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Direct organocatalytic esterification of carboxylic acids and alcohols by redox neutral sulfur(IV) catalysis *via* intramolecularly interrupted Pummerrer intermediates†

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Design, synthesis, and catalytic activity of new sulfur(IV) based organocatalysts for the direct esterification of carboxylic acids and alcohols is unveiled. The polar nature of the sulfoxide in the phenol-tethered catalyst accelerates the formation of an intramolecularly interrupted Pummerrer intermediate that further facilitates the catalytic esterification reaction *via* the activation of carboxylic acids.

Esterification is one of the fundamental reactions in organic chemistry. The ester functionality is widely found in nature, and many critical natural products contain ester groups, such as the antitumor drug quiderone[1] and taxol[2] for treating breast cancer and ovarian cancer. Esterification is a reaction that is also routinely used in the chemical industry to synthesize biodiesel, paints and varnishes, plastics and coatings, and pharmaceuticals. Hence, environmentally benign methods for commercial esterification are in exceptionally high demand. Some of the standard dehydrative Fischer-type esterification methods involve strong Brønsted acids or metal heterogeneous catalysts, which cannot be applied to sensitive organic compounds (Scheme 1a).[3–7] Also, one of the components is usually used in high excess to have decent yields of the ester product. Other methods include an extra step of activating the acid functionality into acid chlorides or anhydrides. However, the most used protocols for esterification methods are the Steglich esterification[8] (employing DCC and DMAP), Mitsunobu[9,10] reaction (employing DEAD and triphenylphosphine) and the Yamaguchi[11–13] esterification (2,4,6-trichlorobenzoyl chloride and DMAP) protocol and all of them involve use of stoichiometric amounts of activating agents and produce stoichiometric amount of waste products (Scheme 1b). Also, the need to remove all of these excess by-products make the purification of the ester products more challenging. Attempts have been made to improve the Mitsunobu protocol by various groups by introducing co-oxidants and co-reductants. However, this results only in replacing one stoichiometric reagent with the other. Nacsa[14] and coworkers reported an excellent tri-methoxy *N*-phenylphenothiazine catalysed electrocatalytic direct esterification of carboxylic acids with alcohols at room temperature.

Recently, Denton[15a–c] and coworkers introduced a very intriguing and ground-breaking phosphine oxide catalyst with phenoxy tether that helps in performing the Mitsunobu type esterification under catalytic redox neutral conditions with only water as the sole by-product, however, also resulting in stereoinversion at the alcohol center. This reaction is facilitated by the strong oxophilicity of the cationic P(v) intermediate and the regeneration of the catalyst, resulting in the formation of a strong P=O bond. On the other hand, the formation of the cationic P(v) intermediate is slow due to the very strong P=O, which results in longer reaction times. We were intrigued to understand the mechanistic difference by replacing P=O with an S=O. We envisaged that a sulfoxide-based catalyst with a phenolic tether would also result in a similar cyclic intermediate *via* an intramolecular interrupted Pummerrer-type intermediate under mildly acidic conditions. However, it would be intriguing to study the reactivity of such an intermediate in esterification reactions. Also, sulfoxide being more polar, we envisaged a mechanistic switch in the esterification reaction.

With this view in mind, herein, we designed the synthesis of sulfoxide-based organocatalysts for the direct esterification of carboxylic acids with alcohols *via* a redox neutral S(IV) catalysis (Scheme 1c). Sulfur(IV) compounds play an extraordinary role in organic chemistry.[16–19] Our synthetic strategy started by reacting 2,4-disubstituted phenols with formaldehyde, resulting in the formation of *ortho*-(hydroxymethyl)phenols (Table 1). Subsequent reactions of these substrates with various thiophenols under acid catalysis followed by oxidation resulted in synthesizing the desired S(IV) catalysts with a phenolic tether. Catalysts **S1–S7**, with variations from both the phenolic and thiol components,

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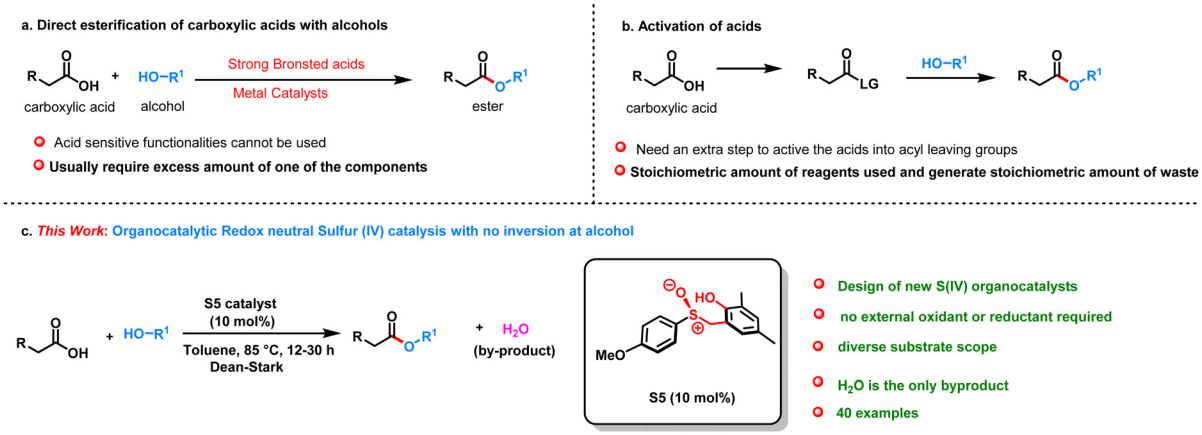
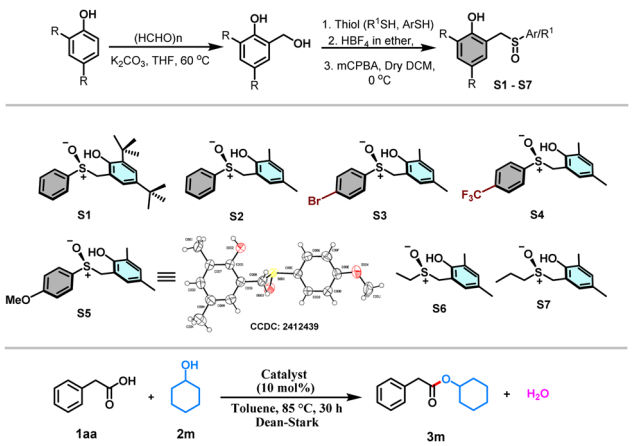
† Electronic supplementary information (ESI) available: Detailed experimental procedures for the synthesis of starting materials and products; their spectroscopic data; NMR, HRMS spectra and X-ray crystallographic data of compounds **S5**. CCDC 2412439. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d5cc00556f**



Scheme 1 (a) and (b) Previous literature on esterification reactions and (c) current work.

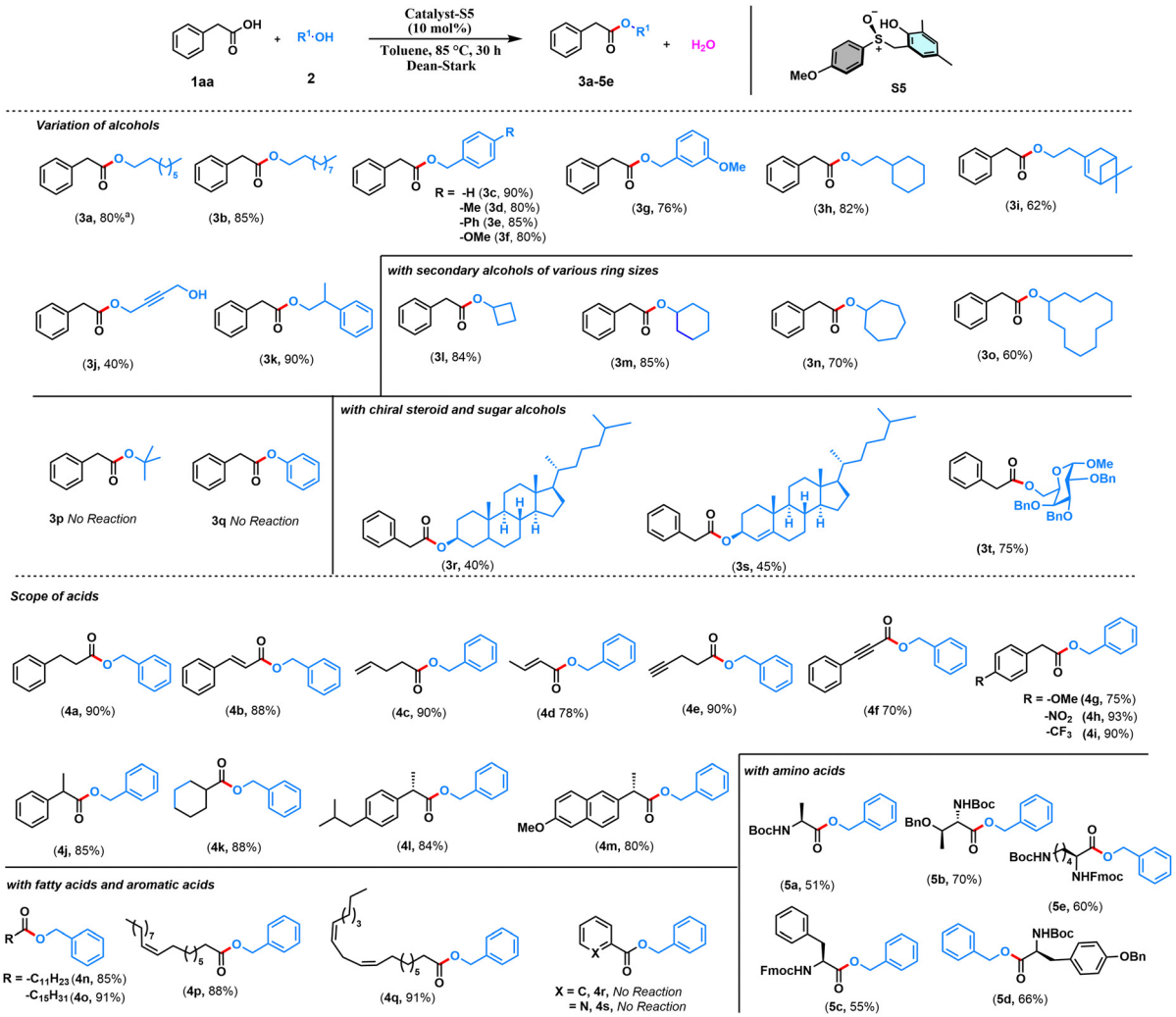
Table 1 Synthesis of the catalysts and optimization of the reaction conditions[a]



Entry	Catalyst	Catalyst (mol%)	Yield[b] (%)
1	**S1**	10	30
2	**S2**	10	45
3	**S3**	10	15
4	**S4**	10	10
5	**S5**	**10**	**85**
6	**S6**	10	20
7	**S7**	10	58
8	**S5**	15	55
9	**S5**	20	65

[a] Reaction conditions: **1aa** (1.0 equiv. 0.7 mmol), **2m** (1.5 equiv. 1.09 mmol), catalyst (10 mol%) in toluene (2 ml) was refluxed in a Dean–Stark apparatus for 30 h. [b] Isolated yield.

have been synthesized to test the efficacy of these catalysts toward the organocatalytic esterification reaction (Table 1). The crystal structure obtained for one of the catalysts **S5** helped the unambiguous characterization of the structures of the catalysts. With the catalysts (**S1–S7**) in hand, we tested their ability toward esterification between 1.5 equiv. of secondary alcohol, cyclohexanol (**2m**) and 1 equiv. of phenylacetic acid (**1aa**) as the model substrates with 10 mol% of the catalyst and toluene as a solvent under Dean–Stark conditions (Table 1). The sterically more hindered **S1** provided the ester product in 30% yield, whereas the sterically less hindered **S2** yielded only 45% of the product (Table 1). Later, the electron-withdrawing groups like Br and CF_3 containing catalysts **S3** and **S4**, respectively, and electron donating OMe group containing catalyst **S5** were tested. Surprisingly, the yield significantly dropped with **S3** and **S4**, whereas the OMe containing **S5** performed the best providing the expected product in 85% yield (Table 1). Later, the catalysts **S6** and **S7** derived from alkyl thiols were also tested. However, the yields of the product were only moderate. Hence, the catalyst **S5** is taken as the optimized catalyst. Surprisingly, the increase in the catalytic amount to 15 and 20 mol% led to a decrease in the yield of the ester product (Table 1). Hence, 10 mol% of **S5** has been taken as the optimized condition for the esterification reaction. A range of alcohols were successfully acylated with phenylacetic acid (Scheme 2). All the primary alcohols tested including functional groups like alkene and alkyne, were successfully coupled to form the ester with phenylacetic acid in moderate to excellent yields (**3a–3k**, 40–90% yields, Scheme 2). The symmetric alkyne diol provided only the mono-esterified product **3j** in a very moderate 40% yield. Secondary alcohols like cyclobutanol, cyclohexanol, cycloheptanol, and cyclododecanol also reacted very well, providing the coupled products in decent yields (**3l–3o**, 60–85%, Scheme 2). The method's ability has also been tested in the ester protection of galactose-derived 6-OH, which gave the product **3t** in a good 75% yield (Scheme 2). Interestingly, the sterically hindered *tert*-butanol and the weakly nucleophilic phenol failed to provide the coupled product. The sterically hindered cholesterol also gave the product in 45% yield (**3s**, Scheme 2) with a retention in stereochemistry. To understand if there is a neighboring group effect by the alkene functionality, the alkene-reduced cholesterol was also subjected to the reaction conditions, providing the ester product in 40% yield (**3r**, Scheme 2) again with the retention of the absolute configuration. Later, we tested the scope of various acids under the current protocol with benzyl alcohol as the standard coupling partner (Scheme 2). A variety of acids with a range of functional groups have been successfully coupled to provide the ester products in good to excellent yields (**4a–4f**, 70–90% yields, Scheme 2). The electron-withdrawing groups NO_2 and CF_3 containing phenylacetic acids provided

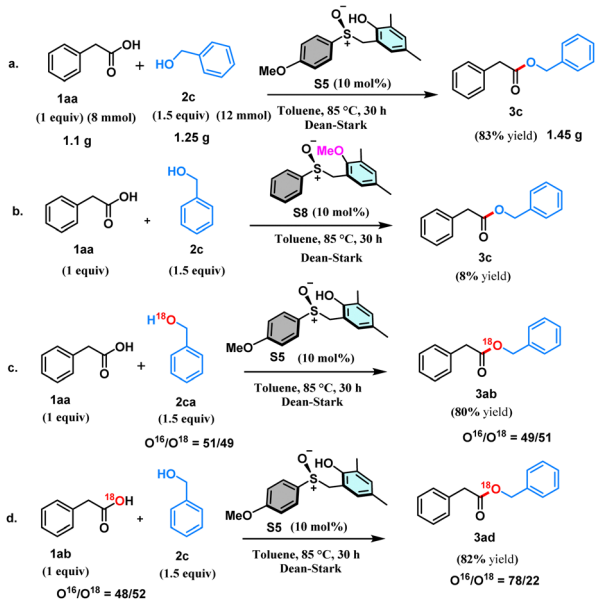


Scheme 2 Substrate scope. Reaction conditions: **1aa** (1.0 equiv. 0.7 mmol), **2** (1.5 equiv. 1.09 mmol), catalyst **S5** (10 mol%) in toluene (2 ml) was refluxed in a Dean–Stark apparatus for 30 h. [a] Isolated yield.

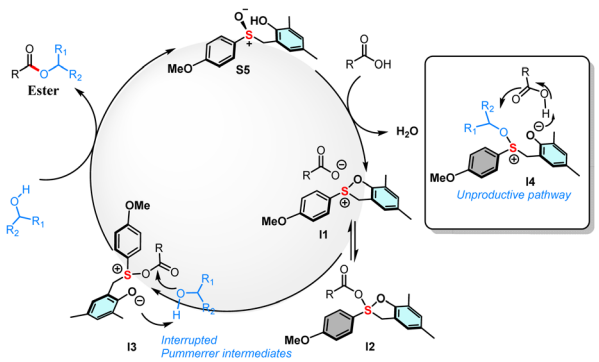
greater yields of the ester product relative to electron-donating (OMe) group containing substrate (**4g–4i**, 75–93% yields, Scheme 2). However, aromatic acids like benzoic acid and heteroaromatic pyridine 2-carboxylic acid failed to react under these conditions. Drug molecules like ibuprofen, naproxen, long-chain carboxylic, and unsaturated fatty acids were esterified in good to excellent yields (**4l–4q**, 84–91%, Scheme 2). Notably, the acid and base-sensitive Boc, Fmoc groups containing amino acids were also tolerated and afforded the ester products in moderate yields (**5a–5e**, 51–70% yields, Scheme 2). The gram scale esterification between **1aa** and **2c** has also provided the product in a good 83% yield (Scheme 3a).

Control experiments were performed to gain insights into the mechanism of this transformation. As expected, the reaction only gave 10% yield of the product in the absence of any catalyst (see the ESI†). Also, the sulfoxide catalyst with OMe group instead of phenolic group gave only 8% yield of the product confirming the importance of the phenolic substituent in the current transformation (Scheme 3b). We also have performed oxygen labelling experiments in order to understand whether the esterification reaction under the current protocol proceeds *via* acid activation or alcohol activation. We have synthesized the O^{18} labelled benzyl alcohol (**2ca**) and O^{18} labelled phenylacetic acid (**1ab**) for the purpose.

Interestingly, when the coupling reaction is performed with O^{18} labelled benzyl alcohol (**2ca**) with unlabelled acid (**1aa**), the same amount of O^{18} labelling is observed in the ester (**3ab**) product (Scheme 3c). In addition, when the coupling experiment is performed with O^{18} labelled phenylacetic acid (**1ab**) unlabelled benzyl alcohol (**2c**), a significant loss of O^{18} labelling is observed within the product (**3ad**) (Scheme 3d). These experiments suggest that the major pathway in the current transformation is *via* the acid activation, not the alcohol activation. Based on all the above experiments, we propose the mechanism of the current transformation as depicted in (Scheme 4). The sulfoxide catalyst **S5** reacts with the acid and forms an initial sulfonium cationic intermediate **I1** that can be in equilibrium with intermediates **I2** and **I3**. The intermediate **I3** can react with nucleophilic alcohol *via* an H-bonding with the phenoxide, thus providing the ester product



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism.

and also regenerating the catalyst **S5** (Scheme 4). Also, the pathway involving an S_N2 attack on alcohol intermediate **I4** is unproductive. Since sulfur is less electronegative, it lacks the driving force for a C–O bond cleavage by a weak nucleophile, unlike the phosphorous analogue.[15a]

In conclusion, we have designed and developed a new redox neutral sulfoxide-based S(IV) organocatalysts with a phenolic tether, that can be used for esterification reactions without inversion at the alcohol stereocenter. The substrate scope is broad for the current protocol and we believe that this new class of organocatalysts may find use in catalysing many other organic transformations as well.

PKK conceived the idea and wrote the manuscript. AB has performed all the experiments, PP and SAW performed the control experiments.

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Data availability

The data underlying this study are available in the published article and its ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 P. A. Sprengeler, *et al.*, *J. Am. Chem. Soc.*, 1991, **113**, 3533–3542.
2 Y. Nakamura and S. Chung-gi, *Chem. Lett.*, 1992, **21**, 49–52.
3 *Comprehensive Organic Synthesis*, ed. P. Knochel, G. A. Molander, Elsevier, Amsterdam, 2nd edn, 2014, vol. 6, pp. 1–841.
4 (*a*) J. W. Bode, *et al.*, *Nature*, 2011, **480**, 471–479; (*b*) J. M. J. Williams, *OH Activation for Nucleophilic Substitution, In Sustainable Catalysis*, John Wiley & Sons, Hoboken, NJ, 2013, pp. 121–138.
5 R. J. Ouellette and J. D. Rawn, *Principles of Organic Chemistry*, Elsevier, Amsterdam, 2014, pp. 699–745.
6 J. Otera, *Esterification: Methods, Reactions, and Applications*, Wiley-VCH, Weinheim, 2003.
7 E. Fischer and A. Speier, *Darstellung der Ester, Ber. Dtsch. Chem. Ges.*, 1895, **28**, 3252–3258.
8 (*a*) W. Steglich, *et al.*, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522–524; (*b*) H. F. Sneddon, *et al.*, *Green Chem.*, 2021, **23**, 6405–6413.
9 G. Boshart, *et al.*, *J. Org. Chem.*, 1961, **26**, 2525–2528.
10 O. Mitsunobu, *et al.*, *Bull. Chem. Soc. Jpn.*, 1967, **40**(50), 2380–2382.
11 P. H. Toy, *et al.*, *J. Am. Chem. Soc.*, 2006, **128**, 9636–9637.
12 (*a*) T. Taniguchi, *et al.*, *Angew. Chem., Int. Ed.*, 2013, **52**, 4613–4617; (*b*) T. Taniguchi, *et al.*, *Chem. Sci.*, 2016, **7**, 5148; (*c*) D. Hirose, M. Gazvoda, J. Košmrlj and T. Taniguchi, *Org. Lett.*, 2016, **18**, 4036–4039.
13 J. A. Buonomo and C. C. Aldrich, *Angew. Chem., Int. Ed.*, 2015, **54**, 13041–13044.
14 E. D. Nacsa, *J. Am. Chem. Soc.*, 2023, **145**(29), 15680–15687.
15 (*a*) R. H. Beddoe, K. G. Andrews, V. Magn, J. D. Cuthbertson, J. Saska, A. L. Shannon-Little, S. E. Shanahan, H. F. Sneddon and R. M. Denton, *Science*, 2019, **365**, 910–914; (*b*) X. Tang, C. Chapman, M. Whiting and R. M. Denton, *Chem. Commun.*, 2014, **50**, 7340–7343; (*c*) Y. Zou, J. J. Wong and K. N. Houk, *J. Am. Chem. Soc.*, 2020, **142**(38), 16403–16408.
16 D. Kaiser, I. Klose, R. Oost, J. Neuhaus and N. Maulide, *Chem. Rev.*, 2019, **119**(14), 8701–8780.
17 T. Wai, H. L. Wang and Y. Tian, *et al.*, *Nat. Chem.*, 2024, **16**, 1301–1311.
18 S. Song, X. Li and J. Wai, *et al.*, *Nat. Catal.*, 2020, **3**, 107–115.
19 B. M. Trost and M. Rao, *et al.*, *Angew. Chem., Int. Ed.*, 2015, **54**, 5026–5043.