# Multi-catalysis reactions: direct organocatalytic sequential one-pot synthesis of highly functionalized cyclopenta[*b*]chromen-1-ones†

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We have developed a new technology called multi-catalysis for the sequential one-pot synthesis of highly functionalized heterocycles. A practical and novel multi-component aniline-, self- and Brønsted acid-catalyzed selective process for the sequential one-pot synthesis of highly substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones, 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones and 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-ones is reported. Direct combination of aniline- and self-catalyzed cascade olefination–hydrogenation (O–H) and Brønsted acid-catalyzed cascade oxy-Michael–dehydration (OM–DH) of 1,3-diones, salicylic aldehydes and organic-hydrides is developed in one-pot to furnish the highly functionalized 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones and 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-ones with high yields.

## Introduction

Heterocycles such as chromanes, chromenes, coumarins and tetrahydroxanthenones are of considerable importance in a variety of industries. As is well known, these heterocycles are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product chemistry, synthetic organic chemistry and polymer science.[1] As such, the development of new and more general catalytic methods for their preparation is of significant interest.[2] Recently nucleophilic amine-catalysis has emerged for the reaction of 2-hydroxybenzaldehyde with substituted enones in the presence of secondary and/or tertiary amines to provide general route to a variety of functionalized 2,3,4,4a-tetrahydro-xanthen-1-ones and 3,3a-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones in moderate to good yields (Scheme 1).[2] But interestingly, there is no direct method for the synthesis of functionalized 2,3,4,9-tetrahydro-xanthen-1-ones and 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones from substituted 2-hydroxy-benzaldehydes and enones, which are highly useful starting materials in natural product synthesis (Scheme 1).

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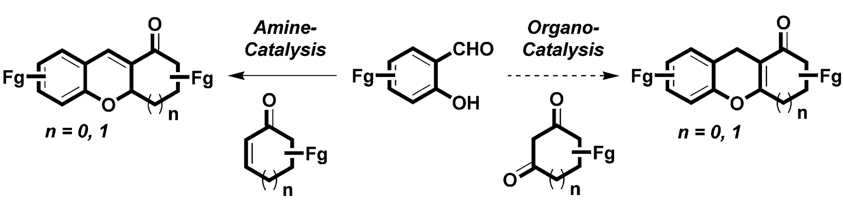
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data ($^1$H NMR, $^{13}$C NMR and HRMS) for all new compounds. CCDC reference numbers 682180 (**6ad**) and 681487 (**10aa**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812551a

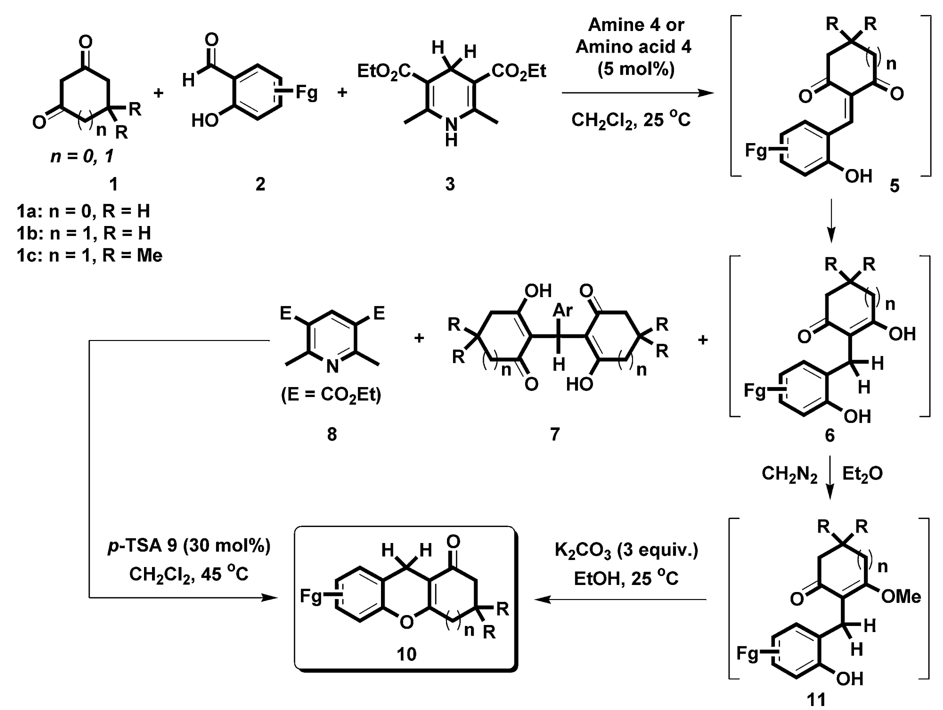
Herein, we discovered a metal-free, novel and multi-catalysis technology for the synthesis of highly substituted 2,3,4,9-tetrahydro-xanthen-1-ones and 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones by using direct organocatalytic sequential one-pot multi-component olefination–hydrogenation–oxy-Michael–dehydration (O–H–OM–DH) and olefination–hydrogenation–alkylation–oxy-Michael–dehydration (O–H–A–OM–DH) reactions from commercially available functionalized 2-hydroxy-benzaldehydes, cyclopentane-1,3-dione or substituted cyclohexane-1,3-dione and Hantzsch ester (organic-hydride) (Scheme 1). Direct combination of amine- or amino acid-catalyzed cascade olefination–hydrogenation (O–H) and Brønsted acid-catalyzed cascade oxy-Michael–dehydration (OM–DH) or combination of amine- or amino acid-catalyzed cascade olefination–hydrogenation (O–H) and self-/base-catalyzed cascade alkylation–oxy-Michael–dehydration (A–OM–DH) of 1,3-diones, salicylic aldehydes, organic-hydride (Hantzsch ester) and diazomethane is developed in one-pot as shown in Scheme 2. 2,3,4,9-Tetrahydro-xanthen-1-ones and 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones are useful starting materials for the synthesis of natural products and their analogues.[1]

In continuation of our recent discovery of bio-mimetic *in situ* reduction of novel active olefins with Hantzsch ester **3** through self-catalysis by decreasing the HOMO–LUMO energy gap between olefins and Hantzsch ester **3** in cascade reactions,[3] we initiated our studies of the cascade O–H reaction of cyclopentane-1,3-dione **1a** with variety of 2-hydroxy-benzaldehydes **2** and Hantzsch ester **3** under amine- or amino acid-catalysis to furnish the reductive alkylation products **6** and their applications in the synthesis of




**Scheme 1** Synthesis of highly substituted 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones.



**Scheme 2** Combining multi-catalysis and multi-component systems for one-pot cascade reactions.

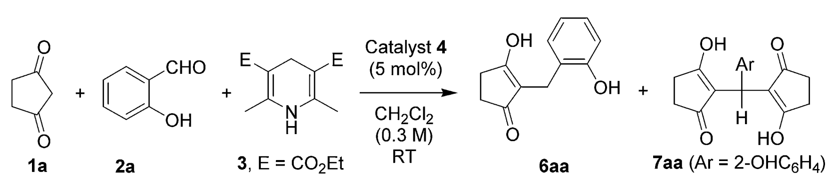
pharmaceutically useful products with good yields in one-pot (see Scheme 2).

## Results and discussion

### Reaction optimization for multi-catalysis reactions in one-pot

First we focused on the optimization for a high yield synthesis of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **6aa** from **1a**, **2a**, **3** and **4** through amine- or amino acid-catalysis, which is a precursor for our designed cascade O–H–OM–DH reaction. For that we initiated our studies of the cascade O–H reaction by screening a number of known and novel organocatalysts for the reductive alkylation of cyclopentane-1,3-dione **1a** with 2-hydroxy-benzaldehyde **2a** and Hantzsch ester **3** as shown in Table 1. Based on our previous experience of the amino acid-promoted reductive alkylation of 1,3-diones with aldehydes and Hantzsch ester *via* cascade O–H reactions,[3] we chose $CH_2Cl_2$ as solvent; and then we decided to investigate the catalyst **4** effect on the cascade O–H reaction of **1a**, **2a** and **3**. It is a well established fact that the self-catalyzed reaction of cyclopentane-1,3-dione **1a** with 3 equiv. of 2-hydroxy-benzaldehyde **2a** furnished only the unexpected bis-adduct **7aa** without the expected olefination product 2-(2-hydroxy-benzylidene)-cyclopentane-1,3-dione **5aa** (result not

**Table 1** Effect of catalyst on the direct amino acid or amine-catalyzed reductive alkylation of **1a** with **2a** and **3**[a]



| Entry | Catalyst **4** (5 mol%) | Time/h | Conversion (%)[b] | Yield (%) product[c] **6aa** | **7aa** |
|---|---|---|---|---|---|
| 1 | Proline **4a** | 28 | >99 | 80 | 20 |
| 2 | Glycine **4b** | 28 | 75 | 50 | 20 |
| **3** | **Aniline 4c** | **2** | **>99** | **80** | **15** |
| 4 | Benzylamine **4d** | 4 | >99 | 80 | 15 |
| 5 | Piperidine **4e** | 24 | >95 | 80 | 15 |
| 6 | Pyrrolidine **4f** | 24 | >95 | 80 | 15 |

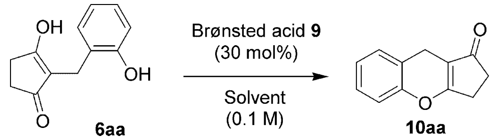
[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **2a** and 1.0 equiv. of **3** relative to **1a** (0.3 mmol) in the presence of 5 mol% of catalyst **4**. [b] Conversion based on the TLC analysis. [c] Yield refers to the column purified product.

shown in Table 1). The same reaction under proline-catalysis also furnished only the bis-adduct **7aa** without product 2-(2-hydroxy-benzylidene)-cyclopentane-1,3-dione **5aa** with a reduced reaction time (result not shown in Table 1). Interestingly, proline-catalyzed reaction of cyclopentane-1,3-dione **1a** and 3 equiv. of 2-hydroxy-benzaldehyde **2a** with Hantzsch ester **3** furnished the expected reductive alkylation product **6aa** with 80% yield accompanied by bis-adduct **7aa** with 20% yield after 28 h at 25 °C in $CH_2Cl_2$ as shown in Table 1, entry 1. These preliminary results prompted us to investigate the catalyst effect on *in situ* trapping of the olefination product of cyclopentane-1,3-dione **1a** with 2-hydroxy-benzaldehyde **2a** through bio-mimetic hydrogenation as shown in Table 1. Interestingly, proline-catalyzed cascade O–H reactions of **1a**, **2a** and **3** are catalyst dependent reactions as shown in Table 1. Simple amino acid glycine **4b** also catalyzed the cascade O–H of **1a**, **2a** and **3** but the result is not as good as proline-catalysis (Table 1, entry 2). The cascade O–H reaction of **1a**, **2a** and **3** catalyzed by simple amines like benzylamine **4d**, piperidine **4e** and pyrrolidine **4f** in $CH_2Cl_2$ are also not as good in comparison to proline-catalysis with respect to yields as shown in Table 1, entries 4–6. Interestingly, the reaction rate for cascade O–H under primary amine, benzylamine **4d**-catalysis is 7-fold enhanced compared to other amine catalysts **4e–f** or amino acid catalyst **4a** as shown in Table 1.

To increase the dynamics of the cascade O–H reaction without generating the by-product bis-adduct **7aa**, a suitable amine catalyst is required. Recently, Dawson and coworkers from the Scripps Research Institute found that aniline is a potent nucleophilic catalyst for imine-type reactions.[4] Aniline is a mild nucleophile, which strongly catalyzes aqueous reactions of aldehydes and ketones with amines to form stable imines (RR′C=NR″) such as hydrazones (RR′C=NNHR″) and oximes (RR′C=NOR″). In a similar fashion, aniline should catalyze the olefination reaction under non-aqueous conditions. Here we show that the dynamics of the cascade O–H reaction can be significantly accelerated by using aniline as a nucleophilic catalyst. Surprisingly, the cascade O–H reaction of **1a**, **2a** and **3** in $CH_2Cl_2$ under 5 mol% of aniline-catalysis furnished the expected hydrogenated reductive alkylation product **6aa** in 80% yield accompanied by a 15% yield of bis-adduct **7aa** within 2 h at 25 °C (Table 1, entry 3). Interestingly, the cascade O–H reaction rate for aniline-catalysis is 14-fold enhanced compare to proline- or secondary amine-catalysis as shown in Table 1. We envisioned the optimized condition to be mixing 3 equiv. of 2-hydroxy-benzaldehyde **2a** with cyclopentane-1,3-dione **1a** and Hantzsch ester **3** at 25 °C in $CH_2Cl_2$ under 5 mol% of aniline-catalysis to furnish the hydrogenated product, 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **6aa** in 80% yield (Table 1, entry 3). The mechanistic aspect of this selective cascade O–H reaction is discussed in the next section.

With an efficient aniline-catalyzed cascade reductive alkylation protocol in hand, we continued our investigation of optimization for the synthesis of functionalized 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-one **10aa** from 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **6aa** under Brønsted acid-catalysis through cascade oxy-Michael–dehydration (OM–DH) reactions as shown in Table 2. The results in Table 2 demonstrate that *p*-TSA **9f** is a suitable Brønsted acid-catalyst for the cascade OM–DH reaction compared to other Brønsted acid catalysts **9a-h** or Lewis acid catalyst **9b**. Treatment of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **6aa** with 30 mol% of $HClO_4$ in $CH_2Cl_2$ at 25 °C furnished the expected cascade product **10aa** in only 20% yield, but interestingly there is no cascade reaction under $BF_3{\cdot}OEt_2$ catalysis even under hot conditions (Table 2, entries 1–2). Cascade OM–DH reaction of **6aa** in $CH_2Cl_2$ at 25 °C under $CH_3SO_3H$-catalysis furnished the **10aa** with only 45% yield, but interestingly there is no cascade reaction under $CF_3SO_3H$-catalysis (Table 2, entries 3–4). (+)-Camphor sulfonic acid catalyzed the cascade OM–DH reaction of **6aa** to furnish the product **10aa** with 70% yield in $CH_2Cl_2$ at 25 °C for 48 h (Table 2, entry 5). Interestingly, the same reaction under *p*-TSA catalysis furnished the expected product **10aa** in 80% yield (Table 2, entry 7). Phosphoric acid-catalysis for the synthesis of cascade product **10aa** is not superior compared to *p*-TSA catalysis (Table 2, entries 9–10). We envisioned the optimized condition to be mixing the 30 mol% of *p*-TSA **9f** with 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **6aa** at 45 °C in $CH_2Cl_2$ for 10 h to furnish the cascade OM–DH product,

**Table 2** Reaction optimization for the Brønsted acid-catalyzed cascade OM–DH reaction of **6aa**[a]

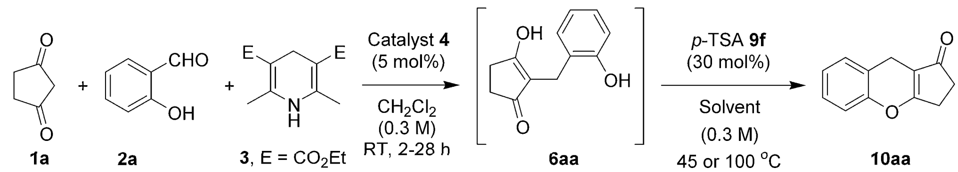



| Entry | Catalyst **9** (30 mol%) | Solvent (0.1 M) | Time/h | Temperature/°C | Yield (%)[b] **10aa** |
|---|---|---|---|---|---|
| 1 | $HClO_4$ **9a** | $CH_2Cl_2$ | 48 | 25 | 20 |
| 2 | $BF_3{\cdot}OEt_2$ **9b** | $CH_2Cl_2$ | 48 | 25 | — |
| 3 | $CH_3SO_3H$ **9c** | $CH_2Cl_2$ | 48 | 25 | 45 |
| 4 | $CF_3SO_3H$ **9d** | $CH_2Cl_2$ | 48 | 25 | — |
| 5 | (+)-CSA **9e** | $CH_2Cl_2$ | 48 | 25 | 70 |
| 6 | *p*-TSA **9f** | $CH_3C_6H_5$ | 10 | 95 | 80 |
| 7 | *p*-TSA **9f** | $CH_2Cl_2$ | 16 | 25 | 80 |
| **8** | ***p*-TSA 9f** | $\mathbf{CH_2Cl_2}$ | **10** | **45** | **90** |
| 9 | $(PhO)_2PO_2H$ **9g** | $CH_2Cl_2$ | 40 | 25 | 73 |
| 10 | (*R*)-BNDHP **9h**[c] | $CH_2Cl_2$ | 48 | 25 | 50 |

[a] Reactions were carried out in solvent (0.1 M) with 30 mol% of catalyst **9**. [b] Yield refers to the column purified product. [c] (*R*)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate **9h** and catalyst **9h** were taken as 5 mol%.

**Table 3** Reaction optimization for the organo–Brønsted acid-catalyzed cascade one-pot synthesis of **10aa**[a]




| Entry | Catalyst **4** (5 mol%) | Time/h | Solvent (0.3 M) | Temperature/°C | Time/h | Conversion (%)[b] | Yield (%)[c] **10aa** |
|---|---|---|---|---|---|---|---|
| 1 | Proline **4a** | 28 | $CH_3C_6H_5$ | 100 | 10 | >99 | 50 |
| 2 | Proline **4a** | 28 | $CH_3C_6H_5$ | 90 | 10 | >99 | 50 |
| 3 | Proline **4a** | 28 | $CH_2Cl_2$ | 45 | 48 | 50 | — |
| 4 | Aniline **4c** | 2 | $CH_3C_6H_5$ | 100 | 10 | >99 | 50 |

[a] See Experimental section. [b] Conversion is based on the TLC analysis. [c] Yield refers to the column purified product.

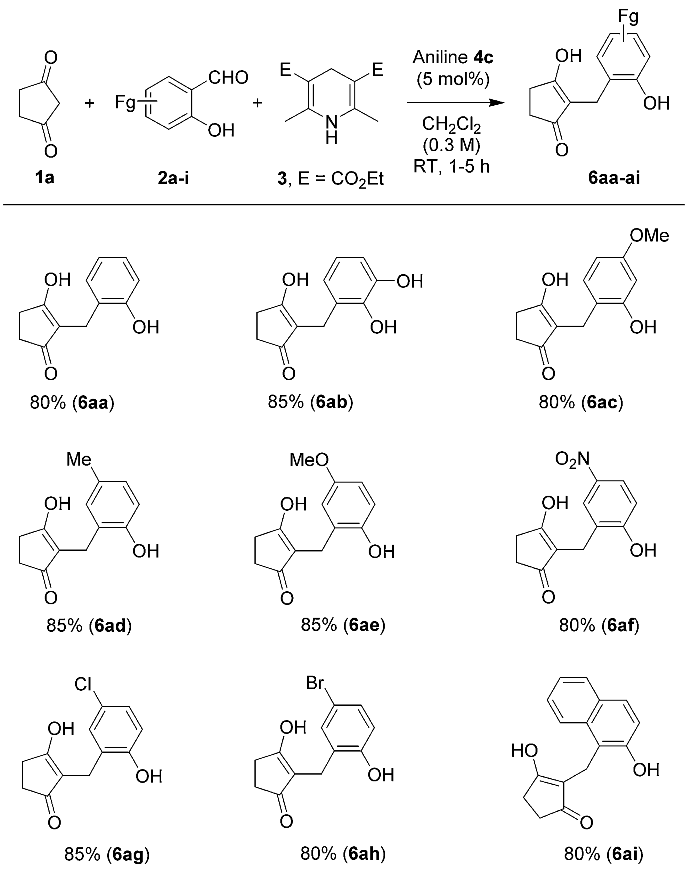
3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-one **10aa** in 90% yield (Table 2, entry 8).

After successful optimization of the aniline-catalyzed cascade O–H and Brønsted acid-catalyzed cascade OM–DH reactions, we decided to investigate the combination of these two cascade reactions in one-pot as shown in Table 3. The cascade O–H reaction of three equiv. of 2-hydroxy-benzaldehyde **2a** with cyclopentane-1,3-dione **1a** and Hantzsch ester **3** under proline-catalysis in $CH_2Cl_2$ at 25 °C for 28 h furnished the expected cascade product **6aa**, which on evaporation of the solvent $CH_2Cl_2$ and treatment with 30 mol% of *p*-TSA **9f** at 100 °C in toluene solvent for 10 h furnished the expected sequential one-pot O–H–OM–DH product **10aa** in >99% conversion with 50% yield as shown in Table 3, entry 1. Combination of two cascade O–H and OM–DH reactions under aniline- and *p*-TSA-catalysis in one-pot also furnished the sequential one-pot product **10aa** in >99% conversion with 50% yield as shown in Table 3, entry 4. Interestingly, combination of two cascade O–H and OM–DH reactions under proline or aniline- and *p*-TSA-catalysis in $CH_2Cl_2$ solvent did not furnish the sequential one-pot product **10aa** with >99% conversion, but furnished it only with ≤50% conversion at 45 °C for 48 h as shown in Table 3, entry 3; this may be due to the strong acid–base interactions of *p*-TSA with pyridine byproduct of 2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester **8**.

### Diversity-oriented synthesis of reductive alkylation products 6aa–6ai

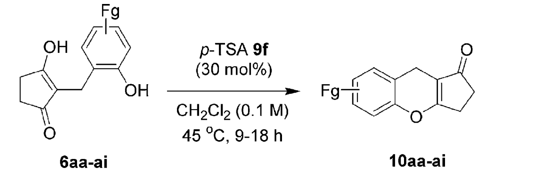
With the three cascade optimized reaction conditions in hand, the scope of the aniline-catalyzed O–H, *p*-TSA-catalyzed OM–DH and aniline–*p*-TSA-catalyzed O–H–OM–DH cascade reactions was investigated with cyclopentane-1,3-dione **1a**, various functionalized 2-hydroxy-benzaldehydes **2a-i** and Hantzsch ester **3** as shown in Tables 4 and 5. A series of functionalized 2-hydroxy-benzaldehydes **2a-i** (3 equiv.) were reacted with cyclopentane-1,3-dione **1a** and Hantzsch ester **3** catalyzed by 5 mol% of aniline at 25 °C in $CH_2Cl_2$ (Table 4). The substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **6aa–6ai** were obtained as single isomers (tautomer) with excellent yields. The cascade reaction of cyclopentane-1,3-dione **1a** with 2,3-dihydroxy-benzaldehyde **2b** and **3** furnished the reductive alkylation product **6ab** as a single isomer (tautomer), in 85% yield after 5 h at 25 °C (Table 4). Synthesis of functionalized 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **6aa–6ai** from **1a**, **2a-i** and **3** at 25 °C under aniline-catalysis requires shorter reaction times (1 to 5 h), compared to proline-catalysis as shown in Tables 1 and 4. Interestingly, the aniline-catalyzed reductive alkylation reaction of cyclopentane-1,3-dione **1a** with 5-chloro-2-hydroxy-benzaldehyde **2g**/5-bromo-2-hydroxy-benzaldehyde **2h** and Hantzsch ester **3** generated the expected cascade products **6ag**/**6ah** in excellent yields with very good selectivity (Table 4). Structure and regio-chemistry of cascade products **6aa–ai** were confirmed by NMR analysis and

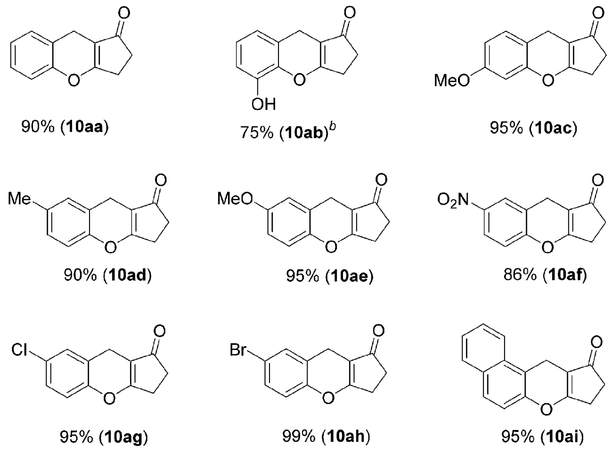
**Table 4** Chemically diverse libraries of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-diones **6**[a]




[a] Yield refers to the column purified product.

**Table 5** Chemically diverse libraries of 3,9-dihydro-2*H*-cyclopenta-[*b*]chromen-1-ones **10**[a]




[a] Yield refers to the column purified product. [b] Reaction performed at 100 °C for 8 h in the toluene solvent.

also by X-ray structure analysis on **6ad** as shown in Fig. 1.[5] Interestingly, these 2-alkyl-cyclopentane-1,3-diones **6** exist as an enol form in both solid and solution state and this may be due to the strong intermolecular hydrogen bonding and this same concept is observed in many other 1,3-diketones.[6] The chemical shifts of the C1 and C3 carbon atoms in the isolated, non-hydrogen-bonded enol forms of 2-alkyl-cyclopentane-1,3-diones **6** can hardly be determined in solution, due to the rapid keto–enol and enol–enol tautomerism.[6] Therefore, in 2-alkyl-cyclopentane-1,3-dione compounds **6aa–ai**, we observed that the $^{13}$C NMR spectra show two of the $CH_2$ carbons α to the carbonyls (*C*=O) including the two carbonyl carbons [2 × $CH_2$ and 2 × *C*=O] at poor resolution even after 2000 scans on standard sampling. This same kind of $^{13}$C NMR pattern was observed for the other 1,3-diketones in the literature due to the rapid keto–enol and enol–enol tautomerism.[6]

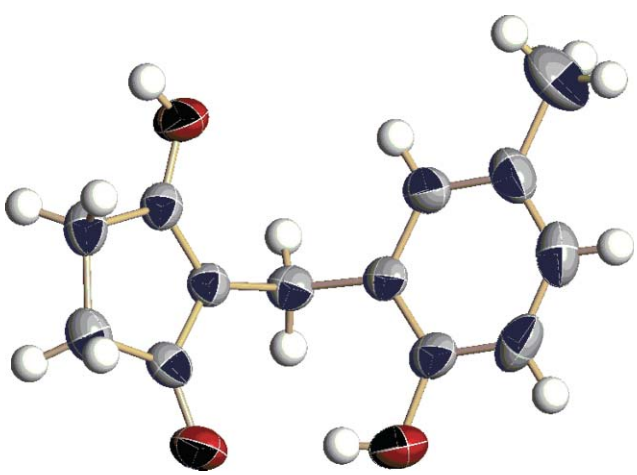


**Fig. 1** Crystal structure of 2-(2-hydroxy-5-methyl-benzyl)-cyclopentane-1,3-dione (**6ad**).

### Diversity-oriented synthesis of heterocycles 10aa–10ai

With the success of cascade synthesis of highly functionalized 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **6**, we continued our investigation for the generation of a highly functionalized diversity oriented library of cascade 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones **10** under acid-catalysis. The results in Table 5 demonstrate the broad scope of this novel green methodology covering a structurally diverse group of 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **6aa–ai**. Cascade OM–DH reaction of 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **6aa–ai** under acid-catalysis furnished the expected 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones **10aa–ai** in 75–99% yield with high selectivity (Table 5). Unexpectedly, cascade product **10ab** only was only produced in moderate yield from **6ab** and **9f**. Interestingly, all 4- and 5-substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones **6ac–ai** furnished the expected products **10ac–ai** with very good yields as a single isomer in acid-catalyzed OM–DH cascade reactions as shown in Table 5. Structure and regiochemistry of cascade products **10** were confirmed by NMR analysis and also by X-ray structure analysis on **10aa** as shown in Fig. 2.[5]

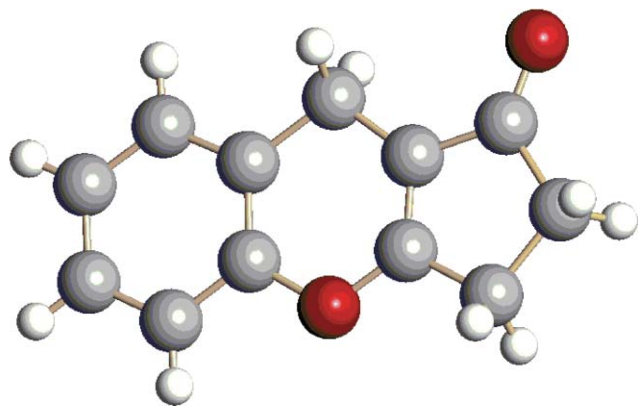
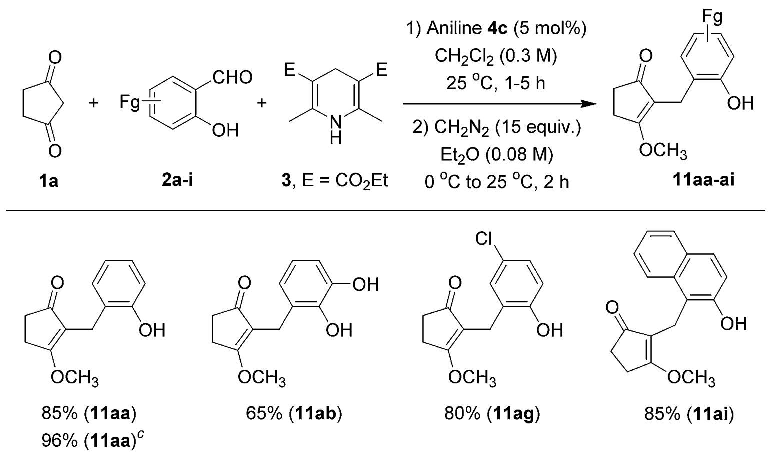


**Fig. 2** Crystal structure of 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-one (**10aa**).

### Diversity-oriented synthesis of 2-alkyl-3-methoxy-cyclopent-2-enones 11aa–11ai

With synthetic applications in mind, we extended the three-component cascade O–H reactions into a novel aniline–self-catalyzed four-component O–H–A reaction of **1a**, **2a-i** and **3** with ethereal solution of diazomethane in one-pot as shown in Table 6. One-pot products **11** were constructed in very good yields with high chemoselectivity as shown in Table 6 and this method should have a great impact on the synthesis of functionalized small molecules. The substituted 2-alkyl-3-methoxy-cyclopent-2-enone unit is a basic building block for a large number of valuable naturally occurring products.[7] Highly substituted 2-alkyl-3-methoxy-cyclopent-2-enones **11** have gained importance

**Table 6** Chemically diverse libraries of 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enones **11**[a,b]

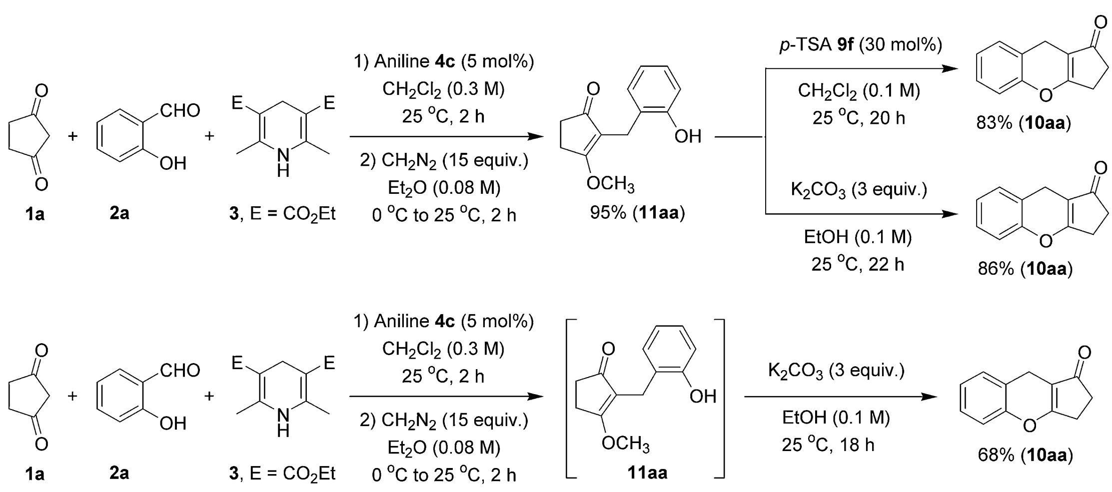



[a] See Experimental section. [b] Yield refers to the column purified product. [c] Yield represents only the etherification reaction.

in recent years as starting materials and intermediates for the synthesis of prostaglandin analogs, which possess a wide range of physiological and pharmacological properties.[7]

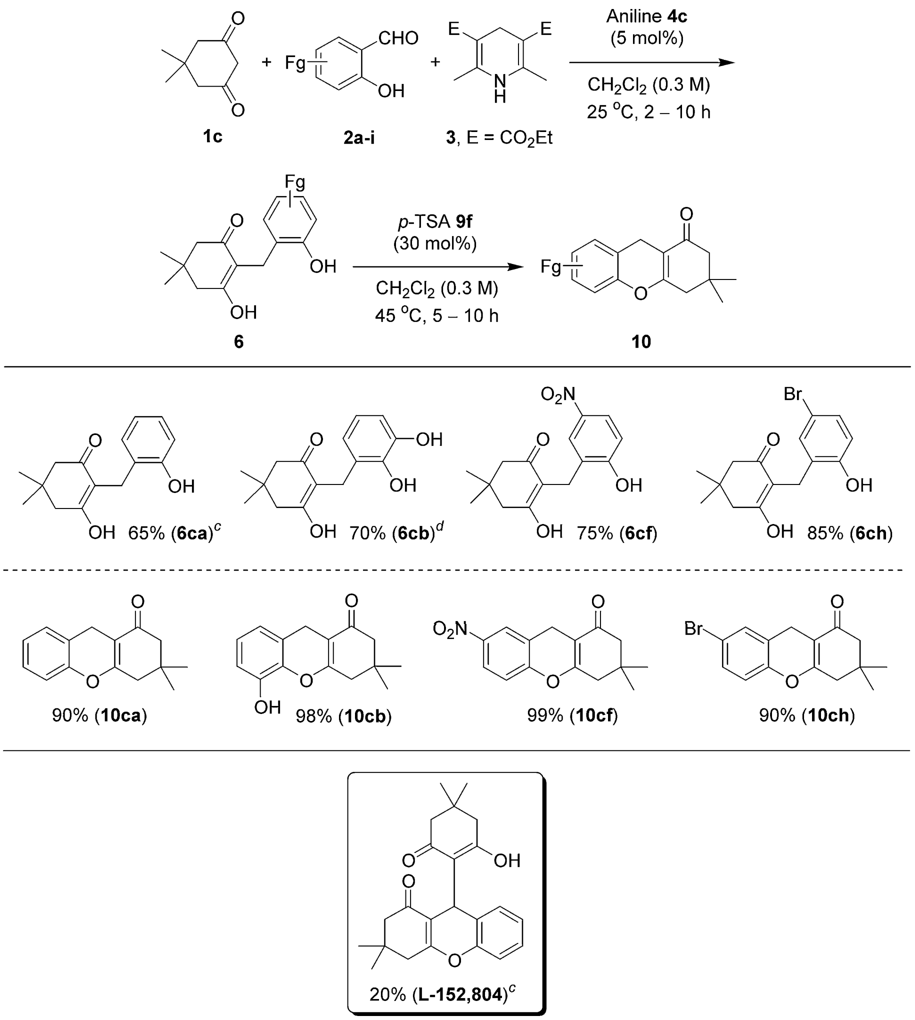
Cascade O–H reaction of **1a**, **2a** and **3** under 5 mol% of aniline-catalysis furnished the substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione **6aa** in good yield, which on treatment with ethereal diazomethane at 0 °C to 25 °C for 2 h furnished chemoselectively the one-pot O–H–A product 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone **11aa** in 85% yield as shown in Table 6. Interestingly, the phenol group is not methylated under these conditions. The acidic or highly enolizable nature of 2-aryl-cyclopentane-1,3-diones **6** is the main driving force to the observed highly chemoselective O-alkylation reaction with diazomethane. Generality of the aniline–self-catalyzed chemoselective one-pot O–H–A reaction was further confirmed by three more examples using 2,3-dihydroxy-benzaldehyde **2b**, 5-chloro-2-hydroxy-benzaldehyde **2g** and 2-hydroxy-naphthalene-1-carbaldehyde **2i** to furnish the expected 2-(2,3-dihydroxy-benzyl)-3-methoxy-cyclopent-2-enone **11ab** in 65% yield, 2-(5-chloro-2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone **11ag** in 80% yield and 2-(2-hydroxy-naphthalen-1-ylmethyl)-3-methoxy-cyclopent-2-enone **11ai** in 85% yield, respectively as shown in Table 6. For the pharmaceutical applications, diversity-oriented library of enones **11** could be generated by using our aniline–self–self-catalyzed, chemoselective one-pot O–H–A reaction.

After successful chemoselective synthesis of 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone **11aa** in good yield, we decided to test the acid–base effect on this cascade product **11aa**. Treatment of **11aa** with both acid (*p*-TSA) or base ($K_2CO_3$) at room temperature furnished the expected 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-one **10aa** in good yield as shown in Scheme 3. Interestingly this same reaction performed in one-pot as a four-component, multi-catalysis (aniline-, self-, self- and base-catalysis) of **1a**, **2a**, **3** and $CH_2N_2$ furnished the one-pot product **10aa** in 68% yield as shown in Scheme 3. The overall yield of one-pot product **10aa** may be less compared to Table 5, but this multi-component–multi-catalysis strategy will have much effect on the synthesis of highly functionalized small molecules like **10** and **11**.




**Scheme 3** Multi-catalysis and multi-component approach to the synthesis of 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-one **10aa**.

**Table 7** Direct organocatalytic synthesis of 2-(2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-diones **6** and 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-ones **10**[a,b]




[a] See Experimental section. [b] Yield refers to the column purified product. [c] 20% of L-152,804; an orally active and selective neuropeptide Y Y5 receptor antagonist was accompanied as by-product with **6ca** in aniline-catalyzed reaction of **1c**, **2a** and **3**. [d] 23% of **10cb** was accompanied as by-product with **6cb** in aniline-catalyzed reaction of **1c**, **2b** and **3**.

### Diversity-oriented synthesis of heterocycles 10ca–10ci

After successful demonstration of the cascade O–H, O–H–A, O–H–OM–DH and O–H–A–OM–DH reactions on cyclopentane-1,3-dione **1a** with **2**, **3** and **4**, then we decided to test the same cascade reactions on other 1,3-diones like cyclohexane-1,3-dione **1b** and dimedone **1c**. Interestingly, cascade O–H reaction of **1b**, **2a** and **3** under proline **4a**- or aniline **4c**-catalysis did not furnish the expected pure product 2-(2-hydroxy-benzyl)-cyclohexane-1,3-dione **6ba** and the reaction itself is not clean. But the same cascade O–H reaction with **1c**, **2a** and **3** under proline **4a**- or aniline **4c**-catalysis furnished the expected product 2-(2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **6ca** in only 65% yield, which on acid-catalysis furnished the expected 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **10ca** in very good yield as shown in Table 7.

Interestingly, cascade product **6ca** was accompanied with byproduct 9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (**L-152,804**) in 20% yield, which is useful compound as an orally active and selective neuropeptide Y Y5 receptor antagonist.[8] But pure product of **L-152,804** was obtained only after two step O–H and OM–DH reactions, because separation of **L-152,804** from **6ca** is tedious job due to the same $R_f$ in TLC plate. In the reaction of **1c**, **2a** and **3** under **4c**-catalysis, the initial byproduct (**L-152,804**) was unchanged after heating with *p*-TSA **9f** in $CH_2Cl_2$. The generality of the aniline- and acid-catalyzed chemoselective cascade O–H and OM–DH reactions of **1c** with **2** and **3** was further confirmed by three more examples using 2,3-dihydroxy-benzaldehyde **2b**, 5-nitro-2-hydroxy-benzaldehyde **2f** and 5-bromo-2-hydroxy-benzaldehyde **2h** to furnish the expected 2-(2,3-dihydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **6cb** in 70% yield, 2-(2-hydroxy-5-nitro-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **6cf** in 75% yield, 2-(5-bromo-2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione **6ch** in 85% yield, 5-hydroxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **10cb** in

98% yield, 3,3-dimethyl-7-nitro-2,3,4,9-tetrahydro-xanthen-1-one **10cf** in 99% yield and 7-bromo-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **10ch** in 90% yield, respectively as shown in Table 7. Interestingly, we could not see the formation of unexpected byproducts like **L-152,804** analogs in the above three reactions. But, cascade product **6cb** was accompanied with byproduct 5-hydroxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one **10cb** in 23% yield. Recently, 5,5-dimethylcyclohexane-1,3-dione derivatives **6ca–ci** were evaluated to show their biological activities like anti-ischemic agents, anti-hypertensive and anti-psychotics.[9]

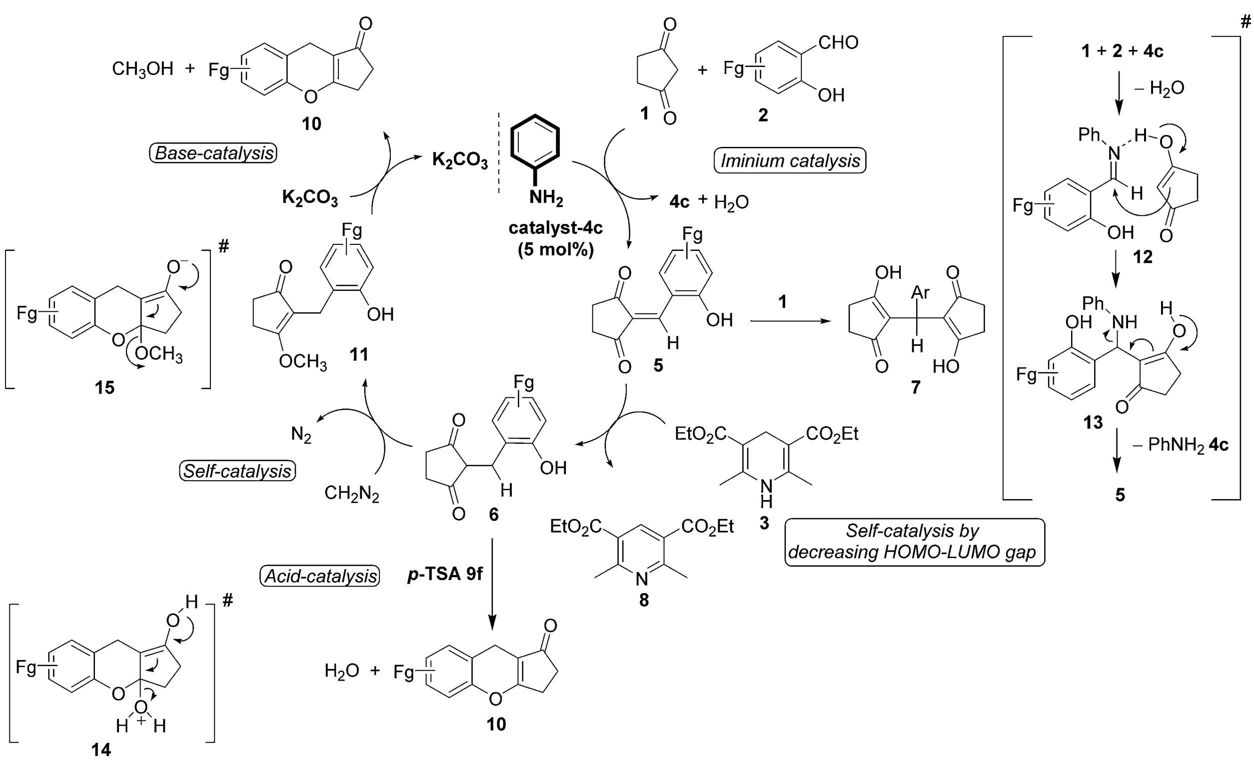
## Mechanistic insights

A possible reaction mechanism for the aniline-, self-, acid- and base-catalyzed chemoselective synthesis of cascade products **6**, **10** and **11** through the reaction of cyclopentane-1,3-dione **1a**, 2-hydroxy-benzaldehydes **2**, Hantzsch ester **3** and diazomethane is illustrated in Scheme 4. This catalytic sequential one-pot, double cascade is a four component reaction comprising a cyclopentane-1,3-dione **1a**, 2-hydroxy-benzaldehydes **2**, Hantzsch ester **3**, diazomethane and a simple catalyst, aniline **4c**. In the first step (Scheme 4), the catalyst **4c** activates component **2** by most likely imine formation, which then selectively adds to the cyclopentane-1,3-dione **1a** *via* a Mannich and retro-Mannich type reaction to generate active olefin **5** (**12** → **13** → **5**). The following second step is bio-mimetic hydrogenation of active olefin **5** by Hantzsch ester **3** to produce **6** through self-catalysis by decreasing the HOMO–LUMO energy gap between **3** and **5** respectively. Highly chemoselective synthesis of cascade hydrogenated products **6** over bis-adduct **7** formation from reactants **1a**, **3** and **5** can be explained by using the HOMO–LUMO energy gaps and enthalpy differences of reactants and products. Recently we published complete mechanistic information about this type of self-catalyzed chemoselective reductive alkylation of 1,3-dione **1a** with **2** and **3** under **4a**-catalysis through PM3 calculations.[3h] For the reductive alkylation of 1,3-diones **1** with **2** and **3** under amine/amino acid **4**-catalysis, the 2-hydroxy group is not essential as demonstrated in our previous work.[3h]

In the subsequent third step, acid-catalyzed oxy-Michael–dehydration of **6** *via* the most likely possible intermediate **14** leads to the formation of one-pot product **10**. In the alternative fourth step, self-catalyzed reaction of **6** with diazomethane leads to the formation of **11**, which on treatment with $K_2CO_3$ generates the expected one-pot product **10** *via* most likely possible intermediate **15**.

## Conclusions

In summary, for the first time we have developed multi-catalysis technology for the synthesis of highly substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-diones **6**, 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones **10** and 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enones **11** from simple starting materials *via* cascade O–H, OM–DH, O–H–OM–DH, O–H–A and O–H–A–OM–DH reactions under combinations of aniline-, self-, base- and Brønsted-acid catalysis. The cascade O–H reaction proceeds in good yields with high selectivity using only 5 mol% of aniline as the catalyst. Furthermore, we have for the first time demonstrated the application of bio-mimetic aniline-catalysis for the olefination of aldehydes **2** with CH-acids like cyclopentane-1,3-dione **1a**. Further work is in progress to utilize novel O–H, OM–DH,




**Scheme 4** Proposed catalytic cycle for the multi-catalysis reactions.

O–H–OM–DH, O–H–A and O–H–A–OM–DH reactions and cascade products **6**, **10** and **11** in synthetic chemistry.

## Experimental

### General methods

The [1]H NMR and [13]C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for [1]H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for [13]C NMR. In the [13]C NMR spectra, the nature of the carbons (C, CH, $CH_2$ or $CH_3$) was determined by recording the DEPT-135 experiment, and is given in parentheses. The coupling constants $J$ are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on a Shimadzu GCMS-QP2010 mass spectrometer. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. LCMS mass spectra were recorded on either a VG7070H mass spectrometer using the EI technique or a Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on a JASCO FT/IR-5300 and a Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonius MACH 3 diffractometer using graphite monochromated, Mo-Kα ($\lambda = 0.71073$ Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube ($\lambda = 0.71073$ Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. $H_2SO_4$ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

### Materials

All solvents and commercially available chemicals were used as received.

### General experimental procedures for the multi-catalysis reactions

**Aniline-catalyzed cascade olefination–hydrogenation reactions.** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **2**, 0.3 mmol of 1,3-dione **1a** and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of dichloromethane, and then the catalyst aniline **4c** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1 to 6. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up, and pure cascade products **6** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

**Acid-catalyzed cascade oxy-Michael–dehydration reactions of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-diones 6.** A solution of substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-diones **6** (0.1 mmol) and *p*-TSA **9f** (0.03 mmol, 30 mol%) in dichloromethane (1.0 ml) was stirred at 45 °C for 9 to 18 h. After cooling, the reaction mixture was washed with water and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure products **10** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

**Amino acid– or aniline–*p*-TSA-catalyzed one-pot double cascade olefination–hydrogenation–oxy-Michael–dehydration reactions.** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **2**, 0.3 mmol of 1,3-dione **1a** and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of dichloromethane, and then the catalyst amino acid **4a** or aniline **4c** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 3. After evaporation of the solvent completely, to the crude reaction mixture was added 1.0 mL of toluene solvent and *p*-TSA **9f** (0.09 mmol, 30 mol%) and the reaction mixture was stirred at 90 °C for 10 h. The crude reaction mixture was worked up with aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. Pure one-pot products **10** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

**General procedure for the direct organocatalytic one-pot synthesis of 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enones 11.** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **2**, 0.3 mmol of 1,3-dione **1a** and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of dichloromethane, and then the catalyst aniline **4c** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 6. After evaporation of the solvent completely, to the crude reaction mixture was added 15 equivalents of an ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for 2 h. After evaporation of the solvent and excess diazomethane completely in fume hood, the crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure one-pot products **11** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

**General procedure for the multi-catalysis synthesis of 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones 10.** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.9 mmol of the aldehyde **2**, 0.3 mmol of 1,3-dione **1a** and 0.3 mmol of Hantzsch ester **3** was added 1.0 mL of dichloromethane, and then the catalyst aniline **4c** (0.015 mmol, 5 mol%) was added and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 3. After evaporation of the solvent completely, to the crude reaction mixture was added 15 equivalents of an ethereal solution of diazomethane and the reaction mixture was stirred at room temperature for the 2 h. After evaporation of the solvent and excess diazomethane completely in a fume hood, to the crude reaction mixture was added 3 equivalents of $K_2CO_3$ and solvent ethanol and the reaction mixture was stirred at room temperature for the 18 h. The crude reaction mixture was worked up with aqueous $NH_4Cl$ solution, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. Pure one-pot products **10** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

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