Chinese Chemical Letters 33 (2022) 5101–5105

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Boron-promoted reductive deoxygenation coupling reaction of sulfonyl chlorides for the C(sp^3)-S bond construction

Shuo Chen[a,1], Qingru Wen[a,1], Yanqing Zhu[a], Yanru Ji[b], Yu Pu[b,*], Zhengli Liu[a], Yun He[a], Zhang Feng[a,b,*]

[a] Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, China
[b] Medical Imaging Key Laboratory of Sichuan Province, North Sichuan Medical College, Nanchong 637000, China

ARTICLE INFO

Article history:
Received 8 February 2022
Revised 4 April 2022
Accepted 8 April 2022
Available online 12 April 2022

Keywords:
C-S bond formation
Reductive deoxygenation coupling
Borane
Organosulfur compounds
Green chemistry

ABSTRACT

Herein, we report a borane-promoted reductive deoxygenation coupling reaction to synthesize sulfides. This reaction features excellent functional group compatibility, high efficiency, broad substrate scope, and application in late-stage functionalization of biomolecules. Preliminary mechanistic studies suggest diaryl sulfides are the intermediates of this reaction. Moreover, the real active aryl sulfide anions may be generated *in situ* with the aid of B_2pin_2 and react with alkyl tosylates through a concerted S_N2 pathway.

Organosulfur compounds, the indispensable chemical substances in our lives, are widely present in many biologically active molecules, materials science, medicine, and agriculture [1–3]. Therefore, the carbon-sulfur bonds formation has attracted much attention in organic synthesis [4–8]. Undoubtedly, the most classic and important synthetic method for building the C(sp^3)-S bond is the substitution reaction of alkyl halides with mercaptans in the presence of strong bases (Scheme 1A) [9,10]. However, this strategy suffers from poor compatibility of functional groups and limited substrate scope. Transition metal-catalyzed cross-coupling of aryl halides with alkyl thiols or alkyl halides with aryl thiols has made great progress so far [11], but the undesirable β-hydride elimination and the metal poisoning problem also restrict its wild applications. Importantly, most mercaptans having unpleasant smells are not commercially available and highly toxic, greatly limiting their applications in organic synthesis. In view of these limitations, much effort has been paid to find new sulfurating agents to replace mercaptans.

In recent years, the use of inorganic sulfur compounds as sulfurating agents has been an alternative strategy for building carbon-sulfur bonds (Scheme 1B) [12–15]. For example, a copper-catalyzed coupling reaction of aryl iodides and alkyl halides with sulfur powder was reported by Ma [16]. In 2018, the Jiang group reported the palladium-catalyzed C-S bond formation using KSAc as a sulfur source [17]. Zhou and coworkers also realized a similar transformation by employing KSCN [18]. $Na_2S_2O_3$ as a sulfurating agent for the construction of carbon-sulfur bonds has also been achieved by Jiang [19]. Another practical protocol is to convert alkyl thiols into electrophiles for the carbon-sulfur bonds formation. For instance, organometallic reagents can react with benzenesulfonothioates to deliver the sulfides through nucleophilic substitution reactions [20]. Nevertheless, most organometallic reagents are sensitive to air and moisture, which restricts this method's application (Scheme 1C). In 2018, a mild and efficient nickel-catalyzed reductive thiolation reaction employing S-phenyl benzenesulfonothioate as the sulfurating electrophiles was reported by Ji and Wang (Scheme 1D) [21]. At present, although metal-free and transition metal-catalyzed methods as mentioned above for the C(sp^3)-S bond formation have made great developments, it is still very necessary to develop simple, environmentally friendly, safe, and practical methods for the C(sp^3)-S bond formation.

Very recently, Radosevich and coworkers found that organophosphines could promote the deoxygenation of sulfonyl chlorides to afford the sulfenyl electrophiles [22]. Inspired by Radosevich's work as well as the role of borane reagents in reductive cross-coupling reactions [23–25], we envisioned that the sulfurating electrophiles would be generated *in situ* from aryl sulfonyl chlorides [26–30] and then underwent the reduc-

* Corresponding authors.
E-mail addresses: puyu@nsmc.edu.cn (Y. Pu), fengzh@cqu.edu.cn (Z. Feng).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cclet.2022.04.022
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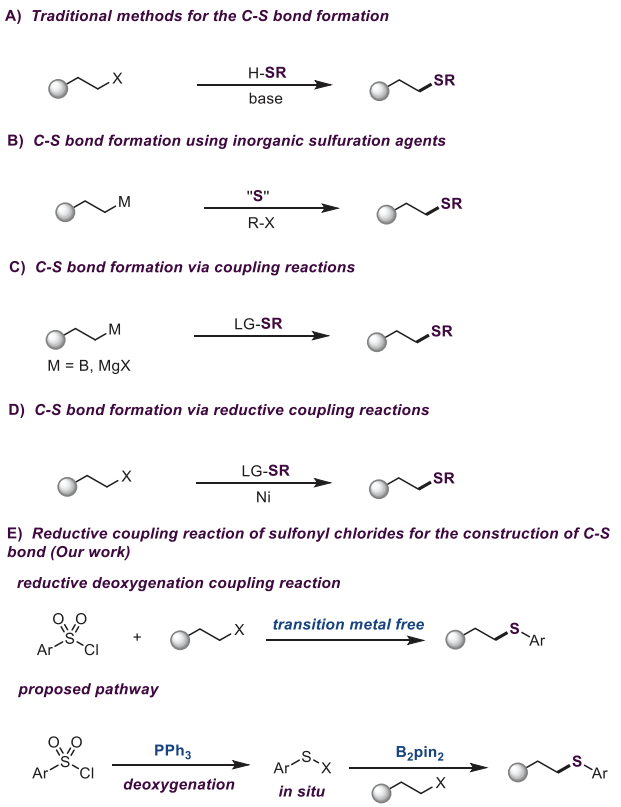
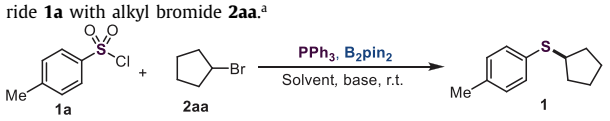


Scheme 1. Methods for the C(sp^3)-S bond formation.

tive cross-coupling reaction with alkyl halides with the aid of the reducing agent boranes (such as B_2pin_2) (Scheme 1E). To our continuing interest in green chemical synthesis [31–38], we sought to develop the first example of borane-promoted reductive deoxygenation coupling reaction of aryl sulfonyl chlorides with alkyl halides and alkyl tosylates for the construction of C(sp^3)-S bond.

With these considerations in mind, we set out to investigate the reductive deoxygenation coupling reaction of aryl sulfonyl chlorides. To our delight, as we anticipated, when B_2pin_2 and PPh_3 were used as additives, this transformation could proceed, and afforded the desired product **1** in 6% yield (Table 1, entry 1). Then, other bases were evaluated, and the best result, 32% yield was provided in the presence of NaOH (Table 1, entry 2; for details, please see Supporting information). We thought that the amount of PPh_3 might be critical to this reaction. Therefore, the loading of PPh_3 was checked, and 48% yield was obtained when 2.0 equiv. of PPh_3 was employed (Table 1, entry 3). Furthermore, increasing the loading of PPh_3 to 3.0 equiv., the 86% yield of desired product was delivered (Table 1, entry 4). After screening other solvents, DME afforded this desired product in 98% yield (Table 1, entries 5 and 6; for details, please see Supporting information). Subsequently, various borane reagents were tested as well. B_2cat_2 and B_2oct_2 could also promote this reaction smoothly, resulting in the corresponding product in moderate yields (Table 1, entries 8 and 9; for details, please see Supporting information). Control experiments were conducted to reveal the importance of the borane reagent and PPh_3 (Table 1, entries 10–12). It was found that the efficiency of this reaction was dramatically affected by the amount of B_2pin_2 (Table 1, entry 10). The desired product **1** was not observed in the absence of the borane reagent and PPh_3, thus demonstrating the necessity of the borane reagent and PPh_3 (Table 1, entries 11 and 12). Gratifyingly, the more commonly used inert substrate, cyclopentyl 4-methylbenzenesulfonate, proved to be a suitable substrate, yielding the corresponding product **1** in 96% yield (Table 1, entries 7). Remarkably, this transformation can be carried out in undried DME under air conditions without losing its efficiency.

Table 1
Representative results for the optimization of the reaction of aryl sulfonyl chloride **1a** with alkyl bromide **2aa**.[a]

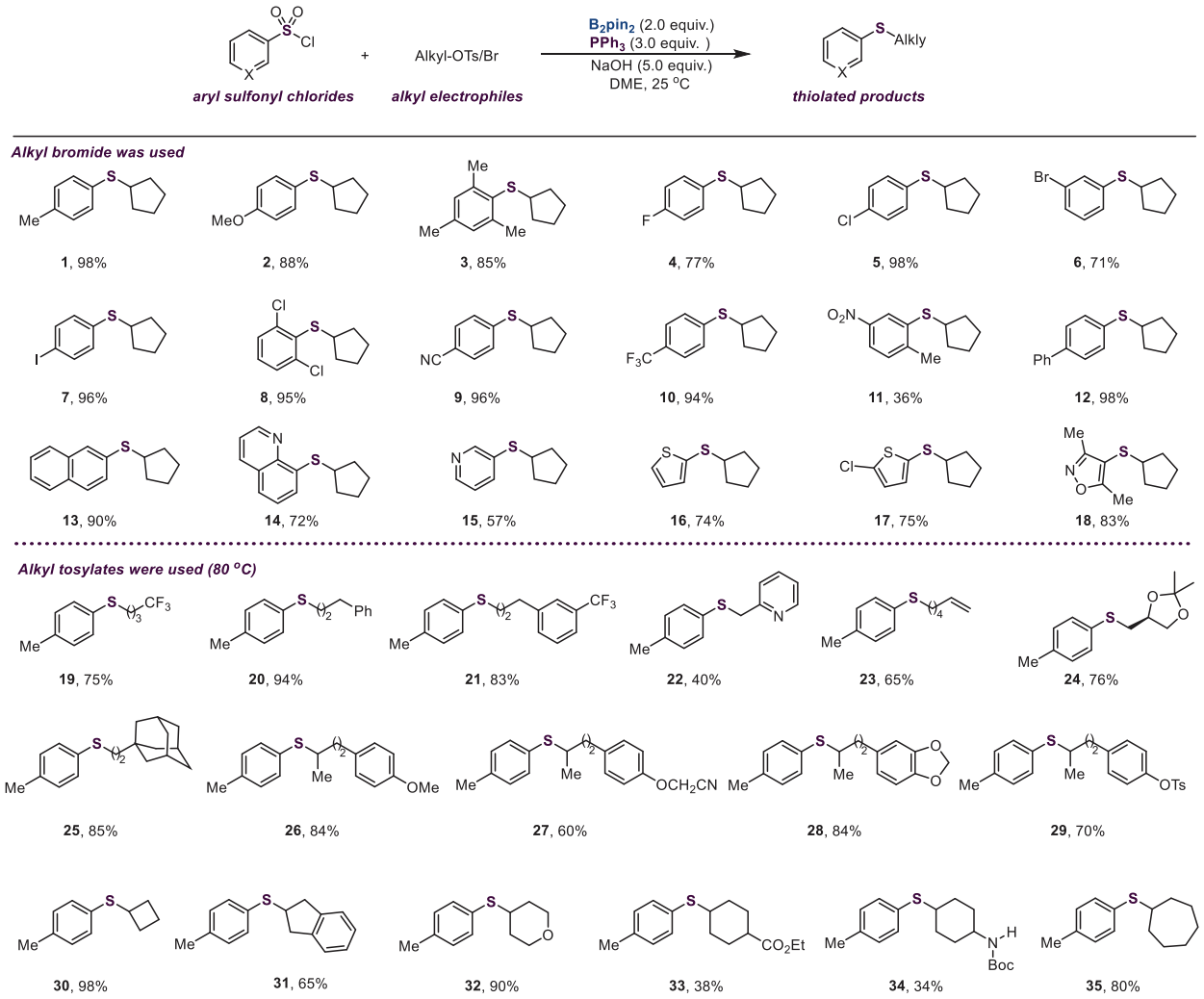


Entry	Borane reagents (equiv.)	PPh_3 (equiv.)	Solvent	Base	Yield (%)[b]
1	B_2pin_2 (2.0)	1.5	THF	KOH	6
2	B_2pin_2 (2.0)	1.5	THF	NaOH	32
3	B_2pin_2 (2.0)	2.0	THF	NaOH	48
4	B_2pin_2 (2.0)	3.0	THF	NaOH	86
5	B_2pin_2 (2.0)	3.0	DMF	NaOH	50
6	B_2pin_2 (2.0)	3.0	DME	NaOH	98 (98)
7[c]	B_2pin_2 (2.0)	3.0	DME	NaOH	96
8	B_2cat_2 (2.0)	3.0	DME	NaOH	60
9	B_2oct_2 (2.0)	3.0	DME	NaOH	60
10	B_2pin_2 (1.0)	3.0	DME	NaOH	56
11	without	3.0	DME	NaOH	0
12	B_2pin_2 (2.0)	without	DME	NaOH	0

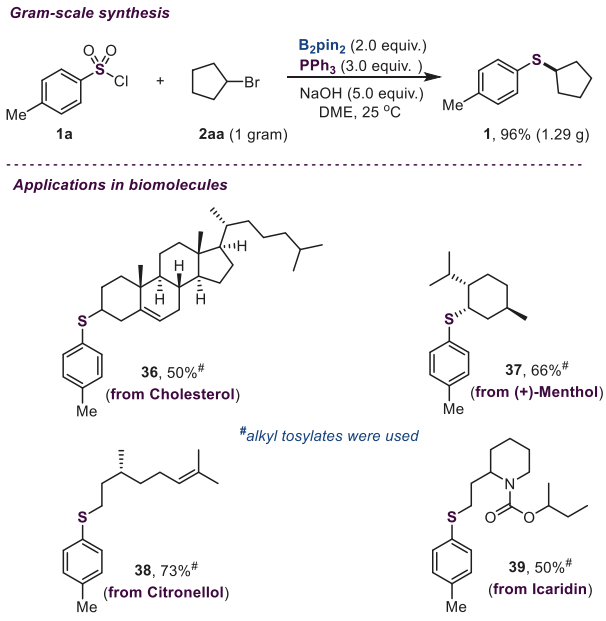
[a] Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv.), bromocyclopentane **2aa** (0.3 mmol, 1.5 equiv.), B_2pin_2 (0.4 mmol, 2.0 equiv.), PPh_3 (0.3 mmol, 1.5 equiv.), base (1.0 mmol, 5.0 equiv.), solvent (1.0 mL), room temperature, 15 h.
[b] Determined by ^1H NMR using mesitylene as an internal standard. The isolated yield is shown in parentheses.
[c] Cyclopentyl 4-methylbenzenesulfonate (0.3 mmol, 1,5 equiv.) was used.

After the reaction conditions were established, we tried to examine the scope of this reaction. As shown in Scheme 2, various aryl sulfonyl chlorides underwent this transformation smoothly, delivering the thiolated products in moderate to excellent yields. Notably, this borane-promoted thiolation reaction features excellent functional group tolerance. Functional group such as F, Cl, Br, I, CN, CF_3, NO_2, OTs, alkenyl, carboxylate, and amine (**4–11**, **23**, **29**, **33**, **34**) could be compatible. Notably, iodo and nitro groups that are always sensitive in transition metal-catalyzed reactions, could be well-tolerated in this protocol (**7**, 96%; **11**, 36%). Substrates bearing an electron-withdrawing group (such as CN, CF_3) on the aromatic ring performed this reaction well, providing the coupling products in excellent yields (**9**, 96%; **10**, 94%). It was worth mentioning that examples with steric hindrance exhibited good efficiency as well. For instance, aryl sulfonyl chlorides having two groups at *ortho*-position of sulfonyl group were suitable for this transformation, affording the desired products in excellent yields (**3**, 85%; **8**, 95%; **18**, 83%). Moreover, the heteroaromatic sulfonyl chlorides were good coupling partners, delivering the desired products in moderate to good yields (**14**–**18**, 57%–83%). With respect to another coupling partner, various alkyl tosylates were further evaluated. The primary and secondary alkyl tosylates carried out this reaction well, while tertiary alkyl tosylates were unsuitable for this conversion. This reaction could proceed using alkyl tosylates containing sensitive groups (such as ester and amine) as substrates, and the synthetically useful yields were obtained (**33**, 38%; **34**, 34%). Additionally, to demonstrate the generality of this borane-promoted thiolation reaction, other alkyl electrophiles were also investigated using 4-methylbenzenesulfonyl chloride **1a** as the coupling partner. Like alkyl bromides, cyclopentyl iodide showed excellent reactivity, affording the desired product in 98% yield, while cyclopentyl chloride only provided 35% yield. However, tertiary alkyl bromides are not suitable for this transformation.

A gram-scale synthesis was carried out to demonstrate the excellent applicability of this borane-promoted thiolation reaction. As shown in Scheme 3, this transformation proceeded well on a 1-gram scale, and 96% yield was afforded. Furthermore, we also



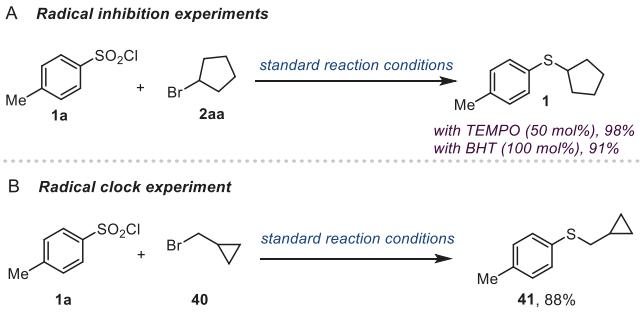
Scheme 2. Scope of the borane-promoted thiolation of (hetero)aryl sulfonyl chlorides. Reaction conditions: aryl sulfonyl chlorides (0.2 mmol, 1.0 equiv.), alkyl tosylates (0.3 mmol, 1.5 equiv.), B_2pin_2 (0.4 mmol, 2.0 equiv.), PPh_3 (0.6 mmol, 3.0 equiv.), NaOH (1.0 mmol, 5.0 equiv.), DME (1.0 mL), 24 h.



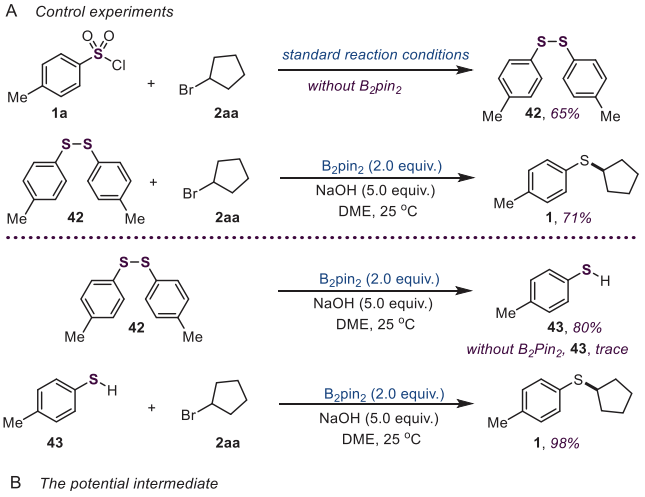
Scheme 3. Gram-scale synthesis and late-stage functionalization of biomolecules.

investigated the late-stage thiolation of biomolecules (Scheme 3). The cholesterol derivative underwent this reaction smoothly, providing the desired product in an acceptable yield (**36**, 50%). The substrate with steric hindrance derived from menthol could react well, and a moderate yield was afforded (**37**, 66%). The citronellol derivative bearing an alkenyl group successfully carried out this coupling reaction, delivering the corresponding product in good yield (**38**, 73%). Notably, when the icaridin derivative containing an ester group was used as the substrate, a reasonable yield was provided (**39**, 50%). These results indicate that this borane-promoted thiolation reaction could provide an efficient method to access valuable molecules in medicinal chemistry.

To understand the mechanism of this borane-promoted cross-coupling reaction, some critical experiments were conducted. In the presence of a radical scavenger TEMPO (50 mol%) or a radical inhibitor BHT (100 mol%), this reaction proceeded well without loss of efficiency (Scheme 4A). Moreover, a radical clock experiment was performed as well, and the coupling product **41** could be obtained in excellent yield instead of the ring-opening product (Scheme 4B). The outcomes suggest that free radicals may not be involved in the reaction system. Furthermore, the EPR experiment also supported no free radical in this reaction (for details, see Supporting information).

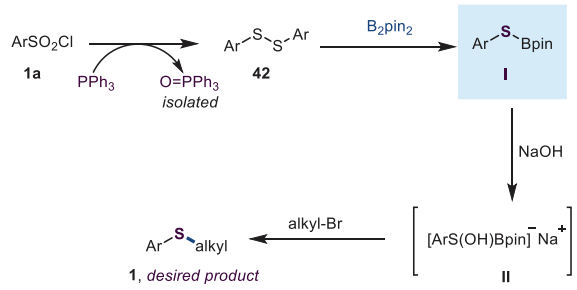


Scheme 4. Mechanistic studies.



Scheme 5. Investigation of the borane effect (A) and the potential intermediate (B).

In our initial studies, we found that the borane reagent was necessary to this reaction. Therefore, control experiments were carried out to illustrate the role of B_2pin_2. Without the borane reagent, the diaryl sulfide **42** could be isolated in 65% yield (Scheme 5A); meanwhile, no thiolated product **1** was obtained. Furthermore, when diaryl sulfide **42** was used as the substrate, the coupling product **1** could be afforded in 71% yield. These results reveal that diaryl sulfide **42** might be an intermediate of this reaction. In addition, we also monitored this reaction and found that in the initial stage of this reaction, intermediate **42** was rapidly formed and then converted into the desired product **1** (Scheme 5B). Importantly, in the presence of B_2pin_2, diaryl sulfide **42** could convert into 4-methylbenzenethiol **43**, which readily reacted with **2aa** to produce the thiolated product **1** in excellent yield. Nevertheless, only a trace amount of 4-methylbenzenethiol **43** was observed in this reaction. Therefore, these results suggest that the aryl sulfide anion might be the real active species generated *in situ* with the aid of B_2pin_2.



Scheme 6. Proposed mechanism.

According to these preliminary results, the mechanism of this borane-promoted thiolation reaction was proposed, as shown in Scheme 6. Firstly, the aryl sulfonyl chloride was reduced by PPh_3 to form a diaryl sulfide, which could be observed in this reaction [39,40]. Subsequently, the resulted diaryl sulfide might react with B_2pin_2 to offer an intermediate **I** [41], which then was triggered by NaOH to deliver a boronate complex **II**. Finally, the *in-situ*-generated aryl sulfide anion reacted with the alkyl bromide through a S_N2 pathway to produce the desired sulfide.

In conclusion, we have developed an efficient borane-promoted reductive deoxygenation coupling reaction to construct the C(sp^3)-S bond. This transformation without the use of unpleasant mercaptans exhibits excellent functional group tolerance and a wide range of substrates, thus providing an excellent strategy to access the valuable sulfide compounds. Moreover, this reaction has also shown good applications in the late-stage thiolation of biomolecules and offers a good platform for drug discovery and development.

Declaration of competing interest

There are no conflicts to declare.

Acknowledgments

We thank for the financial support from Natural Science Foundation of Sichuan (No. 2021YJ0413), Sichuan Key Laboratory of Medical Imaging (North Sichuan Medical College, No. SKLMI201901), Strategic Cooperation of Science and Technology between Nanchong City and North Sichuan Medical College (Nos. 19SXHZ0441, 19SXHZ0227), Chongqing Postdoctoral Science Foundation (No. cstc2020jcyj-bshX0052), and China Postdoctoral Science Foundation (No. 2020M673121). We also thank Analytical and Testing Center of Chongqing University for assistance with NMR spectrum analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.04.022.

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