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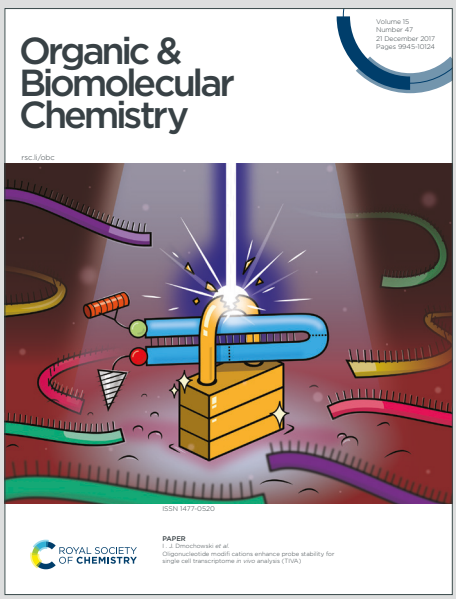

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COMMUNICATION

Phenylboronic Acid-Catalyzed Tandem Construction of S-S and C-S Bonds: A New Entry for the Synthesis of Benzyl Disulfanylsulfone Derivatives from *S*-Benzyl Thiosulfonates†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A unique phenylboronic acid-catalyzed dimerization–sulfonylation of *S*-benzyl thiosulfonates have been disclosed. A metal-free tandem construction of S-S and C-S bonds is an operationally simple to access a wide range of benzyl disulfanylsulfone derivatives in high to excellent yields. Moreover, the robustness of this tandem transformation has been demonstrated by gram-scale reactions, and a plausible mechanism is also proposed.

Disulfanes are widely present in nature[1] where the S-S bridge plays a critical role in protein folding and mediating the biological activity of peptides in the living systems.[2] Additionally, the sulfur-sulfur structural linkage able to release a cellular singling hydrogen sulfide virtue of their pathological and physiological properties.[3] Meanwhile, the disulfide framework found in organic functional materials,[4] food chemistry[5] and pharmaceutical chemistry[6] as presented in Figure 1a. Given the significant importance of disulfanes, the development of a general and metal-free protocol for the synthesis of functionalized disulfanes is always desirable.

Although numerous effective strategies have been developed for the synthesis of both symmetrical and unsymmetrical disulfanes,[7-9] however, the construction of unsymmetrical disulfides still a great interest. Generally, the S-S bond formation[8] involving either S_N2 replacement or oxidative cross-coupling of two different thiols. Alternatively, C-S bond construction[9] is a more straightforward approach through disulfur (RSS) group transfer have been disclosed by Wang[9a] Jiang,[9c-e] Xian[9f] and other groups. Despite these advances, the transition-metal free methodologies are highly desirable due to the unavoidable metal contamination could be a severe problem in the pharmaceutical formulation process.

In contrast, the sulfones are yet another class of privileged functional scaffold due to their widespread applications in biological, agrochemicals and materials chemistry as well as popular therapeutic drugs (Figure 1b).[10] Especially the alkyl sulfones can serve as potential building blocks and also been used in several promising synthetic transformations.[11] With increasing numbers of sulfone-containing bioactive compounds[10a,d,e] has attracted much attention to developing a facile methodology *via* a metal-free sulfonylation from simple and easily available starting materials.

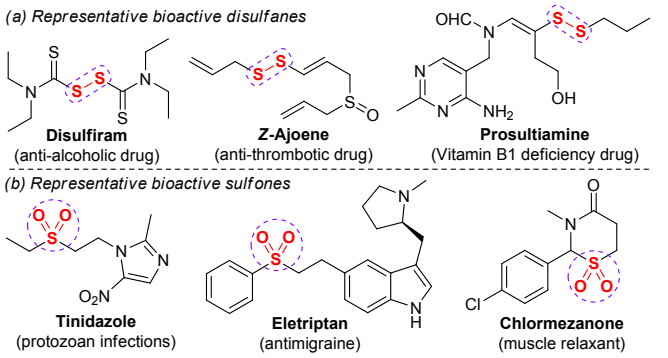

Figure 1. Biologically relevant organosulfur compounds.

Compared with different organosulfur substrates, the thiosulfonates[12] are generally stable crystalline solids, easy to handle and broadly accessible versatile precursors with low toxicity. Recently, Xu and co-workers reported electrophilic disulfuration between *S*-*tert*-butyl *p*-toluenesulfono(dithio-peroxoate) and arylboronic acids could deliver the unsymmetrical disulfanes *via* persulfur transfer reaction (Scheme 1a).[9b] Inspired by the works as mentioned earlier, we envisioned that the *S*-benzyl thiosulfonates would be right starting material to react with phenylboronic acid in the presence of copper-catalysis. The anticipated benzyl phenyl sulfide (**I**) would form by cleavage of weak S-S bond and the construction new C-S bond (Scheme 1b). Instead, we overjoyed to obtain the unprecedented benzyl disulfanylsulfone (**II**) *via* phenylboronic acid (PBA)-catalyzed dimerization-sulfonylation through the tandem construction of S-S and C-S bonds. We have also realized the incorporation of sulfone moiety into disulfane framework may increase their biological properties significantly. Indeed, our attention turns to develop a new and potent method toward sulfonyl derived disulfane variants.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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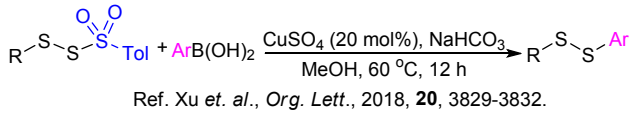
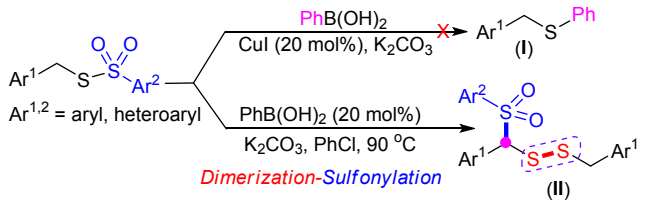
Boronic acid (BA)-catalyzed methodologies offer a powerful platform for rapid and efficient construction of carbon-carbon and carbon-heteroatom bonds in organic synthesis.[13] As part of our ongoing research programme on organosulfur chemistry,[14] herein, we disclose a novel and extremely efficient phenylboronic acid-catalyzed dimerization–sulfonylation of *S*-benzyl thiosulfonates to access a variety of benzyl disulfanyl-sulfones. To the best of our knowledge, the direct assemble of two different sulfur moieties on the same carbon-atom using thiosulfonates is remains underexplored.[14c,15]

***a) Previous work**: Synthesis of disulfanes via C-S bond construction*



Ref. Xu *et. al*., *Org. Lett*., 2018, **20**, 3829-3832.

***b) Present work:** Tandem construction of S-S and C-S bonds*

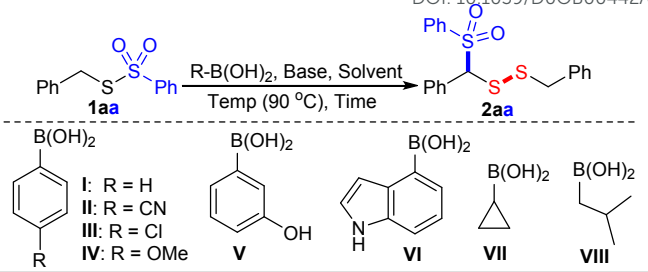


Scheme 1. Stratgies for the synthesis of disulfanes using thiosulfonates.

With a motivation of our previous work on thiosulfonates,[14b-f] we commenced our investigations by choosing *S*-benzyl benzenesulfonothioate (**1aa**) as a model substrate. The optimization results were summarized in Table 1 (also see Table-S1 in the ESI for a detailed survey of reaction conditions). Firstly, the phenylboronic acid (**I**)-catalyzed reaction of **1aa** with K_2CO_3 (1 to 2 equiv) in chlorobenzene (PhCl) gave the desired product **2aa** in high to excellent yields (entries 1-3). Notably, a smooth conversion of **1aa** with 20 mol% PBA and 1.0 equiv K_2CO_3 in PhCl at 90 °C afforded **2aa** in 97% yield (entry 3). Next, a series of boronic acid derivatives (**II** to **VIII**) are also investigated. The use of aryl-substituted boronic acids (**II** to **V**) were unsuccessful in improving the reaction efficiency (entries 4-7). The reaction was slow with indole-5-boronic acid (entry 8), in contrast, the aliphatic boronic acids (**VII** and **VIII**) provided **2aa** in 78% and 73% yields, respectively (entries 9-10). Further, fine-tuning the reaction condition concerning the amount of K_2CO_3 (0.5 equiv); the role of concentration as well as the effect of temperature failed to improve the reaction competency (entries 11-14). Among various bases (Cs_2CO_3, Na_2CO_3, DABCO and DBU) were studied (entries 15-18), the K_2CO_3 found to be an optimal base for this transformation. Changing other chlorinated solvents (DCM and DCE) further evaluated to afford the desired product **2aa** in 53% and 77% yields, respectively (entries 19-20).

With optimized reaction conditions in hand, we next proceeded to explore the generality of the reaction at different substitutions of aryl sulfones (Table 2). A series of *S*-benzyl thiosulfonates **1a(a-l)** were compatible to afford the corresponding disulfanes **2a(a-l)** under the same reaction conditions. Gratifyingly, both electron-donating and electron-withdrawing substituents at the *para* position of thiosulfonates

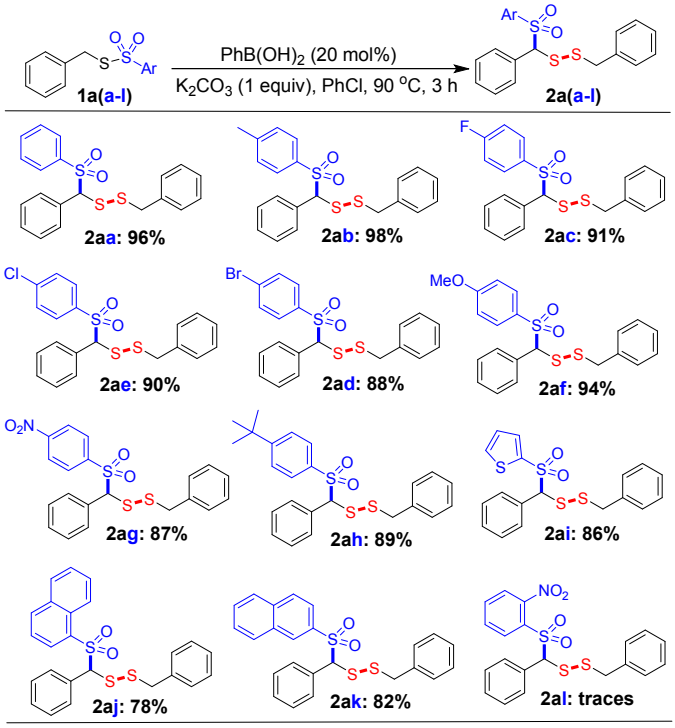
Table 1. Optimization for the synthesis of benzyl disulfanylsulfone.[a]



Entry	$ArB(OH)_2$	Base (equiv)	Solvent	Time	Yield [b]
1	**I** (10 mol%)	K_2CO_3 (2.0 eq)	PhCl	4 h	87%
2	**I** (20 mol%)	K_2CO_3 (2.0 eq)	PhCl	3 h	94%
3	**I (20 mol%)**	**K_2CO_3 (1.0 eq)**	**PhCl**	**3 h**	**97%**
4	**II** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	16 h	71%
5	**III** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	6 h	86%
6	**IV** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	8 h	80%
7	**V** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	16 h	NR
8	**VI** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	24 h	65%
9	**VII** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	4 h	78%
10	**VIII** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	4 h	73%
11	**I** (20 mol%)	K_2CO_3 (0.5 eq)	PhCl	3 h	72%
12[c]	**I** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	3 h	89%
13[d]	**I** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	16 h	71%
14[e]	**I** (20 mol%)	K_2CO_3 (1.0 eq)	PhCl	3 h	85%
15	**I** (20 mol%)	Cs_2CO_3 (1.0 eq)	PhCl	16 h	10%
16	**I** (20 mol%)	Na_2CO_3 (1.0 eq)	PhCl	16 h	traces
17	**I** (20 mol%)	DABCO (1.0 eq)	PhCl	16 h	NR
18	**I** (20 mol%)	DBU (1.0 eq)	PhCl	3 h	mix
19[d]	**I** (20 mol%)	K_2CO_3 (1.0 eq)	DCM	16 h	53%
20[f]	**I** (20 mol %)	K_2CO_3 (1.0 eq)	DCE	6 h	77%

[a] Unless otherwise specified, all reactions performed on a 0.2 mmol scale in solvent (1 mL) at 90 °C. [b] Isolated yield. [c] PhCl (2 mL) used. [d] At 50 °C. [e] At 110 °C. [f] At 80 °C.

Table 2. Substrate scope for the synthesis of benzyl dithiosulfones.[a,b]



[a] All reactions were performed a 0.5 mmol scale of **1a(a-l)** (1.0 equiv), PBA (20 mol%), K_2CO_3 (1.0 equiv) in PhCl (2.5 mL) at 90 °C for 3 h. [b] Isolated yield.

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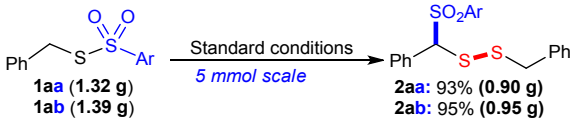
1a(a-h) were well-tolerated and produced the disulfanyl sulfones **2aa**-**ah** in excellent yields. On the whole, a little electronic effect was observed in this transformation (*cf*. **2af** *vs* **2ag**). The 2-thiophenyl and naphthyl derived thiosulfonates (**1ai-k**) gave desired products (**2ai-k**) in 78–86% yields. Surprisingly, the reaction with 2-nitrophenyl derived thiosulfonate **1al** proceeded sluggishly to form **2al** in traces under the same conditions.

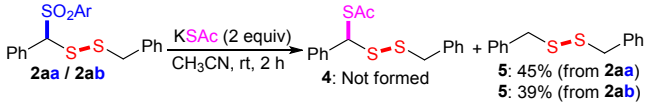
Encouraged by these results, the substrate scope of the reaction was further explored and summarized in Table 3. The tandem process works well for an array of benzyl substituted thiosulfonates. As expected, various 4-alkyl substituted benzyl thiosulfonates **1(b-d)a/b** were smoothly produced desired products **2(b-d)a/b** with no apparent effect on the outcome. The *para*-chloro and *para*-bromobenzyl thiosulfonates (**1e,f/a**) gave desired products **2ea** and **2fa** in 85% and 83% yields, respectively. Unambiguously, the structure of **2fa** was confirmed by single-crystal X-ray data analysis (see the ESI).[16] Pleasingly, the 1- and 2-naphthyl derived thiosulfonates (**1g,h/a**) afforded the anticipated disulfanylsulfones (**2g,h/a**) in high yields. Various 2-halobenzyl thiosulfonate derivatives (**1i,k/a**) were also a suitable substrate for the transformation to provide the pseudosymmetrical dimers (**2i,k/a**) in satisfactory yields. Sterically bulky 2-chloroquinoline derived unsymmetrical disulfane **2la** was obtained in 72% yield with a low purity as compared. Disappointingly, the thiosulfonates (**1ma** and **1nb**) were poor substrates for this transformation to provide the anticipated products. Interestingly, the 2-thiophenyl (**1oa**) and allyl derived (**1pa**) thiosulfonates led to form the corresponding products (**2o,p/a**) with an inseparable mixture of by-products.

To highlight the viability of the tandem process, the reactions performed in a gram-scale under the standard reaction conditions. As shown in Scheme 2, a 5 mmol reaction scale of *S*-benzyl benzenesulfonothioate **1aa** and *S*-benzyl 4-methylphenylsulfonothioate **1ab** were conducted to yield the desired products in 0.90 g (93%) of **2aa** and 0.95 g (95%) of **2ab**; thus the protocol could be readily scalable without any deviation on efficiency.



Scheme 2. Gram-scale reactions for the synthesis of **2aa/b**.

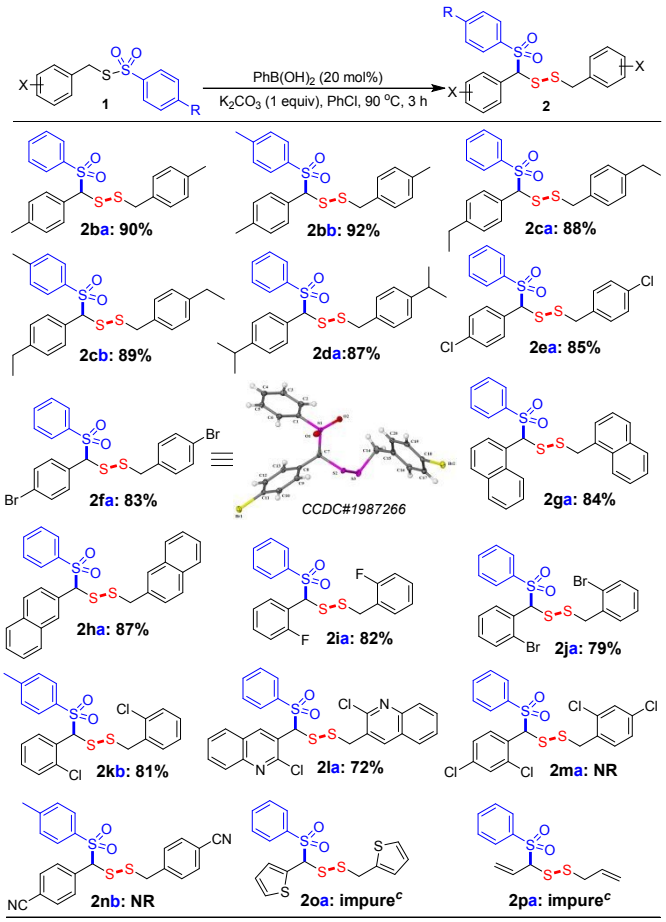
Next, the synthetic usefulness of structurally diverse disulfanylsulfones (**2aa/b**) was examined (Scheme 3). The treatment of potassium acetate (KSAc) in CH_3CN at room temperature and the expected product (**4**) does not form under this condition. To our surprise, the benzyl disulfide (**5**) was obtained in modest yield by simple desulfonylation process.



Scheme 3. Synthesis of benzyl disulfane **5** *via* desulfonylation.

To understanding the reaction mechanism, a few control experiments were conducted for dimerization–sulfonylation reactions (Scheme 4). The reaction performed with a 1:1 mixture **1aa** and **1ab** under standard conditions afforded the 1:2.4 of **2aa** and **2ab,** thus implying the reaction possibly going through an intermolecular fashion (Scheme 4a; see ESI for ^{1}H-NMR). The standard reaction was employed with 1.5 equiv of benzyl mercaptan afforded the unexpected benzyl disulfide (**5**) in 45% yield (Scheme 4b), whereas no reaction the use of benzyl mercaptan alone (Scheme 4c). To worth note the benzyl mercaptan suppressed the formation of disulfanylsulfone **2ab**, it may lead to the formation benzyl disulfide only. Further, the standard reaction was performed in the presence of radical scavengers (Scheme 4d). With BHT the product **2ab** was isolated in 77% yield; however, the reaction with TEMPO entirely not clear. Additionally, the reaction with NBS to produce the disulfone (**6**)[17] in 78% yield (Scheme 4e).

Table 3. Substrate scope for the synthesis of benzyl disulfanylsulfones.[a,b]



[a] All reactions were performed a 0.5 mmol scale of **1a(a-l)** (1.0 equiv), PBA (20 mol%), K_2CO_3 (1.0 equiv) in PhCl (2.5 mL) at 90 °C for 3 h. [b] Isolated yield. [c] The obtained products were not in the pure form.

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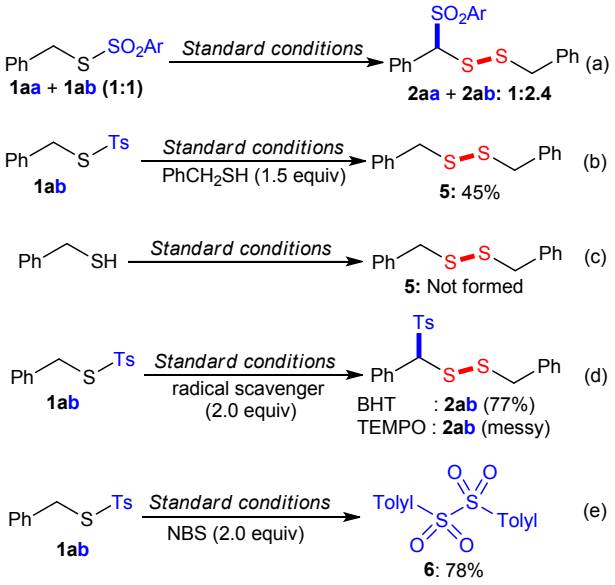
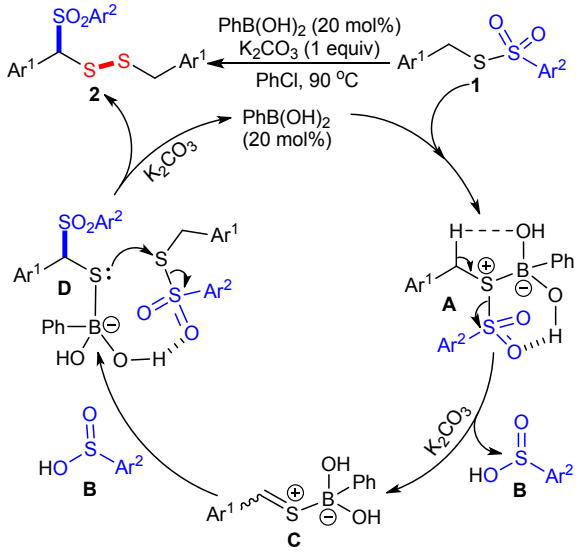


Scheme 4. Control experiments for the formation of disulfanylsulfones.

Based on literature precedents,[13,18] a plausible mechanism was proposed to rationalize the experimental outcome and the control experiments (Scheme 5). The ionic mechanism may initiated by the Lewis acidity of boron species of phenylboronic acid, it may coordinate with a sulfur moiety of thiosulfonate led to form B–S complex **A**.[13,18c] The cleavage of S-SO_2 bond and benzylic proton abstraction[18a,b] in the presence of K_2CO_3 would generate sulfinic acid **B** and boron-sulfonium zwitterion **C**.[18c] Subsequent construction of the C-S bond through the sulfonylation of **C** with sulfinic acid **B** will allow to form intermediary **D**, which prone to react with another unit of benzyl thiosulfonate. Finally, the formation S-S bond lead to desired product **2** and active phenylboronic acid catalyst would be regenerated for the further catalytic process.



Scheme 5. Postulated tentative mechanism catalyzed phenylboronic acid.

Conclusions

We have successfully developed metal-free tandem construction of S-S and C-S bonds for the synthesis of benzyl disulfanylsulfone derivatives using easily accessible *S*-benzyl thiosulfonates as starting materials. An unprecedented phenylboronic acid (PBA)-catalyzed protocol is easy to perform under mild reaction conditions and the obtained products bearing two different sulfur moieties on the same carbon-atom, which were difficult to prepare by other methods. Remarkably, the dimerization–sulfonylation has established by its broad substrate scope and proved at the gram-scale reactions. Further, mechanistic studies and applications are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank CSIR-EMR-II [02(0340)/18/EMR-II] and SERB-ECR [ECR/2015/000053], New Delhi for financial assistance. RJR thanks to UGC for faculty position under Faculty Recharge Programme and Start-up grant (F.4-5/2006/BSR). Our special thanks to OUDST-PURSE (SR/PURSE Phase 2/32/G) programme for partial funding support. MW thank UGC for his Senior Research Fellowship (SRF).

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