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Rhodium(III)-catalyzed diastereo- and enantioselective hydrosilylation/cyclization reaction of cyclohexadienone-tethered α,β-unsaturated aldehydes

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ABSTRACT

A rhodium(III)-catalyzed hydrosilylation/cyclization reaction of cyclohexadienone-tethered α,β-unsaturated aldehydes (1,6-dienes) with triethylsilane is described, providing a series of *cis*-hydrobenzofurans, *cis*-hydroindoles, and *cis*-hydroindenes bearing silyl enol ether in good to excellent yields and excellent stereoselectivities. Additionally, the versatility of this method was demonstrated through a gram-scale experiment and various downstream transformations, highlighting its utility.

Hydrosilylation is an atom-economic reaction for the production of organosilicon compounds that are widely applied in organic synthesis [1,2], material science [3], and polymer chemistry [4]. While UV light irradiation and heat can initiate the reaction [5], transition-metal catalysis is the most widely used method for hydrosilylation [6–11]. Notably, transition metal-catalyzed hydrosilylation/cyclization reactions have become popular in synthesizing carbo- and heterocyclic units bearing a silyl group. Considerable progress has been achieved in the hydrosilylation/cyclization of 1,6-diynes [12,13] and 1,6-enynes [14–26]. However, the reaction involving 1,6-dienes is far less developed, due to their lower reactivity toward transition metals when compared to 1,6-enynes. The exploitation of powerful catalysts merges as a promising way to address this challenge. In that scenario, highly reactive d^0 metals with strong electropositivity and open coordination sites have been employed to enhance the interaction of alkene with the metal center. For instance, Molander pioneered the use of yttrocene to facilitate the hydrosilylation/cyclization of 1,6-dienes, yielding a six-membered ring with a terminal alkyl silane [27,28]. Similar reactivity to the d^0-metallocene was exhibited by the electrophilic group 10 transition-metal complex $[(\mathrm{Phen})\mathrm{Pd}(\mathrm{Me})(\mathrm{OEt_2})]^+[\mathrm{BAr_4}]^-$, as utilized by Widenhoefer *et al.* in 1998. This complex enabled the reaction of 1,6-dienes to afford *trans*-silylated cyclopentanes [29,30]. Thereafter, the asymmetric version of this reaction was realized *via* the catalysis of chiral palladium pyridine-oxazoline complex, leading to heterocycles bearing two adjacent stereocenters with high diastereo- and enantioselectivity (Scheme 1a) [31–33].

Despite the remarkable progress, some perceived challenges remain in this growing area. Notably, there is a need to develop reactions involving electron-deficient 1,6-dienes and explore the regioselectivity of transformations in unsymmetrical 1,6-dienes. In 2021, we disclosed a rhodium(III)-catalyzed asymmetric reductive cyclization of electron-deficient 1,6-dienes, which included cyclohexadienone-tethered α,β-unsaturated ketones, esters, amides, phosphonates, sulfones [34], and terminal alkenes [35]. In these cases, the initial step involved the hydrosilylation/cyclization of the 1,6-diene, transforming the cyclohexadienone unit into a dienol silyl ether. Due to the instability of the dienol silyl ether, it was transformed into enone *via* desilylative workup. Complementing this work, we herein present a rhodium(III)-catalyzed hydrosilylation/cyclization of cyclohexadienone-tethered α,β-unsaturated aldehydes (1,6-dienes) [36–38]. By introducing a more electron-deficient enal group into the side chain, the reaction exhibits a reversed selectivity, allowing for the construction of bicyclo[4.3.0]nonane frameworks bearing a silyl enol ether on the five-membered ring (Scheme 1b). Another advantageous feature of this

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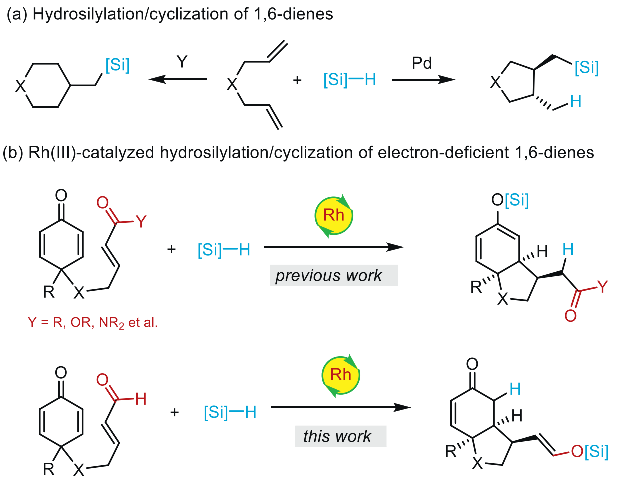
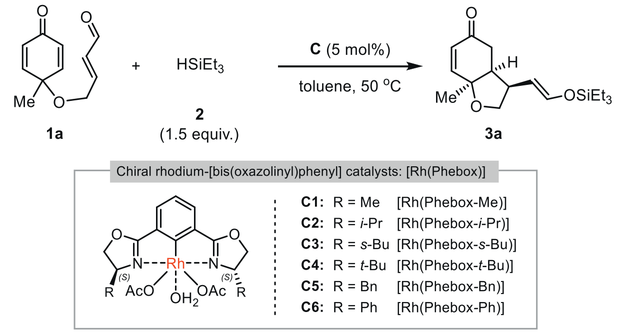


Scheme 1. Transition metal-catalyzed hydrosilylation/cyclization reactions of 1,6-dienes.

reaction is the stability of the silyl enol ether group in the final product, increasing the atom economy of the process and providing a convenient handle for further transformations.

The chiral rhodium-bis(oxazolinyl)phenyl complex developed by the Nishiyama group, has been identified as a powerful catalyst not only for the hydrosilylation of conjugated alkenes [39,40] but also for the desymmetrization of cyclohexadienones [41]. In this context, we initiated our investigation by using a series of rhodium(III) catalysts to promote the hydrosilylation/cyclization of cyclohexadienone-tethered α,β-unsaturated aldehydes **1a** with triethylsilane (**2**). All of the Nishiyama's catalysts, except the sterically hindered catalyst **C4**, resulted in the desired product **3a** with good yield and excellent enantioselectivity (Table 1, entries 1–6). The best outcome was achieved with [(*S*,*S*)-Rh(Phebox-*s*-Bu)(OAc)$_2$·H$_2$O] catalyst (**C3**), giving *cis*-hydrobenzofuran derivative **3a** in 90% yield and 99.9% *ee* (Table 1, entry 3). The addition of ^{t}BuONa, typically thought to accelerate ligand exchange, led to a decreased yield of 80%, even with an extended reaction time of 12 h. This can be attributed to the decomposition of the substrate under basic conditions (Table 1, entry 7). This reaction proved to be less effective at room temperature, and the desired product was obtained in only 56% yield after 36 h (Table 1, entry 8). When THF was used instead of toluene, no further improvement was observed, giving **3a** in 80% yield with 98.3% *ee* (Table 1, entry 9).

Table 1
Evaluation of conditions for hydrosilylation/cyclization of **1a**.[a]



Entry	C	Time (h)	Yield (%)[e]	*ee* (%)[f]
1	**C1**	12	86	99.7
2	**C2**	12	87	98.3
3	**C3**	3.5	90	99.9
4	**C4**	24	<5%	0
5	**C5**	12	87	97.9
6	**C6**	12	78	99.2
7[b]	**C3**	12	80	99.9
8[c]	**C3**	36	56	99.9
9[d]	**C3**	12	80	98.3

[a] Reactions were carried out with **1a** (0.2 mmol), HSiEt$_3$ (0.3 mmol), and **C** (5 mol%) in 2.0 mL of toluene under a N$_2$ atmosphere at 50 °C.

[b] With the addition of NaO^{t}Bu (10 mol%).

[c] Reaction was conducted at r.t.

[d] THF was used as the solvent.

[e] NMR yield.

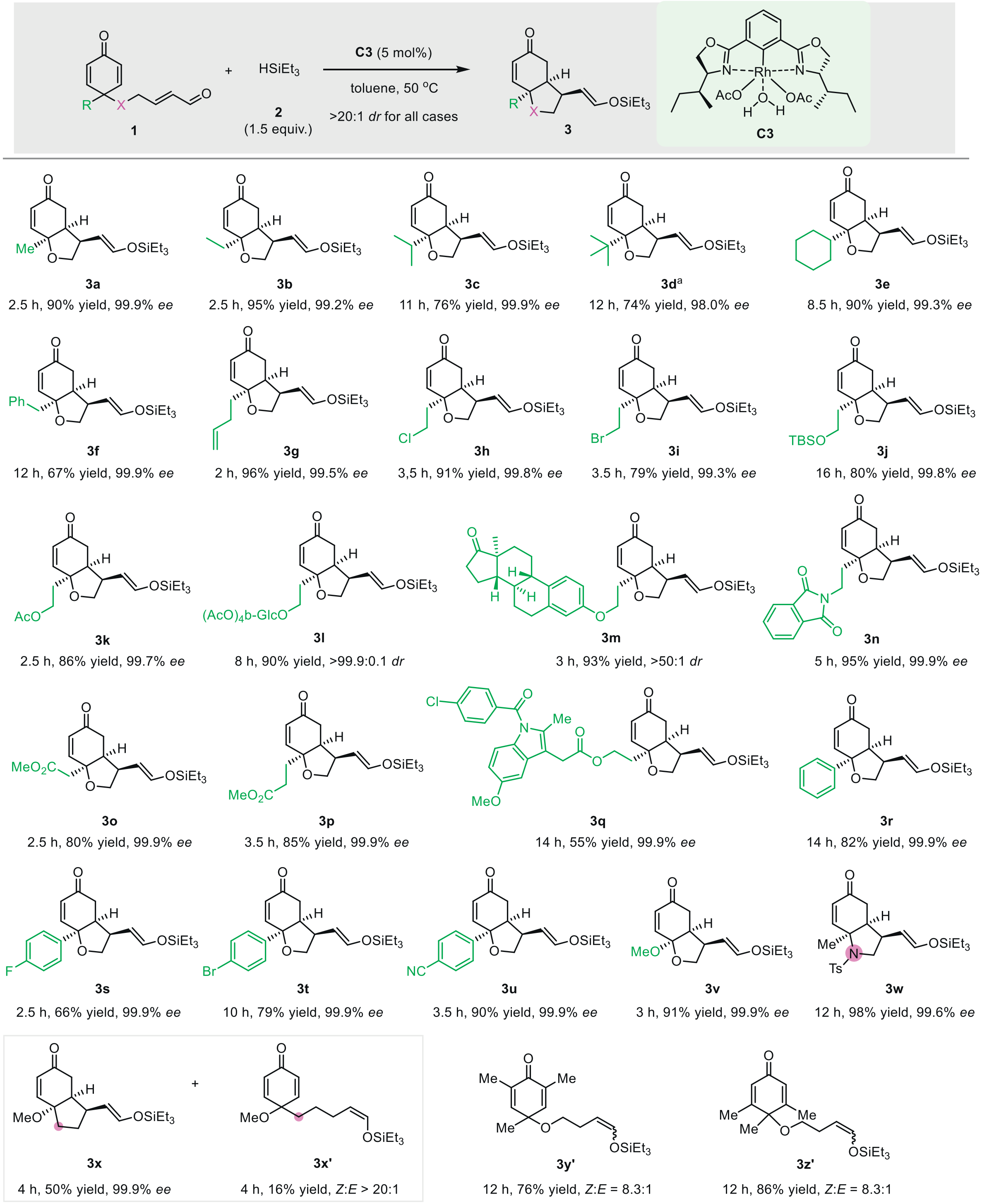
[f] Determined by HPLC analysis using a chiral stationary phase.

With the optimal reaction condition in hand, we proceeded to evaluate the generality of the hydrosilylation/cyclization reaction of cyclohexadienone-containing 1,6-dienes **1** (Scheme 2). The cyclohexadienone scaffolds, with various R substituents including methyl, ethyl, *i*-propyl, *c*-hexyl, benzyl, and homoallyl group, could be converted into the corresponding products **3a**–**3c**, **3e**–**3g** in 67%–96% yield and >99% *ee*. Notably, the terminal alkene in the substrate **1g** remained intact throughout the reaction. Sterically hindered substrate **1d** failed to give the cyclization product under the catalysis of **C3**, but it worked well under the catalysis of **C2**, producing the bicyclic product **3d** with 74% yield and 98.0% *ee*. The reaction proceeded smoothly with substrates **1** featuring a chloro, bromo, OTBS, OAc, glucose, estrone, and phthalimide group as the end of the alkyl chain, giving products **3h**–**3n** in good yields ranging from 79% to 95%, along with excellent enantioselectivity. Enantiopure products **3o**–**3q** were obtained from substrates **1o**–**1q** containing an ester group, although the yield of product **3q** bearing a bulkier indometacin motif, was somewhat lower.

Aryl substituents, such as phenyl, *p*-FC$_6$H$_4$, *p*-BrC$_6$H$_4$, and *p*-CNC$_6$H$_4$, at the quaternary carbon of the cyclohexadienone, were well-tolerated in the reaction, leading to the bicyclic products **3r**–**3u** in 66%–90% yield and 99.9% *ee*. The substrate with a methoxy substituent (**1v**) provided the heterocyclic ketal compound **3v** in 91% yield and 99.9% *ee*. Additionally, the optimized reaction conditions were compatible with TsN- and H$_2$C-linked dienes, providing *cis*-hydroindole **3w** and *cis*-hydroindene **3x** in >99% *ee*. However, the yield of *cis*-hydroindene **3x** was low at 50%, primarily due to the formation of the uncyclized product **3x'**. Substrates featuring methyl groups at the α,α' or β,β' positions of the cyclohexadienone ring did not yield the desired cyclization adducts due to the steric hindrance. Instead, only enals on the side chain participated in the hydrosilylation, delivering uncyclized products **3y'** and **3z'** in 76%–86% yield with an 8.3:1 *Z*/*E* ratio. Interestingly, the enol silyl ethers in **3x'**–**3z'** predominantly adopted the *Z*-form, possibly due to *E* to *Z* isomerization under the catalysis of rhodium (for details, see Supporting information) [42–44].

To probe the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 3). The reaction of cyclohexadienone-tethered α,β-unsaturated aldehyde **1a** with DSiEt$_3$ at 50 °C proceeded slowly. To accelerate the reaction, we elevated the temperature to 80 °C and observed 45% of deuterium incorporation on the cyclohexenone ring. In contrast, the reaction of cyclohexadienone-tethered α,β-unsaturated ester **4** with DSiEt$_3$ resulted in **[D$_1$]**–**5** with a 96% deuterium content on the chain. This outcome indicated that the hydrosilylation/cyclization process differs depending on the substrate, leading to a reversal of selectivity.

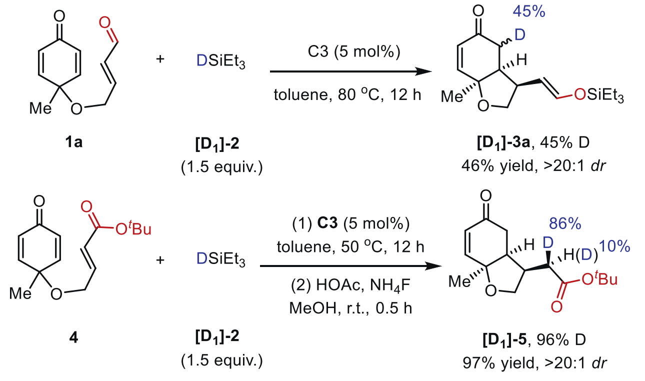
Based on the experiment results, a proposed reaction mechanism is illustrated in Scheme 4. Firstly, the Rh(III) catalyst is reduced by HSiEt$_3$ to generate the Rh(I) species, which may be the catalytic active species and starts the catalytic cycle [45]. Then, coordination and oxidative cyclometalation of the Rh(I) species with **1a** gives the five-membered rhodacycle intermediate **A**, which is in equilibrium with its η_3-oxaallylrhodium structure **A'**. Next, the intermediate **A'** undergoes σ-metathesis with HSiEt$_3$, affording the



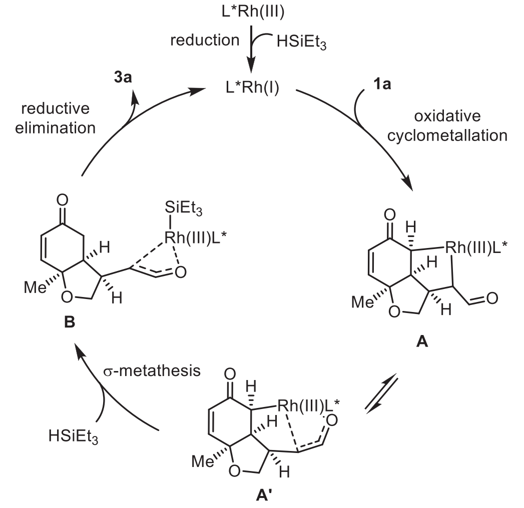
Scheme 2. Substrate scope of cyclohexadienone-tethered α,β-unsaturated aldehydes **1**. Reactions were carried out with **1** (0.2 mmol), $HSiEt_3$ (0.3 mmol), Rh catalyst **C3** (5 mol%), and toluene (2.0 mL) at 50 °C under a N_2 atmosphere. Yield of isolated product. *dr* values were determined by ^1H NMR on the crude reaction mixture before column chromatography. *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] **C2** (5 mol%) was used instead of **C3**.

Rh(III) enolate intermediate **B**. Finally, the stereoselective reductive elimination of the Rh(III) enolate intermediate **B** provides the silyl enol ether product **3a** and regenerates the Rh(I) catalyst. As for the α,β-unsaturated ester **4**, the enolation of the five-membered rhodacycle intermediate would favor the ketone group over the ester group, leading to the opposite selectivity.

To assess the robustness of this rhodium-catalyzed protocol, we carried out a gram-scale reaction. Gratifyingly, the reaction of 1,6-diene **1a** and $HSiEt_3$ on a 5.2 mmol scale proceeded smoothly even at a catalyst loading of 2 mol%, furnishing bicyclic product **3a** (1.47 g, 92% yield, and 99.9% *ee*) without diminishing either yield or enantioselectivity (Scheme 5a). Then, we devoted our efforts to further transformations of the final product. When **3a** was subjected to Luche conditions, the enone group was reduced to the corresponding allylic alcohol, and product **6** was prepared in 92% yield with excellent chemo- and stereoselectivity (Scheme 5b).



Scheme 3. Deuterium-labeling experiments.

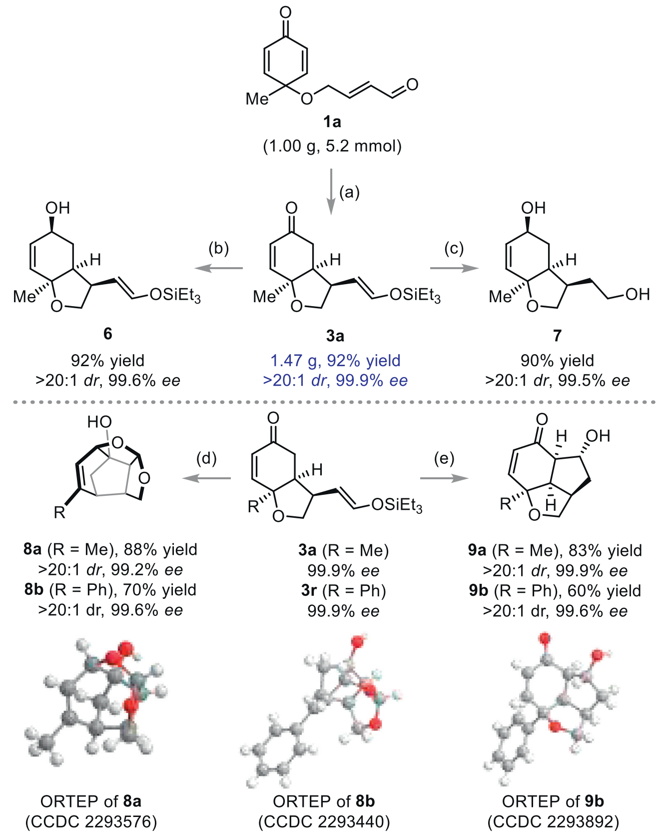


Scheme 4. A plausible mechanism for the hydrosilylation/cyclization of cyclohexadienone-containing 1,6-dienes.

The use of an excess amount of NaBH$_4$ enabled the reduction of both the carbonyl group and silyl enol ether in **3a**, and diol derivative **7** could be attained in 90% yield (Scheme 5c). Moreover, the silyl enol ether provides versatile synthetic handles to design new transformations for the construction of value-added products. For example, a FeCl$_3$-promoted Mukaiyama-aldol/ring-opening rearrangement cascade reaction readily converted **3a** or **3r** into intriguing fused rings **8a** or **8b** (Scheme 5d, for details, see Supporting information). Alternatively, tricyclic skeleton **9a** or **9b** could be built up *via* the removal of the silyl group with TBAF followed by intramolecular aldol condensation (Scheme 5e). Significantly, all the above transformations proceeded smoothly with almost no loss of *ee*.

The structure of **8a**, **8b**, and **9b** was established through X-ray crystallography. Unfortunately, due to the large standard uncertainty associated with the Flack parameters, the absolute configuration of these compounds could not be confidently determined. Therefore, the assignment of absolute configuration was carried out using the electronic circular dichroism (ECD) method. By comparing the calculated ECD with the experimental data, it was determined that compound **8b** has the absolute configuration of (2a*S*,2a^1*S*,3*S*,4a*S*,5*R*,6a*R*) (for details, see the supporting information). Based on these results, the absolute configuration of (+)−**3a** can be inferred as (3*R*,3a*S*,7a*S*).

In conclusion, we have developed a rhodium(III)-catalyzed hydrosilylation/cyclization reaction of cyclohexadienone-tethered α,β-unsaturated aldehydes (1,6-dienes) with triethylsilane, providing a series of *cis*-hydrobenzofurans, *cis*-hydroindoles, and *cis*-hydroindenes bearing silyl enol ether in good to excellent yields and excellent enantioselectivities. Furthermore, the utility of this protocol is highlighted by a gram-scale experiment and versatile downstream transformations.



Scheme 5. Gram-scale preparation and synthetic transformations. Conditions: (a) **1a** (5.2 mmol), HSiEt$_3$ (7.8 mmol), **C3** (2 mol%), and toluene (52 mL) at 50 °C under a N$_2$ atmosphere; (b) NaBH$_4$ (1 equiv.), CeCl$_3$·7H$_2$O (1.2 equiv.), MeOH, 0 °C; (c) NaBH$_4$ (4 equiv.), MeOH, 0 °C; (d) FeCl$_3$ (0.2 equiv.), DCM, −40 °C; (e) TBAF (2 equiv.), DCM, −40 °C.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109520.

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