Biaryls

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# Coupling of Quinone Monoacetals Promoted by Sandwiched Brønsted Acids: Synthesis of Oxygenated Biaryls**

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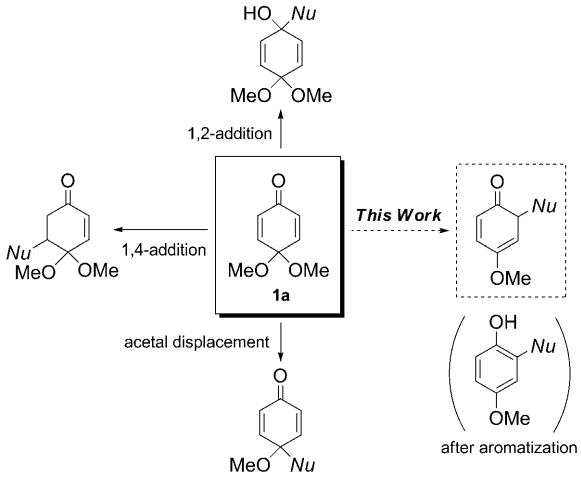
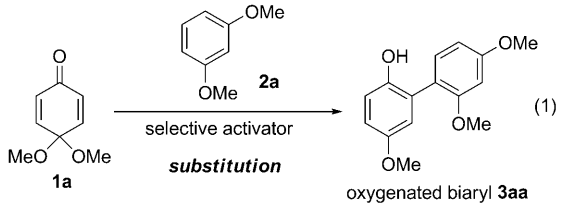
The quinone monoacetal **1a** is a unique molecule having both α,β-unsaturated carbonyl and allyl acetal functionalities in one skeleton (Scheme 1).[1] The structural features of **1a** could potentially lead to a wide array of reactivity, such as, the 1,2-addition to the carbonyl group,[2] conjugated addition to the α,β-unsaturated carbonyl moieties,[3] and others. In contrast to the established addition chemistry of quinone monoacetals regarding the reactivity of the α,β-unsaturated carbonyl group, methods for utilizing the allyl acetal functionality are quite limited for the reactions with nucleophiles. In fact, reactions regarding the introduction of nucleophiles to the allylic position of the acetal units (which also corresponds to the α position of the α,β-unsaturated carbonyl) have rarely been reported,[4,5] thus significant advances in substitution chemistry are possible. Herein, we describe a general protocol for the introduction of nucleophiles to quinone monoacetals by substitution utilizing the unusual protons in polyanions, namely, sandwiched Brønsted acids, as activators. The strategy can provide an attractive new route to the valuable oxygenated biaryl compounds **3** [Eq. (1)].




***Scheme 1.*** Reaction modes of quinone monoacetal **1a** for nucleophiles (*Nu*) based on the four types of electrophilic carbon atoms.




Previously, we studied the reactivity of quinone *O*,*S*-acetals toward aromatic nucleophiles.[6] In the presence of trimethylsilyl triflate (TMSOTf), the quinone *O*,*S*-acetals were activated, and then attack of aromatic nucleophiles occurred at the sulfur atoms in the *O*,*S*-acetals to predominantly give sulfenylated products. We also noted in this investigation that the reactions would be accompanied by an unexpected displacement of the methoxy group at the allyl *O*,*S*-acetal moiety.[6b] The use of the same reaction conditions was thus first envisioned for the quinone acetal **1a**. However, the preliminary experiment of the reaction using **1a** with 1,3-dimethoxybenzene (**2a**) in the presence of TMSOTf in acetonitrile resulted in only trace amounts of **3aa**, which is a substitution product of **1a** and **2a**. Boron trifluoride promoted the expected conjugate addition of **2a** to the α,β-unsaturated carbonyl of **1a** rather than the substitution.[3] The evaluation of magnesium reagents[4a] and typical aluminum Lewis acids, such as $Et_2AlCl$,[4b] did not lead to finding a successful candidate for the substitution. The latter case mainly gave some chlorinated products derived from **1a**. Also, classical Lewis acids ($Ti(OiPr)_4$ and $SnCl_4$) as well as Brønsted acids (AcOH, $CF_3CO_2H$, HCl, triflic acid, and *p*-toluenesulfonic acid at various pH values) were screened in solvents such as dichloromethane, acetonitrile, and hexafluoroisopropanol (HFIP), and in all cases the substituted product **3aa** was not produced in good yield.[7]

Thus, the role of the activator required for the substitution of quinone monoacetals was reconsidered at this stage. We turned our attention to solid acid catalysts derived from earth clays, such as montmorillonites and related polyoxometalates.

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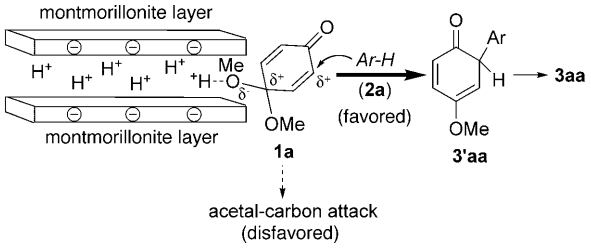
These solid acids are known to consist of higher-order two- and three-dimensional clusters of silicate anions with nanospaces between their layers, in which a number of protons ($H^+$) are absorbed along with polyanion sheets.[8] The unusual protons captured within the interlayers of the solid acids possibly serve as a special Brønsted acid activator of the quinone monoacetal to generate charged species of **1a** that are effectively stabilized by the soft polyanions (Scheme 2).




***Scheme 2.*** Working hypothesis: activation of quinone monoacetal in the montmorillonite layers.

The charged **1a** can thus react with the π-nucleophile **2a** in the allylic manner at the less-hindered carbon atom opposite to the acetal, rather than the sterically encumbered tertiary acetal carbon atom. By using such an activator to produce a smooth and selective substitution of the methoxy group, we hypothesized that the formation of a biaryl **3aa** should occur in good yield via the keto-type tautomer **3′aa**.

Accordingly, we examined the ability of the montmorillonite clays for this type of substitution of the quinone monoacetal **1a** (Table 1). We found that commercial porous montmorillonites (entries 1–4) as well as a series of other solid polyoxometalates, such as the hetero-polyacids (entries 5 and 6), were prominent activators for inducing the unprecedented substitution of **1a**. All of them successfully worked in contrast to the conventional Brønsted and Lewis acids previously tested, but showed unsatisfactory yields of the substitution product **3aa**. Motivated by these significant results, we then optimized the reaction conditions using the MT clay. It is widely accepted that the interlayer distances of the silicate sheets in the montmorillonites expand upon soaking polar solvents.[9] Furthermore, leaching of the interlayer protons should be suppressed in less basic solvents.[10] Thus, one interesting approach to be tried was a screening of protic and polar solvents. For such solvents matching the proposed activation mode of MT clays toward the quinone monoacetal, some fluoroalcohols (e.g., HFIP)[11,12] were found to be applicable, thus yielding the substitution product **3aa** in better yield (entry 7). A mixed solvent system with $CH_2Cl_2$ was finally selected because of the solubility of the reactants in HFIP (entry 8). The once-used insoluble MT clay could be easily removed by filtration from the reaction mixture and recycled without any loss of activity at for at least three cycles; this recyclability excludes participation of some leached species from the MT clay serving as a catalyst during the reaction. Needless to say, no reaction was observed in the absence of the MT clay, and the reactions were sluggish using non-polyoxometalate acids, such as Nafion-H and Amberlyst-15 sulfonic acid resins.

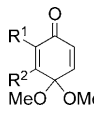
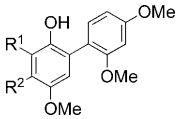
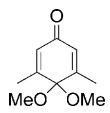
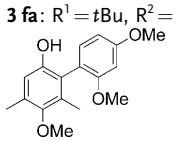
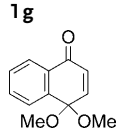
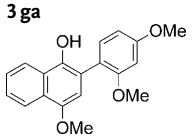
By using the optimized reaction conditions, the influence of the quinone monoacetal structures on the reaction was investigated by using 1,3-dimethoxybenzene **2a** as a model nucleophile (Table 2). Gratefully, we concluded that the ring structures of the quinone monoacetals **1b–h** did not alter the activation mode of the MT clays because the reactions proceeded. Thus, the reactions of **1b–d** having a methyl (entry 1), bulky *tert*-butyl (entry 2), and methoxy (entry 3) group at the neighboring carbon atoms of the acetal group were comparable to that of the simple substrate **1a**, thus giving rise to the desired biaryls **3ba–3da** in good yields. The introduction of **2a** exclusively occurred at the less hindered positions regarding the two allyl acetal moieties in the compounds **1b–d**. Otherwise, the 3,5-dimethyl alternative **1g** could react with **2a** to give a more congested biaryl **3ga** (entry 6). Ring substituents at the α-carbon atom of the

***Table 1:*** Effect of solid acids in the reaction of **1a** and **2a**.[a]

| Entry | Solid acid | Yield of **3aa** [%][b] |
|---|---|---|
| 1 | M-K10 | 44 |
| 2 | M-K5 | 41 |
| 3 | M-KSF | 35 |
| 4 | montmorillonite[c] | 45 |
| 5 | $H_3[PW_{12}O_{40}]\cdot H_2O$ | 43 |
| 6 | $H_4[SiW_{12}O_{40}]\cdot H_2O$ | 35 |
| 7[d] | montmorillonite[c] | 82 |
| 8[e] | montmorillonite[c] | 90 |

[a] Reactions were examined using **1a** and **2a** (2 equiv) in the presence of solid acids (10 mg relative to 1 mL solvent) in $CH_2Cl_2$ at room temperature for 3 h unless otherwise noted. [b] Yield of isolated product. [c] Aluminum pillared clay (purchased from Aldrich). [d] HFIP was used. [e] Mixed solvent system of HFIP and $CH_2Cl_2$ (10:1) was used.

***Table 2:*** Coupling reactions of various quinone monoacetals **1**.[a]

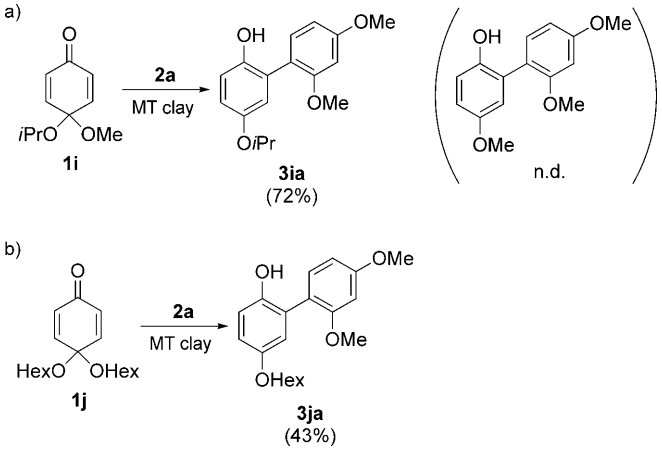
| Entry | Quinone monoacetal **1** | Product **3** | Yield [%][b] |
|---|---|---|---|
| |  |  | |
| 1 | **1b**: $R^1=H$, $R^2=Me$ | **3ba**: $R^1=H$, $R^2=Me$ | 78 |
| 2 | **1c**: $R^1=H$, $R^2=t$Bu | **3ca**: $R^1=H$, $R^2=t$Bu | 67 |
| 3 | **1d**: $R^1=H$, $R^2=OMe$ | **3da**: $R^1=H$, $R^2=OMe$ | 87 |
| 4 | **1e**: $R^1=Cl$, $R^2=H$ | **3ea**: $R^1=Cl$, $R^2=H$ | 76 |
| 5 | **1f**: $R^1=t$Bu, $R^2=H$ | **3fa**: $R^1=t$Bu, $R^2=H$ | 99 |
| 6 |  |  | |
| | **1g** | **3ga** | 76 |
| 7 |  |  | |
| | **1h** | **3ha** | 72 |

[a] Reactions were be performed in an open flask using the conditions of entry 8 in Table 1 and MT clay. [b] Yield of product isolated after purification of the crude reaction mixture.

carbonyl were also not problematic, as exemplified by compounds **1e** and **1f** (entries 4 and 5). The use of the naphthoquinone acetal **1h** should be also noted. These results, to the best of our knowledge, are the first general substitutions of quinone monoacetals with accompanying carbon–carbon bond formation using MT clay.

Diversity of the acetal portion is intriguing regarding the preparation of quinone monoacetals **1**, a process which is quite distinct from the usual acetals.[1] Important information for the present substitution was obtained by using the mixed acetals of **1a** (Scheme 3). The mixed acetal **1i** would, under




***Scheme 3.*** Unique leaving group preferences of the acetal units using a) **1i** and b) **1j** as substrates. n.d. = not determined (below 3% yield).

the standard reaction conditions, only give the biaryl product **3ia** that has an isopropoxy group (Scheme 3a). This accounted for the high leaving group preference of the methoxy group over the larger one. Similarly, a low reaction efficiency was observed in the reaction of **1j** having longer alkyl acetal, thus resulting in a somewhat poor conversion (Scheme 3). These unique leaving group effects of the acetals in **1i** and **1j** were in good agreement with the expected direction of the quinone monoacetal molecules in the MT clay interlayers during their activation, as pictured in Scheme 2.

The aromatic nucleophilic partners **2**, which should have access from the outer-sphere surface of MT clays to interrupt the quinone monoacetal **1** in the clay silicate sandwich, would not limit the scope of the reactions based on our activation concept (Table 3).[13] The oxygenated aromatics **2** could indeed be varied without significant decrease in the biaryl yields in most cases, as seen in **2b–d** toward the quinone monoacetal **1a** (entries 1–3). Although the use of the bulky **2e** tended to circumvent the reaction progress, formation of the biaryl **3ae** that possesses a bulky trimethylsilyl group *ortho* to the biaryl linkage was observed (entry 4). The naphthalene ring of **2f** was reactive at the hindered position (entry 5). The reaction of the phenol **2g** could proceed, and provide a unique hydrophilic biaryl molecule, that is, **3ag** (entry 6). Through extensive investigations, it was clarified that our strategy based on the reagent control of reactivities of quinone monoacetals could afford the highly oxygenated

***Table 3:*** Scope of aryl nucleophiles **2**.[a]

| Entry | Aryl nucleophile **2** | Product **3** | Yield [%][b] |
|---|---|---|---|
| 1 | **2b**: R′ = OMe | **3ab**: R′ = OMe | 82 |
| 2 | **2c**: R′ = Me | **3ac**: R′ = Me | 77 |
| 3 | **2d**: R′ = Br | **3ad**: R′ = Br | 70 |
| 4 | **2e**: R′ = TMS | **3ae**: R′ = TMS | 61 |
| 5 | **2f** | **3af** | 80 |
| 6 | **2g** | **3ag** | 82 |

[a] Reactions were performed in an open flask using quinone monoacetal **1a** and alkoxy arenes **2b–f** or phenol **2g** under the conditions of entry 8 in Table 1 and with MT clay. [b] Yield of product isolated after purification of the crude reaction mixture. TMS = trimethylsilyl.

biaryl families **3** from the quinone monoacetals **1** and oxygenated aromatic rings **2**.

The oxygenated biaryls frequently occur in nature as polyketides, terpenes, lignanes, coumarins, fravonoides, tannins, and many alkaloids,[14] and the natural compounds that show interesting biological properties are considered to be attractive targets. Our new method of synthesizing biaryls involves synthetic handles to obtain them. As part of this study, we recognized that the mixed naphthol/phenol coupling compound **A** would provide a common synthetic module for producing gilvocarcins (Figure 1). Gilvocarcins have a highly oxygenated naphtho[*b*,*d*]benzopyran-6-one structure containing C4 glycosides with a minor change in the C8 substituent. Several studies that require the absence of the sugar moiety for investigating the bioactivities have prompted many synthetic efforts for forming the defucogilvocarcins.[15] In all the syntheses to date, the strategies highlighted as key steps involve the construction of the biaryl linkage to obtain the orthogonally oxygenated precursors.

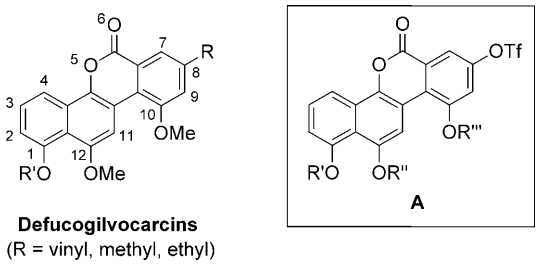
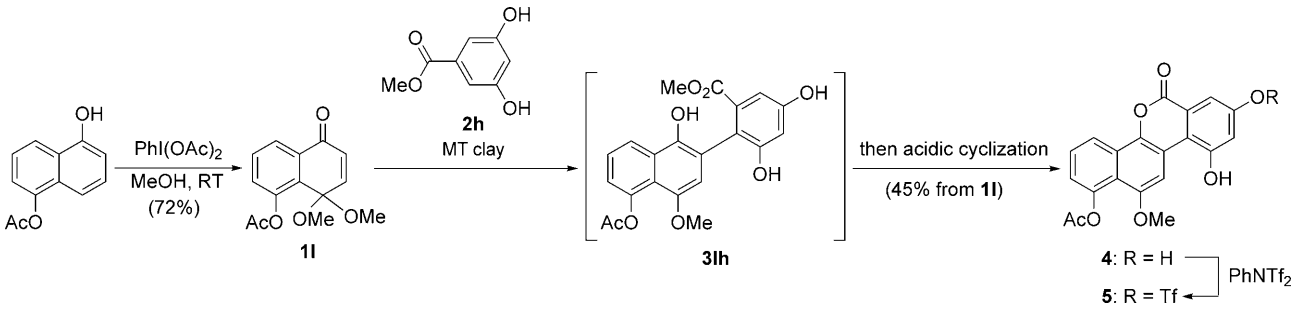



***Figure 1.*** Defucogilvocarcins and their key core structure **A** as orthogonally oxygenated precursors.




***Scheme 4.*** Short synthesis of gilvocarcin intermediates using commercially available **2h**.

The naphthobenzopyran-6-one structure of the defucogilvocarcins was envisioned to arise from the coupling reaction of the naphthoquinone monoacetal **1l** and commercial aromatic nucleophile **2h** using MT clay with subsequent lactonization of the formed biaryl **3lh** (Scheme 4). Accordingly, we prepared the acetal **1l** from a readily available desymmetrized 1,5-dinaphthol, and confirmed the strategy. To our delight, it was shown that the formation of the biaryl **3lh** from **1l** and **2h** using the our method and subsequent cyclization of **3lh** proceeded in one pot. Work-up of the crude reaction mixture afforded the tetracyclic compound **4** including the highly oxygenated target core. Finally, all oxygen atoms were fully differentiated by selective monotriflation of the phenol oxygen atom to achieve the very short synthesis of the Snieckus-type[15a] tetracyclic **5** of defucogilvocarcins. Thus, this convergent route provides facile access to not only the natural products, but also to nonnatural type analogues with the aim for biological screening.

In summary, we have succeeded in controlling the reactivities of quinone monoacetals **1** based on a new activation strategy to realize an unprecedented substitution by nucleophiles. The synthetic utility of the reagent-controlled strategy has been proved by the highly oxygenated mixed biaryl products **3** as well as the tetracyclic compound **4**, the common synthetic intermediate of the natural products. The key to the transformation largely relies on the indispensable involvement of the solid acids, that is, montmorillonites, providing unusual protons ($H^+$) for the selective activation of acetal moieties in combination with the stabilizing effect of the persistent polyanions for generation of the charged species of the the quione monoacetals **1** and protection around the electrophilic acetal carbon atom.

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**Keywords:** biaryls · C–C coupling · chemoselectivity · heterocycles · natural products

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