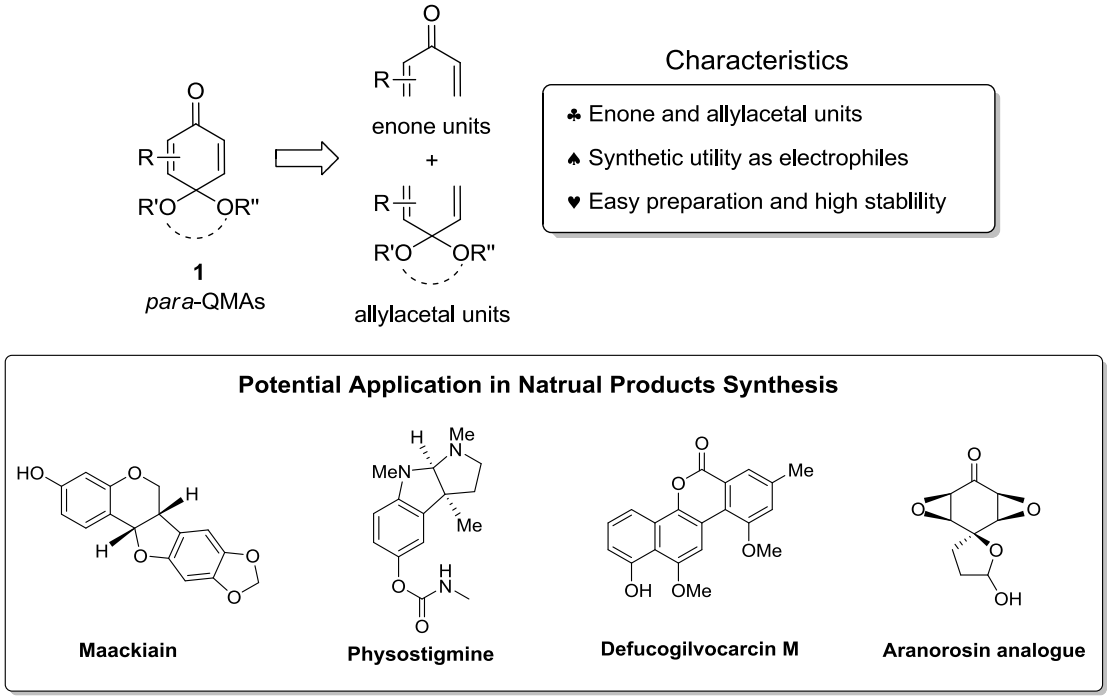
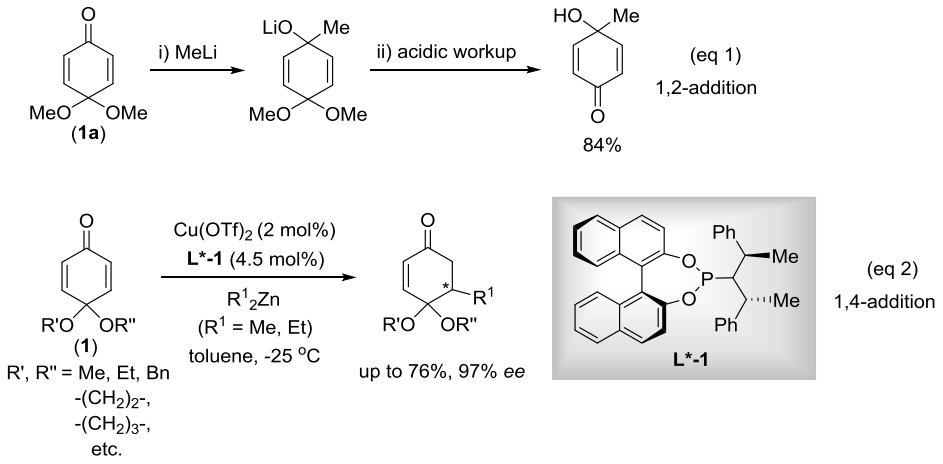


Figure 1

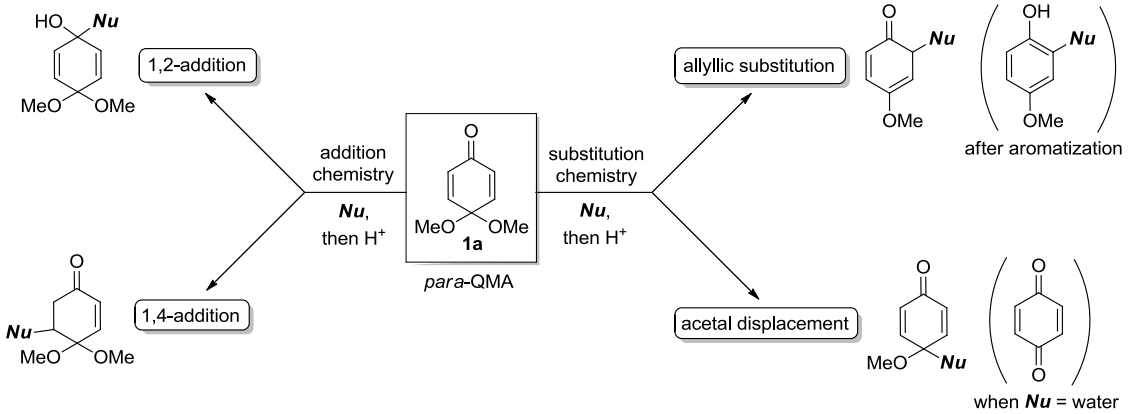
Owing to the uniqueness of the privileged bifunctional structure of QMAs based on the α,β-unsaturated carbonyl and allylacetal moieties in one skeleton as well as their easy and efficient preparations, the rising interest in the development of utilization of QMAs **1** in chemical reactions has been fuelled since the 1970s. For nucleophiles, a

wide array of reactivities toward the enone moieties of QMAs **1** was already revealed to produce the addition reactions, the fundamental theories of which had been extensively studied from 1970 to the 1990s, concluding that the nature of the used hard and soft nucleophiles is the dominant factor that alters the reactivities toward enone group.[9, 10)] For instance, additions to the carbonyl carbon (*i.e.*, 1,2-addition) with the treatment of alkyllithium as a hard nucleophile (eq 1, Scheme 2),[9a)] or the conjugated additions to an enone moiety (1,4-addition) using dialkylzinc reagent as a soft nucleophile (eq 2, Scheme 2),[10a)] as well as other extended cyclizations involving these processes.[11]



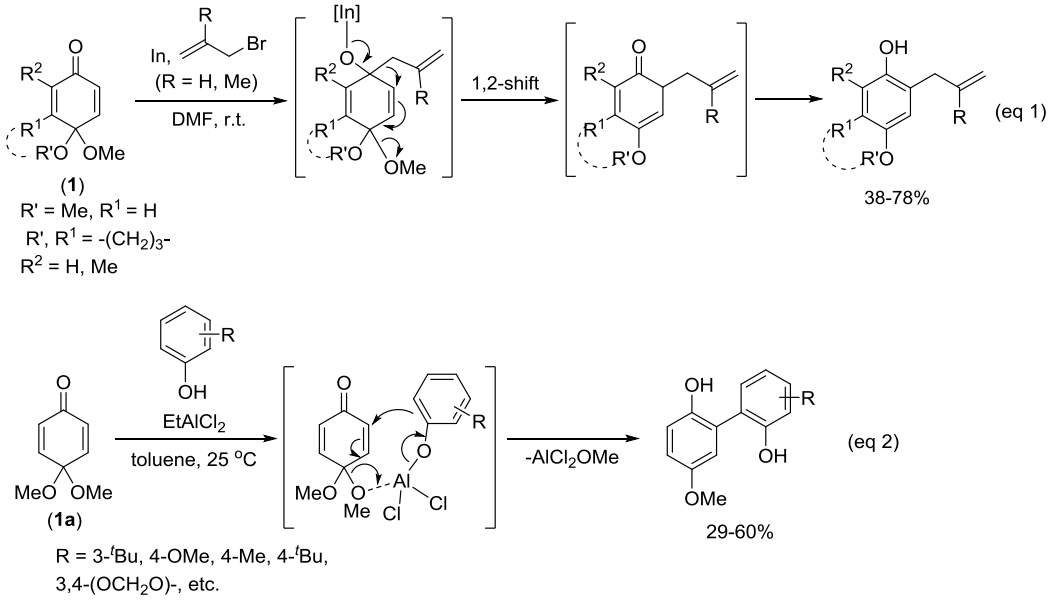
Scheme 2

Besides these addition reactions, it seems that QMAs **1**, in principle, can enjoy the reactivity of the allylacetal functionalities. However, in sharp contrast to the established addition chemistry of QMAs regarding the reactivity at the enone moieties, strategies for utilizing the allylacetals as an electrophilic unit for **substitution reactions** were rarely reported,[12-16)] except for the intramolecular reactions[17)] and well-known acetal deprotection by hydrolysis (Scheme 3).



Scheme 3

One of the typical reports of the substitution for QMAs under basic conditions was demonstrated for introducing the nucleophile to some extent to the allylic position of QMAs **1** with the treatment of the allylindium reagents (In/allyl bromide) only *via* the 1,2-addition of the organometallic species to the carbonyl group followed by rearrangement (eq 1, Scheme 4).[13b] However, the attractive reactivity of QMA **1a** for allylic substitution promoted by the acidic activator of diethylaluminum chloride ($EtAlCl_2$) was demonstrated for few substrates by Sartori's group, who proposed the *pseudo*-intramolecular S_N2' process *via* coordination of the aluminum Lewis acid to both the acetal and the phenol nucleophile as a rare example (eq 2, Scheme 4).[14a]

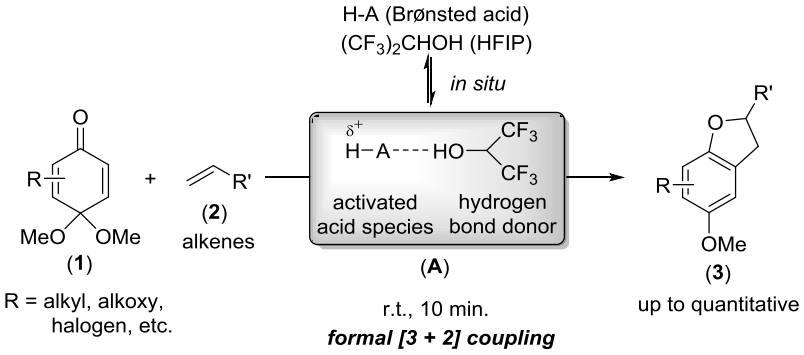


Scheme 4

In contrast to these partial successes, this thesis principally deals with the achievements of novel strategies for developing the chemo- and regio-selective substitution reactions of QMAs **1** with soft and neutral nucleophiles based on the screening of more suitable catalysts under the acidic conditions. To summarize, the following results are newly obtained in this research field.

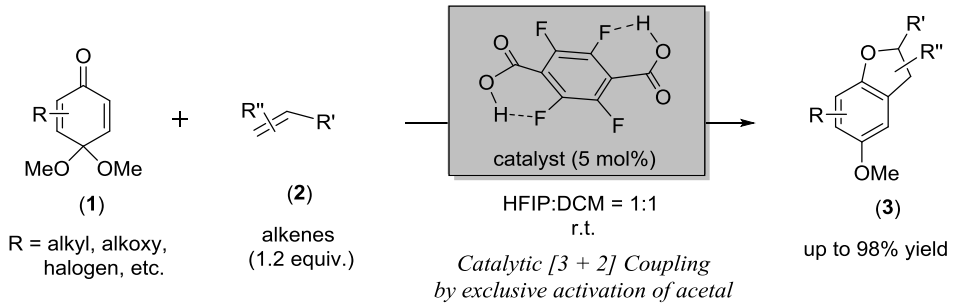
(1) An efficient Brønsted acid-controlled strategy for the [3 + 2] coupling approach of QMAs **1** with a series of alkene nucleophiles **2** has been successfully developed (Scheme 5). The strategy is triggered by the particular use of a specific acid promoter, perfluorobenzoic acid (PFBA), *in situ* generation by the coordination of the hydrogen bond donor solvent, that is 1,1,1,3,3,3-hexafluoro-isopropanol (HFIP). With the

stoichiometric amount of PFBA, the reaction could smoothly proceed with high regio-specificity regarding QMAs **1** for introducing the π-nucleophiles **2** toward only the allylic positions, providing diverse dihydrobenzofuran products and other derivatives **3** with high to quantitative yields under mild conditions in short reaction times (Chapter I).[18a)]



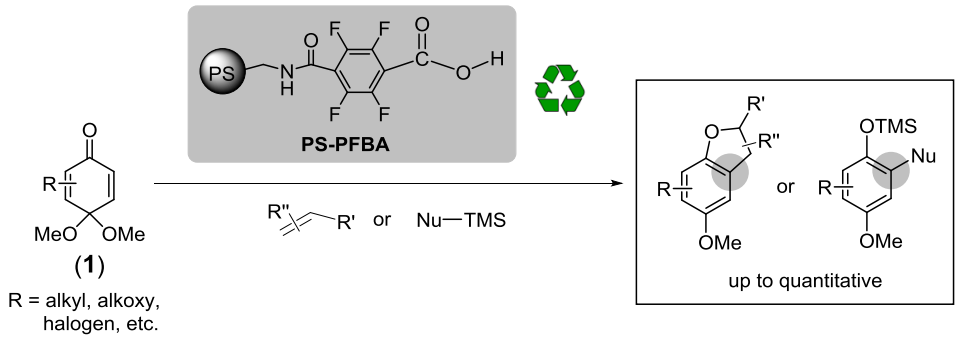
Scheme 5

(2) Aiming at realizing this [3 + 2] coupling reaction in a catalytic way, a further part of our ongoing investigation with regard to the acid tuning has led to finding of an excellent catalytic perfluorinated acid catalyst, which advances our original stoichiometrically controlled couplings to render catalysis of the acid at lower than 5 mol% loading together with the significantly improved stoichiometry of the alkenes **2** lowering to 1.2 equiv. (Scheme 6). The minimal loading of the acid alternative and the save of the amounts of substrates have made this coupling very fascinating from a practical view (Chapter II).[18b)]



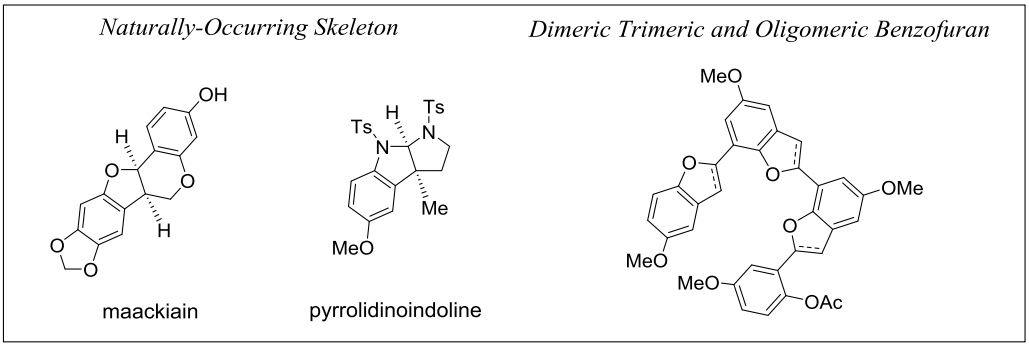
Scheme 6

(3) Despite the high performances of the perfluorinated acid for this [3 + 2] coupling reaction, the used acid catalyst is usually considered to be a waste material after the reactions. To overwhelm this backdrop, a unique solid proton catalyst, so we called PS-PFBA, immobilizing PFBA sites on the polystyrene backbones was successfully prepared and applied as an efficient and reusable solid acid for our controlled activations of QMAs **1** for giving the desired [3 + 2] coupling cycloadducts and other coupling products with a similar efficiency to the homogeneous counterpart, PFBA (Scheme 7). The prepared catalyst is highly stable for additional multiple runs without any loss of activity (Chapter III and IV).[18c)]



Scheme 7

(4) Finally, this novel [3 + 2] coupling approach also shows potency of the extensive applications for the concise synthesis of key modules of phenol and indole-derived natural products, as well as the regio-controlled benzofuran functionalized oligomers (Scheme 8) (Chapter V).



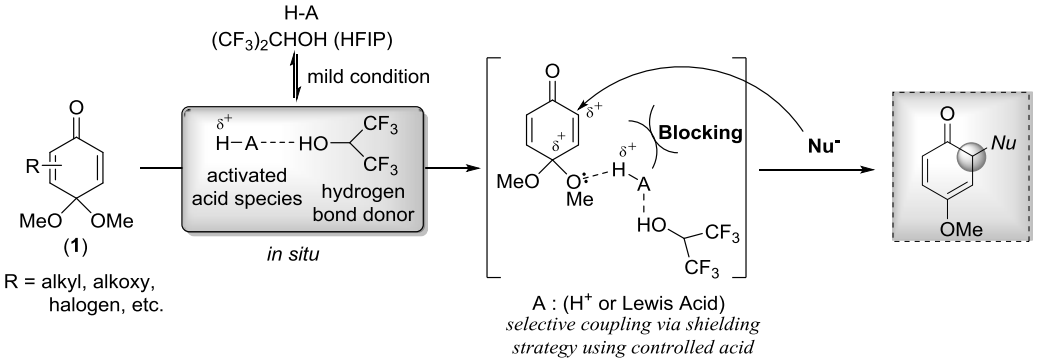
Scheme 8

Results and Discussion

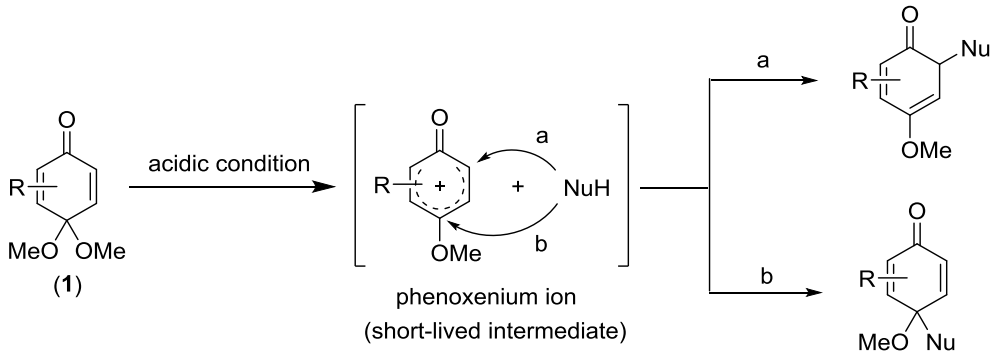
Chapter I. Studies on Controlled Coupling at Allylacetal Moiety of QMAs

Despite the partial success mentioned early works, the limited range of usable nucleophiles under acidic conditions, which typically have lower nucleophilicities than the basic reagents, significantly restricted the scope of the attractive substitution strategy to the allylacetal moiety of QMAs. For expanding the utility, new challenges for developing the substitution reactions of QMAs have thus appeared in recent years by several research groups including us based on the screening of more suitable activators.[12-16)]

At this stage, we first hypothesized the strategy of this regio-specific allylic coupling reaction particularly for the introduction of several soft nucleophiles to QMAs **1** on the behave of the *in situ* controlled reagent of specifically bulky acid promoters by the coordination of the methoxy group of the acetal unit *via* the shielding effect, whereby the nucleophiles would reasonably attack to the less hindered carbon site (which refers to the β-position of the allylacetal moiety) remote from the sterically congested α-position of allylacetal unit and acetal carbon itself (*via pseudo*-S_N2' pathway) (Scheme 9), which is remarkably different to the known phenoxenium ion intermediates by an S_N1 leaving manner (Scheme 10).



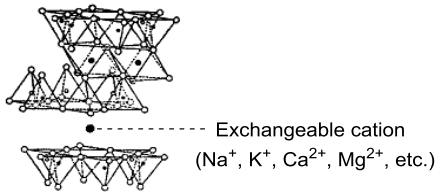
Scheme 9



Scheme 10

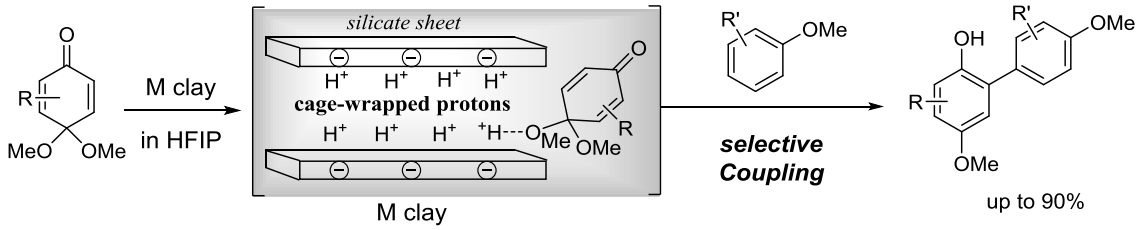
In this course, we recently reported a new method of QMAs **1** with aromatic nucleophiles to obtain oxygenated biaryls which is catalyzed by a solid acid catalyst, montmorillonite K-10 (MT K-10) clay, in a specific solvent, that is 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a rare example for enabling the substitution under acidic conditions (Scheme 11). The montmorillonites are known to consist of higher order 2D and 3D clusters of silicate anions with nanospaces between their layers, in which a number of protons (H^+) are absorbed along with the sheet-like polyanions.[footnote 2] The unusual protons captured in the interlayers of the solid acids could possibly be considered as a special Brønsted acid activator to generate charged species that are effectively stabilized by the soft poly-anion counterparts. It is thus assumed that the charged intermediate can react with an aromatic nucleophile in the allylic manner at the less hindered carbon opposite to the acetal, rather than the sterically blocked tertiary acetal carbon under such reagent control. It should also be noted that the polar medium fluoroalcohol,[footnote 3] HFIP, with high hydrogen bond donor ability,[20,21)] matches the proposed activation mode of the MT clay toward the QMA, probably as a charge-stabilizing polar medium, which thus give the biaryl products in up to 90% yield with high efficiency and broad applicability.

[footnote 2] Montmorillonite with the chemical structure $(Na, Ca)_{0.33}(Al, Mg)_2Si_4O_{10}(OH)_2 \cdot nH_2O$, is a very soft phyllosilicate group of minerals that typically form in microscopic crystal, forming a clay. It is a member of the smectite family, a 2:1 clay, which means that it has two tetrahedral sheets sandwiching a central octahedral sheet, in which the cationic species can be easily replaced by other metal cations and these ion-exchanged montmorillonites have great potential as solid acid catalysts for many environmental friendly reactions because the selection of different cations enables tuning of their acidity, among which the sulfuric acid-treated montmorillonite, K10 has been widely used as a suitable solid acid catalyst in some carbon-carbon bond-forming reactions from a viewpoint of synthetic organic chemistry.[19)]



M-K10

[footnote 3] The fluoroalcohol, *i.e.*, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) with highly polar [$E_T(30)$ = 69.3], but low nucleophility [N = -4.23], are the unique solvent that exhibit a high ionizing power with a *p*Ka [9.3 (HFIP)] higher than that of acetic acid [*p*Ka = 5.2]. In addition, HFIP also has quite excellent hydrogen bond donor abilities [α = 1.96].[20, 21)]



Scheme 11

Section I. Brønsted Acid-Controlled [3 + 2] Coupling of QMAs with Alkene Nucleophiles

Encouraged by the remarkable activation behaviour of the controlled reagent of montomorillonite K-10 with hydrogen bond donor, HFIP, in the oxygenated biaryls coupling reaction of QMAs **1** with aromatic nucleophiles (*vide supra*),[19i, 19j] extensive investigation of this attractive strategy was anticipated. We have now envisioned that the use of the bifunctional molecules of QMAs **1** for other carbon-carbon bond transformation with other potential soft nucelophiles, in particular among which the unactivated alkene nucleophiles for the formal [3 + 2] coupling *via* substitution with the resulting formation of dihydrobenzofurans **3** would probably be possible by further probing the appropriate acid activator and condition. Herein, the investigations for the [3 + 2] coupling of QMAs **1** with a series of alkene nucleophiles **2** by screening of the stoichiometric acid activator by the aid of the the polar medium solvent, fluoroalcohol, was first carried out (Table 1).

We initially examined the [3 + 2] coupling of the QMA **1a** with allyltrimethylsilane **2a**[22] in our reported system along with montmorillonite (MT) or a stoichiometric amount of acetic acid in a mixed solvent with HFIP (Table 1, entries 1 and 9). These reactions indeed produced the coupling adduct, dihydrobenzofuran **3aa**, to some extent (61% and 19%, respectively) at room temperature, but the reactions were very slow and required long times to consume all the starting QMA **1a**.[footnote 4] Considering the pK_a values, several types of Brønsted acids involving a series of carboxylic acids were

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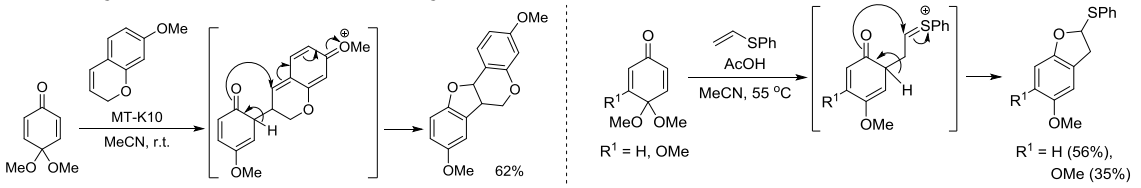
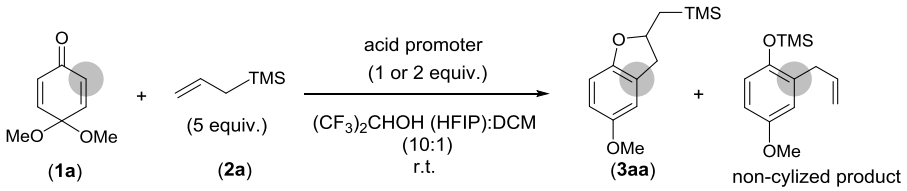
footnote 4 The [3 + 2] coupling utilizing MT clay[16a] and acetic acid[16b] in ordinary solvents were reported as reaction initiators, but these seem to be usable only for a limited number of extremely activated alkenes, *i.e.*, vinyl sulfide and electron-rich chromenes.



systematically evaluated. The results indicated that only the carboxylic acids with suitable acidic proton strength[23] showed good performance in order to develop the

Table 1. Effects of the Stoichiometric Acid Activators for [3 + 2] Coupling Reaction



Sluggish

Other Lewis acids : TMSOTf, $BF_3{\cdot}Et_2O$, $Cu(OTf)_2$, $B(C_6F_5)_3$, etc.

Brønsted acids : CF_3SO_3H, Bentonite, *p*-toluenesulfonic acid, etc.

entry	acid activator[a]	*p*Ka value	yield of **3aa** (%)	time	entry	acid activator[a]	*p*Ka value	yield of **3aa** (%)	time
1	Montmorillonite[b]	-	61	3 days	7	4-Nitrobenzoic Acid	3.42	14	3 days
2	Methanesulfonic Acid	-3.91	Sluggish	2 h	8	Benzoic Acid	4.20	9	2 h
3	CF_3COOH	0.05	72	30 min	9	AcOH*	4.79	19	30 min
4	2,4,6-Trichlorobenzoic Acid	1.40	59	10 min		Solvent			
5[c]	$C_6F_5CO_2H$ (PFBA)	1.60	90	10 min	10	$C_6F_5CO_2H$ (PFBA)	TFE/DCM	21	1 h
					11	//	HFIP/THF	64	1 h
6	Phthalic Acid	2.95	58	10 min	12	//	MeCN/DCM	trace	1 h

[a] 2 equiv. of acids [b] 25 mg relative to 1 mL of the solvent. [c] Pentafluorobenzoic acid (1 equiv.) and **2a** (2 equiv.). Performed at 0 °C. DCM = dichloromethane. TFE = 2,2,2-trifluoroethanol

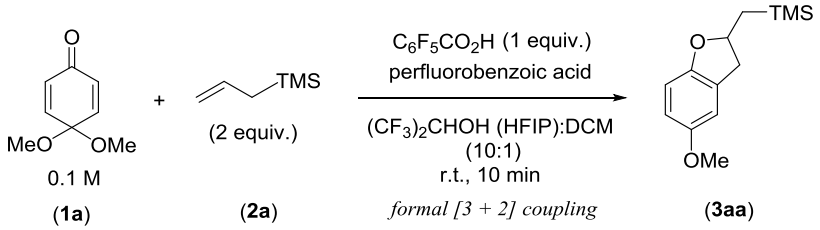
coupling, among which pentafluorobenzoic acid (PFBA; pK_a: ca. 1.5-1.6)[footnote 5] especially gave the most promising results regarding not only the product yield (90%) but also the observed production rate and reaction purity, while lowering the temperature to 0 °C (entry 5). Otherwise, incomplete conversions of the QMA **1a** were usually observed for the less acidic activators (entries 7-9), while the stronger acids, such as trichlorobenzoic and phthalic acids (entries 4 and 6), would considerably decompose QMA **1a**, resulting in poorer yields of the product **3aa**. In particular, trifluoroacetic acid produced the dihydrobenzofuran **3aa** in an acceptable yield (entry 3), but formation of quinone as well as some byproducts derived from the background polymerization of the used alkene **2a** was accompanied by the acid and much stronger

[footnote 5] The p*K*a order of the tested acids is as follows: AcOH, $C_6H_5CO_2H$ > 4-$NO_2C_6H_4CO_2H$ > $C_6F_5CO_2H$ > 2,4,6-Cl-$C_6H_2CO_2H$, phthalic acid > CF_3CO_2H > $MeSO_3H$ > CF_3SO_3H.

methanesulfonic acid (entry 2), which is recognized as a serious problem for future expansion of the scope of the QMAs **1** and alkenes **2**.[24) footnote 6] Some Lewis acids, such as boron trifluoride and trimethylsilyl triflate, are known instead to induce the conjugated addition[10h)] and [5 + 2]-type cyclization[15)] for QMAs **1a** and thus did not produce the desired [3 + 2] coupling as expected.

Due to the good results provided by the perfluorobenzoic acid, we conducted further optimizations of the [3 + 2] coupling. Notably, HFIP has an indispensable role in this new coupling system because the consumption of the QMA **1a** by pentafluorobenzoic acid in other solvents was very slow (entries 10-12), and product **3aa** would not smoothly form, even in the parent but less polar and weaker hydrogen bond donor, 2,2,2-trifluoroethanol (TFE, entry 10). Therefore, the combined use of the perfluorobenzoic acid in HFIP is highly important to achieve an effective reaction.

To sum up, from these observations, we determined the standard conditions for the [3 + 2] coupling of QMAs **1** to be optimized as the use of 2 equiv. of alkene nucleophiles **2** in the presence of 1 equiv. of the acid promoter, PFBA, in a mixed solvent system of HFIP and DCM (Scheme 12).



Scheme 12

Section II. Synthesis of Various Dihydrobenzofuran Derivatives *via* Controlled [3 + 2] Coupling toward Alkene Nucleophiles

With the established conditions in hand, the scopes of both extensive QMAs **1a-i** for the formation of various dihydrobenzoruan derivatives toward **2b** as the counterpart was then evaulated. Many types of the QMAs **1a-i** were applicable in our coupling and afforded the corresponding dihydrobenzofurans **3** in up to quantitative yield (Table 2).

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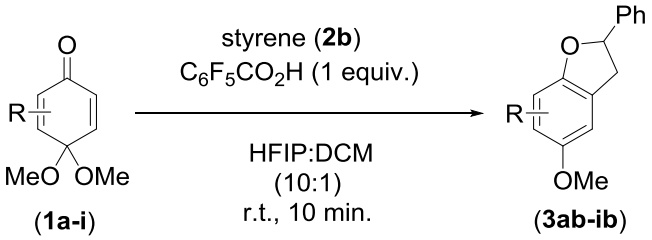
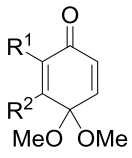
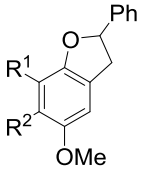
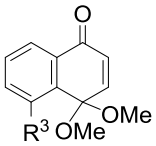
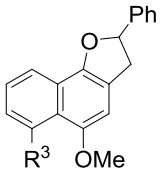
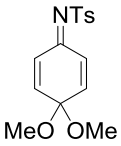
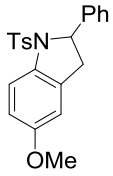
footnote 6 Polymerization of styrenes **2** can occur in the presence of strong Brønsted acids.[24)]

Table 2. Scope of the QMAs 1: Representative Examples



entry	QMA (**1**)	product (**3**)	yield[a]
			
1	$R^1 = R^2 = H$ (**1a**)	(**3ab**)	93%
2	$R^1 = H$, $R^2 = Me$ (**1b**)	(**3bb**)	83%
3	$R^1 = H$, $R^2 = t$-Bu (**1c**)	(**3cb**)	64%
4[b]	$R^1 = H$, $R^2 = OMe$ (**1d**)	(**3db**)	78%
5	$R^1 = {}^t$Bu, $R^2 = H$ (**1e**)	(**3eb**)	quant.
6	$R^1 = Cl$, $R^2 = H$ (**1f**)	(**3fb**)	86%
			
7	$R^3 = H$ (**1g**)	(**3gb**)	quant.
8	$R^3 = OAc$ (**1h**)	(**3hb**)	98%
			
9	(**1i**)	(**3ib**)	82%

[a] Isolated yields of the products **3** after purification by column chromatography. [b] 2 equiv. of the acid activator and 3 equiv. of styrene **2a** were used.

The reactions occurred quite regio-selectively at the less hindered α position of the carbonyl in the QMAs. The *tert*-butyl substituent at the neighboring position of the acetal in the QMA **1c** somewhat hampered the substrate reactivity due to its steric demand (entry 3). The QMAs possessing the substituents of halogen **1e** and a *tert*-butyl moiety **1f** could afford the cyclized coupling products **3eb** and **3fb** with high conversions (entries 5 and 6). The formations of the desired cycloadducts **3gb** and **3ib** were achieved in excellent yields from naphthalene QMAs **1g** and **1h** (entries 7 and 8). Gratefully, the valuable indoline compound **3ib** could also be obtained from iminoquinone acetals **1i** without optimization (entry 9). Such oxygenated indoline structures are found in the natural products showing several interesting biological activities, such as physostigmine and esermethole.[25)]

Subsequently, the scope of the reactions regarding the various alkene coupling partners **2** was investigated by employing QMA **1a** as a unified reaction substrate (Table 3). Fortunately, alkenes **2a-i**, having either electron–donating or withdrawing substituents (entries 1-8), could smoothly react with the QMA **1a** without significant alteration of the reaction efficiencies. Especially, the *trans*-isomer of the dihydrobenzofuran was solely obtained from the *trans*-styrene **2g**. The cyclic styrene **2h** was also applicable to the construction of the fused dihydrobenzofuran structure in the product **3ah** found in the pterocarpan-type natural products (entry 7).[26)] [footnote 7] The use of these alkenes **2** as nucleophiles could afford the corresponding dihydrobenzofurans **3** only in this strategy, while the reported oxidative cyclization methods starting from phenols were somewhat troublesome in terms of the yields to obtain the same products **3**.[27)] Additionally, the vinyl sulfide **2i** was also the appropriate nucleophile, giving the cyclized *O,S*-acetal **3ai** in good yield (entry 8).[footnote 8]

[footnote 7] The member of widely distributed isoflavanoid families showing a broad spectrum of biological properties including sharp responses to fungal infections, COX-2 inhibition, antitumor, LDL-antioxidant, anti-HIV, and anti–snake venom activities.[26), 8a)]

[footnote 8] The cyclized *O,S*-acetal **3ai** could also be utilized for production of the benzofuran **4** as a synthetic module.

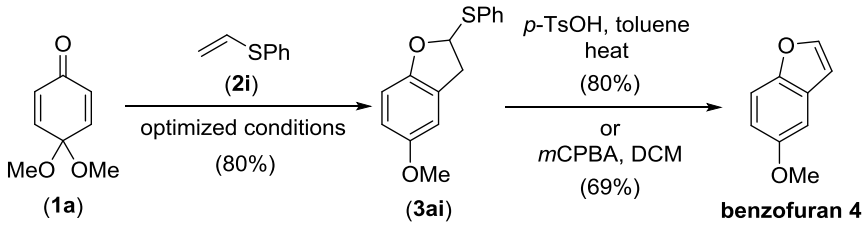
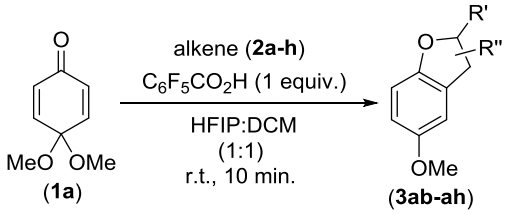
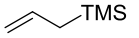
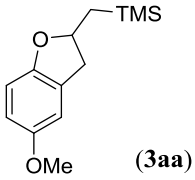
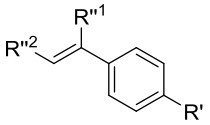
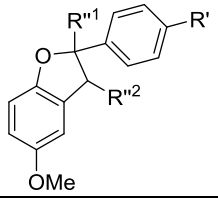
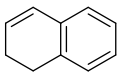
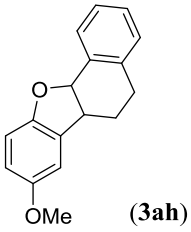
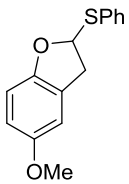


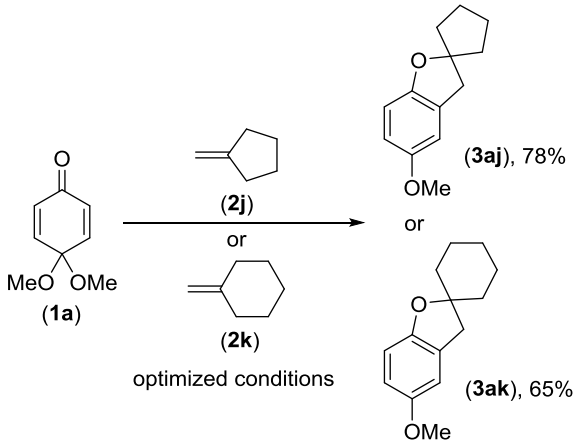
Table 3. [3 + 2] Coupling of Various Alkenes 2a-i Toward QMA 1a



entry	alkene (**2**)	product (**3**)	yield[a]
1	 (**2a**)	 (**3aa**)	89% 90%[b]
			
2	R' = Me, R"1 = R"2 = H (**2c**)	(**3ac**)	83%
3	R' = *t*-Bu, R"1 = R"2 = H (**2d**)	(**3ad**)	92%
4	R' = Cl, R"1 = R"2 = H (**2e**)	(**3ae**)	94%
5	R' = R"2 = H, R"1 = Me (**2f**)	(**3af**)	81%
6	R' = OMe, R"1 = H, R"2 = Me (**2g**)	(**3ag**)[c]	93%
7	 (**2h**)	 (**3ah**)	83%
8	 (**2i**)	 (**3ai**)	80%

[a] See the footnote in Table 2 for the reaction conditions. 2 equiv. of alkenes **2a-i** were used for the reactions. [b] Performed at 0 ^{o}C. [c] Only *trans* isomer produced.

On the other hand, while treating the five- and six-membered *exo*-methylene compounds **2j** and **2k** in excess amounts under the optimized conditions, the two types of ring-sized spirocyclic dihydrobenzofurans **3aj** and **3ak** could be successfully afforded with comparable results, respectively (Scheme 13).[28)] [footnote 9]



Scheme 13

In first conclusion, we have successfully achieved the [3 + 2] coupling of the QMAs **1** with various alkenes **2** on the basis of a new allylic substitution strategy promoted by the stoichiometric amount of perfluorobenzoic acid activator (PFBA) and the hydrogen bond donor, HFIP, affording the final dihydrobenzofuran and other derivatives in good to quantitative yields.

Section III. Mechanistic Considerations

1.3.1 A Plausible Reaction Mechanism

It has been reported that some QMAs **1** would induce [5 + 2] cyclizations with alkenes upon acid treatment.[15)] For the QMA **1d**, the generation of the phenoxenium ion[29)] was reported during the mechanism to exclusively lead to the [5 + 2] cyclization by the trapping with styrene **2b**, giving rise to the product **5** (Scheme 14).[15c)] However, in our reaction system the [5 + 2] adduct **5** would not be produced at all in the presence of the same substrate **1d**, which indicated that our conditions cannot apparently produce the phenoxium ions. Herein, as illustrated in Scheme 14, we hypothesize that our [3 + 2] coupling of the QMA **1a** would instead involve the charged QMA species **A** associated

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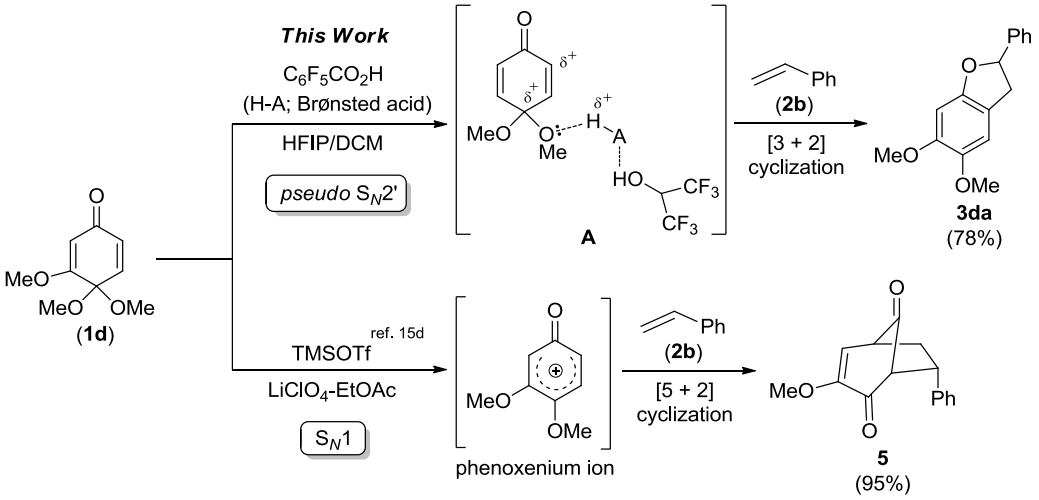
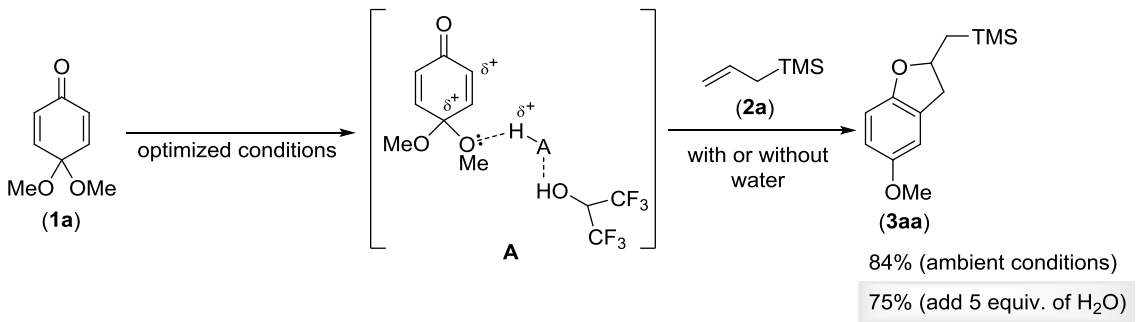
footnote 9 These ring-sized spirocyclic compounds are known to be potentially useful in consideration of the ubiquitous nature of the spirocyclic structures in natural products showing interesting biological activities and of unique physical properties, such as for optoelectronics and asymmetric ligands for catalytic synthesis.[28)]

with the acid species *in situ* generation of the combined acid in equilibrium by the coordination of the hydrogen bond donor solvent, HFIP, as the more stable charged intermediacy **A**.



Scheme 14

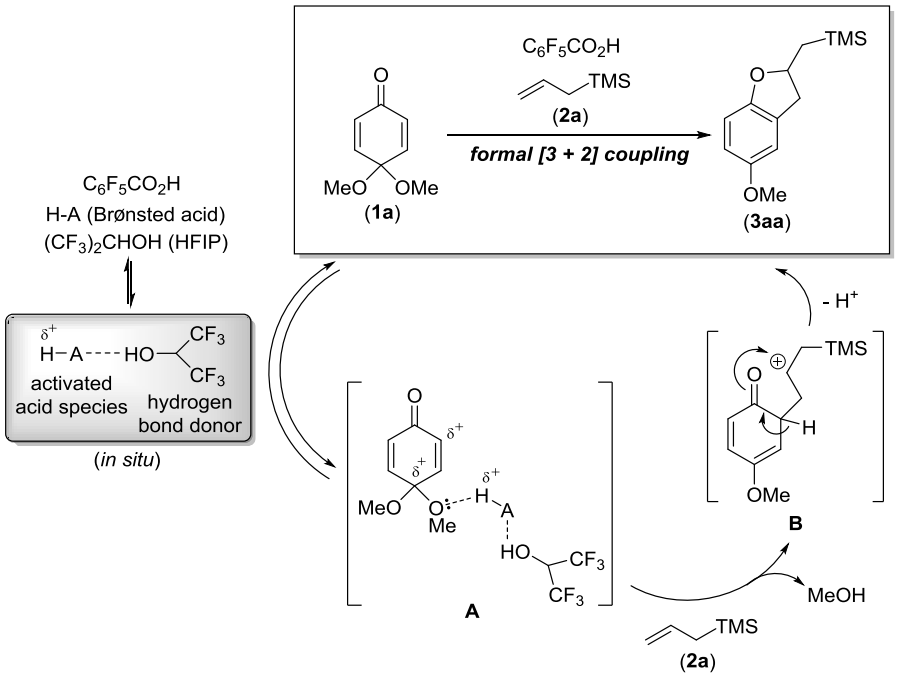
To further prove the existence of our proposed charged QMA species **A,** the following control experiments with an extra addition of 1 equiv. as well as even 5 equiv. of water were conducted under our optimized reaction conditions, against the reactive and unstable phenoxenium ions having low moisture tolerability. As expected, our [3 + 2] coupling of the QMAs **1a** with addition of water did not cause a remarkable decrease in the product yields probably due to the intermediacy of the more stable charged QMA species **A** (Scheme 15), while phenoxenium ions generated under the known conditions[15d] underwent competitive quinone formation by hydrolysis of the acetals in the presence of water (S_N1 pathway).



Scheme 15

After confirmation of the QMA charged species **A,** we subsequently proposed the plausible mechanism for the [3 + 2] coupling reaction using QMAs **1a** and alkene

nucleophile **2a** as the representative coupling substrates (Scheme 16).

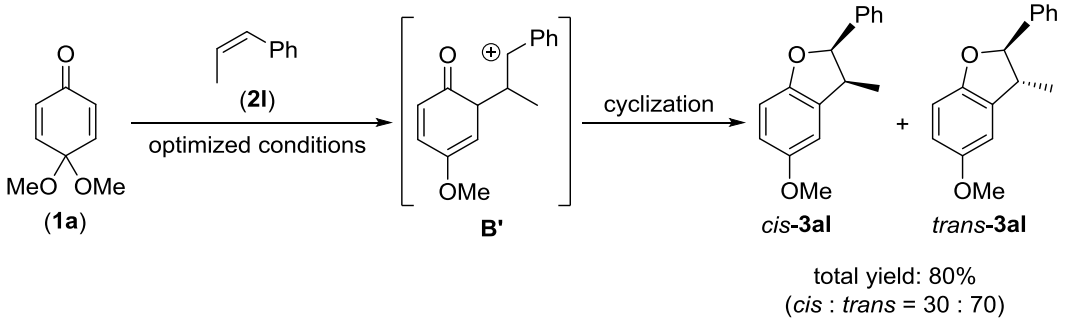


Scheme 16

The initiation step concerns the charged QMA **A** associated with the combined acid species of perfluorobenzoic acid and hydrogen bond donor, HFIP. Pre-activation of the Brønsted acid might first occur by the coordination of HFIP to the Lewis basic functionality of the carbonyl group of the acid (Brønsted acid activation by HFIP).[21] The charged QMA **A** could then react with π-nucleophile **2a** at the allylic carbon of the ring structure, rather than the sterically encumbered tertiary acetal carbon atom. The *pseudo*-S_N2'-like introduction of the nucleophile **2a** by the reagent control could afford the keto-type intermediate **B**, which simultaneously cyclized at the carbonyl moiety of the QMA with accompanying aromatization as a driving force. The stepwise constructions of the carbon-carbon and carbon-oxygen bonds between the QMA **1a** and π-nucleophile **2a** would lead to the formation of the formal [3 + 2] coupling product, dihydrobenzofuran **3aa**. Apparently, the high polar fluoroalcohol is a good match for the solvation of all the charged reaction intermediates.

Finally, to prove the intermediary of the pre-cyclized keto-type tautomer **B**, we presented the following experiment using the *Z*-type styrene **2l** for the coupling (Scheme 17). In fact, the reaction of the QMA **1a** and *cis*-methyl styrene **2l** produced the corresponding cyclized products **3al** as a regio-mixture with an about 30:70 ratio of *cis*- and *trans*-dihydrobenzofurans. One can easily accept that this observation clearly

supports the involvement of the pre-cyclized cationic intermediate **B**, in which the free rotation of the C-C bonds competitively occurred to the cyclizations to form the more thermodynamically-favored latter *trans*-isomer rather than the *cis*-**3al**.



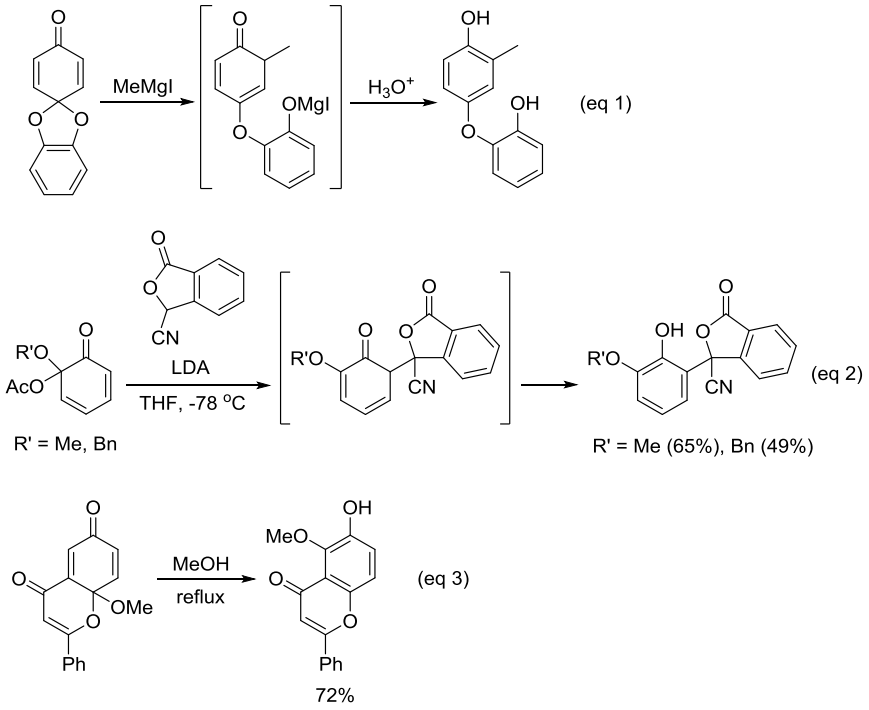
Scheme 17

1.3.2 Comparison with Other Methods

In comparison, we summarize the differences of the reaction pathways between our proposed reaction mechanism under acidic conditions and other representative allylic substitutions of QMAs **1** under basic or neutral conditions, in order to clarify the uniqueness of our *pseudo*-S_N2' reaction mechanism more concrete.

So far, with regard to the other limited strategies promoted under basic and neutral conditions, the first report of an allylic substitution reaction for QMAs **1** with the methyl Grignard reagent (MeMgI) was presented by Coutts and Hamblin over 30 years ago to give the rearomatized diphenyl phenol ether in some extent, where the reaction favored the unusual substitution course due to the formation of the stable magnesium phenoxide consisting of the organometallic reagent and the specific acetal leaving group (Scheme 18, eq 1).[12] Indeed, the introduction of an excellent leaving group, such as the carboxyl group, at the acetal part in some stable and/or electron-deficient QMAs could be promising to bias the reactivity of QMAs for substitution versus the above-mentioned addition preference (eq 2).[30] However, some of the reactive QMAs are too unstable to smoothly handle and 1,3-rearrangement of the acetal methoxy group in a methanol solution might occur *via* the allylic substitution pathway (eq 3).[31]

Although these strategies are useful for directing the reaction to the substitution course under basic and neutral conditions, they might not perfectly eliminate the competitive addition processes and not be applicable to simple and readily accessible QMAs as well as extended nucleophiles.



Scheme 18

Very recently, a S_N2' displacement and cyclizing substitution for the introduction of electron-rich arenes to QMAs similar to that of us has recently been nicely described by Porco *et al.*, who investigated the ABCD ring construction of kibdelones using a novel arylation to produce a complex biphenyl adduct in moderate yield.[14b) footnote10]

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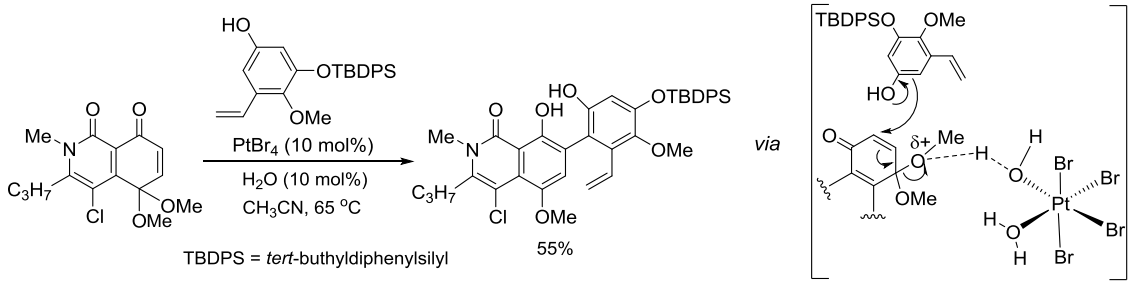
footnote10 This unique arylative substitution could proceed by the action of inorganic platinum(IV) catalysts in the presence of an appropriate amount of water, whereas a number of other screened metal salts as well as Brønsted and Lewis acids did not similarly work so well for the reaction.



In summary, after the extensive mechanistic considerations and investigation of this [3 + 2] coupling reaction including the comparison with other methods, the mechanism of which has been rationalized to principally involve the concerted *pseudo*-S_N2' interaction reacted on the tertiary acetal moiety of QMAs **1** with nucleophilic alkenes **2** *in situ* generation of the acitivated acid species of specific acid (PFBA) in equilibrium by the undesired involvement of coordination of the hydrogen bond donor solvent, fluoroalcohol, at first rather than the 1,2-addition to the carbonyl group followed by rearrangement (aforementioned as an example in eq 1, Scheme 4,)[13b] or through the known phenoxenium ions by an S_N1 leaving manner (mentioned above, Scheme 14)[15d], and then to stepwisely construct the carbon-carbon and carbon-oxygen bonds for cyclizing, leading to the diverse thermo dynamically-favored dihydrobenzofurans **3** and other derivatives.

Chapter II. Controlled [3 + 2] Coupling Reaction of QMAs in a Catalytic System

Despite the general success of the results in this [3 + 2] coupling reaction (*vide supra*), there still exists several critical limitations from the practical view regarding our reported chemical coupling reaction of the QMAs **1** and nucleophilic alkenes **2** with the treatment of PFBA. The reactions usually required a stoichiometric amount of PFBA, which is considered to be a waste material after the reaction process.[32] Additionally, the acid-induced background polymerization of the used alkenes **2** as a problem[24] forced their excess use, typically over 2 equiv., for the couplings, which also refers to the all consumption of the QMAs **1**.

Aiming at realizing a more practical catalytic reaction, several significant advances are expected to be improved, which mainly involves: 1) enhancing the reactivity of our specific perfluorinated acid in order to address the reaction problems needs for its catalytic use, and emerging the reaction more applicability needs improved stoichiometry of the alkenes **2** without any redundant formation of the alkene-derived byproducts.

Herein, we accordingly further attenuate the reactivity of the acid promoter working at a possible minimal loading. Considering that only the acids with the suitable pK_a values could serve as the efficient promoters for the [3 + 2] coupling, we screened a series of perfluorobenzoic acid derivatives **a-h** with the varied pK_a (Figure 2).

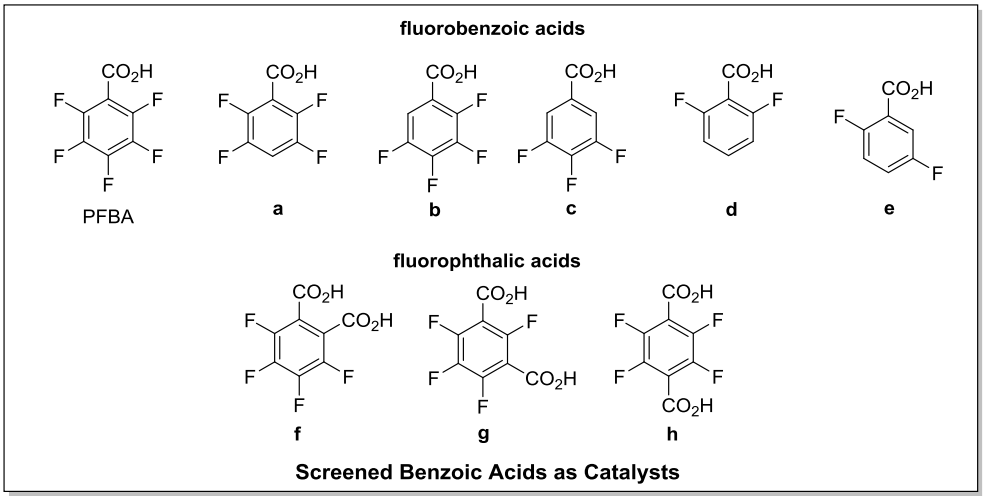
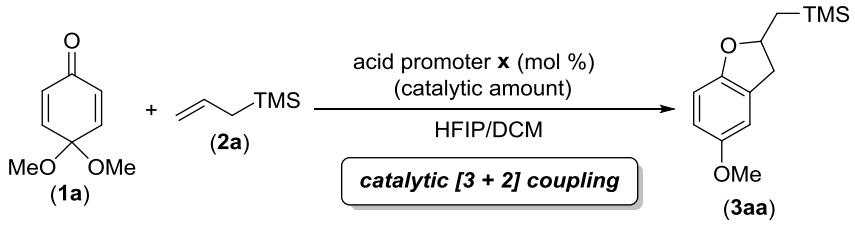


Figure 2

It is thus possible to systematically attenuate the acidity of the perfluorobenzoic acids by modifying the functionality at the ring positions. For the catalytic reaction at 2 mol% loading, all the partially fluorinated benzoic acids **a-e** showed lower efficiencies and slow reaction rates (Table 4, entries 2-6), probably due to their weaker acidities

compared to PFBA itself. Meanwhile, a set of more acidic phthalic acids **f-h** were examined with promising results under the catalytic conditions (entries 7-9), among the three isomers of which fluorinated terephthalic acid **h** showed a best catalytic performance and was capable of providing the coupling product **3aa** in 72% yield even at 1 mol% loading (entry 9). Encouraged by the results with the catalyst **h**, general effects regarding the catalyst loading, reactant ratio, concentration, and temperature were further investigated (entries 11-14). By employing the catalyst **h** at 5 mol%, more promising results were obtained (entry 10). At last, the catalytic reaction at the temperature of 0 ^{o}C has become comparable to the original stoichiometric one (PFBA) for the dihydrobenzofuran **3aa** production when using the fined catalyst **h** at 5 mol% (entry 14).

Table 4. Screening for the Catalytic [3 + 2] Coupling Reaction of 1a and 2a[a]

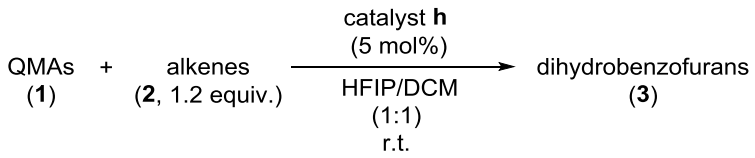


entry	catalyst	**x**	nucleophile **2a** (equiv.)[b]	yield[c]
1	Pentafluorobenzoic acid	2	1.2	48%
2	2,3,5,6-tetrafluorobenzoic acid **a**	2	1.2	45%
3	2,3,4,5-tetrafluorobenzoic acid **b**	2	1.2	24%
4	3,4,5-trifluorobenzoic acid **c**	2	1.2	15%
5	2,6-difluorobenzoic acid **d**	2	1.2	27%
6	2,5-difluorobenzoic acid **e**	2	1.2	18%
7	perfluorophthalic acid **f**	1	1.2	41%
8	perfluoroisophthalic acid **g**	1	1.2	61%
9	perfluoroterephthalic acid **h**	1	1.2	72%
10	perfluoroterephthalic acid **h**	5	1.2	78%
11	perfluoroterephthalic acid **h**	5	1.0	72%
12[d]	perfluoroterephthalic acid **h**	5	1.2	69%
13[e]	perfluoroterephthalic acid **h**	5	1.2	65%
14[f]	perfluoroterephthalic acid **h**	5	1.2	84%

[a] Unless otherwise noted, reactions were examined in HFIP/DCM (1/1 v/v, 0.2 M) at room temperature for 1 hr. [b] Relative to QMA **1a**. [c] Isolated yields after purification. [d] HFIP/DCM (2/1 v/v, 0.2 M). [e] HFIP/DCM (2/1 v/v, 0.2 M). [f] Performed at 0 ^{o}C for 3 hrs.

With the optimal catalyst **h** and conditions, we confirmed the versatility of the catalytic system for the described QMAs **1** and nucleophilic alkenes **2** (Table 5). In comparison, it was found that a series of the dihydrobenzofuran products **3** were successfully produced by employing the 5 mol% catalyst **h** with the improved stoichiometry of the alkenes **2** (lowering to 1.2 equiv. from 2 equiv.). The selected examples are summarized. The good-to-excellent yields (up to 98% for the dihydrobenzofuran **3eb**) have promised the generality of the catalytic method for the practical [3 + 2] couplings of the QMAs **1**.

Table 5. [3 + 2] Coupling by Perfluoroterephthalic Acid Catalyst h[a]

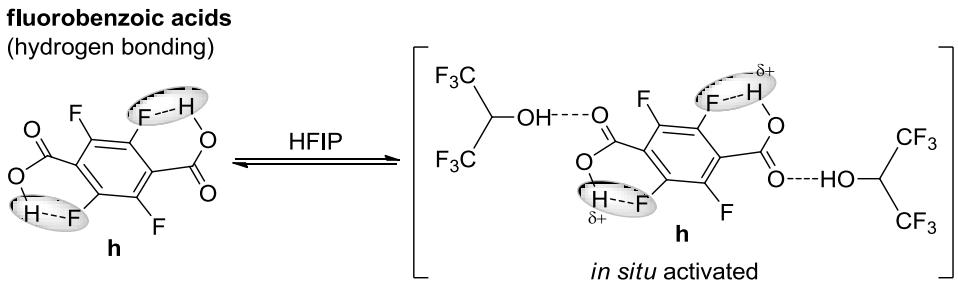


entry	QMA (**1**)	alkene (**2**)	product (**3**)	time	yield[b]
1	**1a**	**2b**	**3ab**	**4h**	82%
2	**1b**	**2b**	**3bb**	**5h**	76%
3	**1c**	**2b**	**3cb**	**5h**	67%
4	**1e**	**2b**	**3eb**	**5h**	98%
5	**1f**	**2b**	**3fb**	**4h**	85%
6	**1h**	**2b**	**3hb**	**5h**	90%
7	**1i**	**2b**	**3ib**	**8h**	94%
8	**1a**	**2c**	**3ac**	**3h**	78%
9	**1a**	**2d**	**3ad**	**4h**	80%
10	**1a**	**2e**	**3ae**	**5h**	88%
11	**1a**	**2f**	**3af**	**5h**	79%
12	**1a**	**2g**	**3ag**[c]	**4h**	84%
13	**1a**	**2h**	**3ah**	**5h**	90%
14	**1a**	**2i**	**3ai**	**4h**	88%
15	**1a**	**2j**[d]	**3aj**	**4h**	74%
16	**1a**	**2k**[d]	**3ak**	**7h**	81%

[a] Reactions were performed using 1.2 equiv. of alkenes **2** in the presence of 5 mol% of the acid catalyst **h** in HFIP/DCM = 1/1 (0.2 M) at room temperature. [b] Isolated yields after purification. [c] Only *trans* isomer was obtained. [d] 3 equiv. of alkene **2j** and **2k** were used.

Nonetheless, the much stronger acids, *e.g.*, toluenesulfonic acid, trifluoroacetic, and methane sulfonic acids, on behalf of the catalyst **h** would provide quite sluggish reaction outcomes, showing much poorer yields of the desired product **3aa**; as already described, such acids were harmful to the QMA **1a** and the alkene **2a** (*vide supra*). Therefore, appropriate acidity is an important factor required for the catalyst.[footnote11]

Although the origin of the higher catalytic activity of the catalyst **h** is yet unclear, one significant difference in the perfluorobenzoic acids relative to others is the presence of the intramolecular H-bonding in the *ortho*-fluorobenzoic acid structure,[33)] which makes the acidic site of the molecule quite bulky. Compared with the less effective catalysts **f** and **g**, the best catalyst **h** has much opportunity for the H-F bondings. It seems that this conformation favorably affected the desired protection of the acetal carbon in the assumed transition state **A** (see the reaction mechanism in Scheme 16) from the nucleophilic attack and thus might exclude the quinone formation by addition of concomitant water as well as other side reactions. In our previous studies, steric blocking of the electrophilic acetal carbon by bulky activator was very important for suppressing the quinone formation.[19i, 19j)] Hence, the perfluorinated benzoic acids would have a superior effect on controlling the coupling reactions in the catalytic cycle because of the bulky shapes compared to the acids having similar pK_as(Scheme 19).



Scheme 19

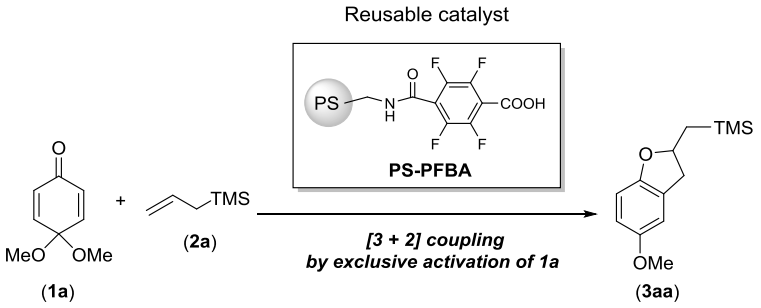
footnote11 Aliphatic carboxylic acids having *p*K$_a$ values similar to that of the catalyst **h**, that is, trichloro- and dichloro-acetic acids, showed somewhat lower efficiencies as the catalysts (below 65% yields of the product **3aa** at 2 mol% loading).

In summary, further investigations in our [3 + 2] coupling strategy with regard to the modification of perfluorinated acid catalyst on their ring structures have been sufficiently conducted, which led to the findings of an excellent catalytic alternative, that is the fluorophthalic acid catalyst **h**, advancing original stoichiometrically controlled couplings to render catalysis of the acid at lower than 5 mol% loading together with the significantly improved stoichiometry of the alkenes (lowering to 1.2 equiv.) for making this controlled coupling reaction more practical.

Chapter III. Controlled Couplings of QMAs Using Reusable Polystyrene-Anchored Specific Proton Catalyst

As we mentioned in the previous chapters, we have succeeded in performing this reagent controlled couplings of QMAs **1** with a series of carbon π-nucleophiles **2** by successfully controlling the formation of carbon-carbon bonds to the quinone architecture. However, with regard to the reaction activator of alkene nucleophiles, the used specific fluorinated acid, that is perfluorobenzoic acid (PFBA) or perfluoroterephthalic acid **h**, is still considered to be a waste material after the reactions.

Encouraged by many positive outcomes in the polymer-supported reagent chemistry[34-36] footnote12, we have become interested in designing a new heterogeneous catalyst carrying the specific PFBA functions as our continuation of effort in developing greener and more attractive strategies in applying the QMAs. We now report the preparation and reactivity of a reusable solid-type PFBA alternative that is extremely valuable for the coupling of QMAs **1** with carbon π-nucleophiles, in which the former electrophiles **1** can be exclusively activated by the solid acid to minimize the formation of alkene-derived byproducts and deactivation of the acid catalyst (Scheme 20).



Scheme 20

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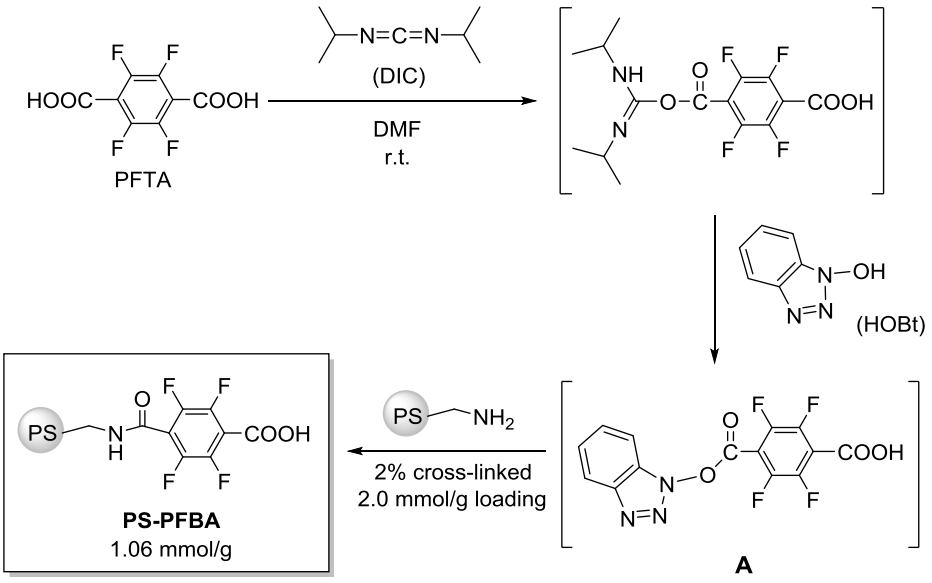
footnote12 Polymer-supported reagents and catalysts, which have emerged from solid-phase organic synthesis (SPOS),[34] have been emerging as a promising tool in modern synthetic research in developing greener methodologies that can meet recent growing demands for establishing ecological and environmentally friendly chemical processes.[35] Generally, the advantages of reagents and catalysts that are immobilized on polymer backbones include enhanced stabilities such as robustness, high tolerance to air and moisture, as well as their convenient handling and recovery, the benefits of which have made them environmentally benign alternatives to conventional reagents and catalysts.[36] Many research studies have revealed that the immobilization of conventional reagents and catalysts is one of the promising ways not only to control their stability, but also to maintain their reactivity for reuse and recycling.

Section I. Preparation of Polystyrene-Supported Perfluorobenzoic Acid

For easy access to the preparative polystyrene-supported perfluorobenzoic acid (PS-PFBA), we first envisioned the following one-pot protocol starting from the commercial perfluoroterephthalic acid (Scheme 21). Relying on well-established procedures in Merrifield's solid-phase peptide synthesis (SPPS),[37] the activated ester **A** was first generated *in situ* in a flask by treatment of the PFBA with diisopropyl carbodiimide (DIC) and hydroxybenzotriazole (HOBt) *via* the amide bond formation,[38] by which the desired polystyrene-anchored PFBA (PS-PFBA) could be finally produced in good efficiency (75%) as white microbeads by rinsing the resins with several solvents. The prepared PS-PFBA is stable under ambient conditions at least for several months without special storage conditions. Characterization for ascertaining the introduction and loading of the PFBA in the polymer backbones was determined by IR and elemental analyses.[footnote13]



Scheme 21

[footnote13] IR spectrum exhibited strong band absorptions at 1698 and 1723 cm^{-1} corresponding to the vibration peaks of the amide linkage and carboxylic acid functionality of the PFBA along with a broad but weak absorption band ranging from 2914 and 3290 cm^{-1} for the NH and COOH groups. Theoretical loading of the PFBA based on the elemental analysis of the nitrogen contents (Found: N, 2.20) averaged 1.06 mmol/g in comparison to the starting aminomethyl polystyrenes (N, 2.88 for 2.0 mmol/g of the free amine sites). The degree of unreacted free NH_2 sites in the polymers (ca. 25%) was also checked by elemental analyses as the corresponding ammonium salt after titration of the prepared PS-PFBA using hydrogen chloride.

Section II. Polystyrene-Supported Perfluorobenzoic Acid as the Specific Promoter for Controlled Couplings of QMAs

The newly prepared polystyrene-supported perfluorobenzoic acid (PS-PFBA) was evaluated with further optimization. It should be noted that, although the reaction of the QMA **1a** and allyltrimethylsilane **2a** at room temperature successfully afforded the coupling product **3aa** in good yield (81%) under the optimized condition, a further approximate 10% increase in the yield was obtained at 0 ^{o}C (90%) probably because the formation of the cationic charged quinone species **A** that occurred *in situ* during the transition states should plausibly occur at that lower temperature. Nonetheless, the used PS-PFBA beads could be quantitatively recovered by filtration of the reaction mixture, and were then repeatedly used for at least several times (*vide infra*).

Encouraged by the remarkable activation behaviour of the PS-PFBA in this [3 + 2] coupling reaction, we subsequently expanded the reaction scopes of various QMAs **1** having different ring substituent patterns and a wide array of carbon π-nucleophiles **2** under the optimized conditions in order to ascertain the versatility of the PS-PFBA as a heterogeneous catalyst (See selected results in Scheme 22). As a result, the PS-PFBA also served as an efficient reusable acid promoter for the reactions to succinctly provide a series of dihydrobenzofuran products **3**[footnote14] in good to excellent yields. The yields in most cases were comparable and sometimes even higher than those for the PFBA and perfluorinated acid **h**. The new polymer acid, PS-PFBA, thus behaved as a powerful and clean promoter with a broad generality.

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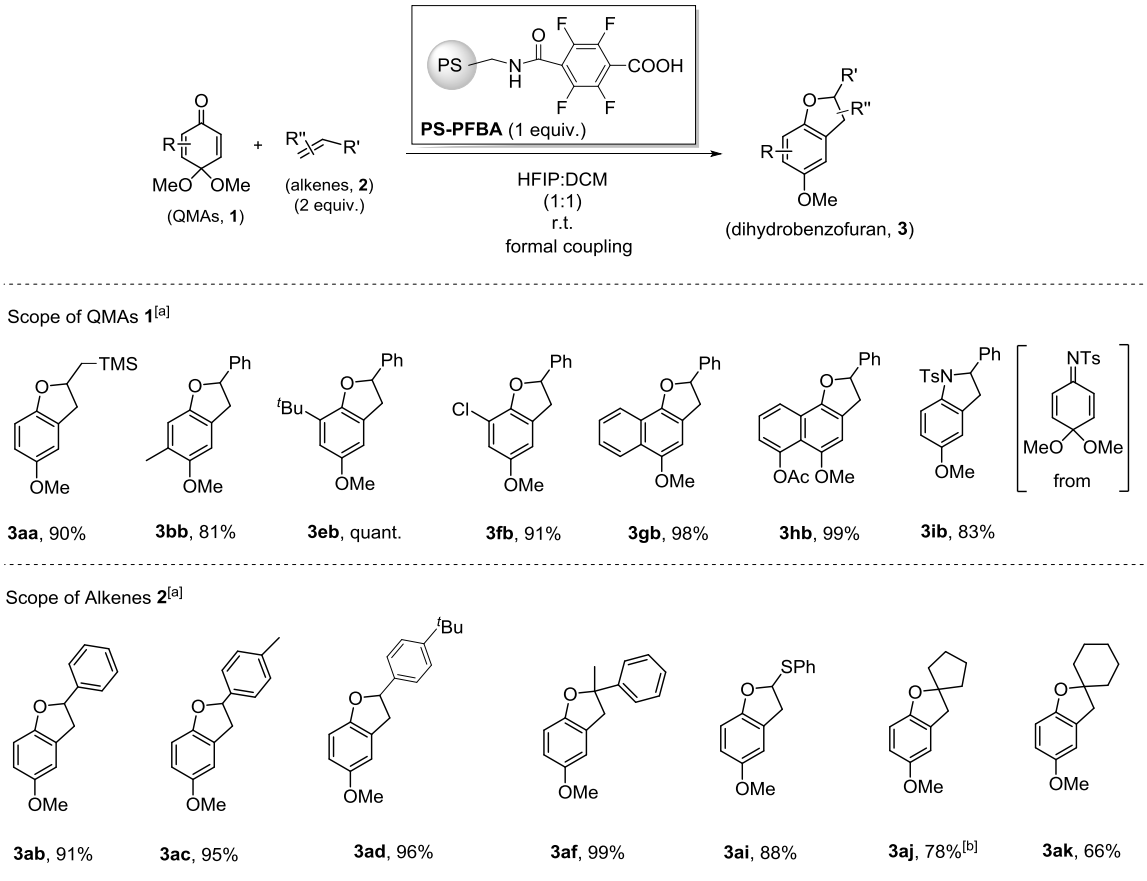
footnote14 The increased yields of the products **3** from the alkene nucelophiles **2** is probably due to the excellent chemo-selectivity of the PS-PFBA toward the QMAs **1** over the alkenes **2** as a milder acid. Since some byproducts derived from the background polymerization of the used alkenes **2** has been confirmed by us as a serious problem of previous homogeneous conditions caused by the acid in chapter I. On the other hand, such byproduct formation was not detected at all based on the NMR detection level when using this newly developed PS-PFBA. The attenuated activity of the PS-PFBA compared with its soluble alternative is mainly due to the heterogeneity of the polymer catalyst.

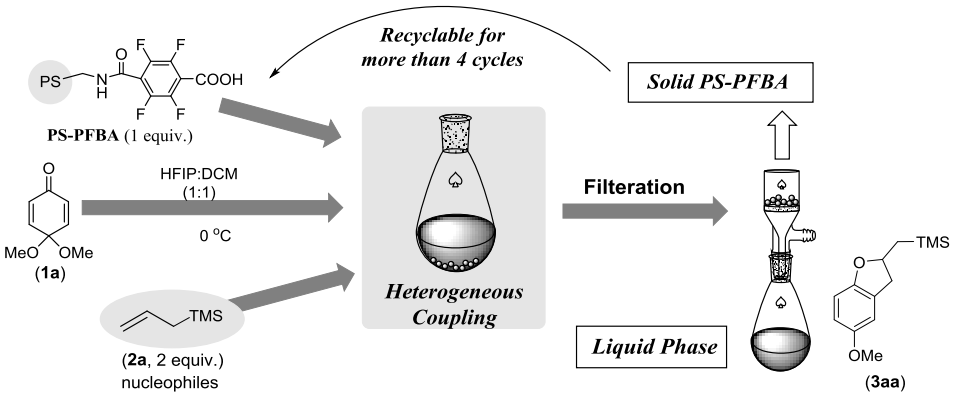


[a] Recycling yield of the polystyrene anchored acid (PS-PFBA) was nearly quantitative. [b] 5.0 equiv. of alkene and 2.0 equiv. of PS-PFBA.

Scheme 22

Since the recyclability is regarded as one of the important criterion for evaluating the applicability of the heterogeneous catalysts, we then attempted to investigate the recovery and recyclability of PS-PFBA in this [3 + 2] coupling reaction. As depicted in Table 6, the recycled catalyst of PS-PFBA was also capable of being reused smoothly for at least four consecutive reuses without any loss of the catalytic activity.

Table 6. [3 + 2] Coupling Product 3aa Using Reused PS-PFBA

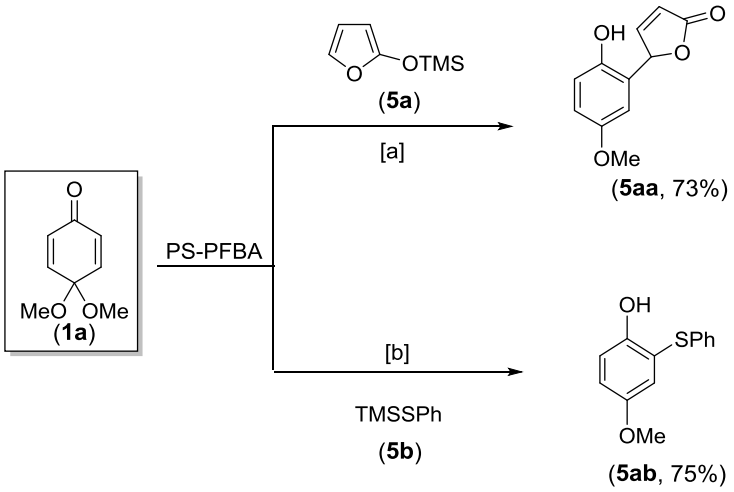


entry	fresh	1st reuse	2nd reuse	3rd reuse	4th reuse
yield **3aa**	91%	90%	90%	91%	89%

To sum up, we have also succeeded in developing a unique solid acid catalyst (PS-PFBA) including immobilized perfluorobenzoic acid sites in the polystyrene backbones, which are capable of behaving as specific promoters for this controlled carbon-carbon bond-forming transformation of QMAs **1**. The polystyrene-anchored protons in the PS-PFBA could successfully induce the [3 + 2] coupling reactions from the diverse π–carbon nucleophiles **2** with a similar efficiency to its homogeneous counterpart PFBA and even catalyst **h**.

Chapter IV. Reactions Using Other Extended Nucleophiles

We finally attempted to broaden the scope of nucleophiles in a brief extension of this study. In evaluating mild conditions of the polymer acid catalyst, other two potential nucleophiles were tested for the reactions to the QMA **1a** using the PS-PFBA. Toward this objective, the furanyl silylether **5a**, and sulfur nucleophile **5b** could behave as good nucleophiles to produce the desired coupling products **5aa** and **5ab** under mild conditions (Scheme 23).



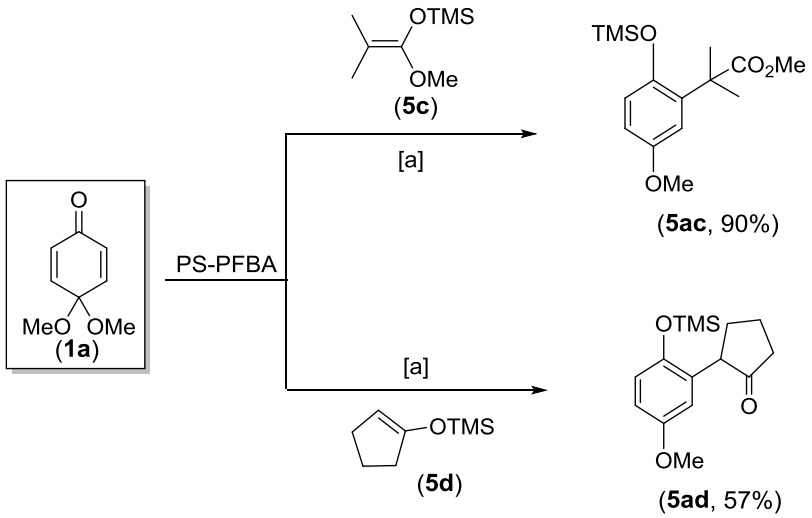
[a] PS-PFBA (0.1 equiv.), nucleophile **5a** (3 equiv.) in HFIP/DCM = 10:1 (0.1 M) at 0 ^{o}C-r.t.

[b] PS-PFBA (1 equiv.), nucleophile **5b** (2 equiv.) in HFIP/DCM = 1:1 (0.2 M) at 0 ^{o}C.

Scheme 23

Since enol silylethers and silyl ketene acetals[39] have become one of the most popular carbon nucleophiles in organic synthesis and are also employed even easily as a relatively weak and soft carbon nucleophiles to form the carbon-carbon bond in other reactions such as Mukaiyama aldol reactions[40], 1,4-additions[41], and others[42]. Therefore, we envisioned that the soft nucleophiles of silyl enolates, which are superior to other metal enolates in terms of their isolation might also be the favorable candidate for our coupling reactions of QMA **1a**.

Finally, investigations in our coupling reactions by utilizing the unique reactivities of the enol silylethers **5c** and silyl ketene acetals **5d** as potential carbon π-nucleophiles was conducted by the aid of our newly developed reusable PS-PFBA for the formation of new carbon-carbon bond for QMA **1a** as the electrophile (Scheme 24). As expected, the reactions were successful for introducing the nucleophiles of enol enolates **5c** and **5d** toward only the allylic position of allylacetal unit of QMA **1a** to provide two types of coupling products **5ac** and **5ad** in moderate to good yields under mild conditions.



[a] PS-PFBA (1 equiv.), nucleophiles **5c** or **5d** (2 equiv.) in HFIP/DCM = 1:1 (0.2 M) at 0 ^{o}C.

Scheme 24

Notably, these two examples of coupling reactions with silyl enolates **5c** and **5d** are the very rare examples of their use in substitution chemistry, showing impressive chemo- and regio-selectivity by using the uniqueness of the privileged bifunctionalities of QMA **1a** (where substitutions toward only the allylic position of allylacetal unit), in comparison with the unique reactivities of silyl enolates and silyl ketene acetals which have been widely applied into the classical Lewis acid catalyzed Mukaiyama-aldol reaction[40d) footnote15] and 1,4-addition reaction[41)], where the α,β-unsaturated enones and ketones are also able to react selectively with different kinds of silyl nucleophiles respectively.

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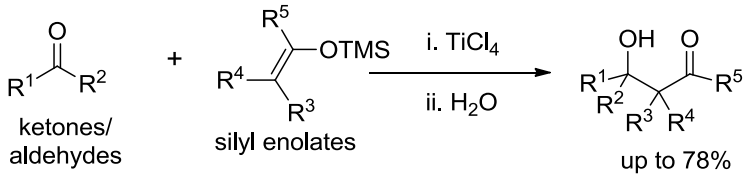
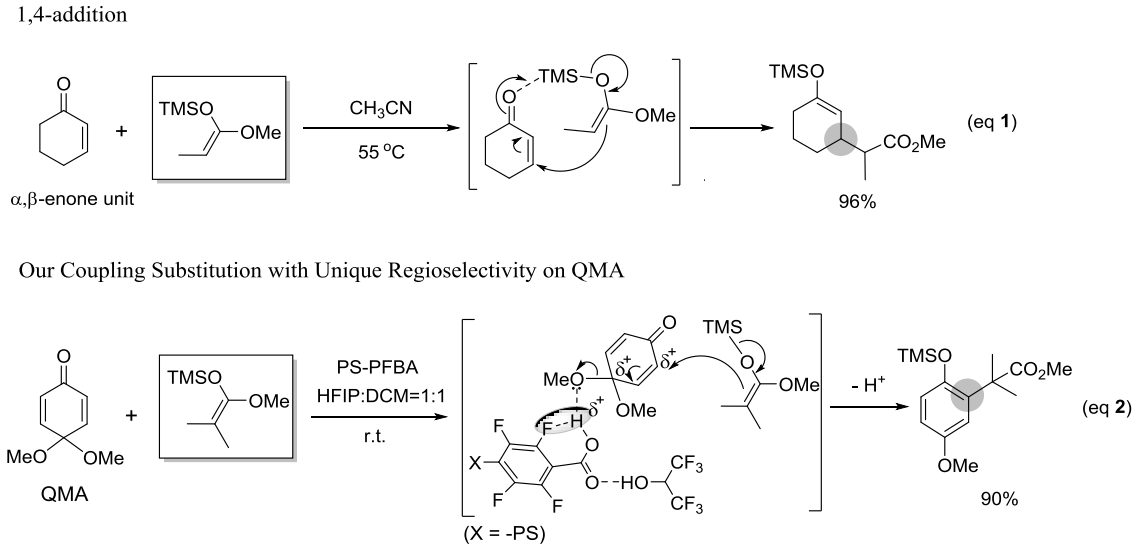
footnote15 To the best of my knowledge, this is a first example for the Mukaiyama-type S_N2'-substitution in the presence of the functionalization for the addition reactions shown below.[40d)]



Indeed, in our previous work, we found that the favorable 1,4-addition of α,β-enone unit could be successfully performed only by utilization of acetonitrile as a solvent without any catalyst to give almost quantitative yields of the corresponding *O*-silylated Michael adducts, in which way the nucleophilic attack would occur toward only β position of the enone moiety with the enol silyl ether nucleophile (eq 1, Scheme 25).[41] However, our [3 + 2] coupling system using the quinone monoacetal as the electrophile could afford the *O*-silylated substitution product in excellent yield with unique regioselectivity, where the enol silyl ether nucleophile would attack to only the α position of enone group (eq 2, Scheme 25).



Scheme 25

I conclude that, the other diverse π–carbon and heteroatom nucleophiles such as furanyl silylether **5a**, sulfur nucleophile **5b**, as well as the enol enolates **5a** and **5b**, are all able to react with the QMA **1a** to produce different types of coupling products **5aa-ad** in moderate to good yields promoted by our newly developed PS-PFBA under mild conditions without any optimization. In particular, two types of coupling products **5ac** and **5ad** from silyl enolates **5c** and **5d** are obtained with impressive regio-selectivity toward the allylic position of allylacetal unit by using the uniqueness of QMA **1a** on contrary to the reaction positions between silyl enolate and enones in 1,4-addition reactions and Mukaiyama-type reaction.

Chapter V. Applications

Section I. Concise Synthesis of Several Naturally Occurring Compounds

Up to date, a great number of naturally occurring biologically active compounds has been described in the literature. In particular, the subset of modules with impressive structures such as the flavonoids derived pterocarpan[26)] [footnote16] and the ring fused indoline-containing pyrrolidinoindoline[25)] [footnote17] (Figure 4) have received substantial interests due to their high biological and medicinal properties *in vitro* and *in vivo* (e.g. antifungal, antimicrobial, antitumoral, and anti-HIV), especially in the area of anticancer drug discovery.

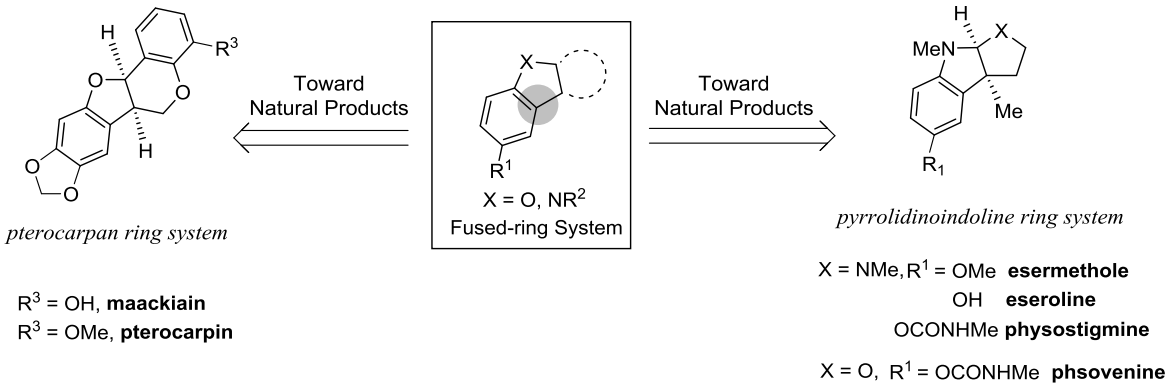


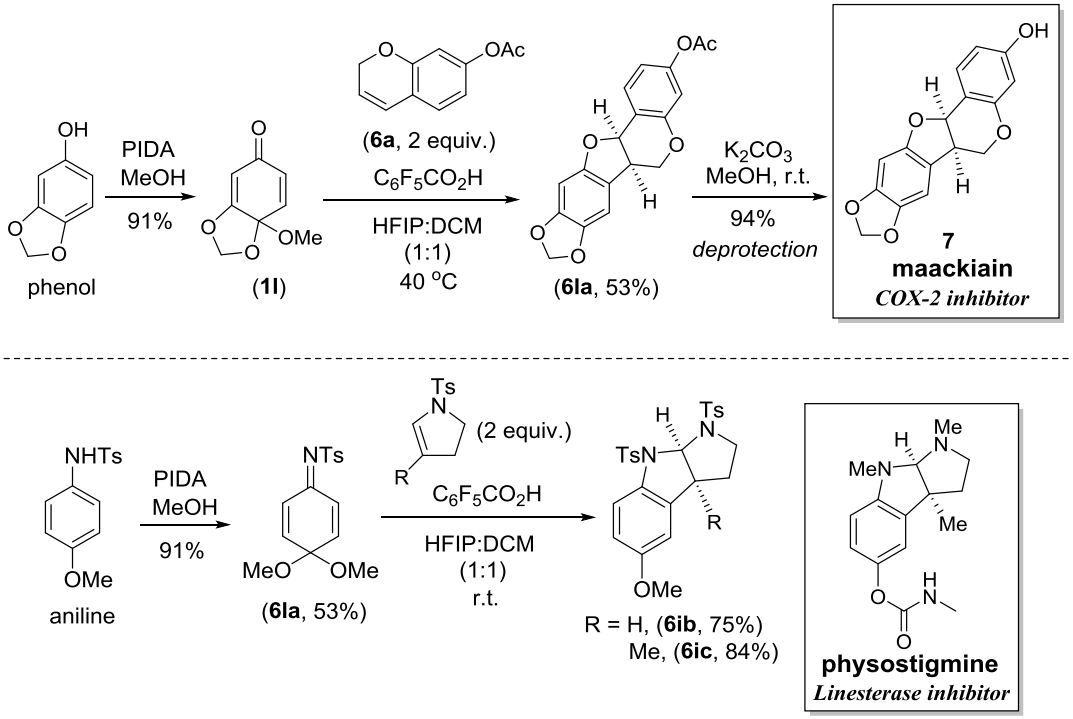
Figure 4

Encouraged by the rare success of the substitution-type chemistry of QMAs **1** to diverse dihydrobenzofuran products **3** as well as the indoline derivatives **3ib** *via* our newly developed appealing reagent-controlled strategy with the involvement of the combined system of the perfluorobenzoic acid promoter and fluoroalcohol solvent, the discovery of more concise and promising route toward these two complex bioactive modules continues to be a vital research for us.

[footnote16] Pterocarpans, the second largest group of natural isoflavonoids produced in plants possessing a 6a,11a-dihydro-6*H*-benzofuro[3,2-c]chromene skeleton (Figure 4) with unusal *cis*-fused dihydrobenzofuran-benzopyran ring juncture, have received considerable attention due to their spectrum of range of biological properties in response to fungal infections, COX-2 inhibition, LDL-antioxidant, anti-HIV, and anti-snake venom activities. Although lots of synthetic methods have been reported recently, many of which are multistep, proceed in poor overall yields, and relying on the uses of specific metal-catalysts.[26)]

[footnote17] Pyrrolidinoindolines, a subset of compounds with a fused indoline motif (Figure 4), mainly exist in the naturally occurring compounds of physovenine showing the acetylcholinesterase inhibitors, such as physostigmine. In most cases, the fused indoline ring system of pyrrolidinoindoline could be obtained in a stepwise fashion by the initial synthesis of a substituted indole or oxindole intermediate, and then further elaborated to the target product of pyrrolidinoindolines.[25)]

To our delight, the further applications of our methodology for the concise synthesis of these naturally occurring pterocarpan and pyrrolidinoindoline has been successfully achieved by the regio-specific [3 + 2] couplings with the involvement of the sequential oxidation/cyclization from phenol or benzenesulfonamide. The corresponding oxidants for the QMAs **1l** and iminoquinone acetals **1i** as key intermediates as well as the designed nucleophiles of 2*H*-chromen **6a**[footnote18], tosyl dihydropyrrole **6b**, and **6c** can thus be utilized for allowing control of the carbon α position for accessing the concise formation of these two valuable naturally occurring skeletons **6la**, **6ib**, and **6ic** in acceptable yields (53%, 75% and 84%), respectively (Scheme 26). Notably, the desired natural product of maackiain **7** could be very concisely synthesized in a good yield (76%), after the deprotection of the pterocarpan **6la**.



Scheme 26

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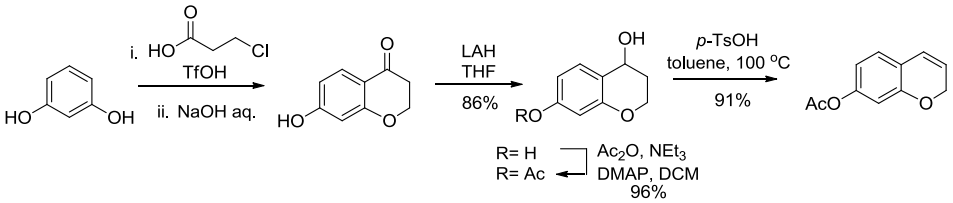
footnote18 2*H*-chromen **6a** was prepared *via* the following methods. Tosyl dihydropyrrole **6b** and **6c** could also be obtained via the similar approach from tosyl pyrrolidinone.



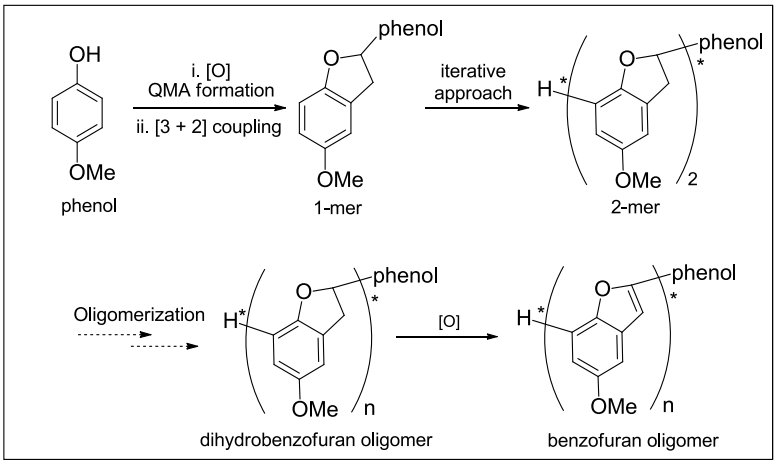
The [3 + 2] coupling could not be succeeded when 2*H*-chromen (R = Me or H) was used probably due to its polymerization under the acidic conditions.

Section II. Preparation of Benzofuran Oligomers

In recent years, benzofuran oligomers are reported as a promising highly fluorescent compounds with the property of organic electroluminescence (OEL) which is an emerging display technology allowing the manufacture of efficient, low-voltage multicolor displays, owning to their highly photoluminescence (PL) quantum efficiency, thermal stability, and also their facile color tenability.[43] However, we noticed that the reports on the series of non-linear *ortho*-benzofuran oligomers are quite limited in contrast to many of the linear ones, described as the good candidate as the promosing highly fluorescent compounds.[44] Therefore, a more concise and iterative route to the non-linear benzofuran oligomers is still in demand, especially a new route that allows regio-control of the reaction.

As a successive effort by utilization of our newly reported [3 + 2] coupling reaction of QMAs **1** with alkene nucleophiles **2**, the further application toward the synthesis of more elongated and structurally defined *ortho*-benzofuran oligomers was thus investigated based on the concept of the iterative oxidation/cyclization strategy involving the following two important steps: 1) the oxidation of phenols to the QMAs by PIDA and 2) a bond-forming cyclization reaction of the QMAs with the designed functionalized alkene nucleophiles (Scheme 27).

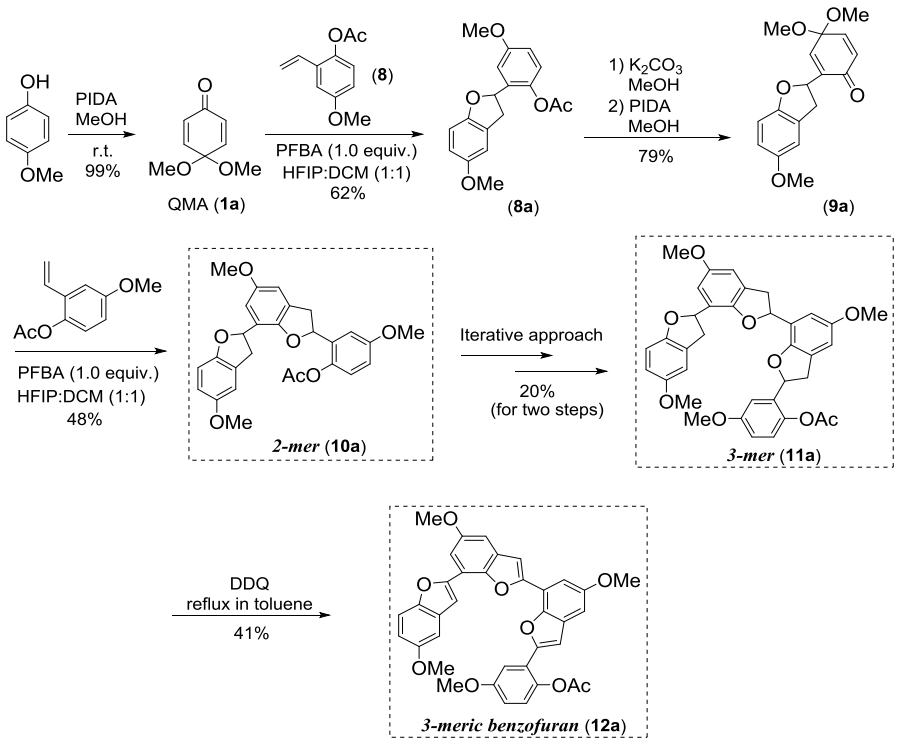
Synthetic Concept



Scheme 27

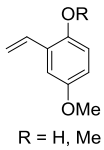
Indeed, the use of this sequential synthetic approach could allow the convergent access to the regio-defined *ortho*-dihydrobenzofuran dimer **10a** and trimer **11a** in acceptable yields, which was also capable of converting into the benzofuran regio-defined *ortho*-benzofuran trimer **12a** in a single step in 41% yield (Scheme 28). In details, the acyl protected dihydrobenzofuranyl phenol **8a** was first obtained through

sequential oxidation/cyclization strategy from *para*-methoxy phenol using acyl protected oxygenated benzoyl alkene **8** as nucleophile.[footnote19] QMA **9a** was then produced by treatment of a solution of dihydrobenzofuranyl phenol in methanol *via* second oxidation after the chemo-selective removal of the acyl group using K_2CO_3 in methanol. Notably, this repetitive oxidation/cyclization strategy should occur before the regeneration of the initial phenol functionality by chemo-selective removal of protected acyl group. Therefore, repetition of the iterative oxidation/cyclization/deprotection process enabled expeditious access to the desired dihydrobenzofuran trimer **11a**, which can be further used for preparing the final promising benzofuran trimer **12a** by treatment of DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) as an oxidant (Scheme 28). Therefore, this is conceptionally applicable for further elongated benzofuran oligomers by further repetitions, potentially becoming a new strategy for the controlled oligo-aromatics.



Scheme 28

[footnote19] Our [3 + 2] coupling reaction of QMA **1a** could not be successfully performed when the other benzoyloxy alkene (R = Me or H) was used as the coupling partner, probably because these two substituents of the corresponding monomer **8a** are less stable than the acyl protected one under the acidic condition.



R = H, Me

Conclusion

In summary, we have succeeded in developing the efficient controlled coupling reactions of the useful unsymmetrized quinone alternatives, quinone monoacetals (QMAs), under specific acidic conditions. The general successes are listed below.

1) At first, the rare success of the substitution-type chemistry of QMAs was achieved based on the development of the appealing reagent-controlled strategy consisting of the combined system of the perfluorobenzoic acid promoter and fluoroalcohol as solvent, which could smoothly proceed with high regio-specificity for introducing the π-nucleophiles toward only at the allylic position of QMAs, providing diverse dihydrobenzofuran products and their derivatives (Chapter I, Sections I, II). The mechanism was also detailed with experimental evidences (Chapter I, Section III).

2) The further investigations with regard to the acid tuning in this controlled [3 + 2] couplings have led to findings of an excellent catalytic alternative (perfluorinated acid catalyst **h**), advancing the original stoichiometrically reactions to render catalysis of the acid at lower than 5 mol% loading along with the significantly improved stoichiometry of the alkenes (lowering to 1.2 equiv.) (Chapter II).

3) A unique solid acid catalyst (PS-PFBA) including immobilized perfluorobenzoic acid sites in the polystyrene backbones has been successfully prepared, which acts as the specific promoters for this controlled coupling reactions of QMAs **1** with diverse π–carbon nucleophiles in high performances with a similar efficiency to its homogeneous counterpart, PFBA (Chapter III, Sections I, II).

4) Other extended nucleophiles could also be utilized for this coupling reaction by the aid of the reusable solid acid catalyst (PS-PFBA) in hexafluoroisopropanol (HFIP) to give the coupling products at the desired positions with excellent regio-selectivities in high performances (Chapter IV).

5) We finally challenged the concise approaches to synthetic modules for natural products (*e.g.* maackiain and pyrrolidinoindoline) as well as the iterative elongation of regio-controlled benzofuran oligomers (*e.g.* dimer and trimer) by utilizing our newly developed controlled [3 + 2] coupling strategy as further applications (Chapter V, Sections I, II).

Main Papers

1) [3 + 2] Coupling of Quinone Monoacetals by Combined Acid–Hydrogen Bond Donor;
   Toshifumi Dohi, ***Yinjun Hu***, Tohru Kamitanaka, Naohiko Washimi, and Yasuyuki Kita, *Org. Lett.*, **2011**, *13*, 4814–4817.
2) Controlled Couplings of Quinone Monoacetals Using Reusable Polystyrene-Anchored Specific Proton Catalyst;
   Toshifumi Dohi, ***Yinjun Hu***, Tohru Kamitanaka, and Yasuyuki Kita, *Tetrahedron*, **2012**, *68*, 8424-8430.
3) Brønsted Acid-Controlled [3 + 2] Coupling Reaction of Quinone Monoacetals with Alkene Nucleophiles: A Catalytic System of Perfluorinated Acids and Hydrogen Bond Donor for the Construction of Benzofurans;
   Yinjun Hu, Toshifumi Dohi, Tohru Kamitanaka, Yusuke Mishima, and Yasuyuki Kita, *J. Org. Chem.*, **2013**, *78*, 5530-5543.

Related Publications

1) Efficient Synthesis of Oxygenated Terphenyls and Other Oligomers: Sequential Arylation Reactions through Phenol Oxidation-Rearomatization;
   Toshifumi Dohi, Tohru Kamitanaka, Shohei Watanabe, ***Yinjun Hu***, Naohiko Washimi, and Yasuyuki Kita, *Chem.-Eur. J.*, **2012**, *18*, 13164-13168.
2) Parallel and Modular Synthesis of P-Chirogenic P,O-Ligands;
   Magnus J. Johansson, Susanne Berglund, ***Yinjun Hu***, Kristian H. O. Andersson, and Nina Kann, *ACS Comb. Sci.*, **2012**, *14*, 304-308.
3) Enantioselective Intramolecular Morita–Baylis–Hillman Reaction Using Chiral Bifunctional Phosphinothiourea as an Organocatalyst;
   Kui Yuan, Hong-Liang Song, ***Yinjun Hu***, Jian-Fei Fang, and Xin-Yan Wu, *Tetrahedron: Asymmetry*, **2010**, *21*, 903-908.
4) Chiral Phosphinothiourea catalyzed Asymmetric Morita–Baylis–Hillman Reactions of Acrylates with Aromatic Aldehydes;
   Kui Yuan, Hong-Liang Song, ***Yinjun Hu***, and Xin-Yan Wu, *Tetrahedron*, **2009**, *65*, 8185-8190.
5) Chiral Phosphinothiourea Organocatalyst in the Enantio-Selective Morita-Baylis-Hillman Reactions of Aromatic Aldehydes with Methyl Vinyl Ketone;
   Kui Yuan, Lei Zhang, Hong-Liang Song, ***Yinjun Hu***, and Xin-Yan Wu, *Tetrahedron Letters*, **2008**, *49*, 6262-6264.

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Experimental Section

General Information

Melting point (mp) was measured by melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded by spectrometers operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR at 25 ^{o}C using $CDCl_3$ as a solvent. Infrared spectra (IR) are reported in reciprocal centimeters (cm^{-1}). High resolution mass spectra (HRMS-EI) were performed by the Elemental Analysis Section of Osaka University Pharmaceutical Sciences. Column chromatography was carried out on silica-gel (230-400 mesh) eluting with hexane and EtOAc for isolation of the QMAs **1** and cycloadducts **3**. The spots and bands were detected by UV light of irradiation (254 and 365 nm) and/or by staining with 5% phosphomolybdic acid followed by heating. Unless otherwise noted, all the experiments were carried out at room temperature in open flask. A series of the perfluorinated acids (PFBA and **a**-**h**) (purchased from TCI), polystyrene, and silica-supported amines (from Sigma-Aldrich) were used as they stand. Other commercial acids for the screening of the reaction promoter were purchased from Aldrich, and TCI and used as they stand. All other chemicals including the commercial alkene nucleophiles **2** and solvents, such as hexafluoroisopropanol (HFIP), were obtained from commercial suppliers and used without further purification.

List of Abbreviations

QMAs	quinone monoacetals
PIDA	phenyliodine(III) diacetate
PFBA	perfluorobenzoic acid
HFIP	1,1,1,3,3,3-hexafluoro-isopropanol
PS-PFBA	polystyrene anchored perfluorobenozic acid
PS	polystyrene
MT	montmorillonite clay
TFE	2,2,2-trifluoroethanol
OTMS	trimethylsilyloxy
DCM	dichloromethane
r.t.	room temperature
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone

Experiments of Chapter I

Experiments of Chapter I, Section I and II

General Procedure for the Preparation of QMAs 1

To a stirred solution of corresponding phenol or *para*-substituted phenol (10 mmol) in suitable anhydrous alcohol (20 mL) at 0 ^{o}C to room temperature was add a solution of $PhI(OAc)_2$ (PIDA, 10 mmol) in the anhydrous alcohol. The mixture was stirred for 10 min, diluted with water, and extracted with EtOAc. The organic layer was washed with aqueous saturated sodium bicarbonate and sodium chloride solution, dried over sodium sulfate, and concentrated by evaporation. The residue was purified by column chromatography on silica-gel with hexane/EtOAc to yield a pure QMA.

The iminoquinone acetal **1i** was also prepared from the corresponding aniline derivative, *p*-methoxy-*N*-tosylaniline, by using the same method.

[3 + 2] Coupling of QMAs 1 with Alkenes 2 (Tables 2 and 3) Promoted by PFBA: A Representative Procedure for the Reaction of QMA 1a and allyltrimethylsilane 2a leading to the dihydrobenzofuran 3aa

To a stirred solution of QMA **1a** (1.0 mmol) and allyltrimethylsilane **2a** (2.0 mmol) in dichloromethane (2.5 mL) was successively added HFIP (2.5 mL) and stoichiometric amount of pentafluorobenzoic acid (1.0 mmol) in open flask under ambient conditions. The reaction mixture was then allowed to stir at room temperature and monitored by TLC. After consumption of the QMA **1a**, the solution was concentrated by evaporation. Isolation of the [3 + 2] coupling cycloadduct **3aa** was directly conducted from the residue by flash chromatography on silica-gel (hexane/EtOAc = 20/1) to give a pure dihydrobenzofuran product **3aa** (0.90 mmol, 89%) as colorless oil. The yields of the other corresponding dihydrobenzofuran products **3** were shown in Table 2 and 3.

2,3-Dihydro-5-methoxy-2-[(trimethylsilyl)methyl]benzofuran 3aa[45)]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (s, 1H), 6.53-6.56 (m, 2H), 4.76-4.84 (m, 1H), 3.65 (s, 3H), 3.14 (dd, 1H, *J* = 15.4, 8.3 Hz), 2.69 (dd, 1H, *J* = 15.4, 8.3 Hz), 1.22 (dd, 1H, *J* = 14.2, 6.1 Hz), 1.01 (dd, 1H, *J* = 14.2, 8.8 Hz), 0.02 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 154.5, 129.3, 113.4, 112.2, 109.8, 83.3, 56.9, 39.5, 26.0, 0.0 ppm; IR (KBr): 2905, 2903, 2831, 1603, 1487, 1433, 1362, 1249, 1213, 1138, 1034, 954, 840, 761, 693 cm^{-1}.

5-Methoxy-2-phenyl-2,3-dihydrobenzofuran 3ab[46)]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.39 (m, 5H), 6.75-6.76 (m, 2H), 6.66-6.74 (m, 1H), 5.70 (t, 1H, *J* = 8.8 Hz), 3.73 (s, 3H), 3.57 (dd, 1H, *J* = 15.6, 9.2 Hz), 3.16 (dd, 1H, *J* = 15.6, 8.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 153.4, 141.6, 128.2, 127.6, 127.1, 125.4, 112.6, 110.8, 108.8, 83.8, 55.6, 38.5 ppm; IR (KBr, cm^{-1}): 3062, 3030, 2937, 2831, 1604, 1487, 1433, 1231, 1203, 1136, 1032, 975, 808, 756, 669 cm^{-1}.

5-Methoxy-6-methyl-2-phenyl-2,3-dihydrobenzofuran 3bb

Yellow sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-7.34 (m, 5H), 6.65 (s, 1H), 6.61 (s, 1H), 5.65 (t, 1H, *J* = 9.2 Hz), 3.71 (s, 3H), 3.53 (dd, 1H, *J* = 15.7, 8.1 Hz), 3.11 (dd, 1H, *J* = 15.7, 8.1 Hz), 2.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 152.3, 142.2, 128.6, 127.9, 126.5, 125.7, 123.6, 111.3, 107.8, 84.1, 56.2, 39.0, 16.6 ppm; IR (KBr): 3062, 3028, 2934, 2855, 2831, 1748, 1602, 1496, 1465, 1415, 1354, 1285, 1256, 1201, 1161, 1096, 1011, 927, 860, 750, 699 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}O_2$ $[M]^+$: 240.1150; found: 240.1149.

6-(*tert*-Butyl)-5-methoxy-2-phenyl-2,3-dihydrobenzofuran 3cb

Colorless solid; mp: 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20-7.39 (m, 5H), 6.78 (d, 2H, *J* = 8.0 Hz), 5.73 (t, 1H, *J* = 9.0 Hz), 3.86 (s, 3H), 3.56 (dd, 1H, *J* = 15.4, 9.3 Hz), 3.18 (dd, 1H, *J* = 15.4, 8.7 Hz), 1.26 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 144.9, 143.4, 141.8, 128.5, 127.9, 127.2, 126.0, 113.9, 109.4, 84.9, 56.2, 39.1, 34.6, 31.7 ppm; IR (KBr): 2959, 2904, 2866, 1767, 1736, 1604, 1490, 1458, 1362, 1325, 1199, 1180, 1110, 1092, 948, 828, 759, 699 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}O_2$ $[M]^+$: 282.1620; found: 282.1621.

5,6-Dimethoxy-2-phenyl-2,3-dihydrobenzofuran 3db

Colorless sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.34 (m, 5H), 6.70 (s, 1H), 6.47 (s, 1H), 5.68 (t, 1H, *J* = 9.0 Hz), 3.79 (s, 3H), 3.77 (s, 3H), 3.52 (dd, 1H, *J* = 15.1, 9.3 Hz), 3.10 (dd, 1H, *J* = 15.1, 8.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 149.4, 143.5, 142.0, 128.6, 128.0, 125.7, 119.0, 116.0, 94.8, 84.6, 56.9, 56.0, 38.6 ppm; IR (KBr): 3027, 2996, 2935, 2832, 1752, 1618, 1504, 1454, 1334, 1217, 1188, 1168, 1104, 996, 856, 762, 700 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}O_3$ $[M]^+$: 256.1099; found: 256.1117.

7-(*tert*-Butyl)-5-methoxy-2-phenyl-2,3-dihydrobenzofuran 3eb

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.43 (m, 5H), 6.73 (d, 1H, *J* = 2.4 Hz), 6.64 (d, 1H, *J* = 2.7 Hz), 5.76 (t, 1H, *J* = 9.0 Hz), 3.78 (s, 3H), 3.58 (dd, 1H, *J* = 15.4, 9.5 Hz), 3.13 (dd, 1H, *J* = 15.6, 8.5 Hz), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 151.6, 142.9, 133.5, 128.5, 127.6, 127.2, 125.4, 111.6, 107.2, 83.4, 55.9, 39.0, 34.2, 29.2 ppm; IR (KBr): 3028, 2954, 2907, 2869, 2832, 1599, 1481, 1427, 1361, 1314, 1264, 1223, 1195, 1125, 1053, 931, 812, 758, 699 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}O_2$ $[M]^+$: 282.1620; found: 282.1622.

7-Chloro-5-methoxy-2-phenyl-2,3-dihydrobenzofuran 3fb

Colorless solid; mp: 65-66 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16-7.33 (m, 5H), 6.58- 6.64 (m, 2H), 5.72 (t, 1H, *J* = 8.5 Hz), 3.66 (s, 3H), 3.57 (dd, 1H, *J* = 15.8, 9.2 Hz), 3.16 (dd, 1H, *J* = 15.8, 8.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 149.6, 141.0, 128.5, 128.4, 127.9, 125.5, 114.1, 112.9, 109.9, 84.4, 55.9, 39.2 ppm; IR (KBr): 3063, 3031, 3001, 2937, 2834, 1595, 1479, 1439, 1365, 1257, 1210, 1115, 1039, 983, 928, 845, 760, 700 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{13}ClO_2$ $[M]^+$: 260.0604; found: 260.0606.

5-Methoxy-2-phenyl-2,3-dihydronaphtho[1,2-b]furan 3gb

Pale green solid; mp: 82-84 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, 1H, *J* = 8.1 Hz), 8.00 (d, 1H, *J* = 8.0 Hz), 7.46-7.53 (m, 4H), 7.32-7.40 (m, 3H), 6.72 (s, 1H), 5.94 (t, 1H, *J* = 9.5 Hz), 3.96 (s, 3H), 3.80 (dd, 1H, *J* = 15.4, 9.7 Hz), 3.36 (dd, 1H, *J* = 15.4, 7.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 148.4, 142.6, 128.6, 127.9, 126.0, 125.7, 125.4, 125.0, 122.5, 121.2, 120.8, 117.9, 101.5, 84.1, 56.0, 40.2 ppm; IR (KBr): 3062, 3027, 2936, 2854, 1640, 1595, 1459, 1402, 1376, 1259, 1235, 1200, 1113, 1081, 1032, 979, 816, 763, 698 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{16}O_2$ $[M]^+$: 276.1150; found: 276.1147.

5-Methoxy-2-phenyl-2,3-dihydronaphtho[1,2-b]furan-6-yl acetate 3hb

Pale pink solid; mp: 150-152 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, 1H, *J* = 8.3 Hz), 7.15-7.35 (m, 6H), 6.96 (d, 1H, *J* = 8.0 Hz), 6.67 (s, 1H), 5.83 (t, 3H, *J* = 8.8 Hz), 3.78 (s, 3H), 3.68 (dd, 1H, *J* = 15.4, 9.7 Hz), 3.23 (dd, 1H, *J* = 15.4, 7.8 Hz), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 149.8, 149.0, 146.7, 142.3, 128.6, 127.9, 125.8, 125.7, 122.7, 120.1, 119.2, 119.1, 118.6, 104.3, 84.2, 56.8, 40.0, 20.9 ppm; IR (KBr): 3061, 3030, 2993, 2938, 2838, 1761, 1602, 1461, 1355, 1249, 1213, 1122, 1061, 985, 862, 815, 755, 700 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{18}O_4$ $[M]^+$:

334.1205; found: 334.1198.

[3 + 2] Coupling Reaction of Iminoquinone Acetal 1i with Styrene 2b (Table 2, entry 9)

By using the similar coupling procedure under the modified reaction conditions, the corresponding indoline skeleton compound **3ib** could also be obtained in 82% yields from iminoquinone monoacetal **1i**.

5-Methoxy-2-phenyl-1-tosylindoline 3ib

Pale brown solid; mp: 57-60 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, 1H, *J* = 8.3 Hz), 7.46 (d, 2H, *J* = 8.8 Hz), 7.10-7.26 (m, 7H), 6.72 (dd, 1H, *J* = 8.8, 3.2 Hz), 6.52 (s, 1H), 5.19-5.23 (m, 1H), 3.69 (s, 3H), 3.02 (dd, 1H, *J* = 16.0, 9.7 Hz), 2.72 (dd, 1H, *J* = 15.8, 8.7 Hz), 2.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 143.8, 142.5, 135.2, 134.9, 133.5, 129.5, 128.6, 127.6, 127.2, 125.9, 118.2, 112.9, 110.8, 64.9, 55.6, 37.8, 21.6 ppm; IR (KBr): 3061, 3027, 2924, 2837, 1739, 1598, 1492, 1454, 1352, 1326, 1256, 1228, 1164, 1090, 1030, 955, 814, 753, 700 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{21}NO_3S$ $[M]^+$: 379.1242; found: 379.1243.

5-Methoxy-2-(*p*-tolyl)-2,3-dihydrobenzofuran 3ac

Colorless solid; mp: 62-63 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09-7.23 (m, 4H), 6.67-6.70 (m, 2H), 6.62 (d, 1H, *J* = 8.8 Hz), 5.63 (t, 1H, *J* = 8.8 Hz), 3.69 (s, 3H), 3.49 (dd, 1H, *J* = 15.7, 9.5 Hz), 3.11 (dd, 1H, *J* = 15.7, 8.4 Hz), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 153. 8, 138.9, 137.8, 129.3, 127.6, 125.8, 112.9, 111.1, 109.1, 84.2, 56.0, 38.8, 21.1 ppm; IR (KBr): 3009, 2948, 2916, 2833, 1609, 1488, 1470, 1428, 1363, 1320, 1296, 1265, 1211, 1138, 1111, 1026, 969, 924, 813, 738, 707 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}O_2$ $[M]^+$: 240.1150; found: 240.1153.

2-(4-(*tert*-Butyl)phenyl)-5-methoxy-2,3-dihydrobenzofuran 3ad

Colorless solid; mp: 46-47 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.40 (m, 4H), 6.68-6.78 (m, 3H), 5.71 (t, 1H, *J* = 8.8 Hz), 3.76 (s, 3H), 3.56 (dd, 1H, *J* = 15.6, 9.3 Hz), 3.22 (dd, 1H, *J* = 15.6, 8.3 Hz), 1.31 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 154.6, 151.9, 139.6, 128.5, 126.5, 126.4, 113.7, 112.0, 110.0, 85.0, 56.8, 39.4, 35.4, 32.1 ppm; IR (KBr): 2961, 2905, 2867, 2830, 1604, 1485, 1433, 1362, 1303, 1230, 1203, 1136, 1033, 977, 808, 748, 708 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}O_2$ $[M]^+$: 282.1620; found: 282.1622.

2-(4-Chlorophenyl)-5-methoxy-2,3-dihydrobenzofuran 3ae

Pale yellow solid; mp: 60-61 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 4H), 6.68-6.77 (m, 3H), 6.69 (t, 1H, *J* = 9.3 Hz), 3.75 (s, 3H), 3.58 (dd, 1H, *J* = 15.8, 9.5 Hz), 3.12 (dd, 1H, *J* = 15.6, 8.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 154.3, 141.3, 134.4, 129.5, 127.9, 127.8, 113.8, 111.9, 110.0, 84.1, 56.7, 39.6 ppm; IR (KBr): 2995, 2940, 2909, 2831, 1601, 1487, 1434, 1231, 1202, 1136, 1090, 1032, 924, 813, 738, 706 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{13}ClO_2$ $[M]^+$: 260.0604; found: 260.0608.

5-Methoxy-2-methyl-2-phenyl-2,3-dihydrobenzofuran 3af

Colorless solid; mp: 53-54 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14-7.40 (m, 5H), 6.71 (d, 1H, *J* = 8.5 Hz), 6.58-6.65 (m, 2H), 3.65 (s, 3H), 3.23-3.36 (m, 2H), 1.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 152.5, 146.4, 127.9, 127.0, 126.5, 124.0, 112.5, 110.9, 108.9, 88.7, 55.5, 44.7, 28.7 ppm; IR (KBr): 3059, 3027, 2973, 2830, 1603, 1487, 1446, 1373, 1270, 1148, 1030, 921, 862, 765, 700 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}O_2$ $[M]^+$: 240.1150; found: 240.1153.

***trans*-5-Methoxy-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran 3ag[47)]**

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, 2H, *J* = 8.0 Hz), 6.40-6.45 (m, 2H), 6.18-6.30 (m, 3H), 4.58 (d, 1H, *J* = 8.0 Hz), 3.31 (s, 3H), 3.29 (s, 3H), 2.90-2.93 (m, 1H), 0.88 (d, 3H, *J* = 8.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 154.4, 153.2, 133.0, 132.6, 127.6, 113.9, 112.8, 110.0, 109.3, 92.5, 56.0, 55.3, 45.6, 17. 5 ppm; IR (KBr): 2996, 2959, 2933, 2833, 1613, 1513, 1484, 1375, 1249, 1202, 1175, 1146, 1034, 970, 829, 772, 741, 710 cm^{-1}.

8-Methoxy-5,6,6a,11a-tetrahydronaphtho[1,2-*b*]benzofuran 3ah (*cis*-stereoisomer)

Pale yellow solid; mp: 81-84 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, 1H, *J* = 8.0 Hz), 7.19-7.30 (m, 2H),7.10-7.14 (m, 1H), 6.80 (s, 1H), 6.64-6.68 (m, 2H), 5.61 (d, 1H, *J* = 8.3 Hz), 3.74 (s, 3H), 3.60-3.62 (m, 1H), 2.61-2.69 (m, 2H), 1.98-2.05 (m, 1H), 1.77-1.81 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 153.4, 138.7, 133.5, 132.4, 130.1, 128.4, 128.2, 126.6, 112.9, 110.7, 109.4, 81.9, 56.0, 41.6, 27.8, 27.6 ppm; IR (KBr): 3063, 3023, 2933, 2832, 1603, 1486, 1434, 1360, 1201, 1137, 1032, 928, 818, 749 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{16}O_2$ $[M]^+$: 252.1150; found: 252.1159.

Synthesis of Benzofuran 4 from the Obtained Coupling Compound Dihydrobenzofuran O,S-Acetal 3ai (Table 3, footnote 8)

The dihydrobenzofuran *O,S*-acetal **3ai** was obtained from QMA **1a** and vinyl sulfide **2i** in 80% yields. Then, upon the treatments of the obtained dihydrobenzofuran **3ai** with

p-toluenesulfonic acid in refluxing toluene or the oxidant (*m*-chloroperbenzoic acid), the benzofuran **4** was formed in 80% or 69% yields, respectively.

5-Methoxy-2-(phenylthio)-2,3-dihydrobenzofuran 3ai[48)]

Colorless solid; mp: 65-66 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.49 (m, 2H), 7.16-7.27 (m, 3H), 6.68-6.70 (m, 2H), 6.60-6.63 (m, 1H), 6.09 (dd, 1H, *J* = 8.8, 4.9 Hz), 3.67 (s, 3H), 3.57 (dd, 1H, *J* = 16.6, 8.8 Hz), 3.07 (dd, 1H, *J* = 17.1, 4.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 152.4, 134.4, 132.1, 129.4, 127.9, 127.3, 113.6, 111.2, 110.7, 89.8, 56.4, 37.6 ppm; IR (KBr): 3057, 2995, 2950, 2909, 2831, 1583, 1485, 1436, 1254, 1222, 1194, 1030, 923, 810, 746, 692 cm^{-1}.

5-Methoxybenzofuran 4[49)]

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, 1H, *J* = 2.0 Hz), 7.31 (d, 1H, *J* = 9.0 Hz), 6.98 (d, 1H, *J* = 2.4 Hz), 6.83 (dd, 1H, *J* = 9.0, 2.7 Hz), 6.63 (d, 1H, *J* = 2.0 Hz), 3.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 150.2, 146.0, 128.2, 113.3, 112.1, 106.9, 103.7, 56.2 ppm; IR (KBr): 2998, 2935, 2832, 1717, 1616, 1596, 1446, 1338, 1283, 1183, 1145, 1131, 1030, 884, 837, 790, 759, 730, 691 cm^{-1}.

Synthesis of the Spirocyclic Dihydrobenzofurans 3aj and 3ak (Scheme 13)

By the similar reaction procedure with other types of nucleophiles **2j** and **2k**, the formation of corresponding **3aj** and **3ak** could also be obtained in 78% and 65% yields under modified reaction conditions, respectively.

5-Methoxy-3*H*-spiro(benzofuran-2,1'-cyclopentane) 3aj

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (s, 1H), 6.56 (s, 2H), 3.67 (s, 3H), 3.10 (s, 2H), 1.98-2.03 (m, 2H), 1.79-1.83 (m, 2H), 1.58-1.69 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 153.2, 128.4, 112.7, 111.4, 109.2, 97.1, 56.1, 40.6, 39.4, 23.9 ppm; IR (KBr): 2956, 2871, 2830, 1603, 1487, 1433, 1337, 1257, 1231, 1169, 1137, 1034, 974, 834, 730 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1150; found: 204.1147.

5-Methoxy-3*H*-spiro(benzofuran-2,1'-cyclohexane) 3ak[50)]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (s, 1H), 6.62 (s, 2H), 3.74 (s, 3H), 2.92 (s, 2H), 1.45-1.78 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 153.0, 127.7, 112.6, 111.6, 109.2, 88.4, 56.0, 41.4, 37.0, 25.1, 23.0 ppm; IR (KBr): 2992, 2932, 2857, 1487, 1447, 1435, 1270, 1215, 1146, 1029, 920, 837, 770, 727 cm^{-1}.

Experiments of Chapter I, Section III

A Representative Procedure: Examination of the [3 + 2] Coupling of QMA 1a and Allyltrimethylsilane 2a for the Effect of Water (Scheme 15)

To a stirred solution of QMA **1a** (1.0 mmol) and allyltrimethylsilane **2a** (1.2 mmol) in dichloromethane (2.5 mL) was successively added HFIP (2.5 mL) and stoichiometric amount of pentafluorobenzoic acid (1.0 mmol) with extra addition of 5 equiv. of water in open flask under ambient conditions. The reaction mixture was then allowed to stir at room temperature. After consumption of the QMA **1a**, the solution was concentrated by evaporation. Isolation of the [3 + 2] coupling cycloadduct **3aa** was directly conducted from the residue by flash chromatography on silica-gel (hexane/EtOAc = 20/1) to give a pure dihydrobenzofuran product **3aa** (0.71 mmol, 71%) as colorless oil.

Reaction of QMA 1a with cis-Methyl Styrene 2l Leading to a Mixture of cis- and trans- Dihydrobenzofuran 3al via the Formation of the Intermediate B (Scheme 17)

The reactions were examined with the general procedures instead using *cis*-methyl styrene **2l** as the alkene nucleophile. The mixture of two inseparable dihydrobenzofuran products **3al** (*cis*- and *trans-isomers*) formed in 80% yield as a mixture of two regio-isomers (*cis*:*trans* = approximate 30:70) using the perfluoroterephthalic acid. The *cis/trans* ratios of the regio- mixtures were determined by the ^{1}H NMR measurement by comparing the authentic samples of *cis*- and *trans*-dihydrobenzofurans **3al**. The proton alpha to the phenyl group in the *cis*-isomer appeared as a doublet (J = 8.8 Hz) at $\delta = 5.71$ ppm in ^{1}H NMR, while the signal for the *trans*-isomer was observed as a doublet (J = 8.5 Hz) as well at $\delta = 5.06$ ppm.

2,3-Dihydro-5-methoxy-3-methyl-2-phenylbenzofuran 3al (a mixture of *cis*- and *trans*-regio-isomers)[51)]

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.41 (m, 5H (*cis* and *trans*)), 7.68–7.81 (m, 3H (*cis* and *trans*)), 5.76 (d, 1H, J = 8.6 Hz (*cis*)), 5.11 (d, 1H, J = 9.0 Hz (*trans*)), 3.76 (s, 3H (*cis* and *trans*)), 3.58–3.68 (m, 1H (*cis*)), 3.36–3.43 (m, 1H (*trans*)), 1.39 (d, 3H, J = 6.8 Hz (*cis*)), 0.78 (d, 3H, J = 7.3 Hz (*trans*)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 154.3, 153.3, 153.1, 140.8, 138.1, 133.8, 132.9, 128.6, 128.2, 127.6, 126.3, 126.1, 112.9, 112.8, 110.8, 110.1, 109.32, 109.28, 92.6, 87.9, 55.99, 55.97, 45.9, 41.3, 17.8, 16.8 ppm; IR (KBr): 3062, 3030, 2961, 2924, 2864, 2831, 1604, 1501, 1432, 1375, 1270, 1210, 1168, 1144, 1034, 972, 866, 804, 740, 700 cm^{-1}.

Experiments of Chapter II

General Procedure for the Catalytic Use of Perfluorinated Terephthalic Acid in [3 + 2] Coupling of QMAs 1 with Alkene Nucleophiles 2 (Table 5)

To a stirred solution of QMA **1** (1.0 mmol) and alkene **2** (1.2 mmol) in DCM (2.5 mL) was successively added HFIP (2.5 mL) and a catalytic amount of perfluorinated terephthalic acid (0.05 mmol, 5 mol% relative to QMA) in open flask under ambient conditions. The reaction mixture was then allowed to stir at room temperature or 0 ^{o}C for 4 to 8 hrs. After confirming consumption of QMA **1** by TLC, the solution was concentrated by evaporation. Isolation of the [3 + 2] coupling cycloadduct was directly conducted from the residue by flash chromatography on silica-gel (hexane/EtOAc) to give the pure dihydrobenzofuran product **3**. The yields of the reactions in this procedure are summarized in Table 5.

Experiments of Chapter III

Typical Procedure for Preparation of Polystyrene-Supported Perfluorobenzoic Acid (PS-PFBA) (Scheme 21)

To a 100 ml round-bottom flask, amino methyl functionalized cross-linked polystyrene resins (1.25 g, 2.0 mmol/g loading, 2% DVB; Sigma-Aldrich Co. LLC) was added in DMF (25 mL) under ambient conditions. To the heterogeneous mixture, tetrafluoroterephthalic acid (4.0 mmol) in DMF (6 mL), 1-hydroxybenzotriazole (HOBt, 3.6 mmol) in DMF (5 mL), and solid 1,3-diisopropylcarbodiimide (DIC, 3.6 mmol) were successively and quickly added. The off-white dispersion turned pale yellow during the reaction. The resulting suspension was vigorously stirred for 16 hrs at room temperature. After the mixture was filtered, the solid on the filter was washed with DMF, THF, and DCM each for three times. After drying under vacuum for overnight, the desired polystyrene-anchored PFBA (PS-PFBA) at a 1.06 mmol/g loading of the PFBA was obtained as off-white beads (calcd. 75% introduction for the starting amino resin).

Elemental analysis of synthetic sample of the prepared PS-PFBA found 2.20% N contents, which corresponds to 1.06 mmol loading of PFBA sites to the polymer. The loading value shows that about 75% of amine sites in the starting PS-NH_2 was functionalized by the PFBA during the preparation.

General Procedure for PS-PFBA Induced Coupling of QMAs 1 with Nucleophiles 2 (Scheme 22)

To a stirred solution of the QMA **1** (1 mmol) and alkenes **2** (2 mmol) in DCM (2.5 mL) was successively added HFIP (2.5 mL) and the PS-PFBA (1 mmol) under ambient conditions. The reaction mixture was then stirred at 0 ^{o}C for 4 to 6 hrs. After confirming consumption of the QMA **1** by TLC, the PS-PFBA was separated by filtration, washed with Et_2O and dried under vacuum, and then reused for the next run. The residue from the concentrated filtrate including the product was purified by column chromatography on silica-gel (hexane/EtOAc) to give the pure dihydrobenzofuran **3**. Reusability of the recovered PS-PFBA was evaluated at least four times using the reactions (Scheme 22).

Experiments of Chapter IV

General Procedure for PS-PFBA Induced Coupling Reactions Using Other Types of Nucleophiles 5 (Scheme 23 and 24)

By the similar treatments of nucleophiles **5a-d** under modified reaction conditions, the corresponding coupling products **5aa-5ad** could be also obtained in moderate to good yields (57-90%).

5-(2-Hydroxy-5-methoxyphenyl)furan-2(5*H*)-one 5aa

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.46 (m, 1H), 6.50-6.60 (m, 3H), 6.10 (s, 1H), 5.88-5.96 (m, 2H), 3.61 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 156.7, 149.9, 149.6, 122.8, 119.9, 115.9, 112.4, 111.6, 80.0, 55.7 ppm; IR (KBr): 3362, 3110, 2956, 2837, 1790, 1739, 1596, 1502, 1460, 1278, 1214, 1176, 1081, 1028, 832, 797 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}O_4$ $[M+H]^+$: 207.0657; found: 207.0654.

4-Methoxy-2-(phenylthio)phenol 5ab[52)]

Pale brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89-7.18 (m, 8H), 6.06 (s, 1H), 3.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 151.2, 135.5, 129.1, 126.7, 126.0, 120.1, 118.7, 116.1, 115.9, 55.7 ppm; IR (KBr): 3435, 3058, 3001, 2938, 2832, 1581, 1486, 1438, 1336, 1276, 1253, 1212, 1181, 1051, 1034, 768 cm^{-1}.

Methyl 2-(5-methoxy-2-(trimethylsilyloxy)phenyl)-2-methylpropanoate 5ac

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41-6.62 (m, 3H), 3.61 (s, 3H), 3.36 (s, 3H), 1.23 (s, 6H), 0.02 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 153.0, 146.4, 136.3, 116.8, 112.8, 110.6, 55.2, 51.5, 43.9, 25.3, 0.0 ppm; IR (KBr): 2950, 2833, 1737, 1497, 1424, 1255, 1234, 1215, 1145, 1078, 1049, 915, 883, 843, 763 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{24}O_4Si$ $[M]^+$: 296.1444; found: 296.1446.

2-(5-Methoxy-2-(trimethylsilyloxy)phenyl)cyclopentanone 5ad

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31-6.47 (m, 3H), 3.47 (s, 3H), 3.04 (dd, 1H, *J* = 10.9, 8.3 Hz), 2.05-2.16 (m, 3H), 1.84-1.90 (m, 2H), 1.57-1.67 (m, 1H, *J* = 14.2, 8.8 Hz), 0.02 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.0, 158.2, 146.6, 130.2, 118.1, 116.0, 112.2, 55.1, 52.5, 37.8, 30.7, 20.9, 0.0 ppm; IR (KBr): 2959, 2834, 1743, 1499, 1465, 1426, 1250, 1225, 1160, 1142, 1040, 937, 904, 889, 845, 757 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_3Si$ $[M]^+$: 278.1388; found: 278.1368.

Experiments of Chapter V

Preparation of the QMAs 1l

To a stirred solution of corresponding *para*-substituted phenol (10 mmol) in methanol (20 mL) at 0 ^{o}C to room temperature was added a solution of $PhI(OAc)_2$ (PIDA, 10 mmol) in methanol (20 mL). The mixture was stirred for 10 min under the same conditions, diluted with water, and extracted with EtOAc. The organic layer was washed with aqueous saturated sodium bicarbonate and sodium chloride solution, dried over sodium sulfate, and concentrated in evaporation. The residue was purified by column chromatography on silica-gel with hexane/EtOAc to yield a pure QMA **1l** in 91% yield.
The iminoquinone acetal **1i** was also prepared in 90% yield from the corresponding aniline derivative, *p*-methoxy-*N*-tosylaniline by using the same method.

Representative Procedure for the Synthesis of Natural Occurring Modules of Pterocarpan 6la, 7 and Pyrrolidinoindoline 6ib, 6ic with Corresponding Nucleophiles 6a, 6b and 6c

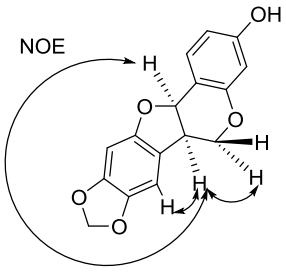
To a stirred solution of QMAs **1l** and nucleophiles of 2*H*-chromen-7-yl acetate **6l** (2 mmol) in DCM (2.5 mL) was successively added HFIP (2.5 mL) and stoichiometric amount of PFBA (1.0 mmol) in open flask under ambient conditions. The reaction mixture was then allowed to stir at room temperature and monitored by TLC. After consumption of the QMAs **1l**, the solution was concentrated by evaporation. Isolation of the [3 + 2] coupling product was directly conducted from the residue by flash chromatography on silica-gel (hexane/EtOAc = 4/1) to give the pterocarpan **6la** (53%) as a pale pink solid. Finally the natural product of maackiain **7** could be successfully synthesized in good yield as a pink solid after the deprotection of the pterocarpan **6la** with 3 equiv. of K_2CO_3 in methanol.
By using the similar procedure, pyrrolidinoindoline **6ib** and **6ic** could also be prepared in good yield (75% and 84%) from the corresponding iminoquinone acetal **1i** with tosyldihydropyrrole **6b** or **6c** by using the same method.

***cis*-6a,12a-Dihydro-6*H*-[1,3]dioxolo[4',5':5,6]benzofuro[3,2-c]chromen-3-yl acetate 6la**

Pale pink solid; mp: 147.7-148.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, 1H, *J* = 8.3 Hz), 6.72 (dd, 1H, *J* = 8.3, 2.2 Hz), 6.66 (s, 1H), 6.64 (s, 1H), 6.37 (s, 1H), 5.85 (d, 2H, *J* = 10.0 Hz), 5.42 (d, 1H, *J* = 7.1 Hz), 4.19 (dd, 1H, *J* = 10.7, 4.9 Hz), 3.59 (t, 1H, *J* = 11.0 Hz), 3.45 (dd, 1H, *J* = 10.7, 4.4 Hz), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 156.2, 154.1, 151.6, 141.8, 131.7, 117.8, 117.6, 115.3, 110.7, 104.7,

101.3, 93.8, 78.0, 66.5, 40.1, 29.3, 21.1 ppm; IR (KBr): 3072, 2891, 2771, 1759, 1617, 1590, 1498, 1459, 1432, 1370, 1338, 1207, 1143, 1116, 1033, 934, 894, 767 cm^{-1}.

cis-6a,12a-Dihydro-6_H_-[1,3]dioxolo[4',5':5,6]benzofuro[3,2-c]chromen-3-ol (maackiain) 7[53)]

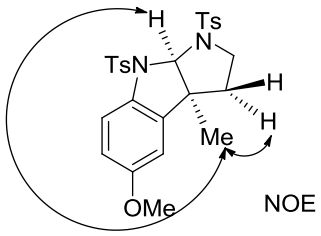


Pink solid; mp: 199.3-201.1 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, 1H, *J* = 8.3 Hz), 6.65 (s, 1H), 6.48 (dd, 1H, *J* = 8.52, 2.7 Hz), 6.37 (s, 1H), 6.34 (d, 1H, *J* = 2.4 Hz), 5.82 (dd, 2H, *J* = 10.0, 1.2 Hz), 5.40 (d, 1H, *J* = 6.8 Hz), 4.77 (br, 1H), 4.15 (dd, 1H, *J* = 10.7, 4.9 Hz), 3.57 (t, 1H, *J* = 11.0 Hz), 3.38-3.43 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 156.9, 154.2, 151.5, 148.1, 132.1, 117.9, 112.7, 110.7, 109.7, 104.7, 103.6, 101.2, 93.8, 78.4, 66.4, 40.1 ppm; IR (KBr): 2923, 1619, 1596, 1508, 1474, 1458, 1181, 1144, 1119, 1033, 912, 741 cm^{-1}.

cis-5-Methoxy-1,8-ditosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole 6ib

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): = 7.86 (d, 2H, *J* = 8.3 Hz), 7.43 (d, 2H, *J* = 8.3 Hz), 7.24-7.27 (m, 2H), 7.22 (s, 1H), 7.10 (d, 2H, *J* = 8.0 Hz), 6.66 (dd, 1H, *J* = 8.8, 2.7 Hz), 6.48 (d, 1H, *J* = 2.4 Hz), 6.18 (d, 1H, *J* = 6.6 Hz), 3.72-3.74 (m, 1H), 3.70 (s, 3H), 3.39 (t, 1H, *J* = 6.8 Hz), 2.64-2.71 (m, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 1.97-2.05 (m, 1H), 1.85-1.89 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 143.8, 143.0, 137.3, 135.0, 134.6, 134.3, 129.2, 129.1, 127.4, 127.3, 118.9, 113.4, 109.4, 81.2, 55.3, 46.6, 46.4, 31.4, 21.32, 21.34 ppm; IR (KBr): 2951, 2079, 1597, 1486, 1348, 1260, 1167, 1092, 1010, 913, 833, 814, 755, 737 cm^{-1}.

cis-5-Methoxy-3a-methyl-1,8-ditosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole 6ic



Pale pink solid; mp: 85.6-88.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, *J* = 8.3 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.22-7.29 (m, 2H), 7.19 (s, 1H), 7.10 (d, 2H, *J* = 8.0 Hz), 6.65 (dd, 1H, *J* = 8.8, 2.7 Hz), 6.42 (d, 1H, *J* = 2.7 Hz), 7.74 (s, 1H), 3.71-3.76 (m, 1H), 3.69 (s, 3H), 3.39 (t, 1H, *J* = 6.8 Hz), 2.63-2.70 (m, 1H), 2.36 (s, 3H), 2.28 (s, 3H), 1.84-1.92 (m, 2H), 0.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 144.1, 143.2, 138.9, 137.7, 135.0, 134.3, 129.6, 129.4, 127.5, 127.4, 118.3, 113.6, 108.5, 86.3, 55.5, 55.0, 47.8, 39.9, 24.6, 21.6, 21.5 ppm; IR (KBr): 2961, 1596, 1485, 1453, 1359, 1233, 1169, 1093, 1032, 914, 844, 813, 735 cm^{-1}.

Synthesis of the Regio-controlled Dihydrobenzofuran Oligomers 10a and 11a

To a solution of the *para*-methoxy phenol (10 mmol) in anhydrous methanol (20 mL) was added a solution of $PhI(OAc)_2$ (PIDA, 10 mmol) in methanol (20 mL) as well. The mixture was stirred for 10 min, diluted with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in evaporation to give the crude QMA **1a** in 99% yield, which could be used for the next step without purification.

After replacing the solvent with a mixture of DCM (10 mL) and HFIP (10 mL), the formed QMA **1a** was reacted with 4-methoxy-2-vinylphenyl acetate **7** (2 equiv.) using the PFBA (1 equiv.) under ambient conditions. The reaction mixture was stirred for 3 hrs. After completion of the reaction, the solution was concentrated by evaporation. Isolation of the [3 + 2] coupling dihydrobenzofuran **8a** was directly conducted from the residue by flash chromatography on silica-gel (hexane/EtOAc = 4/1) to give a pure product **8a** in 62% yield as pale yellow oil.

Next, the selective cleavage of acetyl group in the presence of methoxy groups was successively conducted. Thus, the resulting product was dissolved in methanol (25 mL), which was treated in one portion with potassium carbonate (3 equiv.) and the mixture was stirred at room temperature for 3 hrs. After confirming disappearance of the reactant by TLC, the reaction mixture was concentrated by evaporation to give a dihydrobenzofuranyl phenol product in quantitative yield.

Then the dihydrobenzofuranyl QMA **8a** was sequentially prepared in 79% yield *via* the oxidation with PIDA from dihydrobenzofuranyl phenol using the similar procedure mentioned above, which could be used for the next step directly.

Iterative repetition procedures of the selective cleavage of acetyl group, phenol oxidantion and [3 + 2] cyclization using 4-methoxy-2-vinylphenyl acetate **8** as the coupling partner finally gave the regio-controlled dihydrobenzofuan dimer **10a** and trimer **11a** in moderate yields.

Synthesis of the Regio-controlled Benzofuran Trimer 12a

To a soulution of DDQ (7 mmol, 3.5 equiv.) in dioxane (10 mL) was slowly added to a solution of dihydrobenzofuan trimer **11a** (2 mmol, 1 equiv.) in dioxane (10 mL). Once the addition was complete, the reaction mixture was heated under reflux for 48 hrs. The reaction mixture was then cooled to room temperature and evaporated to dryness under vacuum. The residue was purified by column chromatography on silica-gel (eluent: hexane/AcOEt = 4/1) to give the pure benzofuan trimer **12a** in 41% yield from the dihydrobenzofuan trimer **11a** as a pale orange solid.

Dihydrobenzofuan dimer 10a (as a mixture of diastereomers)

Pale yellow amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99-7.02 (m, 2H), 6.66-6.86 (m, 6H), 5.73-5.90 (m, 2H), 3.72-3.77 (m, 9H), 3.52-3.63 (m, 2H), 3.12-3.27 (m, 2H), 2.05-2.11 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 169.3, 157.23, 157.20, 154.34, 154.32, 154.0, 153.5, 149.95, 149.86, 140.8, 134.7, 127.6, 127.5, 127.3, 127.2, 123.7, 123.5, 123.2, 113.6, 113.5, 112.63, 112.60, 112.1, 112.0, 111.0, 111.34, 111.26, 109,7, 109.6, 118,9, 80.3, 79.6, 79.4, 55.8, 55.7, 55.3, 37.5, 37.4, 37.3, 37.1, 20.40, 20.35 ppm; IR (KBr): 2940, 2835, 1761, 1607, 1486, 1433, 1369, 1137, 1040, 970, 908, 874, 808, 770 cm^{-1}.

Dihydrobenzofuan trimer 11a (as a mixture of diastereomers)

White powder; mp 179.3-181.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.92-6.97 (m, 2H), 6.60-6.80 (m, 8H), 5.67-5.91 (m, 3H), 3.66-3.71 (m, 12H), 3.47-3.60 (m, 2H), 3.07-3.45 (m, 4H), 1.98-2.05 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 157.4, 157.3, 154.52, 154.49, 154.43, 154.37, 154.32, 154.15, 154.14, 153.73, 153.72, 150.2, 149.99, 149.97, 149.86, 141.1, 134.9, 134.8, 128.0, 127.9, 127.8, 127.5, 127.43, 127.37, 124.1, 123.8, 123.7, 123.6, 123.5, 117.3, 113.7, 113.5, 113.44, 113.39, 113.0, 112.80, 112.78, 112.75, 112.2, 111.2, 110.72, 110.68, 110.64, 110.5, 110.3, 109.9, 109.8, 109.7, 109.5, 109.21, 109.19, 109.11, 109.09, 83.4, 80.6, 80.51, 80.45, 80.1, 78.0, 79.9, 79.74, 79.66, 79.64, 56.00, 55.98, 55.7, 55.5, 37.8, 37.63, 37.60, 37.58, 37.54, 37.50, 37.47, 37.36, 37.35, 20.62, 20.57 ppm; IR (KBr): 2940, 2835, 1760, 1607, 1486, 1436, 1369, 1274, 1261, 1196, 1039, 991, 970, 874, 803, 747 cm^{-1}.

Benzofuan trimer 12a

Pale orange solid; mp 215.1-218.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 7.60 (d, 1H, *J* = 2.7 Hz), 7.56 (s, 1H), 7.53-7.55 (m, 2H), 7.44 (d, 1H, *J* = 9.0 Hz), 7.09-7.15 (m, 4H), 7.05 (s, 1H), 6.90-6.96 (m, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.35 (s, 3H) ppm; IR (KBr): 2931, 2834, 2358, 1751, 1614, 1474, 1433, 1205, 1169, 1040, 912, 843, 799, 745 cm^{-1}. HRMS (EI) calcd for $C_{36}H_{28}O_9Na$ $[M]^+$: 627.1626; found: 627.1631.

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