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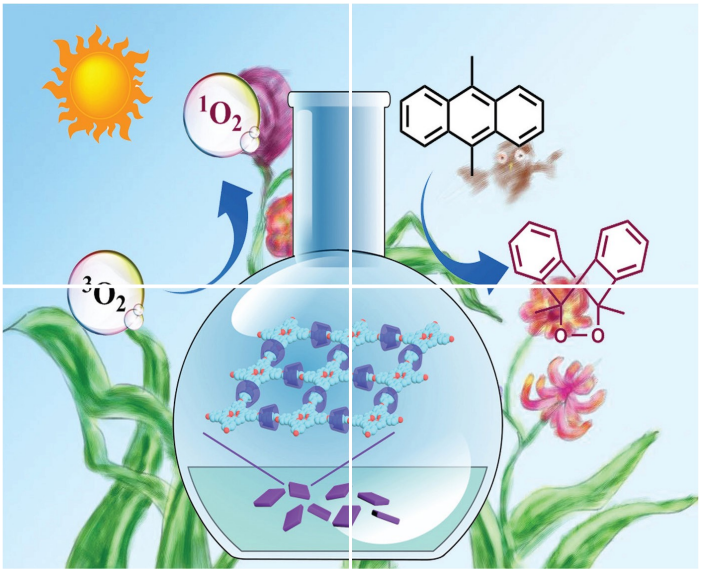

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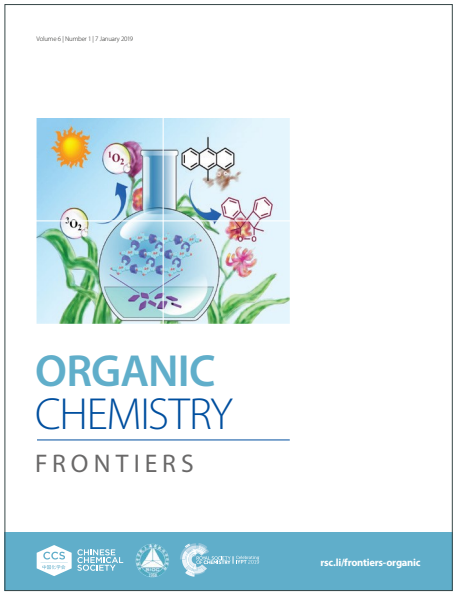

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ARTICLE

Tandem indium(III)-catalyzed cyclization and intermolecular hydrofunctionalization of 1,6-enynes

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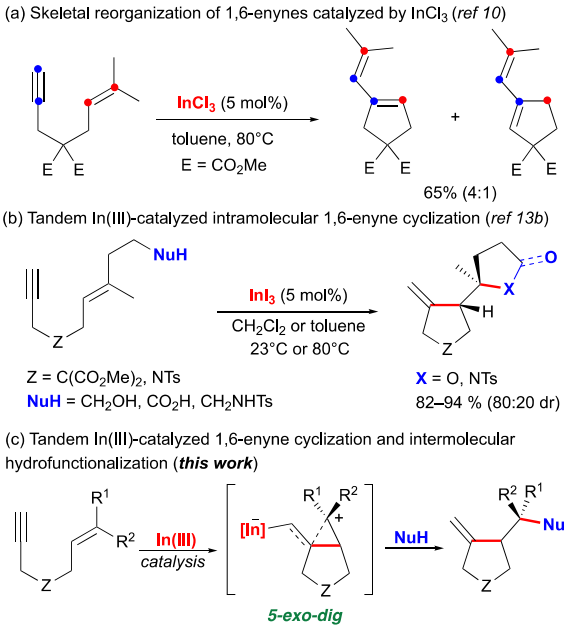
A tandem indium(III)-catalyzed cyclization and intermolecular hydrofunctionalization of 1,6-enynes for the stereoselective synthesis of functionalized carbo- and heterocycles is reported. The synthetic transformation involves a regio- and stereoselective *5-exo-dig* 1,6-enyne cyclization followed by intermolecular nucleophilic addition of alcohols (including water), carboxylic acids, arenes and trimethylsilyl azide. Remarkably, the reaction proceeds under mild reaction conditions with low catalyst loading using unexpensive commercial indium(III) halides in good yields with broad chemoselectivity and high regio- and stereoselectivity.

Introduction

Metal-catalyzed 1,n-enyne cyclizations provide an efficient and atom-economical method for the synthesis of architecturally complex cyclic frameworks, with generally good levels of regio- and stereoselectivity and reasonable versatility.[1] In addition, tandem processes in which a nucleophilic addition occurs after the cyclization step provides direct access to more elaborated chemical structures in a single operation.[2] This chemical transformation starts with the electrophilic activation of the alkyne (π-acid catalysis), though the reaction mechanism varies depending on the metal catalyst.[3] Usually, catalysis is associated to precious transition metals such as palladium, platinum, and gold due to their unique chemical properties.[4] However, some main group elements, particularly post-transition metals, such as indium, gallium or bismuth have been postulated as valuable and economical alternatives, although their reactivity and synthetic utility are still underexplored.[5]

Indium(III) is a low-cost Group 13 element with attractive chemical properties for catalysis.[6] Its larger size comparing to boron or aluminum renders it as a softer Lewis acid with oxophilic and carbophilic character, enabling dual catalytic activity. Over the years, indium(III) has proven to be an effective σ-Lewis acid in fundamental organic transformations such as Diels-Alder cycloadditions or carbonyl additions, and more recently as π-acid in the electrophilic activation of C–C unsaturated bonds, mostly alkynes.[7] Interestingly, the alkynophilicity can be tuned through ligand modification, although a reduced number of synthetic examples have been developed yet.[8] In this field of research, we have recently shown indium(III) iodide as particularly efficient π-acid catalyst in intramolecular alkyne hydroarylation, hydroalkoxylation and hydroamination reactions.[9] The cycloisomerization reaction of enynes under indium(III) catalysis was first studied by Chatani,[10] showing that 1,6-enynes proceeds with *5-exo-dig* regioselectivity affording a variable mixture of cyclopentene dienes through a metathesis skeletal rearrangement (Scheme 1a).[11] The power of indium(III) catalysis, particularly cationic indium(III) iodide, in enynic cyclizations was highlighted by Corey in the synthesis of polycyclic structures through cascade polyenyne cyclization reactions.[12] In addition, our group has also reported In(III)-catalyzed enyne cyclizations such as the regio-, stereoselective and stereospecific synthesis of tricyclic frameworks by tandem indium-catalyzed cyclization/hydroarylation of aryl 1,5-enynes and 1,6-enynes withexcellent chemoselectivity (Scheme 1b).[13] Herein, we



Scheme 1. Previous and current research on In(III)-catalyzed 1,6-enyne cycloisomerization reactions.

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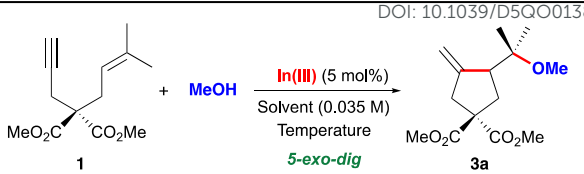
disclose the first tandem 1,6-enyne cyclization and intermolecular nucleophilic addition under indium(III) catalysis. This approach demonstrates the feasibility of trapping the cycloisomerization intermediate with an external nucleophile under In(III) catalysis broadening the synthetic utility of main group metals in the electrophilic activation of C–C unsaturated bonds under π-acid catalysis. Although these synthetic transformations have been reported under transition metal catalysis, this communication uncovers the first such examples using main group catalysis.[2]

Results and discussion

According to our previous experience,[13b] our research started exploring the indium(III)-catalyzed 1,6-enyne cycloisomerization of **1** in the presence of methanol as external nucleophile with the aim to trap the proposed zwitterionic cyclopropyl-like intermediate formed during the cycloisomerization (Scheme 2). Interestingly, the treatment of **1** with 5 mol% InI_3 in toluene (0.035 M) and MeOH (5 equiv.) at 80°C afforded the methoxycyclization product **3a** in 56% isolated yield in just 3 h along with cycloisomerization product **1a** (entry 1, table 1). The reaction also proceeded using CH_2Cl_2 as solvent at 23°C in the same chemical yield and short reaction time (entry 2). However, increasing concentration (0.1 M in CH_2Cl_2) at 23°C only produced a mixture of cycloisomerization products (**1a** and **1b**) (entry 3). On the other hand, a larger excess of methanol inhibited the catalytic reaction at 23°C even with 20 mol% the InI_3 (entry 4) while 10 equiv of MeOH and InI_3 in CH_2Cl_2 at 23°C gave **3a** in 72% yield (entry 5). Catalysis using indium diiodonium cation (InI_2^+) generated by treatment of InI_3 (5 mol%) with $AgSbF_6$ (5 mol%) provided **3a** in a modest 32% yield (entry 6). On the other hand, $In(OTf)_3$ or $In(NTf_2)_3$ (5 mol%) produced a complex mixture of products (entries 7 and 8). Finally, we found that setting up the reaction at -20°C and slow warm up to 23°C prevents the skeletal rearrangement giving rise the desired product **3a** in 80% isolated yield in just 4 h (entry 10).

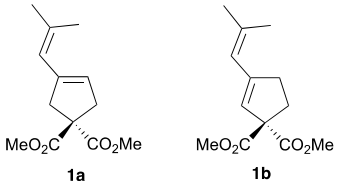
With the optimal reaction conditions in hand, we explored the versatility of the protocol employing other organic nucleophiles and 1,6-enynes (Scheme 2). Starting from alcohols, we were delighted that the alkoxycyclization of **1** can be extended to the allylic alcohol 3-methyl-2-buten-1-ol, or phenol which were regioselectively incorporated in good yields (**3b–d**, 47–86%). In addition, the hydroxycyclization was successfully achieved using tap water as nucleophile giving rise the corresponding alcohol **3e** (86%). These results demonstrate the synthetic utility of indium(III) catalysis in hydroxy- and hydroalkoxylations of 1,6-enynes providing novel examples uncovered under transition metal catalysis. Encouraged by these results, we tested carboxylic acids as nucleophiles for a selective hydroacyloxylation reaction which have been elusive using transition metal catalysis. Gratifyingly, following the previous experimental protocol developed, we found that indium(III) iodide catalyze this tandem intermolecular transformation

Table 1. In(III)-catalyzed methoxycyclization of 1,6-enyne **1**



Entry	InX_3[a]	T (°C)	Solvent	MeOH[b]	t (h)[c]	Yield[d]
1	InI_3	80	Toluene	5	3	56
2	InI_3	23	CH_2Cl_2	5	3	56
3	InI_3	23	CH_2Cl_2[e]	5	24	–
4	InI_3	23	CH_2Cl_2	50	72	nr
5	InI_3	23	CH_2Cl_2	10	24	72
6	InI_3[f]	23	CH_2Cl_2	5	4	32
7	$In(OTf)_3$	23	CH_2Cl_2	5	24	–
8	$In(NTf_2)_3$	23	CH_2Cl_2	5	24	–
9	InI_3	-20	CH_2Cl_2	5	24	nr
10	InI_3	-20–23	CH_2Cl_2	5	4	80

[a] 5 mol% except entries 4 (20 mol%) and 5 (10 mol%); [b] Equivalent amount with respect to 1,6-enyne; [c] Monitored by TLC; [d] Isolated yield (%); [e] 0.1 M of CH_2Cl_2; [f] Using $AgSbF_6$ (5 mol%) as cocatalyst.



efficiently with a variety of novel aromatic and aliphatic carboxylic acids such as benzoic acid, cyclohexane carboxylic acid, 3,3-dimethylacrilic acid or pivalic acid giving rise a novel set of esters (**3f–i**) in moderate yields (45–53%). It is highly remarkable the compatibility of indium(III) catalysis with the carboxylic acid functional group.

Next, we focused our attention on the tandem intermolecular addition using arenes as external nucleophiles. Therefore, we were pleased to find the tandem intermolecular cyclization/hydroarylation reaction using 1,3,5-trimethoxybenzene afforded **3j** in 61% yield and the reaction with *N*-methyl indole gave the corresponding product **3k** in 92% yield. Our efforts to perform the hydroamination reaction using amines gave poor yields, but the versatile azide functional group was introduced using $TMSN_3$ and 10 mol% of InI_3 (**3l**, 60%, Scheme 2).[14] Overall, we demonstrate that the tandem indium(III)-catalyzed cyclization of 1,6-enynes and intermolecular nucleophilic addition can be performed with alcohols, carboxylic acids, arenes or azide ion regioselectively (*5-exo-dig*) in good yields. As next step, we plan to extend this methodology to other 1,6-enynes like **2** bearing a *N*-tosyl group as 1,6-enyne bridge. As previously, the tandem reaction also took place efficiently with *5-exo-dig* regioselectivity with a variety of oxygenated nucleophiles such as methanol or benzyl alcohol, carboxylic acids as benzoic acid or arenes as 1,3,5-trimethoxybenzene or *N*-methylindole affording the corresponding pyrrolidines **3m–q** in 43–76% yields.

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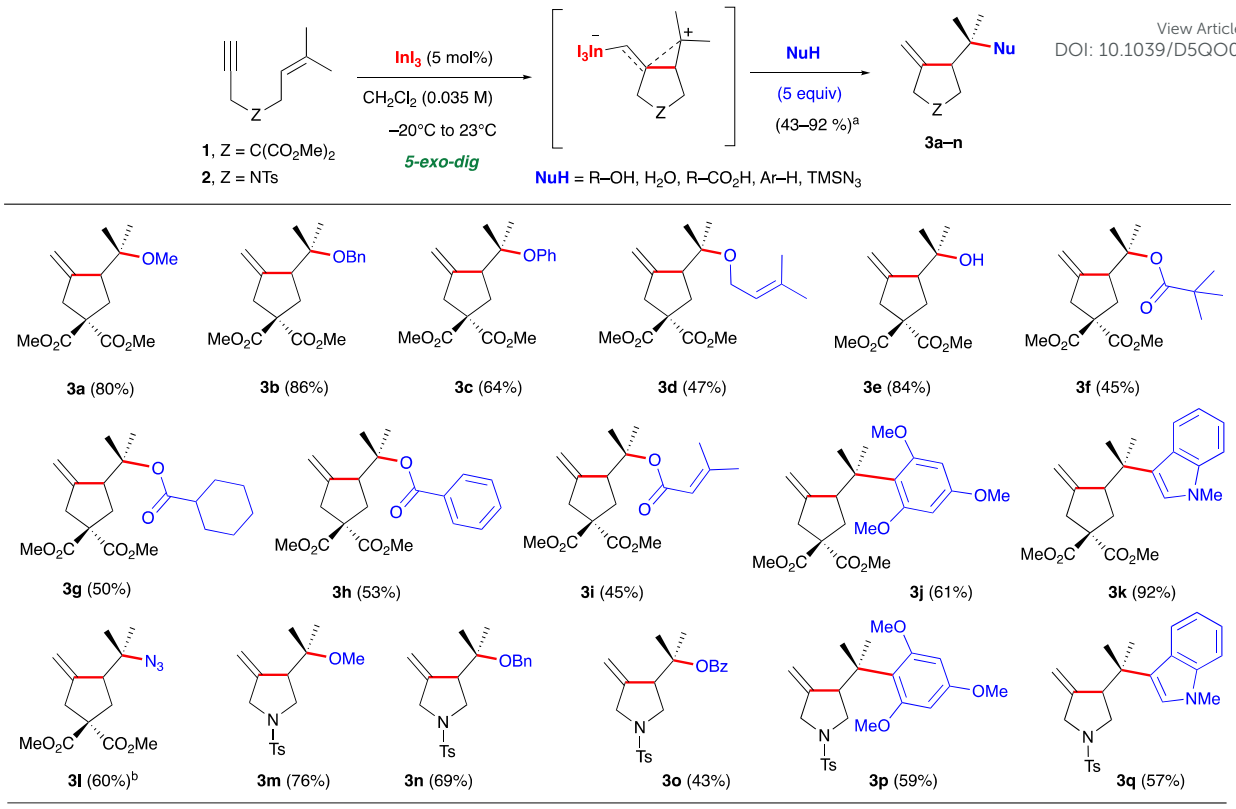

[a] Isolated yields; [b] 10 mol% of catalyst employed

Scheme 2. Indium(III)-catalyzed cyclization/intermolecular hydrofunctionalization reactions of 1,6-enynes **1** and **2**.

To explore the synthetic scope and stereoselectivity of this novel tandem indium(III)-catalyzed intermolecular nucleophilic addition to 1,6-enynes, we tested the styryl 1,6-enyne **4** presenting a 1,2-disubstituted alkene. Under the previously optimized reaction conditions, we found that the treatment of *(E)*-**4** with InI_3 (5 mol%) and benzyl alcohol (5 equiv.) in CH_2Cl_2 at 23°C gave the desired benzyloxycyclization product **5a** in 75% isolated yield as a single diastereoisomer.[15] Analogously, the reaction of benzoic acid also provided the diastereomerically pure benzoate **5b** in 62% yield. In addition, the reaction using *N*-methylindole or 1,3,5-trimethoxybenzene as nucleophiles afforded the expected cyclopentenes **5c** and **5d** stereoselectively in 88 and 78% isolated yield with complete diastereoselectivity. Furthermore, the reaction using $TMSN_3$ also gave the azide **5e** derivative in 80% yield.

Furthermore, the stereochemical outcome of this diastereoselective 1,6-enyne cyclization was explored using *(Z)*-1,6-enyne **4**. Under the same experimental conditions, *(Z)*-**4** showed lower reactivity than *(E)*-**4** being necessary to increase the temperature up to 60°C and extend the reaction time (24h) for a complete conversion. Interestingly, the tandem reaction using different organic nucleophiles such as benzyl alcohol, benzoic acid, 1,3,5-trimethoxybenzene or trimethylsilyl azide also gave the expected reaction products **5a–e** as single diastereoisomer in 25–75% yields. Distinctly to the indium-catalyzed intramolecular sequence (Scheme 1b),[13b] this transformation showed stereoconvergent probably due to the thermal isomerization of the chiral intermediate during the 1,6-enyne cyclization through an open carbocation structure, as it can be deduced monitoring the reaction of (*Z*)-**4** with 1,3,5-trimethoxybenzene at different temperatures by ^1H NMR (see Supplementary Information). This behaviour contrasts with the stereospecific outcome observed under platinum(II) or gold(I) catalysis.[2a,2j]

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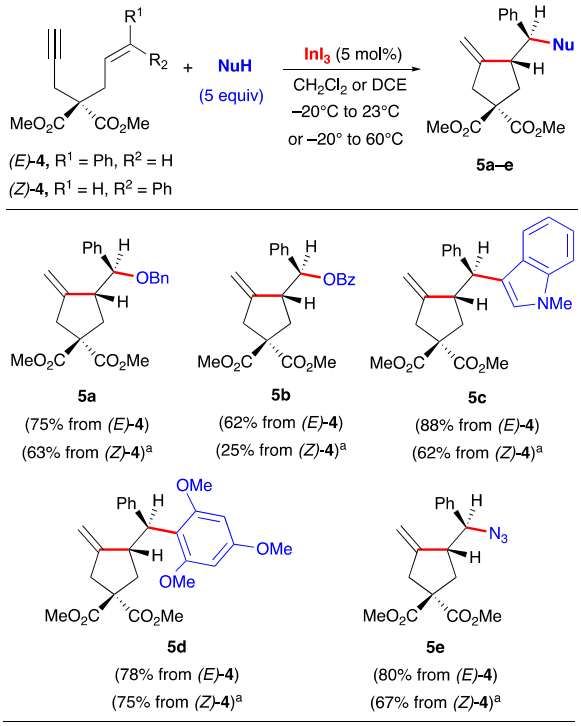
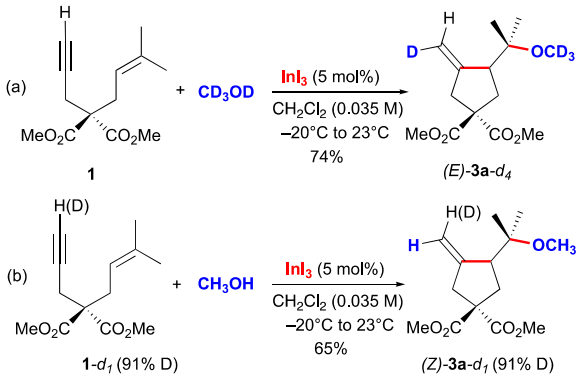


[a] Reactions set up at –20°C and heated to 60°C in DCE

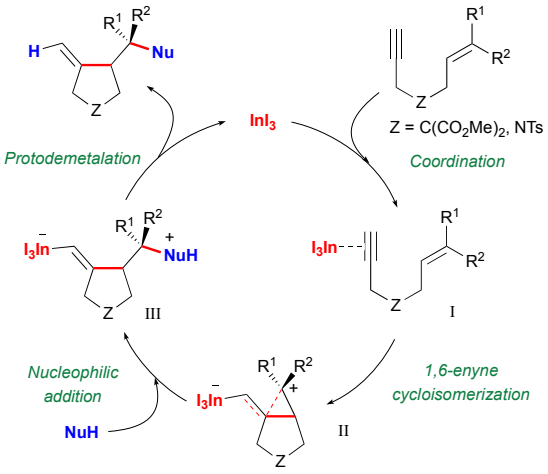
Scheme 3. Diastereoselective In(III)-catalyzed cyclization/intermolecular hydrofunctionalization reactions using 1,6-enynes (*E*)-**4** and (*Z*)-**4**.

To shed light about the mechanism of these tandem process some experiments with deuterated 1,6-enyne **1** and nucleophiles were performed. Under the previously developed reaction conditions, the reaction of **1** with deuterated methanol gave (*E*)-**3a**-d_4 as a single stereoisomer in 74% yield (Scheme 4a).[16] In addition, the reaction of 1,6-enyne deuterated at the terminal alkyne **1**-d_1 (91% D) with non-deuterated methanol, under the same reaction conditions, gave (*Z*)-**3a**-d_1 in 65% yield and identical deuterium percentage (91% D, Scheme 4b). These overall results are in accordance with a *trans*-attack of the alkene to the (η²-alkyne)-indium complex and demonstrates that the carbon-deuterium bond is not broken throughout the cyclization process.



Scheme 4. In(III)-catalyzed cyclization/intermolecular hydrofunctionalization reactions using deuterated methanol-d_4 and 1,6-enyne **1**-d_1.

According to our previous experimental and computational studies on indium(III)-catalyzed alkyne hydrofunctionalization, and 1,6-enyne cycloisomerization reactions,[13b] we postulate a stepwise reaction mechanism initiated by the formation of a (η²-alkyne)-indium complex (**I**) that promotes the cyclization. Then, the enyne cyclization occurs with *5-exo-dig* regioselectivity and *anti*-stereoselectivity, giving rise to a chiral zwitterionic transition state that involves indium-stabilized homoallylic cationic species (**II**). Finally, the stereoselective nucleophilic addition affords an indium organometallic species (**III**) which suffers a protodemetalation to give the corresponding cyclization product (Scheme 5).



Scheme 5. Mechanistic proposal

Conclusions

In summary, herein we report the first tandem indium(III)-catalyzed 1,6-enyne cyclization and intermolecular nucleophilic addition for the synthesis of carbo- and heterocyclic structures. The reaction takes place under mild conditions using InI_3 (5 mol%) in good yields. Remarkably, indium(III) catalysis exhibits high chemoselectivity enabling the incorporation of a variety of carbon-, oxygen- and nitrogen- nucleophiles such as alcohols, water, carboxylic acids, arenes and azide allowing the formation of C–C , C–O and C–N bonds in a wide number of functionalized carbo- and heterocyclic compounds. Furthermore, the synthetic transformation is highly regioselective (*5-exo-dig*) and stereoselective probing the synthetic potential of indium(III) catalysis and opening the possibility of developing novel applications in organic synthesis and enantioselective transformations using other 1,n-enynes.

Author contributions

J.P.S. conceived the project and wrote the manuscript with contributions of all authors. R. P-G., D. F-I., and L. A-M. performed the experimental work. M. M. M and J. P. S. supervised the experimental work. All authors have given approval to the final version of the manuscript.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article (experimental procedures and copies of the NMR for all compounds prepared) has been included as part of the Supplementary Information.

Acknowledgements

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Data availability

The data supporting this article (experimental procedures and copies of the NMR for all compounds prepared) have been included as part of the Supplementary Information.