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Tin Tetrachloride-Catalyzed Regiospecific Allylic Substitution of Quinone Monoketals: An Easy Entry to Benzofurans and Coumestans

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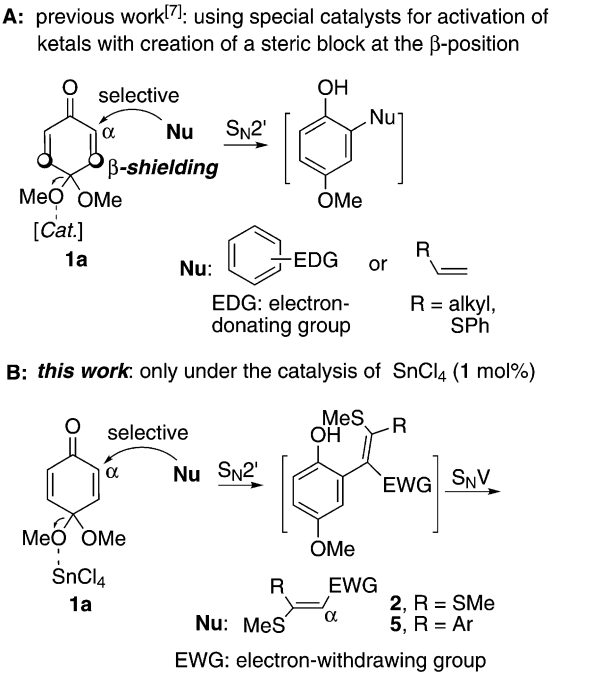
Abstract: A highly regioselective allylic substitution of quinone monoketals with α-oxoketene dithioacetals is achieved under the catalysis of only tin tetrachloride (1 mol%). The advantages of the reaction, including its simplicity, rapidity, low catalyst loading of inexpensive tin tetrachloride, mild conditions and; in particular, the regiospecificity, is proposed to be due to a pseudo-intramolecular process. This new synthetic method provides a facile [3+2]cycloaddition route to benzofurans and is highlighted by the synthesis of coumestans.

Keywords: allylic substitution; cycloaddition; heterocycles; quinone monoketals; regioselectivity

The achievement of complete chemo- and regioselectivity is a major issue in synthetic organic chemistry.[1] In the reactions of quinone monoketals bearing both enone and allyl ketal functionalities (such as, **1a** in Scheme 1) with nucleophiles, 1,2- and 1,4-additions at the enone moiety are dominant.[2] Additionally, their synthetic potential has also been exploited in double conjugate additions,[3a] Diels–Alder reactions[3b] and Deslongchamps annulations.[3c] In contrast, thedirect addition to the α-position of their enone moiety leading to the allylic substitution (S_N2') products has been seldom reported.[2,4–6]

It was found that the reaction of quinone monoketals with vinyl sulfide in acetate acid could proceed in the allylic manner but with unimpressive efficiency.[5] Sartori realized an S_N2' reaction of quinone monoacetals and phenols in the presence of a stoichiometric amount of $EtAlCl_2$ leading to the coupling products only in 25–60% yields.[6] Significantly, an attractive strategy has been established recently for controlling the regioselectivity of the S_N2' reactions of quinone monoketals with electron-rich arenes[7a,c] or alkenes[7b] (Scheme 1, **A**). In these reactions, the ketal moiety was required to be activated, depending on the nature of nucleophiles, by an unusaul sandwiched solid acid,[7a] a Brønsted acid activated by a hydrogen bond donor (perfluorinated alcohol)[7b] or by a Pt(IV)-aqua complex.[7c] The high selectivity of these reactions is believed to lie in the steric block of the β-position arising from the activation, which leads to an attack of nucleophiles at the less hindered α-carbon of quinone monoketals.[7] This strategic protocol proved to be efficient and has been successfully applied in the synthesis of natural products.[7a,c] Undoubtedly, a new

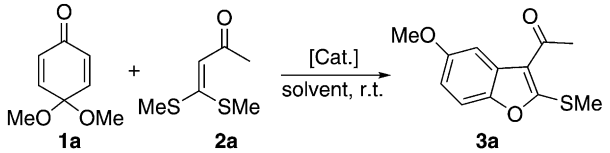


Scheme 1. Regiospecific S_N2' reactions of quinone monoketals.

method for selective S_N2' reactions of quinone monoketals that can be applied to a range of different classes of nucleophiles, especially allowing access to valuable chemicals, is desired but remains a challenge.

During our ongoing interest in ketene dithioacetal chemistry,[8] the nucleophilicity of the α-carbon atom of functionalized ketene dithioacetals (for example, **2** in Scheme 1) has been well recognized.[9,10] Taking into consideration the versatile reactivity of quinone monoketals **1** as electrophiles and ketene dithioacetals **2** as nucleophiles, the reaction between **1** and **2** was examined in this work. Surprisingly, the addition of **2a** to **1a** in an initial attempt exclusively occurred at the α-position of **1a** followed by an intramolecular S_NV[8,9] reaction to afford benzofuran **3a** in nearly quantitative yield under the catalysis of only 1 mol% of $SnCl_4$ (Table 1, entry 1). In sharp contrast to the previous work[5–7] in which usual acidic catalysts, including $SnCl_4$, proved to be inefficient for the S_N2' reactions of quinone monoacetals, the simple $SnCl_4$-catalyzed reaction in our experiment shows high reactivity and regiospecificity without the assistance of the steric block of the β-position. This might indicate a new catalytic reactivity mode in this catalytic process. Thus, the scope of the reactions was investigated in detail. In this communication, we describe this new S_N2' reaction between quinone monoketals and α-oxoketene dithioacetals under the catalysis of a classical Lewis acid (Scheme 1, **B**). The method allows a rapid and regiospecific synthesis of substituted benzofurans[11] and is highlighted by the one-pot preparation of bioactive coumestans[12] under mild conditions.

Table 1. Screening the acid catalysts for the reaction.[a]



1a **2a** **3a**

Entry	Cat. (equiv.)	Solvent	Time	Yield [%][b]
1	$SnCl_4$ (1%)	MeCN	10 min	99
2	$SnCl_4 \cdot 5H_2O$ (1%)	MeCN	5 min	94
3	$SnCl_4$ (0.5%)	MeCN	24 h	54[c]
4	$TiCl_4$ (1%)	MeCN	24 h	nr[d]
5	$CuBr_2$ (1%)	MeCN	24 h	nr[d]
6	TFA (1%)	MeCN	24 h	nr[d]
7	HBr (1%)	MeCN	24 h	nr[d]
8	HBr (10%)	MeCN	24 h	nd[e]
9	$SnCl_4$ (1%)	CH_2Cl_2	20 min	92
10	$SnCl_4$ (1%)	THF	24 h	nr[d]
11	$SnCl_4$ (1%)	DMF	24 h	nr[d]
12	$SnCl_4$ (1%)	MeOH	24 h	nr[d]

[a] *Reaction conditions:* **1a** (0.45 mmol), **2a** (0.25 mmol), solvent (3 mL).
[b] Isolated yields.
[c] **2a** was recovered in 41% yield.
[d] No reaction.
[e] Not detected. Only a trace amount of a complex was detected in this case.

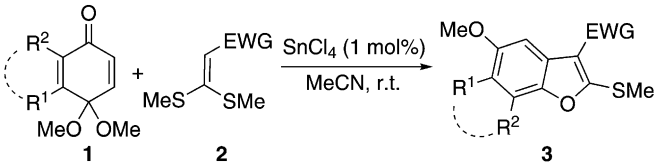
Initial investigations (Table 1) showed that benzofuran **3a** was obtained in excellent yields from the reaction of **1a** (0.45 mmol) with **2a** (0.25 mmol) in dry acetonitrile at room temperature for 5–10 min in the presence of $SnCl_4$ (1 mol%, entry 1) or $SnCl_4 \cdot 5H_2O$ (1 mol%, entry 2). Interestingly, $TiCl_4$ was found to be an ineffective catalyst for this allylic substitution initiated [3+2]cycloaddition under identical conditions (entry 4). $CuBr_2$, trifluoroacetic acid (TFA), especially hydrobromic acid which proved to be able to significantly improve the nucleophilicity of ketene dithioacetals,[9c] were inefficient as well (entries 5–8). It was found that decreasing the amount of $SnCl_4$ led to a lower yield and longer reaction time (entry 3). Among the solvents examined, acetonitrile was the best. Benzofuran **3a** was also obtained in high yield with dichloromethane as the solvent (entry 9). However, no reaction was observed in THF, DMF and MeOH, respectively (entries 10–12).

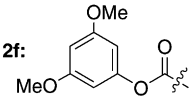
The successful synthesis of **3a** provides a new and mild route to substituted benzofurans.[11] More importantly, it exhibits a highly efficient and regiospecific S_N2' reaction never before associated with quinone monoketals under normal acidic conditons.[5–7] Thus, the optimal reaction conditions (Table 1, entry 1) were applied to assess the scope of the reaction. As described in Table 2, **1a** could react smoothly with **2** having a wide range of electron-withdrawing groups (EWG), including acetyl (**2a**), benzoyl (**2b**), cinnamoyl (**2c**), cyano (**2d**), and alkoxycarbonyl (**2e**), to give the desired polysubstituted benzofurans **3a–e** in 83–99% yields (entries 1–5). To test the generality of the quinone monoketal components, substrates **1** bearing either electron-withdrawing or electron-donating substituents were explored. Pleasingly, all the reactions of **2a–e** with 2-bromoquinone monoketal **1b** could give benzofurans **3f–j** in high yields (entries 6–10). In addition, the reaction was further extended to the synthesis of benzofurans **3k–q** in high to excellent yields from the corresponding **1c–f** and **2a–e** (entries 11–17).

Remarkably, all of the above reactions proceeded very rapidly, reaching completion within 20 min (Table 2). In the cases of using α-cinnamoyl dimethyl thioacetal **2c** as substrate, 3 mol% of $SnCl_4$ were often required to provide higher yields (entries 3, 8 and 14). Whereas, under identical conditions, no desired product **3r** was detected when the reaction of **1a** with ketene dithioacetal **2f** having a bulky 3,5-dimethoxyphenoxycarbonyl group was carried out[13] even using up to 10 mol% of $SnCl_4$ for 12 h (entry 18).

Encouraged by the successful synthesis of polysubstituted benzofurans **3**, the reaction between quinone monoketals **1** and vinylogous thioester **5**[14] was exam-

Table 2. Synthesis of substituted benzofurans **3**.[a]

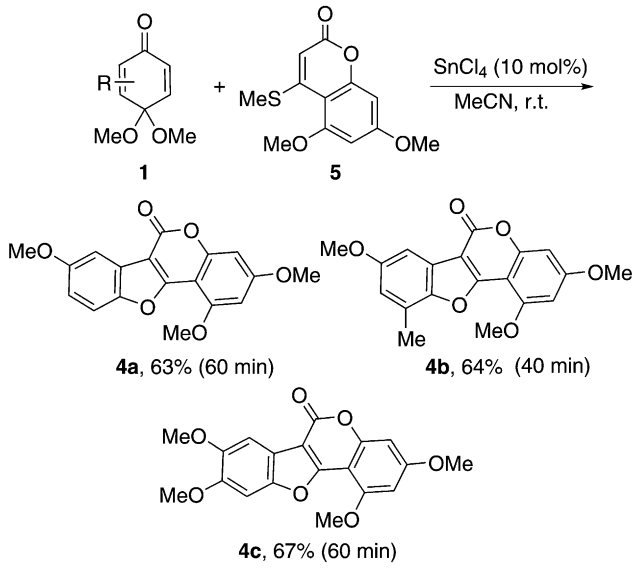


Entry	**1**	**2**: EWG	Time [min]	**3**, Yield [%][b]
1	**1a**: $R^1=R^2=H$	**2a**: MeCO	10	**3a**, 99
2	**1a**	**2b**: PhCO	15	**3b**, 97[c]
3	**1a**	**2c**: PhCH=CHCO	20	**3c**, 99[c]
4	**1a**	**2d**: CN	20	**3d**, 87
5	**1a**	**2e**: CO_2Et	10	**3e**, 83
6	**1b**: $R^1=H$, $R^2=Br$	**2a**	10	**3f**, 99
7	**1b**	**2b**	10	**3g**, 99
8	**1b**	**2c**	15	**3h**, 99[c]
9	**1b**	**2d**	15	**3i**, 91
10	**1b**	**2e**	10	**3j**, 89
11	**1c**: $R^1=H$, $R^2=Cl$	**2a**	10	**3k**, 99
12	**1c**	**2d**	15	**3l**, 93
13	**1d**: $R^1=H$, $R^2=Me$	**2a**	10	**3m**, 94
14	**1d**	**2c**	10	**3n**, 99[c]
15	**1e**: $R^1=OMe$, $R^2=H$	**2a**	20	**3o**, 85
16	**1e**	**2e**	20	**3p**, 80
17	**1f**: R^1, $R^2=(CH=CH)_2$	**2b**	15	**3q**, 88
18	**1a**	**2f:** 	720	**3r**, nd[d]

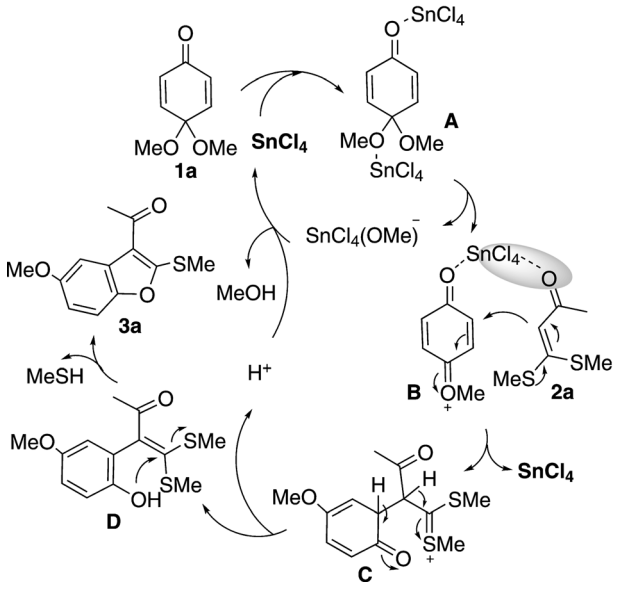
[a] *Reaction conditions:* **1** (0.45 mmol), **2** (0.25 mmol), MeCN (3 mL).
[b] Isolated yields.
[c] 3 mol% of $SnCl_4$ were used.
[d] 10 mol% of $SnCl_4$ were used, but **3r** was not detected.

ined, both to extend the scope of the formal [3+2] cycloaddition and to find an efficient synthesis of coumestans,[13] which were isolated from plant extracts (for example, split peas, pinto beans, alfalfa and clover sprouts) and shown to be new lead compounds for the regulation of the AMP-activated protein kinase.[12] Fortunately, coumestans **4a–c** were successfully prepared in 63–67% yields, respectively, from **5** (4 equiv.) with selected quinone monoketals **1a**/**1d**/**1e** in MeCN by using 10 mol% of $SnCl_4$ as catalyst at room temperature (Scheme 2).

On the basis of the experimental results and related reports,[5–7] a proposed mechanism for the formation of benzofurans **3** is outlined in Scheme 3 (with the reaction of **1a** and **2a** as an example). At first, intermediate **A** is formed, in which both ketal moiety and carbonyl of **1a** are activated by $SnCl_4$.[15] Then oxonium **B** is afforded with the elimination of $SnCl_4(OMe)^-$ to the reaction system. Subsequently, attack of **2a** at the α-position of **B** delivers intermediate **C** and further to **D** along with the release of the proton to complete the catalytic cycle. Finally, benzofuran **3a** is formed *via* an intramolecular S_NV process.[8,9]



Scheme 2. Synthesis of coumestans **4**.



Scheme 3. Proposed mechanism for the formation of benzofuran **3a**.

The above transformation represents a tandem allylic substitution, intramolecular cyclization, and elimination of thiol process. The high efficiency and selectivity of **2a** in the nucleophilic attack at the α-position of the carbonyl of intermediate **B** should be noted. Besides the strong nucleophilicity of **2**, a pseudo-intramolecular[6] process might be involved to well explain the selectivity although it remains to be clarified. Coordination of $SnCl_4$ to the carbonyls of both **B** and **2a** can put **2a** close to the α-position of **1a** (shaded part in Scheme 3). It facilitates the following allylic substitution. In fact, it has been found that the structural nature of the carbonyl in **2** plays a key role for the reaction (Table 2, entries 1–17 versus entry 18).[16] From the point of view of the pseudo-intramolecular process, it is easy to understand that **2f** is sluggish in the above process due to the inefficient coordination of its bulky carbonyl group with an unsatisfying conformation (Table 2, entry 18).[13]

In conclusion, a new allylic substitution of quinone monoacetals has been developed. Accordingly, a range of substituted benzofurans was synthesized in high to excellent yields from quinone monoacetals and ketene dithioacetals *via* a formal [3+2] cycloaddition under mild conditions. The reaction is anticipated to involve a pseudo-intramolecular process which leads to high regioselectivity and efficiency of the reactions. Additionally, the method was extended to allow the synthesis of bioactive coumestans in a single step from the reaction of quinone monoacetals and vinylogous thioesters. Further studies on mechanism and applications are in progress.

Experimental Section

General Procedure for the Synthesis of Benzofurans 3a–q (3a as Example)

To a stirred solution of 4,4-dimethoxycyclohexa-2,5-dienone **1a** (69 mg, 0.45 mmol) and 4,4-bis(methylthio)but-3-en-2-one **2a** (40.5 mg, 0.25 mmol) in dry acetonitrile (2 mL) was added an acetonitrile solution of $SnCl_4$ (1 mL, $c = 0.0025$ mol/L, 0.0025 mmol) at room temperature. The reaction mixture was stirred for 10 min to consume the starting material **2a** as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (10 mL), neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3× 10 mL). The combined organic phase was washed with water (3×10 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash silica gel chromatography (petroleum ether:ethyl acetate = 40:1, v/v) to give **3a** as a white solid; yield: 59 mg (99%).

Acknowledgements

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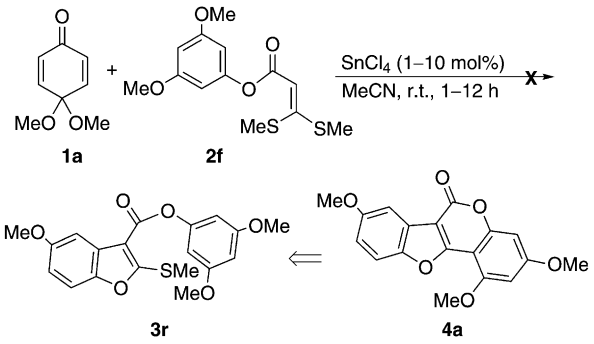
[13] Aiming to synthesize coumestan **4** (also see Scheme 2), we also designed the following process. But it failed.

[14] For the preparation of **5**, please see the Supporting Information.



[15] ^{13}C NMR (125 MHz, $CDCl_3$) for **1a**: $\delta = 185.0$, 143.2 (2C), 129.9 (2C), 92.4, 50.3 (2C). The ^{13}C NMR analysis of **1a** in the presence of 0.1 equiv. of $SnCl_4$ was performed as follows: to a solution of **1a** (39 mg) in 0.5 mL of $CDCl_3$ was added $SnCl_4$ (0.29 ul, 0.1 equiv.). Then, ^{13}C NMR spectra of the resulting solution were recorded at 25 °C on a Varian 125 MHz. It was found that the ^{13}C NMR spectra of **1a** in the presence of 0.1 equiv. of $SnCl_4$ were complex. The peaks of δ***C***O and δ***C***$(OMe)_2$ of **1a** turned out to be weak and some new peaks, such as those at 187.2 ppm, 157.3 ppm, 136,5 ppm, 99.6 ppm, and 55.5 ppm, were observed. These results show clearly the interactions of both the carbonyl oxygen and methoxy oxygen of **1a** with $SnCl_4$ and supported the formation of intermediate **A**.

[16] A comparative reaction between **1a** and vinyl sulfide was carried out under identical conditions. However, no reaction was detected with 1 mol% of $SnCl_4$. In the presence of 3 mol% of $SnCl_4$, the reaction gave cycloaddition product 5-methoxy-2-(phenylthio)-2,3-dihydrobenzofuran in 42% yield in 30 min. In addition, we also prepared [2-(4-chlorophenyl)ethene-1,1-diyl]bis(methyl sulfane) to react with **1a** under the catalysis of 1 mol% of $SnCl_4$ in MeCN at room temperature. However, no reaction was detected after 3 h at room temperature.

