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A metal-free or metal e-waste catalysed alkyne hydration–condensation–decarboxylation cascade reaction in water gives access to (fused) carbocycles

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We show here that the ester-assisted hydration of alkynyl β-ketoesters does not require any commercial metal catalyst but just protons in water (either in solution or on a recyclable solid) or metals recycled from e-waste (typically Au) to give not the expected ketones but a variety of polymethylated carbocycle compounds (hydroindanes, decalines, cyclohexanones and fluorenes) in good yields and selectivity, after a three-to-five step cascade reaction.

Introduction

The neighboring-assisted hydration of alkynes is a representative reaction in Au-catalyzed chemistry, since the corresponding γ-ketoester products are of high interest both as synthons and as products themselves.[1] Fig. 1 shows that a long-sought objective for the alkyne hydration reaction is to substitute Au (or any other metal catalyst) by a simple H^+, but keeping the mild reaction conditions of the former, in order not only to decrease the price but also to increase the sustainability/viability of the process.[2] Some of the most representative processes reported in the literature for Brønsted (H^+)-catalyzed alkyne hydration reactions (Table S1 in the SI) require either high amounts of harsh strong soluble acids or reaction temperatures >150 °C, or even both,[3a] although other procedures operate under milder reaction conditions.[3b,c] It is difficult to find anyway a H^+-catalyzed neighboring-assisted hydration of alkynes, and the few examples found are with other oxygenated groups, since esters are readily hydrolyzed under aqueous acid conditions.[4]

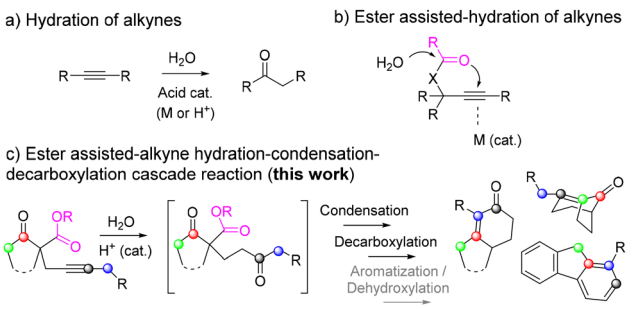

Fig. 1 (a) Catalytic hydration reaction of alkynes. (b) Neighbouring (ester)-assisted hydration of alkynes. (c) The work reported here.

Here we show that the ester-assisted hydration of alkynyl β-ketoester is mediated by simple H^+ catalysts (HCl, HOAc, H_2SO_4 or the solid catalyst Amberlyst) and that the reaction does not stop in the product ketone but evolves to different alkyl-substituted (fused) carbocycles, as a function of the substitution pattern in the starting material and the acid catalyst employed. The inclusion of an enolizable ketone in α-position to the ester group and δ-position to the nascent ketone functionality (after the hydration reaction) triggers a series of cascade reactions otherwise difficult to achieve concomitantly with separate synthons.[5] Cascade reactions are an effective and sustainable strategy to intensify organic synthetic routes, avoid separations/purifications and achieve complex organic compounds from simple starting materials.[6]

Results and discussion

Acid-mediated reaction of alkynyl β-ketoester 1

Table 1 shows the results for the reaction of alkynyl β-ketoester **1** to products **2–5** in acid media, the former prepared in high yield by nucleophilic substitution reaction of widely-available

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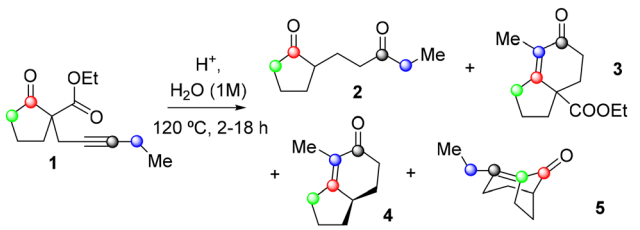
Table 1 Results for the H^+-mediated alkyne hydration–condensation–decarboxylation cascade reaction of the β-ketoester **1**



Entry	H^+ catalyst (equiv., pK_a)	Time (h)	Conv. **1** [a] (%)	Yield[a] (%)			
				2	**3**	**4**	**5**
1	None	18	23	—	—	—	—
2	HCl (4, −5.8)	18	87	22	—	40	—
3	HOAc (13, +4.5)	18	14	2	—	—	—
4	HCl + HOAc (1 + 1)	18	>99	60	—	24	—
5	HCl + HOAc (10 + 10)	18	>99	29	—	55	—
6	H_2SO_4 (1, −3.0)	2	>99	—	—	**67**	—
7	H_2SO_4 (10, −3.0)	2	>99	—	—	57	—
8		18	>99	—	—	62	**37**
9	H_3PO_4 (10, +2.2)	18	>99	43	—	56	—
10	Zeolite HZSM-5[b]	72	35	—	—	—	—
11	Zeolite HUSY[b]	72	41	17	—	4	—
12	Amberlyst 15[b]	18	97	32	—	25	—
13	Amberlyst 16[b]	18	10	10	—	—	—
14	Amberlyst 20[b]	18	12	12	—	—	—
15	Amberlyst 15[b,c]	18	>99	23	**76**	—	—

Reaction conditions: **1** (1 mmol), water (1 mL), acid catalyst, 120 °C (oil bath temperature), 18 h. [a] Double-checked results by GC-MS and ^{1}H-NMR, average of two runs. The mass balance is completed with intermediates during the cascade reaction (see kinetics ahead). [b] 100 wt%. [c] EtOH : toluene (1 : 1 v : v) and 4 equiv. of H_2O.

commercial reagents (Fig. S1). The reactions were concomitantly monitored by gas chromatography coupled to mass spectrometry (GC-MS) and ^{1}H nuclear magnetic resonance (^{1}H-NMR), in order to double-check the structure and yields of the products observed, and the results correspond to the average of two runs. The use of concentrated HCl (4 equiv.) gave a 87% conversion of **1** after 18 h reaction time, with 22% of diketone **2** and 40% of hydroindane **4**, both decarboxylated products, in contrast to the non-catalyzed experiment where the conversion was only 23% (compare entries 1 and 2, and see kinetics ahead). A combination of simulated ^{1}H NMR spectra, comparison with the existing literature and experimental 2D nuclear Overhauser enhancement spectra (NOESY, see the compound characterization section in the SI) allowed us to assign with quite confidence the structure of **4** exclusively to the *cis*-hydroindane compound, the one thermodynamically more stable and present in natural products.[7]

HOAc barely gives any product, combined or not with HCl (entries 3–5), but the use of H_2SO_4 (1 equiv., referred to the first deprotonation, 100 mol% of acid relative to the substrate, pH < 0) gave **4** as the only product in 67% yield after just 2 h reaction time (entry 6). Notice that the conversion of **1** is >99% and that the mass balance is completed with intermediate products. A higher amount of H_2SO_4 (10 equiv.) did not improve the yield to **4** after 2 h (entry 7) but longing the reaction time to 18 h allowed the formation of the carbonyl-bridged [5,6] carbocycle **5** in 37% yield together with **4** (62% yield), thus with total selectivity to products **4** + **5** (entry 8). H_3PO_4 was less effective than H_2SO_4 to form carbocycles (compare entries 8 and 9), and gave a 43% of **2** and a 56% of **4**.

Solid acid catalysts are a sustainable solution to soluble acids in organic synthesis,[8] however, solid acids tend to be not active at the moderate temperatures required in complex organic synthesis, when mineral acids with pK_a > 0 are not active (as here HOAc and H_3PO_4 are not).[9] Indeed, the acid zeolites HZSM-5 and H-USY gave low conversion of **1** even after 72 h reaction time (entries 10 and 11) but, gratifyingly, Amberlyst 15 (4.5 mmol H^+ per g) gave a 97% conversion with 25% of product **4** and, remarkably, a 32% of product **3** (not decarboxylated), under identical conditions to the soluble acid catalysts (entry 12). It must be noticed that the microporous structure of the zeolite is not a limiting factor here since the diffusion of **1** is allowed into, at least, the H-USY zeolite.[10] Besides, the Lewis sites in the zeolite should not play a determinant role neither since water is used as a solvent, thus Brønsted acidity might take over.[9c–e] The structure of **3** is a common scaffold in natural product synthesis.[11] Amberlysts 16 and 20, more resistant to water and with a different degree of acid functionalization to Amberlyst 15 (4.8 and 1.9 mmol H^+ per g, respectively),[12] were much less active (entries 13 and 14). In view of this, different organic solvents were tested for Amberlyst 15, and the results (Table S2) showed that a combination of toluene and EtOH enabled a 76% yield of product **3**. The use of a base (NaOH) did not give any product, even after using 24 equivalents (Fig. S2).

Reaction mechanism

The mechanism of the reaction was then studied by kinetic, isotopic and reactive experiments, and the proposed reaction mechanism is shown in Fig. 2. First, the soluble acid (HCl/HOAc, H_3PO_4, and H_2SO_4)-mediated reactions were monitored by GC, and the kinetic profiles (Fig. S3–S5) show that the inter-

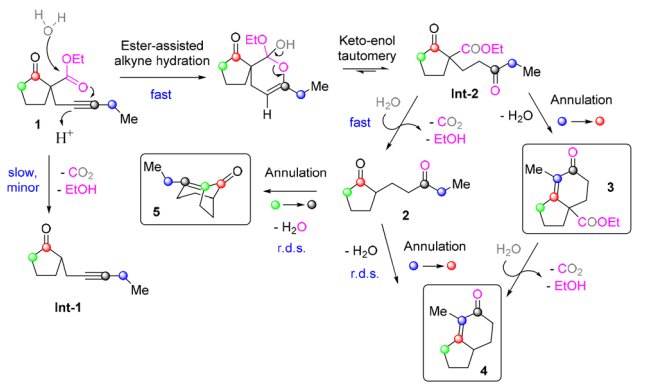


Fig. 2 Proposed reaction mechanism for the H^+-catalyzed alkyne hydration–condensation–decarboxylation cascade reaction of the β-ketoester **1**.

mediate ketone **2** is formed in all cases from the very beginning of the reaction, to smoothly transform to either product **4** (all acid catalysts) and product **5** (only with H_2SO_4). The latter can be easily seen in Fig. 3. The carboxylated product **3** is also formed but rapidly transformed to product **4**, regardless the soluble acid catalyst employed. The linear relationship found between the rate formation of **2** and the pK_a of the acid catalyst (Fig. S6) strongly supports the dependency and tunability of the reaction on the acid catalyst, and the accumulation of intermediate **2** during reaction in all cases, without the alkyne **Int-1** or ketone **Int-2**, indicates that the ester-assisted hydration and the decarboxylation reaction occurs on **Int-2** very fast, and that the hydration of alkyne **Int-1** is much more difficult.

The alkene counterpart of β-ketoester **1** was prepared and tested under optimized reaction conditions with H_2SO_4, and the results (Fig. S8, top) show that only the decarboxylated product was found, in 40% yield after extended reaction times. Besides, we also performed the reaction with alkyne **Int-1** directly, under optimized reaction conditions, and the results (Fig. S8, bottom) showed that neither product **2** nor any other product in the cascade reaction are formed with H_2SO_4, and only after employing Amberlyst 15 (100 wt%), the ketone **2** could be observed, but just in 30% yield. In any case, this conversion is much lower than with alkyne **1**, in line with the neighboring assistance required for the (cascade) reaction to proceed. These results confirm the need of a previous hydration reaction of the alkyne to efficiently perform the decarboxylation and the intramolecular condensation reactions, and, all the above results together, strongly support the rapidness of the ester-assisted alkyne hydration and the decarboxylation reactions with protons.

The combined use of DCl/DOAc in D_2O shows that product **4-*d*^{5}** is exclusively formed (Fig. S9), *i.e.* all the expected enolizable positions are deuterated, including the decarboxylation position. This result showcases the role played here by the carbon skeleton of the β-ketoester, which helps to the cyclization/decarboxylation reactions after the condensation reactions. Therefore, it can be accepted that the *in situ* formed new ketone functionality in **2** triggers a intramolecular aldol condensation annulation reaction with the starting cyclopentanone, to generate product **4**, the major product at long reaction times with all the soluble acids, and which is the rate-determining step (r.d.s.) of the cascade reaction. The alternative intramolecular aldol condensation annulation occurs only at high amounts of H_2SO_4, to give product **5**.

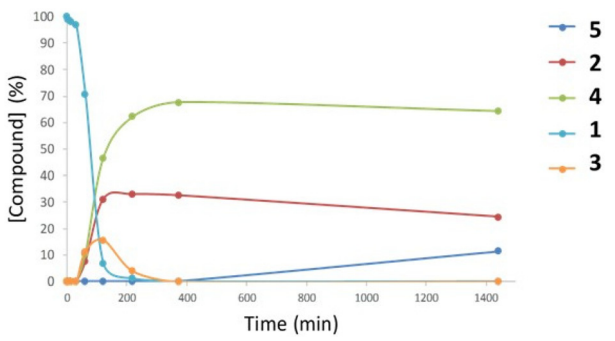


Fig. 3 Kinetics for the H^+-catalyzed alkyne hydration–condensation–decarboxylation cascade reaction of the β-ketoester **1**. Reaction conditions: **1** (1 mmol), water (1 mL), H_2SO_4 (10 equiv.), 120 °C. Combined GC and ^{1}H-NMR results. Error bars account for a 5% uncertainty. Lines are a guide to the eye.

Metal e-waste-catalysed reaction

The rapidness of the H^+-catalyzed ester-assisted alkyne hydration reaction was further assessed by using $NaAuCl_4$ or $AuPPh_3Cl$ as a catalyst, both well-known Au catalysts for this reaction.[13] Au catalysts have been used in cascade reactions,[14] but barely in an ester-assisted alkyne hydration reaction. The results (Fig. S7) show that the Au catalyst started to be active only at >5 mol% amounts and that, with even a 10 mol% loading, the only product found with the Au catalyst was **Int-2** in 36% yield, with an initial conversion rate of 0.5% of **1** min^{-1}, nearly two orders of magnitude lower than with H_2SO_4 (30% of **1** min^{-1}). Any cyclized or decarboxylated product was not found, and other metal catalysts such as $FeCl_3$ did not give any conversion even at >10 mol% amount.[15] In accordance, mixing $NaAuCl_4$ and H_2SO_4 in the same reaction give an identical kinetic profile to H_2SO_4 alone (compare Fig. S5 and S7). These results corroborate that the alkyne hydration reaction proceeds in a much efficient way with H^+ than with a state-of-the-art metal catalyst, besides triggering the cascade reaction. Remarkably, the solid catalyst Amberlyst 15 enables a mixed reactivity, with the preferential formation of product **3** without evolving (decarboxylating) to product **4**, in a reaction that can be considered as a hybrid version between the strong soluble acids and $NaAuCl_4$. In agreement with this, the combination of Amberlyst 15 and $NaAuCl_4$ gave product **3** as the major product, in similar yields to Amberlyst 15 alone. However, product **2** is still formed with Amberlyst 15, indeed, is the only product observed together with **3** or **4**, since **Int-2** rapidly evolves to the latter (entries 12 and 15 in Table 1, and Table S2).

We have recently published that the metal contained in the random-access memories (RAMs) of discarded electronic devices (such as laptops) can be directly used as catalytic metal precursors in reactions involving strong acids, which is the case here.[14b] Thus, we wondered if these recycled RAM contacts would be active for the cascade reactions. For that, first, we tested the ability of the metal chloride salts contained in the RAM contacts to catalyse or not the cascade reaction. The results (Table S3) show that AuCl, $CuCl_2$ or $NiCl_2$ converts into very active catalysts for the cascade reaction after adding the acid and also oxidizing agent H_2SO_4, requiring just 0.6 mol% of Au to get a 91% of the cascade product **4** (see entry 2). This result is much better than when using H_2SO_4 alone (67%, entry 1) or Au as $NaAuCl_4$ or $AuPPh_3Cl$ (compare the above results and entry 5 in Table S3). This marked catalytic effect does not occur for Cu (compare entries 3 and 6) nor Ni (compare entries 4 and 7), since the final yield of **4** is not better than with H_2SO_4 alone. Thus, we tested the RAM con-

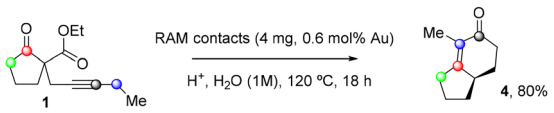


Fig. 4 Results for the e-waste (RAM contacts) catalyzed alkyne hydration–condensation–decarboxylation cascade reaction of the β-ketoester **1**. Reaction conditions: **1** (1 mmol), water (1 mL), mineral acid combination (1.8 equiv.: 10 μL HCl, 10 μL HNO_3, 100 μL H_2SO_4), 120 °C (oil bath temperature), 18 h. Double-checked results by GC-MS and ^{1}H-NMR, average of two runs. The mass balance is completed with intermediates during the cascade reaction.

tacts extracted from an e-waste bin in our Institute to catalyze the reaction. The results are shown In Fig. 4.

A 80% of the cascade product **4** is obtained under the optimized reaction conditions with H_2SO_4 but now with the RAM contacts added (keeping the amount of acid constant after combining small amounts of HCl and HNO_3 to better dissolve the RAM contacts), with just 0.6 mol% of Au, in contrast to the 10 mol% of Au required to get similar results without acid. Besides, the RAM contacts-catalysed system is also effective with other cascade products, such as product **17** (see Fig. 5 ahead, scope of the reaction). These results showcase that the acid-catalyzed system is not only able to bring the cascade reaction to good yields but also to transform Au residues into a very active catalyst for the reaction.

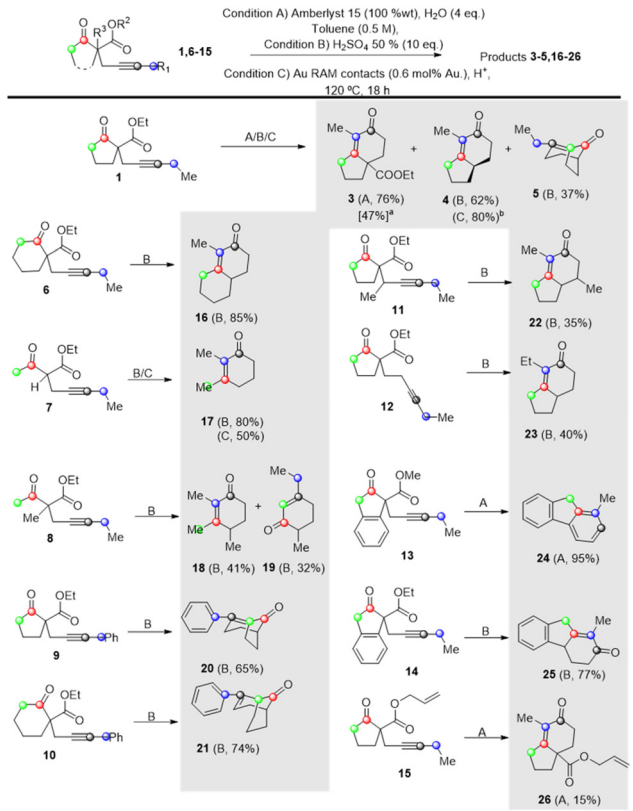


Fig. 5 Results for the H^+-mediated alkyne hydration–condensation–decarboxylation cascade reaction of β-ketoesters. Isolated yields. 120 °C refers to the oil bath temperature. [a] After 6 reuses of the solid catalyst. [b] See exact conditions for the RAM contacts in Fig. 3.

Scope of the reaction

The different β-ketoesters **6–15** were then prepared and used as starting materials for the cascade reaction. The results in Fig. 5 show that polymethylated conjugated cyclohexenones and (fused) carbocycles are obtained in good yields. Hydroindanes **3** and **4** give access to a whole family of natural products[16,17] and resembles the ubiquitous Hajos-Parrish ketone. The solid Amberlyst 15 catalyst could be used seven times with some decrease of the activity after the first use (Fig. S10). The selectivity to product **3** decreases after first use, being the **Int-2** the major product observed. The decaline **16** also give access to a variety of natural products[17,18] and might substitute the Wieland-Miescher ketone as a starting material. The cyclohexenones **17–19** are decorated with methyl and ethyl groups in difficult to achieve positions by conventional synthetic methods. The use of phenylacetylene-substituted β-ketoesters (starting materials **9** and **10**) blocks one of the enolizable positions and directs the cascade reaction exclusively to carbonyl-bridged bis-cycles (such as **5**), to give **20** and **21** in good yields. These bridged carbocycles are of high interest in the synthesis of natural products,[19] and it is noteworthy to point out that product **21** shows the alkene in a non-conjugated position to the ketone, in contrast to **20**, since apparently this disposition is more favorable in the [6,6] bridged bicycle. The use of methyl ester indane **11** as a starting material is particularly relevant, since 1-methyl-9*H*-fluorene **24** is the only product observed in 95% yield when using Amberlyst 15 as a catalyst (H_2SO_4 produced polymerization), after the cascade reaction has been extended with aromatization/dihydroxylation steps. This result opens a new way to prepare alkyl-substituted fluorenes[20] in excellent yields with a simple reusable solid catalyst. However, if we start with **14**, the complete aromatization/dihydroxylation does not take place, obtaining the corresponding ketone **25** (products **23** and **25** tend to polymerize once formed due to the high amount of H_2SO_4 in the reaction mixture, however, this can be palliated by stopping the reaction at the right time). If we modify the ester substituent with an allyl (**15**), we are not able to observe the decarboxylation, obtaining a new kind of compound with an allyl substituent (**26**) together with compound **4** in 15% yield.

Structure–activity relationships (SARs)

With the reactivity of different β-ketoesters in hand, we further studied the structural factors governing the cascade reactions. Kinetic experiments with the starting materials **1** (cyclopentanone), **6** (cyclohexanone), **7** (acetone) and **8** (metylacetone) show that the reactivity order assessed by initial reaction rates are **1** ≫ **6** *ca.* **8** > **7** (30.0, 2.9, 2.8, and 1.0% conversion per min). Density-functional theory (DFT) calculations were then performed to find possible structure-(reactivity) activity relationships (SAR). After optimization of the starting materials' structures (Fig. S14), the initial reaction rates could not be correlated neither with the alkyne bond length nor the

electronics/distance to the reactive ester group (scattered points), but a linear relationship might be interpreted from the correlation with the quaternary carbon angle (the carbon atom between carbonyl groups in **1** and **6–8**, Fig. S15). The wider the angle is, the better the cascade reaction proceeds. These results clearly indicate that the reactivity of the β-ketoester does not obey to any Thorpe-Ingold effect,[1a] which often appears during the ester-assisted hydration reaction but that should follow the opposite trend. Indeed, any clear correlation with the initial rate could not be found neither for the expected hydrate nor the alkoxyhydroxylated intermediates during the ester-assisted hydration reaction of **1** and **6–8**, beyond a correlation with the quaternary carbon angle, after computing the corresponding structures (Fig. S16–S18). The calculation of the relative energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of **1**, **6–8** and the corresponding intermediates during the hydration reaction, and the calculation of the relative Gibbs energies, did not show any correlation neither (Fig. S19–S21). These results strongly support that the ester-assisted alkyne hydration reaction is not the controlling step of the cascade reaction, in good agreement with the experimental results shown above. However, kinetic studies with the starting materials **9** and **10** (Fig. S22) confirms that the substitution of the alkyne with an electron-withdrawing phenyl ring equals the rate of formation of the cascade products **20** and **21** (0.22 conversion per min) regardless the initial β-ketoester structure, which supports that the final condensation reaction is the r.d.s. of the cascade reaction, since the delocalization in the starting alkyne bond ultimately facilitates the enolization of the reactive ketones.

Conclusions

In summary, we have shown here that the ester-assisted alkyne hydration of easily-accessible alkynyl β-ketoesters proceeds without any metal catalyst under acid conditions in water,[21–23] to trigger a series of reactions in cascade which include, at least, the decarboxylation and intramolecular aldol condensation annulation reactions, but also aromatization and dehydroxylation reactions, to produce (fused) carbocycles of interest in organic synthesis. The nature of the final product can be controlled not only by the starting material structure but also by the acid mediator employed, and the solid catalyst Amberlyst 15 can be recycled at least seven times after reaction. These results bring the ester-assisted alkyne hydration into a valuable tool to prepare natural products' cores without involving expensive and toxic metals, through a sustainable cascade reaction in water.

Author contributions

A. L.-T. performed and analyzed the catalytic experiments and synthesized some of the scope products, D. P. dlC.-P. synthesized some of the scope products, S. H.-A. carried out the DFT calculations, J. O.-M. supervised the project and A. L.-P. conceived the idea and supervised the project. All the authors designed the experiments, analysed the data, discussed the results and contributed to the writing the manuscript.

Conflicts of interest

There is not any conflict of interest to declare.

Data availability

The data underlying this study are available in the published article and its supplementary information (SI). Supplementary information: experimental details, Tables S1–S3 and Fig. S1–S22. See DOI: **https://doi.org/10.1039/d5qo01729g**.

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