3.1 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. As such, the development of new and more general catalytic methods for their preparation is of significant interest. Recently nucleophilic amine-catalysis is emerging for the reactions of 2-hydroxy-benzaldehyde with substituted enones under 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-2H-cyclopenta[b]chromen-1-ones in moderate to good yields (Scheme 1). But interestingly, there is no direct method for the synthesis of functionalized 2,3,4,9-tetrahydro-xanthen-1-ones and 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones from substituted 2-hydroxy-benzaldehydes and enones, which are highly useful starting materials in natural product synthesis (Scheme 1).

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-2H-cyclopenta[b]chromen-1-ones by using direct organocatalytic sequential one-pot three-component reductive alkylation/oxy-Michael/dehydration (TCRA/OM/DH) and three-component reductive alkylation/alkylation/oxy-Michael/dehydration (TCRA/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 three-component reductive alkylation (TCRA) and Brønsted acid-catalyzed cascade oxy-Michael/dehydration (OM/DH) or combination of amine- or amino acid-catalyzed cascade three-component reductive alkylation (TCRA) 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-2H-cyclopenta[b]chromen-1-ones are useful starting materials for the synthesis of natural products and their analogues.\textsuperscript{17}

In continuation of our recent discovery of bio-mimetic in situ reduction of novel active olefins with Hantzsch ester \textsuperscript{15} through self-catalysis by decreasing HOMO-LUMO energy gap between olefins and Hantzsch ester \textsuperscript{15} in cascade reactions,\textsuperscript{16} we initiated our studies of the cascade TCRA reaction of cyclopentane-1,3-dione \textsuperscript{3d} with variety of 2-hydroxy-benzaldehydes \textsuperscript{37} and Hantzsch ester \textsuperscript{15} under amine- or amino acid-catalysis to furnish the reductive alkylation products \textsuperscript{41} and their applications in the synthesis of pharmaceutically useful products with good yields in one-pot (see Scheme 2).
**Scheme 2:** Combining Multi-Catalysis and Multi-Component Systems for the One-Pot Cascade Reactions.

\[
\begin{align*}
3d: & \quad n = 0, R = H \\
3e: & \quad n = 1, R = H \\
3g: & \quad n = 1, R = Me
\end{align*}
\]

**3.2 Results and Discussion**

**3.2.1 Reaction Optimization for the Multi-catalysis Reactions in One-pot:**

First we focused on the optimization for high yield synthesis of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione \(41da^*\) from 3d, 37a, 15 and 4c through amine- or amino acid-catalysis, which is precursor for our designed cascade TCRA/OM/DH reaction. For that we initiated our studies of the cascade TCRA reaction by screening a number of known and novel organocatalysts for the reductive alkylation of cyclopentane-1,3-dione 3d with 2-hydroxy-benzaldehyde 37a and Hantzsch ester 15 as shown in Table 1. Based on our previous experience in the amino acid-promoted reductive alkylation of 1,3-diones with aldehydes and Hantzsch ester via cascade TCRA reactions,\(^{16}\) we chose \(\text{CH}_2\text{Cl}_2\) as solvent; and then we decided to investigate the catalyst effect on cascade TCRA reaction of 3d, 37a and 15. It is well established that self-catalyzed reaction of

\(^*\)In all compounds denoted 41xy, \(x\) is incorporated from reactant CH-acids 3 and \(y\) is incorporated from the reactant salicyladehydes 37.
cyclopentane-1,3-dione 3d with 3 equiv. of 2-hydroxy-benzaldehyde 37a furnished only the unexpected bis-adduct 42da without the expected olefination product 2-(2-hydroxy-benzylidene)-cyclopentane-1,3-dione 40da (result not shown in Table 1). The same reaction under proline-catalysis also furnished only the bis-adduct 42da without the product 2-(2-hydroxy-benzylidene)-cyclopentane-1,3-dione 40da, with reduced reaction time (result not shown in Table 1). Interestingly, proline-catalyzed reaction of cyclopentane-1,3-dione 3d and 3 equiv. of 2-hydroxy-benzaldehyde 37a with Hantzsch ester 15 furnished the expected reductive alkylation product 41da in 80% yield accompanied by the bis-adduct 42da in 20% yield after 28 h at 25 °C in CH2Cl2 as shown in Table 1, entry 1. These preliminary results prompted us to investigate the catalyst effect on in situ trapping of olefination product of cyclopentane-1,3-dione 3d with 2-hydroxy-benzaldehyde 37a through bio-mimetic hydrogenation as shown in Table 1. Interestingly, proline-catalyzed cascade TCRA reactions of 3d, 37a and 15 are catalyst dependent reactions as shown in Table 1. Simple amino acid glycine 4f also catalyzed the cascade TCRA of 3d, 37a and 15 but result is not superior as compared to proline-catalysis (Table 1, entry 2). The cascade TCRA reaction of 3d, 37a and 15 catalyzed by simple amines like benzylamine 4h, piperidine 4i and pyrrolidine 4b in CH2Cl2 are also not superior as compared to proline-catalysis with respect to yields as shown in Table 1, entries 4-6. Interestingly, the reaction rate for cascade TCRA under primary amine, benzylamine 4h-catalysis is 7-fold enhanced compare to other amine catalysts 4b, 4i or amino acid catalyst 4c, 4f as shown in Table 1. To increase the dynamics of the cascade TCRA reaction without generating the by-product of bis-adduct 42da, 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. 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 all compounds denoted 40xy and 42xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicylaldehyde 37.
In a similar fashion, aniline should catalyze olefination reaction under non-aqueous conditions. Here we show that the dynamics of the cascade TCRA reaction can be significantly accelerated by using aniline as a nucleophilic catalyst.

**Table 1:** Effect of Catalyst on the Direct Amino Acid or Amine-Catalyzed Reductive Alkylation of 3d with 37a and 15

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst 4 (5 mol%)</th>
<th>time (h)</th>
<th>conversion (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>products yield (%)&lt;sup&gt;c&lt;/sup&gt; 41da</th>
<th>42da (Ar = 2-OHC6H4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>proline 4c</td>
<td>28</td>
<td>&gt;99</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>glycin 4f</td>
<td>48</td>
<td>75</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>aniline 4g</td>
<td>2</td>
<td>&gt;99</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>benzylamine 4h</td>
<td>4</td>
<td>&gt;99</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>piperidine 4i</td>
<td>24</td>
<td>&gt;95</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>pyrrolidine 4b</td>
<td>24</td>
<td>&gt;95</td>
<td>80</td>
<td>15</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out in solvent (0.3 M) with 3.0 equiv of 37a and 1.0 equiv of 15 relative to the 3d (0.3 mmol) in the presence of 5 mol% of catalyst.

<sup>b</sup> Conversion based on TLC analysis. <sup>c</sup> Yield refers to the column purified product.

Surprisingly, the cascade TCRA reaction of 3d, 37a and 15 in CH2Cl2 under 5 mol% of aniline-catalysis furnished the expected hydrogenated reductive alkylation product 41da in 80% yield accompanied with 15% yield of bis-adduct 42da within 2 h at 25 °C (Table 1, entry 3). Interestingly, cascade TCRA reaction rate for aniline-catalysis is 14-fold enhanced compared to proline- or secondary amines-catalysis as shown in Table 1.
Figure-1: $^1$H NMR and $^{13}$C NMR Spectrum of Product 41da.
We envisioned the optimized condition to be mixing the 3 equiv. of 2-hydroxybenzaldehyde 37a with cyclopentane-1,3-dione 3d and Hantzsch ester 15 at 25 °C in CH₂Cl₂ under 5 mol% of aniline-catalysis to furnish the hydrogenated product, 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione 41da* in 80% yield (Table 1, entry 3). A mechanistic aspect of this selective cascade TCRA 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-2H-cyclopenta[b]chromen-1-one 38da* from 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione 41da 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 35a is the suitable Brønsted acid-catalyst for cascade OM/DH reaction compared to other Brønsted acid catalysts 35a-h or Lewis acid catalyst 35c. Treatment of 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione 41da with 30 mol% of HClO₄ in CH₂Cl₂ at 25 °C furnished the expected cascade product 38da in only 20% yield, but interestingly there is no cascade reaction under BF₃.OEt₂ catalysis even at hot conditions (Table 2, entries 1-2). Cascade OM/DH reaction of 41da in CH₂Cl₂ at 25 °C under CH₃SO₃H-catalysis furnished 38da in only 45% yield, but interestingly there is no cascade reaction under CF₃SO₃H-catalysis (Table 2, entries 3-4). (+)-Camphor sulfonic acid catalyzed the cascade OM/DH reaction of 41da to furnish the product 38da with 70% yield in CH₂Cl₂ at 25 °C for 48 h (Table 2, entry 5). Interestingly, same reaction under p-TSA catalysis furnished the expected product 38da in 80% yield (Table 2, entry 7). Phosphoric acid-catalysis for the synthesis of cascade product 38da is not superior as compare to p-TSA catalysis (Table 2, entries 9-10). We envisioned the optimized condition to be mixing the 30 mol% of p-TSA 35a with 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione 41da at 45 °C in CH₂Cl₂ for 10 h to furnish the cascade

---

17
In all compounds denoted 41xy and 38xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicyldehydes 37.

OM/DH product, 3,9-dihydro-2H-cyclopenta[b]chromen-1-one 38da in 90% yield (Table 2, entry 8).

Table 2: Reaction Optimization for the Brønsted acid-Catalyzed Cascade OM/DH Reaction of 41da

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst 35 (30 mol%)</th>
<th>solvent (0.1 M)</th>
<th>time (h)</th>
<th>temperature (°C)</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt; 38da</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HClO&lt;sub&gt;4&lt;/sub&gt; 35b</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>48</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·OEt&lt;sub&gt;2&lt;/sub&gt; 35 c</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>48</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;3&lt;/sub&gt;H 35 d</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>48</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;3&lt;/sub&gt;H 35 e</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>48</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>(+)-CSA 35 f</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>48</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>p-TSA 35 a</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>10</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>p-TSA 35 a</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>16</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>p-TSA 35 a</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>10</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>(PhO)&lt;sub&gt;2&lt;/sub&gt;PO&lt;sub&gt;2&lt;/sub&gt;H 35 g</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>(R)-BNDHP 35 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>48</td>
<td>25</td>
<td>50</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out in solvent (0.1 M) with 30 mol% of catalyst 35.<sup>b</sup>

Yield refers to the column purified product. <sup>c</sup>(R)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate 35h and catalyst 35h was taken as 5 mol%.

After successful optimization of the aniline-catalyzed cascade TCRA 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. Cascade TCRA reaction of three equiv. of 2-hydroxy-benzaldehyde 37a with cyclopentane-1,3-dione 3d and Hantzsch ester 15 under proline-catalysis in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C for
28 h furnished the expected cascade product 41da, which on evaporation of the solvent CH₂Cl₂ and treatment with 30 mol% of p-TSA 35a at 100 °C in toluene solvent for 10 h furnished the expected sequential one-pot TCRA/OM/DH product 38da in >99% conversion with 50% yield as shown in Table 3, entry 1. Combination of two cascade TCRA and OM/DH reactions under aniline- and p-TSA-catalysis in one-pot was also demonstrated to furnish the sequential one-pot product 38da in >99% conversion with 50% yield as shown in Table 3, entry 4. Interestingly, combination of two cascade TCRA and OM/DH reactions under proline or aniline- and p-TSA-catalysis in CH₂Cl₂ solvent did not furnish the sequential one-pot product 38da with >99% conversion, but furnished only with ≤50% conversion at 45 °C for 48 h as shown in Table 3, entry 3 may be due to the strong acid-base interactions of p-TSA with the pyridine byproduct of 2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester 43.

**Table 3**: Reaction Optimization for the Organo-/Brønsted acid-Catalyzed One-Pot Synthesis of 38da

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (5 mol%)</th>
<th>time (h)</th>
<th>solvent (0.3 M)</th>
<th>temperature (°C)</th>
<th>time (h)</th>
<th>conversion (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>proline 4c</td>
<td>28</td>
<td>CH₃C₆H₅</td>
<td>100</td>
<td>10</td>
<td>&gt;99</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>proline 4c</td>
<td>28</td>
<td>CH₃C₆H₅</td>
<td>90</td>
<td>10</td>
<td>&gt;99</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>proline 4c</td>
<td>28</td>
<td>CH₂Cl₂</td>
<td>45</td>
<td>48</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>aniline 4g</td>
<td>2</td>
<td>CH₃C₆H₅</td>
<td>100</td>
<td>10</td>
<td>&gt;99</td>
<td>50</td>
</tr>
</tbody>
</table>

* See Experimental Section. *b* Conversion based on TLC analysis. *c* Yield refers to the column purified product.
3.2.2 Diversity-Oriented Synthesis of Reductive Alkylation Products 41da-41di: With the three cascade optimized reaction conditions in hand, the scope of the aniline-catalyzed TCRA, ρ-TSA-catalyzed OM/DH and aniline-ρ-TSA-catalyzed TCRA/OM/DH cascade reactions was investigated with cyclopentane-1,3-dione 3d, various functionalized 2-hydroxy-benzaldehydes 37a-i and Hantzsch ester 15 as shown in Tables 4 and 5. A series of functionalized 2-hydroxy-benzaldehydes 37a-i (3 equiv.) were reacted with cyclopentane-1,3-dione 3d and Hantzsch ester 15 catalyzed by 5 mol% of aniline at 25 °C in CH₂Cl₂ (Table 4). The substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones 41da-41di* were obtained as single isomers (tautomer) with excellent yields. The cascade reaction of cyclopentane-1,3-dione 3d with 2,3-dihydroxy-benzaldehyde 37b and 15 furnished the reductive alkylation product 41db as 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 41da-41di from 3d, 37a-i and 15 at 25 °C under aniline-catalysis has taken shorter reaction times (1 to 5 h), compared to proline-catalysis as shown in Tables 1 and 4. Interestingly, aniline-catalyzed reductive alkylation reaction of cyclopentane-1,3-dione 3d with 5-chloro-2-hydroxy-benzaldehyde 37g/5-bromo-2-hydroxy-benzaldehyde 37h and Hantzsch ester 15 generated the expected cascade products 41dg/41dh in excellent yields with very good selectivity (Table 4). Structure and regio-chemistry of cascade products 41da-di were confirmed by NMR analysis [for example see Fig. 1 & 2] and also by X-ray structure analysis on 41dd as shown in Scheme 3. Interestingly, these 2-alkyl-cyclopentane-1,3-diones 41 existed as an enol in both solid and solution state may be due to the strong intermolecular hydrogen bonding and this same concept is observed in many other 1,3-diketones. 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 41 can hardly be determined in solution, due to the rapid keto-enol and enol-enol tautomerism. Therefore, in 2-alkyl-cyclopentane-1,3-dione compounds 41da-di, we observed that 13C NMR
shows two of CH₂ carbons α to the carbonyls (C=O) including the two carbonyl carbons [2 x CH₂ and 2 x C=O] are poor resolution even after 2000 scans on

In all compounds denoted 41xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicyladehydes 37.

standard sampling [see Fig. 1 & Fig. 2]. This same kind of ¹³C NMR pattern was observed for the other 1,3-diketones in the literature due to the rapid keto-enol and enol-enol tautomerism.²¹

**Table 4:** Chemically Diverse Libraries of 2-(2-Hydroxy-benzyl)-cyclopentane-1,3-diones 41

---

²¹ In all compounds denoted 41xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicyladehydes 37.
Synthesis of Highly Functionalized Cyclopenta [b]chromen-1-ones via MCC Reactions

\[
\begin{align*}
3d + \text{Fg-CHO} + 15, E = \text{CO}_2\text{Et} & \rightarrow \text{41da-df} \\
\text{Aniline 4g (5 mol\%)} & \text{CH}_2\text{Cl}_2 (0.3 \text{ M}) \\
\text{RT, 1-5 h} & \text{80\% (41da) 85\% (41db) 80\% (41dc)} \\
\text{85\% (41dd) 85\% (41de) 80\% (41df)} \\
\text{85\% (41dg) 80\% (41dh) 80\% (41di)}
\end{align*}
\]

\[\hat{\text{a}} \text{ Yield refers to the column purified product.}\]

\[\text{41db}\]

\[\text{41db}\]

\[\text{41db}\]
Figure-2: $^1$H NMR and $^{13}$C NMR Spectrum of Product 41db.

Scheme 3: Crystal Structure of 2-(2-Hydroxy-5-methyl-benzyl)-cyclopentane-1,3-dione (41dd).
3.2.3 Diversity-Oriented Synthesis of Heterocycles 38da-38di: With the success of cascade synthesis of highly functionalized 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones 41, we continued our investigation for the generation of highly functionalized diversity oriented library of cascade 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones 38 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 41da-di*. Cascade OM/DH reaction of 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones 41da-di under acid-catalysis furnished the expected 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones 38da-di* in 75-99% yield with high selectivity (Table 5). Unexpectedly, cascade product 38db only was obtained with moderate yield from 41db and 35a. Interestingly, all the 4- and 5-substituted 2-(2-hydroxy-aryl)-cyclopentane-1,3-diones 41dc-di furnished the expected products 38dc-di with very good yields as single isomer in acid-catalyzed OM/DH cascade reactions as shown in Table 5. Structure and regio-chemistry of cascade products 38 were confirmed by NMR analysis [for example see Fig. 3] and also by X-ray structure analysis on 38da as shown in Scheme 4.20

Table 5: Chemically Diverse Libraries of 3,9-Dihydro-2H-cyclopenta[b]chromen-1-ones 38

---

In all compounds denoted 41xy and 38xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicylaldehydes 37.
Synthesis of Highly Functionalized Cyclopenta[bf]chromen-1-ones via MCC Reactions

\[ \text{41da-di} \xrightarrow{\text{p-TSA 35a (30 mol\%)}} \text{38da-di} \]

- 90% (38da)
- 75% (38db)<sup>b</sup>
- 95% (38dc)
- 90% (38dd)
- 95% (38de)
- 86% (38df)
- 95% (38dg)
- 99% (38dh)
- 95% (38di)

<sup>a</sup> Yield refers to the column purified product.  <sup>b</sup> Reaction performed at 100 °C for 8 h in the toluene solvent.
Figure-3: $^1$H NMR and $^{13}$C NMR Spectrum of Product 38di.

3.2.4 Diversity-Oriented Synthesis of 2-Alkyl-3-Methoxy-Cyclopent-2-enones 44da-44di: With synthetic applications in mind, we extended the three-component cascade TCRA reactions into a novel aniline/self-catalyzed four-component TCRA/A reaction of 3d, 37a-i and 15 with ethereal solution of diazomethane in one-pot as shown in Table 6. One-pot products 44 were constructed in very good yields with high chemoselectivity as shown in Table 6 and this method will be showing much impact on 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. Highly substituted 2-alkyl-3-methoxy-cyclopent-2-enones 44 have gained importance in recent years as starting materials and intermediates for the synthesis of prostaglandin analogs, which possess a wide range of physiological and pharmacological properties.

Cascade TCRA reaction of 3d, 37a and 15 under 5 mol% of aniline-catalysis furnished the substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-dione 41da in good yield, which on treatment with ethereal diazomethane at 0 °C to 25 °C for 2 h furnished the chemoselectively one-pot TCRA/A product 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone 44da* in 85% yield as shown in Table 6. Interestingly, phenol group is not methylated under these conditions. Acidic or highly enolizable nature of 2-aryl-cyclopentane-1,3-diones 41 is the main driving force to observe high chemoselective O-alkylation reaction with diazomethane. Generality of the aniline-/self-catalyzed chemo-

*In all compounds denoted 44xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicyladehydes 37.

selective one-pot TCRA/A reaction was further confirmed by three more examples using 2,3-dihydroxy-benzaldehyde 37b, 5-chloro-2-hydroxy-benzaldehyde 37g and 2-hydroxy-naphthalene-1-carbaldehyde 37i to furnish the expected 2-(2,3-dihydroxy-
benzyl)-3-methoxy-cyclopent-2-enone $44\text{db}$ in 65% yield, 2-(5-chloro-2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone $44\text{dg}$ in 80% yield and 2-(2-hydroxy-naphthalen-1-ylmethyl)-3-methoxy-cyclopent-2-enone $44\text{di}$ in 85% yield, respectively as shown in Table 6. For the pharmaceutical applications, diversity-oriented library of enones $44\text{a}$ could be generated by using our aniline-/self-/self-catalyzed, chemoselective one-pot TCRA/A reaction.

**Table 6**: Chemically Diverse Libraries of 2-(2-Hydroxy-benzyl)-3-methoxy-cyclopent-2-enones $44\text{a,b}$

\[
\begin{align*}
\text{3d} & + \text{37a-i} + \text{15, } E = \text{CO}_2\text{Et} \\
& \overset{1)}{\text{Aniline 4g (5 mol%)}} \quad \text{CH}_2\text{Cl}_2 (0.3 \text{ M}) \\
& \quad \text{25 °C, 1-5 h} \\
& \overset{2)}{\text{CH}_3\text{N}_2 (15 \text{ equiv})} \\
& \quad \text{Et}_2\text{O (0.08 M)} \\
& \quad 0 \text{ °C to 25 °C, 2 h} \\
& \rightarrow 44\text{da-di}
\end{align*}
\]

\[
\begin{align*}
& \text{85% (44da)} \\
& \text{96% (44da)}^{c}
\end{align*}
\]

\[
\begin{align*}
& \text{65% (44db)} \\
& \text{80% (44dg)} \\
& \text{85% (44di)}
\end{align*}
\]

\[\text{a See Experimental Section. b Yield refers to the column purified product. c Yield represents only etherification reaction.}\]
Figure-4: $^1$H NMR and $^{13}$C NMR Spectrum of Product $44\text{da}$.

After successful chemoselective synthesis of 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enone $44\text{da}^*$ in good yield, we decided to test the acid/base effect on this cascade product $44\text{da}$. Treatment of $44\text{da}$ with either acid ($p$-TSA) or base ($K_2\text{CO}_3$) at
room temperature furnished the expected 3,9-dihydro-2H-cyclopenta[b]chromen-1-one 38da* in good yield as shown in Scheme 5. Interestingly this same reaction when performed in one-pot as four-component, multi-catalysis (aniline-, self-, self- and base-catalysis) of 3d, 37a, 15 and CH₂N₂ furnished the one-pot product 38da in 68% yield as shown in Scheme 5. Even though overall yield of one-pot product 38da may be less compared to Table 5, this multi-component/multi-catalysis strategy will show much effect on the synthesis of highly functionalized small molecules like 38 and 44.


3.2.5 Diversity-Oriented Synthesis of Heterocycles 38ga-38gi: After successful demonstration of the cascade TCRA, TCRA/A, TCRA/OM/DH and TCRA/A/OM/DH reactions on cyclopentane-1,3-dione 3d with 37, 15 and 4, then we decided to test the same cascade reactions on other 1,3-diones like cyclohexane-1,3-dione 3e and dimedone 3g. Interestingly, cascade TCRA reaction of 3e, 37a and 15 under proline 4c- or aniline 4g-catalysis did not furnish the expected pure product 2-(2-hydroxy-benzyl)-cyclohexane-1,3-dione 41ca* and the reaction was not clean. But the
same cascade TCRA reaction with 3g, 37a and 15 under proline 4c- or aniline 4g-catalysis furnished the expected product 2-(2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione 41ga in only 65% yield, which on acid-catalysis furnished the expected 3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one 38ga* in very good yield as shown in Table 7. Interestingly, cascade product 41ga 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 45ga* (L-152,804) in 20% yield, which is useful as an orally active and selective neuropeptide Y Y5 receptor antagonist. But the pure product, L-152,804 was obtained only after two step TCRA and OM/DH reactions, because separation of L-152,804 from 41ga is a tedious job due to the same Rf in TLC plate. In the reaction of 3g, 37a and 15 under 4g-catalysis, the initial byproduct 45ga (L-152,804) was unchanged after heating with p-TSA 35a in CH2Cl2. Generality of the aniline- and acid-catalyzed chemoselective cascade TCRA and OM/DH reactions of 3g with 37 and 15 was further confirmed by three more examples using 2,3-dihydroxy-benzaldehyde 37b, 5-nitro-2-hydroxy-benzaldehyde 37f and 5-bromo-2-hydroxy-benzaldehyde 37h to furnish the expected 2-(2,3-dihydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione 41gb in 70% yield, 2-(2-hydroxy-5-nitro-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione 41gf in 75% yield and 2-(5-bromo-2-hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione 41gh in 85% yield and 5-hydroxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one 38gb in 98% yield, 3,3-dimethyl-7-nitro-2,3,4,9-tetrahydro-xanthen-1-one 38gf in 99% yield and 7-bromo-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one 38gh in 90% yield, respectively as shown in Table 7.

*In all compounds denoted 41xy, 38xy and 45xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicyladehydes 37.

Table 7: Direct Organocatalytic Synthesis of 2-(2-Hydroxy-benzyl)-5,5-dimethyl-cyclohexane-1,3-diones 41 and 3,3-Dimethyl 2,3,4,9-tetrahydro-xanthen-1-ones 38a,b
Synthesis of Highly Functionalized Cyclopenta[b]chromen-1-ones via MCC Reactions

\[
\text{Aniline 4g (5 mol\%)} \\
\text{CH}_2\text{Cl}_2 (0.3 \text{ M}) \\
25 \degree \text{C}, 2 - 10 \text{ h}
\]

\[
\text{p-TSA 35a (30 mol\%)} \\
\text{CH}_2\text{Cl}_2 (0.3 \text{ M}) \\
45 \degree \text{C}, 5 - 10 \text{ h}
\]

\[
\begin{array}{cccc}
\text{OH} & \text{OH} & \text{O}_2\text{N} & \text{Br} \\
65\% \ (41\text{ga})^c & 70\% \ (41\text{gb})^d & 75\% \ (41\text{gf}) & 85\% \ (41\text{gh})
\end{array}
\]

\[
\begin{array}{cccc}
\text{OH} & \text{OH} & \text{OH} & \text{OH} \\
90\% \ (38\text{ga}) & 98\% \ (38\text{gb}) & 99\% \ (38\text{gf}) & 90\% \ (38\text{gh})
\end{array}
\]

\[
\begin{array}{cccc}
\text{OH} & \text{OH} & \text{OH} & \text{OH} \\
20\% \ (45\text{ga} \ (L-152,804))^c
\end{array}
\]

\(^a\) 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 41\text{ga} in aniline-catalyzed reaction of 3g, 37a and 15. \(^d\) 23\% of 38\text{gb} was accompanied as by-product with 41\text{gb} in aniline-catalyzed reaction of 3g, 37b and 15.
Syrhesis of Highly Functionalized Cyclopenta [b]chromen-1-ones via MCC Reactions

Figure-5: $^1$H NMR and $^{13}$C NMR Spectrum of Product 41ga.
Figure-6: $^1$H NMR and $^{13}$C NMR Spectrum of Product 38ga.
Figure-7: $^1$H NMR and $^{13}$C NMR Spectrum of Product 45ga.
Interestingly, we could not see the formation of unexpected byproducts like L-152,804 analogs in the above three reactions. But, the cascade product 41gb* was accompanied with the byproduct 5-hydroxy-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one 38gb* in 23% yield. Recently, 5,5-dimethylcyclohexane-1,3-dione derivatives 41ga-41gi were evaluated for their biological activities like anti-ischemic agents, anti-hypertensive and anti-psychotics.\(^{24}\)

\[
\text{3g} + \text{37a} \overset{\text{Morpholine 4 (20 mol\%)}\, \text{EtOH (0.5 M)}\, 25^\circ\, \text{C}, 2\, \text{h}}{\longrightarrow} \text{45ga} \quad \text{yield: 81%}
\]

9-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one 45ga is an useful compound as an orally active and selective neuropeptide Y Y5 receptor antagonist, accompanied as a byproduct in TCRA reaction of dimedone 3g, salicylaldehyde 37a and Hantzsch ester 15. With the pharmaceutical applications of product 45ga* (L-152,804) in mind, we optimized the condition for the synthesis of this useful compound in very good yields under eco-friendly conditions as shown in eq. 10. The reaction of dimedone 3g and 2-hydroxy benzaldehyde in the presence of morpholine furnished the product 45ga in 2h with 81% yield as shown in eq. 10.

### 3.3 Mechanistic Insights

The possible reaction mechanism for the aniline-, self-, acid- and base-catalyzed chemoselective synthesis of cascade products 41, 38 and 44 through reaction of cyclopentane-1,3-dione 3d, 2-hydroxy-benzaldehydes 37, Hantzsch ester 15 and diazomethane is illustrated in Scheme 6. This catalytic sequential one-pot,

---

*In all compounds denoted 41xy, 38xy and 45xy, x is incorporated from reactant CH-acids 3 and y is incorporated from the reactant salicyldehydes 37.*

---

36
double cascade is a four component reaction comprising of cyclopentane-1,3-dione 3d, 2-hydroxy-benzaldehydes 37, Hantzsch ester 15, diazomethane and a simple catalyst, aniline 4g. In the first step (Scheme 6), the catalyst 4g activates component 37 by most likely imine formation, which then selectively adds to the cyclopentane-  

Scheme 6: Proposed Catalytic Cycle for the Multi-Catalysis Reactions.

1,3-dione 3d via a Mannich and amine elimination reaction to generate active olefin 40 (46 → 47 → 40). The following second step is bio-mimetic hydrogenation of active olefin 40 by Hantzsch ester 15 to produce 41 through self-catalysis by decreasing HOMO-LUMO energy gap between 15 and 40 respectively. Highly chemoselective synthesis of cascade hydrogenated products 41 over the bis-adduct 42 formations from reactants 3d, 15 and 40 can be explained by using HOMO/LUMO energy gaps and enthalpy differences of reactants and products.
Recently we published the complete mechanistic information about this type of self-catalyzed chemoselective reductive alkylation of 1,3-dione 3d with 37 and 15 under 4c-catalysis through PM3 calculations.\textsuperscript{12} For the reductive alkylation of 1,3-diones 3 with 37 and 15 under amine/amino acid 4-catalysis, 2-hydroxy group is not essential as demonstrated in our previous work.\textsuperscript{12}

In the subsequent third step, acid-catalyzed oxy-Michael/dehydration of 41 via most likely possible intermediate 48 leads to the formation of one-pot product 38. In the alternative fourth step, self-catalyzed reaction of 41 with diazomethane leads to the formation of 44, which on treatment with $\text{K}_2\text{CO}_3$ generates the expected one-pot product 38 via most likely possible intermediate 49.

### 3.4 Conclusion

In summary, for first time we have developed the multi-catalysis technology for the synthesis of highly substituted 2-(2-hydroxy-benzyl)-cyclopentane-1,3-diones 41, 3,9-dihydro-2H-cyclopenta[b]chromen-1-ones 38 and 2-(2-hydroxy-benzyl)-3-methoxy-cyclopent-2-enones 44 from simple starting materials via cascade TCRA, OM/DH, TCRA/OM/DH, TCRA/A and TCRA/A/OM/DH reactions under the combinations of aniline-, self-, base- and Brønsted-acid catalysis. The cascade TCRA reaction proceeds in good yields with high selectivity using only 5 mol\% of aniline as the catalyst. Furthermore, we have demonstrated the application of bio-mimetic aniline-catalysis for the olefination of aldehydes 37 with CH-acids like cyclopentane-1,3-dione 3d. Further work is in progress to utilize novel TCRA, OM/DH, TCRA/OM/DH, TCRA/A and TCRA/A/OM/DH reactions and cascade products 41, 38 and 44 in synthetic chemistry.