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CO/O_2 Assisted Oxidative Carbon–carbon and Carbon-heteroatom Bond Cleavage for the Synthesis of Oxosulfonates from DMSO and Olefins

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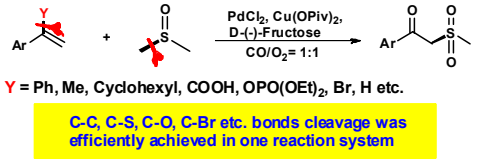
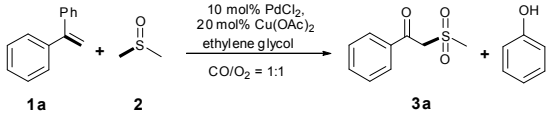
A selective carbon–carbon and carbon-heteroatom bond cleavage was achieved in one reaction system. With this strategy a novel Pd/Cu-catalyzed aerobic oxidative oxosulfonation of olefins with DMSO has been developed. Preliminary mechanistic investigation indicated that CO/O_2 assisted the bond cleavage and the leaving groups from the starting materials were trapped by O_2 and underwent a hydroxylation process.

In the past few years, transition-metal-catalyzed carbon–carbon and carbon-heteroatom bond activation (cleavage) has attracted much attention, due to not only its fundamental scientific interest but also its potential usage in organic synthesis.[1] Methods for these strategies mainly involving strain-release, aromatization, and chelation-assistance, and the research topics mainly focus on stoichiometric reactions such as transition-metal insertion into carbon–carbon bonds via stable metallacycle formation.[1e, 2] Although significant progress has been made in this emerging field, the reactivity, selectivity, and efficiencies in these strategies are still far from satisfactory due to the thermodynamic stability of the unstrained C–C and C-heteroatom bonds; furthermore, few examples could be compatible with a variety of bonds cleavage in one transformation.[3] Hence, the development of an efficient catalytic system towards unstrained C-C and C-heteroatom bonds cleavage is always highly attractive. Due to continuous research interests in the C-C and C-heteroatom bond cleavage, we discovered a transformation in which C-C, C-S, C-O, C-Br etc bonds cleavage were efficiently achieved in one reaction system. The leaving groups could be phenyl, methyl, cyclohexyl, carboxyl, phosphate and bromine (Scheme 1).

With the combination of ethene-1,1-diyldibenzene, $PdCl_2$, $Cu(OAc)_2$ and ethylene glycol in the presence of 1 atm CO/O_2 at 80 °C, unexpected β-oxo sulfone compound **3a** and phenol were isolated and identified (Scheme 2 and Table 1), which indicated that C-S/C-C bond cleavage and O_2 fixation process were involved. To our knowledge, the selective cleavage of unactivated C-S, C-C bond is still a challenging topic up to date;[4] Furthermore, the β-oxo sulfone derivatives are important chemical feedstocks which are commonly used precursors in the synthesis of a series of useful biologically active molecules and basic scaffolds of numerous pharmaceutically important molecules.[5] No examples have been described in literature of β-oxo methyl sulfones being prepared using a Pd/Cu catalyst from the direct cleavage of C-C and C-S bonds. Therefore, we decided to further investigate this transformation by utilizing the commercially available dimethyl sulfoxide to realize the synthesis of β-oxo methyl sulfones derivatives.



Scheme 1. The synthesis of oxosulfonation via C-C/C-S bond cleavage



Scheme 2. The reaction between ethene-1,1-diyldibenzene and dimethyl sulfoxide.

Our efforts started with treating ethene-1, 1-diyldibenzene with DMSO in the presence of catalytic Pd/Cu salts and polyhydroxy additives. Notably, the use of polyhydroxy compounds, such as ethylene glycol and glycerol are essential for the reaction, in addition, CO is also indispensable (Table 1, entry 1-3 and 17). Removing or replacing polyhydroxy

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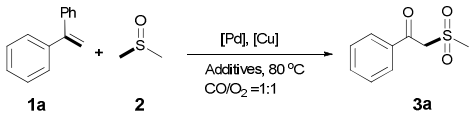
compounds with other ligands, such as 1, 10-phen, PPh_3, L-proline both turned out to be ineffective (Table 1, entry 4-6). It is well known that the carbohydrates are commonly available and widely existed in nature and could also be used in organic synthesis because of the polyhydroxy function groups.[6] Hence, we next screened a series of carbohydrates as the additives. To our delight, the D-(-)-Fructose could afford the product in 80% yield and D-(-)-Glucose could also afford the product in 77% yield (Table 1, entry 8 and 9). When sucrose was used, a lower yield was obtained (Table 1, entry 7). Pd and Cu salts were also essential in this transformation. After a series of condition screening, we found $Cu(OPiv)_2$ and $PdCl_2$ were the best catalysts in this reaction (Table 1, entries 10-16). After considerable effort, the combination of $PdCl_2$ (0.1 eq.), $Cu(OPiv)_2$ (0.2 eq.) and D-(-)-Fructose (0.4 eq.) in the presence of 1 atm CO/O_2 (1:1) at 80 °C was found to be the best reaction conditions for this aerobic oxidative cross-coupling (Table 1, entry 13).

Table 1: Optimization of Conditions for the Reaction of Ethene-1,1-diyldibenzene 1a and DMSO. [a]

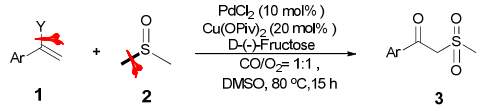


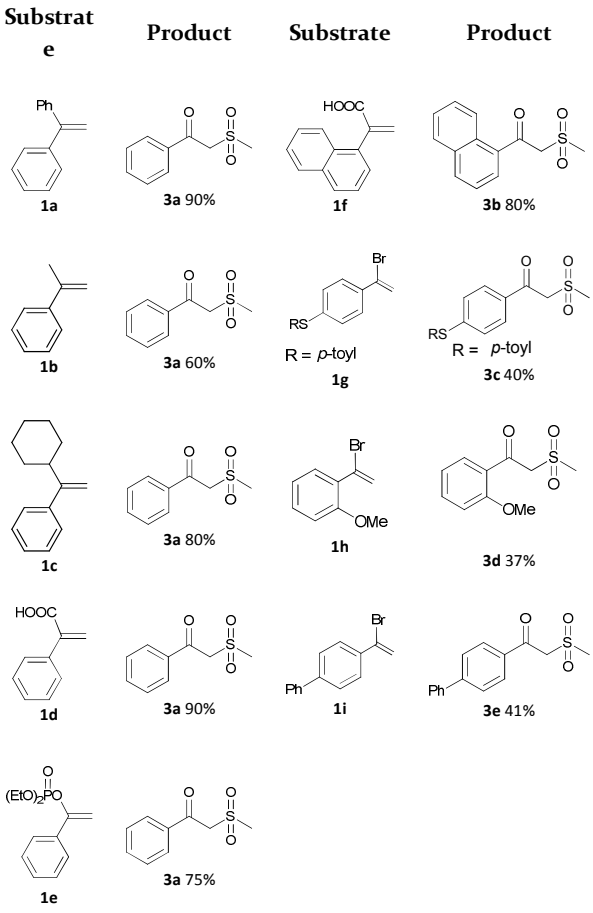
Entry	[Pd]	[Cu]	Additives	Yield [%][b]
1	$PdCl_2$	$Cu(OAc)_2$-	–	N.R
2	$PdCl_2$	$Cu(OAc)_2$	glycol	30
3	$PdCl_2$	$Cu(OAc)_2$	glycerol	44
4	$PdCl_2$	$Cu(OAc)_2$	1,10-phen	trace
5	$PdCl_2$	$Cu(OAc)_2$	PPh_3	N.R
6	$PdCl_2$	$Cu(OAc)_2$	L-proline	trace
7	$PdCl_2$	$Cu(OAc)_2$	sucrose	41
8	$PdCl_2$	$Cu(OAc)_2$	D-(-)-Glucose	77
9	$PdCl_2$	$Cu(OAc)_2$	D-(-)-Fructose	80
10	$PdCl_2$	-	D-(-)-Fructose	trace
11	$PdCl_2$	CuCl	D-(-)-Fructose	15
12	$PdCl_2$	CuOAc	D-(-)-Fructose	35
13	**$PdCl_2$**	**$Cu(OPiv)_2$**	**D-(-)-Fructose**	**90**
14	-	$Cu(OPiv)_2$	D-(-)-Fructose	N.R
15	$Pd(OAc)_2$	$Cu(OPiv)_2$	D-(-)-Fructose	70
16	Pd/C	$Cu(OPiv)_2$	D-(-)-Fructose	40
17[c]	$PdCl_2$	$Cu(OPiv)_2$	D-(-)-Fructose	N.R

[a] Reactions were carried out on a scale of 0.20 mmol of **1a** and 1 mL of **2a** in the presence of 10 mol% [Pd], 20 mol% [Cu] and 40 mol% additives in 1 atm CO/O_2 (1:1) for 15 h. [b] Isolated yields. [c] without CO.

With the optimized conditions in hand, various α-substituted phenylethylenes **1** were tested to react with dimethyl sulfoxide (Table 2). To our delight, the reaction was readily extended to a variety of α-substituted phenylethylenes **1**, no matter methyl, phenyl, cyclohexyl or carboxyl substituted phenylethylene could provide 2-(methylsulfonyl)-1-phenylethanone **3a** in good yields, which C-C and C-S bonds

Table 2: Aerobic Oxidative Oxosulfonation of Different α-substituted Phenylethylene with DMSO [a]





[a] Reaction conditions: 1 (0.25 mmol), 2 (1 mL), $PdCl_2$ (10 mol%), $Cu(OPiv)_2$ (20 mol%), D-(-)-Fructose (40 mol%) 1 atm CO/O_2 (1:1) at 80 °C for 15 h. Isolated yields.

cleavage were involved (Table 2, **1a**, **1b**, **1c**, **1d** and **1f**). In addition, diethyl (1-phenylvinyl) phosphate **1e** was also found to be suitable reaction partners with dimethyl sulfoxide in the reaction, in which C-O and C-S bonds cleavage were involved. It was noteworthy that various α-bromostyrene derivatives, such as (4-(1-bromovinyl)phenyl)(ptolyl)sulfane **1g**, 4-(1-bromovinyl)-1,1'-biphenyl **1i** and 1-(1-bromovinyl)-2-methoxybenzene **1h** could also be employed to the β-oxo sulfone without any difficulties, in which C-Br and C-S bonds cleavages were involved.

Since the products are β-oxo sulfone, an undisputable advancement is the application of simple olefins in this

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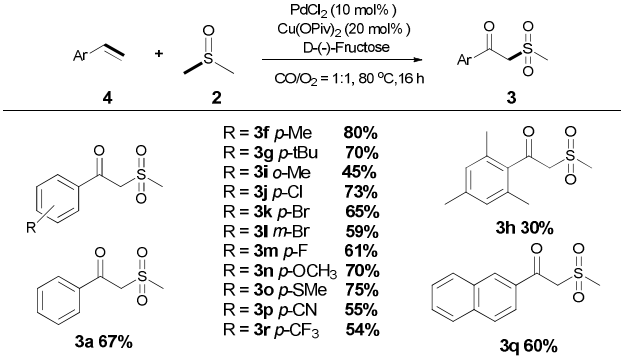
reaction. To our delight, the reaction was readily extended to a variety of simple aryl alkenes, either electron-withdrawing and electron-donating substituted groups or halogen groups at the aromatic ring could be introduced into the desired product under the standard reaction conditions (Scheme 3, **3f**, **3g**-**3r**). Styrenes bearing alkyl substituents, such as methyl and tert-butyl, afforded the desired products in moderate to good yields (Scheme 3, **3f**, **3g**–**3i**). It was noteworthy that the position of substituent seems to have influence on the product yield (Scheme 3, **3f**, **3h** and **3i**). Several typical functional groups such as sulfydryl, trifluoromethyl and cyano group were well tolerated (Scheme 3, **3o**, **3p**, **3r**). Meanwhile, 2-vinylnaphthalene 4q could also be transformed into the target product in 60% yield (Scheme 3, **3q**).

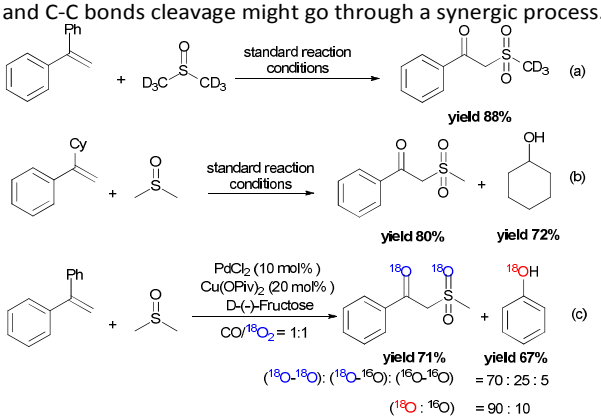


Scheme 3. Reactions of alkenes 4 and dimethyl sulfoxide 2. Reaction conditions: 4 (0.20 mmol), 2 (1 mL), $PdCl_2$ (10 mol%), $Cu(OPiv)_2$ (20 mol%), D-(-)-Fructose (40 mol%) 1 atm CO/O_2 (1:1) at 80 °C for 15 h. Isolated yields.

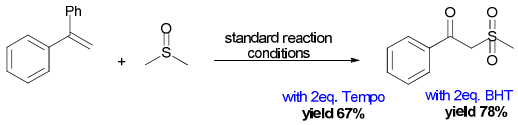
To gain preliminary mechanistic information about this transformation, the styrene reacted with deuterated DMSO generated the desired deuteriumlabeled product in 88% yield under the standard reaction conditions (Scheme 4a). From 1H NMR spectrum, the resonance at δ = 2.0–4.0 ppm was not observed. However, the resonance at δ = 4.61 ppm still existed, which demonstrated that the methylene of the product was from styrene. The leaving Ph group was transformed into phenol (GC yield 82%). Meanwhile, (1-cyclohexylvinyl)benzene has also been tested in the reaction, and the leaving cyclohexyl group was also transformed into cyclohexanol (Scheme 4b). Furthermore, the by-product of diethyl (1-phenylvinyl) phosphate **1e** was also identified by LC-MS (See more details in the Supporting Information). The isotopic labeling experiments with $^{18}O_2$ were also performed (Scheme 4c), the results demonstrated that two additional oxygen present in the product and the oxygen present in phenol all came from $^{18}O_2$.

The radical-trapping experiments have been tested under the standard conditions. The addition of radical scavenger TEMPO and BHT only reduced the reaction yields slightly, which suggests that radical intermediates might not be the active species in this oxidative transformation (Scheme 5).

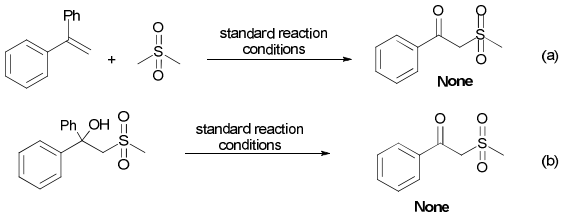
By employing dimethyl sulfone as the substrate instead of DMSO to react with **1a** under the standard conditions, no corresponding β-oxo sulfone product was produced (Scheme 6a). This indicates that the lone pair of electrons on DMSO is essential to the C-S bond cleavage. Furthermore, 2-(methylsulfonyl)-1, 1-diphenylethanol did not lead to the desired product under our reaction conditions (Scheme 6b), which suggests that the formation of carbonyl and C-C bonds cleavage might go through a synergic process.



Scheme 4. Labelling and trapping experiment



Scheme 5. Radical inhibiting experiment



Scheme 6. Control experiment

On the basis of above results and previous studies,[7] we proposed a mechanism for this oxidative transformation (Scheme 7): (1) the deprotonation of DMSO by Pd(II) affords the intermediate 5 (The DFT calculation was also performed, see more details in the Supporting Information); (2) the insertion of CO leads the intermediate **6**; (3) the β-heteroatom ($SOCH_3$) elimination via 7 produces intermediate 8 and the ketene; (4) the insertion of **1a** to **8** give the alkylpalladium intermediate **9**. (5) although the detailed mechanism is not clear yet，via intermediate **10**, the oxidative C-C or C-X bond cleavages and C-O bond formation took place in the presence of copper, oxygen and carbohydrate.

As shown in the mechanism, the ketene was from C-S bond cleavage and the insertion of CO. The ketene easily reacted with H_2O to form acetic acid. Hence, we performed the acetic acid trapping experiment (Scheme 8). 2-(bromomethyl)naphthalene was added into the solution after the reaction was accomplished, and deuteriumlabeled naphthalen-2-ylmethyl acetate was produced, which suggests the formation of ketene.

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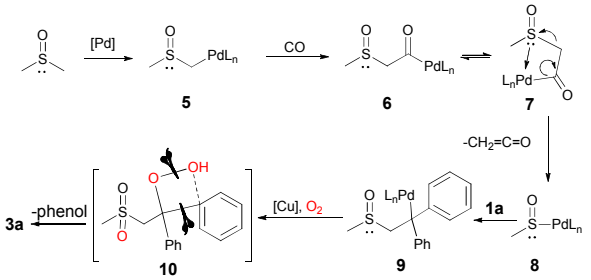
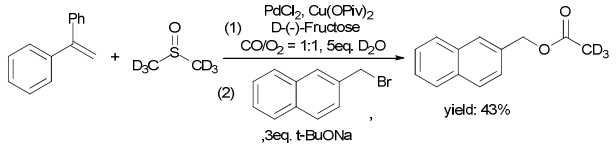


Scheme 7. Proposed mechanism of C-S and C-C bond cleavage.



Scheme 8. Acetic acid trapping experiment.

In summary, we have demonstrated an efficient and attractive aerobic oxidative oxosulfonation of olefins with DMSO, in which C-C, C-S, C-O, C-Br etc. bonds cleavage are involved. A diverse collection of valuable β-oxo sulfones were easily synthesized by this protocol. Preliminary mechanistic investigation was also performed, indicating that the CO and O_2 assisted this oxidative carbon–carbon and carbon-heteroatom bond cleavage and the leaving groups from the starting materials were trapped by O_2 and underwent a hydroxylation process.

Acknowledgements

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