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Tetranuclear Zn₂Ln₂ coordination clusters as catalysts in the Petasis borono-Mannich multicomponent reaction†

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We report herein for the first time the efficiency of heteronuclear Zn/Ln coordination clusters (CCs) as catalysts for the multicomponent Mannich-type condensation that involves amines, aldehydes and boronic acids, known as the Petasis borono-Mannich (RBR) reaction. The reaction proceeds in very good to excellent yields (84–98%, 17 products) at room temperature with catalyst loadings as low as 1.0 mol%.
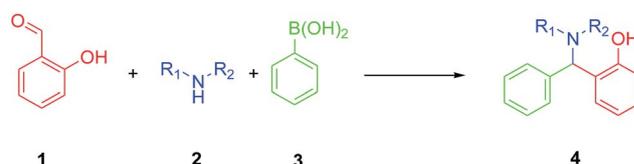
Introduction

The coordination chemistry of 3d and 4f polynuclear coordination clusters (CCs) offers many opportunities to connect Chemistry and Materials Science. The possibility of combining the properties of 3d as well as 4f elements within one molecule has received tremendous attention due to the fascinating structures[1–3] and properties ranging from molecular magnetism,[4–6] magnetic resonance[7] and luminescence.[8,9] So far, however, there are few examples of bimetallic 3d/4f CCs as efficient catalysts for water[10] or alcohol oxidation,[11] and our group has showcased the efficiency of isoskeletal[12] 3d/4f CCs in domino electrocyclization[13,14] and Friedel–Crafts alkylation reactions.[15,16]

Multicomponent reactions (MCRs) dominate synthetic chemistry for the following reasons: they yield products from simple starting materials, in fewer steps, and in a shorter time when the reactions are carried out in a combinatorial way.[17–28] Among these transformations the Mannich-type condensation that involves amines, aldehydes and boronic acids, developed by Petasis,[29] known as the Petasis borono-Mannich (PBR) reaction has received considerable attention because it produces skeletons that can easily be converted to amino acids, heterocycles and alkylaminophenols.[30]

More specific, the reaction shown in Scheme 1 in which aryl boronic acids react with amines and salicylaldehydes yield in a single step novel aminophenol derivatives[31] which are suitable for the preparation of dihydro-1,3-oxazines,[32,33] triarylmethanes,[34] and polycyclic *N,O*-acetals.[30] It is worth noting that aldehydes lacking an OH group in position 2 failed to deliver the desired product, showcasing the importance of the hydroxyl

group in the aldehyde to activate the boronic acid.[30] The first report for the specific transformation shown in Scheme 1 incorporated a reaction at 90 °C, in dioxane as solvent, in 16 hours and in absence of catalyst in very good yields.[35] In 2004, Tye *et al.* developed a rapid, microwave assisted protocol for carrying this reaction that required a 10 min reaction time.[36] In 2009, Gois *et al.*, reported the synthesis of several alkylaminophenols in moderate to good yields, in water, at 80 °C, in absence of catalyst.[37] Recently, an effective and rapid synthesis was carried out using protonated trititanate ($H_2Ti_3O_7$) nanotubes as a heterogeneous solid–acid catalyst.[38] However, these methods suffer from a number of disadvantages such as high temperatures, high catalyst loadings (10%) and long-time reactions.

We recently started to study the catalytic properties of 3d/4f CCs stabilized by the Schiff base organic ligand [(*E*)-(2-hydroxy-3-methoxybenzylidene-amino)phenol], H_2L.[39] These CCs are very easily accessible in two steps. The first step involves the synthesis of the ligand H_2L (yield > 98%) from cheap and commercially available materials (*o*-vanillin and 2-aminophenol) and the second step involves the synthesis of the CC in high yields (>80%) at ambient conditions. We showed that compounds $[Zn_2^{II}Ln_2^{III}L_4(NO_3)_2(DMF)_2]$ (**5**)[15] (Fig. 1) where Ln is Y (**5Y**),[40] Nd (**5Nd**), Gd (**5Gd**), Dy (**5Dy**), Tb (**5Tb**) and Yb (**5Yb**) retain their core intact in solution as confirmed by ESI-MS, EPR and NMR[15] and are highly efficient catalysts in two Friedel–Crafts type reactions of indole; with aldehydes[15] and with substituted nitro-styrenes.[16] In both cases, the reactions

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Scheme 1 An example of the Petasis borono-Mannich (PBR) reaction used in this study.
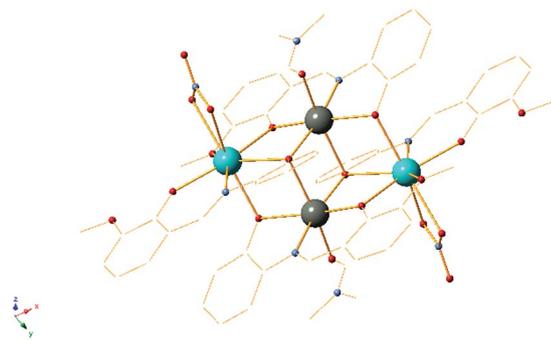
Fig. 1 Molecular structure of **5Ln**. Colour code: Zn^{II}: grey; Ln^{III}: light blue; O: red; N: blue. C and H atoms are omitted for clarity.

proceed smoothly with as low as 1 mol% catalyst loadings, in environmentally friendly solvents, with excellent yields (80–100%) and with wide substrate scope. Having in mind that the Zn–Y/Ln metals are very close (~3.3 Å) in this specific topology and observing a chelation preference of aldehydes[15] to Y/Ln metals in **5**, we envisioned that these catalysts would be an ideal synergistic template for the MCR reaction shown in Scheme 1. Therefore, we employed compounds **5** as catalysts in the title reaction (Scheme 1) and the results of this study are presented herein.

Experimental section

General methods

All data supporting this study are provided as ESI accompanying this paper.† All chemicals and solvents were purchased from Sigma Aldrich, S. D. Fine Chemicals, and commercial suppliers. The progress of the reaction was monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates. Products were purified by column chromatography on silica gel (60–120 mesh). NMR spectra were collected using a Bruker Advance III HD 500 MHz spectrometer. The ^{1}H and ^{13}C NMR spectroscopic data were analysed with a 500 MHz spectrometer in either CDCl$_3$. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as the internal standard. The coupling constants (J) are reported in Hz, and the splitting patterns of the proton signals are described as s (singlet), d (doublet), t (triplet), and m (multiplet).

Synthesis of complexes. All CCs were synthesised according to the literature.[15]

General procedure for the multicomponent reaction. All experiments were carried out in the open atmosphere and on a mmol scale. A 10 mL round bottom flask was charged with catalyst **1Dy** (1.0 mol%), 2-hydroxybenzaldehyde, secondary amine and boronic acid. Solvent (5 mL) was added and the reaction mixture was stirred for 12–16 h at room temperature. The product was purified by silica gel column chromatography.

Single crystal X-ray structure determinations. Crystals suitable for single crystal X-ray diffraction analyses were obtained for compound **4aba**. Preliminary data on the space group and unit cell dimensions as well as intensity data were collected on

an Agilent Xcalibur Eos Gemini Ultra diffractometer with CCD plate detector under a flow of nitrogen gas at 173(2) K using Mo Kα radiation ($\lambda = 0.71073$ Å). CRYSALIS CCD and RED software. Reflection intensities were corrected for absorption by the multi-scan method. Structure solution and refinement were accomplished using Olex2,[41] solved using either Superflip[42] and refined with SHELXL.[43] The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were geometrically fixed and allowed to refine using riding model. Geometric/crystallographic calculations were performed using Olex2,[41] package; graphics were prepared with Crystal Maker.[44] CCDC 1486441.†

Results and discussion

Our first step was to optimize the reaction conditions for the multicomponent reaction. Thus, we tested several reaction parameters, such as the use of solvents (Table 1), different catalysts (Table 2), temperature (Table 3) and catalyst loading

Table 1 Influence of the solvent^a

Entry	Solvent	Yield^b [%]
1	Toluene	34
2	Water	28
3	THF	40
4	Ethanol	80
5	DME	96
6	DMSO	12
7	DMF	14

^{a} Reaction conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), **3a** (0.50 mmol), 5 mL solvent, 1.0 mol% **5Dy** catalyst, room temperature. ^{b} Isolated yield by column chromatography.

Table 2 MCR of 2-hydroxybenzaldehyde **1a**, indoline **2a**, phenylboronic acid **3a** catalyzed by **5Ln** complexes^a

Entry	Catalyst	Yield^b%
1	None	40
2	Zn(OTf)$_2$	56
3	Dy(OTf)$_3$	36
4	**5Y**	74
5	**5Nd**	55
6	**5Gd**	54
7	**5Dy**	96
8	**5Tb**	66
9	**3Yb**	57

^{a} Reaction conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), **3a** (0.50 mmol), 5 mL solvent, 1.0 mol% **5Dy** catalyst, room temperature. ^{b} Isolated yield by column chromatography.

Table 3 Influence of the temperature[a]

Entry	Temperature [°C]	Yield[b] [%]
1	0	0
2	rt	96
3	60	76
4	80	72
5	100	65
6	120	62

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), **3a** (0.50 mmol), 5 mL solvent, 1.0 mol% **5Dy** catalyst, room temperature. [b] Isolated yield by column chromatography.

(Table 4). In previous studies **5Y** and **5Dy** showed similar catalytic efficacy at room temperature,[15,16] thus we decided to perform the solvent screening reactions with **5Dy**. We studied the reaction between salicylic aldehyde (0.50 mmol) **1a**, indoline (0.50 mmol) **2a** and phenylboronic acid (0.50 mmol) **3a** and a catalyst loading of 1.0% mmol% at room temperature. As can be seen from Table 1, 1,2-dimethoxyethane (DME) appears to be the most suitable solvent (entry 5, Table 1). An almost full conversion is achieved. The use of THF, toluene or ethanol, gave the anticipated product in substantially lower yields (entries 1–4, Table 2), showcasing an inhibitory influence on the reaction. Interestingly, the use of DMSO or DMF yielded very low conversions (entries 6 and 7, Table 2).

We then examined the catalytic efficiency of compounds **5**. The results are summarized in Table 1. The desired product **4aaa** was obtained in moderate to excellent yields. A blank experiment in the absence of the 3d/4f CCs catalyst showed 40% conversion (Table 1, entry 1). Moderate conversions were obtained in the presence of Dy or Zn salts (Table 2, entries 2 and 3). Both **5Dy** and **5Y** show higher activity than **5Gd**, **5Nd**, **5Yb** and **5Tb** (Table 1, entries 4–9). Therefore, we selected **5Dy** for the following experiments. Efforts to recover the catalyst after the MCR completion were not successful.

We then decided to identify the influence of the temperature on the catalytic performance. The reactions were carried out at various temperatures ranging from room temperature to 120 °C (Table 3, entries 1–6). At room temperature (Table 3), the yield of **4aaa** was 96%, but 0% at 0 °C. Lower yields were obtained at 60,

Table 4 Catalyst **5Dy** loading[a]

Entry	Catalyst loading [**5Dy** mol%]	Yield[b]%
1	—	40
2	0.5	57
3	1.0	96
4	1.5	70
5	2.0	40
6	5.0	24

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), **3a** (0.50 mmol), 5 mL solvent, 1.0 mol% **5Dy** catalyst, room temperature. [b] Isolated yield by column chromatography.
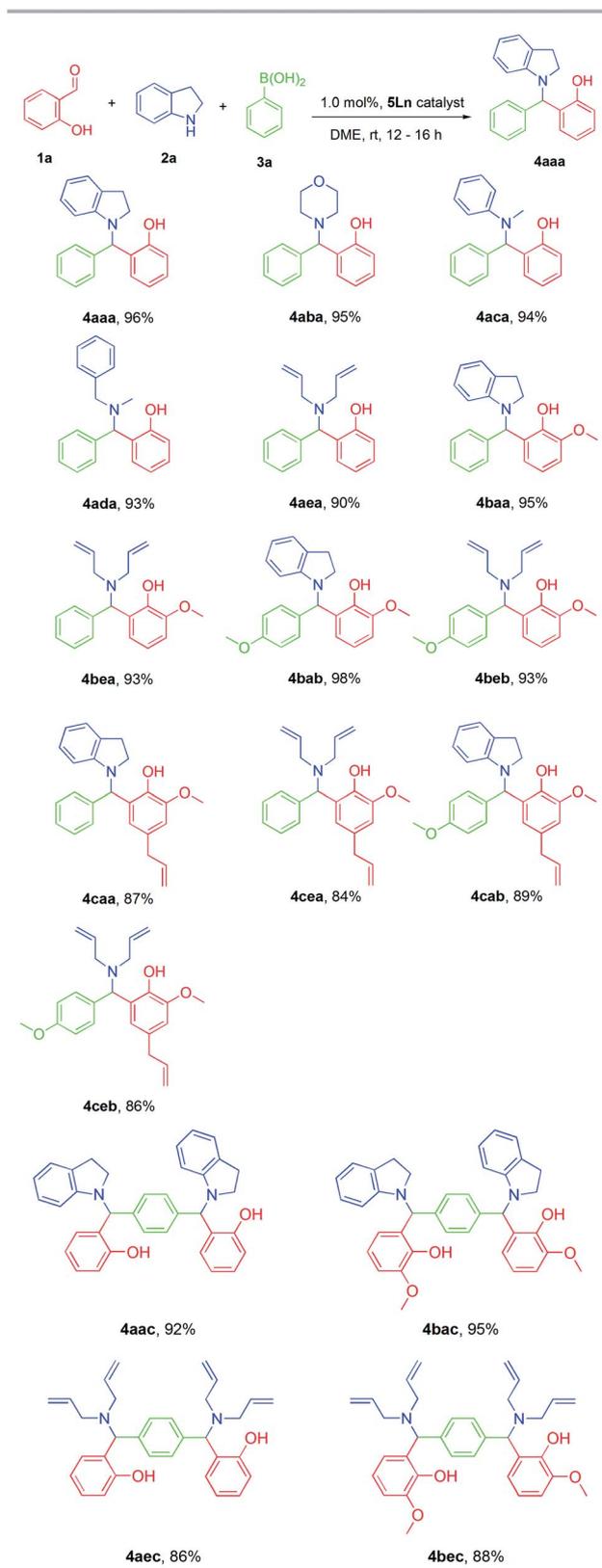

Fig. 2 **5Dy** catalysed MCR of aldehydes, amines and boronic acids. Reaction conditions; aldehyde, 0.5 mmol; substituted indole, 1 mmol; DME 10 mL; room temperature; 12–16 h. 1.0% loading of **5Dy**.

80, 100 and 120 °C (Table 3, entries 3–6), therefore the following reactions were performed at temperature.

After optimizing the reaction conditions, we varied the loadings of catalyst **5Dy** (Table 4). It was sufficient to use a catalyst loading of 1.0 mol% to obtain a yield up to 96% (Table 4, entry 3). An increase of the catalyst loading from 1.0 mol% to 5 mol% led to remarkable decrease in the yield of the desired product **4aaa** (Table 4, entries 3–6).

Further, a decrease in the catalyst loading to 0.5 mol% also showed lower yield of desired product **4aaa** (Table 4, entry 2). In absence of catalyst a 40%conversion is observed (Table 4, entry 1). Finally, we determined that the use of 1.0 mol% **5Dy**, in DME and at room temperature were the optimal conditions to further explore the scope of the MCR.

To demonstrate the applicability of the optimised reaction conditions, different secondary amines, aldehydes and boronic acids were employed in this MCR, using **5Dy** as catalyst (Fig. 2). The reaction proceeds in very good to excellent yields (84–98%, 17 products) at room temperature with catalyst loading 1.0 mol%. Compound **4aba** was characterized *via* single crystal X-ray crystallography (see Fig. S1†). Very good yields were obtained for the reaction involving indoline as secondary amine (Fig. 2), whereas the reaction with *N*-methylaniline, and *N*-benzylmethylamine, gave very good yields, 94 and 93%, respectively (Fig. 2). The presence of an electron donating group in the *para* position of boronic acid gives the multicomponent product in very good yields, whereas the nature of secondary amine influences the total yield (Fig. 2). Compounds **4cab**, **4cea**, **4cab** and **4ceb** (allyl functional group) were isolated in moderate yields. Moreover, the MCRs between salicylic aldehyde or *o*-vanillin, secondary amines and benzene 1,4-diboronic acid afforded products **4aac**, **4bac**, **4aec** and **4bec** in very good yields (Fig. 2). To the best of our knowledge, this is the first time that benzene 1,4-diboronic acid is successfully involved in the titled reaction. It is worth mentioning that the reaction does not proceed with the use of primary amines or benzaldehyde indicating the importance of the hydroxyl group in the aldehyde to activate the boronic acid.[31]

Notwithstanding, the MCR with 2-methoxy-benzaldehyde, indoline and boronic acid yields the desired product (as shown by the presence of a peak in the region of 5.30 ppm in the ^{1}H NMR spectra, corresponding to the tetra substituted carbon atom), however all efforts to purify it by column chromatography were not successful.

Altering the 4f centres without changing the core topology in **5Ln**, allows the use of a pallet of techniques [NMR (for **5Y**), EPR (for **5Gd**), UV-Vis] to study *in situ* a catalytic reaction. In the present case, to gain further information on the plausible mechanism we attempted to monitor the reaction by NMR and UV-Vis. Efforts to monitor the catalytic cycle by NMR, using the diamagnetic **5Y** as catalyst, were not successful due to solubility issues. Salicylic aldehyde shows a broad peak in the UV region prohibiting thus a complete study, however according to our previous UV-Vis binding studies, aldehydes prefer coordination to Ln over Zn.[15] Having all these in mind, we envision the plausible mechanism shown in Scheme 2. The first step of the cycle involves the coordination of aldehyde to Ln metal and secondary amine to Zn metal centres and giving rise to *N*-substituted Zn-complex in step 2. Then, the reaction of the boronic acid with *N*-substituted Zn-complex (step 2) affords the desired final compounds with the release of boronic acid (steps 3–5) with the formation of transition state in step 5.
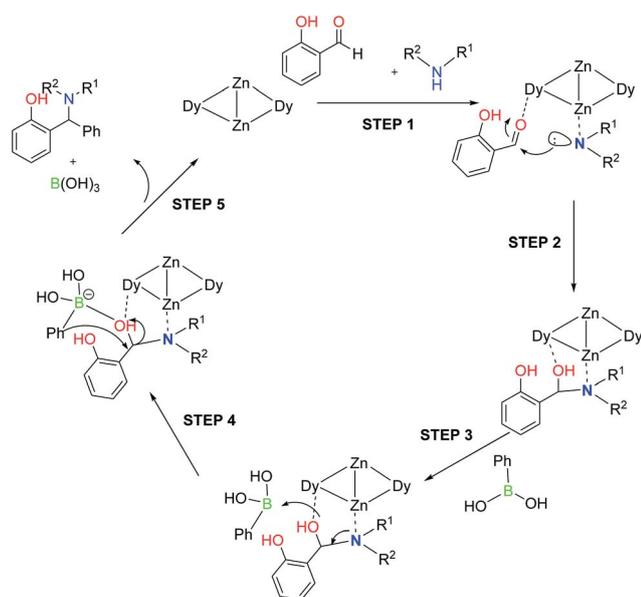
Conclusions

Compound **5Dy** was successfully employed for the first time as catalyst in the PBR MCR (Scheme 1) exhibiting excellent efficacy at room temperature, in short time, with 1% loading and excellent yields. The present successful paradigm adds value on the usefulness of **5Ln** CCs as catalysts. These species can efficiently catalyse at room temperature and low loadings, two different type of transformations, Friedel–Crafts alkylation[15,16] and the present MCR, thus opening new directions in 3d/4f coordination chemistry. We currently exploring the catalytic efficiency of **5Ln** to other MCRs and organic transformations as well to domino reactions. Involvement of chiral ligands for the synthesis of 3d/4f CCs to achieve enantioselectivity and immobilization of **5Ln** are also currently under investigation in our laboratory.

Scheme 2 Proposed reaction mechanism.

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