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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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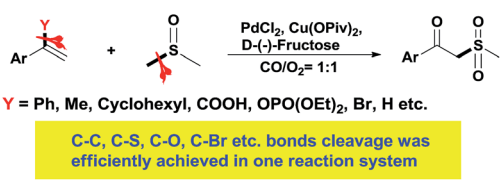
Selective carbon–carbon and carbon–heteroatom bond cleavage was achieved in a one reaction system. With this strategy a novel Pd/Cu-catalyzed aerobic oxidative oxosulfonation of olefins with DMSO has been developed. Preliminary mechanistic investigations indicated that CO/O_2 assisted the bond cleavage 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 not only to its fundamental scientific interest but also its potential usage in organic synthesis.[1] Methods for these strategies mainly involve 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 are compatible with a variety of bond cleavages in one transformation.[3] Hence, the development of an efficient catalytic system towards unstrained C–C and C–heteroatom bond cleavage is always highly attractive. Due to continuous research interests into C–C and C–heteroatom bond cleavage, we discovered a transformation in which C–C, C–S, C–O, C–Br *etc.* bond cleavage was efficiently achieved in a one reaction system. The leaving groups could be phenyl, methyl, cyclohexyl, carboxyl, phosphate or 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, the 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 an O_2 fixation process were involved. To the best of our knowledge, the selective cleavage of unactivated C–S/C–C bonds is still a challenging topic to date.[4] Furthermore, 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 the 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 commercially available dimethyl sulfoxide to realize the synthesis of β-oxo methyl sulfone derivatives.

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, is essential for the reaction and CO is also indispensable (Table 1, entry 1–3 and 17). Removing or replacing the polyhydroxy compounds with other ligands, such as 1,10-phen, PPh_3, or L-proline, both turned out to be ineffective (Table 1, entry 4–6). It is well known that carbohydrates are commonly available and exist widely in nature so could also be used in organic synthesis because of the polyhydroxy functional groups.[6] Hence, we next screened a series of carbohydrates as the additives. To our delight, 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



Scheme 1 The synthesis of oxosulfonates *via* C–C/C–S bond cleavage.

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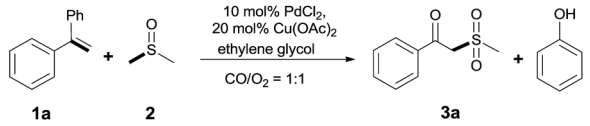
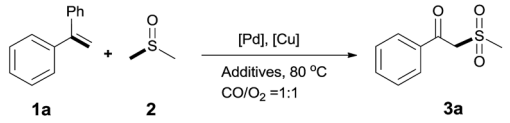


Scheme 2 The reaction between ethene-1,1-diyldibenzene and dimethyl sulfoxide.

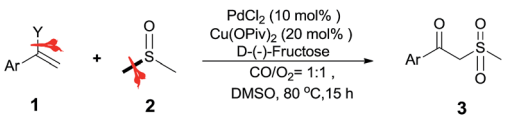
Table 1 Optimization of conditions for the reaction of ethene-1,1-diyldibenzene (**1a**) and DMSO[a]

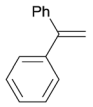
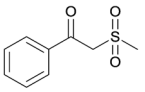
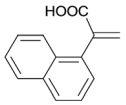
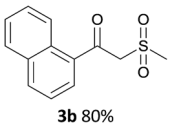
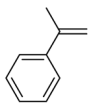
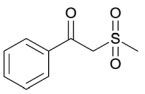
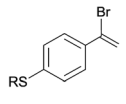
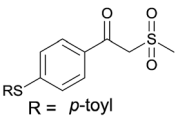
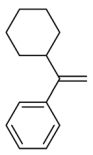
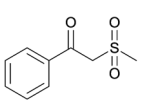
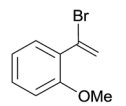
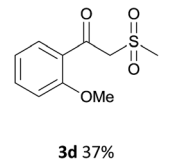
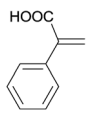
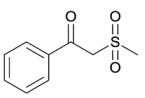
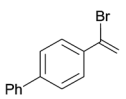
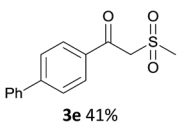
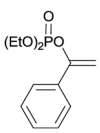
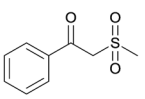


Entry	[Pd]	[Cu]	Additive	Yield[b] [%]
1	$PdCl_2$	$Cu(OAc)_2^-$	—	N.R
2	$PdCl_2$	$Cu(OAc)_2$	Glycol	30
3	$PdCl_2$	$Cu(OAc)_2$	Glycerol	44
4	$PdCl_2$	$Cu(OAc)_2$	1,10-Phen	Trace
5	$PdCl_2$	$Cu(OAc)_2$	PPh_3	N.R
6	$PdCl_2$	$Cu(OAc)_2$	L-Proline	Trace
7	$PdCl_2$	$Cu(OAc)_2$	Sucrose	41
8	$PdCl_2$	$Cu(OAc)_2$	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% additive in 1 atm CO/O_2 (1 : 1) for 15 h. [b] Isolated yields. [c] Without CO.

Table 2 Aerobic oxidative oxosulfonation of different α-substituted phenylethylenes with DMSO[a]



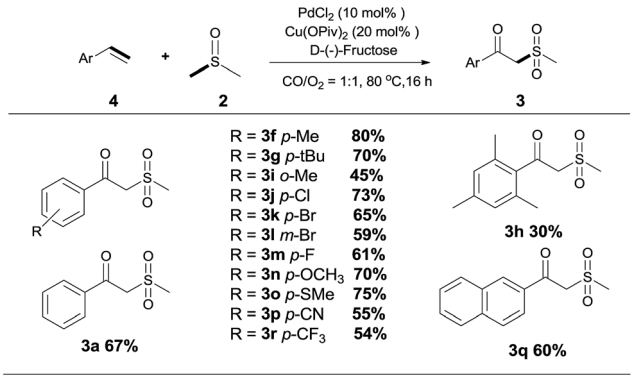
Substrate	Product	Substrate	Product
 **1a**	 **3a** 90%	 **1f**	 **3b** 80%
 **1b**	 **3a** 60%	 R = *p*-toyl **1g**	 R = *p*-toyl **3c** 40%
 **1c**	 **3a** 80%	 **1h**	 **3d** 37%
 **1d**	 **3a** 90%	 **1i**	 **3e** 41%
 **1e**	 **3a** 75%		

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

transformation. After screening a series of conditions, we found that $Cu(OPiv)_2$ and $PdCl_2$ were the best catalysts in this reaction (Table 1, entries 10–16). After considerable efforts, 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).

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**, and methyl, phenyl, cyclohexyl or carboxyl substituted phenylethylene could provide 2-(methylsulfonyl)-1-phenylethanone **3a** in good yields, in which C–C and C–S bond cleavage was involved (Table 2, **1a**, **1b**, **1c**, **1d** and **1f**). In addition, diethyl (1-phenylvinyl)phosphate **1e** was also found to be a suitable reaction partner with dimethyl sulfoxide in the reaction, in which C–O and C–S bond cleavage was involved. It was noteworthy that various α-bromostyrene derivatives, such as (4-(1-bromovinyl)phenyl)(*p*-tolyl)sulfane **1g**, 4-(1-bromovinyl)-1,1′-biphenyl **1i** and 1-(1-bromovinyl)-2-methoxybenzene **1h**, could also be added to the β-oxo sulfone without any difficulties, in which C–Br and C–S bond cleavage was involved.

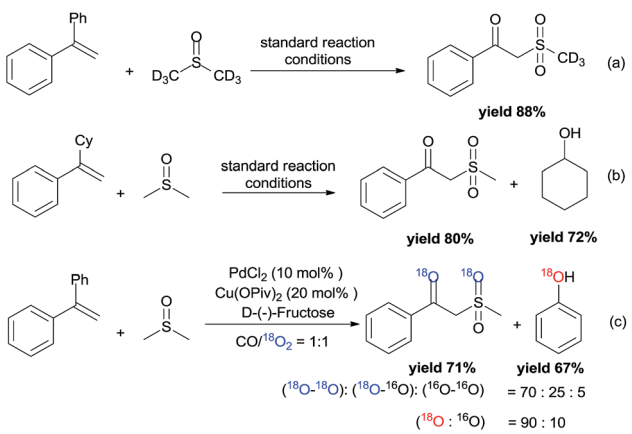
Since the products are β-oxo sulfones, an indisputable advancement is the application of simple olefins in this reaction. To our delight, the reaction was readily extended to a variety of simple aryl alkenes, either electron-withdrawing or electron-donating substituted groups or halogen groups at the 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 groups, afforded the desired products in moderate to good yields (Scheme 3, **3f**, **3g–3i**). It was noteworthy that the position of the substituent seems to have an influence on the product yield (Scheme 3, **3f**, **3h** and **3i**). Several typical functional groups such as sulfhydryl, trifluoromethyl and cyano groups 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**).



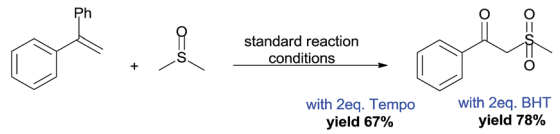
Scheme 3 Reactions of alkenes **4** and dimethyl sulfoxide **2**. Reaction conditions: **4** (0.20 mmol), **2** (1 mL), $PdCl_2$ (10 mol%), $Cu(OPiv)_2$ (20 mol%), D-(−)-fructose (40 mol%) and 1 atm CO/O_2 (1 : 1) at 80 °C for 15 h. Isolated yields.

To gain preliminary mechanistic information about this transformation, the styrene was reacted with deuterated DMSO to generate the desired deuterium labeled product in 88% yield under the standard reaction conditions (Scheme 4a). From the ^{1}H NMR spectrum, the resonance at $\delta = 2.0$–4.0 ppm was not observed. However, the resonance at $\delta = 4.61$ ppm still existed, which demonstrated that the methylene of the product was from the styrene. The leaving Ph group was transformed into phenol (GC yield 82%). Meanwhile, (1-cyclohexylvinyl)benzene was also 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 ESI†). Isotopic labeling experiments with $^{18}O_2$ were also performed (Scheme 4c), and the results demonstrated that the two additional oxygen atoms present in the product and the oxygen present in phenol all came from $^{18}O_2$.

Radical-trapping experiments were carried out under the standard conditions. The addition of the radical scavengers 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).



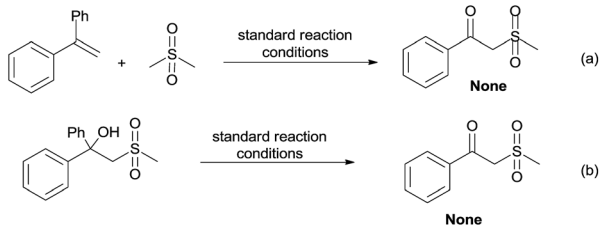
Scheme 4 Labelling and trapping experiments.



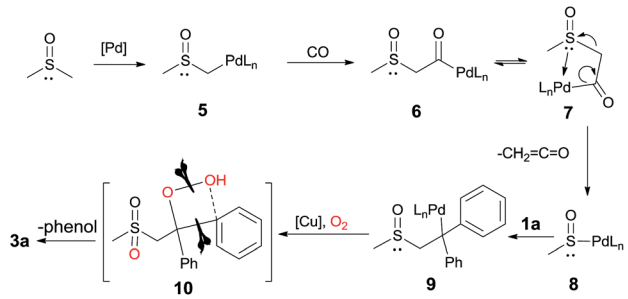
Scheme 5 Radical inhibiting experiment.

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 the carbonyl and the C–C bond cleavage might go through a synergistic process.

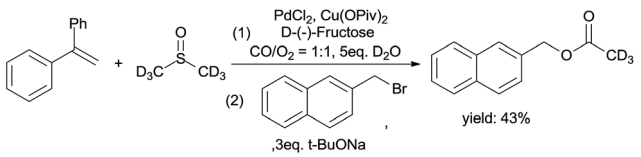
On the basis of the above results and previous studies,[7] we proposed a mechanism for this oxidative transformation (Scheme 7): (1) the deprotonation of DMSO by Pd(II) affords the intermediate **5** (DFT calculations were also performed, see more details in the ESI†); (2) the insertion of CO leads to the intermediate **6**; (3) the β-heteroatom ($SOCH_3$) elimination *via* **7** produces intermediate **8** and the ketene; (4) the insertion of **1a** into **8** gives the alkylpalladium intermediate **9**; (5) although the



Scheme 6 Control experiment.



Scheme 7 Proposed mechanism for C–S and C–C bond cleavage.



Scheme 8 Acetic acid trapping experiment.

detailed mechanism is not clear yet, *via* intermediate **10**, the oxidative C–C or C–X bond cleavage and the C–O bond formation takes place in the presence of copper, oxygen and the carbohydrate.

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

In summary, we have demonstrated the efficient and attractive aerobic oxidative oxosulfonation of olefins with DMSO, in which C–C, C–S, C–O, C–Br *etc.* bond cleavage is involved. A diverse collection of valuable β-oxo sulfones was easily synthesized by this protocol. Preliminary mechanistic investigation was also performed, indicating that 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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Notes and references

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