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# *L*-Lysine/imidazole-catalyzed Multicomponent Cascade Reaction: Facile Synthesis of C5-substituted 3-Methylcyclohex-2-enones

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A facile and simple route for the direct preparation of substituted 3-methylcyclohex-2-enone *via* Aldol-Robinson cascade reaction of aldehydes and acetones catalyzed by the new catalytic system of *L*-lysine/imidazole in *n*-heptane with 0.5% water was reported. A variety of substrates can participate in the process efficiently. The merits of this method included inexpensive and easily available starting materials and catalyst, the good yield of products and the straightforward work-up.

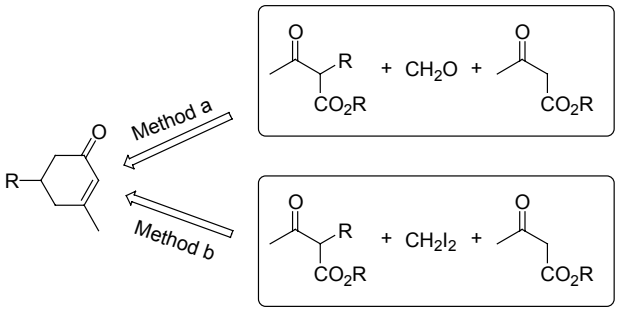
**Keywords** *L*-lysine, cascade reactions, imidazole, cyclohexanone-2-ene, aldehydes

## Introduction

Compounds containing cyclohex-2-enone exhibit significant biological activities and are widely utilized as pheromone,[1] food additives[2] and antitumor.[3] Substituted 3-methylcyclohex-2-enone structural motifs have been found in many natural products and pharmacologically active compounds.[4] In the last few years, these compounds have conventionally been prepared through Hagemann's or Knoevenagel's approach under severe reaction conditions (Scheme 1, Method a and b).[5] In 1998, Martínez and co-workers reported the reductive cyclization of 2,6-dimethyl-3,5-dicarboxyethyl-4-aryl-1,4-dihydropyridines to give the corresponding cyclohex-2-enone in 25%—40% yields using sodium and methanol as solvent.[6] Moreover, List *et al*. have transformed 4-substituted 2,6-heptandiones, which were obtained by multi-step synthesis, into cyclohex-2-enone using a primary amine-catalyzed reaction with acetic acid as the additive.[7] Although cyclohex-2-enone could be prepared by these synthetic methods, most of them suffer from harsh reaction conditions, low yield and longer synthesis step.

Recently, Multicomponent cascade reactions, where a series of reactions proceed in a defined order in one sequence, have emerged as a powerful tool that allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, and facile automation.[8] In 2000, Barbas and co-workers have reported the generation of the Wieland-Miescher ketone through domino Michael-aldol reaction of methyl vinyl ketone and 2-methyl 1,3-cyclohexanedione catalyzed by *L*-proline.[9] Since then, many studies for the development of new multicomponent cascade reactions have been reported.[10]

**Scheme 1** Synthetic route to cyclohexanone-2-ene




As a part of our continued efforts in the development of novel and efficient catalytic system, especially enzyme or organic small molecule, for cascade reaction,[11] we turned our attention to search the new catalyst for the direct synthesis of cyclohex-2-enone from available starting materials by a one-pot strategy. The previous experiments showed that *L*-lysine had good catalytic activity for the direct reaction of enone with acetones into cyclohexanone-2-ene in presence of imidazole (Scheme 2, path *a*). Promoted by these results, we envisioned that aldehyde could also be utilized as starting substrates for the synthesis of cyclohex-2-enone (Scheme 2, path *b*) *via* Aldol-Robinson cascade reaction. To the best of our knowledge, there are few reports about the catalytic systems which have the ability of catalyzing direct Aldol-Robinson cascade reactions of

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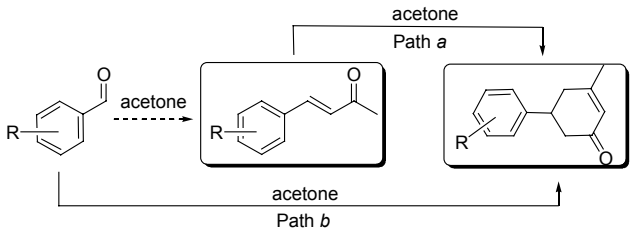
aldehyde and acetone to produce cyclohex-2-enone.[12] In this paper, we described a new catalytic system of *L*-lysine/imidazole for the direct synthesis of substituted 3-methylcyclohex-2-enone by a one-pot strategy.

**Scheme 2** Synthetic route to cyclohexanone-2-ene




## Experimental

### General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCE DMX-500 spectrometer at 400 MHz and 100 MHz in $CDCl_3$, respectively. Chemical shifts are reported relative to the internal standard of tetramethylsilane (TMS). IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. HR-MS were obtained on a Bruker 7-Tesla FT-ICR MS equipped with an electrospray source (Billelica, MA, USA).

### Syntheses

A mixture of **1a**—**1m** (0.20 mmol), acetone (0.4 mL), imidazole (0.18 mmol), *L*-lysine (0.06 mmol) and water (10 μL) was added to *n*-heptane (2 mL) and it was stirred at 50 ℃ for 36 h. After the completion of the reaction, the yields were detected by HPLC using area-external standard method.

5-(4'-Nitropheny1)-3-methylcyclohex-2-enone CAS No: 62596-10-5, **5a**: Yield: 37.9 mg (82%); light yellow solid. m.p. 131—135 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.23 (d, $J$=8.8 Hz, 2H), 7.43 (d, $J$=8.4 Hz, 2H), 6.03 (s, 1H), 3.48—3.42 (m, 1H), 2.71—2.56 (m, 4H), 2.05 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 197.6, 160.8, 150.5, 147.1, 127.7, 126.7, 124.1, 43.2, 40.5, 38.2, 24.3; IR (KBr) $v$: 3060, 3029, 1661, 1606, 1596, 1521, 1346, 853 cm$^{-1}$.

5-(3'-Nitropheny1)-3-methylcyclohex-2-enone CAS No: 10323-98-5, **5b**: Yield: 33.3 mg (72%); light yellow solid. m.p. 100—105 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.15—8.13 (m, 2H), 7.60 (d, $J$=8.0 Hz, 1H), 7.61—7.52 (m, 1H), 6.02 (s, 1H), 3.52—3.44 (m, 1H), 2.68—2.56 (m, 4H), 2.05 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 197.8, 160.9, 148.5, 145.1, 133.0, 129.8, 126.7, 122.1, 121.7, 43.3, 40.3, 38.3, 24.3; IR (KBr) $v$: 3069, 2922, 1662, 1633, 1528, 1352, 887 cm$^{-1}$.

5-(4'-Fluoropheny1)-3-methylcyclohex-2-enone CAS No: 1222312-10-8, **5c**: Yield: 22.4 mg (55%); light yellow solid. m.p. 43—47 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.22—7.12 (m, 2H), 7.06—6.96 (m, 2H), 5.96 (s, 1H), 3.33—3.25 (m, 1H), 2.58—2.46 (m, 4H), 1.99 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 198.4, 162.7, 161.2, 138.9, 128.1, 126.8, 115.0, 43.8, 39.8, 38.9, 24.1; IR (KBr) $v$: 3041, 2916, 1666, 1602, 1511, 1225, 890 cm$^{-1}$.

5-(4'-Chloropheny1)-3-methylcyclohex-2-enone CAS No: 54795-01-6, **5d**: Yield: 15.4 mg (35%); light yellow solid. m.p. 53—55 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.30 (d, $J$=8.4 Hz, 2H), 7.17 (d, $J$=8.4 Hz, 2H), 5.97 (s, 1H), 3.34—3.26 (m, 1H), 2.64—2.47 (m, 4H), 2.00 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 199.2, 161.7, 143.3, 128.8, 127.0, 126.8, 126.6, 43.9, 40.8, 39.0, 24.4; IR (KBr) $v$: 3031, 1663, 1633, 1594, 1490, 1379, 827 cm$^{-1}$.

5-(2'-Chloropheny1)-3-methylcyclohex-2-enone CAS No: 10323-89-4, **5e**: Yield: 15.8 mg (36%); light yellow solid. m.p. 61—64 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.33 (d, $J$=8.0 Hz, 1H), 7.25—7.14 (m, 2H), 7.40 (d, $J$=8.0 Hz, 1H), 5.92 (s, 1H), 3.81—3.73 (m, 1H), 2.59—2.43 (m, 4H), 1.95 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 198.5, 161.3, 142.1, 131.8, 128.4, 127.5, 127.3, 126.5, 120.6, 43.5, 40.1, 38.6, 24.3; IR (KBr) $v$: 3058, 1669, 1633, 1612, 1475, 1380, 696, 754 cm$^{-1}$. HR-MS [EI]$^+$ calcd for $C_{13}H_{13}ClO$: 220.0656; found 220.0655.

5-(3'-Chloropheny1)-3-methylcyclohex-2-enone CAS No: 10323-90-7, **5f**: Yield: 20.7 mg (47%); light yellow liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.39—7.37 (m, 2H), 7.22—7.14 (m, 2H), 5.96 (s, 1H), 3.34—3.25 (m, 1H), 2.60—2.46 (m, 4H), 2.00 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 198.7, 161.5, 140.1, 136.4, 129.9, 128.0, 127.2, 127.0, 126.4, 42.2, 37.1, 29.6, 24.3; IR (KBr) $v$: 3031, 2917, 1664, 1625, 1593, 1430, 888 cm$^{-1}$.

5-(4'-Bromopheny1)-3-methylcyclohex-2-enone CAS No: 211876-67-4, **5g**: Yield: 22.3 mg (42%); white solid. m.p. 66—69 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.47 (d, $J$=8.4 Hz, 2H), 7.13 (d, $J$=8.4 Hz, 2H), 5.99 (s, 1H), 3.33—3.26 (m, 1H), 2.66—2.48 (m, 4H), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 161.3, 142.1, 131.8, 128.4, 126.5, 120.6, 98.5, 43.5, 40.1, 38.6, 24.3; IR (KBr) $v$: 3030, 2915, 1663, 1634, 1488, 1379, 890 cm$^{-1}$.

5-(4'-Cyanopheny1)-3-methylcyclohex-2-enone **5h**: Yield: 27.4 mg (65%); light yellow solid. m.p. 55—59 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.65 (d, $J$=8.0 Hz, 2H), 7.37 (d, $J$=7.6 Hz, 2H), 6.01 (s, 1H), 3.48—3.36 (m, 1H), 2.68—2.51 (m, 4H), 2.03 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 197.73, 160.78, 148.45, 132.60, 127.57, 126.68, 118.55, 110.97, 43.31, 40.38, 38.48, 24.45; IR (KBr) $v$: 3036, 2921, 2227, 1664, 1635, 1608, 1380, 891 cm$^{-1}$. HR-MS [EI]$^+$ calcd for $C_{14}H_{13}NO$: 211.0997; found 211.0996.

5-(4'-Trifluoromethylpheny1)-3-methylcyclohex-2-enone **5i**: Yield: 46.7 mg (92%); light yellow liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.59 (d, $J$=8.0 Hz, 2H), 7.35 (d, $J$=8.0 Hz, 2H), 5.99 (s, 1H), 3.44—3.34 (m,

1H), 2.74—2.51 (m, 4H), 2.01 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 198.0, 160.9, 147.1, 131.3, 129.2, 128.8, 127.4—125.3, 122.7, 43.4, 40.5, 38.5, 24.2; IR (KBr) $v$: 3027, 2921, 1667, 1619, 1420, 1326, 1122, 891 cm$^{-1}$; HR-MS [EI]$^+$ calcd for $C_{14}H_{13}F_3O$: 254.0918; found 254.0919.

5-Pheny1-3-methylcyclohex-2-enone CAS No: 5337-88-2, **5j**: Yield: 15.6 mg (42%); light yellow liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.35 (d, $J$=7.6 Hz, 2H), 7.29—7.25 (m, 3H), 6.00 (s, 1H), 3.38—3.30 (m, 1H), 2.68—2.03 (m, 4H), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 199.8, 162.3, 144.0, 129.5, 127.7, 127.4, 127.3, 44.6, 41.5, 39.7, 25.1; IR (KBr) $v$: 3308, 3063, 3029, 1663, 1630, 1609, 1496, 1379, 758, 700 cm$^{-1}$.

5-(4'-Methylpheny1)-3-methylcyclohex-2-enone CAS No: 5337-88-2, **5k**: Yield: 6.4 mg (16%); light yellow liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.20—7.13 (m, 4H), 5.98 (s, 1H), 3.34—3.26 (m, 1H), 2.63—2.50 (m, 4H), 2.35 (s, 3H), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 199.9, 162.4, 159.2, 136.2, 128.3, 127.2, 114.8, 56.0, 44.8, 40.7, 40.0, 25.0; IR (KBr) $v$: 3024, 2949, 2921, 2853, 1666, 1611, 1568, 1515, 1379, 800 cm$^{-1}$.

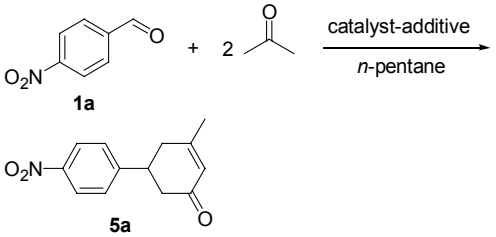
3-Methyl-5-(pyridin-3-yl)cyclohex-2-enone CAS No: 53295-89-9, **5m**: Yield: 29.2 mg (80%); light yellow solid. m.p. 60—64 ℃. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.54 (s, 1H), 8.52 (d, $J$=4.4 Hz, 1H), 7.57 (d, $J$=7.6 Hz, 1H), 7.30—7.27 (m, 1H), 6.00 (s, 1H), 3.41—3.33 (m, CH, 1H), 2.64—2.53 (m, 4H), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 198.7, 161.5, 140.1, 129.9, 128.0, 127.2, 127.0 126.4, 42.2, 37.1, 29.6, 24.3; IR (KBr) $v$: 3032, 2923, 2852, 1667, 1612, 1576, 1549, 1380, 804, 715 cm$^{-1}$. HR-MS [EI]$^+$ calcd for $C_{12}H_{13}NO$: 187.0997; found 187.0996.

The spectroscopic data were consistent with those reported in the literature.

## Results and Discussion

Initial experiment revealed that the reaction of **1a** and acetone catalyzed by a substoichiometric amount (33 mol%) of *L*-lysine gave only 5% yield of **5a** in *n*-pentane after 48 h at 50 ℃ (Table 1, Entry 1), while other amino acids have no catalytic activity (Table S1, Supporting Information (SI)). To obtain the optimal catalytic effect, the influence of various additives on the efficiency of this process was tested. A dramatic change in reaction outcome was observed and the yield of **5a** increased up to 41% when three equivalents of imidazole (relative to amount of *L*-lysine) were added as the additive (Table 1, Entry 3 and Table S2, SI). It was worthwhile to mention that no reaction happened under the catalysis of imidazole without *L*-lysine (Table 1, Entry 6). It has suggested to us that both *L*-lysine and imidazole are necessary for this cascade reaction. While switching to AcOH, $Et_3N$ or DMAP as additives, the reaction of **1a** with acetone only resulted in the formation of **5a** in 8%, 7% and 9% yield, respectively (Table 1, Entries 2, 4, 5). The examination of catalytic loading revealed that a reduction of *L*-lysine amount from 33 mol% to 10 mol% led to the decrease of **5a** yields from 41% to 15% (Table 1, Entries 3, 7, 8). Further increase of the *L*-lysine amount did not give better results than that of 33 mol% *L*-lysine (Table S3, SI).

**Table 1** Screening of the additive conditions for the cascade reaction[a]




| Entry | Catalyst–additive | Yield[b]/% |
|---|---|---|
| 1 | Lysine | 5 |
| 2 | Lysine-AcOH | 8 |
| 3 | Lysine-Imidazole | 41 |
| 4 | Lysine-$Et_3N$ | 7 |
| 5 | Lysine-DMAP | 9 |
| 6 | Imidazole | ＜1 |
| 7 | Lysine-Imidazole[c] | 15 |
| 8 | Lysine-Imidazole[d] | 27 |

[a] Reaction conditions: *p*-nitrobenzaldehyde (0.2 mmol), acetone (0.4 mL), *L*-lysine (0.06 mmol), additive (0.18 mmol) in 2 mL *n*-pentane, 50 ℃, 24 h; [b] yields were determined by HPLC; [c] *L*-lysine (0.02 mmol), additive (0.06 mmol); [d] *L*-lysine (0.05 mmol), additive (0.12 mmol).

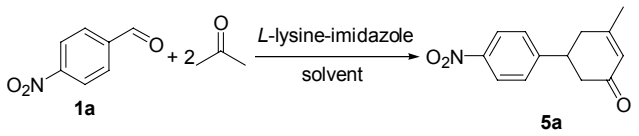
With optimal catalyst system in hand, the influence of different solvents on the lysine/imidazole-catalyzed cascade reaction of **1a** with acetone was also investigated. As described in Table 2, the efficiency of solvents was of overwhelming distinction. *n*-Heptane was extremely superior to others (Table 2, Entries 1 and 7). Only very poor yield was obtained when *n*-heptane was substituted by other solvent, such as $CH_3CN$, EtOH, $H_2O$ and toluene. Thus, *n*-heptane was selected as the reaction solvent to test the ratio of substrates.

Considering the advantages of water,[13] we screened the range of water concentration from 0% to 50% for the Aldol-Robinson cascade reaction and the results are shown in Figure 1. The best yield of 89% was obtained for **5a** after 48 h when 10 μL water was added to the reaction system. It may be due to the fact that the addition of trace water was helpful to hydrolysis of Schiff base and thus promoted the reaction. At last, the effect of reaction time was studied. The experimental results indicated that the yield increased up to 86% after 36 h, and while prolonging the reaction time to 48 h did not help to improve yield of **5a** (Figure 2).

Having established an effective catalytic system for the selective cyclization reactions, in order to explore the scope of the cascade reaction under the optimized

**Table 2** Optimization of reaction conditions using different solvents[a]




| Entry | Solvent | Yield[b]/% |
|---|---|---|
| 1 | *n*-Pentane | 41 |
| 2 | $CH_3CN$ | <1 |
| 3 | EtOH | 3 |
| 4 | $H_2O$ | 7 |
| 5 | Toluene | <1 |
| 6 | 1,4-Dioxane | <1 |
| 7 | *n*-Heptane | 57 |

[a] Reaction conditions: *p*-nitrobenzaldehyde (0.2 mmol), acetone (0.4 mL), *L*-lysine (0.06 mmol), imidazole (0.18 mmol) in 2 mL solvent, 50 ℃, 24 h; [b] yields were determined by HPLC.

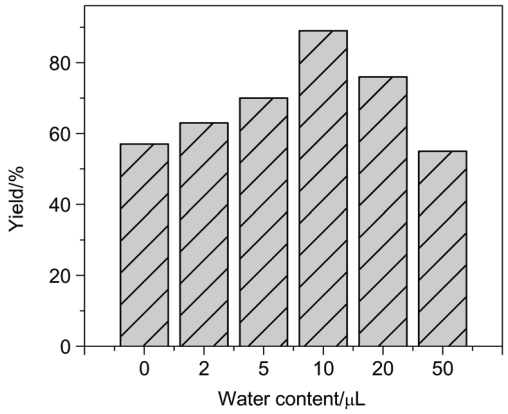



**Figure 1** Effect of water content on the reaction.

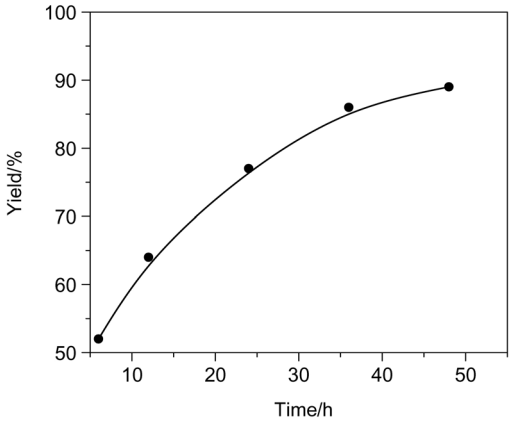
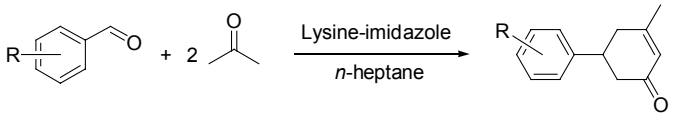
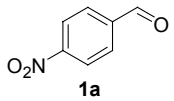
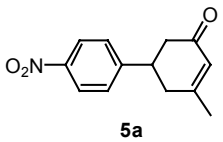
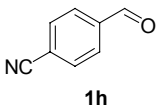
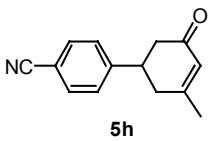
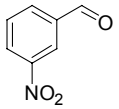
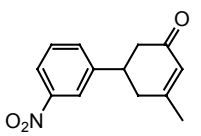
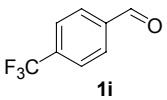
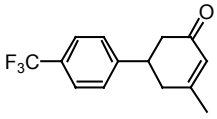
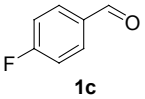
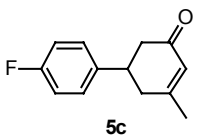
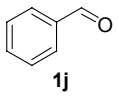
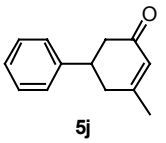



**Figure 2** Influence of reaction time on reaction.

conditions, a variety of C5-substituted 3-methylcyclohex-2-enones were synthesized and the results were summarized in Table 3. It was notably found the electronic effects of the substituents on the aromatic ring had an influence on the reaction. Aldehydes with electron-withdrawing groups, such as $-NO_2$ (Table 3, Entries 1, 2), $-CF_3$ (Table 3, Entry 9), –CN (Table 3, Entry 8) reacted with acetone to give the corresponding products in high yields while the one with electron-donating groups, such as $-CH_3$ (Table 3, Entry 11) afforded the desired products in poor yields. The reason for this result might be the reduction in the electron density of carbonyl carbon atom as a result of the strong electron-withdrawing effect of electron-withdrawing groups, thus increasing the reactivity of the carbonyl group. In addition, this reaction was also applicable to heterocyclic aldehyde and acetone, producing the desired product with a yield up to 80% (Table 3, Entry 12).

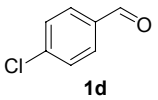
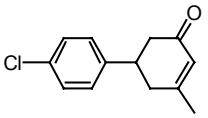
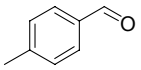
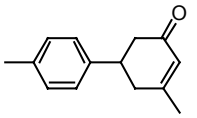
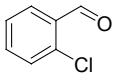
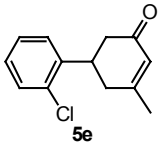
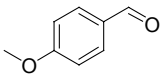
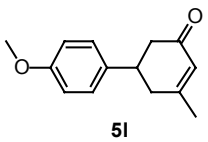
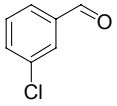
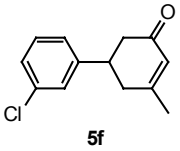
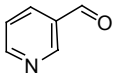
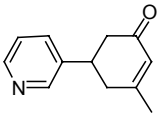
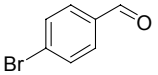
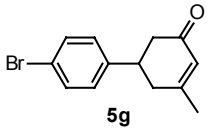
**Table 3** Synthesis of substituted cyclohexanone-2-ene[a]




| Entry | Substrate | Product | Yield[b]/% | Entry | Substrate | Product | Yield[b]/% |
|---|---|---|---|---|---|---|---|
| 1 |  **1a** |  **5a** | 86 | 8 |  **1h** |  **5h** | 65 |
| 2 |  **1b** |  **5b** | 72 | 9 |  **1i** |  **5i** | 92 |
| 3 |  **1c** |  **5c** | 55 | 10 |  **1j** |  **5j** | 42 |

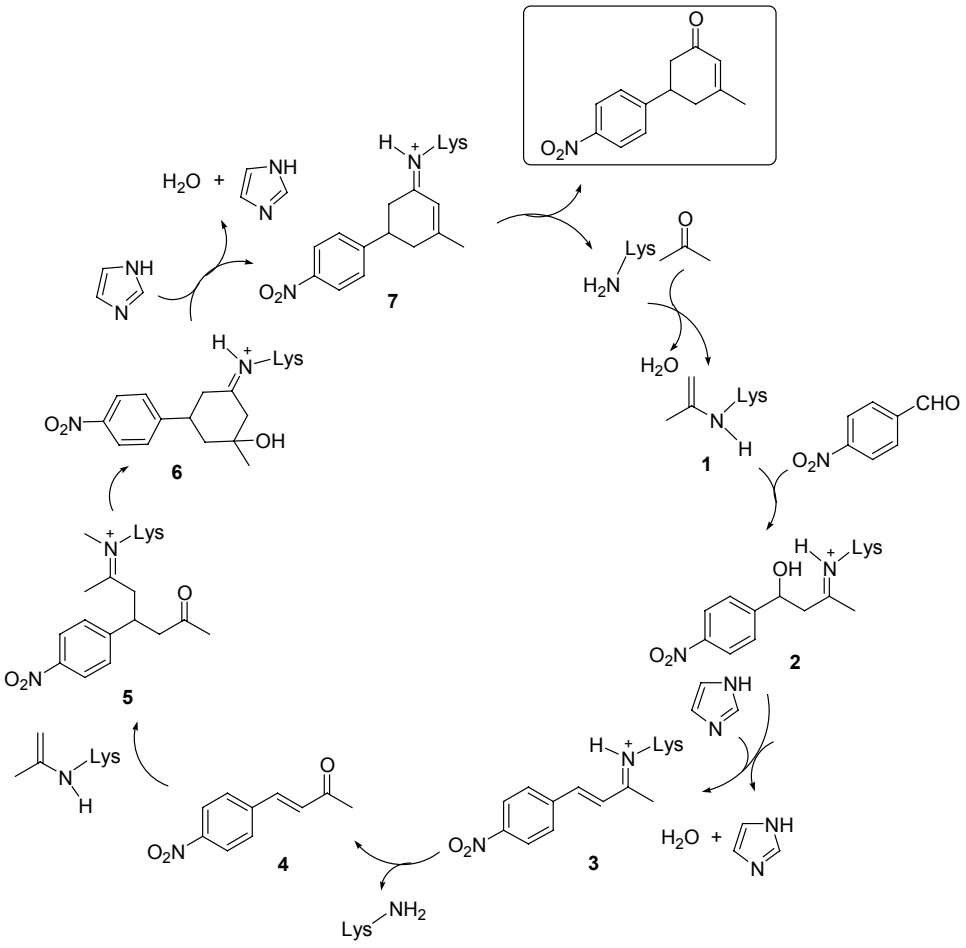
  

Continued

| Entry | Substrate | Product | Yield[b]/% | Entry | Substrate | Product | Yield[b]/% |
|---|---|---|---|---|---|---|---|
| 4 |  **1d** |  **5d** | 35 | 11 |  **1k** |  **5k** | 16 |
| 5 |  **1e** |  **5e** | 36 | 12 |  **1l** |  **5l** | N. D.[c] |
| 6 |  **1f** |  **5f** | 47 | 13 |  **1m** |  **5m** | 80 |
| 7 |  **1g** |  **5g** | 42 | | | | |

[a] Reaction conditions: aldehyde (0.2 mmol), acetone (0.4 mL), *n*-heptane (2 mL), water (10 μL), *L*-lysine (0.06 mmol), imidazole (0.18 mmol) in 2 mL solvent, 50 ℃, 36 h; [b] yields were determined by HPLC; [c] not detected.

**Scheme 3** Proposed mechanism of the cascade reaction between aldehyde and acetone



Based on the catalysis mechanism of type-I aldolase whose active center was the 6-amino group of a lysine,[14] a possible proposal for this domino process was presented in Scheme 3. In the first step acetone was activated as the iminium ion **1** by *L*-lysine, with which aldehyde performed the first Aldol addition reaction and afforded the enamine **2**. The resulting enamine **2** was dehydrated in the presence of base (imidazole) to give the enamine **3**. Subsequent hydrolysis of the enamine **3** generated the enone **4**, which reacted with the iminium ion **1** to give the enamine intermediates **5**. After an intermolecular enamine-mediated aldol reaction, intermediates **6** were formed, which underwent dehydration and hydrolysis to afford the desired product, while the catalyst was regenerated for the next catalytic cycle.

## Conclusions

In summary, we have developed a new catalytic system of *L*-lysine/imidazole for the direct synthesis of C5-substituted 3-methylcyclohex-2-enones *via* the direct Aldol-Robinson cascade reactions. A variety of substrates can participate in the process with moderate to good yields. Therefore, the use of simple and readily available materials, mild reaction conditions, simple execution, good yields, and wide synthetic potential of the products, make this new catalytic system attractive for academic research and practical applications. Unfortunately, although many reaction conditions have been investigated in full, no enantioselectivity was observed toward this reaction. Further research to prepare C5-substituted 3-methylcyclohex-2-enones with optical activity is under way.

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