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Ligand-enabled C–H borylation of diverse classes of arenes

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ABSTRACT

Here we report a new 6,6′-bipyridine based ligand framework for the iridium-catalysed regioselective ortho borylation of diverse classes of arenes containing different functional groups. Moreover the developed method is highly selective for the directed C(sp (Altus and Love, 2021) [3]-H borylation of the 2-pyridyl amines as well as benzyl and homobenzyl amides directed by pyridine group and amide directed borylation of N-adjacent C–H bond of amides.

1. Introduction

Transition metal-catalysed C–H bond functionalisation [1] is one of the modern day's powerful synesthetic tools for the diversification of unreactive C–H bonds to prepare high-valued materials [2]. Selective functionalisation of inert C–H bond is always challenging due to the high bond dissociation energies and low polarity [3]. Despite these difficulties, so many efficient methods have been discovered to functionalise these inert C–H bonds from proximal to remote C–H bonds [4]. Among the various C–H bond functionalizations, Iridium-catalysed C–H bond borylation [5] has received tremendous attention owing to its versatile synthetic utility [6]. Organoboron compounds are valuable organic linchpins for the various cross-coupling reactions and transformations of other functionalities [6].

In this context, among various metal-catalysed C–H borylation reactions, the employment of iridium-metal-catalysed C–H borylation is the major contributing factor. Moreover, while directed ortho metalation (DoM) strategy is a widely accepted synthetic approach, many C–H borylation catalysts have been discovered, which have enabled to activate and functionalise arene's C–H bonds [7] with high selectivity and thus considered as a complementary approach to DoM [8]. Apart from an initial report [9] of the benzamide ortho borylation, the first example of the ortho C–H borylation of phenol was reported by the Hartwig group [10] utilising Si-chelation to the iridium metal using bidentate dtbpy ligand under homogeneous conditions. Subsequently, Sawamura and co-workers [11] came up with a powerful strategy by employing solid-supported monodentate phosphine ligand for the ortho borylation under iridium-catalysed heterogeneous conditions. Notably, by the passing of time, this ligand showed huge utility for the ortho borylation [12] of a large array of substrates including aliphatic borylations [13]. Subsequently, electron-deficient monodentate phosphine and arsine ligand was introduced by the Ishiyama and Miyaura for the ortho borylation of esters [14] and ketone [15] functionalities respectively.

To this continuous development of the ortho borylation, Lassaletta and Farnandez [16] introduced an elegant concept using hemilabile ligand for the selective ortho borylation of hydrazones and 2-phenyl pyridines. These are the seminal reports where iridium-catalysed regioselective borylation occurred through the formation of Iridium tris(boryl) complex [17]. Aside from the several reports of ortho borylation through chelation [18], another type of concept was developed by the Smith [19], Kanai [20], and Reek group [21] for the selective ortho borylation of specific substrates by the modification of the bidentate bipyridine ligand using noncovalent interactions. On the other hand in 2014, Smith and coworkers reported an approach [22] for the ortho borylation of diverse classes of substrates using P/N–Si ligand and the reaction underwent through the formation of iridium bis(boryl) complex. After that, Li et al. [23] reported N,B-bidentate ligand for the ortho borylation of arenes containing several functional groups. Recently, our group [24] developed a method for the ortho and directed aliphatic borylation of diverse classes of substrates by using simplified N–C monoanionic bidentate ligand (PYT ligand). In these above-mentioned reports where heterobidentate [25, 26] or monodentate ligand [11] were used for the ortho borylation of diverse classes of substrates, there was no report for the bipyridine-based systems for the ortho borylation of diverse classes of arenes irrespective

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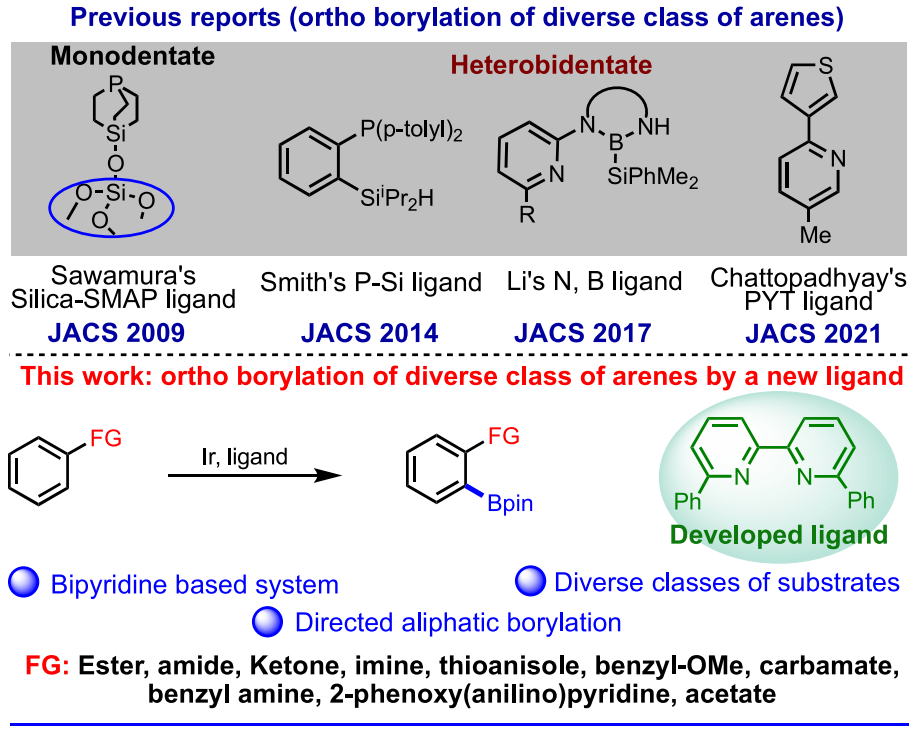

Fig. 1. Previous developments and present study.

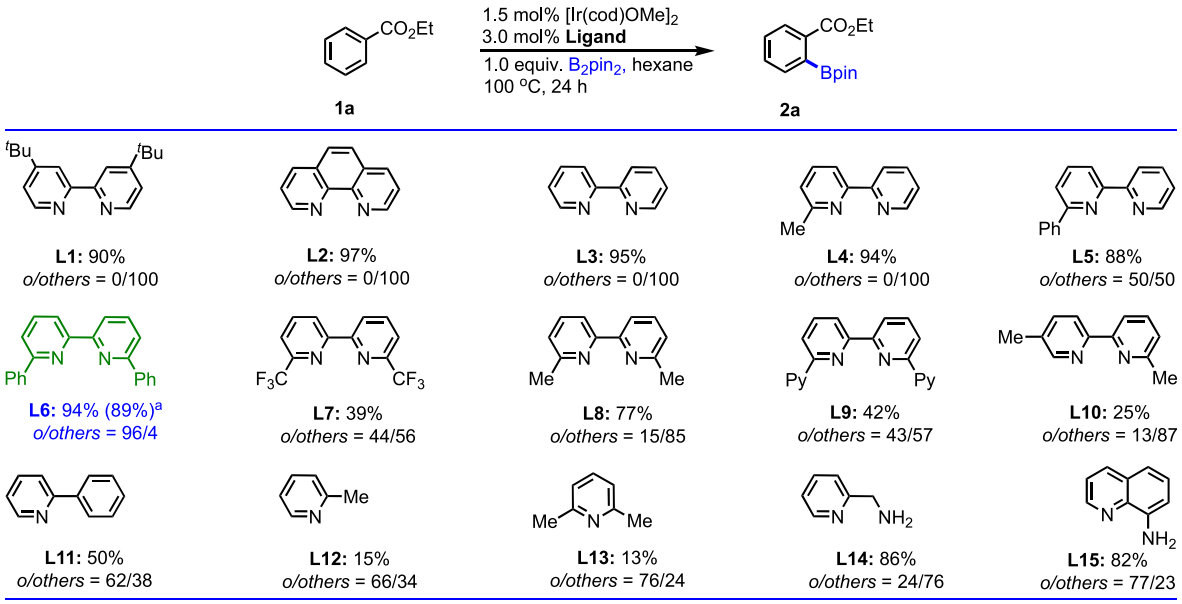

Fig. 2. Ligand screening. Reactions are in 0.5 mmol scale. In parenthesis isolated yield is reported. Conversions and ratios are determined from the GC/MS analysis. [a]1.5 equiv. B_2pin_2 was used (with 1.0 equiv. B_2pin_2 76% conversion (*o/others* = 96/4)). See SI for details.

of their electronic nature.

Herein, we report a simple bidentate bipyridine ligand having phenyl groups at 6,6′- position of bipyridine ligand, which showed high regioselectivity towards ortho as well as aliphatic borylations (Fig. 1).

2. Results and discussions

To get the optimised reaction conditions, we first tested the borylation with ethyl benzoate (1a) as a model substrate (Fig. 2). Initial investigation with the conventional bidentate ligands (L1-L3) with $[Ir(cod)OMe]_2$ showed that there was no ortho selective borylation, rather resulted mixture of meta and para borylated products. Next, we tested various ring-substituted bpy derived ligands and found that while the 6-substituted ligand **L5** gave 50% ortho selectivity but the 6-methyl substituted ligand **L4** gave no ortho borylation under the same reaction conditions. Based on this result, we have designed and synthesized 6,6′-diphenyl substituted bpy ligand (**L6**) and employed in the borylation reaction. Interestingly, we found this developed ligand showed very high

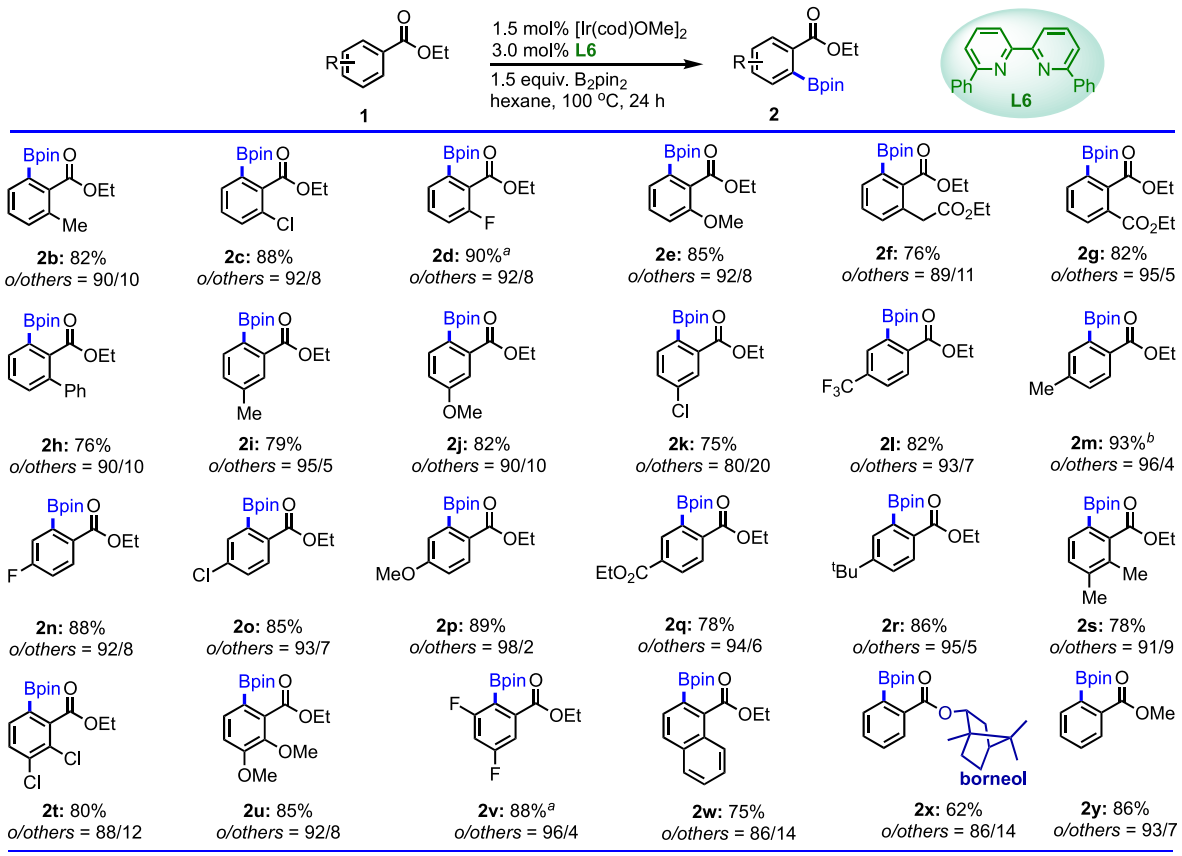

Fig. 3. Substrates scope for aromatic esters. Reactions are in 0.5 mmol scale. Isolated yields are reported. Ratios are determined from the GC/MS analysis. [a]1.0 equiv. B_2pin_2 was used. [b]1.2 equiv. B_2pin_2 was used. See SI for details.

ortho selective borylation (96%) with 76% conversion. With increasing the amount of B_2pin_2 to 1.5 equiv., the conversion was increased to 94%. Then to see any effect of other substitution at the 6-position, **L7-L9** ligands were tested and resulted lower ortho selectivity. Also, it was observed that 5,6′-disubstituted ligand **L10** gave very poor ortho selectivity. Moreover, testing some monodentate ligands (**L11-L13**) in the borylation also found to be nonselective. Notably, to see the effect of the hemilabile ligands, we performed borylation using **L14** [27] and **L15** [18a] which also gave nonselective borylation. Frome the above screening it is concluded that the optimised ligand is **L6**.

Next ortho borylation of a series of aromatic esters were performed under the developed reaction conditions (Fig. 3). It was observed that arenes containing substitution at ortho positions (1b-1h) were well tolerated. The developed conditions were also compatible for arenes containing meta (**1i-1k**), para (**1l-1r**) substituents and as well as disubstituted arenes(1s-1w) with good isolated yield and selectivity. Ester derived from bioactive borneol (1x) gave 86% ortho borylation. The developed reaction condition was applicable for the ortho borylation of methyl benzoate substrate (1y).

To this end, we have found that the developed conditions exhibited excellent outcomes for the regioselective ortho borylation of a range arenes containing different functional groups (Fig. 4). For example, the developed ligand (**L6**) was compatible for the ortho borylation of N, N disubstituted amide (**3a**), acetophenone (**3b**), benzophenone (**3c**), thioanisole [20] (**3d**), benzyl ether (**3e**), imine (**3f**), carbamate (**3g**), *N, N*-disubstituted benzylamine (**3h**), 2-phenoxypyridine (**3i**), 2-anilinopyridine (**3j**) and 8-aryl quinoline (**3k**) and phenyl acetate (**3k**). The developed ligand system was also examined for the aliphatic borylations. For example, the aliphatic borylation of N-substituted 2-pyridylamines (**3m-3o**), where directed aliphatic borylation occurred by the coordination of the pyridyl nitrogen to the iridium center with a decent number of isolated yields (Fig. 4). This developed method also equally effective for the amide-directed sp [3] C–H borylation [28] of C–H bond adjacent to the nitrogen atom of *N,N*-dimethyl benzyl amide and homologous benzyl amides.

The practical utility of the developed methodology was showcased by the transformation of the in-situ generated boronate ester to various functional groups. Thus, ortho borylated product (**2a**) was converted into ethyl 2-hydroxybenzoate (**5,** 86%), Pd-catalysed arylation (**1h,** 82%), Cu-catalysed bromination (**6,** 87%) and chlorination (**1c,** 85%) could also be performed. By treatment with $AgNO_3$ and D_2O, deuteration (**7,** 90%) was also be performed (Fig. 5, see SI for details).

To understand the mechanism of the ortho selectivity of benzoate ester with 6,6′-diphenyl bipyridine ligand (**L6**), we looked into some ligand screening results including 2-phenyl pyridine (**L11**) with other ligand systems (Fig. 6). We observed that while the ligand (**L11**) resulted in 62% ortho borylated product, the ligand 2-methyl pyridine (**L12**) gave almost same amount of ortho borylation (66%), which indicated a monodentate behaviour of the **L11** ligand. Moreover, we noticed that 6-substituted ligands **L5** and **L16** also gave almost 42–50% ortho selectivity, which is same result with the **L7** and **L9** ligands. These results indicated that **L6** ligand may act as a hemilabile ligand (one N-coordination acts as labile due to the sterically crowded phenyl substitution at the nitrogen binding site) during the C–H activation process (oxidative addition). From these results, we proposed a mechanism where **L6** acts as a hemilabile ligand (Fig. 6). Also, there may be other possible mechanism where N, C bidentate coordination may play role in the ortho selectivity, which is matter of further study.

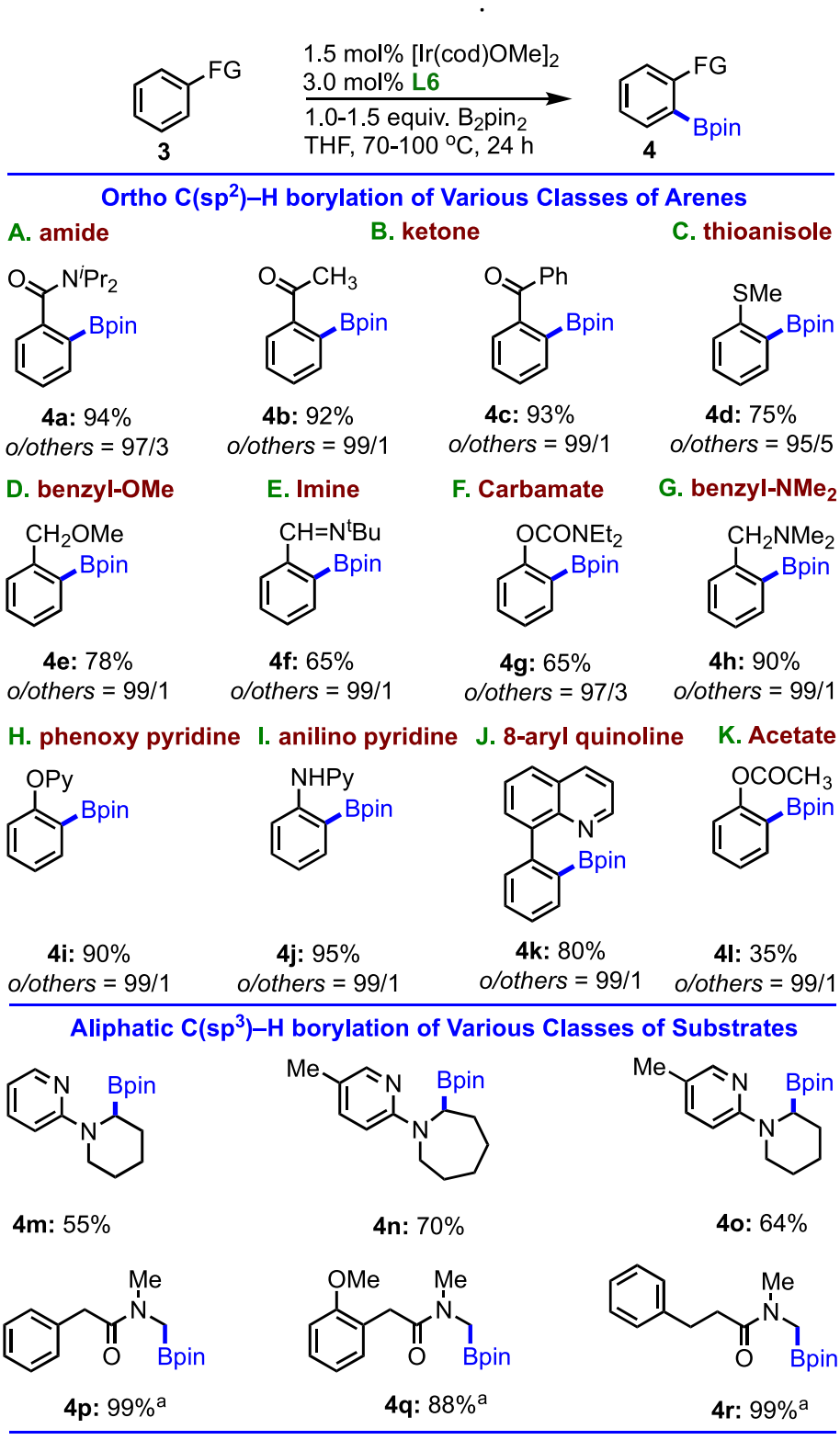

Fig. 4. Substrate scopes for other classes. Reactions are in 0.5 mmol scale. Ratios are determined by GC/MS analysis. [a]NMR conversions are reported. See SI for details.

3. Conclusion

In summary, we have developed a new ligand framework for the ortho borylation of a diverse class of arenes containing different functional groups along with aliphatic borylation. The developed method showed excellent functional group tolerance and site selectivity. We believe that the developed method will find wide application for the C–H functionalisation reactions.

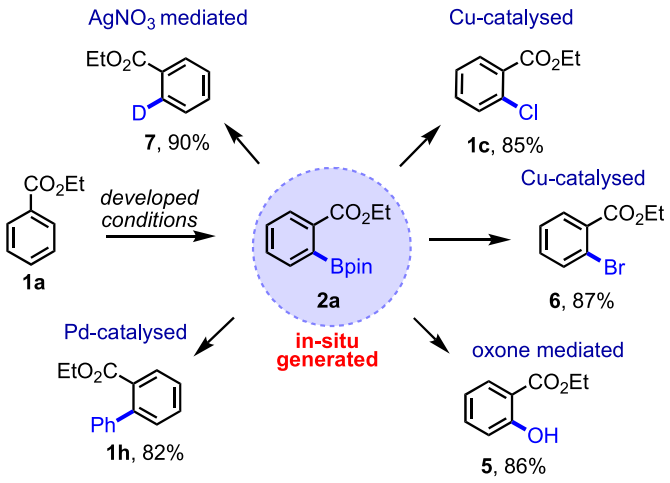

Fig. 5. In-situ synthetic transformations. See SI for details.

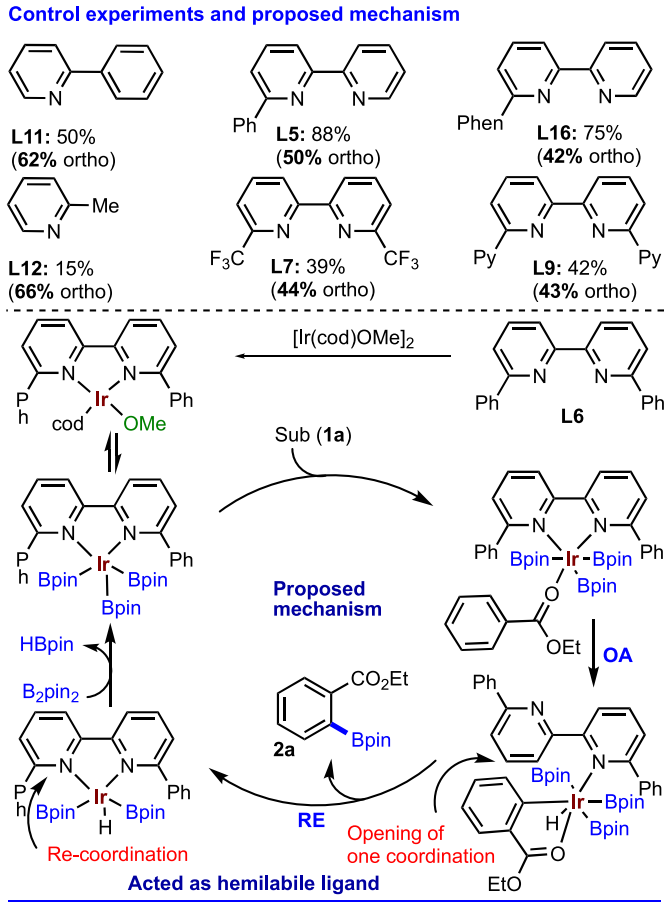

Fig. 6. Control experiments and proposed mechanism.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tchem.2022.100028.

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