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Metal- and additive-free oxygen-atom transfer reaction: an efficient and chemoselective oxidation of sulfides to sulfoxides with cyclic diacyl peroxides†

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Metal- and additive-free oxidation of a series of sulfides/thioketones has been achieved using cyclic diacyl peroxides as mild oxygen source. This protocol features simple manipulation, high chemo- and diastereoselectivity, and a broad substrate scope (up to 42 examples), tolerates many common functional groups, and is scalable and applicable to late-stage sulfoxidation strategy. A preliminary mechanistic study by quantum mechanical calculations suggests that single two-electron transfer process is energetically more favorable, and indicates reactivity of cyclic diacyl peroxides distinct from conventional acyclic acyl peroxides.

Introduction

The pivotal role of sulfoxides as very important structural motifs has attracted considerable interest from researchers working in a variety of different fields due to their unique properties, such as central chirality at the sulfur, high configurational stability and the strongly polarized S−O bond. In addition, organic sulfoxides have been also successfully employed as steering ligands in transition-metal catalysis,[1] as versatile synthetic intermediates in the generation of numerous natural products and biologically active compounds,[2] as well as new pharmacophores in drug discovery (Fig. 1).[3] To date, four well-established approaches to generate sulfoxides are the partial oxidation of sulfides,[4] the nucleophilic substitution,[5] palladium-catalyzed Suzuki coupling or alpha-arylation,[6] and palladium-catalyzed arylation of sulfenate anions (Scheme S-1 in the supporting information).[7] Undoubtedly the selective oxidation of sulfides is the most straightforward and frequently used method for the synthesis of the corresponding sulfoxides. Although a wide range of oxidizing systems can be used in sulfoxidation, most of them might prove to be unsatisfactory for medium- to large-scale synthesis because of the utilization of expensive or heavy metal containing oxidants, the existence of environmentally

unfavorable toxic wastes, and the possibility of an over-oxidation to sulfones.[8] In fact, over-oxidation coupled with functional group liability severely limits the widespread synthetic utility of the selective oxidation of sulfides. Specifically speaking, the most wide used hydrogen peroxide and *m*-chloroperbenzoic acid usually cause undesired over oxidation of sulfoxide products, require specialized catalysts or additives under relatively severe reaction conditions (e.g. acidic, basic or aqueous media), and are not   for the sulfoxidation of sulfides bearing bulky groups or highly electron-withdrawing substituents.[4] Therefore, there are still appreciable emphases on the investigation and formulation of suitable chemoselective sulfoxidation approaches to efficiently actualize the desired chemical transformations, especially for medium- to large-scale production.

Although the cyclic diacyl peroxides have been investigated in detail by Greene and Adam from the mid-1950s to the 1970s,[9] there have been few studies examining their reactivity and practicality for methodology development and synthetic application until lately (Scheme S-2 in the supporting information). In this regard, Tomkinson and Siegel have recently made some significant advances in the metal-free dihydroxylation of alkenes,[10] and metal-free arene oxidation[11] in a two-step reaction sequence by the utilization of cyclic diacyl peroxides as mild oxygen source. Subsequently, we[12a] and Torres-Alacan[12b] independently realized photocyclization of phthaloyl peroxide derivatives as the aryne precursors. Very recently, a collaborative work[13] by Terent'ev and Adam demonstrated the lanthanide-catalyzed oxidative C−O coupling of 1,3-dicarbonyl compounds with cyclic malonoyl peroxides. In contrast, only one case[14] involving metal-free heteroatom oxidation using cyclic diacyl peroxides as electrophilic oxidants is the oxidation of triphenylphosphine to date. In this paper, we present the first investigation of the reactivity of cyclic diacyl peroxides in metal- and additive-free heteroatom oxidation with a range of

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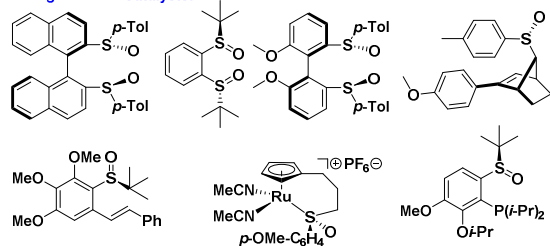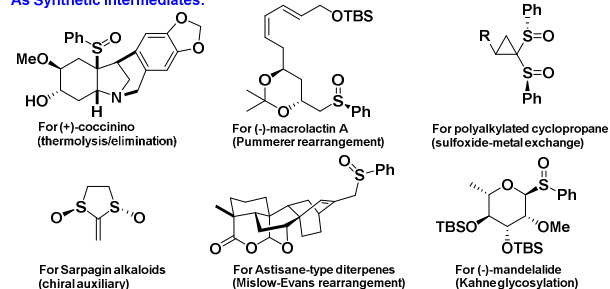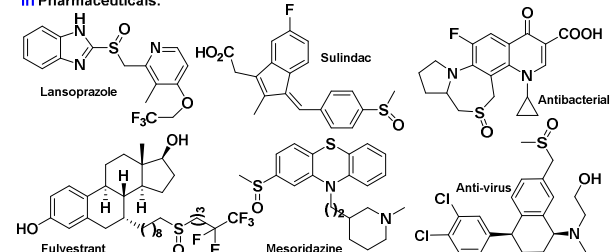
Fig. 1 Representative examples of applications of sulfoxides in organic chemistry and drug discovery.
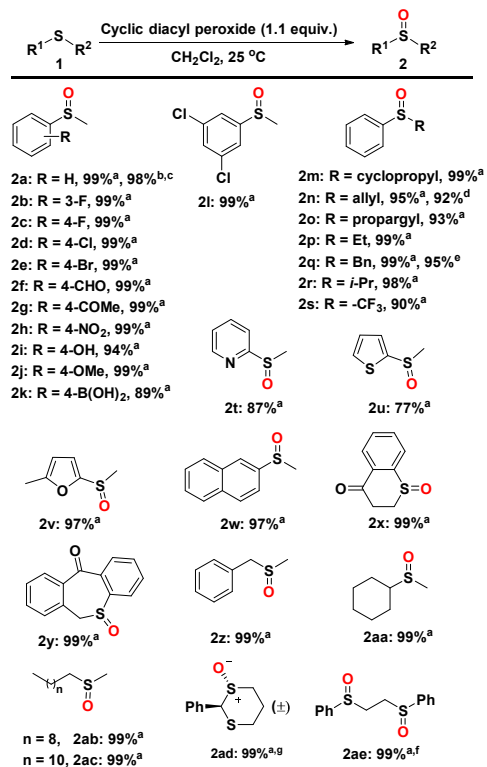
structurally diverse sulfides. Compared to the known sulfoxidation approaches, this new protocol features excellent chemo- and diastereoselectivity with the tested cases, a broad substrate scope and a high degree of functional group tolerance, and it is operationally simple and applicable to metal-free late-stage sulfoxidation of complex small molecules. To the best of our knowledge, sulfoxidation with cyclic diacyl peroxides in the absence of catalysts and additives is currently one of the most practical, efficient and chemoselective method to obtain a large variety of sulfoxides on gram and smaller scales with no need for the exclusion of oxygen and water.

Results and discussion

The feasibility of oxygen atom transfer to sulfide substrates was readily established by a treatment of sulfide **1a** with 1.1 equiv. of phthaloyl peroxide (PPO) in dichloromethane at 25 °C for 8 hours, and an almost quantitative yield (99%) of the desired sulfoxide **2a** was isolated. The direct hydroxylation of arenes[11] and the over-oxidation to sulfones were not found to be competitive. It is noteworthy that a gram-scale synthesis of **2a** (10 mmol of **1a**, 1.24 g) was performed and maintained the similar yield (98%) and perfect chemoselectivity without any
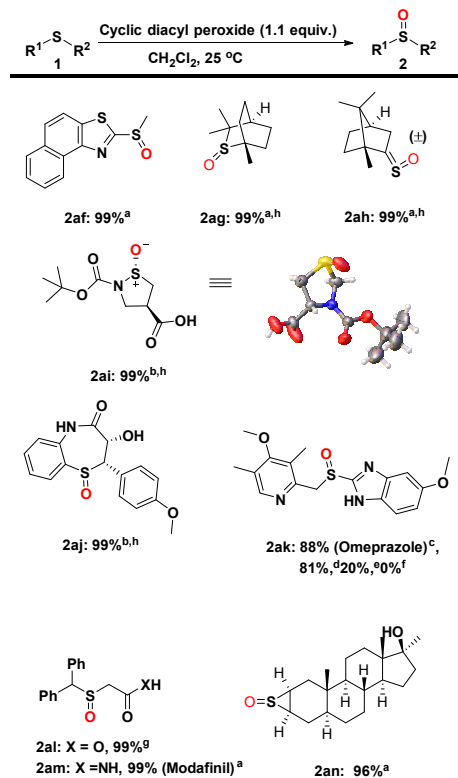
detectable over oxidation to sulfones, which illustrated that our procedure can provide analytically pure sulfoxides from suitable organic sulfides on gram scale. Interestingly, cyclopentyl malonoyl peroxide (MPO) can also get a similar yield (98%). It is important to emphasize that phthaloyl peroxide and malonoyl peroxide are easily synthesized in one or three steps from cheap, commercially available phthaloyl chloride[10a] or diethyl malonate[10b] using solid sodium percarbonate or urea hydrogen peroxide, and can be also achieved on 30-80 gram scale to deliver the corresponding cyclic diacyl peroxides without the occurrence of an explosion. Both peroxides can be stored under nitrogen in a freezer cooled to -20 °C for prolonged periods of time (months up to one year) without degradation or loss of reactivity.

As illustrated in Table 1, a diverse set of important functional groups is well tolerated, including synthetically valuable fluoro (**2b**, 99% and **2c**, 99%), chloro (**2d**, 99% and **2l**, 99%), bromo (**2e**, 99%), carbonyl (**2f**, 99% and **2g**, 99%), nitro (**2h**, 99%), hydroxy (**2i**, 94%), methoxy (**2j**, 99%), and boronic (**2k**, 89%) groups. Both electron-releasing and electron-withdrawing substituents can be very well accommodated under particularly mild oxidative conditions. Notably, an efficient and selective sulfoxidation of 4-(methylthio)benzaldehyde (**1f**) and 4-(methylthio)phenylboronic acid (**1k**) containing two different oxidizable groups occurred in our oxygen-atom transfer reactions without any changes in another easily oxidizable group,[15] which provides a synthetic handle for further carbon-carbon bond forming reactions for further chemical manipulation. In a similar fashion, several phenyl alkyl sulfides smoothly reacted with 1.1 equiv. of phthaloyl peroxide, affording the corresponding desired products **2p-s** in high yields. Strained ring system including cyclopropyl (**2m**) remain intact and do not undergo ring opening. More remarkably, sulfides **1n** and **1o** were chemoselectively oxidized to sulfoxides **2n** and **2o** without further oxidation of the double or triple bond moiety, in 95% (92% even in 2 grams-scale synthesis) and 93% yields, respectively. Other acyclic and cyclic aromatic sulfides (**1t**, **1u**, **1v**, **1w**, **1x** and **1y**) are also competent substrates, and it is particularly interesting that the heteroaromatic part of the sulfides (**1u**) is unaffected by oxidation. Similarly, dialkyl sulfides (**1z**, **1aa**, **1ab** and **1ac**) also underwent efficient sulfoxidation to afford the corresponding products in excellent yields. In addition to monothio derivatives, dithio derivatives (**1ad** and **1ae**) selectively delivering the corresponding trans mono-oxidation (with almost complete diastereoselectivity, trans/cis > 20/1)[16] or bis-oxidation products in excellent yields. It is worth noting that a mixture of the meso and racemic 1, 2-bis(phenylsulfinyl)ethane **2ae** can be produced in higher yield (99% in gram-scale synthesis versus 92% in the previous literature[17]) and with easier work up than previously disclosed known method[17] on gram scale (4.05 mmol of **1ae**) under our optimized reaction conditions, which is most often employed as ligand for a mild and highly selective palladium-catalyzed allylic oxidation of terminal olefins.[17]

Journal Name

ARTICLE

Table 1 Sulfoxidation of various substituted sulfide derivatives

2a: R = H, 99%[a], 98%[b,c]
2b: R = 3-F, 99%[a]
2c: R = 4-F, 99%[a]
2d: R = 4-Cl, 99%[a]
2e: R = 4-Br, 99%[a]
2f: R = 4-CHO, 99%[a]
2g: R = 4-COMe, 99%[a]
2h: R = 4-NO₂, 99%[a]
2i: R = 4-OH, 94%[a]
2j: R = 4-OMe, 99%[a]
2k: R = 4-B(OH)₂, 89%[a]

2l: 99%[a]

2m: R = cyclopropyl, 99%[a]
2n: R = allyl, 95%[a], 92%[d]
2o: R = propargyl, 93%[a]
2p: R = Et, 99%[a]
2q: R = Bn, 99%[a], 95%[e]
2r: R = i-Pr, 98%[a]
2s: R = -CF₃, 90%[a]

2t: 87%[a]

2u: 77%[a]

2v: 97%[a]

2w: 97%[a]

2x: 99%[a]

2y: 99%[a]

2z: 99%[a]

2aa: 99%[a]

n = 8, 2ab: 99%[a]
n = 10, 2ac: 99%[a]

2ad: 99%[a,g]

2ae: 99%[a,f]

Reaction conditions: [a] **1a** (1 mmol), PPO (1.1 mmol), DCM (2 mL), 25 °C, 8 h, isolated yields. [b] **1a** (1 mmol), MPO (1.1 mmol), DCM (2 mL), 25 °C, 8 h. [c] **1a** (10 mmol), PPO (11 mmol) DCM (25 mL), 25 °C, 15 h. [d] **1n** (13.3 mmol), PPO (14.63 mmol), DCM (30 mL), 25 °C, 15 h. [e] **1q** (11.5 mmol), PPO (12.6 mmol), DCM (30 mL), 25 °C,15 h. [f] **1ae** (4.05 mmol), PPO (4.46 mmol), DCM (20 mL), 25 °C, 15 h. [g] Diastereoisomeric ratio (> 20:1) was determined by ¹H NMR analysis (400 MHz).

Table 2 Late-stage sulfoxidation of complex/sensitive substrates

2af: 99%[a]

2ag: 99%[a,h]

2ah: 99%[a,h] (±)

2ai: 99%[b,h]

2aj: 99%[b,h]

2ak: 88% (Omeprazole)[c], 81%,[d]20%,[e]0%[f]

2al: X = O, 99%[g]
2am: X =NH, 99% (Modafinil) [a]

2an: 96%[a]

Reaction conditions: [a] sulfide (1 mmol), PPO (1.1 mmol), DCM (2 mL), 25 °C, 10 h, isolated yields. [b] **1ai-j** (1 mmol), PPO (1.1 mmol), DCM(1 mL) and CH₃OH (1 mL), 25 °C, 8 h. [c] **1ak** (1 mmol), MPO (1.1 mmol), CH₃OH (2 mL), 8 h. [d] **1ak** (3.03 mmol), MPO (3.3 mmol), CH₃OH (20 mL), 25 °C, 8 h. [e] **1ak** (1 mmol), PPO (1.1 mmol), CH₃OH (2 mL), 25 °C, 8 h. [f] **1ak** (1 mmol), BPO (1.1 mmol), CH₃OH (2 mL), 25 °C, 8 h. [g] **1al** (1 mmol), PPO (1.1 mmol), CH₃OH (2 mL), 25 °C, 10 h. [h] Diastereoisomeric ratio (> 20:1) was determined by ¹H NMR analysis (400 MHz) or ¹³C NMR analysis (600 MHz).

In light of these above-mentioned results, we anticipated that our sulfoxidation event could be applied for the more challenging late-stage diversification of drug-like molecules and advanced sulfide intermediates. To our delight, it was found that the present sulfoxidation protocol could readily be employed for the introduction of sulfoxide functionality in complex molecules (Table 2). As shown in Table 2, these sulfides derived from biologically active, synthetically valuable and structurally fascinating molecules (such as sulfur-containing cyclic monoterpenoids, naphthothiazoles, amino acids, benzothiazepinones and steroids) are fully compatible with sulfoxidation, and the desired sulfoxides **2af**-**2an** as the exclusive products were achieved in 88%-99% yields. As seen previously for highly diastereoselective sulfoxidation of cyclic dithioacetal **1ad**, the high diastereomer ratio of cyclic sulfoxides (**2ag**, **2ah**, **2ai** , **2aj and 2an**) were isolated in high yields with an extremely excellent level of diastereoselectivity (more than 20:1 dr (diastereoisomeric ratio)). A noteworthy observation is the absolute and relative configuration of sulfoxidation product **2ai** was determined by X-ray single crystal diffraction analysis.[18] Interestingly enough, S-mono-

oxidation of thioketones (**2ah**) was carried out with phthaloyl peroxides to selectively provide the corresponding thiocarbonyl S-oxides (sulfines) in almost quantitative yields without any detectable over-oxidation to sulfenes, which is a unique class of sulfur-centered heterocumulenes with Z/E isomerism constituting valuable synthetic intermediates in organic chemistry.[19] Even more instructive was the successful preparation of drugs, such as Modafinil (**2am**, 99%) and Omeprazole (**2ak**, 88%, 1 mmol **1ak** with 1.1 equiv. of cyclopentyl malonoyl peroxide in methanol at room temperature for 8 hour), evidencing the perfect chemoselectivity profile among multiple potential reaction sites. To demonstrate the potential application of our sulfoxidation in future synthesis, we tested the scalability of our protocol in course of preparation of Omeprazole on gram scale. When the sulfide **1ak** with cyclic diacyl peroxides was scaled to 3 mmol (1.0 g), the expected product **2ak** was
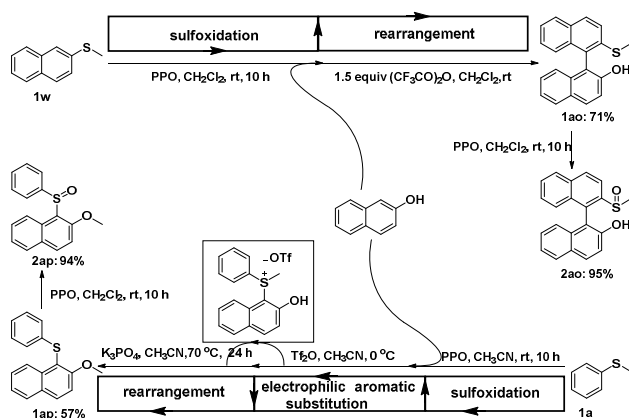
Scheme 1 Application in one-pot construction of functionalized sulfur-containing phenol derivatives.

successive one-electron transfer (radical pathway, route **B**) have been proposed for the formation of intermediate **3**,[23] but
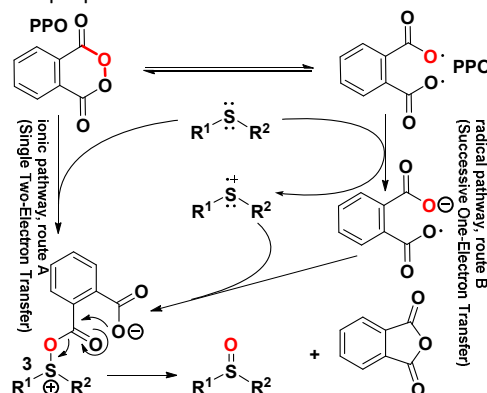

Scheme 2 Possible reaction mechanism.

isolated in 20% (using phthaloyl peroxide) or 81% (using cyclopentyl malonoyl peroxide) yield. In the course of preparation of Omeprazole on gram scale, this reactivity highlighted a marked difference between cyclic diacyl peroxides and acyclic analogs such as benzoyl peroxide (BPO) which has been shown not to react directly with the precursors/substrates under identical conditions. Taken together, the results compiled in Table 2 clearly demonstrate the enabling power prospective impact of our sulfoxidation methodology to late-stage functionalization without touching the other functional groups in a straightforward fashion, thus significantly increasing the overall synthetic practical utility of cyclic diacyl peroxides as new platforms for oxygen-atom transfer reactions. It needs to be addressed that, to the best of our knowledge, this represents the first examples of the sulfur atom oxidation using cyclic diacyl peroxides as mild oxygen source.

To demonstrate the potential synthetic utility and practicality of our methodology, several sequential one-pot multi-step transformations of aryl sulfides (**1a** and **1w**) with 2-naphthol were carried out (Scheme 1) without intermediate isolation. These one-pot stepwise procedures furnished the desired sulfide products **1ao** and **1ap** in 71% and 57% overall yields (for experiment details, see the Supporting Information), which have been recently synthesized and explored by the groups of Yorimitsu[20] and Huang,[21] respectively, albeit in slightly diminished yields. Fortunately, the subsequent reactions were not affected by the existence of phthaloyl anhydride as the by-product. Then, the isolated sulfide products **1ao** and **1ap** was subjected to our standard sulfoxidation to afford the corresponding sulfoxides **2ao** and **2ap** in 95% and 94% yields.

Mechanistic study

On the basis of the aforementioned observations and previous reports,[10,22] two different mechanisms, the single one-step two-electron transfer (ionic pathway, route **A**) and the

they differ in the initial electron demand from sulfide (two electrons via route A, one electron via route B, as shown in Scheme 2). Subsequently intermediate **3** can undergo the intramolecular nucleophilic attack (route **C**) to afford the sulfoxide product and phthaloyl anhydride. By contract, it can also undergo the intramolecular hydrogen abstraction (route **D**) or intermolecular hydrogen abstraction (route **E**) to generate the different product, add the name of **P-D** (Scheme 3). DFT calculations were performed to investigate the detailed reaction mechanism for this reaction at the (U)B3LYP/6-31+G(d) level.[24] which has been previously proven to be suitable and reasonable for this kind of reactions.[11a] The vibrational frequencies of each stationary point were computed at the same level to check whether the optimized structure is an energy minimum or a transition state and to evaluate the zero-point vibration energy and thermal corrections at 298.15 K. Solvent effects were also evaluated by a self-consistent reaction field (SCRF) using the CPCM model[25,26] at the same level with the gas phase optimized structures, where dichloromethane was used as the solvent and UFF radii were used. All calculations in the current study were performed with the Gaussian 03 program package.[27] As shown in Fig. S-1 in the supporting information, the single one-step two-electron transfer pathway (ionic pathway, route **A**) requires an energy barrier of 9.5 kcal/mol, which is 11.7 kcal/mol lower than that for the successive one-electron transfer pathway(radical pathway, route **B**), clearly showing that the single one-step two-electron transfer pathway is more energetically favorable for the formation of intermediate **3**. The relative high energy barrier for the successive one-electron transfer pathway is contributed by the direct C─C bond cleavage to generate a biradicals molecule in **PPO'**. Subsequently, sulfonium-carboxylate inner salt **3** can undergo a barrierless intramolecular nucleophilic attack pathway to generate the sulfoxide product and phthaloyl anhydride. However, the overall energy barriers for the intramolecular and intermolecular hydrogen abstractions are calculated to be 13.3 and 14.3 kcal/mol, respectively, indicating that the intramolecular nucleophilic attack pathway is the main pathway and both hydrogen abstractions hardly occur. It is in good agreement with the fact that only **P-C** product is experimentally observed.

Similarly, we speculated that unstable cyclopentyl malonoyl anhydride was formed as an unwanted side-product using cyclopentyl malonoyl peroxide as oxygen source base on the malodour from the finished reaction mixture. Considering that generation of malonoyl anhydride should be less-favored due to the formation of a four membered ring, an alternative reaction pathway was proposed that subsequent decarboxylation of the analogous intermediate **4** leads to the formation of cyclopentane ketene, which is subsequently trapped with water to give the cyclopentane carboxylic acid (Scheme 4).

While phthaloyl peroxide, benzoyl peroxide and *tert*-butyl peroxybenzoate share similarities in atom connectivity, phthaloyl peroxide possessing the increased strain exhibits heightened thermal stability.[28] Compared to our novel approaches, the sulfoxidation using benzoyl peroxide[29] or *tert*-butyl peroxybenzoate[30] is hopelessly impractical and difficult

to handle because the generated benzoate anion or *tert*-butoxide can act as a base towards hydrogen rather than a nucleophile towards carbon may accommodate the formation of ylide which can subsequently provide access to the unexpected α-acyloxylated product. The increased reactivity of cyclic diacyl peroxides versus acyclic peroxides might been attributed to repulsion between non-bonded electron pairs of the peroxy-oxygen atoms[9a] and the generated sulfonium-carboxylate inner salts.

Conclusions

In conclusion, we have described the first use of cyclic diacyl peroxides as mild oxygen source to provide access to various sulfoxides and sulfine derivatives in the absence of catalysts
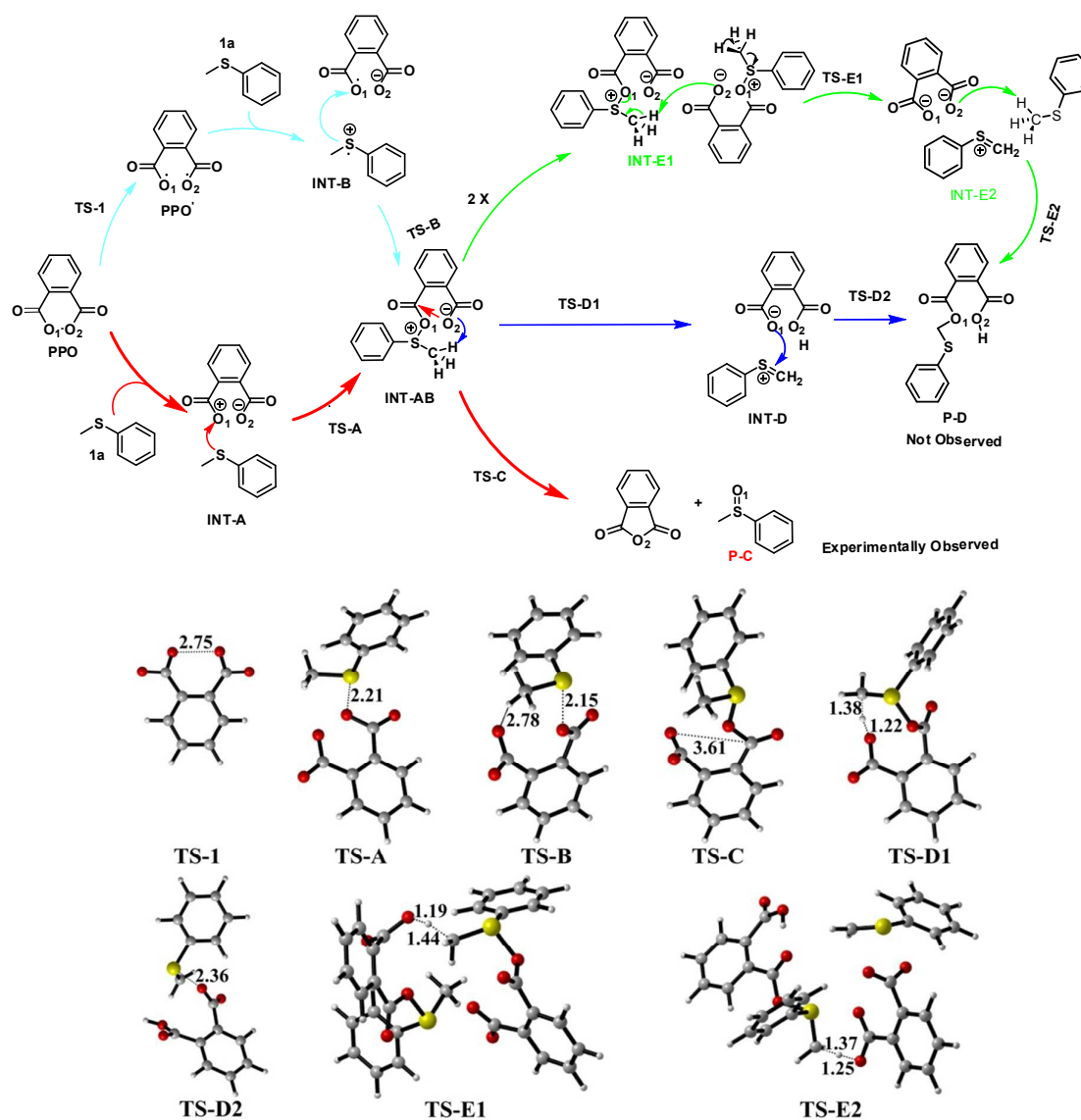
Scheme 3 Proposed mechanism and the optimized geometries of the transition state.
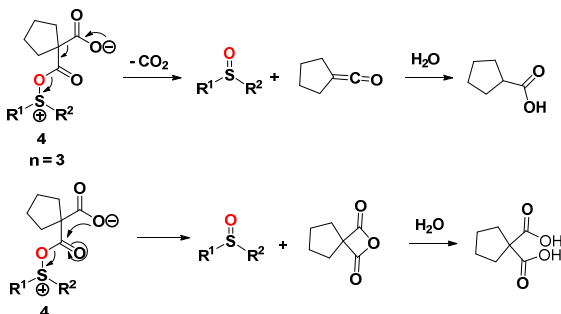
Scheme 4 Possible reaction pathway.

and additives. It should be mentioned for the procedure that the unprecedented selectivity from sulfides/thioketones to sulfoxides/sulfines could be perfectly controlled without the need for special exclusion of air or moisture. Particularly illustrative is the chemoselectivity profile of our protocol, as heterocycles (**1t**, **1u**, **1v**), amides (**1am**), ketones (**1g**), and even aldehydes (**1f**) were tolerated. Notably, unprotected aliphatic alcohols (**1aj**), phenols (**1i**), and carbonyl compounds containing relatively acidic α-protons (**1ai**) did not compete with the efficacy of the sulfoxidation event, thus providing ample opportunities for subsequent manipulation. High levels of substrate-directed diastereocontrol in the sulfoxidation was observed when a chiral center is present in the specific cyclic sulfur-containing substrates. The excellent functional group compatibility, broad substrate scope, and high chemo- and diastereoselectivity of this transformation provide the general method for the direct metal-free late-stage sulfoxidation of complex and/or sensitive molecules important molecular scaffolds, which make it a synthetically valuable method for the synthesis of organic sulfoxides. In our opinion, the operationally simple, multigram-scale sulfoxidation with cyclic diacyl peroxides is currently one of the most practical methods to obtain a large variety of sulfoxides on multigram and smaller scales, but it requires stoichiometric amounts of cyclic diacyl peroxides. A disadvantage of the transformation is the generation of a stoichiometric amount of waste, the phthaloyl anhydride and cyclopentanecarboxylic acid byproduct. Fortunately, based on the literatures[31,10a,10b] phthaloyl anhydride and cyclopentanecarboxylic acid can be used to re-synthesized corresponding peroxides. We believe that the distinct cyclic diacyl peroxides-based reactivity shown here may contribute to the meaningful development of more general oxidation reactions. The other performance of cyclic diacyl peroxides and the development of the corresponding catalytic or asymmetric variant are currently under investigation.

Acknowledgements

Experimental section

General procedure for the synthesis of the sulfoxidition of the corresponding sulfide.
A solution of an appropriate sulfide (1 mmol) and PPO (1.1 mmol) in CH_2Cl_2 (2 mL) was stirred in a standard schlenk tube at room temperature (8-10 h). The resulting reaction mixture was concentrated in vacuum and purified by column chromatography using petroleum ether/ethyl acetate to afford corresponding products.

Notes and references

1   For recent reviews on chiral sulfoxide ligands for asymmetric catalysis, see: (a) M. Mellah, A. Voituriez and E. Schulz, *Chem. Rev.*, 2007, **107**, 5133–5209; (b) B. M. Trost and M. Rao, *Angew. Chem., Int. Ed.*, 2015, **54**, 5026–5043; (c) G Sipos, E. E. Drinkel and R. Dorta, *Chem. Soc. Rev.,* 2015, **44**, 3834–3860; (d) S. Kobayashi, C. Ogawa, H. Konishi and M. Sugiura, *J. Am. Chem. Soc.*, 2003, **125**, 6610–6611; (e) R. Mariz, X. Luan, M. Gatti, A. Linden and R. Dorta, *J. Am. Chem. Soc.*, 2008, **130**, 2172–2173; (f) J. Chen, J. Chen, X. Zhang, L. Cun, J. Zhu, J. Deng and J. Liao, *J. Am. Chem. Soc.*, 2010, **132**, 4552–4553; (g) Q.-A. Chen, X. Dong, M.-W. Chen, D.-S. Wang, Y.-G. Zhou and Y.-X. Li, *Org. Lett.*, 2010, **12**, 1928–1931; (h) T. Thaler, L.-N. Guo, A. K. Steib, M. Raducan, K. Karaghiosoff, P. Mayer and P. Knochel, *Org. Lett.*, 2011, **13**, 3182–3185; (i) W.-Y. Qi, T.-S. Zhu and M.-H. Xu, *Org. Lett.*, 2011, **13**, 3410–3413; (j) B. M.Trost, M. Rao and A. P. Dieskau, *J. Am. Chem. Soc.*, 2013, **135**, 18697–18704; (k) T. Jia, P. Cao, B. Wang, Y. Lou, X. Yin, M. Wang and J. Liao, *J. Am. Chem. Soc.*, 2015, **137**, 13760–13763.

2   For reviews on the application of sulfoxides as versatile synthetic intermediates, see: (a) M. C. Carreño, *Chem. Rev.*, 1995, **95**, 1717–1760; (b) E. N. Prilezhaeva, *Russ. Chem. Rev.*, 2001, **70**, 897–920; (c) I. Fernández and N. Khiar, *Chem. Rev.*, 2003, **103**, 3651–3705; (d) S. K. Burr and A. Padwa, *Chem. Rev.*, 2004, **104**, 2401–2432; (e) M. C. Carreño, G. Hernández-Torres, M. Ribagorda and A. Urbano, *Chem. Commun.*, 2009, 6129–6144; (f) W. H. Pearson and B. W. Lian, *Angew. Chem., Int. Ed.*, 1998, **37**, 1724–1726; (g) J. P. Marino, M. S. McClure, D. P. Holub, J. V. Comasseto and F. C. Tucci, *J. Am. Chem. Soc.*, 2002, **124**, 1664–1668; (h) A. Abramovitch, L. Fensterbank, M. Malacria and Marek, I. *Angew. Chem., Int. Ed.*, 2008, **47**, 6865–6868; (i) S. Krüger and T. Gaich, *Angew. Chem., Int. Ed.*, 2015, **54**, 315–317; (j) H. Cheng, F.-H. Zeng, X. Yang, Y.-J. Meng, L. Xu and F.-P. Wang, *Angew. Chem., Int. Ed.*, 2016, **55**, 392–396; (k) H. Lei, J. Yan, J. Yu, Y. Liu, Z. Wang, Z. Xu and T. Ye, *Angew. Chem., Int. Ed.*, 2014, **53**, 6533–6537; (l) M. H. Nguyen, M. Imanishi, T. Kurogi and A. B. Smith III, *J. Am. Chem. Soc.*, 2016, **138**, 3675–3678.

3   (a) S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan and D. H. B. Ripin, *Chem. Rev.*, 2006, **106**, 2943–2989; (b) E. R. Yera, A.

E. Cleves and A. N. Jain, *J. Med. Chem.*, 2011, **54**, 6771-6785; (c) S. Liao, I. Čorič, Q. Wang and B. List, *J. Am. Chem. Soc.*, 2012, **134**, 10765–10768; (d) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (e) Achaogen Inc. WO2009/137130A2, 2009. (f) Combinatorx (Singapore) Pte. Ltd. US2010/9970A1, 2010.

4   For reviews, see: (a) H. L. Holland, *Chem. Rev.*, 1988, **88**, 473–485; (b) M. Madesclaire, *Tetrahedron*, 1986, **42**, 5459–5495; (c) Bolm, C. *Coord*. *Chem. Rev.*, 2003, **237**, 245–256; (d) P. Kowalski, K. Mitka, K. Ossowka and Z. Kolarska, *Tetrahedron*, 2005, **61**, 1933–1953; (e) K. Kaczorowska, Z. Kolarska, K. Mitka and P. Kowalski, *Tetrahedron*, 2005, **61**, 8315–8327; (f) E. Wojaczyńska and J. Wojaczyński, *Chem. Rev*., 2010, **110**, 4303–4356; (g) F. A. Davis, R. T. Reddy, W. Han and Patrick J. Carroll, *J. Am. Chem. Soc.*, 1992, **114**, 1428–1437; (h) R. Cibulka, *Eur. J. Org. Chem.* 2015, **2015**, 915; (i) H. Iida, Y. Imada and S.-I. Murahashi, *Org. Biomol. Chem.* 2015, **13**, 7599. (j) X.-Y. Gu, X. Li, Y.-H. Chai, Q. Yang, P.-X. Li and Y.-M. Yao; *Green Chem.* 2013, **15** 357; (K) T. Neveselý, E. Svobodová, J. Chudoba, M. Sikorski and R. Cibulka, *Adv. Synth. Catal.* 2016, **358**, 1654.

5   For selected recent examples, see: (a) Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang, X. Su, H. S. Wilkinson, Z.-H. Lu, D. Magiera and C. H. Senanayake, *Tetrahedron,* 2005, **61**, 6386–6408; (b) F. Xue, D. Wang, X. Li and B. Wan, *J. Org. Chem.,* 2012, **77**, 3071–3081; (c) T. Miao, P. Li, Y. Zhang and L. Wang, *Org. Lett.,* 2015, **17**, 832–835.

6   (a) C. Mollar, M. Besora, F. Maseras, G. Asensio and M. Medio-Simón, *Chem.−Eur. J.* 2010, **16**, 13390–13397; (b) T. Jia, A. Bellomo, K. EL. Baina, S. D. Dreher and P. J. Walsh, *J. Am. Chem. Soc.*, 2013, **135**, 3740–3743.

7   (a) G. Maitro, S. Vogel, G. Prestat, D. Madec and G. Poli, *Org. Lett.*, 2006, **8**, 5951–5954; (b) G. Maitro, S. Vogel, M. Sadaoui, G. Prestat, D. Madec and G. Poli, *Org. Lett.*, 2007, **9**, 5493–5496; (c) E. Bernoud, G. L. Duc, X. Bantreil, G. Prestat, D. Madec and G. Poli, *Org. Lett.*, 2010, **12**, 320−323; (d) F. Gelat, J.-F. Lohier, A.-C. Gaumont and S. Perrio, *Adv. Synth. Catal.*, 2015, **357**, 2011−2016; (e) F. Izquierdo, A. Chartoire and S. P. Nolan, *ACS Catal.*, 2013, **3**, 2190–2193; (f) T. Jia, A. Bellomo, S. Montel, M. Zhang, K. EL. Baina, B. Zheng, P. J. Walsh, *Angew. Chem., Int. Ed.*, 2014, **53**, 260−264; (g) T. Jia, M. Zhang, I. K. Sagamanova, C. Y. Wang, P. J. Walsh, *Org. Lett.*, 2015, **17**, 1168−1171; (h) T. Jia, M. Zhang, H. Jiang, C. Y. Wang and P. J. Walsh, *J. Am. Chem. Soc.*, 2015, **137**, 13887−13893; (i) H. Jiang, T. Jia, M. Zhang, P. J. Walsh, *Org. Lett.*, 2016, **18**, 972−975.

8   R. Noyori, M. Aoki and K. Sato, *Chem. Commun.*, 2003, 1977−1986.

9   (a) F. D. Greene, *J. Am. Chem. Soc.*, 1956, **78**, 2246−2250; (b) W. Adam and R. Rucktaeschel, *J. Am. Chem. Soc.*, 1971, **93**, 557−559; (c) W. Adam, *Acc. Chem. Res.*, 1979, **12**, 390−396.

10 (a) C. Yuan, A. Axelrod, M. Varela, L. Danysh and Siegel, D. *Tetrahedron Lett.*, 2011, **52**, 2540–2542; (b) J. C. Griffith, K. M. Jones, S. Picon, M. J. Rawling, B. M. Kariuki, M. Campbell and N. C. O. Tomkinson, *J. Am. Chem. Soc.*, 2010, **132**, 14409–14411; (c) K. M. Jones and N. C. O. Tomkinson, *J. Org. Chem.*, 2012, **77**, 921–928; (d) S. Picon, M. Rawling, M. Campbell, N. C. O. Tomkinson, *Org. Lett.*, 2012, **14**, 6250–6253; (e) M. J. Rawling, J. H. Rowley, M. Campbell, A. R. Kennedy, J. A. Parkinson and N. C. O. Tomkinson, *Chem. Sci.*, 2014, **5**, 1777–1785; (f) C. Alamillo-Ferrer, S. C. Davidson, M. J. Rawling, N. H. Theodoulou, M. Campbell, P. G. Humphreys, A. R. Kennedy and N. C. O. Tomkinson, *Org. Lett.,* 2015, **17,** 5132–5135; (g) M. Schwarz and O. Reiser, *Angew. Chem., Int. Ed.*, 2011, **50**, 10495–10497.

11 (a) C. Yuan, Y. Liang, T. Hernandez, A. Berriochoa, K. N. Houk and D. Siegel, *Nature*, 2013, **499**, 192–196; (b) A. Dragan, T.

M. Kubczyk, J. H. Rowley, S. Sproules and N. C. O. Tomkinson, *Org. Lett.*, 2015, **17**, 2618–2621.

12 (a) D. Chang, D. Zhu and L. Shi, *J. Org. Chem.*, 2015, **80**, 5928–**5933**; (b) J. Torres-Alacan, *J. Org. Chem.*, 2016, **81**, 1151–**1156**.

13 A. O. Terent'ev, V. A. Vil', E. S. Gorlov, G. I. Nikishin, K. K. Pivnitsky and W. Adam, *J. Org. Chem.*, 2016, **81**, 810–823.

14 W. Adam and J. W. Diehl, *J. Chem. Soc., Chem. Commun.,* 1972, **13**, 797-798.

15 (a) H. Marom, S. Antonov, Y. Popowski and M. J. Gozin,*J. Org. Chem.*, 2011, **76**, 5240–5246; (b) S. Meninno, A. Parrella, G. Brancatelli, S. Geremia, C. Gaeta, C. Talotta, P. Neri and A. Lattanzi, *Org. Lett.*, 2015, **17**, 5100–5103.

16 (a) J. Fujisaki, K. Matsumoto, K. Matsumoto and T. Katsuki, *J. Am. Chem. Soc.*, 2011, **133**, 56–61; (b) Y. Wu, F. Mao, F. Meng and X. Li, *Adv. Synth. Catal.*, 2011, **355**, 1707–1712.

17 J. H. Delcamp and M. C. White, *J. Am. Chem. Soc.*, 2006, **128**, 15076–15077.

18 CCDC 1510240 contains the supplementary crystallographic data for compound **2ai**. See ESI† for details.

19 (a) B. *J.* Zwanenburg, *J. Sulfur Chem.*, 2013, **34**, 142–157; (b) A. J. Sánchez-Arroyo, Z. D. Pardo, F. Moreno-Jiménez, A. Herrera, N. Martín and D. García-Fresnadillo, *J. Org. Chem.,* 2015, **80**, 10575–10584.

20 T. Yanagi, S. Otsuka, Y. Kasuga, K. Fujimoto, K. Murakami, K. Nogi, H. Yorimitsu and A. Osuka. *J. Am. Chem. Soc.* 2016, **138**, 14582–14585.

21 (a) D. Chen, Q. Feng, Y. Yang, X. Cai, F. Wang and S. Huang, *Chem. Sci.,* 2017, 10.1039/c6sc04504a;(b) E. L. Clennan, *Tetrahedron*, 2000, **56**, 9151-9179. (c) D. M. Camp, P. C. Vasquez and A. L. Baumstark, *Heterocycl. Commun.* 2015; **21** 47–53.

22 (a) J. Park, Y. Morimoto, Y.-M. Lee, W. Nam and S. Fukuzumi, *J. Am. Chem. Soc.*, 2011, **133**, 5236–5239; (b) W. Nam, Y.-M. Lee and S. Fukuzumi, *Acc. Chem. Res.*, 2014, **47**, 1146–1154; (c) A. Barbieri, R. D. C. Chimienti, T. D. Giacco, S. D. Stefano, O.,Lanzalunga, A. Lapi, M. Mazzonna, G. Olivo and M. Salamone, *J. Org. Chem.*, 2016, **81**, 2513–2520.

23 C. Wang, L. Sim, D. R. Rose and B. M. Pinto, *Carbohydr. Res.*, 2007, **342**, 1661−1667.

24 Ab Initio Molecular Orbital Theory, Ed. W. J. Hehre, L. Radom, P. V. R. Schleyer and J. A. Pople, New York, 1986.

25 V. Barone, and M. Cossi, *J. Phys. Chem. A.*, 1998, **102**, 1995−2001.

26 M. Cossi, N. Rega, G. Scalmani and V. Barone, *J. Comput. Chem.*, 2003, **24**, 669−681.

27 Frisch, M. J. et al. Gaussian 03, Revision B.03, Gaussian, Inc., Wallingford CT, 2004.

28 K. Fujimori, Y. Oshibe, Y. Hirose and S. Oae, *J. Chem. Soc., Perkin Trans. 2*, 1996, 413−417.

29 (a) L. Horner, E. Jürgen and Annalen, *Liebigs Ann. Chem.*, 1957, **602**, 135−153; (b) H. B. Henbest, J. A. W. Reid and C. J. M. Stirling, *J. Chem. Soc.*, 1964, 1220−1223; (c) D. I. Davies, D. H. Hey and B. Summers, *J. Chem. Soc. C.*, 1970, 2653−2660; (d) W. A. Pryor, H. T. Bickley, *J. Org. Chem.*, 1972, **37**, 2885−2893.

30 W. A. Pryor and W. H. Jr. Hendrickson, *J. Am. Chem. Soc.*, 1983, **105**, 7114−7122.

31 (a) R. D. Gandour, M. Coyne, V. J. Stella and R. L. Schowen, *J. Org. Chem.*, 1980, **45**, 1733−1737; (b) C. R. Davis, D. C. Sweson and D. J. Burton, *J. Org. Chem.*, 1972, **37**, 2885−2893.