Reagent-Controlled [3+2] Coupling of Quinone Monoacetals with Alkene Nucleophiles

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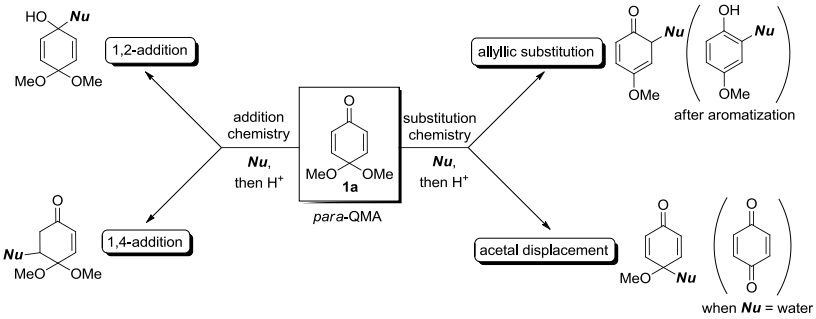
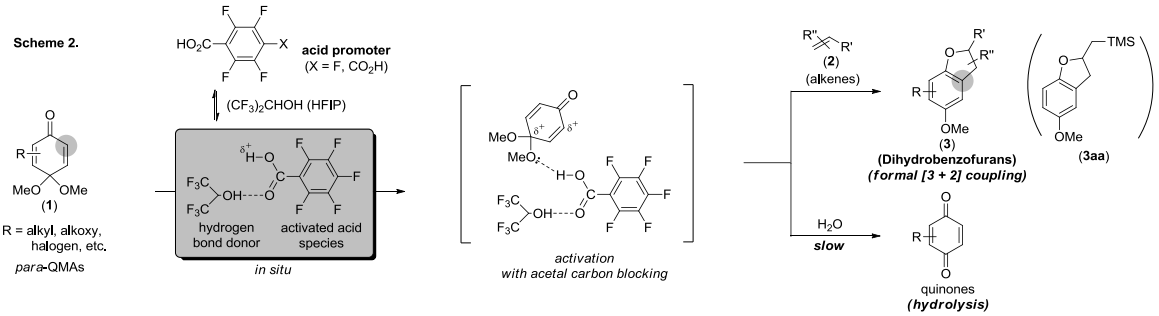
【Purpose】Quinone monoacetal (QMA) **1** is a desymmetrized and mono-protected quinone compound, which possesses synthetically useful privileged bifunctionalities of unsaturated carbonyl and allylacetal moieties in one skeleton.[1] Encouraged by the synthetic utility regarding the promising solutions to the chemo- and regio-selectivity issues of quinone compounds based on its electronically differentiated enone and allylacetal moieties, a wide array of reactivities toward nucleophilic attack on QMAs **1** was already revealed to produce the addition reactions with hard or soft nucleophiles (Scheme 1), for instance, additions to the carbonyl carbon and conjugated additions. However, strategies for utilizing the allylacetal functionality as an electrophilic unit for the success of substitution reactions are quite limited.[2] In this proceeding, we herein developed an efficient reagent-controlled strategy for [3+2] couplings of QMAs **1** with a series of nucleophilic alkenes **2**, which is triggered by the particular use of the catalytic system of the specific perfluorinated acids by the coordination of the hydrogen bond donor solvent, fluoroalcohol, for in situ generation of pre-activated catalytic species in equilibrium (Scheme 2).



Scheme 1. Reactivities of QMAs **1a** toward nucleophiles based on the four electrophilic carbons.



【Results and Discussion】To validate the potency of various proton promoters, we initially examined the [3+2] coupling of QMA **1a** with allyltrimethylsilane **2a** along with solid acid, montmorillonite (MT)[2], or acetic acid in a mixed solvent with hexafluoroisopropanol (HFIP) (Table 1, entries 1 and 2). However, the yields were moderate and long reaction times were needed for the consumption of the QMA **1a**. Considering the pKa values, accordingly, several types of acid activators including a series of carboxylic acids were systematically evaluated (Table 1). The results indicated that only the carboxylic acids with suitable acidic proton strength showed good performance in order to develop the coupling (entries 3-7), among which pentafluorobenzoic acid (PFBA) (p*K*a: ca. 1.5-1.6) especially gave the most promising results regarding

Table 1. Effect of the acid activators for the [3 + 2] coupling [a]

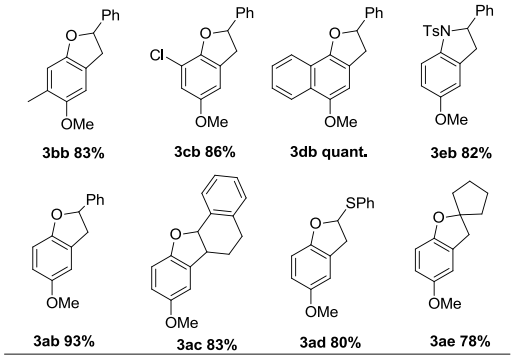
entry	activator[b]	solvent	time	yield of **3aa**
1	montmorillonite	HFIP/DCM=10:1	1 day	61%
2	acetic acid	//	2 h	19%
3	benzoic acid	//	2 h	9%
4	4-nitrobenzoic acid	//	2 h	14%
5	***pentafluoro benzoic acid***	//	10 min.	84% ***90%***[c]
6	2,4,6-trichloro benzoic acid	//	10 min.	59%
7	phthalic acid	//	10 min.	58%
8	trifluoromethane sulfonic acid	//	1 day	n.d.
9	$BF_3 \cdot Et_2O$	//	1 h	25%

[a] Unless otherwise noted, reactions were conducted with 2 equiv. of acid, 5 equiv. of allyltrimethylsilane **2a** at room temperature. [b] Tested Brönsted acids were arranged by the pKa vaule. [c] Acid (1 equiv.) and **2a** (2 equiv.) at 0 °C

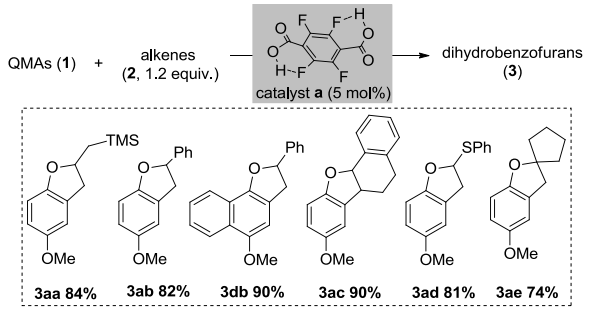
not only the product yield but also the observed production rate and reaction purity with complete regio-selectivity by the catalysis of this specific controlling fluorinated acid (entry 3).

With the established acid promoter and reaction conditions in hand, the scopes of both QMAs **1** and various alkene coupling partners **2** were evaluated for identifying the versatility of this coupling method. It is clearly indicated that many coupling patterns with different substituents in this [3+2] coupling reaction would not limit the reaction scope (Figure 1), giving the desired coupling products **3** in good to quantitative yields. The results especially included important structure of indoline derivatives (**3eb**), pterocarpan-type fused dihydrobenzofuran (**3ac**), cyclized O,S-acetal products (**3ad**), as well as the spirocyclic compounds (**3ae**).

Figure 1. Examples of Substrates Scope



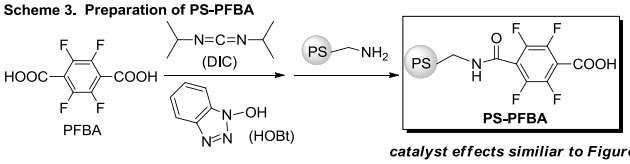
In spite of the general success of the above-mentioned results, several limitations still remained in this coupling reaction from the practical view. A stoichiometric amount of the PFBA and excess uses (over 2 equiv.) of alkenes **2** were usually needed for the complete conversion of the reaction using perfluorobenzoic acid. To our delight, further modifying the functionality at the ring positions of the set of more acidic fluorinated phthalic acids, the isomer of acid **a** (Scheme 2) led to finding of an excellent catalytic alternative, which showed a best catalytic performance at less than 5 mol% loading together with the significantly improved stoichiometry of the alkenes **2** (lowering to 1.2 equiv.). The catalyst **a** was capable of providing the coupling products **3** in comparative results to that of its counterpart (PFBA) while still maintaining the complete regioselectivities with the promising generality of the reaction scope.



Scheme 2. catalystic results of products **3** by using perfluoroterephthalic acids **a**

In addition, a solid proton by attaching the proton function to an insoluble polymer was newly developed as recyclable alternative to PFBA as acid promoter in this coupling reaction. This developed reusable solid-type alternative that was synthesized by the one-pot amide formation (Scheme 3), could also smoothly induce this coupling reactions with a similar efficiency to the counterpart itself and is also highly amenable for being recovered in multiple runs without any loss of reactivity.[4a]

Scheme 3. Preparation of PS-PFBA



catalyst effects similiar to Figure 1

【Summary】 A complete regio-specific [3+2] coupling of QMAs **1** with a variety of carbon π-nucleophiles **2** by the reagent control strategy with the specific fluorinated acid promoters in combination with the transition state stabilizing solvent, HFIP, has been successfully developed to provide diverse dihydrobenzofuran products **3** and derivatives with high yields up to quantitative under mild conditions in short reaction times. In particular, the minimal loading of the perfluorinated acid, development of this recyclable polymer-immobilized acid, the use of the readily available substrates, and the deep understanding of the reaction scope, especially, with the highly regioselectivity manner by the reagent control strategy have made this coupling very fascinating from a practical view. By utilizing this strategy, We recently challenge concise preparation of several oligomers of dihydrobenzofurans **3** for further applications.

【References】

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