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Catalytic [3+3] Annulation of β-Ketoethers and Cyclopropenones via C(sp^3)-O/C-C Bond Cleavage Under Transition-metal Free Conditions

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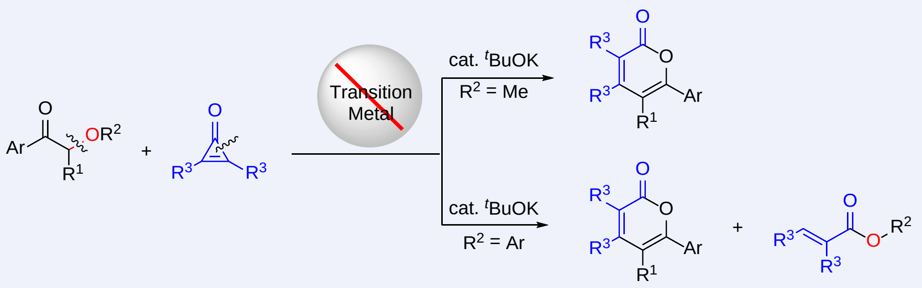
Keywords

C-O/C-C activation | [3+3] annulation | β-ketoethers | cyclopropenones | transition-metal free conditions

Main observation and conclusion

The efficient cleavage of carbon-oxygen (C-O) bond is highly important for the transformation of oxygen-rich biomass and industry chemicals. Herein, an efficient [3+3] annulation of β-ketoethers with cyclopropenones in presence of catalytic base has been developed, which proceed through the C(sp^3)-O bonds cleavage in β-ketoethers and C-C bond cleavage in cyclopropenones under transition-metal free conditions. The cleavage of C(sp^3)-O bonds in alkyl alkyl ethers and aryl alkyl ethers were realized. The reaction featured excellent functional group compatibility and chemoselectivity, affording various 2-pyrones in good to excellent yields under mild conditions and simple operation.

Comprehensive Graphic Content



- C-C/C-O bond cleavage
- [3+3] annulation reaction
- Transition-metal free condition
- Broad substrate scope
- Excellent chemoselectivity
- Mild reaction condition

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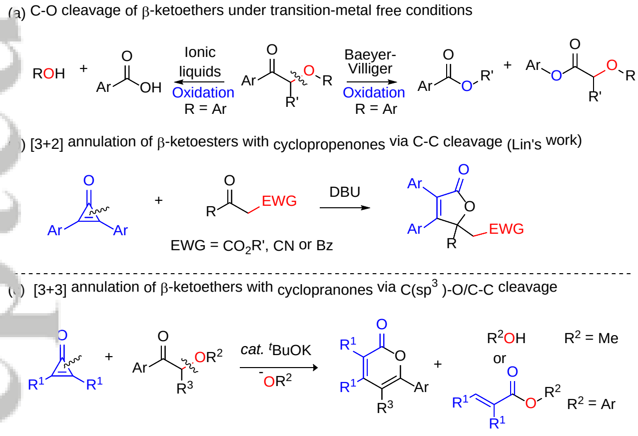
Background and Originality Content

The ubiquity of C-O bond in nature has stimulated efforts towards their efficient transformation to afford diverse organic platforms.[1] Although the direct conversion of C-O bonds of esters, carbonates, carbamates and sulfates are studied very well, the cleavage of C-O bonds in inexpensive ethers is more challenge because of its low polarity and reactivity.[2] In the past several decades, many efforts have been developed for the chemical conversion of the C-O bonds in ethers into value-added chemicals.[3] Among these investigations, the cleavage of sp^2 C-O bonds in aryl aryl ethers, aryl alkyl ethers and sp^3 C-O bonds in aryl alkyl ethers, benzyl alkyl ethers or benzyl allyl ethers have been the main focus,[1-3] while the sp^3 C-O bonds activation in other alkyl alkyl ethers are rarely reported. In this regard, the C-O cleavage in β-ketoethers has attracted great attention, as the keto aryl alkyl ethers are often utilized as the model compounds to disclose the chemical transformation of lignin.[4] Some representative approaches have been reported to convert the lignin model compounds (keto aryl alkyl ethers) using nickel catalysts, ruthenium complexes, vanadium complexes and so on.[5] These strategies usually require harsh conditions or transition-metal-based catalysis. Only some transition-metal catalysis free routes for the C-O bond cleavage in keto aryl ethers were developed in recent years,[6-9] through ionic liquid inducing oxidation process or classic Baeyer-Villiger oxidation reaction with stoichiometric oxidant reagent (Scheme 1a).[8]

Scheme 1 Selected examples of C-O cleavage of β-ketoethers and C-C cleavage of cyclopropenones in absence of transition-metal catalysis.

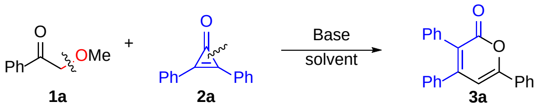


On the other hand, the cyclopropenones have been utilized as important building skeletons with transition-metal or organo-catalysis via C-C bond cleavage process,[10] which could server as a 3C synthon in the [3+n] annulation reaction with various coupling partners.[11] Recently, Lin group reported the [3+2] annulation of cyclopropenones with β-ketoesters under base conditions, the electron-withdrawing group in the ketoester is crucial to the reaction transformation(Scheme 1b).[11c] Herein, we report the [3+3] annulation of β-ketoethers with cyclopropenones via C(sp^3)-O/C-C bond fission in presence of catalytic potassium t-butoxide without the using of transition-metal catalysis, affording various 2-pyrones in good to excellent yields with excellent chemoselectivity (Scheme 1c). 2-pyrones constitute the key structural units of numerous natural products and pharmaceuticals. [12] This general, mild and clean method for cleavage of sp^3 C-O bonds of the alkyl alkyl ethers were furthermore expand to lignin models β-O-4 linkage (keto aryl alkyl ethers) for synthetic transformations. Compared to other C-O bond activations, there are three issues to overcome: 1) The oxygen or carbon atom of *keto* group could both be nucleophilic site after the deprotonation (α-position) as the enolization. The mixture of geometric isomers may complicate the annulation process; 2) The C-O bonds in the β-ketoethers are highly insert, which may lead to low efficiency; 3) The protonation of the reaction intermediate can be a competitive reaction after the ring-opening of cyclopropenone.

Results and Discussion

We initiated set out to explore the possibility of C(sp^3)-O cleavage in β-ketoethers by investigating the coupling of commerical available material **1a** with diphenylcyclopropenone **2a** (Table 1). When the reaction was performed in MeO^{t}Bu at 30℃ for 12h, the [3+3] annulation product **3a** was not observed using the base of CH_3COOK, K_2CO_3, NEt_3 or DBU (Table 1, entries 1-4), only CH_3ONa gave the product **3a** in 13% yield (Table 1, entry 5). To our delight, when ^{t}BuOK was used, the cyclic product **3a** could be obtained in 93% yield (Table 1, entry 6). The yield decreased slightly when the reaction performed under the air atmosphere (Table 1, entry 7), and higher temperature resulted slight lower yield as the decomposition of cyclopropenone **2a** (Table 1, entry 8). Screening of the solvent revealed that the yield of **3a** could be isolated in 98% when DME was used as the solvent (Table 1, entry 9). The reaction in dioxane, THF and toluene as well as polar solvent such as EtOH, DMA also resulted in good to excellent yields of **3a** (Table 1, entries 10-15), while no desired product observed when 1,2-dichloroethane (DCE) was used as solvent (Table 1, entry 16). Furthermore, only starting materials **1a** and **2a** were recovered in the absence of ^{t}BuOK (Table 1, entry 17)

Table 1 Optimization of Reaction Conditions.

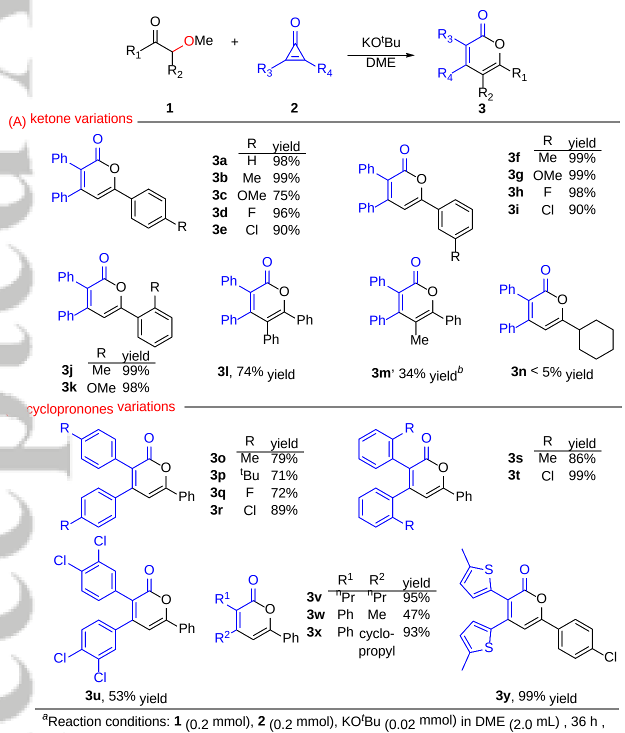


Entry	Base (10 mol %)	Solvent	T (°C)	Yield (%)
1	CH_3COOK	MeO^{t}Bu	30	NR
2	K_2CO_3	MeO^{t}Bu	30	NR
3	$N(Et)_3$	MeO^{t}Bu	30	NR
4	DBU	MeO^{t}Bu	30	NR
5	CH_3ONa	MeO^{t}Bu	30	13
6	^{t}BuOK	MeO^{t}Bu	30	93
7[b]	^{t}BuOK	MeO^{t}Bu	30	80
8[c]	^{t}BuOK	MeO^{t}Bu	60	85
9	^{t}BuOK	DME	30	98
10	^{t}BuOK	dioxane	30	85
11	^{t}BuOK	THF	30	90
12	^{t}BuOK	toluene	30	82
13	^{t}BuOK	$PhCF_3$	30	85
14	^{t}BuOK	EtOH	30	74
15	^{t}BuOK	DMA	30	86
16	^{t}BuOK	DCE	30	NR
17	--	MeO^{t}Bu	30	NR

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), base (0.02 mmol) in solvent (2.0 mL), 12 h, 30 °C, argon. [b] Under the air. [c] 60 °C.

The scope and generality of this [3+3] annulation reaction was evaluated with the optimized conditions (Scheme 2). First, the compatibility of β-ketoethers was investigated. The β-ketoethers bearing methyl-, methoxyl-, fluoro-, chloro- groups at the *para*-position of the benzene ring were all tolerated, giving the desired products in high to excellent yield (**3a-3e**, 75-99% yield). The reaction also worked smoothly in the presence of methyl-, methyoxyl-, fluoro- and chloro- groups at the *meta*-position of the benzene ring (**3f-3i**, 90-99% yield). The cyclic products with *ortho*-methyl (**3j)** or methoxyl group (**3k)** at the benzene ring were obtained in 99% yield and 98% yield respectively. The presence of phenyl group at the α-position of the β-ketoether afforded the *tetra*-phenyl-substituted 2-pyrone **3l** in 74% yield. The β-ketoether with a methyl group at the α-position resulted in decreased reactivity (**3m**, 34% yield). The coupling of 1-cyclohexyl-2-methoxyethan-1-one **2n** with diphenylcyclopropenone **2a** failed to give the cyclic product. Further exploration demonstrated the scope of cyclopropenones in this reaction system. Diphenylcyclopropenone bearing methyl-, ^{t}Bu-, fluoro- and chloro- groups at the C4-position of the benzene ring underwent smooth transformation, and the desired annulation products **3o-3r** were isolated in 71-89% yields. Several other cyclopropenones were also briefly examined, affording the desired products **3s-3u** in 53-99% yields. The dialkyl- substituted cyclopropenones could proceed very well (**3v**, 95% yield). Meanwhile, this coupling system can be extended to the nonsymmetrical cyclopropenones with excellent regioselectivity (**3w**, 47% yield and **3x**, 93% yield). Low yield of **3w** as the decomposition of cyclopropenone. The cyclopronones containing heterocyclic ring such as thiophene could be converted to the desired product **3y** in 99% yield.

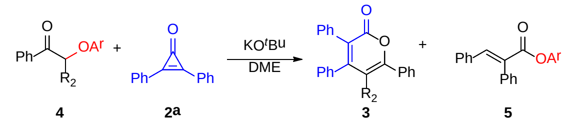
Scheme 2 Substrates Scope.

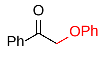
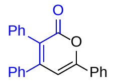
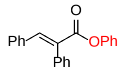
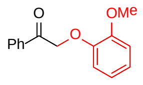
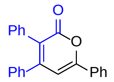
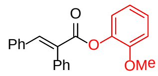
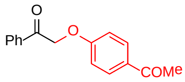
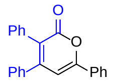
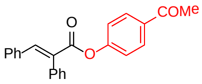
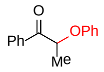
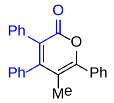
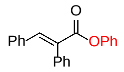
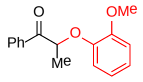
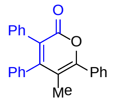
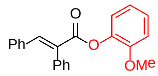
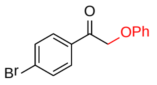
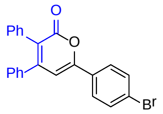
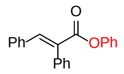


^{a}Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), KO^{t}Bu (0.02 mmol) in DME (2.0 mL), 36 h, 30 °C, argon. ^{b}Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), and KO^{t}Bu (0.1 mmol) in DME (1.0 mL), 36 h, 30 °C, argon.

We then turned our attention to the transformation of β-O-4 linkage **4** (keto aryl alkyl ether) which were used as the lignin model compounds. The present base conditions allowed the direct conversion of the lignin model **4a** to 2-pyrone **3a** in 99% yield along with formation of phenyl (*E*)-2,3-diphenylacrylate **5a** in 83% yield just using two equiv cyclopropenone **2a** at slightly higher temperature (Table 2, entry 1). Installation of the methoxyl- or acetyl- group on the benzene ring resulted in excellent conversion (Table 2, entries 2 and 3). It is worthy of note that the presence of methyl group at α-position in the β-ketoethers allowed direct conversion of lignin model **4d** and **4e** to corresponding products in moderate to excellent yields (Table 2, entries 4 and 5). The *bromo*-substituted compound **4f** gave corresponding products 2-pyrone **3z** in 99% yield and ester **5a** in 58% yield (Table 2, entry 6).

Table 2 Scope of lignin model compounds.

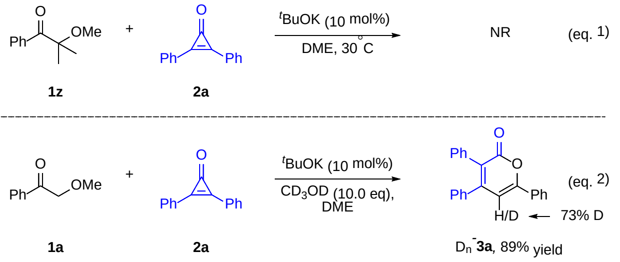


Entry	Ketone **4**	Product **3**	Product **5**
1^a	 **4a**	 **3a**, 99% yield	 **5a**, 83% yield
2^a	 **4b**	 **3a**, 99% yield	 **5b**, 76% yield
3^a	 **4c**	 **3a**, 99% yield	 **5c**, 98% yield
4^b	 **4d**	 **3m**, 99% yield	 **5a**, 72% yield
5^b	 **4e**	 **3m**, 71% yield	 **5b**, 72% yield
6^a	 **4f**	 **3z**, 99% yield	 **5a**, 58% yield

^{a}Reaction conditions: **2a** (0.2 mmol), **4** (0.1 mmol), KO^{t}Bu (0.01 mmol) in DME (1.0 ml), 36 h, 50 °C, argon. ^{b}Reaction conditions: **2a** (0.2 mmol), **4** (0.1 mmol), KO^{t}Bu (0.01 mmol) in DME (1.0 ml), 36 h, 80 °C, argon.

Then we briefly explored the reaction mechanism (Scheme 3). No corresponding product was observed when 2,2-dimethyl-1-phenylpropan-1-one **1z** reacted with cyclopropenone **2a** even at higher temperature (Scheme 3, eq. 1), and this result demonstrated that the enol intermediate under base condition is crucial for the reaction conversion. Moreover, the H/D exchange reaction was performed, when CD_3OD was added into the coupling system of **1a** with **2a**, H/D exchanged was observed at the 5-position of the product **3a** with partial deuteration (73% D), indicating that protonation of the enolization intermediate occoured before the ring-opening of cyclopropenone and not likely involved in the turnover-limiting step (Scheme 3, eq. 2).

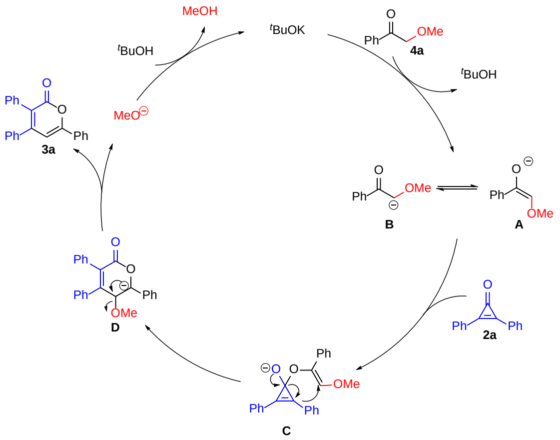
Scheme 3 Mechanism studies.



On the base of our mechanism experiments results and previous related reports,[10, 14] proposed mechanistic possibilities of this

[3+3] annulation is shown in Scheme 4. Deprotonation of β-ketoether **4a** by ^{t}BuOK generated the enol intermediate **A** and **B**, the *in-situ* formed nucleophilic oxygen anion attacks the carbonyl group of cyclopropenone **2a** gave intermediate **C**, subsequently ring-opening process and intramolecular cyclization reaction delivered the anion species **D**. Finally, the β-O elimination process gave the final product **3a** and regenerated the base.

Scheme 4 Proposed Reaction Mechanism.



Conclusions

We have developed an unprecedented base catalyzed [3+3] annulation of β-ketoethers with cyclopropenones via C(sp^3)-O and C-C cleavage under mild conditions, giving various 2-pydones with broad substrates scope and excellent chemoselectivity. This method obviated the need of transition-metal catalysis and proceeded well with simple operation. The sp^3 C-O bonds cleavage in keto alkyl alkyl ethers and keto aryl alkyl ethers were realized in this annulation reaction. Further efforts will be made to apply the present strategy to the conversion of the nature lignin.

Experimental

General procedure：^{t}BuOK (2.24 mg, 0.02 mmol) in DME (2.0 mL) were charged into a pressure tube under argon, followed by addition of cyclopropenone (0.200 mmol, 1.0 equiv) and keto ether (0.200 mmol, 1.0 equiv). The reaction tube was then sealed and placed into an oil bath at 30 °C. After reaction for 36 h, the reaction mixture was filtered through a pad of celite. The mixture was eluted with ethyl acetate, concentrated, and purified by silica gel chromatography (PE : EA = 10:1) to give the indicated product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement

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Catalytic [3+3] Annulation of β-Ketoethers and Cyclopropenones via C(sp³)-O/C-C Bond Cleavage Under Transition-metal Free Conditions

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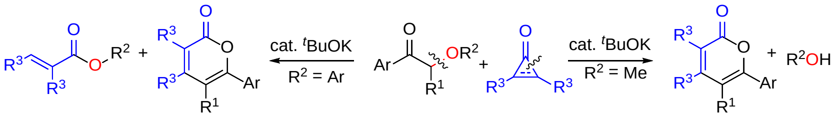

- Transition-metal free catalysis
- C-C/C-O bond cleavage
- [3+3] annulation reaction
- Broad substrate scope
- Excellent chemoselectivity
- Mild reaction condition

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