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Ruthenium(II)-catalyzed chemoselective deacylative annulation of 1,3-diones with sulfoxonium ylides *via* C-C bond activation†

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The first successful example of deacylative annulation of 1,3-diones with sulfoxonium ylides was achieved through Ru(II)-catalyzed C-C bond activation. The excellent chemoselectivity and broad substrate scope render this method a practical and versatile approach for the preparation of (hetero)aryl and alkenyl substituted furans, which are valuable units in many biologically active compounds and functional materials. A preliminary mechanistic study reveals that this process involves a deacylative α -ruthenation to generate key alkyl Ru(II) intermediates with the release of a benzoic acid fragment.

Introduction

Carbon-carbon bonds are the most extensive and basic chemical bonds in organic molecules. The selective cleavage of C-C bonds in a constructive manner enables the reconstitution of the molecular skeleton and introduction of new functional groups, thus attracting great attention. In the past decade, chemoselective C-C(CO) bond cleavage has been extensively studied by employing the strategies of chelation assistance,2 ring-strain release,3 and aromatization.4 However, the selective cleavage of unstrained C-C(CO) moieties without an auxiliary directing group still remains an unmet challenge. 5,6 Recently, transition metal-catalyzed C-C(CO) bond functionalization of 1,3-diones has been achieved by Jiao,6a Bolm,6b Peng,6c and Wu.6d These methods are understood to proceed through oxidative α-functionalization of 1,3-diones, followed by retro-Claisen condensation to provide α-substituted ketones (Scheme 1a). However, Lei's work demonstrated an alternative reaction pathway for the C-C(CO) bond cleavage of 1,3-diones, in which deacylative α-cupration could occur to form alkyl Cu(III) complexes that subsequently underwent cross-coupling to give α-aryl ketones (Scheme 1b). Inspired by Lei's work, we questioned whether this open shell deacylative α-cupration mechanism might be translated to other transition metals, such as ruthenium, thereby allowing catalytic formation of alkyl Ru intermediates that can be captured by suitable coupling partners. In continuation of our research on C-C(CO) bond cleavage reactions,8 herein we disclose the first ruthenium-catalyzed deacylative annulation of 1,3-diones with sulfoxonium ylides

(Scheme 1c). This method provides a practical and mild synthetic route to substituted furans, which are essential structural moieties in many biologically active compounds, natural products, and functional materials. 10

On the other hand, sulfoxonium ylides are readily available and bench-stable carbene precursors, which have been extensively explored for the transition metal-catalyzed functionalization of C-H bonds. However, sulfoxonium ylide carbene-involved C-C bond functionalization has not yet been realized due to it being challenging to control the chemoselectivity from the same starting materials. ¹²

Results and discussion

We initiated our investigation on the model reaction of 1,3-diphenylpropane-1,3-dione (1a) with sulfoxonium ylide (2a) to optimize various reaction parameters. The results are summarized in Table 1. With $[RuCl_2(p\text{-cymene})]_2$ as the catalyst,

College of Materials Science & Engineering, Huaqiao University, Xiamen 361021, China. E-mail: glcheng@hqu.edu.cn R² Cu, Ag or Fe functionalization R¹ R² H₂O retro-Claisen R¹ FG

a) Transition metal-catalyzed C-H functionalization/retro-Claisen condensation

FG = OR, SR, $PO(R)_2$, or CH_2CN

b) Deacylative C-C cupration/cross-coupling

$$R^{1} \xrightarrow{\bigcirc} R^{2} + Ar - I \xrightarrow{Cu^{l}} R^{1} \xrightarrow{\bigcirc} Cu^{|||} Ar \xrightarrow{} R^{1} \xrightarrow{\bigcirc} Ar$$

c) This work: deacylative C-C ruthenation/annuation

$$R^{1} \xrightarrow{R^{2}} R^{2} + R^{3} \xrightarrow{R^{4}} R^{4} \xrightarrow{R^{1}} R^{1} \xrightarrow{R^{1}} R^{1} \xrightarrow{R^{2}} R^{1}$$

Scheme 1 Transition metal-catalyzed C-C bond activation of 1,3-diones.

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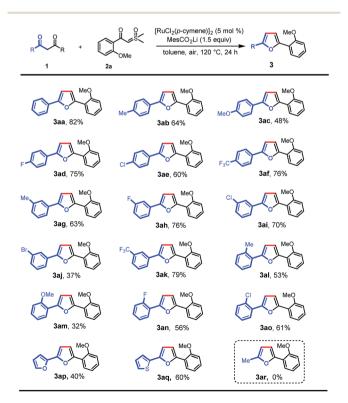
Table 1 Selected optimization studies^a

Entry	Solvent	Base	Yield ^b (%)	
			3aa	4a + 5a (4a : 5a)
1	HFIP	Na ₃ PO ₄	23	45 (1:6)
2	i PrOH	Na ₃ PO ₄	26	8 (1:3)
3	DMF	Na ₃ PO ₄	30	20 (1:3)
4	CH_3CN	Na_3PO_4	25	14(1:2)
5	DCE	Na_3PO_4	15	24 (1:5)
6	Toluene	Na ₃ PO ₄	35	Trace
7	Toluene	Na_2CO_3	30	Trace
8	Toluene	K_2CO_3	20	Trace
9	Toluene	Cs_2CO_3	25	Trace
10	Toluene	NaHCO ₃	24	0
11	Toluene	KH_2PO_4	52	0
12	Toluene	^t BuOLi	72	Trace
13	Toluene	_	10	0
14^c	Toluene	^t BuOLi	Trace	0
15 ^c	Toluene	$MesCO_2Li$	71	Trace
$16^{c,d}$	Toluene	MesCO ₂ Li	78	Trace
$17^{c,e}$	Toluene	$MesCO_2Li$	40	Trace
$18^{c,d,f}$	Toluene	MesCO ₂ Li	$85(82)^g$	Trace
$19^{c,d,h}$	Toluene	MesCO ₂ Li	66	Trace
$20^{c,d,i}$	Toluene	$MesCO_2Li$	0	0

 a Reaction conditions: except where otherwise noted, all of the reactions were performed with 1a (0.1 mmol), 2a (0.2 mmol), base (0.15 mmol), MesCO₂H (0.15 mmol), and [RuCl₂(p-cymene)]₂ (5 mol%) in a solvent (1 mL) at 110 °C in air for 24 h. b The yields were determined by $^1\mathrm{H}$ NMR analysis of the crude product using CH₂Br₂ as the internal standard. c Without MesCO₂H. d Reaction was carried out at 120 °C. e Reaction was carried out at 130 °C. f 2 mL of toluene was used. g Isolated yield. h 3 mL of toluene was used. i Without [RuCl₂(p-cymene)]₂. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. DMF = *N*,*N*-dimethylformamide. DCE = 1,2-dichloroethane. MesCO₂H = 2,4,6-trimethylbenzoic acid.

MesCO₂H as the additive, and Na₃PO₄ as the base, the desired reaction occurred in HFIP to afford the desired furan product (3aa) in 23% yield (entry 1). However, the C-H carbene insertion product $(4a)^{12a,b}$ and the C-C carbene insertion product $(5a)^{12b,c}$ were also obtained as an inseparable mixture in 45% combined yield with 1:6 chemoselectivity. Investigations on various solvents indicated that toluene performed better than others, affording 3aa in a yield of 35% with excellent chemoselectivity (Table 1, entries 1-6). The use of a proper base was crucial for this reaction, and the exploration of different bases revealed that ^tBuOLi provided the best yield of 72% (entries 7–12). Only 10% yield of 3aa was obtained in the absence of a base (entry 13). The MesCO₂H additive was proved to be necessary to ensure the generation of 3aa. In the absence of MesCO₂H, trace 3aa was observed (entry 14). A comparative yield was observed when MesCO₂Li was used instead of ^tBuOLi and MesCO₂H (entry 15). The yield of 3aa could be improved to 78% when the reaction was run at an elevated temperature (entry 16). However, a lower yield was obtained when the reaction was carried out at 130 °C (entry 17). Excitedly, when the solvent volume was increased to 2 mL, the desired product (3aa) was obtained in 85% yield (entry 18), but when the solvent volume was further increased to 3 mL, the yield of 3aa was reduced to 66% (entry 19). Finally, in the absence of a catalyst, no desired product was observed (entry 20). Then, the optimized reaction conditions were identified as follows: 1a (0.1 mmol), 2a (2 equiv.), [RuCl₂(*p*-cymene)]₂ (5 mol%), MesCO₂Li (1.5 equiv.) in toluene (2 mL) at 120 °C in air for 24 h (entry 18).

With the optimal conditions in hand, we turned our attention to the scope of 1,3-diones for this transformation (Scheme 2). It was found that the 1,3-diones bearing methyl, -methoxy, -halogen, and -CF₃ groups could all be smoothly transformed to afford the substituted furan products in moderate to good vields (3aa-ao). The structure of 3ak was unambiguously verified by single-crystal X-ray diffraction.¹³ The reactivity of this transformation was significantly influenced by the steric hindrance. 1,3-diones with ortho-substituted phenyl rings (3alao) generally gave lower yields of desired products than those with meta- and para-substituents (3ab-af). The electronic properties of the phenyl rings in 1,3-diones were observed to affect the reaction efficiency obviously. The substrates with electron-withdrawing groups (3ad-af, 3ah, 3ai, and 3ak) gave higher yields than those with electron-donating groups (3ab, 3ac, and 3ag). However, a lower yield was observed when 1,3dione with a bromo group was used (3aj). It is noteworthy that



Scheme 2 Scope of 1,3-diones. Reaction conditions: $\mathbf{1}$ (0.1 mmol), $\mathbf{2a}$ (0.2 mmol), MesCO₂Li (0.15 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in toluene (2 mL) at 120 °C in air for 24 h.

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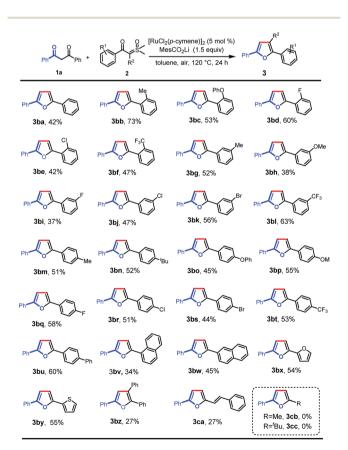
furan and thiophene rings were also tolerated, giving the desired products in moderate yields (3ap and 3aq), which could be expected to find wide applications in organic electronics. ^{10b,14} Finally, this reaction was not applicable to pentane-2,4-dione (3ar).

Next, we further investigated the reaction of 1,3diphenylpropane-1,3-dione with a variety of aroyl sulfoxonium ylides under the optimal reaction conditions (Scheme 3). Various valuable functional groups were tolerated, such as methyl, phenyl, phenoxyl, methoxyl, halogen, and trifluoromethyl. The reactivity was not sensitive to the steric hindrance and electronic properties of the phenyl rings on the sulfoxonium ylides. Substrates with ortho-substituted phenyl rings, having electron-donating moieties (3ba-bc) and electronwithdrawing groups (3bd-bf), gave the desired products in moderate to good yields. The substrates with meta- and parasubstituted phenyl rings could be smoothly converted into the desired products in moderate yields (3bg-bt). Then, a phenyl group was introduced at the para-position which formed the tetra(aryl ring)-containing product 3bu in 60% yield. In addition, 1-naphthalenyl (3bv), 2-naphthalenyl (3bw), 2-furyl (3bx), and 2-thienyl (3by) substrates were also tolerated, giving the corresponding products in the yields of 34%, 45%, 54%, and 55%, respectively. Importantly, triphenyl substituted furan (3bz) could also be obtained using α -phenyl sulfoxonium ylide

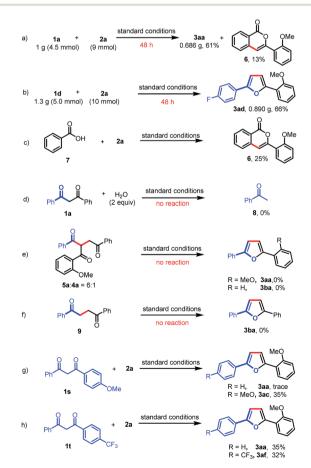
as the substrate, albeit in low yield due to the increased bulkiness. Alkenoyl sulfoxonium ylide was also a capable substrate, giving 2-alkenyl substituted furan (3ca) in 27% yield. The aryl/alkenyl groups in conjugation with carbonyl are indispensable moieties for the successful formation of the corresponding furans, and the sulfoxonium ylides with alkanoyl groups failed to provide the desired products (3cb and 3cc).

A gram-scale experiment of this deacylative annulation was demonstrated employing **1a** and **2a** as model substrates; the product **3aa** was obtained in 61% yield, along with an isocoumarin byproduct (**6**) (Scheme 4a). The 5 mmol scale reaction of **1d** and **2a** could give the product **3ad** in 66% yield (Scheme 4b). Ackermann recently reported Ru(II)/Ag(I)-catalyzed C-H activation/annulation of benzoic acids with sulfoxonium ylides for the synthesis of isocoumarins. ^{11f} Indeed, we notice that isocoumarin (**6**) could also be generated under the silver-free conditions in 25% yield from benzoic acid (**7**) and **2a** (Scheme 4c). These results indicated that benzoic acid might be generated during the C-C bond cleavage process.

To further understand the reaction mechanism, the reaction of 1,3-dione (1a) and $\rm H_2O$ was investigated under the standard reaction conditions. No reaction was observed, which indicated that the Ru($\rm II$)-catalyzed C-C activation could not occur in the absence of a sulfoxonium ylide (Scheme 4d). Furthermore, a mixture of 5a and 4a (6:1) could not afford furan products



Scheme 3 Scope of sulfoxonium ylides. Reaction conditions: 1a (0.1 mmol), 2 (0.2 mmol), MesCO₂Li (0.15 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in toluene (2 mL) at 120 °C in air for 24 h.



Scheme 4 Gram-scale reactions and control experiments.

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Scheme 5 Plausible catalytic cycle

(3aa or 3ba) under the standard reaction conditions (Scheme 4e). To rule out the possibility that Paal–Knorr furan synthesis is involved in our transformation, we also prepared 1,4-diphenylbutane-1,4-dione (9); however, no desired product (3ba) was obtained when this 1,4-dione was subjected to the standard reaction conditions (Scheme 4f). Finally, the intramolecular competitive reactions of unsymmetrical 1,3-diones (1s or 1t) with 2a indicated that the chemoselectivity of this reaction was affected by the electron density of aryl-groups, and the C–C bond cleavage tended to occur at the less electron-rich moieties (Scheme 4g and h). The electron-deficient carbonyls are more likely to be attacked by a nucleophile, such as H₂O, which may induce the subsequent C–C bond cleavage.

On the basis of these results, we proposed that the reaction would proceed as shown in Scheme 5. The transformation begins with the generation of Ru complex **A** under basic conditions, which is subsequently captured by sulfoxonium ylide to form Ru carbene complex **B**. Then, C–C bond activation occurs in the presence of H_2O , giving Ru complex **C**. Migratory insertion of **C** affords intermediate **D**. Finally, intramolecular annulation of **D** results in intermediate **E**, followed by β -O elimination to furnish the furan products (3) and regenerate the Ru(π) catalyst.

Conclusions

In conclusion, we have demonstrated the first example of Ru(II)catalyzed chemoselective deacylative annulation of 1,3-diones with sulfoxonium ylides. A series of substituted furans have been synthesized in reasonable yields by this novel method. This protocol which uses unstrained C–C(CO) bonds as nucleophiles in transition metal-catalyzed cross coupling should be expected to find wide applications. More work to better understand the mechanistic information on this strategy is currently underway.

Conflicts of interest

There are no conflicts to declare.

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