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# Organocatalyst-mediated Aldol–Robinson Cascade Reactions: A Convenient Synthesis of Substituted Cyclohex-2-enones

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A convenient organocatalytic process for the chemoselective synthesis of substituted cyclohex-2-enones was developed. The cascade reaction involves a remarkable Michael addition of an acyclic ketone-based enamine onto unmodified enones. The enamine-mediated aldol–Robinson cascade reactions of aromatic and aliphatic aldehydes with acetone produced substituted cyclohex-2-enones in moderate to high yields under mild reaction conditions.

In recent years, secondary amine catalyzed reactions have drawn much attention. Most research in this area has been focused on the development of novel methodologies for asymmetric aldol reactions or conjugated additions.[1]

Enamine-mediated Michael reactions, however, have been very restricted, particularly for the intermolecular version. To the best of our knowledge, the enamine-mediated conjugate addition of unactivated ketones and unmodified enones is very rare and has only been presented very recently by Wang and Li independently.[2] Additionally, two other reports have only mentioned such transformations as minor side-reactions.[3]

During the course of our research, we have been attracted by the enone side-products **5** produced by enamine-mediated aldol reactions (Figure 1). We were intrigued by the possibility that the in situ generated iminium form of the enone side-products **4** could be utilized as excellent Michael acceptors for intermolecular Michael reactions or Robinson annulations to provide substituted cyclohex-2-enones, a family of biologically active molecules and important synthetic building blocks (Figure 1).[4]

In our preliminary investigations, we employed 4-hydroxybenzaldehyde (**7**) as the model substrate and pyrrolidine/propionic acid as the cocatalysts.[5] Under 20 °C, the reaction provided approximately 1:3.76 molar ratio of enone **9** and the aldol–Robinson product cyclohex-2-enone **10** (Entry 1, Table 1).

As depicted in our proposed cascade process (Figure 1), the thermodynamically favored enone intermediate **5** is crucial for the cascade reaction, we then decided to carry out our reaction optimizations at elevated temperature to facilitate the formation of enones and complete the conversion of starting materials to the cyclohex-2-enone **10**. Under 45 °C and 50 mol % of catalysts, the reaction was dramatically improved, and only aldol–Robinson cascade product **10** was produced (Entry 2, Table 1). Furthermore, we found that reactions with lower catalytic loadings had longer reaction times and provided a lower ratio of the desired cyclohex-2-enone **10** versus the enone **9**, and consequently lower yield of **10** was obtained (Entries 3–5, Table 1). Our proposed intermediate, enone **9**, increasing in prevalence at low catalytic loading highly suggests that the cyclohex-2-enone **10** was derived from a Robinson reaction of **9**, providing further support for our proposed reaction pathway (Figure 2).

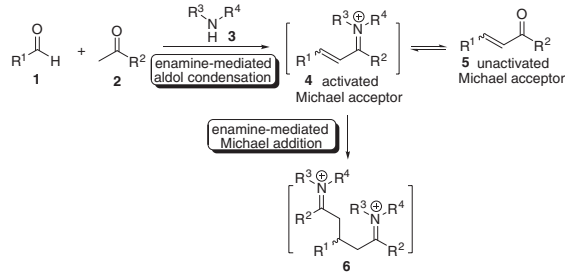
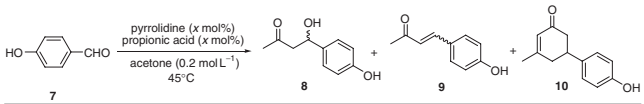



**Figure 1.** Our proposed cascade process.

**Table 1.** Reaction optimizations[a]




| Entry | Catalytic loading $x$/mol % | Time /h | **8**:**9**:**10** molar ratio[b] | Yield /%[c] |
|---|---|---|---|---|
| 1[d] | 50 | 24 | —:21:79 | 47 |
| 2 | 50 | 24 | —:—:100 | 73 |
| 3 | 30 | 24 | —:6:94 | 68 |
| 4 | 20 | 30 | —:8:92 | 66 |
| 5 | 10 | 48 | —:25:75 | 58 |

[a]All reactions were performed on a 1.0 mmol scale. [b]The molar ratios were calculated based on $^1$H NMR integrations. [c]Yield of pure and isolated product **10**. [d]The reaction was carried out under 20 °C.

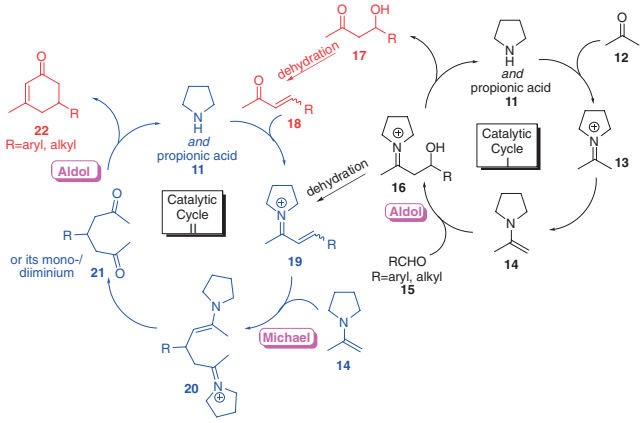
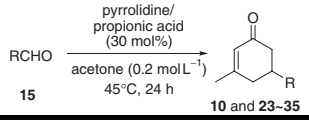



**Figure 2.** Proposed reaction mechanism for the cascade process.

In the proposed reaction mechanism (Figure 2), iminium ion intermediate **13** deprotonates into enamine **14**, which undergoes an aldol condensation with aldehyde **15** to give iminium **19**.

**Table 2.** Reaction scope of the organocatalytic cascade process[8]




| Entry | R | Products | Yields/%[a] |
|---|---|---|---|
| 1 | 4-$HOC_6H_4$ | **10** | 68[c] |
| 2[b] | 4-$CH_3OC_6H_4$ | **23** | 50 |
| 3 | 4-$(CH_3)_2NC_6H_4$ | **24** | 81 |
| 4 | 2-$CH_3OC_6H_4$ | **25** | 52 |
| 5 | 4-$ClC_6H_4$ | **26** | 90 |
| 6 | 2,6-$Cl_2C_6H_4$ | **27** | 66[c] |
| 7 | 4-$CH_3C_6H_4$ | **28** | 76 |
| 8 | 3-$HOC_6H_4$ | **29** | 62 |
| 9[d] | 4-$NO_2C_6H_4$ | **30** | 53 |
| 10 | 2-Furanyl | **31** | 52 |
| 11 | 2-Thienyl | **32** | 91 |
| 12 | 2-Pyrryl | **33** | 64 |
| 13 | 2-Naphthyl | **34** | 56 |
| 14 | Propyl | **35** | 53 |

[a]Yield of pure and isolated product. [b]50 mol % catalysts, 96 h. [c]3% and 26% of aldol condensation products were isolated in Entries 1 and 6, respectively. Prolonged reaction time only resulted in complex mixtures. [d]50 mol % catalysts, 10 h.

Alternatively, **19** could also be formed via the dehydration of $\beta$-hydroxyketone **17** followed by formation of iminium ion. The Michael addition between the acyclic ketone-derived enamine **14** and the enone iminium intermediate **19** delivers intermediate **20**, which is then hydrolyzed to form 4-substituted-2,6-heptanediones **21** (or its mono-/diiminium forms). Intramolecular aldolization (The Amagi cyclization)[6] of **21** produces the desired product **22**.

We then examined the scope of our methodology by screening structurally diverse aldehydes, as shown in Table 2. Benzaldehyde derivatives with various substituents in the *ortho*-, *meta*-, and *para*-positions of the phenyl ring all provided the corresponding cyclohex-2-enones with moderate to high yields (Entries 1–9). Remarkably, benzaldehyde derivatives with *para* and *ortho* electron-donating groups proceeded efficiently in the reaction despite the relatively low reactivity of the carbonyl group, which has been extremely rarely reported in enamine-mediated aldol reactions. Moreover, *p*-nitrobenzaldehyde[7] offered us a 53% yield of the corresponding cyclohex-2-enone derivative **30** very efficiently in only 10 h (Entry 9). This is in sharp contrast to Nhien and co-workers' recent report,[3] in which they used 100 mol % of catalyst, but only obtained a 4% yield of the cyclohex-2-enone **30** as a side product.

The substrates of this new cascade reaction were not limited to functionalized benzaldehydes. Heterocyclic aldehydes (Entries 10–12) and 1-naphthaldehyde (Entry 13) were all transformed into the corresponding cyclohex-2-enones. These results were of particular interest as cyclohex-2-enones bearing heterocycles (e.g., **32**) have shown biological activity (e.g., sedative properties).[4g]

An aliphatic aldehyde, *n*-butanal was also successfully employed in the synthesis (Entry 14), to produce (±)-celery ketone, an artificial flavoring ingredient. It should be noted that this is the first example of an organocatalytic one-step synthesis of (±)-celery ketone from inexpensive, readily available starting materials.

In summary, we have successfully developed an efficient organocatalytic aldol–Robinson cascade reaction from commercially available and inexpensive starting materials. This reaction proceeded chemoselectively to produce substituted cyclohex-2-enones in moderate to high yields. A variety of cyclohex-2-enones with different substituted groups were readily accessed. This cascade process has disclosed a novel intermolecular Michael addition that will be employed in future studies. An enantioselective version of this cascade reaction, as well as the synthetic applications of its products are currently under investigation.

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7 We thank a reviewer for the suggestion that benzaldehyde with a strong electron-withdrawing group should also be tried for the cascade process.

8 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

  