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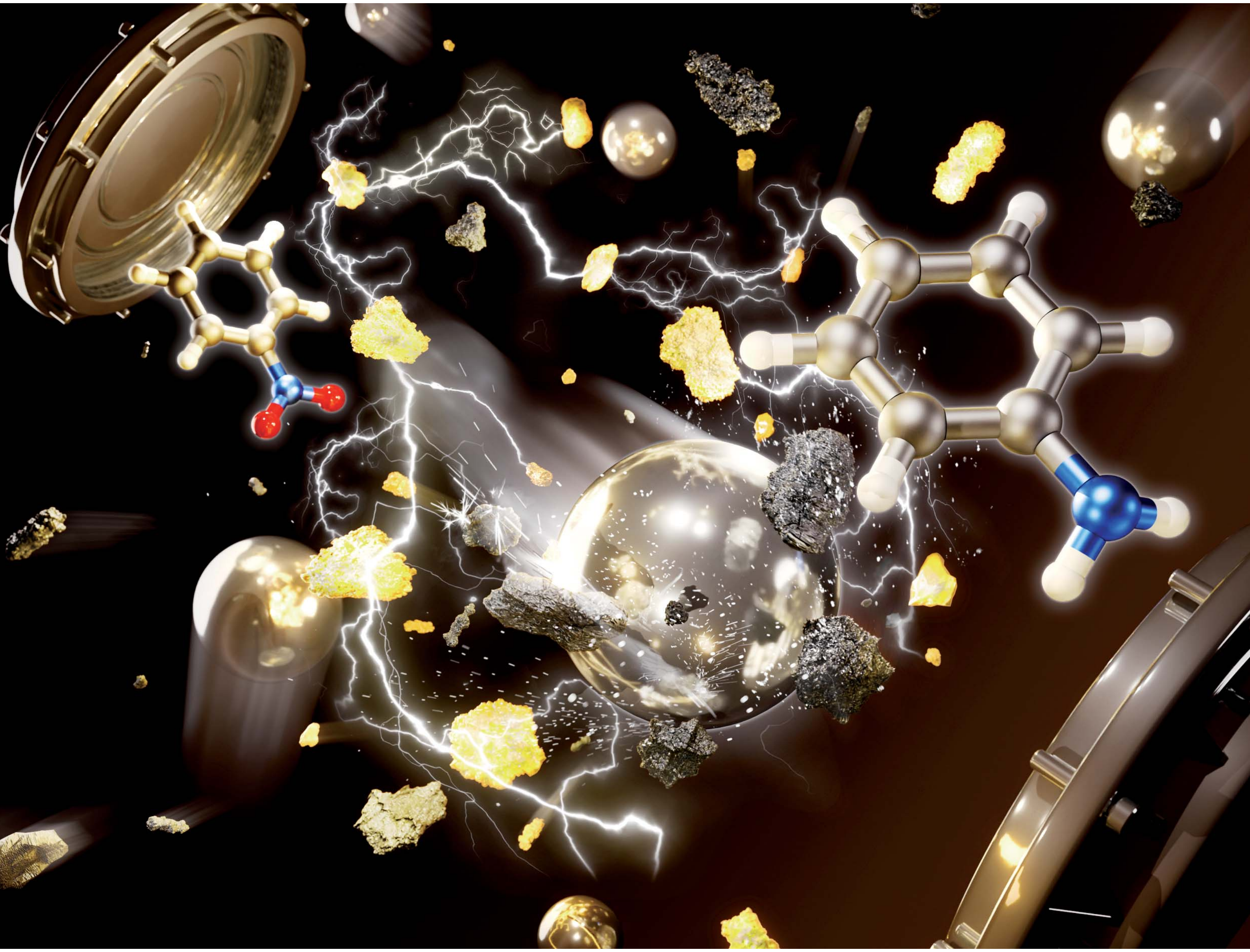

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Solvent-free zinc-mediated Béchamp reduction using mechanochemistry†

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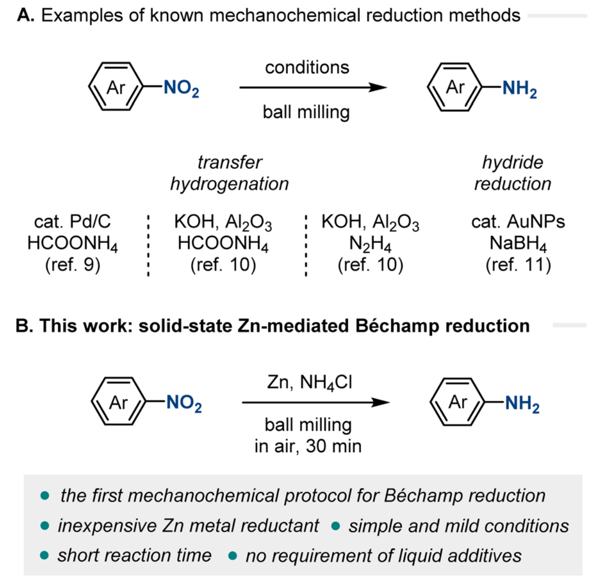
In this study, we report the first mechanochemical protocol for highly efficient solvent-free Béchamp reduction using inexpensive Zn metal as a reductant in combination with NH_4Cl. This reaction is considerably faster than previous solution-based reactions. Herein, a variety of nitroarenes were chemoselectively reduced to the corresponding primary aromatic amines in good yields within 30 min. Notably, the present solvent-free protocol does not require an organic solvent or air-sensitive and/or expensive reagents, and all synthetic operations can be performed under ambient conditions, greatly enhancing its practical utility. Furthermore, the feasibility of the gram-scale reaction as well as the synthesis of an important intermediate of the muscle relaxant tizanidine were demonstrated.

The chemoselective reduction of nitroarenes is an important transformation in the synthesis of many aromatic amines, which are indispensable components of pharmaceutical drugs and bioactive molecules.[1] Numerous methods for reducing nitroarenes have been reported previously.[1] Among these, zero-valent-metal-mediated reduction under acidic conditions, also known as the Béchamp reduction, has been widely used in academic and industrial settings.[1,2] Typical metals used in these reductions are Fe,[3] Sn,[4] In,[5] and Zn[6] in combination with several proton sources. Although many useful Béchamp conditions have been developed, conventional reductions are commonly performed in potentially harmful organic solvents and often require corrosive HCl, high temperatures, and prolonged reaction times. Recently, several modified procedures for the Béchamp reduction in the presence of NH_4Cl as a mild proton source have been developed; however, these require expensive reagents such as surfactants or ionic liquids.[6e,f] Therefore, the development of a highly efficient, time-saving, cost-effective, and sustainable Béchamp process remains an important challenge in synthetic chemistry.

Mechanochemistry using ball milling has attracted significant attention as a promising alternative to solution-based organic synthesis.[7,8] The effectiveness of mechanochemical methods is reflected in the minimal solvent use, high efficiency, short reaction times, operational simplicity, low energy consumption, and cost efficiency; however, despite recent advances in this field, the development of a mechanochemical protocol for Béchamp reduction remains unexplored. Other mechanochemical methods for the reduction of nitroarenes, such as palladium-catalyzed[9] or base-mediated transfer hydrogenation[10] and gold-nanoparticle-catalyzed hydride reduction,[11] have been reported (Scheme 1A). However, these methods require precious metal catalysts,[9,11] liquid additives,[9] potentially hazardous reductants such as hydrazine,[10] and highly basic



Scheme 1 Mechanochemical protocols for reduction of nitroarenes.

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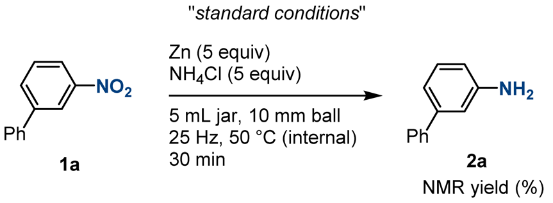
Table 1 Optimization study on the solvent-free Béchamp reduction under mechanochemical conditions[a]



Entry	Deviation from "standard conditions"	Conv. of **1a** [b](%)	Yield (%) of **2a**[b]
1	None	>99	95
2	Room temperature	34	18
3	Zn (1.0 equiv.)	5	9
4	Zn (3.0 equiv.)	63	51
5	NH_4Cl (1.0 equiv.)	32	16
6	NH_4Cl (3.0 equiv.)	65	63
7	Fe instead of Zn	5	<1
8	Mn instead of Zn	21	3
9	Sn instead of Zn	40	11
10	In instead of Zn	95	22

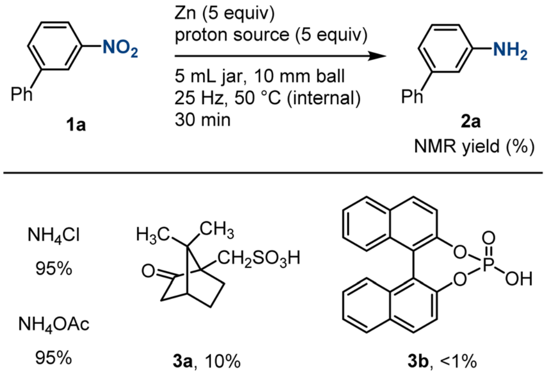
[a] Conditions: **1a** (0.5 mmol), Zn (2.5 mmol), and NH_4Cl (2.5 mmol) were added to a stainless-steel ball mill jar (5 mL) with a stainless steel ball (diameter: 10 mm). [b] Determined by ^1H NMR analysis of the crude reaction mixture using an internal standard.

conditions.[10] Therefore, the development of a simple and mild mechanochemical protocol for the Béchamp reduction can offer a more practical choice for the synthesis of aromatic amines and address the aforementioned limitations associated with traditional solution-based Béchamp processes.[1–6]

Herein, we report a highly efficient mechanochemical Béchamp reduction method using inexpensive Zn metal as the reductant (Scheme 1).[12] These reactions are rapid, and various nitroarenes can be reduced to afford the desired aromatic amines in good yields within 30 min. Notably, this simple and mild mechanochemical method does not require bulk solvents or even small amounts of liquid additives and air-sensitive and/or expensive reagents. Additionally, all synthetic operations can be performed under ambient conditions. The practical utility of this protocol was further demonstrated by an efficient gram-scale reaction as well as by the synthesis of the intermediate tizanidine.[13,14]

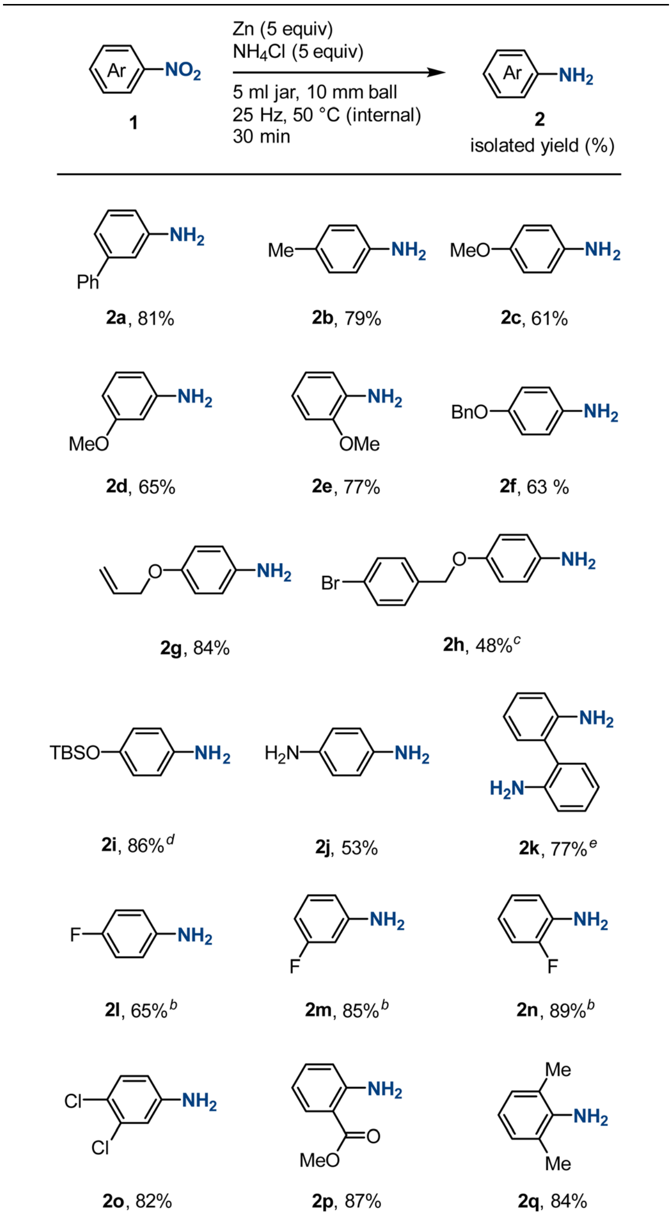
Initially, we conducted a study to optimize the mechanochemical conditions for Béchamp reduction (Table 1). With 3-nitro-1,1′-biphenyl (**1a**) as the model substrate, all reactions were performed in a Retsch MM400 mixer mill (stainless-steel milling jar: 5 mL; stainless-steel ball: 10 mm in diameter). We used a commercially available temperature-controllable heat gun placed directly above the ball-milling jar to control the reaction temperature.[8e] Based on traditional solution-based conditions,[6] the mechanochemical reaction was initially conducted for 30 min using Zn (5 equiv.) and NH_4Cl (5.0 equiv.) as proton sources. All reactions were conducted under atmospheric conditions, and all reagents were purchased from common commercial suppliers and used as received. Under the applied conditions, the desired product (**2a**) was obtained in excellent yield (95%) with a heat gun preset to 70 °C (entry 1). The internal temperature of the reaction mixture (50 °C) was confirmed using thermography immediately after the milling jar was opened. Without external heating, the reaction was slow, and **2a** was obtained in a lower yield (18%, entry 2). Decreasing the amount of Zn or NH_4Cl yielded poor results (entries 3–6). Next, other metal reductants were tested (entries 7–10). Fe metal, which is most widely used in Béchamp reduction,[3] did not yield the desired product (**2a**) (entry 7). Other metals such as Mn and Sn also showed poor reactivity under the applied mechanochemical conditions (entries 8 and 9). The reaction with In resulted in low product yield (22%), despite the high conversion of the starting materials (entry 10). These results suggest that the use of Zn is crucial for achieving a highly efficient mechanochemical Béchamp reduction. Traditional

Table 2 Effect of proton sources[a,b]



[a] Conditions: **1a** (0.5 mmol), Zn (2.5 mmol), and a proton source (2.5 mmol) were added to a stainless-steel ball mill jar (5 mL) with a stainless-steel ball (diameter: 10 mm). [b] Determined by ^1H NMR analysis of the crude reaction mixture using an internal standard.

Table 3 Substrate scope[a,b]

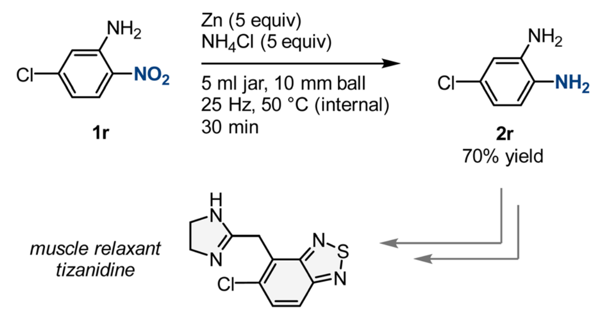


[a] Conditions: **1** (0.5 mmol), Zn (2.5 mmol), and NH_4Cl (2.5 mmol) were added to a stainless-steel ball mill jar (5 mL) with a stainless-steel ball (diameter: 10 mm). [b] ^1H NMR yield. [c] 60 min. [d] 6.0 equivalents of Zn were used. [e] Zn (5.0 mmol) and NH_4Cl (5.0 mmol) were used.

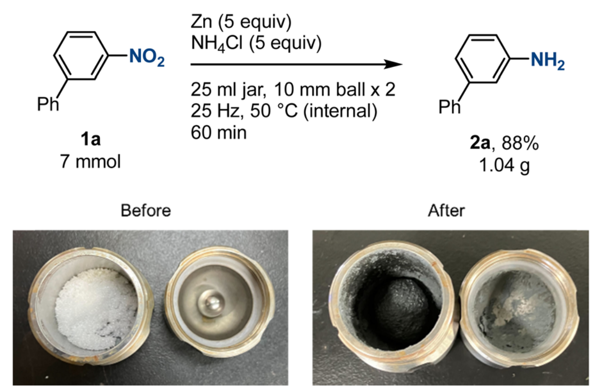
solution-based conditions for Béchamp reduction typically require several hours to complete,[1–6] whereas the proposed mechanochemical protocol significantly accelerates the reaction, achieving completion within 30 min. Moreover, this reaction does not require air-sensitive or expensive reagents, significantly enhancing its practical utility.

Subsequently, the effect of the proton sources was investigated (Table 2). The use of NH_4OAc[6f] instead of NH_4Cl also afforded **2a** in excellent yield (95%). Next, we tested other solid, easy-to-handle Brønsted acid reagents, such as (+)-10-camphorsulfonic acid (**3a**) and BINOL-based phosphoric acid (**3b**), although these have not been previously used in Béchamp reduction in solution. The reaction with **3a** proceeded and produced a considerably low yield of **2a** (10%). No reaction was observed when **3b** was used. These results suggest that the use of ammonium salts is essential for efficient reduction. Given the high moisture sensitivity of NH_4OAc, we used NH_4Cl, which can be easily handled in air, as the optimal proton source.

Using the optimized mechanochemical conditions, we explored the substrate scope of the mechanochemical solvent-free Béchamp reduction (Table 3). Overall, the scope of this mechanochemical method is comparable to that of the solution protocols for Béchamp reduction. The reactions of methyl-, methoxy-, and benzyloxy-substituted substrates (**1b–1f**) proceeded smoothly to afford the desired products (**2b–2f**) in moderate to good yields (61–79%). The position of the methoxy group on the benzene ring did not affect the reactivity. Substrates containing terminal alkene (**1g**), bromo group (**1h**), and silyl ether moiety (**1i**) did not interfere with the reduction process, affording the corresponding products (**2g–2i**) in moderate to good yields (84%, 48%, and 86%, respectively). This protocol is suitable for the synthesis of diamine compounds (**2j** and **2k**) in good yields (53% and 77%, respectively). The reactions of substrate bearing electron-withdrawing substituents, such as fluoro (**1l–1n**), chloro (**1o**), and ester (**1p**) groups, afforded the desired products (**2l–2p**) in good to high

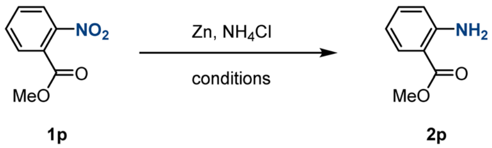


Scheme 2 Mechanochemical Béchamp reduction for the synthesis of the intermediate **2r** of tizanidine. Details of the reaction conditions are provided in the ESI.†



Scheme 3 Solvent-free mechanochemical Béchamp reduction on a gram scale. Details of the reaction conditions are provided in the ESI.†

Table 4 Comparison of *E*-factors[a]



1p **2p**

Entry	Conditions	*E*-factor
1	Zn (5 equiv.), NH_4Cl (5 equiv.) 50 °C, 30 min	4.1
2	Zn (5 equiv.), NH_4Cl (10 equiv.) 40 °C, acetone/H_2O (4 : 1, 0.1 M), 24 h	60.9

[a] For details of the E-factor calculations, see the ESI.

yields (65–89%). Sterically hindered nitro compound (**1q**) underwent efficient reduction to produce the corresponding aniline (**2q**) in high yield (84%).

To demonstrate the synthetic utility of this reaction, we investigated the synthesis of the important intermediate **2r** of the muscle relaxant tizanidine (Scheme 2).[13,14] The reaction of **1r** under the optimized conditions afforded the desired product **2r** in good yield (70%). **2r** can be converted into tizanidine in seven steps.[14] This result showcases the potential of this solvent-free protocol for the preparation of bioactive compounds in a more sustainable manner.

To demonstrate the practical utility of this reaction, we investigated the gram-scale synthesis of **2a** (Scheme 3). A 7 mmol-scale reaction was conducted in a 25 mL stainless-steel jar with two 10 mm stainless-steel balls. The gram-scale reaction proceeded smoothly to afford **2a** in 88% yield (1.04 g), which was comparable to the yield obtained in the small-scale reaction. This result emphasizes the practical utility of the solvent-free Zn-mediated Béchamp reduction protocol.

To quantify the environmental benefits of this mechanochemical approach, we compared the E-factor of the present mechanochemical conditions to that of the previously reported representative solution-based conditions (Table 4).[15] The E-factor is an index for the quantitative evaluation of the environmental impact of a chemical process.[16] For our mechanochemical reduction of **1p**, the E-factor is 4.1 (entry 1), whereas the *E*-factor of the representative solution-based method using acetone/H_2O (4 : 1, 0.1 M)[15] is 60.9 (entry 2). This difference is primarily attributed to the absence of bulk solvents under our mechanochemical conditions. Based on these results, the current mechanochemical approach is significantly more eco-friendly than traditional solution-based methods.

In conclusion, we demonstrated a simple mechanochemical protocol that enables highly efficient and rapid solvent-free Zn-based Béchamp reduction without the use of bulk solvents or a complicated reaction setup involving inert gases. Notably, most nitroarenes were reduced within 30 min to produce the desired aromatic amines in good to high yields. A gram-scale reaction under mechanochemical conditions was also demonstrated. Compared to existing mechanochemical reduction protocols for nitroarenes,[9–11] this new method uses inexpensive, safe, and easy-to-handle Zn metal as the reductant and eliminates the need for transition metal catalysts. These results suggest that this study serves as an important proof of concept, demonstrating the feasibility of sustainable, solvent-free Béchamp reduction through mechanochemistry. However, it is important to highlight that the key limitations of this method include the need for external heating, as well as the use of excess Zn metal and NH_4Cl to achieve efficient nitroarene reduction. Further studies toward the development of a room-temperature version of the mechanochemical Béchamp reduction without using excessive reagents are currently underway in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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