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1	Catalytic Synthesis of Methacrolein via the Condensation of		
2	Formaldehyde and Propionaldehyde with L-proline		
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13	Abstract		
14	Methacrolein (MAL) is an important chemical for the manufacture of methyl		
15	methacrylate and a key monomer in many polymerization reactions. In this study, L-		
16	proline was investigated as catalyst for the aldol condensation of formaldehyde and		
17	propionaldehyde to produce MAL. The catalytic activity of the reaction system was		
18	closely related to the competition between the main reaction synthesizing MAL and the		
40			

side reaction producing 2-methyl-2-pentenal, which could be modified by adjusting the 19 20 operating parameters. The influences of several operating conditions, including 21 temperature, reaction time and water content, on the catalytic performance of the system 22 were systematically studied via a series of single-factor experiments, and the optimized 23 reaction conditions were obtained. The mechanism discussion via ESI indicated that 24 the reaction pathway followed the Mannich route. Experimental and theoretical kinetic 25 analyses of the L-proline-catalyzed aldol condensation reaction were performed, and 26 the reaction orders of the reactants were obtained by regression. The results showed that L-proline was an efficient catalyst for the production of MAL via aldol 27 condensation under mild condition. 28

29 Keywords: methacrolein, aldol condensation, L-proline, kinetics

View Article Online DOI: 10.1039/D0GC00726A

30 1. Introduction

Methacrolein (MAL) is a key chemical widely used in the production of polymers 31 and resins.^{1,2} It is also applied as a raw material for the synthesis of unsaturated esters^{3,4} 32 and diacetates^{5,6}, which act as monomers for thermoplastics⁷ and intermediates for 33 34 various chemical reactions. MAL production is mainly realized via two routes: the direct oxidation of isobutene and the aldol condensation of formaldehyde (FA) and 35 propionaldehyde (PA).⁸ The isobutene direct-oxidation route, generally catalyzed with 36 Mo-Bi composite, is limited by its low yield of MAL.⁹ While the aldol condensation 37 process, which can occur at mild conditions with relatively high yield, is a clean 38 technological route with good industrial prospects, the development of an efficient 39 catalyst and technology is required. 40

Acidic or alkaline substances can enhance the reaction of the aldehydes via the 41 direct aldol condensation pathway, but they can also act as catalysts for the self-42 condensation of PA and the polymerization of the unsaturated aldehydes, the selectivity 43 for the target product MAL is unsatisfactory.¹⁰ More efficient catalytic process was 44 expected to accomplish the MAL synthesis. The amine-assisted aldol condensation 45 process to prepare MAL with FA and PA first came into use in the 1950s, when molten 46 salts of monoamine were introduced as catalysts by Bortnick et al.¹¹ Since then, several 47 48 attempts to realize the commercial production of MAL via the amine-assisted Mannich reaction have been carried out, and many catalytic systems have been proposed. 49 Mironov et al.¹² argued that the pH of the reaction system was directly related to its 50 51 catalytic activity, and obtained a yield of 97 % at 313-323 K in the pH range of 6-7. Dashko et al.¹³ reported that increased basicity of the amino catalysts and the solvents 52 favored the cross-condensation reaction in the system. Erkkila et al.¹⁴ reported the 53 54 catalytic abilities of different secondary amine/carboxylic acid combinations on the 55 condensation of diverse aldehydes and FA under mild conditions and obtained a MAL 56 yield of 90% in the pyrrolidine/propionic acid co-catalyst system. Besides, the acidities of co-catalysts were found to be closely related with the catalytic performance.¹⁵ Lei et 57

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al.¹⁶ investigated the possibility of preparing MAL with high selectivityDvia0.1the/D0GC00726A 58 condensation of aldehydes at temperatures in the range of 373-483 K and short 59 residence times of a few seconds; the results of this group indicated that appropriately 60 shortened residence time increased the selectivity of MAL with 99.9% conversion of 61 PA. Li et al.¹⁷ found diethylamine/acetic acid was the optimal catalyst for the Mannich 62 synthesis of MAL from FA and PA, among the various combinations of secondary 63 amines and acetic acid, with a conversion of 97% and yield of 94%. The experimental 64 65 kinetic results indicated that the reaction activation energy of the diethylamine catalyzed process was 62.45 kJ/mol.¹⁸ Compared with the direct aldol condensation 66 pathway, the Mannich route shows obvious superiority on the high catalytic efficiency 67 and relatively lower harm on environment. Unfortunately, the stability of secondary 68 69 amine/carboxylic acid catalysts during recycling was challenged because the carboxylic acids drained away during distillation. To overcome this issue, amines were 70 immobilized on cation exchange resins and applied to the MAL synthesis process, yet 71 low conversions of aldehvdes were obtained.¹⁹ Pvo et al.²⁰ found more aldehvde were 72 73 transformed into a β -hydroxy aldehyde, the selectivity of the dehydration product MAL 74 was quite low.



(b)

(c)

1/202

acid/base

R₁ decomposition

ОН

dehydration

75



Considering the above researches, homogeneous single-molecular catalysts 78 containing both a secondary amine group and a carboxyl group may be an effective 79

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View Article Online means to complete the aldol condensation reaction. L-proline and its derivatives can be/DOGC00726A

introduced to the synthesis of MAL on account of their ability to form iminiums.²¹ 81 82 These organocatalysts are green and environmentally benign compounds, which act as enzymes, may potentially catalyze the synthesis reaction of MAL under mild conditions 83 with high efficiency and low toxicity to humans and the environment. This reaction 84 85 process presents competitiveness in aspects of efficiency, safety, and sustainability, satisfies the green chemistry criteria highlighted in the recent catalytic 86 87 methodologies.22-25

88 In this work, L-proline was proposed as a single-molecular catalyst for the 89 synthesis of MAL from the aldol condensation of FA and PA. The optimal reaction 90 parameters for the system were investigated using a series of single-factor experiments. 91 Furthermore, a kinetic model of the reaction was established based on experimental and 92 theoretical analyses, the reaction mechanism was verified and the rate-controlling step 93 was determined. L-proline catalyzed condensation reaction was discovered as an efficient process for MAL synthesis. 94

2. Experimental section 95

2.1 Materials 96

FA (about 37%), methanol (\geq 99.5%), ethanol (\geq 99.9%), sodium sulfite 97 anhydrous ($\geq 97\%$), diethylamine ($\geq 99\%$) were purchased from Xilong Scientific 98 Co., Ltd. (China), while acetic acid (\geq 99.5%), sulfuric acid (\geq 97%) were provided 99 100 by Beijing Chemical Factory (China), PA ($\geq 97\%$) was obtained from Aladdin Industrial Inc. L-proline ($\geq 99\%$), sarcosine ($\geq 99\%$), L-pipecolic ($\geq 99\%$), 101 hydroxyproline (\geq 99%) were also supplied by Aladdin Industrial Inc. and used as 102 catalysts. All these chemicals were used without further purification. The concentration 103 of FA was determined with the sodium sulfite titration method before each experiment. 104

2.2 General synthesis experiments 105

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The synthesis experiments were conducted in a 250 ml three necked round bottom

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flask at atmospheric pressure. The reaction temperature was controlled to 30803230K/D0GC00726A 107 by a water bath with a magnetic stirrer. The diffusion resistance had been eliminated. 108 109 L-proline crystals (0.15 mol) were dissolved in water (30 g) and then injected into the flask. An aqueous mixture of PA and FA (37 wt%) was dripped into the L-proline 110 solution while stirring at a speed of 1.2 ml/min, avoiding any abrupt temperature 111 112 increase in the system (The optimization of the drop rate was shown in Supporting Information). The molar ratio of FA/PA/L-proline was 1:1:1, and the resulting system 113 114 was stirred for 10 min. After completion of the reaction, methanol (0.5 mol) was added to the system with mixing to form a homogeneous solution. The product was collected 115 116 and analyzed with gas chromatography (GC).

The catalytic performance of the catalyst was evaluated based on the conversion
of PA, the selectivity of MAL and the yield of MAL. The corresponding expressions of
these parameters were as followed:

120 Conversion of PA:

$$X_{PA} = \frac{n_{PA,in} - n_{PA,out}}{n_{PA,in}} \times 100\%$$
 Eq. 1

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121 Selectivity to MAL:

$$S_{MAL} = \frac{n_{MAL,out}}{n_{PA,in} - n_{PA,out}} \times 100\%$$
 Eq. 2

122 Yield of MAL:

$$Y_{MAL} = \frac{n_{MAL,out}}{n_{PA,in}} \times 100\%$$
 Eq. 3

123 In these equations, $n_{PA,in}$ and $n_{PA,out}$ is the moles of PA existing in the system 124 before and after the reaction respectively, $n_{MAL,out}$ is the moles of MAL synthesized 125 in this reaction.

126 2.3 Kinetic study

127 The kinetic study was carried out in a 500 ml three-necked glass-jacketed reactor.

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The experiments were conducted in the temperature range of 273–293 K controlled by/DOGC00726A the ethanol bath pumped into the jacket. Mechanical stirring was utilized to ensure the uniform mixing of the reaction solution. Exactly 0.75 mol of L-proline, aqueous FA solution containing 0.75 mol of the aldehyde, and the corresponding amount of PA were quickly mixed with distilled water to obtain a mixture with a total volume of 240 ml. Samples (0.5 g) were regularly collected from this reaction system and analyzed by GC. The weights of the products and sampling times were recorded accurately.

The reaction rate for the aldol condensation reaction of FA 1 with PA 2 to produce
MAL 3 and water 4 can be expressed with a power-law equation as:

137
$$CH_20(1) + C_3H_60(2) \xrightarrow{L-\text{proline}} C_4H_60(3) + H_20(4)$$

$$r = -\frac{d[\mathbf{2}]}{dt} = k_T [\mathbf{1}]^a [\mathbf{2}]^b - k_{-T} [\mathbf{3}]^c [\mathbf{4}]^d$$
 Eq. 4

138 where, *r* represents the reaction rate with a unit of mol \cdot L⁻¹ \cdot min⁻¹, k_T and k_{-T} is 139 the forward and reverse rate constants of the aldol condensation reaction, *a,b,c,d* is the 140 reaction order of FA, PA, MAL and water respectively.

Besides, the MAL synthetic process could be considered as an irreversible reaction
in the current system as no PA was detected when MAL and L-proline solution were
mixed at 293 K. The equation could be simplified as:

The reaction orders of PA and FA were determined in sequence based on the concentration changes of PA. Three runs of experiments with FA in excess were designed to measure the order of PA. The molar ratios of FA and PA were set to 1:0.1, 1:0.15, and 1:0.2. Under this circumstance, the concentration change of FA was quite small, and hence considered constant. The reaction rate equation was converted to:

$$r = -\frac{d[\mathbf{2}]}{dt} = (k_T[\mathbf{1}]^a)[\mathbf{2}]^b = k'[\mathbf{2}]^b$$
 Eq. 6

$$\ln r = \ln k' + b \ln[2]$$
 Eq. 7

149 where k' was the rate constant.

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Linear fitting was conducted for the ln*r*-ln[2] plot, and the slope intrinsically indicatesthe reaction order of PA in the tests with FA in excess.

Tests were then conducted under various temperatures in the range of 273-293 K with the molar ratio of FA and PA set as 1:1 to investigate the reaction order of FA. Under this condition, the conversion of FA could be described via the PA concentration, the reaction rate equation was rearranged as Eq 8.

$$r = k_T [\mathbf{1}]^a [\mathbf{2}]^b = k_T [\mathbf{2}]^{a+b}$$
 Eq. 8

157 According to the Arrhenius equation (Eq. 9), the linear regression of $\ln k$ as a 158 function of 1/T provides the frequency factor and E_a of the L-proline catalyzed 159 process as shown in Eq. 10.

$$k_{\rm T} = A \times e^{-\frac{E_a}{RT}}$$
 Eq. 9

$$\ln k_{\rm T} = -\frac{E_a}{R} \times \frac{1}{T} + \ln A$$
 Eq. 10

where *A* is the frequency factor, E_a is the activation energy (J/mol), *T* is the temperature (K), and *R* is the gas constant, (8.314 J/(mol K)).

162 2.4 Analytical methods

The sodium sulfite titration method was used to detect the amount of FA in the 163 aqueous solution. GC analysis was employed to analyzed the amount of PA, MAL and 164 MP in the system, with ethanol as the internal standard. A Q-HT chromatographic 165 166 column (27.5 m×0.32 mm×10 µm) was selected. He (30 mL/min) was used as the carrier gas with a split ratio of 300:1, and the front inlet temperature was set as 523 K. 167 The oven had an initial temperature of 393 K, and was heated at a rate of 30 K/min to 168 513 K, and then held for 10 min. A FID detector with a temperature of 573 K was also 169 used. The accuracy of MAL analysis was confirmed with its isolated yield obtained by 170 extraction separation (see Supporting Information). 171

The ESI-MS spectra were obtained on a Bruker micrOTOF-QII mass spectrometer.

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174 **3.1 Screening of the catalyst**

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3. Results and discussion

Previous work conducted by our group verified that diethylamine/acetic acid could effectively catalyze the MAL synthesis process¹⁷, however, the acidic catalytic component was lost during recycling. To overcome this problem, several bifunctional molecules containing both a secondary amine group and a carboxyl group were selected as catalysts and tested in the present system. The results of these experiments were shown in Table 1.

Entry	Catalyst	X _{PA} /%	<i>S_{MAL}</i> /%
1	И ОН	92.0	84.3
2	OH OH	52.2	87.0
3	И ОН	96.5	96.8
4	HO OH	94.1	91.9

181 Table 1. MAL production with different catalysts

182 Reaction condition: content of reaction system, $n_{FA}=0.15$ mol, $n_{PA}=0.15$ mol, $n_{catalyst}=0.15$ 183 mol; water content = 40 wt%; reaction temperature, 316 K; reaction time, 30 min.

As expected, the investigated single-molecular organocatalysts were effective for 184 the aldol condensation reaction with satisfactory yield of MAL.²⁶ L-proline (entry 3) 185 exhibited the best result among the catalysts investigated. While moderate conversion 186 was observed for L-pipecolic acid (entry 2), a small amount of by-products, i.e., dimers 187 of the aldehydes, was also detected; this result indicated that the reaction rate of this 188 system was relatively slow and that the hexatomic ring structure suppressed the activity 189 190 of the secondary amine. Sarcosine (entry 1) has a straight-chain structure and features the simplest molecular structure among the selected catalysts; however, the selectivity 191 of this catalyst was far from optimal. The data of these two entries indicated that the 192 five-membered pyrrolidine ring containing a secondary amine in L-proline was the 193

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most suitable structure to catalyze the aldol condensation reaction, likely because the/DOGC00726A 194 spatial proximity of the acid and base of this structure was beneficial to the catalytic 195 reaction.²⁷ The L-proline derivative hydroxyproline (entry 4) showed no improvement 196 in compared with the result of L-proline, probably because the hydroxyl group had little 197 effect on the dissociation constant and steric hindrance of the catalyst.²⁸ 198

3.2 Optimization of aldol condensation with L-proline 199

The effects of reaction temperature, solvent content, reaction time and molar ratio 200 201 of reactants were studied to determine the optimal reaction conditions resulting in the 202 maximum yield of MAL.

203 3.2.1 Effect of reaction temperature

Temperature exerted significant influences on the reaction rate and preference 204 between main and side reactions. Detailed results of the changes observed at low 205 temperatures were illustrated in Figure 1(a). 206

Conversion of PA increased gradually to 99.0% at 323 K. By contrast, MAL 207 selectivity first increased with increasing temperature and then abruptly decreased at 208 reaction temperatures higher than 320 K, giving a maximum yield of 97.4%. The 209 selectivity for the by-product 2-methyl-2-pentenal (MP) followed a raising trend, 210 reached 8.13% at 323 K. 211

The rising trend of PA conversion with temperature is expected because the 212 reaction rate for most systems is accelerated at high temperatures. Competition between 213 214 main and side reactions is responsible for the trend observed in MAL selectivity. At relatively low temperatures, the main aldol condensation reaction dominates the system, 215 216 and no obvious peak of the side product MP could be detected. However, the selectivity obtained is lower than expected because the intermediate Mannich base is not fully 217 decomposed into MAL at low temperatures. At high reaction temperatures, side 218 219 reactions are preferred even though the overall reaction rates are enhanced. These 220 findings are in accordance with the results of Lei et al.¹⁶, who investigated the 221 continuous synthesis of MAL and showed that the contents of impurities varied with

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222 temperature.

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223 3.2.2 Effect of water content

The presence of water is known to affect the species and contents of intermediates formed with L-proline and aldehydes and promote the aldol condensation reaction.^{29,30} The effect of water content on the present MAL formation reaction is illustrated in Figure 1(b).



Figure 1. Catalytic performance as a function of various reaction parameters. (a) Effect of reaction temperature (n_{FA} = 0.15 mol, n_{PA} = 0.15 mol, $n_{L-\text{ proline}}$ = 0.15 mol, water content = 40 wt%, 25 min). (b) Effect of initial water content (n_{FA} = 0.15 mol, n_{PA} = 0.15 mol, $n_{L-\text{ proline}}$ = 0.15 mol, 320 K, 25 min) (c) Effect of reaction time (n_{FA} = 0.15 mol, n_{PA} = 0.15 mol, $n_{L-\text{ proline}}$ = 0.15 mol, water

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content = 37 wt%, 320 K) (d) Effect of reactant ratio (n_{FA} = 0.15 mol, $n_{L-proline} = 0.15$ mol, water/D0GC00726A content = 37 wt%, 320 K, 25 min)

The performance of L-proline in this aldol condensation reaction was approximately unaltered as the water content of the system increased from 36% to 43%; in particular, the conversion of PA was close to 100%. This result indicates that the water content and reactant concentration have little effect on the aldol condensation reaction under the chosen operating conditions.

The pH of the reaction solutions was measured with a pH indicator. The L-proline 239 solutions were under approximately neutral conditions, and pH values decreased from 240 7.06 to 6.65 with increasing amount of water in the current systems. The same operation 241 242 was conducted on the mixtures obtained after the reaction, and pH values between 5 and 6 were obtained. These findings verify the existence of intermediates formed with 243 L-proline and aldehyde. The secondary amine forms bonds with the reactants, and the 244 hydrogen proton of the carboxyl group dissociates, thereby slightly increasing the 245 246 acidity of the system.

247 3.2.3 Effect of reaction time

The reaction time shown in Figure 1(c) refers to the sum of the dripping times of the reactants (about 20 min) and the time these reactants are maintained in the flask.

A slight increase in conversion was observed in the time interval of 20–35 min, 250 251 and conversion plateaued after 35 min. The occurrence of reversible elementary reactions inhibited the reactants from converting completely, and the equilibrium 252 conversion was 99.3%. The curve for MAL selectivity followed an inverted U shape, a 253 maximum selectivity of 99.4% was achieved at 25 min, while the selectivity for MP 254 255 changed little in this time interval. When the reaction time was too short, a large amount of the Mannich base, an intermediate, was observed in the system. With increasing time, 256 257 the side reaction consuming MAL molecules by self-polymerization became more vigorous and led to the decline of reaction selectivity to MAL. 258

259 3.2.4 Effect of molar ratio of reactants

The ratio of substrates added is a key element, especially for reversible reactions,/DOGC00726A 260 because this parameter would determine the conversion of the reaction under chemical 261 equilibrium. Ganapati et al.³¹ observed enhancements in the yield of jasminaldehyde in 262 the vapor-phase aldol condensation of heptanal and benzaldehyde by adjusting the 263 molar ratio of substrates; the team attributed this finding to the competitive adsorption 264 of reactants on catalytic sites and dilution of substrates, which led to the displacement 265 of chemical equilibrium. To examine the optimal molar ratio of FA to PA, a set of 266 267 experiments was performed with different amounts of PA injection (Figure 1(d)).

Higher conversions were observed when less PA was injected into the system. The curve for selectivity peaked at 99.4% under the 1:1 reactant ratio condition. While the amounts of MAL detected were approximately the same, in the experiments in which the amounts of PA added were in no shortage. This result means increases in PA input would not lead to higher production of MAL, but an ascending yield of the by-product MP, because the content of FA in the system limited the conversion to MAL.

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3.3 Recyclability of the catalyst

275 The stability and life cycle of a catalyst are key considerations determining its 276 commercial application prospects. Low-pressure distillation was applied to the mixture obtained after aldol condensation to obtain an L-proline aqueous solution. The excess 277 aldehydes, methanol and water in the system were separated by distillation at 323 K 278 under 13 kPa until the weight of the solution remaining in the round flask was less than 279 280 that of the L-proline solution added at the beginning of synthesis. The concentration of L-proline was detected by liquid chromatography, and the amounts of catalyst in the 281 282 mixture were found to remain the same in over six runs. Water was added to the system to maintain the same concentration of L-proline. The 6 runs of stability tests followed 283 the same procedure of the reactions discussed above, and the results are shown in Figure 284 2. 285

The catalytic performance of L-proline was essentially maintained after six repeated runs. This finding reveals that L-proline has relatively good recyclability and

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can be reused via distillation at reduced pressure. 288



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Figure 2. Recycling performance of L-proline on the MAL synthetic reaction (n_{FA} = 0.15 mol, n_{PA} = 290 291 0.15 mol, $n_{\rm L-proline} = 0.15$ mol, water content = 37 wt%, 320 K, 25 min)

292 3.4 Reaction mechanism

The mechanisms of various L-proline-catalyzed C-C bond formation reactions 293 294 have been investigated in several studies, and generally two main mechanisms are accepted for these L-proline catalyzed processes: the enamine pathway and the iminium 295 pathway.^{21,32-34} Based on the previous researches, two possible mechanisms were 296 proposed for this MAL synthesis process, as shown in Scheme 2. 297

In the enamine pathway, PA attacked the L-proline, forming the iminium ion 7, 298 299 which further transformed to enamine 8. A transition state is synthesized with the 300 activated enamine and FA, giving the aldol product 10. The aldol product 10 can 301 dehydrate to MAL **3**.

302 The iminium pathway, which could also be called as Mannich route in this system, start with the nucleophilic addition of FA and L-proline, generating the iminium ion 12, 303 and a molecule of water 4 is released. PA then reacts with the iminium ion 12 to form 304 305 the Mannich base 13, which later dissociates into MAL 3.

ESI-MS spectra were employed to verify the mechanism of the condensation 306 307 reaction. If the reaction follows the enamine route, the enamine 8 and aldol product 10

View Article Online could be detected in the reaction system. While if the intermediates 11, the iminium impunation/DOGC00726A 308 309 12 and the Mannich base 13 exist, the Mannich mechanism applies to the condensation reaction. As presented in Figure S1, the intermediates 8, 11, 12 and 13 were all observed 310 in the reaction system, but the intensity of enamine 8 was quite low, about 1/40 of the 311 312 iminium ion 12. This supported the claim that the L-proline catalyzed process followed the Mannich pathway. This was also implied by the high selectivity of the MAL 313 synthesis reaction, as more aldol product 10 would be detected if the reaction followed 314 315 the enamine pathway. The existence of enamine 8 in the system may also devoted to the production of by-product MP. The relative higher intensity of peak corresponding 316 to iminium ion 12 than intermediates 11 indicated that intermediates 11 tended to 317 transformed to rather stable iminium ion 12 in the system. 318



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(a)

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319 Scheme 2. Proposed catalytic cycle for the aldol reaction (a) the enamine pathway and (b) the
320 Mannich pathway

321 **3.5 Kinetic study**

322 The kinetic study of this condensation reaction was conducted both experimentally 323 and theoretically to further understand this reaction and the mechanism.

324 3.5.1 Experimental kinetic model

As illustrated before, three runs of experiments with FA in excess were conducted to discuss the order of PA. Because the conversion of PA slowed with time, as shown in Figure 3, a positive reaction order was suggested for PA. The approximately overlapping straight lines in the ln*r*-ln[**2**] plots (Figure S2) indicated that the simplification of the power-law model was reasonable and the mean value of the reaction order of PA was calculated as 0.980.

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Figure 3. Kinetic profiles for the L-proline catalyzed aldol reaction with $[1]_0$ in different levels of excess with respect to $[2]_0$ (n_{FA} = 0.75 mol, $n_{L-\text{ proline}} = 0.75$ mol, total volume = 240 ml, 273 K) The reaction profile in the range of 273-293 K with the same initial concentrations of FA and PA were shown in Figure 4. The nearly parallel linear fittings presented in the Figure S3 indicated that the total order of the reaction was 1.494 and that the reaction

337 order of FA was 0.514.

The power-law kinetic model for the L-proline catalyzed process was:

$$r = k_T [\mathbf{1}]^{0.514} [\mathbf{2}]^{0.980}$$
 Eq. 11



339

338

340 Figure 4. Kinetic profiles for the L-proline catalyzed aldol reaction at different temperatures (n_{FA} =

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The relationship of the rate constant $k_{\rm T}$ and reaction temperature was described in

0.75 mol, n_{PA} = 0.75 mol, $n_{L-proline}$ = 0.75 mol, total volume = 240 ml)

346 experimental kinetic calculation were included in Supporting information.



Figure 5. Arrhenius curve of $\ln k_{\rm T}$ versus 1/T

349 3.5.2 Theoretical derivation of kinetic model

Knowledge of the reaction order of the reactants may help in the construction of 350 351 the reaction mechanism and determination of the rate-controlling step. According to the power-law kinetic rate expression obtained in the discussion above, the reaction order 352 of PA is close to 1, which means it may be directly involved in the rate-determining 353 step. The reversible reaction of FA may contribute to its rate order, which is less than 354 1. Based on the information and knowledge of the reaction mechanism shown in 355 Scheme 2 (b), a more detailed rate equation for the reaction process is deduced as in 356 Eq. 12 (More information please see Supporting information). 357

$$r = \frac{k_1 k_2 k_3 k_4 [\mathbf{1}] [\mathbf{5}]_{tot} [\mathbf{2}]}{k_{-1} k_{-2} (k_{-3} + k_4) [\mathbf{4}] + k_1 [\mathbf{1}] [k_2 (k_{-3} + k_4) + k_2 k_3 [\mathbf{2}] + k_{-2} (k_{-3} + k_4) [\mathbf{4}]]}$$
Eq. 12

In Eq. 12, $[5]_{tot}$ is the initial concentration of L-proline, [4] is the concentration of water, which could be regarded as a constant since water is the solvent of the system. As Mannich base 13 is a poorly stable species, k_4 is much greater than k_{-3} , and the equation simplifies to Eq. 13:

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$$r = \frac{k_1 k_2 k_3 [\mathbf{1}] [\mathbf{5}]_{tot} [\mathbf{2}]}{k_{-1} k_{-2} [\mathbf{4}] + k_1 [\mathbf{1}] [k_2 + \frac{k_2 k_3 [\mathbf{2}]}{k_4} + k_{-2} [\mathbf{4}]]}$$
Eq. 13

362 This equation agrees with the rate expressions of Blackmond and Orlandi.^{35,36} As the concentrations of FA 1 and PA 2 are observed in the denominator of the expression. 363 364 the observed reaction orders may be less than 1. The reaction order of FA 1 is more severely deviated from 1 when compared with that of PA 2. When k_4 is characterized 365 with larger orders of magnitude, the coefficient for PA in the denominator is reduced 366 to zero, and a nearly first-order reaction of PA is realized. The nonnegligible term of 367 the FA concentration in the denominator leads to its non-integer reaction order in the 368 current experimental kinetic analysis. The apparent dependence of the reaction on water 369 370 in the proposed system would show a negative order because of the existence of [4] 371 in the denominator of Eq. 12. The addition of extra water shifts the chemical equilibriums shown in Scheme 2 (b) and drives the intermediates decomposed back to 372 L-proline. Thus supposition is in accordance with a report by Zotova²⁹. The 373 correspondence of the experimental kinetic data with the mechanism deduced 374 theoretical kinetic model supported the proposed Mannich mechanism for the L-proline 375 376 catalyzed reaction.

Comparing the experimental and theoretical equations obtained, the rate determining step of the aldol condensation was determined. If the first step, i.e., nucleophilic addition of L-proline, is the rate-determining step, a first order of FA concentration would be expected as shown in Eq. 14. If the iminium ion **12** formation step acts as the rate-limiting step, the reaction rate could be given by Eq. 15 and the reaction order of FA would be 1. These two assumptions do not match with the noninteger reaction order of FA **1** obtained in the experimental rate equation.

$$r = k_1[\mathbf{1}][\mathbf{5}]$$
 Eq. 14

$$r = k_2[\mathbf{11}] = \frac{k_1 k_2[\mathbf{1}][\mathbf{5}]}{k_{-1}}$$
 Eq. 15

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step is the controlling step, the rate could be described by Eq. 16 and 17 separately:

$$r = k_3[12][2]$$
 Eq. 16

$$r = k_4[13]$$
 Eq. 17

Both the two equations satisfy the observed nearly first order of PA and the fractional order of FA in the rate expressions obtained. The final controlling step in the practical reaction process is related with the operating conditions, which affect the corresponding rate constant of the two steps. Hence, the Mannich base **13** formation and dissociation step were deduced to be the rate-determining steps of aldol condensation of FA and PA, and the actual rate-limiting step was the slower step of the two under the corresponding reaction condition.

393 4. Conclusion

In summary, the application of several single-molecular bifunctional catalysts to 394 395 form MAL from the aldol condensation of FA and PA was investigated, and the results 396 showed that L-proline was an effective catalyst for the aldol condensation to produce MAL via Mannich pathway. Parameters with the most significant effects on MAL yield 397 398 were determined, and a high-yielding reaction was established. The catalytic yield of 399 MAL retained at 98% after six runs. A nearly first-order dependence on PA was 400 observed in the kinetic study, and the reaction order of FA was fractional with a value of approximately 0.5. The apparent E_a of the proposed L-proline catalyzed aldol 401 402 reaction was calculated to be 61.1 kJ/mol. Hence, L-proline is an efficient and 403 recyclable catalyst for the aldol condensation reaction to synthesize MAL.

- 404 Conflicts of interest
- 405 There are no conflicts of interest to declare.
- 406 Acknowledgements

407 The authors gratefully acknowledge the financial supports of the National Natural

- 408 Science Funds (21878293), Science Funds for Creative Research Groupson Of the DogCoor26A
- 409 National Natural Science Foundation of China (21921005), and Key Research Program
- 410 of Frontier Sciences (CAS QYZDB-SSW-SLH022).

411 List of abbreviations and symbols

FA	Formaldehyde
PA	Propionaldehyde
MAL	Methacrolein
MP	2-methyl-2-pentenal
k	Rate constant
A	Pre-exponential factor
Т	Temperature (K)
E_a	Activation energy (J/mol)
R	Gas constant, (8.314 J/(mol K))
n	Molar amount of chemical (mol)
X_{PA}	Conversion of propionaldehyde
S_{MAL}	Selectivity to methacrolein
Y _{MAL}	Yield of methacrolein

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