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# Dynamic Kinetic Resolution Enabled by Intramolecular Benzoin Reaction: Synthetic Applications and Mechanistic Insights

Guoxiang Zhang, Shuang Yang, Xiaoyan Zhang, Qiqiao Lin, Deb. K. Das, Jian Liu, and Xinqiang Fang\*

<sup>†</sup>State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, University of Chinese Academy of Sciences, Fuzhou, Fujian 350002, P. R. China

<sup>‡</sup>Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, University of Chinese Academy of Sciences, Fuzhou, Fujian 350002, P. R. China

Supporting Information Placeholder

**ABSTRACT:** The highly enantio-, diastereo-, and regioselective dynamic kinetic resolution of  $\beta$ -ketoesters and 1,3-diketones was achieved via a chiral N-heterocyclic carbene catalyzed intramolecular cross-benzoin reaction. A variety of tetralone derivatives bearing two contiguous stereocenters and multiple functionalities were liberated in moderate to excellent yields and with high levels of stereoselectivity (> 95% ee and > 20:1 dr in most cases). In addition, the excellent regioselectivity control for aryl/alkyl 1,3diketones, and the superior electronic differentiation of 1,3diarylketones were highlighted. Moreover, a set of new mechanistic rationale that differs with the currently widely accepted understanding of intramolecular benzoin reactions was established to demonstrate the superior preference of benzoin over aldol transformation: (1) a co-existence of competitive aldol and benzoin reactions was detected, but a retro-aldol-irreversible benzoin process performs a vital role in the generation of predominant benzoin products; (2) the most essential role of an N-electronwithdrawing substituent in triazolium catalysts was revealed to be accelerating the rate of the benzoin transformation, rather than suppressing the aldol process through reducing the inherent basicity of the catalyst.

#### INTRODUCTION

The asymmetric benzoin reaction enabled by chiral *N*heterocyclic carbenes (NHCs) has been a longstanding research focus since 1966.<sup>1</sup> The Enders, Rovis, Suzuki, Leeper, You, Cannon, Gravel, and Johnson groups, etc. have made great contributions in this arena through exploiting novel chiral NHC catalysts and discovering innovative benzoin reaction patterns, therefore promoted significantly the development of this named reaction.<sup>2</sup> Since there has been an increasing demand in assembling molecules with stereo-diversity and structural complexity in a highly selective and efficient manner both in basic organic research and practical chemical industry, the discovery of protocols allowing access to optically enriched substances with two or more stereocenters via one-step benzoin reaction is thus urgent and indispensable. However, despite the enormous progress being made, it still remains a significant challenge for the current stage of benzoin

reactions to well address the above issue. In 2009, Ema and coworkers reported the asymmetric desymmetrization of cyclic 1,3diketones affording bicyclic tertiary alcohols through an intramolecular cross-benzoin reaction.<sup>3</sup> In 2014, Johnson group disclosed a graceful intermolecular two stereocenters forming benzoin transformation through the dynamic kinetic resolution (DKR)<sup>5</sup> of  $\beta$ -stereogenic  $\alpha$ -keto esters.<sup>4</sup> An asymmetric desymmetrization of acyclic 1,3-diketones was also achieved by our group recently.<sup>6</sup> Based on these pioneering reports, we envisioned that the introduction of an electron-withdrawing group (EWG) into a ketonealdehyde substrate (e.g.,  $\beta$ -keto ester 1a and 1,3-diketone 3 in Scheme 1a and 1c respectively) should provide a new opportunity in achieving a DKR through an NHC catalyzed intramolecular benzoin reaction, wherein enantioenriched tetralone products with two stereocenters and multiple functional groups will also be built simultaneously.

# Scheme 1. Key Challenges in Achieving DKR through NHC Catalyzed Intramolecular Benzoin Reaction



However, comparing with the previous reports especially those from the Suzuki2g-h, Enders2f and You2i,2l groups, at least two formidable challenges (Scheme 1) must be addressed to achieve an ideal outcome: (1) the competing aldol-type side reactions must be suppressed. In Suzuki, Ender, and You's early studies, two main strategies were utilized to suppress an aldol process: first, the amounts of bases were controlled accurately to be equal to or less than those of the catalysts to minimize aldol side reactions;<sup>2f-</sup> <sup>1,21,7</sup> second, because the inherent basicity of a free carbene can also promote an aldol process,<sup>2h,8</sup> Suzuki and co-workers modified the NHC catalyst through replacing N-phenyl group with an Nelectron-withdrawing 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub> group, thereby reduced the capability of the catalyst in enolizing substrates.<sup>2h</sup> This approach proved successful, but when substrates with relatively strong acidic protons adjacent to carbonyl groups were utilized, aldol products were still unavoidable (Scheme 1b). For example, in Suzuki's report,<sup>2h</sup> the treatment of S1 or S2 with phenyl substituted Rovis catalyst C1 afforded aldol-type products in 82% and 37% yields respectively; although the side reactions can be significantly suppressed by using electron-poor  $N-3,5-(CF_3)_2C_6H_3$  catalyst C2, a 27% combing yield of the byproducts was still obtained when S1 was tested (Scheme 1b). Thus, considering that the substrates used in this study (e.g., 1a and 3 in Scheme 1) contain more acidic protons than those in S1/S2 (the Ka value of 1a is about 4-5 orders of magnitude greater than that of S1 according to the Bordwell's pKa table<sup>9</sup>), it can be reasoned that an aldol process should be inevitable and even be predominant.<sup>10</sup> Also to be noted, in all the known successful NHC catalysis mediated DKR reports, such as those from the Scheidt,<sup>11a</sup> Johnson<sup>4,11b</sup> and Wang<sup>11c-d</sup> groups, excess amounts of bases relative to the catalysts were utilized to achieve efficient DKRs, so this contradiction also increases the difficulty of reducing aldol-type byproducts to get an ideal outcome. (2) furthermore, when 1,3-diketone 3 was employed as the substrate, new challenge of regioselectivity control during the benzoin reaction arises and must be well handled besides the diastereo- and enantioselectivity, otherwise a mixture of maximal eight stereoisomers could be obtained from the benzoin process, thereby making this methodology synthetically useless (Scheme 1c). However, the regiochemistry of the intramolecular benzoin reaction remains an underexploited field thus far, therefore different to the first challenge, no readily available approaches or even hints can be drawn from the currently known reports<sup>1,2</sup> regarding the question that which ketone moiety will be attacked preferentially.

To address all the above challenges, we recently conducted the DKR of ketones with  $\alpha$ -EWGs via an intramolecular benzoin reaction. To our delight, through the elaborate screening of reaction conditions, aldol-type side reactions were completely "suppressed", furnishing 1-tetralone products with two contiguous stereocenters in moderate to high yields and with high degrees of stereoselectivity. To be noted, the enantioenriched tetralone products are useful building blocks in organic synthesis and privileged structural motifs in a broad range of natural products and pharmaceuticals (Scheme 2).<sup>12</sup> What's more, in contrast to the wellknown strategy of trying to suppress aldol reactions to guarantee a smooth benzoin process,<sup>2f-h,7</sup> the mechanistic study of this protocol revealed a competitive aldol process occurring together with the benzoin one, but the reversible aldol and irreversible benzoin processes jointly enabled the formation of the desired products in high yields. Moreover, different to the widely accepted viewpoint,<sup>2h,i,l,n</sup> the most important role of N-electron-withdrawing groups in catalysts was proved to be not reducing the basicities of catalysts but accelerating the rates of benzoin transformations. All these findings provided a number of new insights into the investigation of the intramolecular benzoin reaction at a fundamental level. Herein we report our results.

#### Scheme 2. Natural Products Containing Tetralone Units



#### **RESULT AND DISCUSSION**

As illustrated in Table 1, we commenced by selecting readily available  $\beta$ -ketoester 1a and a series of aminoindanol-derived carbene catalysts developed initially by the Rovis group to test our hypothesis. Unsurprisingly, aldol product 2a' was produced predominantly in 76% yield when triazolium  $A^{13}$  (15 mol%) was used as the catalyst and  $K_2CO_3$  (1.0 eq.) as the base, and only 10% yield of benzoin product 2a was obtained, albeit with an excellent diastereoselectivity and a promising 84% ee (Table 1, entry 1). Mesityl-substituted catalyst  $\mathbf{B}^{14}$ , first reported by the Bode group, was also tested but no better result than that of A was obtained (Table 1, entry 2). Catalyst C, bearing a 4-bromo-phenyl group, induced an excellent ee of 99%, however, the aldol product was still predominant (Table 1, entry 3). The strong electron-withdrawing  $C_6F_5$  group in catalyst  $\mathbf{D}^{15}$  was proved to be essential in tuning the distribution of products, with benzoin adduct 2a isolated in 66% yield, but with a low 61% ee (Table 1, entry 4). A variety of chiral catalysts F-I with diverse skeletons were further examined, and different ratios of benzoin to aldol products were observed with varying degrees of enantioselectivity (Table 1, entries 5-8). To our delight, a search for alternative electronwithdrawing substituents in Rovis type catalysts revealed that triazolium  $\mathbf{E}^{16}$ , with an *N*-trichlorophenyl group, was optimal regarding both the yield (88%) and ee (99%) (Table 1, entry 9). Further effort to suppress the aldol byproduct by evaluating other reaction parameters such as bases and solvents didn't lead to better results (Table 1, entries 10-13). Cheerfully, we found that lowering the reaction temperature to 0 °C was beneficial to diminish the aldol adduct (Table 1, entry 14). Thus finally, the optimal result was established by setting the temperature at -20 °C and benzoin product 2a was produced in almost quantitative yield and with 99% ee (Table 1, entry 15). To be noted, the use of substoichiometric K<sub>2</sub>CO<sub>3</sub> retarded the reaction and led to an increased amount of 2a' significantly (Table 1, entries 16).

With the optimal conditions in hand, we set on exploring the generality and limitations of this NHC catalyzed DKR process (Table 2). A variety of aromatic ketones with  $\alpha$ -ethoxycarbonyl group performed very well, and both electron-donating and withdrawing substituents on the aryl rings were tolerated, with extremely excellent 99% ee observed in most cases (Table 2, 2a-2h). Replacement of the phenyl ring at the ketone moiety with a hetero-aromatic thienyl group had little effect on the yield (89%) and enantioselectivity (99% ee) (Table 2, 2i). Introduction of a fluoro substituent into the formylphenyl ring did not encumber the reaction considering both the yield and ee (Table 2, 2i). The change of electron-withdrawing CO2Et group to a phenyl group allowed access to the benzoin product with excellent ee (95%), albeit in a moderate yield (Table 2, 2k). We also surveyed the aliphatic methyl and ethyl ketone substrates and moderate ee (75% and 65%, respectively) was detected (Table 2, 2l and 2m). Unfortunately, efforts to expand this protocol to substrates with aliphatic formal groups were not successful; mixtures of two diastereomers were obtained in low yields (< 20%) and with low ee (< 30%).

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Table 1. Initial Studies and Reaction Optimization <sup>a</sup>			
Ph Co 1a (i	CHO 2Et base (1 eq.) conditions E racemic)	to <sub>2</sub> c (> 20:1 dr ) <b>2a</b> (cross-benzoin)	HO DC 2C <sup>44</sup> <b>2a'</b> (aldol)
	$\begin{array}{c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$	$F^{\Theta} \rightarrow N^{\Theta} \rightarrow N^{O} \rightarrow N^{O$	F4 N⊕ N BF4 N Ph
entry	conditions	yield ( <b>2a/2a'</b> , %) <sup>b</sup>	ee ( <b>2a</b> , %) <sup>c</sup>
1	A, K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	10/76	84
2	<b>B</b> , K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	6/53	68
3	C, K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	8/81	99
4	<b>D</b> , K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	66/23	61
5	F, K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	29/51	49
6	G, K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	42/20	-98
7	H, K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	25/46	-8
8	I, K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	1/84	99
9	E, K <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	88/7	99
10	E, DIPEA, THF, 23 °C	65/22	99
11	E, Cs <sub>2</sub> CO <sub>3</sub> , THF, 23 °C	72/4	92
12	E, K <sub>2</sub> CO <sub>3</sub> , Toluene, 23 °C	74/6	97
13	E, K <sub>2</sub> CO <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 23 °C	81/5	99
14	<b>E</b> , K <sub>2</sub> CO <sub>3</sub> , THF, 0 °C	90/3	99
15	E, K₂CO₃, THF, −20 °C	99/0	99
16 <sup>d</sup>	<b>E</b> , K <sub>2</sub> CO <sub>3</sub> , THF, −20 °C	68/16	99

<sup>*a*</sup>Reaction conditions: **1a** (0.2 mmol), NHC (15 mol %), solvent (2 mL), base (0.2 mmol), argon protection, 12h. Diastereomeric ratios were determined via <sup>1</sup>H NMR analysis of reaction mixtures. <sup>*b*</sup>Isolated yields based on **1a**. <sup>*c*</sup>Determined via HPLC analysis on a chiral stationary phase; the absolute configuration was assigned by analogy to the X-ray single crystal structure of **2f**<sup>17</sup>. <sup>*d*</sup>K<sub>2</sub>CO<sub>3</sub> (0.75 eq.) was used.

Having achieved an efficient DKR of  $\beta$ -ketoesters through the highly selective intramolecular benzoin reaction, we wondered whether this methodology can be extended to 1,3-diketone substrates such as **3a** (Scheme 3). As has been illustrated in Scheme 1c, it's more challenging because besides the resolution efficiency, the regioselectivity control is also an arduous mission to be accomplished. It's well-known that regioselective transformations play a vital role in organic synthesis,<sup>18</sup> but to the best of our knowledge, even in the whole domain of asymmetric catalysis, there are very limited successful DKR reports using 1,3-diketones as substrates, most probably owning to the enormous difficulties in controlling the regioselectivity study is one of the fundamental aspects in the research field of the intramolecular benzoin reaction, hitherto the related reports are scarcely seen. So, to test

#### Table 2. Scope of α-Ketoesters<sup>4</sup>



<sup>*a*</sup>All reactions were run on a 0.2 mmol scale; all yields were of isolated products; in all cases, only one diastereomer was observed via <sup>1</sup>H NMR analysis; ee values were determined via HPLC analysis on a chiral stationary phase. The absolute configuration was determined via the X-ray single crystal structure analysis of **2g**<sup>17</sup>. <sup>*b*</sup>CH<sub>2</sub>Cl<sub>2</sub> was used as the solvent.

the possibility of achieving the efficient DKR of 1,3-diketones via an intramolecular benzoin reaction, we first examined the reactivity of 3a under the standard conditions utilized in Table 2. Cheerfully, an excellent regioselectivity was detected, with 4a as the single benzoin product among eight possible stereomers, albeit with moderate ee; no any other possible isomers such as 4a' were observed from the <sup>1</sup>H NMR analysis of the reaction mixture (Scheme 3a). Moreover, further evaluation of propionyl substituted 3b showed somewhat surprising outcome because 4b was isolated as the only product, with the phenyl ketone moiety attacked by the acyl anion equivalent (Scheme 3b). It's worthwhile to mention that 4b was furnished with a high degree of enantioselectivity (99% ee). From the observed results, the regioselectivity sequence in this DKR mediated intramolecular benzoin reaction can be defined as Me>Ph>Et with respect to the reactivities of ketone units. At the current stage, we speculate that the superposition of both electronic and steric factors of different ketone substituents is responsible for the excellent regioselectivity observed, and the powerfulness of NHC catalysts in distinguishing minute reactivity differences (such as Me and Et) was distinctly illustrated.<sup>20</sup> More insights into this regioselectivity preference will be one of the focuses in our ongoing investigation.

#### Scheme 3. Reactions of Me/Ph and Et/Ph 1,3-Diketones



The scope of this NHC catalyzed DKR of 1,3-diketones proved very general. First, product **4a** can be gotten with 83% ee under slightly modified conditions using  $CH_2Cl_2$  as the solvent (Table 3, **4a**). Second, variations on the substitution pattern at the aryl ketone moiety of **2b** were possible. For example, electron-donating Me or OMe groups had little effect on the enantioselectivities (Table 3, **4c**-**4d**); introduction of a phenyl substituent was also







<sup>*a*</sup>See footnote *a* in Table 2. The absolute configuration was determined via the X-ray single crystal structure analysis of  $4h^{17}$ . <sup>*b*</sup>CH<sub>2</sub>Cl<sub>2</sub> was used as the solvent.

amenable, affording **4e** in 55% yield and with excellent 98% ee (Table 3, **4e**); substrates equipped with electron-withdrawing F, Cl or Br groups at the *para*-position of the aryl ring were tolerated, releasing the annulation products in moderate to good yields (59% –82%) and with excellent enantioselectivities (97–99% ee, Table 3, **4f–4h**). The substrate diversity was further evaluated by introducing a fluoro group into the formyl aromatic ring and no any erosion in enantioselectivity was detected (Table 3, **4i**). A heteroaromatic furyl group substituted ketone was compatible under the standard conditions (Table 3, **4j**). The replacement of the propionyl moiety with a butyryl or cyclopropanecarbonyl group had no significant influence on the regio- and enantioselectivities (99% ee in both cases, Table 3, **4k** and **4l**). It's noteworthy that in all cases the benzoin products were obtained with excellent > 20:1 dr and no any other possible benzoin adducts were perceived.

The substrate scope of this methodology was further expanded to 1,3-diaryketones such as **5a**. To our delight, the subjection of **5a** to the standard conditions exhibited excellent electronic differentiation, with the electron-poor aryl ketone unit being attacked preferentially. However, two diastereomers of **6a** (35% yield, 99% ee) and **6b** (53% yield, 14% ee) were generated, and their structures were confirmed unambiguously via the X-ray crystal analysis<sup>17</sup> (Scheme 4). Disappointingly, attempts to explore the reaction of 1,3-dialkylketones (e.g., Me/Et or Et/cyclopropyl substituted 1,3-diketones) was not successful; complicated reaction mixtures were obtained and no possible benzoin products were identified. Anyway, we have provided useful information for the first time with respect to the regiochemistry of the intramolecular benzoin reaction.

#### Scheme 4. Reaction of Diaryl Substituted 1,3-Diketone



To showcase the synthetic applications of this protocol, further transformations based on the enantioenriched benzoin products were performed in highly chemo- and stereoselective manners (Scheme 3). For instance, the diastereoselective nucleophilic attack of chiral **2a** by vinylmagnesium bromide furnished function-

alities congested 1,2-diol **7a** in 89% yield and with 99% ee (Scheme 5a).<sup>21</sup> Moreover, the ethyl ketone moiety of **4b** underwent the chemoselective reaction with hydroxylamine to form the oxime, and then after the Beckmann rearrangement, chiral amide **7b** was delivered without any erosion in enantioselectivity (Scheme 5b).<sup>22</sup>

Scheme 5. Derivatization of Benzoin Products



# MECHANISTIC STUDIES

Control Experiments. As has been speculated in the first challenge (Scheme 1a-b), and based on the current understanding of the intramolecular benzoin reaction, an aldol side reaction in this methodology should be inevitable owning to the easily enolizing feature of the substrates under basic conditions. Thus it is really puzzling since an excellent outcome was obtained in view of the preference of benzoin over aldol transformations. To clarify this perplexity and gain more insights into this highly selective process, we conducted the control experiments depicted in Scheme 6. First, despite the well-known reversible feature of benzoin reactions,<sup>23</sup> the exposure of compound 2a to the standard conditions with catalysts ent-E or A did not resulted in any erosion of the ee value or the formation of aldol products, indicating an irreversible benzoin  $process^{24}$  in this protocol (Scheme 6, eq 1 and 2). However, the treatment of aldol product 2a' with trichloro-catalyst E led to a full conversion of 2a' to the benzoin product 2a under the standard conditions, presumably through a retroaldol-benzoin process (Scheme 6, eq 3). This result also suggests the possibility of using aldol adducts as aldehyde surrogates to undergo NHC catalyzed reactions. In contrast to catalyst E, phenyl-catalyst A cannot facilitate an aldol to benzoin transformation within 12h at room temperature, but we did observe the formations of small amounts of benzoin product 2a and starting material 1a in an extended reaction time (48h), which unambiguously demonstrated the existence of a retro-aldol process<sup>25</sup> (Scheme 6, eq 4).

#### **Scheme 6. Control Experiments**



**NMR Monitoring Experiments.** Furthermore, to get an intuitive understanding of the reaction profile, we performed NMR tracking experiments through detecting the concentrations of the starting material and the benzoin/aldol products (Figures 1–2). The reaction diagram of **1a** with trichloro-catalyst **E** (Figure 1) reveals a competitive aldol process against the benzoin one occurring at the initial stage, and then aldol product **2a**' even predominates over benzoin adduct **2a** at the point of the 30th minute. Thereafter, **2a**' gradually diminishes accompanied by an increasing amount of **2a**, therefore confirming that part of **2a** is produced through a retro-aldol-benzoin process (Figure 1).<sup>26</sup> In contrast, the

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59 60 reaction profile of **1a** under the catalysis of phenyl-catalyst **A** (Figure 2) shows a continuous formation of aldol product **2a'** together with a slow generation of **2a** in the initial several hours. But to be noted, the amount of **2a'** slightly decreases in the 6th hour, accompanied by a small increase in the amount of benzoin product **2a** (Figure 2). Hence in both cases, the aldol reactions are absolutely not suppressed, and the main difference between them lies in the rates of the benzoin products formation, with a superior one from catalyst **E** than that from **A**. Therefore, entirely distinct from the presently widely accepted and utilized aldol-suppression strategy,<sup>2FI</sup> a retro-aldol-benzoin process lays the foundation of the success of this intramolecular benzoin reaction.<sup>27</sup>



Figure 1. Reaction profile of 1a under the catalysis of E at -20 °C. All conditions were the same as that in Table 2.



Figure 2. Reaction profile of **1a** under the catalysis of **A** at 23 °C. Other conditions were the same as that in Table 2.

Evaluation of the Role of N-EWG in the Catalyst. Smith et al. have reported a range of 16.5-18.5 for the pKa values of triazolium salts with different N-substituents in aqueous solution (the pKa of triazolium A is 16.5; pKa of D is 18.5).<sup>28</sup> However, the pKa values of acetylacetone and ethyl acetoacetate in water are 9.0 and 10.7 respectively.<sup>29</sup> These data indicate that the free carbenes derived from both catalysts A and E have stronger basicities than that from deprotonated 1a; plus with the stoichiometric K<sub>2</sub>CO<sub>3</sub> employed in the reaction, we reason that the distinction between A and E in suppressing aldol processes caused by their different basicities should be unconspicuous, thereby not decisive for the formation of benzoin products in this work. The Smith group has revealed markedly superior rates performed by Nelectron-deficient aryl triazolium precatalysts than those with Nelectron-rich substituents in intramolecular Stetter reactions.<sup>30</sup> Bode et al. have also studies comprehensively the reactivity distinction of differently substituted triazoliums.<sup>31</sup> Electron deficient

and sterically more hindered N-substituents were considered to be beneficial for the reactivity promotion in acyl anion related reactions.<sup>30,31</sup> Based on these important reports and the data depicted in Figures 1-2, we concluded that the most important role of an N-EWG in catalysts such as E is to enhance the rate of benzoin process to be capable of competing with, rather than suppressing the aldol reactions. In contrast, phenyl catalyst A acts on the benzoin reaction in a much slower fashion, caused probably by both the relatively slow Breslow intermediate formation and the sluggish catalyst turnover in the final benzoin product formation step,<sup>30,31</sup> therefore no remarkable benzoin product can be isolated within the reaction time (12h). However, it can be reasoned that, given enough time, the full conversion of 1a to 2a can be realized. <sup>1</sup>H NMR analysis of the reaction in Scheme 7 confirmed this deduction: <sup>1</sup>H NMR analysis of the reaction mixture showed that the ratio of 2a versus 2a' increased from 1:7 to 1:3 when the reaction time was extended to 48 h. As a whole, this new finding-an N-EWG in catalyst is to accelerate the benzoin reaction, not to suppress the aldol one-is another sharpest contrast to the intramolecular benzoin reaction related early reports.2f-1,7

## Scheme 7. Reaction of 1a Under the Catalysis of A in Different Times



**Proposed Mechanism.** On the basis of the above analysis, the mechanistic profile of the whole reaction system can be briefly described in the following Scheme 8. At the initial stage, enoalte *Int-1* is formed in a fast and reversible way from both enantiomers of 1a under basic conditions, followed by the rapid release of aldol product 2a'. Simultaneously, the Breslow intermediate *Int-2* is also generated quickly and reversibly<sup>30</sup> from (S)-1a and finally afford 2a via an irreversible benzoin reaction. In contrast, (R)-1a acts on the NHC catalyst much more slowly, hence the minor isomer 2a'' was not perceived. To be noted, although the retro-aldol step occurs in a slow fashion, it exists throughout the entire dynamic reaction system since the formation of aldol product 2a'.

#### Scheme 8. Mechanistic Profile



# CONCLUSION

In summary, we have demonstrated both the synthetic applications and mechanistic insights of the challenging DKR of  $\alpha$ -EWGs substituted ketones enabled by the highly selective intramolecular cross-benzoin reaction for the first time. A variety of enantioenriched tetralones bearing two contiguous stereocenters and multiple functionalities were assembled with high diastereoand enantioselectivities. In addition, this work shed light on the excellent regioselectivity control for aryl/alkyl 1,3-diketones, and the superior electronic differentiation of 1,3-diarylketones. Furthermore, a set of new mechanistic rationale was established to clarify the preference of the benzoin over aldol process: (1) despite the widely accepted aldol-suppression strategy, a coexistence of both aldol and benzoin reactions was revealed and a retro-aldol-benzoin mechanism enables the generation of benzoin products in a predominant manner; (2) the N-electronwithdrawing substituents in NHC catalysts play a vital role in accelerating the transformation of aldehyde-ketone substrates to benzoin products, rather than diminishing aldol products through reducing the basicities of carbene catalysts. Overall, despite the well-known investigations established almost ten years ago, we provided herein a number of new insights into the fundamental research of the intramolecular benzoin reaction. Further study focusing on the regiochemistry and new reaction modes discovery of the benzoin reaction is ongoing.

## ASSOCIATED CONTENT

#### Supporting Information

Experimental procedures, spectral data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

# AUTHOR INFORMATION

#### **Corresponding Author**

\*xqfang@fjirsm.ac.cn

#### Notes

The authors declare no competing financial interests.

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