JOC The Journal of Organic Chemistry

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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

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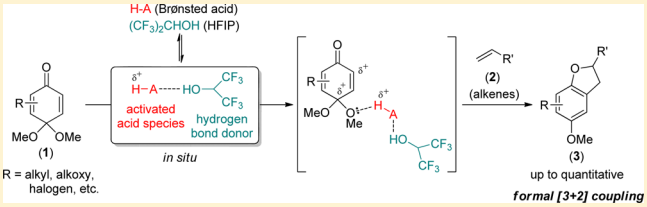
Supporting Information

ABSTRACT: We have developed an efficient Brønsted acid-controlled strategy for the [3 + 2] coupling reaction of quinone monoacetals (QMAs) with nucleophilic alkenes, which is triggered by the particular use of a specific acid promoter, perfluorinated acid, and a solvent, fluoroalcohol. This new coupling reaction smoothly proceeded with high regiospecificity in regard with QMAs for introducing π-nucleophiles to only the carbon α to the carbonyl group, thereby providing diverse dihydrobenzofurans and derivatives with high yields, up to quantitative, under mild conditions in short reaction times. The choice of Brønsted acid enabled us to avoid hydrolysis of the QMAs, which gives quinones, and the formation of discrete cationic species from the QMAs. Notably, further investigations in this study with regard to the acid have led to the findings that the originally stoichiometrically used acid could be reduced to a catalytic amount of 5 mol % loading or less and that the stoichiometry of the alkenes could be significantly improved down to only 1.2 equiv. The facts that only a minimal loading (5 mol %) of perfluoroterephthalic acid is required, readily available substrates can be used, and the regioselectivity can be controlled by the acid used make this coupling reaction very fascinating from a practical viewpoint.



INTRODUCTION

Quinones belong to a unique class of molecules in which all of the carbon atoms constituting the ring structures are electrophilic. Furthermore, they ubiquitously exist in nature and are frequently included in commercial and industrial chemicals having many broad and attractive applications.[1,2] As a result, these quinone-type compounds are of importance in organic chemistry as synthetic intermediates and building blocks.[2] Regarding their reactivity, many types of reactions have been developed utilizing the unsaturated enone structure as a versatile electrophile, especially in cycloaddition reactions with various nucleophiles and dienes. On the other hand, because of the electrophilic nature of all of the ring carbons, chemo- and regioselectivity issues arise, sometimes limiting the utility of quinones themselves in organic synthesis.

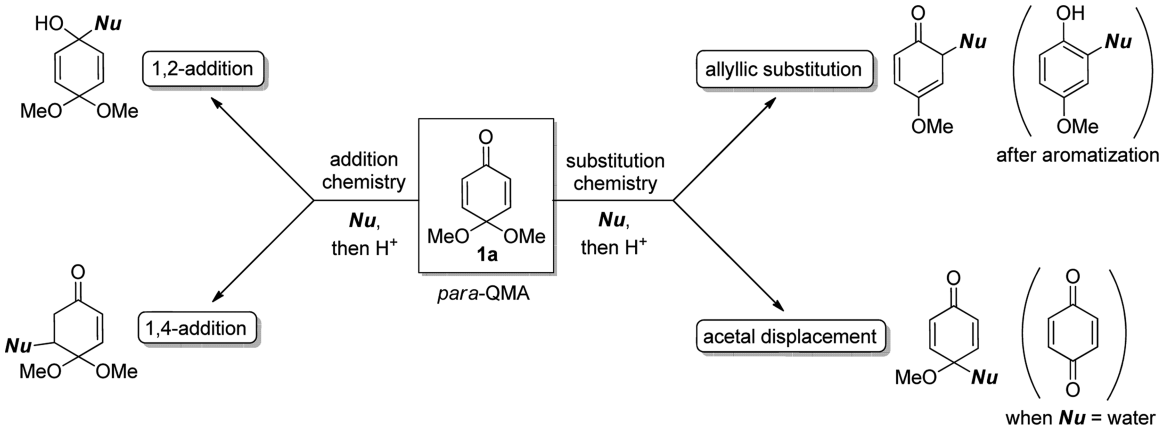
As one promising solution to the selectivity issues, quinone monoacetals (QMAs, for example, **1a**), i.e., monoprotected quinones, have been used for differentiating the two carbonyl groups. The desymmetrized quinones serve as a useful alternative to selective chemical transformations in controlling the reactivity of quinones, and thus are frequently called "masked" quinones.[3] These compounds can be readily obtained from phenols, quinones, and quinone bisacetals by utilizing any of the many procedures, among which methods involving chemical oxidations, specifically those using hypervalent iodine reagents in a suitable alcohol solvent, are straightforward and attractive.[4] Because of the uniqueness of the bifunctional structure of the QMAs based on the α,β-unsaturated carbonyl and allylacetal moieties in one skeleton as well as their easy and efficient preparations, QMAs have been attracting interest since the 1970s. Regarding the reactivities, both chemo- and regioselective reactions have been reported (Scheme 1), for instance, additions to the carbonyl carbon (i.e., 1,2-additions),[5] conjugated additions (1,4-additions, etc.),[6] and cyclizations involving these processes.[7]

In addition to these addition reactions, it seems that QMAs, in principle, can participate in the chemistry and 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 electrophilic units for *substitution reactions* were rarely reported,[8−12] except for the intramolecular reactions[13] and well-known acetal deprotection by hydrolysis. The earliest report of the substitution for QMAs with the methyl Grignard reagent (MeMgI) was demonstrated more than 30 years ago for introducing the nucleophile to some extent to the carbon α to the carbonyl group of the QMAs (which also corresponds to the allylic-position of the allylacetal group).[8] The reactions unexpectedly favored the substitution course instead of the additions by depending on the formation of the stable magnesium phenoxide. These strategies under basic conditions

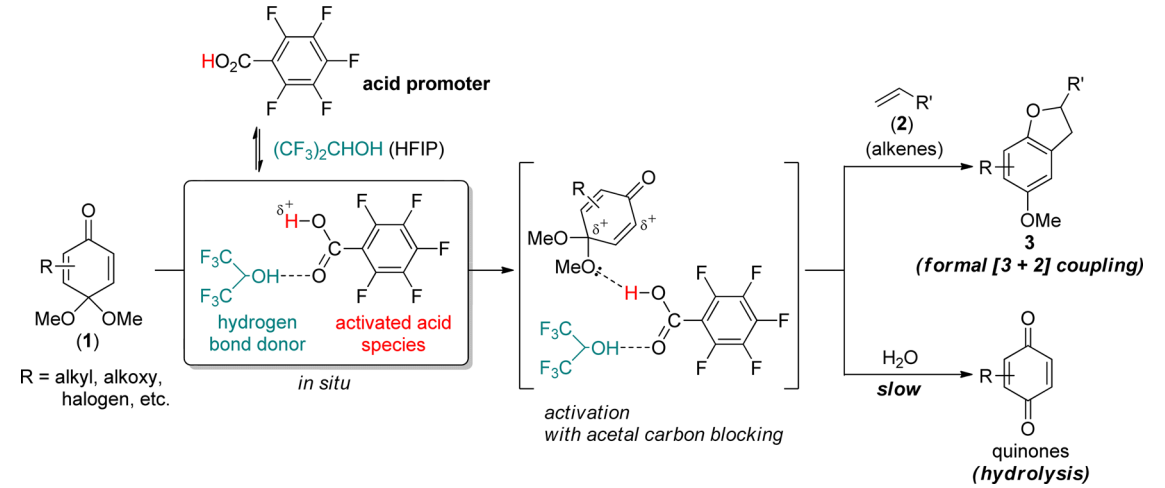
Received: March 28, 2013
Published: May 14, 2013

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530−5543

Scheme 1. Reactions of QMAs 1a toward Nucleophiles Based on the Four Electrophilic Carbons



Scheme 2. Brønsted Acid-Controlled [3 + 2] Coupling Reaction of QMAs by Specific Acid Promoters



cannot usually perfectly exclude the competitive addition processes. Indeed, the S_N2' displacement of the simple QMA dimethyl acetals for the allylation and propargylation are known to occur only via the 1,2-addition of the organometallic species to the carbonyl group followed by rearrangement.[9]

Considering the addition reactivities promoted under basic conditions, acidic activations of QMAs for substitution chemistry have recently been considered as an alternative strategy, though such examples are quite limited. The attractive reactivity of QMAs for substitution promoted by diethyl aluminum chloride ($EtAlCl_2$) was demonstrated by Sartori's group, who proposed the pseudo-intramolecular S_N2' process via coordination of the aluminum Lewis acid to the acetal as well as the phenol nucleophile.[10] In addition, the phenoxenium ions, generated from QMAs by treatment with the appropriate strong acids, were demonstrated by Büchi and other research groups for the [5 + 2]-type cycloadditions resulting from the tandem substitution−annulation sequence.[11] On the other hand, only a few QMAs and activated π-nucleophiles were reported for an alternative [3 + 2] coupling reaction promoted by Brønsted acids leading to dihydrobenzofurans.[12]

Despite their partial success, 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 strategy. 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 on the basis of the screening of more suitable activators.[14−17] We recently developed a new method promoted in a specific solvent, that is, hexafluoroisopropanol (HFIP), for the controlled substitution of QMAs **1** with aromatic nucleophiles to give biaryl compounds in the presence of a solid acid catalyst.[14] Further investigation of this appealing strategy in the specific solvent system has led to the finding of the controlled [3 + 2] coupling reaction of QMAs **1** and alkene nucleophiles **2** (Scheme 2).[15] The specific use of the acid promoter, perfluorobenzoic acid, and the fluoroalcohol solvent concerns the involvement of activated acid species in situ formed in equilibrium with the aid of the hydrogen bond donor, HFIP.[18,19] By the associating acid, the expeditious and efficient coupling reaction would include the attack of the nucleophiles **2** at the less hindered carbon site of the QMAs **1** remote from the acetal rather than the sterically protected acetal carbon; otherwise, the hydrolysis of the acetals by concomitant water usually occurs. As a result, the new system utilizing the specific Brønsted acid and HFIP has extremely improved the [3 + 2] coupling strategy for the remarkably extensive QMAs **1** and π-nucelophiles **2**.

In this paper, we fully summarize our further efforts on the new [3 + 2] coupling reaction of QMAs **1** and alkenes nucleophiles **2** in the specific reaction systems with special emphasis on the reaction scope, mechanism, and extension of the stoichiometric strategy to the catalytic coupling reactions. These further investigations led to the conclusion that the

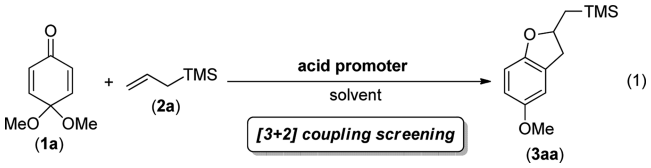
dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530−5543

reactions would proceed in a pseudo-S_N2' interaction of QMAs **1** and alkenes **2**, and stepwise construction of the two carbon−carbon and carbon−oxygen bonds would lead to the thermodynamically favored dihydrobenzofuran products **3**.[20] The significant advances based on the further catalyst tuning have now enabled the controlled coupling reactions with improved stoichiometry of the alkenes **2** (1.2 equiv) under catalysis with the acid promoter at less than 5 mol % loading.

RESULTS AND DISCUSSION

Optimization of the Reaction Conditions and Acid Promoters for the [3 + 2] Coupling Reaction in HFIP. On the basis of our previous success regarding the controlled coupling reaction of QMA **1a** with aromatic nucleophiles,[14] we initially examined the [3 + 2] coupling reaction of the QMA **1a** with allyltrimethylsilane **2a**[21] in our reported system along with montmorillonite (MT) or a stoichiometric amount of acetic acid in a mixed solvent with HFIP (Table 1, eq 1). These reactions indeed produced the coupling adduct, dihydrobenzofuran **3aa**, to some extent (61 and 19%, respectively) at room temperature (entries 1 and 2), but the reactions were very slow and required long times to consume all the starting QMA **1a**. For the [3 + 2] coupling reaction, the MT clay and acetic acid in ordinary solvents were reported as reaction initiators,[12] but these seem to be usable only for a limited number of extremely activated alkenes, i.e., vinyl sulfide and electron-rich chromenes. Accordingly, we screened a more suitable acid activator to allow more efficient reactions and an extensive substrate scope. Considering the pK_a values, several types of Brønsted acids involving a series of carboxylic acids (2 equiv relative to the QMA **1a**) were systematically evaluated. The results indicated that only the carboxylic acids with suitable acidic proton strengths[22] showed a good performance in order to develop the coupling reactions (entries 3−15), among which pentafluorobenzoic acid (pK_a: ca. 1.5−1.6)[22b] especially gave the most promising results regarding not only the product yield, but also the observed production rate and reaction purity (entry 5). Otherwise, incomplete conversions of the QMA **1a** were usually observed for the less acidic activators (entries 2−4), while the stronger acids, such as trichlorobenzoic and phthalic acids (entries 12 and 13), would significantly decompose the QMA **1a**, resulting in poorer yields of the product **3aa**. In particular, trifluoroacetic acid produced the dihydrobenzofuran **3aa** in an acceptable yield (entry 14), but formation of the quinone as well as some byproducts derived from the background polymerization of the used alkene **2a** was accompanied by the acid and much stronger methanesulfonic acid (entry 15) and Nafion resin,[23] which is recognized as a serious problem for future expansion of the scope of the QMAs **1** and alkenes **2**.[24] Lewis acids, such as boron trifluoride and trimethylsilyl triflate, are known instead to induce the conjugated addition[6h] and [5 + 2]-type cyclization[11] for the QMAs **1a** and others, but did not produce the desired [3 + 2] coupling reaction, as expected (entries 16 and 17).

Table 1. Effects of the Reaction Promoters for [3 + 2] Coupling Reaction of 1a and 2a (eq 1)[a]



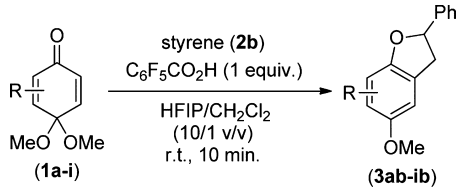
entry	acid	solvent	time	yield of 3aa[b] (%)
1	MK-10[c]	HFIP/DCM	3 days	61
2	acetic acid	HFIP/DCM	7 h	19
3	benzoic acid	HFIP/DCM	2 h	9
4	4-nitrobenzoic acid	HFIP/DCM	2 h	14
5	pentafluorobenzoic acid	HFIP/DCM	10 min	84
6[d]	pentafluorobenzoic acid[e]	HFIP/DCM	10 min	75
7[d,f]	pentafluorobenzoic acid[e]	HFIP/DCM	10 min	90
8[d,g]	pentafluorobenzoic acid[e]	HFIP/DCM	10 min	67
9[d]	pentafluorobenzoic acid[e]	TFE/DCM (10/1)	1 h	21
10[d]	pentafluorobenzoic acid[e]	MeCN/DCM (10/1)	1 h	trace
11[d]	pentafluorobenzoic acid[e]	HFIP	1 h	66
12	2,4,6-trichlorobenzoic acid	HFIP/DCM	10 min	59
13	phthalic acid	HFIP/DCM	10 min	58
14	trifluoroacetic acid	HFIP/DCM	30 min	72
15	trifluoromethanesulfonic acid	HFIP/DCM	2 h	n.d.
16	boron trifluoride·Et_2O	HFIP/DCM	1 h	25
17	trimethylsilyl triflate	HFIP/DCM	2 h	n.d.

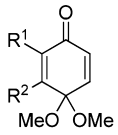
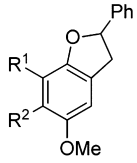
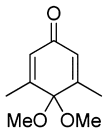
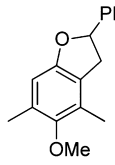
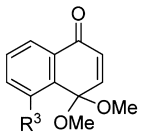
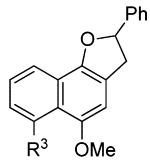
[a]Unless otherwise noted, the screenings were carried out with 2 equiv of acids in HFIP/DCM (10/1 v/v, 0.1 M of QMA **1a**) at room temperature. 5 equiv of allyltrimethylsilane **2a** was used for the reactions. [b]Isolated yields after purification. Formation of very small amounts of noncyclized allylation product was observed. For the details, see Supporting Information. [c]25 mg relative to 1 mL of the solvent. [d]Allyltrimethylsilane **2a** (2 equiv) in HFIP/DCM (10/1 v/v, 0.2 M of QMA **1a**). [e]Pentafluorobenzoic acid (1 equiv). [f]Performed at 0 °C. [g]1.2 equiv of allyltrimethylsilane **2a** was used. n.d. = not determined due to low formation of the product **3aa**. DCM = dichloromethane.

For the perfluorobenzoic acid affording the good results, we conducted further optimizations of the [3 + 2] coupling reaction with respect to the solvent, substrate concentration, temperature, and reagent and substrate stoichiometries. Regarding the solvent, a considerable decrease in the yield of the product **3aa** was observed upon reducing the HFIP ratio relative to dichloromethane (DCM). Meanwhile, the reaction at a higher HFIP ratio permitted the reduction of the perfluorobenzoic acid to 1 equiv and allyltrimethylsilane **2a** to 2 equiv (entry 6). Lowering the temperature to 0 °C has led to a further approximately 10% increase in the product yield (entry 7 for 90%). However, the excess use of the alkene **2a** (2 equiv) was still essential, and 1.2 equiv of allytrimethylsilane **2a** would cause a considerable decrease in the yield of the product **3aa** (entry 8). Finally, the solvent was re-examined for the reaction. HFIP remained indispensable under the optimized conditions, and the consumption of the QMA **1a** by pentafluorobenzoic acid in other solvents was still very slow; the product **3aa** was not smoothly formed, even in the parent but less polar and weaker hydrogen bond donor, 2,2,2-trifluoroethanol (entries 9 and 10). On the other hand, the use of DCM as a cosolvent for HFIP was plausible for dissolving the reactants to obtain the reproducible results (entry 11). A subtle change in the concentration of the substrate **1a** in the range of 0.1−0.5 M had only a slight effect on the product yields. From these observations, we determined the optimized standard conditions for the [3 + 2] coupling reaction of the QMAs **1** to be the use of 2 equiv of alkene nucleophiles **2** in the presence of 1 equiv of the acid promoter,

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530−5543

Table 2. Scope of the QMAs 1: Representative Examples[a]



entry	QMA (**1**)	product (**3**)	yield[b]
			
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[c]	$R^1 = H$, $R^2 = OMe$ (**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	 (**1g**)	 (**3gb**)	trace
			
8	$R^3 = H$ (**1h**)	(**3hb**)	quant.
9	$R^3 = OAc$ (**1i**)	(**3ib**)	98%

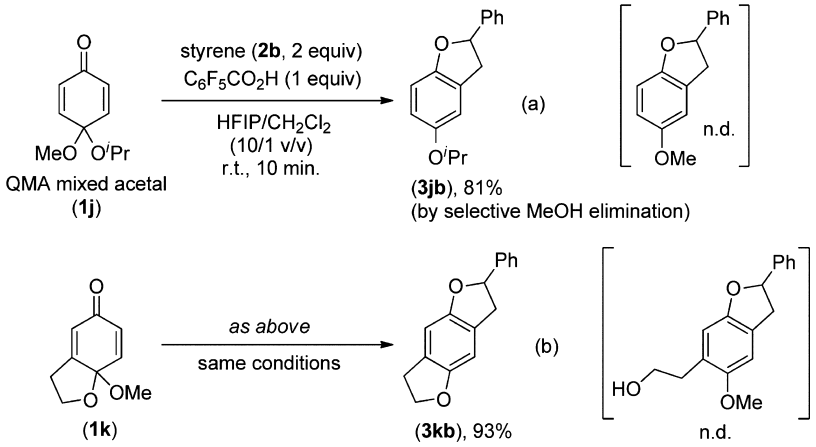
[a]Reactions were conducted using 1 equiv of perfluorobenzoic acid (relative to QMAs **1**) in HFIP/DCM solvent (10/1 v/v, 0.2 M) in the presence of 2 equiv of styrene **2b** at room temperature for 10 min. [b]Isolated yields of the products **3** after purification by column chromatography. [c]2 equiv of the acid activator and 3 equiv of styrene **2a** were used.

perfluorobenzoic acid, in a mixed solvent system of HFIP and DCM.

Scope of the Reactions. Examination of Extended Series of QMAs 1 and Alkene Nucleophiles 2 for the [3 + 2] Coupling Reactions. With the optimal conditions in hand, we then evaluated the extensive QMAs **1a–i** with the diversity of their ring substituent pattern and functionalities for the reactions toward **2b** as the counterpart (Table 2). Unless otherwise noted, all the experiments were carried out at room temperature in an open flask. It was confirmed that many types of QMAs **1** were applicable and afforded the corresponding dihydrobenzofurans **3** in up to quantitative yield at room temperature without competitive formation of other regioisomers and remarkable byproducts. The cyclizations with styrene **2b** and the QMAs **1b–d** having both electron-withdrawing or -donating groups smoothly proceeded, all the

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530–5543

Scheme 3. Unique Leaving Group Preferences of the Acetal Units of QMAs 1j and 1k[a]



[a]n.d. = not determined due to low-yield formation.

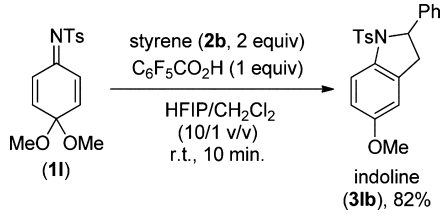
reactions of which exclusively occurred at the less hindered positions of the two carbons α to the carbonyl group of the QMA structures (entries 2−4). The QMA **1c** with a *tert*-butyl substituent at the neighboring carbon atom of the acetal moiety seemed to slightly hamper the substrate reactivity because of its steric hindrance (entry 3). Meanwhile, the less electrophilic methoxy QMA **1d** reacted with the alkene **2b** as do the more electrophilic QMAs **1a** and **1b**, though higher amounts of the acid and a higher concentration of the alkene **2b** were needed (entry 4). The substituents of a *tert*-butyl and halogen moiety at the neighboring side of the carbonyl group were intact, and the QMAs **1e** and **1f** afforded the cyclized coupling products **3eb** and **3fb** with high conversions and efficiencies (entries 5 and 6). On the other hand, the disubstituted QMA **1g** was not reactive at all in this [3 + 2] coupling reaction, probably because of the severe steric requirement of the transition state (entry 7), which was in accord with the observed perfect regioselectivity for the QMAs **1b−d** during the reactions. To our delight, the formations of the desired cycloadducts **3hb** and **3ib** were achieved in excellent yields from the naphthalene QMAs **1h** and **1i** (entries 8 and 9). Remarkably, all of the reactions except for the QMA **1g** were finished within 10 min at room temperature with the indicated good efficiencies.

In addition to the above-mentioned QMAs **1** based on the dimethyl acetal, the QMAs **1j** and **1k** having mixed acetals would participate in the [3 + 2] coupling reaction under the standard reaction conditions, giving only the single products after the selective release of the methoxy group (Scheme 3). Specifically, the reaction of the QMA **1j** accounted for the high leaving preference for the methoxy group rather than the larger isopropoxy one (Scheme 3a). One plausible explanation for the unique recognitions of the acetals is the facile interaction of the small methoxy group toward the perfluorinated acid species during their activation.

For the QMA derivatives, we found that the valuable indoline compound **3lb** was also obtained from iminoquinone acetals **1l** in a similar transformation without optimization (Scheme 4). Such oxygenated indoline structures are found in 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** for the QMAs was investigated by employing QMA **1a** as a unified reaction substrate (Table 3). Fortunately, not only the activated alkene

Scheme 4. Construction of Indoline Skeleton from Iminoquinone Acetal 1l

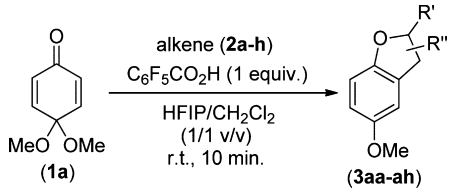


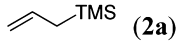
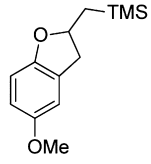
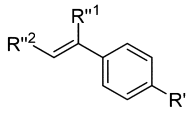
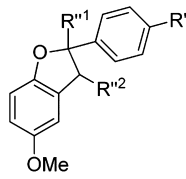
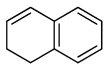
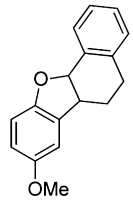
2a (entry 1), but also many styrene derivatives **2c−g**, having either electron-donating or -withdrawing substituents on the aromatic ring (entries 2−6), smoothly reacted with the QMA **1a** without significant alteration of the reaction efficiencies. Especially, the *gem*- and disubstituted styrenes **2f** and **2g** were similarly converted to the desired cyclocoupling products, **3af** and **3ag** (entries 5 and 6); in the latter, the *trans*-isomer of the dihydrobenzofuran was solely obtained from the *trans*-styrene **2g**. The cyclic styrene **2h** was also applicable for the construction of the fused dihydrobenzofuran structure in the product **3ah** found in the pterocarpan-type natural products (entry 7), a member of the 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] These coupling reactions thus proceeded very fast within 10 min and provided the expected products **3** in good yields at room temperature. It should be noted that the use of these alkenes **2** as nucleophiles afforded the corresponding dihydrobenzofurans **3** only in this strategy, while the reported oxidation methods starting from phenols were somewhat troublesome in terms of the yields to obtain the same products **3**.[27]

The alkene nucleophiles having the cation-stabilizing substituents (β-cation by TMS and α-cation by aryl) eventually coupled with the QMAs **1** in the effective manners. Encouraged by the results, we examined several aliphatic alkenes for the coupling reaction with the QMAs **1**. It should be noted that treating the five- and six-membered *exo*-methylene compounds **2i** and **2j** in excess amounts under the optimized conditions successfully afforded the two types of ring-sized spirocyclic dihydrobenzofurans **3ai** and **3aj** with comparable results, 78 and 65%, respectively (Scheme 5). These compounds are

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530−5543

Table 3. [3 + 2] Coupling Reaction of Various Alkenes 2a–h toward QMA 1a[a]



entry	alkene (**2**)	product (**3**)	yield[b]
1	 (**2a**)	 (**3aa**)	89% 90%[c]
			
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**)[d]	93%
7	 (**2h**)	 (**3ah**)	83%

[a]See the footnote in Table 2 for the reaction conditions. 2 equiv of alkenes **2a–h** were used for the reactions. [b]Isolated yields of the products **3** after purification. [c]Performed at 0 °C. [d]Only *trans* isomer produced.

known to be potentially useful in consideration of the ubiquitous nature of the spirocyclic structures in natural products showing interesting biological activities and unique physical properties, such as for optoelectronics, and as asymmetric ligands for catalytic synthesis, attributed to their spirocyclic core structures.[28] Meanwhile, the mono- and vicinal-substituted alkenes, i.e., the 1- and 2-octenes, did not smoothly react with the QMAs **1**.

Because of the mildness of the reaction conditions, dihydrobenzofuran **3ak** having a cyclized *O*,*S*-acetal was obtained in good yield by using the vinyl sulfide **2k** as an appropriate π counterpart for the coupling reaction (Scheme 6). This extended the utility of the [3 + 2] coupling reaction for production of the benzofurans **4** from the products **3** as synthetic modules by utilizing the known elimination of the phenyl sulfide group. Indeed, successive treatments of the formed dihydrobenzofuran product **3ak** with acid and heating or an oxidant,[29] such as *m*-chloroperbenzoic acid (*m*CPBA), were confirmed for the conversion to the benzofuran **4**.

The above-mentioned results using various QMAs **1** and alkene nucleophiles **2** validated the extended scope of the [3 + 2] coupling reaction in the present systems in comparison to the reported procedures.[12] The dramatic improvements in the product yields and the reaction rates now have promise for the catalysis of perfluorobenzoic acid in HFIP.

Mechanistic Considerations. It is known that some QMAs would cause [5 + 2] cyclizations with alkenes upon acid treatment.[11] For the QMA **1d**, the generation of the

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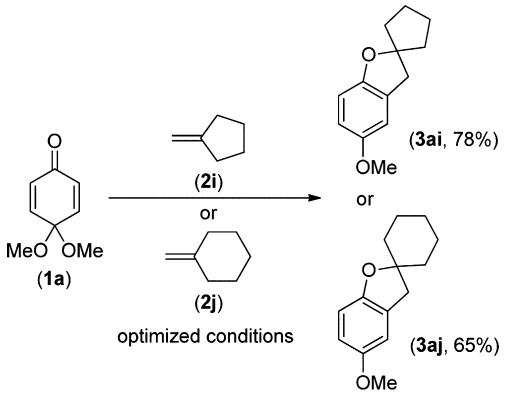
Scheme 5. Formation of Spirocyclic Dihydrobenzofurans 3ai and 3aj[a]



[a]3 equiv of alkene was used for each case.

phenoxenium ion[30] was reported during the reaction to exclusively lead to the [5 + 2] cyclization by the trapping with styrene **2b**, giving rise to the product **5** (Scheme 7).[11c] On the other hand, our reaction system did not produce the [5 + 2] adduct **5** at all with the treatment of the same substrates **1d** and **2b**, which indicated that our conditions apparently cannot produce the phenoxeium ions. Because the QMAs **1** were not consumed in the absence of the alkenes **2** in our reaction systems, it seems that the [3 + 2] coupling reaction would instead involve the charged QMA species **A** associated with the acid species for the activation and is considered to be initiated by the pseudo-concerted attack of the alkenes **2** and elimination of the methanol.

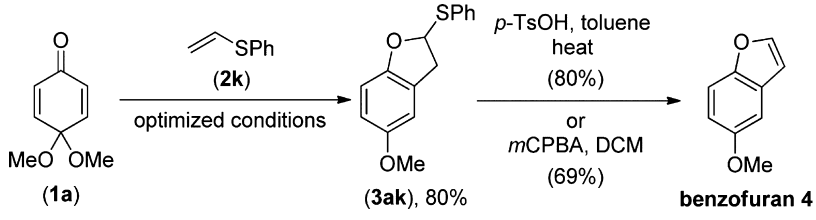
Apparently, the important tolerance toward moisture for our reactions has come from the lack of involvement of the reactive and unstable phenoxenium ions. The [3 + 2] coupling reaction of the QMAs **1** proceeded without the use of the absolutely dehydrated HFIP, and the control experiments with the extra addition of 1 equiv as well as even 5 equiv of water did not cause a remarkable decrease in the product yields due to the intermediacy of the more stable charged QMA species **A** (Scheme 8), which is the significant merit of the nondiscrete mechanism (pseudo-S_N2' pathway). However, phenoxenium ions generated under the known conditions underwent competitive quinone formation by hydrolysis of the acetals in the presence of water (S_N1 pathway).

The plausible mechanism for the [3 + 2] coupling reaction of the QMAs **1** with alkene nucleophiles **2** is suggested in Scheme 9 for the representative coupling substrates, QMA **1a** and alkene **2a**. For the activation of the QMA **1a**, the initiation step involves the charged QMA **A** associated with the combined acid species of perfluorobenzoic acid and HFIP. Because of the super hydrogen bond donor ability of the fluoroalcohol solvent, preactivation of the Brønsted acid might first occur by the coordination of HFIP to the Lewis basic functionality of the acid's carbonyl group (Brønsted acid activation by HFIP).[19] The charged QMA **A** can now react with the π-nucleophile **2a** at the ring carbon α to the carbonyl group, rather than the sterically encumbered tertiary acetal carbon atom, the concerted course of which seems to enhance the observed steric trends and regioselectivities for the reaction of the substituted QMAs **1** discussed in Table 2. The pseudo-S_N2'-like introduction of the nucleophile **2a** by the reagent control afforded 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 highly polar fluoroalcohol is a good match for the solvation of all the charged reaction intermediates.

To prove the intermediary of the precyclized keto-type tautomer **B**, we presented the following experiment using the *Z*-type styrene **2l** for the coupling reaction (Scheme 10). In fact, the reaction of the QMA **1a** and *cis*-methyl styrene **2l** produced the corresponding cyclized products **3al** as a regiomixture with an about 30:70 ratio of *cis*- and *trans*-dihydrobenzofurans. After prolonged stirring of the reaction mixture, epimerization of the two isomeric products was not observed. In addition, no isomerization of the *cis*-olefin to *trans* one occurred during the reaction. One can easily accept that these observations clearly support the involvement of the precyclized cationic intermediate **B′**, in which the free rotation of the C−C bonds competitively occurred to the cyclizations to form the more thermodynamically favored *trans* isomer rather than the *cis*-**3al**.

Extension to the Catalytic Systems. Despite the general success of the above-mentioned results, several drawbacks still remained from the practical view regarding the chemical reaction for the [3 + 2] coupling reaction of the QMAs **1** and nucleophilic alkenes **2** using perfluorobenzoic acid. The reactions usually required a stoichiometric amount of the acid, which is considered to be a waste material after the reactions.[31] In addition, the acid-induced background polymerization of the used alkenes **2** as a problem[23] forced their excess use, typically over 2 equiv, for the coupling reactions. Designing a recyclable alternative to perfluorobenzoic acid by attaching the acid function to an insoluble polymer partially alleviated these drawbacks,[15b] but the catalysis of the acid promoter with improved stoichiometry of the used alkenes **2** in the coupling reactions had not been accomplished by this approach. Indeed, the use of a semistoichiometric amount of the alkene **2a** (1.2 equiv) with catalytic use of the acid promoter (20 mol %) under the stated optimized conditions significantly decreased

Scheme 6. Formation of Cyclized *O,S*-Acetal Compound 3ak from Vinyl Sulfide 2k and Successive Conversion of the Product to Benzofuran 4



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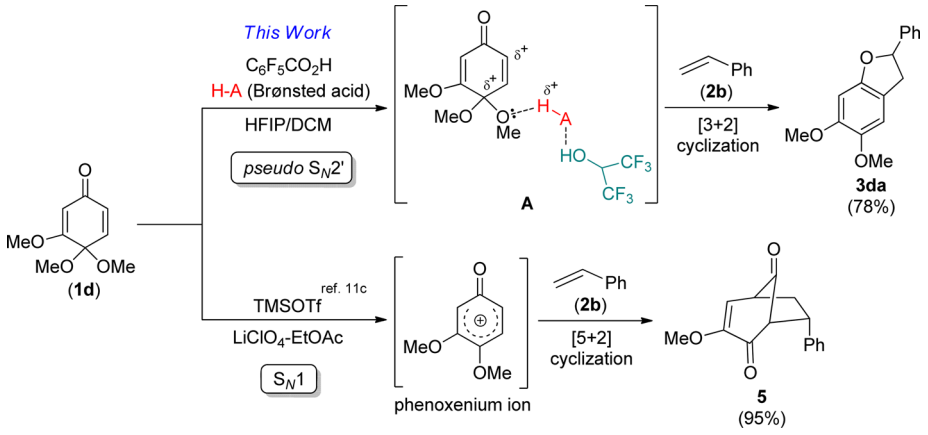
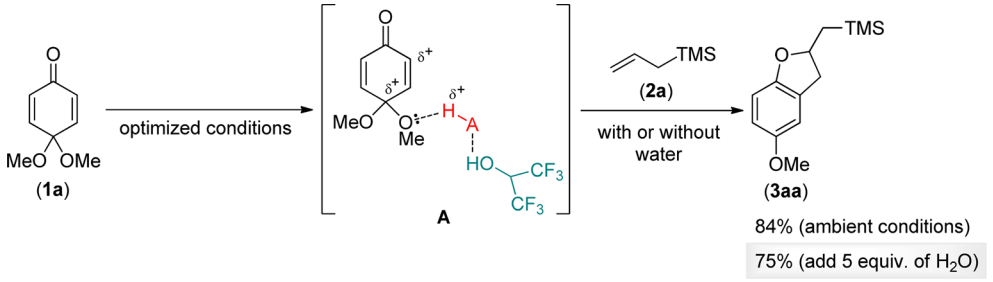
Scheme 7. Alternation of the Reaction Mechanisms by the Acid Promoters[a]

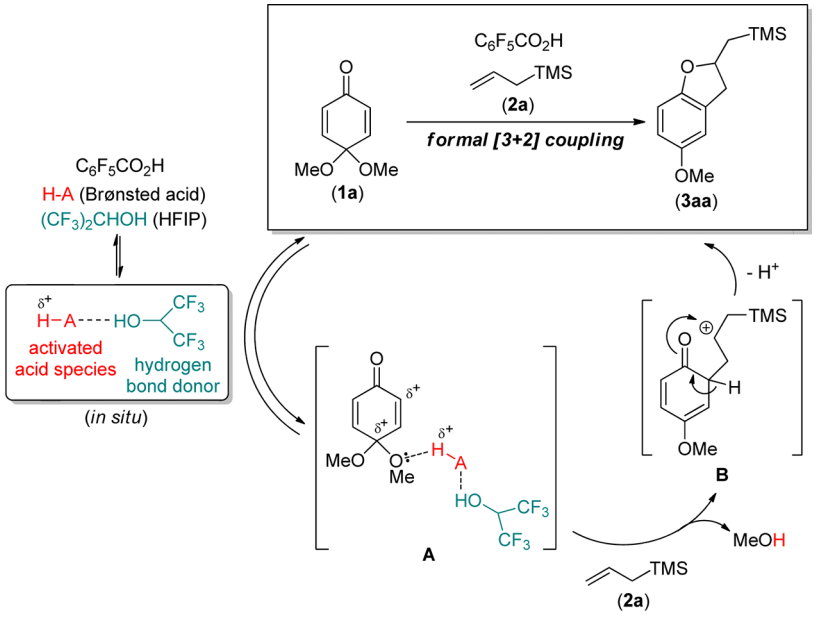


[a]H-A: perfluorobenzoic acid.

Scheme 8. Examination of the Effect of Water



Scheme 9. Plausible Mechanism for the [3 + 2] Coupling Reaction of QMA 1a Initiated by Perfluorobenzoic Acid



the yield of the [3 + 2] product **3aa** (Table 4, eq 2, entries 1 and 2). Reoptimizing the solvent ratio for the catalytic conditions somewhat positively affected the reaction efficiency (entry 3), but the benefit was limited only to a relatively high catalyst loading (entry 4).

Aimed at realizing a more practical catalytic reaction, we accordingly had to further attenuate the reactivity of the acid promoter working with a possible minimal loading. Considering that only the acids with the suitable pK_a values served as the efficient promoters for the [3 + 2] coupling reaction, we screened a series of perfluorobenzoic acid derivatives **a**–**h** with various pK_a values (Figure 1, all commercially available materials). 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 a 2 mol % loading, all the partial fluorinated benzoic acids **a**–

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Scheme 10. Formation of the Regiomixture via the Stepwise Cyclization Mechanism

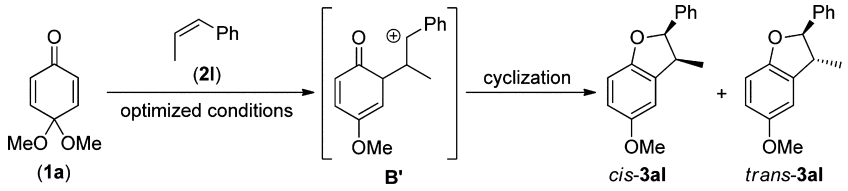
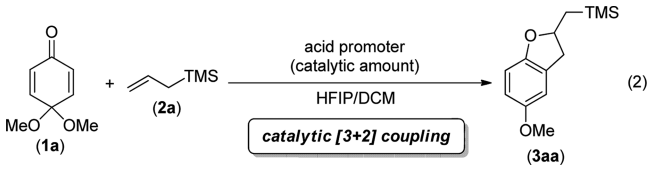


Table 4. Screening for the Catalytic [3 + 2] Coupling Reaction of 1a and 2a (eq 2)[a]



entry	perfluorobenzoic acid [mol %]	2a (equiv)[b]	yield of 3aa[c] (%)
1[d]	pentafluorobenzoic acid [100]	1.2	67
2[d]	pentafluorobenzoic acid [20]	1.2	56
3	pentafluorobenzoic acid [20]	1.2	72
4	pentafluorobenzoic acid [2]	1.2	48
5	2,3,5,6-tetrafluorobenzoic acid **a** [2]	1.2	45
6	2,3,4,5-tetrafluorobenzoic acid **b** [2]	1.2	24
7	3,4,5-trifluorobenzoic acid **c** [2]	1.2	15
8	2,6-difluorobenzoic acid **d** [2]	1.2	27
9	2,5-difluorobenzoic acid **e** [2]	1.2	18
10	perfluorophthalic acid **f** [1]	1.2	41
11	perfluoroisophthalic acid **g** [1]	1.2	61
12	perfluoroterephthalic acid **h** [1]	1.2	72
13	perfluoroterephthalic acid **h** [5]	1.2	78
14	perfluoroterephthalic acid **h** [5]	1.0	72
15[e]	perfluoroterephthalic acid **h** [5]	1.2	69
16[f]	perfluoroterephthalic acid **h** [5]	1.2	65
17[g]	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 h. [b]Relative to QMA **1a**. [c]Isolated yields after purification. Formation of very small amounts of noncyclized allylation product was observed. [d]HFIP/DCM (10/1 v/v, 0.2 M of QMA **1a**). [e]HFIP/DCM (2/1 v/v, 0.2 M). [f]HFIP/DCM (1/2 v/v, 0.2 M). [g]Performed at 0 °C for 3 h.

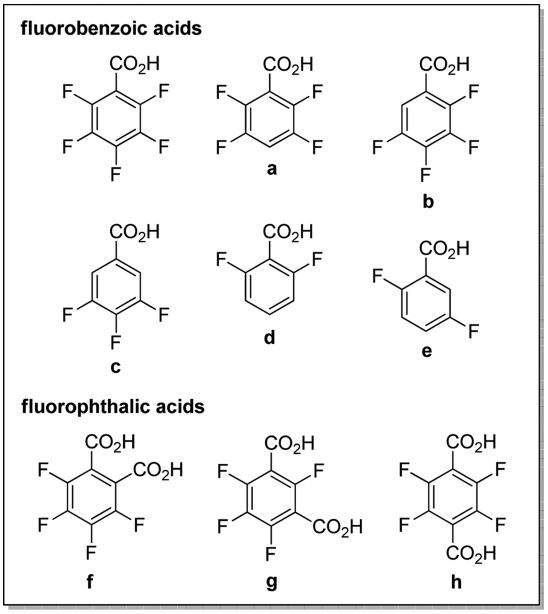


Figure 1. Screened fluorobenzoic acids as catalysts.

e showed lower efficiencies and slow reaction rates (entries 5–9), probably due to their weaker acidities in comparison to perfluorobenzoic acid itself. Meanwhile, a set of more acidic phthalic acids **f**–**h** were examined with promising results under the catalytic conditions (entries 10–12); among the three isomers, the fluorinated terephthalic acid **h** showed the best catalytic performance and was capable of providing the coupling product **3aa** in 72% yield even at a 1 mol % loading (entry 12).

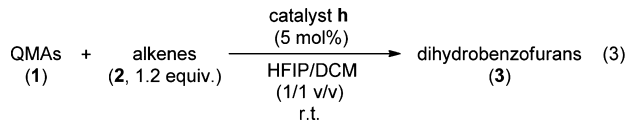
Encouraged by the results with the catalyst **h**, the general effects regarding the catalyst loading, reactant ratio, concentration, and temperature were further investigated (entries 13–17). By employing the catalyst **h** at 5 mol %, more promising results were obtained (entry 13), which maintained the product yield at over 70% even with strict use of the alkene **2a** at 1.0 equiv (entry 14). The catalytic reaction at the temperature of 0 °C has now become comparable to the original stoichiometric one for the dihydrobenzofuran **3aa** production when using the best catalyst **h** at 5 mol % (entry 17).

With the optimal catalyst **h** and conditions determined, we confirmed the versatility of the catalytic system for the described QMAs **1** and nucleophilic alkenes **2** in Tables 2, 3, and Scheme 6. 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** (1.2 equiv). The resultant examples are summarized in Table 5. The excellent-to-good yields (up to 98% for the QMA **1e** and alkene **2b**) compatible with the stoichiometric reactions (note: the stoichiometric reactions in Tables 2 and 3 used 2 equiv of the alkenes **2**) while maintaining the regioselectivities have promised the generality of the catalytic method for the practical [3 + 2] coupling reactions of the QMAs **1**.

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, the appropriate acidity is an important factor required for the catalyst, while interestingly, aliphatic carboxylic acids having pK_a values similar to that of the catalyst **h**, that is, the trichloro- and dichloroacetic acids, showed somewhat lower efficiencies as the catalysts (below 65% yields of the product **3aa** at 2 mol % loading). Although the origin of the higher catalytic activity of the catalyst **h** is still

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530–5543

Table 5. [3 + 2] Coupling Reactions by Perfluoroterephthalic Acid Catalyst h (eq 3)[a]



entry	QMA (1)	alkene (2)	product (3)	time (h)	yield[b] (%)
1	**1a**	**2b**	**3ab**	4	82
2	**1b**	**2b**	**3bb**	5	76
3	**1c**	**2b**	**3cb**	5	67
4	**1e**	**2b**	**3eb**	5	98
5	**1f**	**2b**	**3fb**	4	85
6	**1h**	**2b**	**3hb**	5	90
7	**1i**	**2b**	**3ib**	8	94
8	**1j**	**2b**	**3jb**	4	85
9	**1k**	**2b**	**3kb**	4	84
10	**1a**	**2c**	**3ac**	3	78
11	**1a**	**2d**	**3ad**	4	80
12	**1a**	**2e**	**3ae**	5	88
13	**1a**	**2f**	**3af**	5	79
14	**1a**	**2g**	**3ag**[c]	4	84
15	**1a**	**2h**	**3ah**	5	90
16	**1a**	**2i**[d]	**3ai**	4	74
17	**1a**	**2j**[d]	**3aj**	7	81
18	**1a**	**2k**	**3ak**	4	88

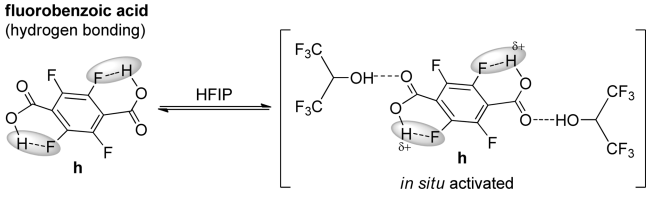
[a]Reactions were performed using 1.2 equiv of alkenes **2** in the presence of 5 mol % of the acid catalyst **h** in HFIP/DCM=1/1 (0.2 M) at room temperature. [b]Isolated yields after purification. [c]Only *trans* isomer was obtained. [d]3 equiv of alkene **2i** and **2j** was used.

unclear, one significant difference in the perfluorobenzoic acids relative to the others is the presence of the intramolecular H-bonding in the *ortho*-fluorobenzoic acid structure,[32] 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 mechanism in Scheme 9) from the nucleophilic attack and thus might exclude the quinone formation by the addition of concomitant water as well as other side reactions. In our previous studies, steric blocking of the electrophilic acetal carbon by a bulky activator was very important for suppressing quinone formation.[14] Hence, the perfluorinated benzoic acids would have a superior effect on controlling the coupling reactions in the catalytic cycle compared to the acids having similar pK_as (Scheme 11).

CONCLUSIONS

In summary, we have demonstrated in this study that the quinone monoacetals (QMAs), which have recently emerged as useful quinone alternatives for controlling the addition and substitution chemistries due to their unique bifunctional structures based on both the α,β-unsaturated carbonyl and allylacetal moieties in one skeleton, are versatile electrophiles for the efficient [3 + 2] coupling reaction with nucleophilic alkenes under specific acidic conditions. The rare success of the substitution-type chemistry of QMAs should appear because of the appealing Brønsted acid-controlled strategy consisting of the combined system of a specific acid promoter and solvent, that is, perfluorobenzoic acid and fluoroalcohol. This new and expeditious [3 + 2] coupling reaction smoothly proceeded with a high regiospecificity for the QMAs by introducing the π-nucleophiles toward only the carbons α to the carbonyl group, providing diverse dihydrobenzofuran products and their derivatives with yields up to quantitative in short reaction times at room temperature. This investigative report details the estimated reaction scope and mechanism for their deep understandings and the extension of the preliminary study (2 equiv of alkenes, 100 mol % acid promoter)[15] to develop the coupling reactions at minimal catalyst loadings with improved stoichiometry of the substrates. Interestingly, the mechanism was rationalized to proceed via the concerted addition manner including the charged QMA species in the transition state by coordination of the specific acid promoter, which is activated by the hydrogen-bond donor fluoroalcohol, rather than the discrete phenoxenium ions. In addition, the observation of the thermodynamically favored dihydrobenzofurans accounts for the stepwise construction of the carbon−carbon and carbon−oxygen bonds of the products via the resulting precyclized keto-intermediate (Scheme 9, intermediate **B**). As the reaction promoter, the perfluorinated benzoic acids with the intramolecular H-bonding seem to be plausibly effective for controlling the coupling reactions in the desired substitution manner. Hence, the potent reactivities for additions to the conjugated enone moiety and quinone formation from QMAs can be excluded by the reagent control. Ongoing studies with respect to the diversity of the nucleophiles might be expected as the advanced work on this Brønsted acid-controlled [3 + 2] coupling reaction and the basis of the inherent ambident reactivities of the QMAs.

Scheme 11. Conformation of the Perfluoroterephthalic Acid



EXPERIMENTAL SECTION

General Methods. Melting point (mp) was measured by melting point apparatus. ^{1}H NMR (and ^{13}C NMR) spectra were recorded by spectrometers operating at 400 or 300 MHz (100 or 75 MHz for ^{13}C NMR) at 25 °C using $CDCl_3$ as a solvent. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00 ppm) with the solvent resonance as an internal standard ($CDCl_3$, δ = 7.24 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR). The data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, sep = septet, m = multiplet), and coupling constant (Hz). Absorptions of infrared spectra (IR) are reported in reciprocal centimeters (cm^{-1}). Column chromatography and analytical thin-layer chromatography (TLC) were carried out on silica gel (230−400 mesh) eluting with hexane and ethyl acetate for isolation of the quinone monoacetals (QMAs) **1** and cycloadducts **3**. The spots and bands were detected by UV light of irradiation (254, 365 nm) and/or by staining with 5% phosphomolybdic acid followed by heating. A series of the perfluorinated acids, perfluorobenzoic acid and compounds **a**−**h** are commercially available and were used as they were received. The QMAs (**1a** and other substituted derivatives) were prepared from the corresponding phenols or *para*-alkoxy phenols by the conventional oxidation procedures using phenyliodine diacetate (PIDA, $PhI(OAc)_2$) in suitable alcohol solvents.[4] Imino quinone acetal **1l** was prepared from the corresponding aniline derivative, i.e., *p*-methoxy-*N*-tosyl

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530−5543

aniline, by the same method.[4h] Other commercial acids for the screening of the reaction promoter in Table 1 were purchased and used as they stand. All other chemicals including the commercial alkene nucleophiles **2** and solvents, such as hexafluoroisopropanol (HFIP), for the reactions were obtained from commercial suppliers and used as received without further purification.

[3 + 2] Coupling Reaction of QMAs 1 with Alkenes 2 Promoted by Perfluorobenzoic Acid (Tables 2 and 3): A Representative Procedure for the Reaction of QMA 1a and Allyltrimethylsilane 2a. To a stirred solution of quinone monoacetal **1a** (154 mg, 1.0 mmol) and allyltrimethylsilane **2a** (0.32 mL, 2 mmol) in dichloromethane (0.45 mL) were successively added HFIP (4.5 mL) and a stoichiometric amount of pentafluorobenzoic acid (215 mg, 1.0 mmol) in an open flask at 0 °C. The reaction mixture was then stirred for 10 min and monitored by TLC. After consumption of the quinone monoacetal **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/ethyl acetate = 20/1) to give a pure dihydrobenzofuran product **3aa** (215 mg, 0.90 mmol, 90%) as a colorless oil (Table 1, entry 7). Typically, theoretical amount of unreacted QMA was recoverable during this purification procedure.

2,3-Dihydro-5-methoxy-2-[(trimethylsilyl)methyl]-benzofuran (3aa).[21c] Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (1H, s), 6.53−6.56 (2H, m), 4.76−4.84 (1H, m), 3.65 (3H, s), 3.14 (1H, dd, J = 15.4, 8.3 Hz), 2.69 (1H, dd, J = 15.4, 8.3 Hz), 1.22 (1H, dd, J = 14.2, 6.1 Hz), 1.01 (1H, dd, J = 14.2, 8.8 Hz), 0.02 (9H, s) 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}.

2,3-Dihydro-5-methoxy-2-phenylbenzofuran (3ab).[33a] 42.1 mg of **3ab** obtained as a colorless oil in 93% isolated yield (Table 2, entry 1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.39 (5H, m), 6.75−6.76 (2H, m), 6.66−6.74 (1H, m), 5.70 (1H, t, J = 8.8 Hz), 3.73 (3H, s), 3.57 (1H, dd, J = 15.6, 9.2 Hz), 3.16 (1H, dd, 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) 3062, 3030, 2937, 2831, 1604, 1487, 1433, 1231, 1203, 1136, 1032, 975, 808, 756, 669 cm^{-1}.

2,3-Dihydro-5-methoxy-6-methyl-2-phenylbenzofuran (3bb). 39.9 mg of **3bb** obtained as a yellow sticky oil in 83% yield (Table 2, entry 2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.34 (5H, m), 6.65 (1H, s), 6.61 (1H, s), 5.65 (1H, t, J = 9.2 Hz), 3.71 (3H, s), 3.53 (1H, dd, J = 15.7, 8.1 Hz), 3.11 (1H, dd, J = 15.7, 8.1 Hz), 2.13 (3H, s) 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-QMS) Calcd for $C_{16}H_{16}O_2$ [M]$^+$, 240.1150, found 240.1149.

2,3-Dihydro-6-(*tert*-butyl)-5-methoxy-2-phenylbenzofuran (3cb). 36.2 mg of **3cb** obtained as a colorless solid in 64% yield (Table 2, entry 3): mp 47−49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.39 (5H, m), 6.78 (2H, d, J = 8.0 Hz), 5.73 (1H, t, J = 9.0 Hz), 3.86 (3H, s), 3.56 (1H, dd, J = 15.4, 9.3 Hz), 3.18 (1H, dd, J = 15.4, 8.7 Hz), 1.26 (9H, s) 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-QMS) Calcd for $C_{19}H_{22}O_2$ [M]$^+$, 282.1620, found 282.1621.

2,3-Dihydro-5,6-dimethoxy-2-phenylbenzofuran (3db). 40.0 mg of **3db** obtained as a colorless sticky oil in 78% yield (Table 2, entry 4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.34 (5H, m), 6.70 (1H, s), 6.47 (1H, s), 5.68 (1H, t, J = 9.0 Hz), 3.79 (3H, s), 3.77 (3H, s), 3.52 (1H, dd, J = 15.1, 9.3 Hz), 3.10 (1H, dd, 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, 116.0, 119.0, 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-QMS) Calcd for $C_{16}H_{16}O_3$ [M]$^+$, 256.1099, found 256.1117.

2,3-Dihydro-7-(*tert*-butyl)-5-methoxy-2-phenylbenzofuran (3eb). 56.4 mg of **3eb** obtained as a slightly yellow oil in quantitative yield (Table 2, entry 5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.43 (5H, m), 6.73 (1H, d, J = 2.4 Hz), 6.64 (1H, d, J = 2.7 Hz), 5.76 (1H, t, J = 9.0 Hz), 3.78 (3H, s), 3.58 (1H, dd, J = 15.4, 9.5 Hz), 3.13 (1H, dd, J = 15.6, 8.5 Hz), 1.42 (9H, s) 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-QMS) Calcd for $C_{19}H_{22}O_2$ [M]$^+$, 282.1620, found 282.1622.

2,3-Dihydro-7-chloro-5-methoxy-2-phenylbenzofuran (3fb). 44.9 mg of **3fb** obtained as a colorless solid in 86% yield (Table 2, entry 6): mp 65−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.33 (5H, m), 6.58−6.64 (2H, m), 5.72 (1H, t, J = 8.5 Hz), 3.66 (3H, s), 3.57 (1H, dd, J = 15.8, 9.2 Hz), 3.16 (1H, dd, 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-QMS) Calcd for $C_{15}H_{13}ClO_2$ [M]$^+$, 260.0604, found 260.0606.

2,3-Dihydro-5-methoxy-2-phenyl-naphtho[1,2-*b*]furan (3hb). 55.2 mg of **3hb** obtained as a pale-green solid in quantitative yield (Table 2, entry 8): mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, d, J = 8.1 Hz), 8.00 (1H, d, J = 8.0 Hz), 7.46−7.53 (4H, m), 7.32−7.40 (3H, m), 6.72 (1H, s), 5.94 (1H, t, J = 9.5 Hz), 3.96 (3H, s), 3.80 (1H, dd, J = 15.4, 9.7 Hz), 3.36 (1H, dd, 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-QMS) Calcd for $C_{19}H_{16}O_2$ [M]$^+$, 276.1150, found 276.1147.

2,3-Dihydro-5-methoxy-2-phenyl-naphtho[1,2-*b*]furan-6-yl acetate (3ib). 65.5 mg of **3ib** obtained as a pale-pink solid in 98% yield (Table 2, entry 9): mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, J = 8.3 Hz), 7.15−7.35 (6H, m), 6.96 (1H, d, J = 8.0 Hz), 6.67 (1H, s), 5.83 (3H, t, J = 8.8 Hz), 3.78 (3H, s), 3.68 (1H, dd, J = 15.4, 9.7 Hz), 3.23 (1H, dd, J = 15.4, 7.8 Hz), 2.28 (3H, s) 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-QMS) Calcd for $C_{21}H_{18}O_4$ [M]$^+$, 334.1205, found 334.1198.

2,3-Dihydro-5-methoxy-2-(*p*-tolyl)benzofuran (3ac). 39.9 mg of **3ac** obtained as a colorless solid in 83% yield (Table 3, entry 2): mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09−7.23 (4H, m), 6.67−6.70 (2H, m), 6.62 (1H, d, J = 8.8 Hz), 5.63 (1H, t, J = 8.8 Hz), 3.69 (3H, s), 3.49 (1H, dd, J = 15.7, 9.5 Hz), 3.11 (1H, dd, J = 15.7, 8.4 Hz), 2.28 (3H, s) 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-QMS) Calcd for $C_{16}H_{16}O_2$ [M]$^+$, 240.1150, found 240.1153.

2,3-Dihydro-2-(4-(*tert*-butyl)phenyl)-5-methoxybenzofuran (3ad). 52.0 mg of **3ad** obtained as a colorless solid in 92% yield (Table 3, entry 3): mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.40 (4H, m), 6.68−6.78 (3H, m), 5.71 (1H, t, J = 8.8 Hz), 3.76 (3H, s), 3.56 (1H, dd, J = 15.6, 9.3 Hz), 3.22 (1H, dd, J = 15.6, 8.3 Hz), 1.31 (9H, s) 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-QMS) Calcd for $C_{19}H_{22}O_2$ [M]$^+$, 282.1620, found 282. 1622.

2,3-Dihydro-2-(4-chlorophenyl)-5-methoxybenzofuran (3ae). 49.0 mg of **3ae** obtained as a slightly yellow solid in 94% yield

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530−5543

(Table 3, entry 4): mp 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (4H, s), 6.68−6.77 (3H, m), 6.69 (1H, t, J = 9.3 Hz), 3.75 (3H, s), 3.58 (1H, dd, J = 15.8, 9.5 Hz), 3.12 (1H, dd, 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-QMS) Calcd for $C_{15}H_{13}ClO_2$ [M]$^+$, 260.0604, found 260.0608.

2,3-Dihydro-5-methoxy-2-methyl-2-phenylbenzofuran (3af). 38.9 mg of **3af** obtained as a colorless solid in 81% yield (Table 3, entry 5): mp 53−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.40 (5H, m), 6.71 (1H, d, J = 8.5 Hz), 6.58−6.65 (2H, m), 3.65 (3H, s), 3.23−3.36 (2H, m), 1.68 (3H, s) 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-QMS) Calcd for $C_{16}H_{16}O_2$ [M]$^+$, 240.1150, found 240.1153.

2,3-Dihydro-*trans*-5-methoxy-2-(4-methoxyphenyl)-3-methylbenzofuran (3ag).[27b] 50.3 mg of **3ag** obtained as a colorless oil in 93% yield (Table 3, entry 6): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (2H, d, J = 8.0 Hz), 6.40−6.45 (2H, m), 6.18−6.30 (3H, m), 4.58 (1H, d, J = 8.0 Hz), 3.31 (3H, s), 3.29 (3H, s), 2.90−2.93 (1H, m), 0.88 (3H, d, 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}.

5,6,6a,11a-Tetrahydro-8-methoxy-benzo[*b*]naphtho[2,1-*d*]furan (3ah, *cis*-stereoisomer). 41.9 mg of **3ah** obtained as a slightly yellow solid in 83% isolated yield (Table 3, entry 7): mp 81−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 8.0 Hz), 7.19−7.30 (2H, m), 7.10−7.14 (1H, m), 6.80 (1H, s), 6.64−6.68 (2H, m), 5.61 (1H, d, J = 8.3 Hz), 3.74 (3H, s), 3.60−3.62 (1H, m), 2.61−2.69 (2H, m), 1.98−2.05 (1H, m), 1.77−1.81 (1H, m) 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-QMS) Calcd for $C_{17}H_{16}O_2$ [M]$^+$, 252.1150, found 252.1159. The stereochemistry was determined by referring reported data in the literatures.[33b,c]

5-Methoxy-spiro[benzofuran-2(3*H*),1′-cyclopentane) (3ai). 31.9 mg of **3ai** obtained as a colorless oil in 78% yield (Scheme 5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, s), 6.56 (2H, s), 3.67 (3H, s), 3.10 (2H, s), 1.98−2.03 (2H, m), 1.79−1.83 (2H, m), 1.58−1.69 (4H, m) 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-QMS) Calcd for $C_{13}H_{16}O_2$ [M]$^+$, 204.1150, found 204.1147.

5-Methoxy-3*H*-spiro(benzofuran-2,1′-cyclohexane) (3aj).[33d] 28.4 mg of **3aj** obtained as a colorless oil in 65% yield (Scheme 5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (1H, s), 6.62 (2H, s), 3.74 (3H, s), 2.92 (2H, s), 1.45−1.78 (10H, m) 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}.

2,3-Dihydro-5-methoxy-2-(phenylthio)benzofuran (3ak).[12a] 103 mg of **3ak** obtained as a colorless solid in 80% yield (Scheme 6): mp 65−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.49 (2H, m), 7.16−7.27 (3H, m), 6.68−6.70 (2H, m), 6.60−6.63 (1H, m), 6.09 (1H, dd, J = 8.8, 4.9 Hz), 3.67 (3H, s), 3.57 (1H, dd, J = 16.6, 8.8 Hz), 3.07 (1H, dd, 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}.

Leaving Group Preferences of the Acetal Unit: Reactions of Quinone Mixed Acetals 1j and 1k with Styrene 2b (Scheme 3). The reactions were performed with the same procedure as described for quinone dimethylacetals **1a−h** in Tables 2 and 3. The selective releases of the methoxy group in the mixed acetals were observed during the reactions. No formation of other dihydrobenzofuran products was confirmed by ^{1}H NMR measurement of the crude reaction mixtures after the reactions.

2,3-Dihydro-5-isopropoxy-2-phenylbenzofuran (3jb). 41.2 mg of **3jb** obtained as a pale-yellow oil in 81% yield (Scheme 3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.43 (5H, m), 6.70−6.78 (3H, m), 5.73 (1H, t, J = 8.8 Hz), 4.36−4.41 (1H, sep, J = 5.8 Hz), 3.58 (1H, dd, J = 15.6, 9.3 Hz), 3.18 (1H, dd, J = 15.6, 8.3 Hz), 1.31 (6H, d, J = 5.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.3, 142.0, 128.6, 127.9, 127.4, 125.7, 116.1, 113.9, 109.1, 84.2, 71.3, 38.8, 22.1 ppm; IR (KBr) 3024, 2976, 2937, 1739, 1604, 1485, 1371, 1218, 1115, 969, 764, 669 cm^{-1}; HRMS (MALDI-TOF) Calcd for $C_{17}H_{18}O_2$ [M]$^+$, 254.1307, found 254.1301.

6,7-Dihydro-6-phenylfuro[2,3-*f*]-1,3-benzodioxole (3kb). 44.3 mg of **3kb** obtained as a white solid in 93% yield (Scheme 3): mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.35 (5H, m), 6.65 (1H, s), 6.56 (1H, s), 5.66 (1H, t, J = 9.0 Hz), 4.46−4.50 (2H, m), 3.48 (1H, dd, J = 15.4, 9.2 Hz), 3.05−3.11 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 153.7, 142.1, 128.6, 127.9, 126.2, 125.7, 125.4, 105.9, 105.8, 84.4, 71.5, 38.8, 30.3 ppm; IR (KBr) 3061, 3029, 2924, 2855, 1739, 1483, 1448, 1311, 1223, 1140, 982, 945, 913, 859, 746, 700 cm^{-1}; HRMS (MALDI-TOF) Calcd for $C_{16}H_{14}O_2$ [M]$^+$, 238.0994, found 238.0988.

[3 + 2] Coupling Reaction of Iminoquinone Acetal 1l with Styrene 2b (Scheme 4). By a similar coupling procedure, the corresponding indoline product **3lb** was obtained in 82% yield from iminoquinone monoacetal **1l**.

2,3-Dihydro-5-methoxy-1-[(4-methylphenyl)sulfonyl]-2-phenylindole (3lb). 62.2 mg of **3lb** obtained as a pale-brown solid in 82% yield (Scheme 4): mp 57−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 8.3 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.10−7.26 (7H, m), 6.72 (1H, dd, J = 8.8, 3.2 Hz), 6.52 (1H, s), 5.19−5.23 (1H, m), 3.69 (3H, s), 3.02 (1H, dd, J = 16.0, 9.7 Hz), 2.72 (1H, dd, J = 15.8, 8.7 Hz), 2.30 (3H, s) 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-QMS) Calcd for $C_{22}H_{21}NO_3S$ [M]$^+$, 379.1242, found 379.1243.

Reaction of QMA 1a with *cis*-Methyl Styrene 2l Leading to a Mixture of *cis*- and *trans*-Dihydrobenzofurans 3al via the Formation of the Intermediate B (Scheme 10). The reaction was examined with the general procedure instead using *cis*-methyl styrene **2l** as the alkene nucleophile. Usually, the mixture of two inseparable dihydrobenzofuran products **3al** (*cis*- and *trans*-isomers) formed in 80% yield as a mixture of two regioisomers (*cis*/*trans* = approximately 30:70) under the stoichiometric conditions using perfluorobenzoic acid. The *cis*/*trans* ratio of the regiomixtures was determined by the ^{1}H NMR measurement by comparison with the authentic samples of *cis*- and *trans*-dihydrobenzofurans **3al**.[33e] The proton alpha to the phenyl group in the *cis*-isomer appeared as a doublet (J = 8.8 Hz) at δ = 5.71 ppm in ^{1}H NMR, while the signal for the *trans*-isomer was observed at δ = 5.06 ppm (d, J = 8.5 Hz).

2,3-Dihydro-5-methoxy-3-methyl-2-phenylbenzofuran (3al, a mixture of *cis*- and *trans*-regioisomers).[33e] 38.5 mg of *cis*- and *trans*-**3al** obtained as a mixture (Scheme 10); Pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.41 (5H, m (*cis* and *trans*)), 7.68−7.81 (3H, m, (*cis* and *trans*)), 5.76 (1H, d, J = 8.6 Hz (*cis*)), 5.11 (1H, d, J = 9.0 Hz (*trans*)), 3.76 (3H, s (*cis* and *trans*)), 3.58−3.68 (1H, m (*cis*)), 3.36−3.43 (1H, m (*trans*)), 1.39 (3H, d, J = 6.8 Hz (*cis*)), 0.78 (3H, d, J = 7.3 Hz (*trans*)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.42, 154.37, 153.25, 153.13, 140.81, 138.09, 133.78, 132.90, 128.57,128.15, 127.55, 126.28, 126.05, 112.87, 112.80, 110.76, 110.06, 109.32, 109.28, 92.60, 87.86, 55.99, 55.97, 45.92, 41.34, 17.83, 16.80 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}.

Catalytic Use of Perfluorinated Terephthalic Acid in [3 + 2] Coupling Reaction of QMAs 1 (Table 5). To a stirred solution of QMA **1** (1.0 mmol) and alkene **2** (1.2 mmol) in dichloromethane (2.5 mL) were successively added HFIP (2.5 mL) and a catalytic amount of

dx.doi.org/10.1021/jo400613z | J. Org. Chem. 2013, 78, 5530−5543

perfluorinated terephthalic acid **h** (12 mg, 0.05 mmol, 5 mol % relative to QMA) in an open flask under ambient conditions. The reaction mixture was then allowed to stir at room temperature or 0 °C for 4−8 h. After confirming the consumption of QMA **1** by TLC, the solution was concentrated by evaporation. Isolation of the [3 + 2] coupling cycloadduct **3** was directly achieved from the residue by flash chromatography on silica gel (hexane/ethyl acetate) to give the pure dihydrobenzofuran product **3**. The yields of the reactions in this procedure are summarized in Table 5.

Synthesis of Benzofuran 4 from the Obtained Coupling Compound 3ak (Scheme 6). The dihydrobenzofuran O,*S*-acetal **3ak** was obtained from QMA **1a** and vinyl sulfide **2k** in 80 and 88% yields, respectively, under the stoichiometric and catalytic conditions. Upon treatments of the obtained dihydrobenzofuran **3ak** with *p*-toluenesulfonic acid in refluxing toluene or the oxidant (*m*-chloro perbenzoic acid), the benzofuran **4** was formed in 80% (23.7 mg) or 69% (20.5 mg) yield, respectively.

5-Methoxybenzofuran (4).[33f] Pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, d, J = 2.0 Hz), 7.31 (1H, d, J = 9.0 Hz), 6.98 (1H, d, J = 2.7 Hz), 6.83 (1H, dd, J = 9.0, 2.7 Hz), 6.63 (1H, d, J = 2.0 Hz), 3.77 (3H, s) 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}.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental and detailed spectroscopic data including ^{1}H and ^{13}C NMR spectra charts for all the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (A) and Encouragement of Young Scientists (A) from JSPS, a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT, and Ritsumeikan Global Innovation Research Organization (R-GIRO) project. T.D. is thankful for financial support from the Asahi Glass Foundation and the Industrial Technology Research Grant Program from NEDO of Japan.

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