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Metal- and oxidant-free electrochemical synthesis of sulfinic esters from thiols and alcohols†

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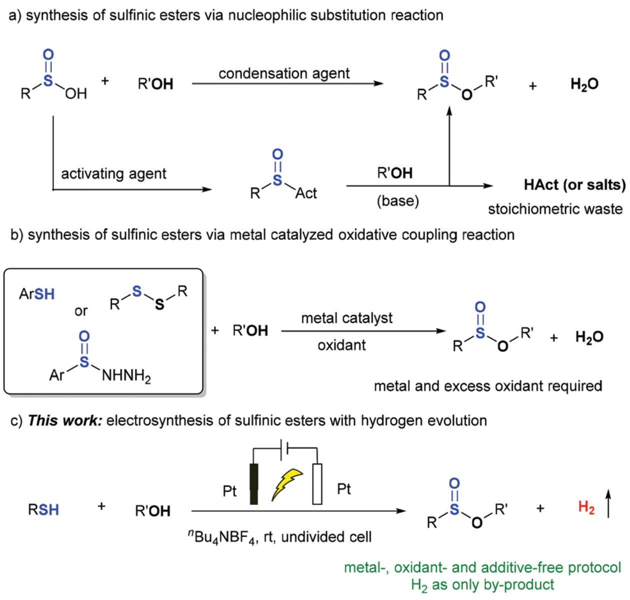
An efficient and eco-friendly electrochemical synthesis of various sulfinic esters from thiols and alcohols *via* sequential S–H/S bond cleavage and double S–O bond formation under mild reaction conditions has been developed. Stoichiometric oxidants, metal catalysts, activating agents and even added bases were avoided in this method, and the only by-product generated from this reaction was dihydrogen gas which could serve as a green source of energy. Various functional groups are compatible with this green protocol which can be easily conducted on a gram-scale.

Development of practical methodologies for the preparation of sulfinic esters is an important issue in organic synthesis because these compounds not only exhibit diverse biological and therapeutic activities,[1] but also act as valuable synthons for the preparation of functional sulfone-containing products.[2] To date, numerous synthetic methods have been successfully developed to produce these skeletons. The nucleophilic substitution reactions of sulfur compounds (sulfinic acids,[3] sulfinyl chlorides,[4] and sodium sulfinates[5]) with alcohols offered convenient ways to synthesize sulfinic esters (Scheme 1a). However, the employment of stoichiometric amounts of condensation agents or activating agents resulted in a lot of undesired waste, which is environmentally unfriendly. In this context, the oxidative coupling reactions provided useful alternatives for the synthesis of these compounds, since these methods avoided the use of activating or condensation agents (Scheme 1b). The early representative protocols are mainly based on the oxidation of diaryl disulfides in the presence of alcohols using excess *N*-bromosuccinimide (NBS),[6a] Br_2 [2b] or $PhI(OCOCF_3)_2$ [6b] as oxidants. In 2016, the groups of Pan and Jang independently developed the coupling reaction of alcohols with sulfonyl hydrazides[7] or thiols[8] in the presence of copper salts for the preparation of sulfinic ester derivatives. Very recently, Zhang's group has also developed an efficient route to access sulfinic esters *via* the Co/N-SiO_2-AC-mediated cross-dehydrogenative coupling reaction of thiols and alcohols.[9] Despite these great advances, the use of metal catalysts and excess oxidants has limited their further applications. Thus, there is a high demand for new, efficient and environmentally benign methods for the synthesis of sulfinic esters from readily available starting materials under catalyst-, oxidant- and additive-free conditions.

Organic electrosynthesis has been demonstrated to be an eco-friendly synthetic tool since it can avoid the use of oxidants, reducing agents, toxic bases or even catalysts, thus decreasing waste and pollution.[10] Under constant current conditions, thiols will lose one electron to generate thiol



Scheme 1 Methods for the synthesis of sulfinic esters.

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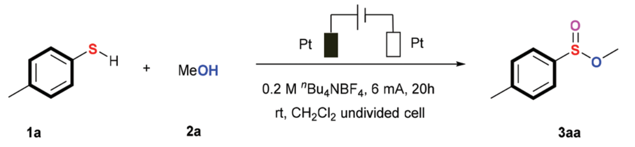
radical species, which could undergo radical–radical coupling,[11] metal-catalyzed thiolation with aryl halides[12] or ketones,[13] difunctionalization of alkenes,[14] and oxidation reactions,[15] leading to a variety of useful sulfur-containing compounds, such as disulfides, sulfides, methyl sulfoxides and sulfonamides. To the best of our knowledge, the synthesis of sulfinic esters ($R^1SO\text{-}OR^2$) from thiols using electricity has not been reported yet, since it is difficult to avoid the overoxidation to sulfonate esters. Herein, we describe a versatile and efficient electrochemical oxidative reaction of thiols with alcohols to afford sulfinate esters as products under metal catalyst- and oxidant-free undivided electrosynthetic conditions (Scheme 1c).

At the outset of this study, 4-methylthiophenol (**1a**) and methanol (**2a**) were chosen as the starting materials (Table 1). The initial reaction was performed in an undivided cell with platinum plates as electrodes under 6 mA constant current at room temperature using ^{n}Bu$_4$NBF$_4$ as the electrolyte and CH_2Cl_2 as the solvent. Fortunately, the desired product **3aa** was obtained in 87% yield (Table 1, entry 1). Subsequently, a series of solvents were investigated, and replacement of CH_2Cl_2 with CH_3CN or THF gave a slightly decreased yield, while only a trace amount of the product was observed when using DMF as the reaction solvent (Table 1, entries 2–4). Next, various supporting electrolytes such as $LiClO_4$, ^{n}Bu$_4$NBF$_4$, ^{n}Bu$_4$NPF$_6$, and ^{n}Bu$_4$NI were explored (Table 1, entries 5 and 6). ^{n}Bu$_4$NBF$_4$ was found to be the most efficient electrolyte for this reaction. In addition, using graphite rod as an anode electrode resulted in a much poorer yield, while nickel turned out to be an unsuccessful cathode in this transformation (Table 1, entries 8 and 9). Notably, the constant current affected the reaction dramatically; either increasing or decreasing the constant current led to a lower yield (Table 1, entries 10 and 11). Furthermore, changing the reaction temperatures did not improve the product yield (Table 1, entries 12 and 13). It was noteworthy that the reaction with air instead of N_2 under the standard conditions also afforded the desired product **3aa** in 84% yield (Table 1, entry 14). In contrast, no desired product was obtained without an electric current (Table 1, entry 15). Interestingly, this protocol could be easily conducted at the 12 mmol scale to produce **3aa** in 1.67 g, 82% yield (Table 1, entry 16).

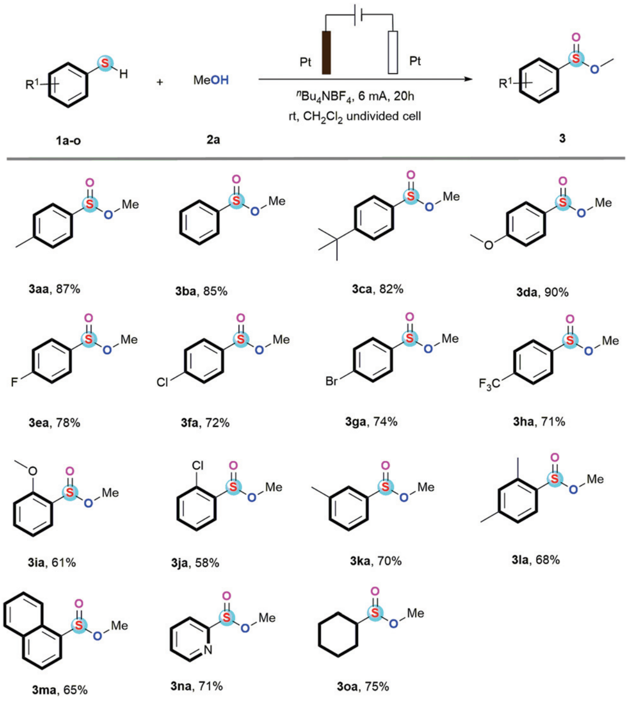
Table 1 Optimization of the reaction conditions[a]



Entry	Variation from the standard conditions	Yield[b] (%)
1	**None**	**87**
2	CH_3CN instead of CH_2Cl_2	74
3	THF instead of CH_2Cl_2	71
4	DMF instead of CH_2Cl_2	Trace
5	$LiClO_4$ instead of ^{n}Bu$_4$NBF$_4$	72
6	Bu$_4$NPF$_6$ instead of ^{n}Bu$_4$NBF$_4$	78
7	^{n}Bu$_4$NI instead of ^{n}Bu$_4$NBF$_4$	70
8	Graphite rod as an anode	68
9	Nickel as a cathode	NR
10	3 mA instead of 6 mA	64
11	10 mA instead of 6 mA	83
12	40 °C	75
13	10 °C	58
14	Air instead of N_2	84
15	No electric current	0
16	12.0 mmol instead of 1.0 mmol	82

[a] Reaction conditions: Undivided cell, Pt anode (1 cm × 1 cm), Pt cathode (1 cm × 1 cm), **1a** (1.0 mmol), **2a** (1.0 mL), *n*-Bu$_4$NBF$_4$ (1.0 mmol), CH_2Cl_2 (4.0 mL), N_2, 20 h. [b] Isolated yields.

After identifying the optimum reaction conditions, we next set out to determine the versatility of this reaction system in the electrochemical oxidative coupling of various thiophenols and alcohols. The scope of this reaction was initially explored with a range of thiophenols **1** and methanol (**2a**). As depicted in Scheme 2, various sulfinic esters could be synthesized with satisfactory yields (58–90%). The substituents on the aryl ring of aryl thiols affected the desired product yields to some extent. *para*-Substituted substrates with electron-donating groups on the thiols, such as –Me (**1a**), –^{t}Bu (**1c**) and –OMe (**1d**), gave better yields than those with electron-withdrawing groups (**1e–h**). Moreover, the substitution patterns on the aryl rings of thiols had a slight effect on this reaction, forming **3ia–ka** from *ortho*- and *meta*-substituted substrates in relatively lower yields. In addition, disubstituted thiols also underwent this reaction smoothly to provide **3la** in 68% yield. Notably, other aromatic skeletons were also tolerated, such as naphtha-

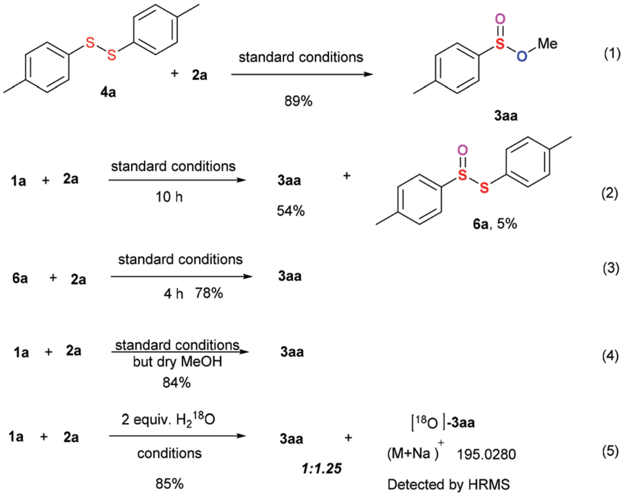


Scheme 2 Substrate scope of thiols. Reaction conditions: Undivided cell, Pt anode (1 cm × 1 cm), Pt cathode (1 cm × 1 cm), **1** (1.0 mmol), **2a** (1.0 mL), *n*-Bu$_4$NBF$_4$ (1.0 mmol), CH_2Cl_2 (4.0 mL), N_2, 20 h. Isolated yields.

lene and pyridine, leading to the corresponding products **3ma** and **3na** being obtained in 65% and 71% yields, respectively. Delightfully, the less-reactive cyclohexanethiol (**1o**) was still compatible with this transformation to produce the targeted product **3oa** in a moderate yield.

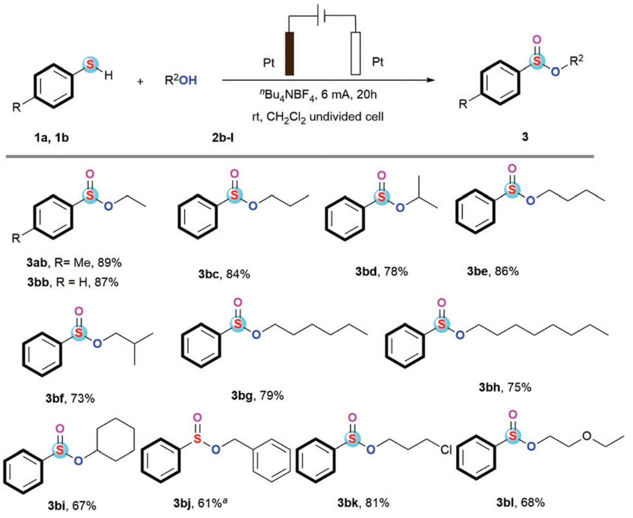
Next, the scope of this reaction with respect to various alcohols was studied, furnishing the sulfinic esters in 61–89% yields (Scheme 3). High yields (73–89%) were obtained when using primary aliphatic alcohols as substrates, such as ethanol (**2b**), *n*-propanol (**2c**), *n*-butanol (**2e**), *n*-hexanol (**2g**), *etc.* Furthermore, the reactions were also conducted efficiently with secondary aliphatic alcohols (**2d** and **2i**), delivering the sulfinic ester derivatives **3bd** and **3bi** in 78% and 67% yields, respectively. It is noteworthy that benzyl alcohol turned out to be an efficient substrate, affording the corresponding product **3bj** in 61% yield. Delightfully, functionalized alcohols containing heteroatoms such as 3-Cl (**2k**) and 2-OEt (**2l**) were also tolerated in this reaction with moderate yields, thereby providing an opportunity for further manipulations.

To gain mechanistic insight into this transformation, some control experiments were performed (Scheme 4, see the ESI† for more details). We observed that the thiol was first converted into disulfane **4**, and then **4a** reacted with **2a** smoothly to give **3aa** in 89% yield under the standard conditions (Scheme 4, eqn (1)). In addition, reducing the reaction time to 10 h led to **3aa** in 54% yield accompanied by **6a** in 5% yield (Scheme 4, eqn (2)). Subjecting **6a** to the standard conditions led to the formation of the desired product **3aa** in 78% yield within 4 h (Scheme 4, eqn (3)). The experimental results strongly suggested that disulfane **4a** and thiosulfinate **6a** were the key intermediates in this transformation. Furthermore, this reaction still proceeded smoothly when dry methanol was used as the solvent under a N_2 atmosphere (Scheme 4, eqn (4)), which indicated that the alcohols may act not only as reactants but also as oxidants to oxidize the S(II) to S(IV) species. More importantly, an isotopic labelling reaction was carried out by the treatment of **1a** and **2a** in the presence of $H_2{}^{18}O$ (Scheme 4, eqn (5)) under the standard conditions, leading to a mixture of **3aa** and [^{18}O]-**3aa** (1 : 1.25) in 85% yield. The isotopic labelling experimental results indicated that oxygen in sulphur could also come from water.

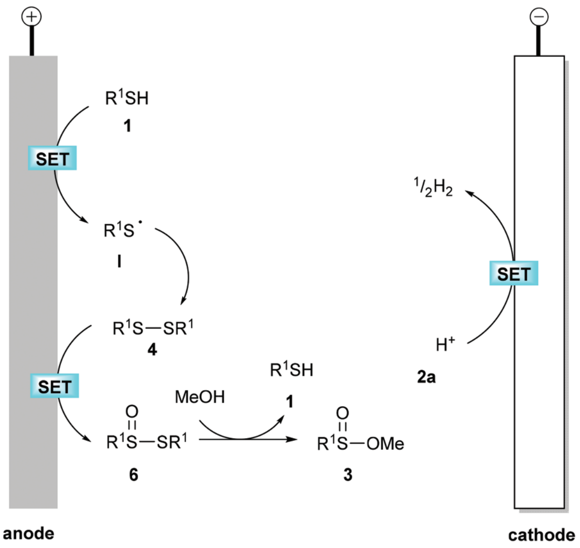


Scheme 4 Control experiments.

On the basis of the control experiments and literature reports,[11–15] a plausible mechanism is depicted in Scheme 5. Initially, thiol **1** is oxidized to a thiol radical **I** in the anode. Subsequently, the homo-coupling of thiol radical **I** forms the disulfide **4** *in situ*, followed by the oxidation of **4**, leading to the generation of thiosulfinates **6**. Finally, the nucleophilic attack of **6** by methanol gives the desired product **3**, with the release of **1**. On the other hand, the hydrogen ion was reduced to dihydrogen gas in the cathode.



Scheme 3 Substrate scope of alcohols **2**. Reaction conditions: Undivided cell, Pt anode (1 cm × 1 cm), Pt cathode (1 cm × 1 cm), **1a** or **1b** (1.0 mmol), **2** (1.0 ml), *n*-Bu_4NBF_4 (1.0 mmol), CH_2Cl_2 (4.0 mL), N_2, 20 h. Isolated yields. ^{a} CH_3CN as the solvent.



Scheme 5 Proposed reaction mechanism.

Conclusions

In summary, we have developed an eco-friendly electron induced oxidative S–O coupling reaction which avoids the use of metals, oxidants and additives. Readily available alcohols and thiols could be used as substrates under constant conditions in an undivided electrochemical cell equipped with a platinum anode and a platinum cathode, providing versatile sulfinic esters in good yields. Furthermore, this reaction could be conducted on a gram scale easily. We anticipate that this novel and efficient synthetic protocol used to prepare sulfinic esters will find applications in both academic research and industrial development settings.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) J. H. Kim, J. O. Lee, S. K. Lee, J. W. Moon, G. Y. You, S. J. Kim, S. H. Park, J. M. Park, S. Y. Lim, P. G. Suh, K. O. Uhm, M. S. Song and H. S. Kim, *J. Biol. Chem.*, 2011, **286**, 7567; (*b*) J. Blackinton, M. Lakshminarasimhan, K. J. Thomas, R. Ahmad, E. Greggio, A. S. Raza, M. R. Cookson and M. A. Wilson, *J. Biol. Chem.*, 2009, **284**, 6476.

2 (*a*) J. A. Lujan-Montelongo, A. O. Estevez and F. F. Fleming, *Eur. J. Org. Chem.*, 2015, 1602; (*b*) J. E. Resek and A. I. Meyers, *Tetrahedron Lett.*, 1995, **36**, 7051; (*c*) F. Yuste, J. García Ruano, A. Parra and V. Mastranzo, *Synthesis*, 2008, 311; (*d*) M. Funes Maldonado, F. Sehgelmeble, F. Bjarnemark, M. Svensson, J. Åhman and P. I. Arvidsson, *Tetrahedron*, 2012, **68**, 7456; (*e*) F. Yuste, A. H. Linares, V. M. Mastranzo, B. Ortiz, R. Sanchez-Obregon, A. Fraile and J. L. Ruano, *J. Org. Chem.*, 2011, **76**, 4635; (*f*) N. T. Nguyen, H. T. Vo, F. Duus and T. X. T. Luu, *Molecules*, 2017, **22**, 1458; (*g*) R. R. Tata, C. S. Hampton and M. Harmata, *Adv. Synth. Catal.*, 2017, **359**, 1232.

3 A. R. Hajipour, A. R. Falahati and A. E. Ruoho, *Tetrahedron Lett.*, 2006, **47**, 2717.

4 I. Fernandez, N. Khiar, A. Roca, A. Benabra, A. Alcudia, J. L. Espartero and F. Alcudia, *Tetrahedron Lett.*, 1999, **40**, 2029.

5 A. Tranquilino, S. R. C. P. Andrade, A. P. M. da Silva, P. H. Menezes and R. A. Oliveira, *Tetrahedron Lett.*, 2017, **58**, 1265.

6 (*a*) P. Brownbridge and I. C. Jowett, *Synthesis*, 1988, 252; (*b*) M. Xia and Z. C. Chen, *Synth. Commun.*, 1997, **27**, 1321.

7 B. Du, Z. Li, P. Qian, J. Han and Y. Pan, *Chem. – Asian J.*, 2016, **11**, 478.

8 P. K. Shyam, Y. K. Kim, C. Lee and H. Y. Jang, *Adv. Synth. Catal.*, 2016, **358**, 56.

9 C. Zhou, Z. Tan, H. Jiang and M. Zhang, *Green Chem.*, 2018, **20**, 1992.

10 For selected reviews, see: (*a*) J.-I. Yoshida, K. Kataoka, R. Horcajada and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265; (*b*) B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099; (*c*) R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492; (*d*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230; (*e*) Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, 2018, **118**, 4485; (*f*) S. Liang, K. Xu, C.-C. Zeng, H.-Y. Tian and B.-G. Sun, *Adv. Synth. Catal.*, 2018, **360**, 4266; (*g*) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086; (*h*) Z.-W. Hou, Z.-Y. Mao and H.-C. Xu, *Synlett*, 2017, **28**, 1867; (*i*) Q.-L. Yang, P. Fang and T.-S. Mei, *Chin. J. Chem.*, 2018, **36**, 338.

11 (*a*) P. Huang, P. Wang, S. Tang, Z. Fu and A. Lei, *Angew. Chem., Int. Ed.*, 2018, **57**, 8115; (*b*) Y. Li, Q. Yang, L. Yang, N. Lei and K. Zheng, *Chem. Commun.*, 2019, **55**, 4981; (*c*) Z.-Y. Mo, T. R. Swaroop, W. Tong, Y.-Z. Zhang, H.-T. Tang, Y.-M. Pan, H.-B. Sun and Z.-F. Chen, *Green Chem.*, 2018, **20**, 4428; (*d*) S. Tang, Y. Liu, L. Li, X. Ren, J. Li, G. Yang, H. Li and B. Yuan, *Org. Biomol. Chem.*, 2019, **17**, 1370; (*e*) D. Li, S. Li, C. Peng, L. Lu, S. Wang, P. Wang, Y.-H. Chen, H. Cong and A. Lei, *Chem. Sci.*, 2019, **10**, 2791; (*f*) Y. Yuan, Y. Cao, J. Qiao, Y. Lin, X. Jiang, Y. Weng, S. Tang and A. Lei, *Chin. J. Chem.*, 2019, **37**, 49; (*g*) F. Lu, Z. Yang, T. Wang, T. Wang, Y. Zhang, Y. Yuan and A. Lei, *Chin. J. Chem.*, 2019, **37**, 547.

12 S. Liang, C.-C. Zeng, H.-Y. Tian, B.-G. Sun, X.-G. Luo and F.-Z. Ren, *Adv. Synth. Catal.*, 2018, **360**, 1444.

13 (*a*) D. Liu, H.-X. Ma, P. Fang and T.-S. Mei, *Angew. Chem.*, 2019, **58**, 5033; (*b*) Y. Wang, L. Deng, X. Wang, Z. Wu, Yi Wang and Y. Pan, *ACS Catal.*, 2019, **9**, 1630.

14 For a review, see: (*a*) G. M. Martins, B. Shirinfar, T. Hardwick and N. Ahmed, *ChemElectroChem*, 2019, **6**, 1300. For selected examples, see: (*b*) Y. Yuan, Y. Chen, S. Tang, Z. Huan and A. Lei, *Sci. Adv.*, 2018, **4**, eaat5312; (*c*) Y. Wang, L. Deng, H. Mei, B. Du, J. Han and Y. Pan, *Green Chem.*, 2018, **20**, 3444.

15 (*a*) G. Laudadio, N. J. W. Straathof, M. D. Lanting, B. Knoops, V. Hessel and T. Noël, *Green Chem.*, 2017, **19**, 4061; (*b*) K.-S. Du and J.-M. Huang, *Green Chem.*, 2018, **20**, 1405; (*c*) G. Laudadio, E. Barmpoutsis, C. Schotten, L. Struik, S. Govaerts, D. L. Browne and T. Noël, *J. Am. Chem. Soc.*, 2019, **141**, 5664.