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# A new arylation of silyl enol ethers by quinone monoacetal substitution

Toshifumi Dohi, Tohru Kamitanaka, Hitoho Takamuro, Yusuke Mishima, Naohiko Washimi, Yasuyuki Kita *

*College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu, Shiga 525-8577, Japan*

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Dedicated to the memory of Professor Harry H. Wasserman

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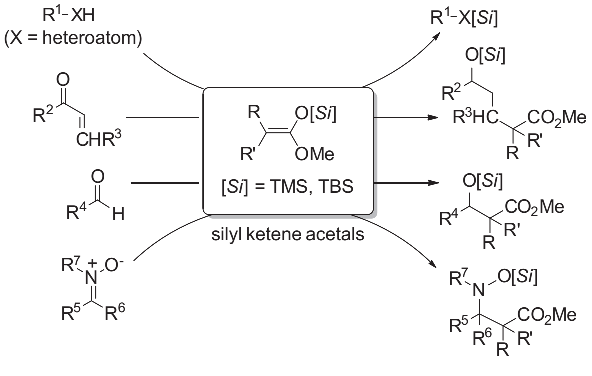
## ABSTRACT

Quinone monoacetals (QMAs) were found to be convenient substrates for a unique arylation reaction of enol silyl ethers. This arylation process of QMAs typically proceeds through the acetal activation of the QMAs by a hydrogen-bond donor solvent, such as a fluoroalcohol, for the initiating step. The silyl transfer from silyl enol ethers to the carbonyl oxygen of the QMAs appears to be involved in the C–C coupling step, followed by QMA aromatization. By this method, valuable α-aryl carbonyl compounds containing *o*-phenol moieties can be obtained directly under mild conditions without lactone formation.

Ketene acetal derivatives such as silyl enol ethers[1a–c] and alkoxy vinyl esters[1d,e] belong to the family of O-functionalized enols of esters. Upon nucleophilic attack on the silyl or acyl group, they easily revert to the stable original ester. By taking advantage of this powerful driving force and the attractiveness of having only the ester as a coproduct, these ketene acetal derivatives have been used since the 1970s as efficient and clean silyl and acyl group transfer agents in organic synthesis, as first reported by our research group.[2–8] Indeed, more than 40 years ago our research group first pioneered the silyl transfer chemistry for the direct and efficient silylations of alcohols, carboxylic acids, mercaptans, and amides under very mild conditions by utilizing O-silylated ketene acetals.[3,4] These silyl group transfer processes were further applied to carbon–carbon bond-forming reactions, that is, 1,4-addition to α,β-unsaturated ketones,[5] 1,2-additions to aldehydes,[6] and 1,3-additions to nitrones,[7] all of which involved activation of the enolate through the transfer of the silyl group to the nucleophilic oxygen of the coupling partner. These addition reactions proceed even without the presence of an external activator or catalyst (Scheme 1). Thanks to advances in the synthetic routes to alkoxy vinyl esters,[9] these compounds have become more readily available. Similarly, we have also reported the acyl group transfer ability of alkoxy vinyl esters in the 1980s and applied this process to organic syntheses.[8]



**Scheme 1.** Ketene silyl acetals as versatile silyl transfer agent in organic transformations. (TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl).

As a continuation of our research, we became interested in the possibility of new carbon–carbon forming reactions of these ketene silyl acetals and silyl enol ethers and the synthetic applications of this chemistry. We focused our efforts on a new α-arylating

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* Corresponding author. Tel./fax: +81 (77)5615829.
*E-mail address:* kita@ph.ritsumei.ac.jp (Y. Kita).

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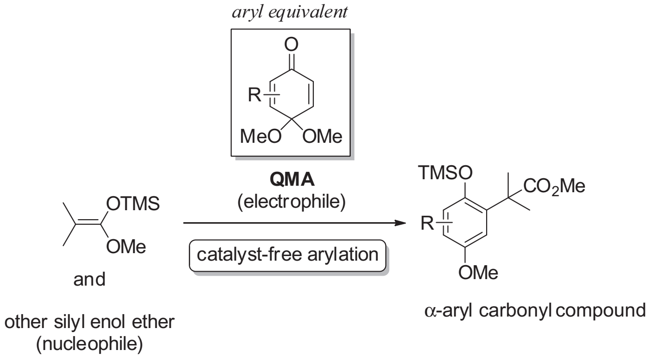
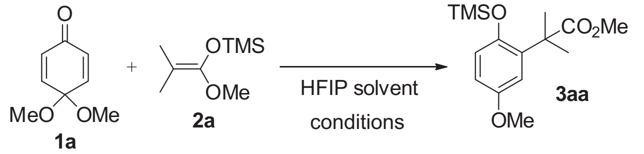


**Scheme 2.** A new α-arylation strategy by quinone monoacetal (QMA) substitution utilizing silyl enol ethers.

**Table 1**
Screening of the conditions for arylation using QMA **1a**



| Entry[a] | Acid (equiv) | Time (h) | Yield[b] of **3aa** (%) |
|---|---|---|---|
| 1 | Perfluoroterephthalic acid (0.05) | 1.5 | 72 |
| 2 | Perfluoroterephthalic acid (0.5) | 1.5 | Complex |
| 3 | Pentafluorobenzoic acid (1) | 3 | 45 |
| 4 | Acetic acid (1) | 3 | 81 |
| 5 | None | 24 | 91 |
| 6[c] | None | 24 | 95 |
| 7[d] | None | 24 | 89 |
| 8[e] | None | 24 | 43 |

[a] The reactions were examined using QMA **1a** (1 equiv) and silyl enol ether **2a** (2 equiv) in a mixture of hexafluoroisopropanol (10 mL relative to 1 mmol of QMA **1a**) and dichloromethane (1 mL relative to 1 mmol of QMA **1a**) at 0 °C unless otherwise noted.

[b] Isolated yield based on QMA **1a** used.

[c] HFIP/DCM = 5.5 mL/5.5 mL.

[d] HFIP/DCM = 1 mL/10 mL.

[e] Dichloromethane (**1a**: 0.10 M) was used as solvent together with 2 equiv of HFIP.

method of carbonyl compounds under mild and metal catalyst-free conditions, following our recent studies of the substitution chemistry of quinone monoacetals (QMAs).[10] These quinone derivatives have been found to react as powerful and regiospecific electrophiles, their reaction being followed by rapid rearomatization.[11,12] Accordingly, we now report the first results of an extended study of a new coupling reaction of silyl enol ether nucleophiles with QMAs, facilitated by a strong hydrogen-bond donor solvent, that is, a fluoroalcohol, under mild conditions (Scheme 2).[13]

Since the discovery of the Mukaiyama-aldol reaction, the use of silyl enol ethers has greatly expanded beyond the scope of the aldol reaction to form new complex products.[14] As part of these efforts, the α-arylation of carbonyl compounds utilizing silyl enol ethers has emerged as a powerful synthetic process.[15] Since α-aryl carbonyl motifs are present in a large number of nature-made molecules and fine chemicals, introducing aryl moieties to keto compounds, or rather to a form of the corresponding metal enolates, has been intensively studied. In particular, the transition metal-catalyzed coupling strategies employing aryl halides and related electrophiles were the focus of much attention during the early stages of research in this area.[16] New synthetic developments for this reaction have involved the uses of silyl enol ethers as convenient equivalents of these basic enolates, because of their characteristics as stable, neutral, and regiocontrolling nucleophiles.[17]

These silyl nucleophiles have been found to be effective in several metal catalyst-free approaches for providing α-arylated carbonyl compounds,[18] though the methods were limited only to specific types of aryl substrates, that is, activated aryl electrophiles, such as diaryl iodonium salts, arylbismuth agents,[19] among others.[20,21]

We recently developed conditions for the substitution reactions of QMAs promoted by Brønsted acids in a specific solvent, hexafluoroisopropanol (HFIP), for the coupling reactions with aromatic and alkene nucleophiles.[11,12] QMAs are readily available, mono-protected quinone derivatives, which have recently attracted interest due to their broad utility in selective organic transformations, effectively acting as desymmetrized quinones.[10] Hence, we started our QMA arylation study of silyl enol ethers in order to establish a new arylation process for the production of α-arylated carbonyl compounds under metal catalyst-free conditions by examining our reported reaction conditions, that is, the use of perfluorinated benzoic acids in HFIP (Table 1).[22] As expected, the coupling of the representative QMA **1a** with ketene silyl acetal **2a** proceeded smoothly under our standard conditions in the fluoroalcohol solvent in the presence of a catalytic amount of phthalic acids (5 mol %),[12c] producing the α-aryl ester **3aa**,[23] accompanied by silylation of the phenol group, in 72% yield (entry 1). Interestingly, the corresponding lactone was prevented by the O-silylation of the phenol. This coupling rapidly proceeded at room temperature, and the reaction went to completion in 1.5 h. Consistent with our previous observations,[11,12] the nucleophile **2a** attacked the QMA **1a** selectively at the α-position of the carbonyl group and did not touch the other electrophilic ring carbons of QMA **1a**.[24] To further improve the yield, we then examined the stoichiometric use of acid activators. However, this attempt to use perfluorinated terephthalic and benzoic acids[12a,b] failed, resulting in drastic decreases in product yields, despite the complete consumption of both reaction substrates **1a** and **2a** (entries 2 and 3). Based on these experiments, we concluded that the low yields were probably caused by the degradation of the acid-labile ketene silyl acetal **2a** by the action of the acids, thereby preventing the desired coupling reaction of QMA **1a** and silyl nucleophile **2a**. This situation prompted us to study a milder reaction system with a weaker Brønsted acid. Hence, acetic acid was used as the activator instead of the above-mentioned stronger acids, and to our delight, we observed complete consumption of QMA **2a** after stirring in HFIP for 3 hours and the product was obtained in good yield (entry 4). At that time, we were also aware of the formation of some product **3aa** in the absence of catalyst, presumably promoted by the hydrogen-bond donating fluoroalcohol medium, HFIP. The reaction progress in the absence of the acid additives was thus monitored by TLC. We reasoned that the fluoroalcohol as a solvent or possibly even as an additive could act as a promoter for the coupling of the silyl enol ether **2a** with QMA **1a**. In the event, using HFIP either as a solvent or additive, with QMA **1a** concentrations ranging from 0.10 to 0.01 M, provided the product **3aa** in good yields (entries 5 and 6), however decreasing the proportion of HFIP with respect to the dichloromethane solvent caused the yield to significantly drop (entry 7). Needless to say, no reaction was observed in the absence of HFIP. Other reaction factors, such as concentration (doubling and halving the amount of the solvents) and temperature (0 °C), had little influence on product formation and yield. However, as in the reported metal-catalyzed reactions,[17] this metal catalyst-free method was similarly sensitive to the stoichiometry of the silyl enol ether **2a**, and the product **3aa** was obtained in very low yield when employing an equimolar amount of the ketene silyl acetal **2a** with QMA **1a**. According to our careful examinations, the use of other activators ($Et_2AlCl$, $SnCl_4$, $PtBr_4$, $BF_3 \cdot Et_2O$, TMS-triflate)