Iron-catalyzed cross-aldol reactions of *ortho*-diketones and methyl ketones†

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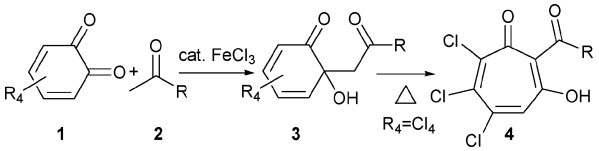
Iron-catalyzed cross-aldol reactions of *ortho*-diketones and methyl ketones were developed and the thus formed aldol products were efficiently transformed into cyclohepta-2,4,6-trienone derivatives (tropones) under thermal conditions *via* ring-expansion.

The aldol reaction is a particularly valuable carbon–carbon bond formation in organic synthesis. The aldol products, β-hydroxy aldehydes or ketones, are multifunctional products and versatile intermediates. Extensive studies on the aldol reaction have produced various efficient methods for the reactions between aldehydes and ketones. Due to the low electrophilic reactivity and steric hindrance of ketones, aldehydes are commonly used as the electrophilic partner in the aldol reaction. To achieve cross-aldol reactions of two different ketones is still a great challenge in synthetic chemistry.[1]

The applications of iron catalysts are attracting much attention in organic chemistry due to their advantages of being inexpensive, easily available and nontoxic.[2] Some pioneering works in iron-catalyzed organic reactions have been reported, which were effectively catalyzed by noble metal catalysts.[3–10] To the best of our knowledge, there are no reports on iron-catalyzed aldol reactions between two ketones.[11] Herein, we report an efficient iron-catalyzed cross-aldol reaction of *ortho*-diketones and methyl ketones. Significantly, the cross-aldol products smoothly transform into multifunctional cyclohepta-2,4,6-trienone derivatives (tropones) under thermal conditions *via* ring-expansion (Scheme 1).

In 1956, an interesting result of the gas HCl-promoted aldol reaction of *o*-chloranil and acetone was reported.[12] Acetone was used as both a reactant and solvent in this transformation. Unfortunately, there are no further investigations on this reaction.[13] We hypothesized that the reaction would be useful in organic synthesis if other ketones could be applied under the catalytic and mild reaction conditions. According with our research,[10a,b] we investigated the iron-catalyzed reaction of *o*-chloranil **1a**[14,15] and acetophenone. To our delight, the desired product **3a** was obtained in 91% yield using 5 mol% $FeCl_3$ at room temperature (Table 1, entry 1).‡ The yield of **3a** depended dramatically on the solvent. Polar solvents led to low yields of the desired product. Cyclohexane and petroleum ether (PE) were suitable solvents for this transformation. We chose PE as a solvent due to its low price. $FeCl_2$ and $AlCl_3$ were much less effective than $FeCl_3$ in the present aldol reactions. No product was observed in the absence of a catalyst.



Scheme 1 $FeCl_3$-catalyzed cross-aldol reactions and ring-expansion.

Subsequently, the scope of the aldol reaction was investigated and the representative results are listed in Table 1. Both electron-donating substituted and electron-withdrawing substituted acetophenones reacted smoothly with **1a** (Table 1, entries 3–8). Low reaction rates were observed when α- and β-acetyl naphthalenes were used. Moderate yields of **3h** and **3i** were obtained with prolonged reaction time (Table 1, entries 9 and 10). The desired product **3j** was obtained with good yield when 2-acetyl-5-methylfuran was used (Table 1, entry 11). 6 equivalents of acetone had to be used in order to increase the conversion of **1a** (Table 1, entry 12). Importantly, 10 mmol scale aldol reactions went smoothly under the standard reaction conditions (Table 1, entries 2 and 13). Moreover, the reactions of **1b** and **1c** with acetone afforded the corresponding products in good yields, albeit when excess acetone was used as a solvent (Scheme 2). Asymmetric *ortho*-diketone **1b** gave two regioisomeric products **3l** and **3l′** with the ratio of 3 : 4.

Due to its unique non-benzenoid aromatic structure and broad spectrum of biological properties, the synthesis of the tropone skeleton has attracted great attention.[16] With the cross-aldol products in hand, we explored the generality and selectivity of thermal ring-expansion.[12,17] After countless failures, we found that the expected seven-membered cyclic compounds **4** were selectively obtained as single isomers with good yields at 130 °C for 40 min (Table 2).§ The structure of **4b** (CCDC 714817) was unambiguously confirmed by crystal X-ray diffraction.[18] These tropone derivatives with multiple functional groups are potentially useful building blocks for further elaboration.

A tentative mechanism for the formation of the tropone skeleton is proposed in Scheme 3. Intramolecular aldol reaction of **3** led to bicyclic intermediate **A**. A 6π electrocyclic ring-opening reaction gives seven-membered intermediate **B**. Two sequential keto–enol tautomerizations afford the intermediate **D** *via* **C**. Tropone **4** is formed as the final product by elimination of one chloro atom from **D**. The relatively high thermostability of enol form **4** contributes to the isolation of

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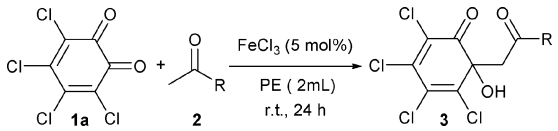
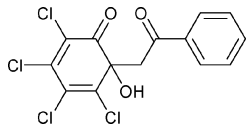
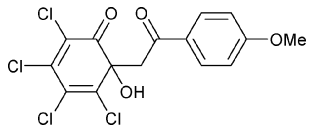
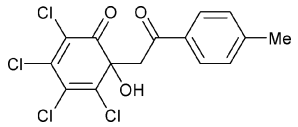
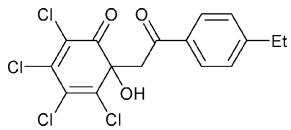
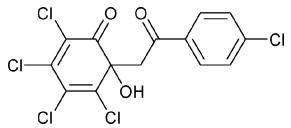
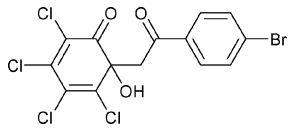
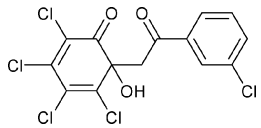
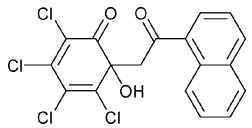
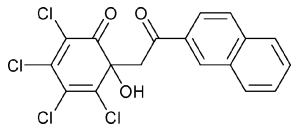
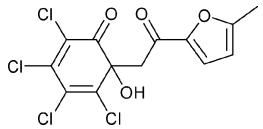
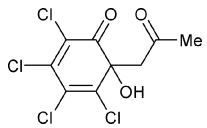
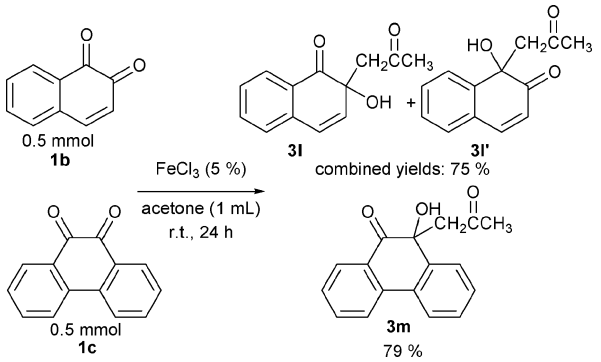
† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for isolated compounds, and X-ray data for **4b**. CCDC 714817. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b903515j

Table 1 Aldol reactions of *o*-chloranil **1a** and ketones **2**[a]



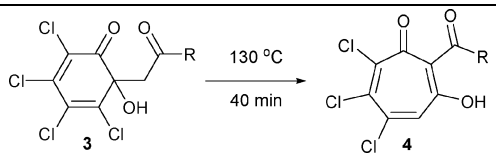
Entry	Product		Yield (%)[b]
1		**3a**	91
2		**3a**	75[c]
3		**3b**	81
4		**3c**	68
5		**3d**	66
6		**3e**	84
7		**3f**	87
8		**3g**	71
9		**3h**	60[d]
10		**3i**	61[d]
11		**3j**	82
12		**3k**	85[e]
13		**3k**	82[f]

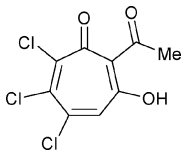
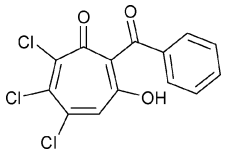
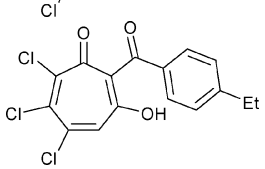
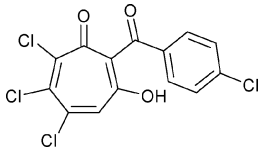
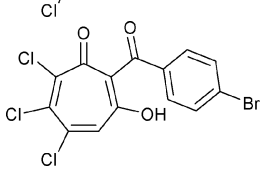
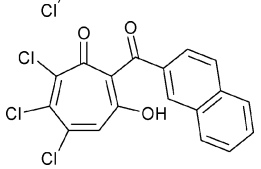
[a] **1a** (0.5 mmol) and $FeCl_3$ (0.025 mmol), **2** (0.75 mmol); unless otherwise noted. [b] Isolated yield. [c] **1a** (10 mmol), **2** (15 mmol), PE (40 mL). [d] 48 h. [e] **2** (3.0 mmol). [f] **1a** (10 mmol), **2** (30 mmol), PE (40 mL).



Scheme 2 The reactions of **1b** and **1c** with acetone.

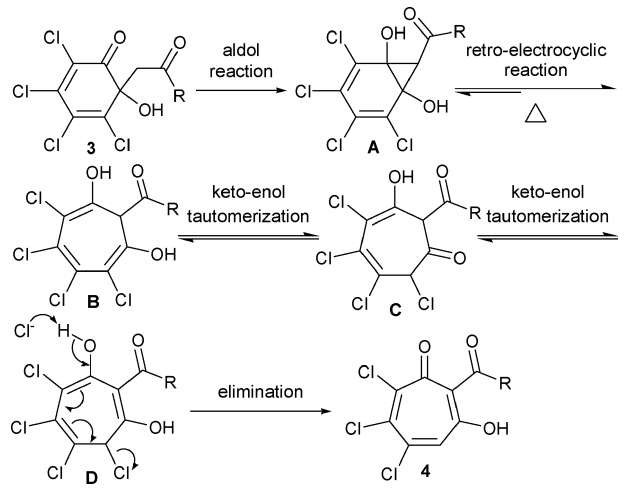
Table 2 Ring-expansion reactions of **3**[a]



Entry	Product		Yield (%)[b]
1		**4a**	81 (77)
2		**4b**	82 (64)
3		**4c**	88 (74)
4		**4d**	79 (68)
5		**4e**	76 (64)
6		**4f**	85 (74)

[a] **3** (0.2 mmol). [b] NMR yields are determined by ^1H NMR spectroscopy using mesitylene as an internal standard; isolated yields are given in parentheses.

only the single isomer.[19,20] However, some structurally uncharacterized solids were obtained when the temperature of the ring-expansion was above 150 °C.



Scheme 3 A tentative mechanism for ring-expansion reactions.

In summary, we have demonstrated an efficient iron-catalyzed cross-aldol reaction between two ketones under mild reaction conditions. Multifunctional tropones were efficiently and selectively obtained *via* ring-expansion of the aldol products under thermal conditions. Further studies into the applications of these tropones in synthetic chemistry are in progress.

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Notes and references

‡ **A typical procedure for the preparation of 3**. To a 2.0 mL solution of **1** (0.5 mmol) in petroleum ether (PE) under N_2 at room temperature was added **2** (0.75 mmol, 1.5 equiv.). The resulting mixture was stirred for 24 h at room temperature. The resulting reaction solution was mixed with silica gel and evaporated *in vacuo*. The residue was purified by flash column chromatography using silica gel (ethyl acetate : PE = 1 : 5) to afford the desired product **3**.

§ **A typical procedure for the preparation of 4**. An oven-dried Schlenk tube was charged with **3** (0.2 mmol) under N_2 at room temperature. The Schlenk tube was put into a pre-heated oil bath at 130 °C for 40 min. The reaction mixture was quenched with saturated $NaHCO_3$ and washed with 10 mL diethyl ether. The resulting aqueous phase was acidified with 2 mL 3 N HCl and extracted with 15 mL diethyl ether. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to afford the desired products **4**.

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