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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201601505

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601505

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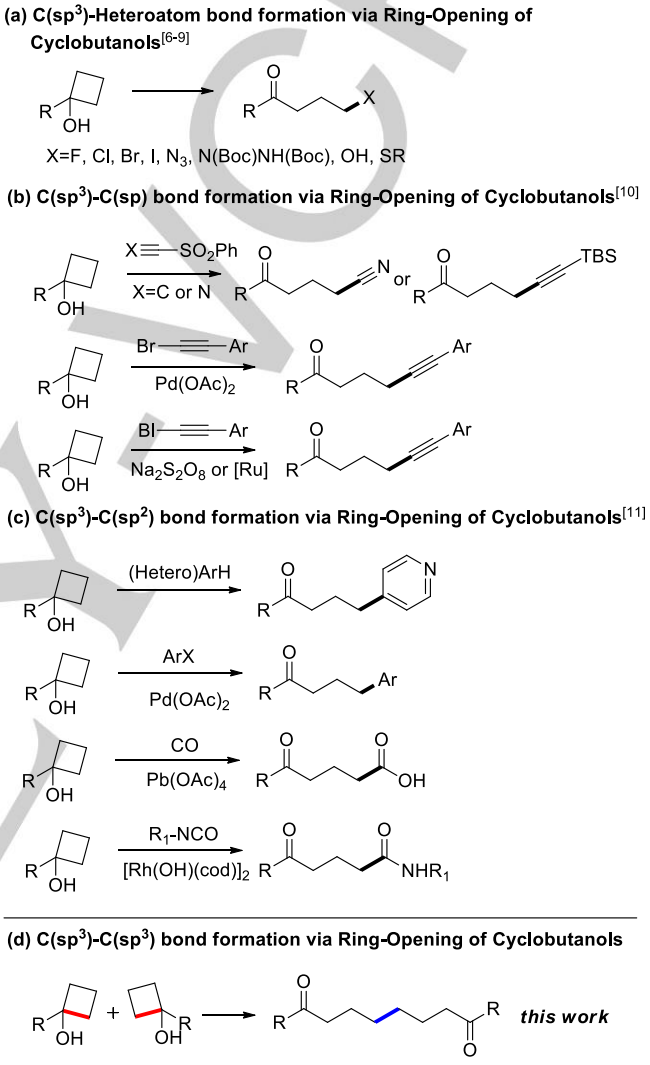
C–C Bond Formation via Oxidative Ring-opening Homo-coupling of Cyclobutanol

Huiying Zeng,*[a] Pan Pan,[a] Jinping Chen,[b] Hang Gong*[b] and Chao-Jun Li*[a],[c]

Abstract: *A C(sp³)–C(sp³) bond formation via oxidative ring-opening homo-coupling of cyclobutanol is reported. A broad scope of 1-substituted-cyclobutanols are transformed into C(sp³)–C(sp³) bond formation products via oxidative ring-opening in good to high yields under exceptionally mild conditions with open flask in just 30 seconds.*

Introduction

Selective C–C bond activation is one of the most fundamental processes in chemistry owing to its potential utility in organic synthesis.[1] Furthermore, C–C bond cleavage is one of the most important reactions for reforming long chain alkanes and degrading polymers and biomass.[2] Due to the strained cyclic C–C bonds, tertiary cycloalkanols as good precursors for regiospecific synthesis of chain ketones via C–C bond cleavage were achieved.[3] Cyclopropanols are the most small ring compounds, have been broadly used as useful synthons in various coupling reactions.[4] Owing to a lower ring strain energy, cyclobutanol is relatively more difficult than cyclopropanol.[5] Some important achievments for oxidizing ring-opening of cyclobutanol include: a) C(sp³)–heteroatom bond formation (Scheme 1a) (for example, C–halogen (F, Cl, Br, I) bond[6], C–N bond,[7] C–S bond[8], C–O bond[9]), b) C(sp³)–C(sp) bond formation[10] (Scheme 1b), c) C(sp³)–C(sp²) bond formation[11] (Scheme 1c). Despite all these important progresses, the efficient formation of C–C bond via C–C bond activation of cyclobutanols, especially more challenger C(sp³)–C(sp³) formation, continues to attract the interest of chemists. Herein we would like to report a oxidative ring-opening C(sp³)–C(sp³) homo-coupling for forming a new σ-C(sp³)–C(sp³) bond product under exceptionally mild conditions with open flask in just 30 seconds (Scheme 1d).



Scheme 1. Ring-opening σ-C(sp³)–Hetero, σ-C(sp³)–C(sp) and σ-C(sp³)–C(sp² bond formation *VS* ring-opening σ-C(sp³)–C(sp³) bond formation

To begin our study, 1-phenylcyclobutanol was reacted with 2.5 equiv of MnO_2 in acetonitrile and water at room temperature under open flask (Table 1). Gratifyingly, a trace amount of the desired homo-coupling product 1,8-diphenyloctane-1,8-dione was obtained (Table 1, entry 1). Encouraged by this preliminary result, we then examined different oxidants, and found that $Mn(OAc)_3$ was beneficial to this reaction (Table 1, entry 2)[12], with the desired product being obtained in 15% yield. However, strong oxidizing reagents such as $KMnO_4$, as well as organic oxidizing reagent DDQ, did not produce any desired product at all (Table 1, entries 3 and 4). Further investigation of the oxidants showed that high valent cerium (IV) gave better results (Table 1, entries 5-7).

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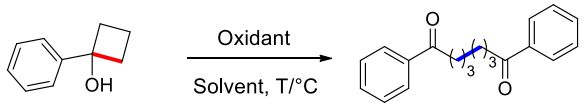
With CAN as oxidant, the desired product was obtained in 45% yield (Table 1, entry 7). Increasing the reaction temperature to 40 ˚C resulted in a slightly lower yield (Table 1, entry 8). When the temperature was downed to 0˚C, an improved yield (73%) was obtained (Table 1, entry 9). Then, we investigated different solvents which revealed that it is less effective ether in acetonitrile or water[13] alone as solvent (Table 1, entries10-11). In the use of other co-solvent was also less effective (Table 1, entries12-14). Both increasing or reducing the equiv of CAN, led to lower yields of this reaction (Table 1, entries15-17). Prolonging the reaction time, it also decreased the product yield (Table 1, entry18).

Table 1. C–C bond formation via ring-opening homo-coupling of 1-phenylcyclobutanol under various conditions[a]

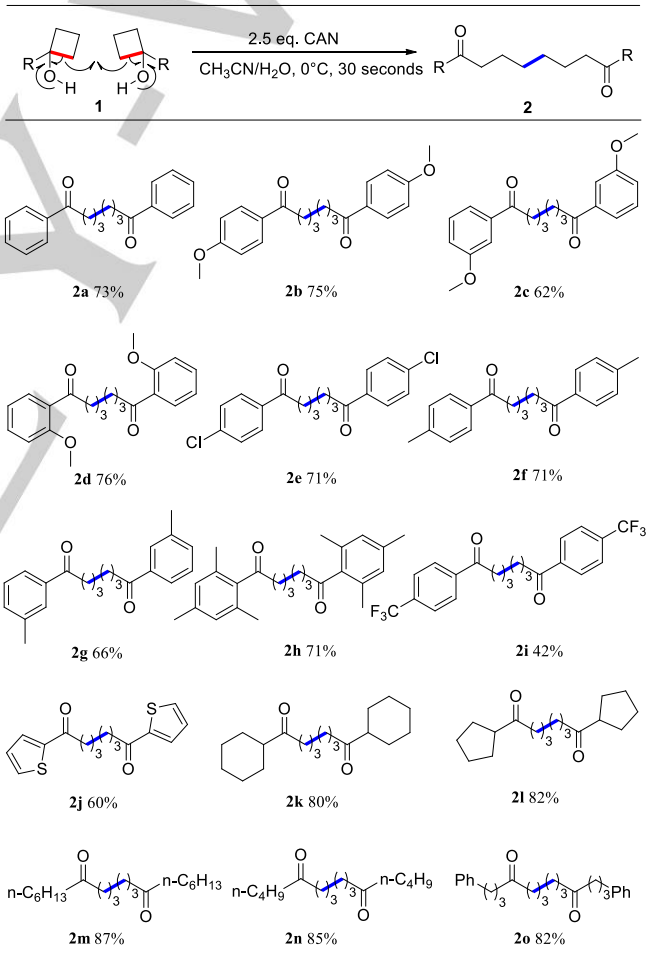


Entry	Oxidant	Solvent	T/°C	Yield/%
1	MnO_2	CH_3CN/H_2O	rt	trace
2	$Mn(OAc)_3$	CH_3CN/H_2O	rt	15
3	$KMnO_4$	CH_3CN/H_2O	rt	0
4	DDQ	CH_3CN/H_2O	rt	0
5	$Ce(SO_4)_2$	CH_3CN/H_2O	rt	15
6	$(NH_4)_4Ce(SO_4)_4$	CH_3CN/H_2O	rt	16
7	CAN	CH_3CN/H_2O	rt	45
8	CAN	CH_3CN/H_2O	40	32
9	CAN	CH_3CN/H_2O	0	73
10	CAN	CH_3CN	0	trace
11	CAN	H_2O	0	8
12	CAN	Toluene/H_2O	0	trace
13	CAN	THF/H_2O	0	28
14	CAN	DCM/H_2O	0	0
15[b]	CAN	CH_3CN/H_2O	0	48
16[c]	CAN	CH_3CN/H_2O	0	62
17[d]	CAN	CH_3CN/H_2O	0	50
18[e]	CAN	CH_3CN/H_2O	0	55

[a] All reactions were conducted at 0.2 mmol scale with 2.5 eq. CAN under open flask in the solvents (1.6 mL) (the mixture solvent ratio is 1:1) in 30 seconds, all yields were determined by using nitromethane as an internal standard. [b] 1.5 eq. CAN was added. [c] 2.0 eq. CAN was added. [d] 3.0 eq. CAN was added. [e] reaction time is 2 minutes.

With the optimized conditions in hand, we then evaluated the substrate scope at 0 ˚C using 2.5 equiv of CAN as the oxidant in acetonitrile/H_2O under open flask in only 30 seconds. As shown in Table 2, the reaction proceeded efficiently with various aryl and alkyl groups. Diverse substituents on the aryl groups had little effect on the outcome of the reactions, and the corresponding1,8-diaryloctane-1,8-diones were obtained in good to high yields in all cases (Table 2, **2a** - **2j**). While 1-phenylcyclobutanol gave a high yield of the desired product (Table 2, **2a**), the presence of an electron-donating group (Table 2, **2b**-**2d**) on different positions (para-, meta-, ortho-) of the phenyl group had little effect for this reaction, and the corresponding homo-coupling products were obtained in good to high yields. The chloro-substituted phenyl group gave a same result under the standard conditions (Table 2, **2e**). The presence of a weak electron-donating group on different positions of the phenyl group had the similar results (Table 2, **2f**-**2g**). With a more sterically hindered substituent on the phenyl ring, 1-mesitylcyclobutanol also gave the coupled product in high yield (Table 2, **2h**). On the other hand, the presence of a strong electron-withdrawing group (Table 2, **2i**) on the phenyl moiety

Table 2. The scopes of ring-opening homo-coupling of cyclobutanols[a]



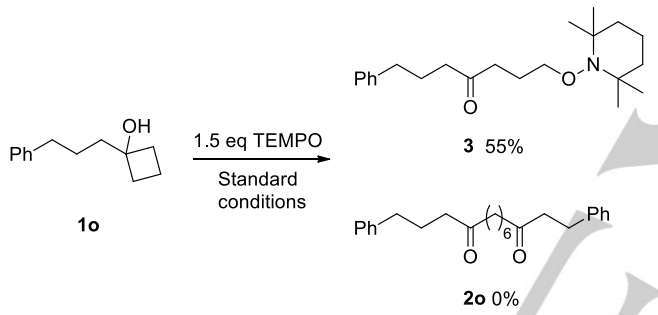
[a] Reaction conditions: 1-alkylcyclobutanol (0.2 mmol), CAN (0.5 mmol), in acetonitrile (0.8 mL) and water (0.8 mL); all reactions were carried out at 0°C in open flask for 30 seconds; the yield of isolated product.

was found to be less favorable to this transformation. It is interesting to note that the use of a heteroarylcyclobutanol, 1-(thiophen-2-yl)cyclobutanol, also led to the corresponding product

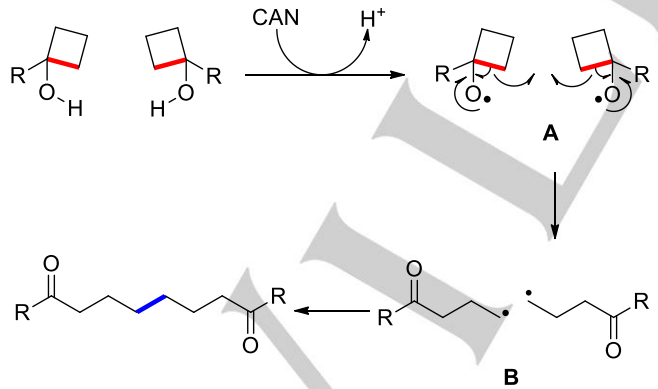
in good yield (Table 2, **2j**). Besides aryl substituted derivatives, the 1-alkylcyclobutanols were found to be even more effective for this transformation, giving the desired products in better yields than with the 1-arylcyclobutanols (Table 2, **2k**-**2o**). The different ring sizes of the 1-cycloalkylcyclobutanols had the same results for this reaction, high yields were obtained in all cases (Table 2, **2k**-**2l**). The 1-linearalkylcyclobutanols with different chain length also reacted very well (Table 2, **2m-2n**), including the one with a phenyl substituent at the terminal position of the chain (Table 2, **2o**).

To explore the reaction mechanism, 1.5 equiv of TEMPO was added with an attempt to trap the intermediate under the standard conditions. Compound **3** was isolated in 55% yield, with no homo-coupling product being detected (Scheme 2).

Based on this experimental result, a tentative mechanism is proposed in Scheme 4: Initially, 1-phenylcyclobutanol reacts with CAN via a single electron transfer process to form the oxygen free radical intermediate **A**. Subsequently, with the ring strain as the driving force, homolytic C–C cleavage forms free radical **B**[14], which homo-coupled rapidly to form the desired product (Scheme 3).



Scheme 2. Experiments for mechanistic elucidation with radical scavenger



Scheme 3. Tentative mechanism for the homo-coupling of 1-substituted-cyclobutanol

In conclusion, we have discovered a C–C bond formation via a ring-opening homocoupling of cyclobutanols under mild reaction conditions. The method allowed the direct formation of 1,8-disubstituted-1,8-diketone from the oxidation of 1-substituted-cyclobutanol. A tentative mechanism is proposed for this novel process. The scope, mechanism and application of this transformation is undergoing in our lab.

Experimental Section

A typical experimental procedure is as follows: cyclobutanol **1a** (30 mg, 0.2mmol, 1.0 equiv) was loaded in a flask. A mixed solvent CH_3CN/H_2O (0.8 mL : 0.8 mL) was then added, which was followed the addition of cerium ammonium nitrate (274 mg, 0.5mmol, 2.5 equiv). The mixture was stirred in an ice bath for 30 seconds, and then the reaction was quenched by adding 10% sodium thiosulfate aqueous solution. The mixture was extracted with ethyl acetate 3x20mL, and the combined organic extracts were washed by brine, dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash chromatography on silica gel (PE/EA=8:1) to give product **2a**.

Acknowledgements

We thank the National Science Foundation of China (Nos. 21302073 and 21402168), the Fundamental Research Funds for the Central Universities (lzujbky-2016-53) and Lanzhou University the Recruitment Program of Global Experts (to C.J.L.) for their support of our research.

Keywords: cyclobutanol • homo-coupling • C–C bond formation

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Radical Homo-coupling

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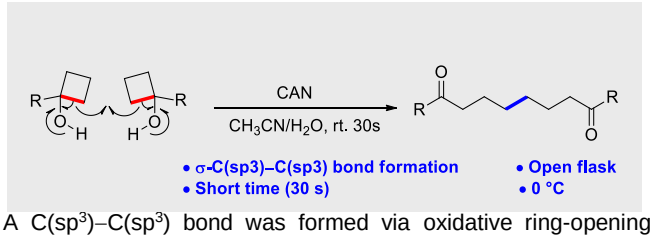

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C–C Bond Formation via Oxidative Ring-opening Homo-coupling of Cyclobutanol

A C(sp^3)–C(sp^3) bond was formed via oxidative ring-opening homo-coupling of cyclobutanol. 1,8-disubstituentoctane-1,8-diones were obtained efficiently with homo-coupling of 1-substituted-cyclobutanol.