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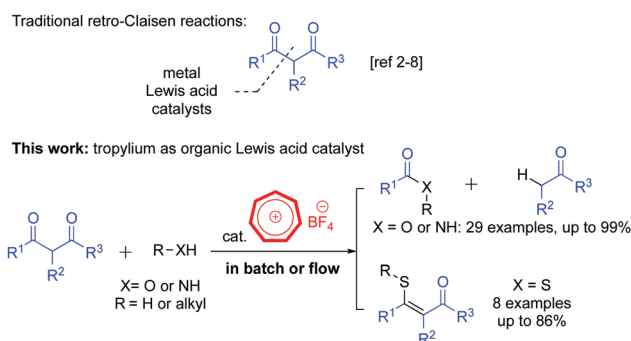
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An efficient method for *retro*-Claisen-type C–C bond cleavage of diketones with tropylium catalyst†

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The *retro*-Claisen reaction is frequently used in organic synthesis to access ester derivatives from 1,3-dicarbonyl precursors. The C–C bond cleavage in this reaction is usually promoted by a number of transition-metal Lewis acid catalysts or organic Brønsted acids/bases. Herein we report a new convenient and efficient method utilizing the tropylium ion as a mild and environmentally friendly organocatalyst to mediate *retro*-Claisen-type reactions. Using this method, a range of synthetically valuable substances can be accessed via solvolysis of 1,3-dicarbonyl compounds.

In recent years, the *retro*-Claisen reaction (Scheme 1) has often been used as an alternative approach to access ester products from dicarbonyl compounds.¹ Esters from *retro*-Claisen reactions normally have different structural features to their analogues produced by other traditional esterification methods, hence offering a unique synthetic value for this type of chemical transformation.² The C–C bond cleavage³ in this reaction has been promoted by a wide range of transition metal Lewis acids⁴ such as In(III),^{2,5} Fe(III),⁶ Pd(0)⁷ and Ag(I) catalysts.⁸ More recently, there have been a number of interesting movements to use non-transition metal Brønsted bases⁹ or organocatalytic systems¹⁰ to trigger the *retro*-Claisen reaction to reduce environmental footprints. These new developments have significantly advanced the field, however there are still limitations in the efficiency, regioselectivity and substrate scope of the *retro*-Claisen reaction. Herein we report a new method utilizing a tropylium salt to mediate this chemical transformation. The method can be used for the synthesis of alkenyl thioethers and it can be conveniently implemented in flow chemistry for the large-scale solvolysis of 1,3-dicarbonyl compounds (Scheme 1).

Scheme 1 *retro*-Claisen reactions.

The tropylium ion¹¹ possesses an interesting combination of stability and reactivity due to its unique non-benzenoid aromatic cation structure.¹² Based on our recent works with tropylium ion-promoted chemistry¹³ and reactions of carbonyl compounds,¹⁴ we believed that the tropylium ion could act as a Lewis acid catalyst to activate 1,3-dicarbonyl substrates for *retro*-Claisen reactions. The tropylium ion could also enhance the Brønsted acidity of protic reagents to promote the reaction via a Lewis acid assisted Brønsted acid catalytic pathway,^{13g} which has been rarely studied in the past.¹⁵

Thus, we set out to investigate the catalytic activity of tropylium tetrafluoroborate (**1**) in the *retro*-Claisen type solvolysis of 2-acetylcyclopentanone (**2a**) as a model substrate. Our initial reactions on the hydrolytic transformation of **2a** using 10 mol% catalyst **1** met with very promising outcomes (Table 1, entries 1–4). Similar to a range of other catalytic *retro*-Claisen reactions, elevated temperatures were required to effectively promote the C–C bond cleavage. A quick optimization study on catalyst loadings and solvents showed that 10 mol% of catalyst **1** delivered the best efficiency (Table 1, entries 4–13). The optimal reaction conditions were reflected in entry 4 where we were able to carry out the ring-opening hydrolysis of diketone **2a** within 16 hours and obtain product **4a** in 99%

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Table 1 Optimization of tropylium-promoted hydrolysis reaction of substrate **2a**^a

Entry	Mol% cat.	Solvent	T (°C)	Time ^b	Yield ^c (%)
1	10	No solvent	rt	48	18
2	10	No solvent	60	24	52
3	10	No solvent	80	24	96
4	10	No solvent	100	16	99
5	5	No solvent	100	16	62
6	2.5	No solvent	100	16	56
7	1	No solvent	100	16	38
8	No cat.	No solvent	100	16	Traces
9 ^d	10	Water as solvent	100	16	80
10	10	MeCN	Reflux	16	45
11	10	Toluene	Reflux	16	46
12	10	DCE	Reflux	16	70
13	10	TFE	Reflux	12	99
14	10	TFE	rt	24	98
15	10	Water as solvent	rt	48	21
16	10	MeCN	rt	48	62
17	10	Toluene	rt	48	37
18	10	DCE	rt	48	64
19 ^e	10% HBF ₄	No solvent	100	24	67
20 ^e	10% TfOH	No solvent	100	24	78
21 ^e	10% HBF ₄	TFE	rt	48	59
22 ^e	10% TfOH	TFE	rt	48	76

^a Conditions: diketone **2a** (1 mmol), water (**3a**, 2 mmol) and cat. **1** (0.1 mmol) in the indicated solvent (0.6 mL) under N₂ atmosphere. ^b Reaction time (hour) until no further or total consumption of substrate **2a**. ^c Yield of the isolated product. ^d 0.5 mL water was used. ^e 10 mol% of a Brønsted acid catalyst was used instead of tropylium catalyst **1**.¹⁶

yield after purification. Increasing the amount of water actually disfavoured the formation of this product (entry 9, Table 1).

We subsequently examined the possibility of performing this chemical transformation at ambient temperature, which is more desirable for sustainable synthetic protocols. Based on our prior experience with tropylium-promoted chemistry, we identified the highly ionizing solvent trifluoroethanol (TFE) as an effective medium for this reaction. Indeed, TFE solvent could not only mediate the reaction smoothly at high temperature (Table 1, entry 13) but also at room temperature, albeit taking longer reaction time (entry 14). Other organic solvents gave unsatisfactory reaction outcomes at room temperature even with extended reaction times (entries 15–18). In brief, we established two practical protocols to facilitate the *retro*-Claisen type hydrolysis of 2-acetylcyclopentanone (**2a**), the solvent-free method requires elevated temperature (Table 1, entry 4, procedure A) while the use of TFE can mediate the reaction at room temperature with similar reaction efficiency (Table 1, entry 14, procedure B).

We subsequently used these newly developed procedures to perform a range of hydrolysis, alcoholytic and aminolytic reactions on cyclic diketones (Scheme 2). 2-Acetylcyclopentanone (**2a**), 1,3-cyclohexanedione (**2b**, also see page S18 in the ESI†)¹⁷ and 2-methyl-1,3-cyclohexanedione (**2c**) were smoothly ring-opened with water, alcohols and amines to afford the corresponding products in good to excellent yields (**2a** → **4a–o**, **2b** → **4p–r** and **2c** → **4s–w**, respectively). Secondary alcohols (**4g**, **4i**) and secondary amines (**4m**, **4n**, **4w**) generally gave lower product yields than their primary analogues.¹⁷ Treatment of substrate **2a** with the sterically challenging *tert*-butyl alcohol under reaction conditions in procedure A led to the formation of hydrolysis product **4a**, presumably due to water being formed from the tropylium ion-catalyzed dehydration reaction of the tertiary alcohol.

Tropylium ion can also promote the *retro*-Claisen solvolysis of acyclic substrates such as dibenzoylmethane (**2d**) and acetylacetone (**2e**). However, the reactions proved to be sluggish





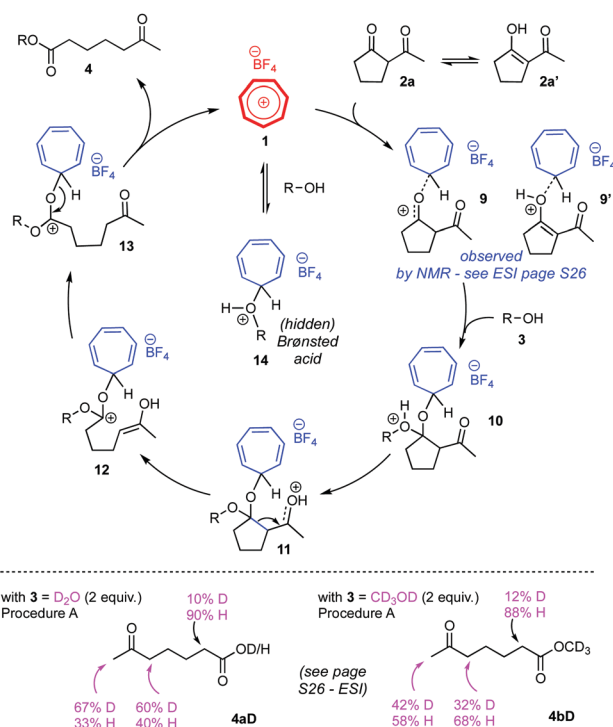
Scheme 3 (left) *retro*-Claisen alcoholysis and aminolysis in continuous flow chemistry; (right) thio-enolization with mercaptan reagents.

using procedures A or B so we adapted the conditions specified in entry 13 (Table 1, procedure C), which worked to give the cleaved products (**4y-z**) with moderate efficiency.

Our newly developed tropylium-catalyzed *retro*-Claisen method was amenable to large-scale synthesis using continuous flow chemistry setup. Indeed, after some reaction parameter optimization,¹⁶ we were able to carry out the alcoholysis and aminolysis of selected diketone substrates on multi-gram scale (Scheme 3, left). The tropylium catalyst loading could be reduced to 5 mol%, which is another improvement from batch conditions. Six products **4c-4w** were synthesized in high to excellent yields by flowing a mixture of the reagents and tropylium catalyst in TFE solutions into a 10 mL tubular reactor heated to 150 °C with retention time of 30 minutes. This simple and efficient flow protocol offers an alternative practical approach to the *retro*-Claisen solvolysis reactions of diketone substrates.

When we explored the possibility of using thiols as nucleophiles in this transformation, the outcomes were interesting. Instead of cleaving off the C-C bond to form the corresponding ketothioesters **7**, we obtained thio-enol ether products **8** (Scheme 3, right), most likely *via* the nucleophilic addition of thiols to the carbonyl group followed by dehydration reaction. The position of the C-C double bond was confirmed by 2D-NMR.¹⁶ This reactivity is common for a range of diketone and thiol substrates,¹⁸ as we obtained their condensation products **8** in good to high yields. Although this reaction looked rather simple, this is, to the best of our knowledge, the first time thio-enol ethers are produced directly from diketones in a dehydrative fashion. These products belong to a broader family of alkenyl thioethers, which are interesting structural scaffolds¹⁹ and valuable synthetic precursors for C-C coupling reactions.²⁰ Our protocol could serve as an alternative approach to access tetrasubstituted alkenes with thioether substituent instead of the addition of thiols to alkyne.²¹

To gain more information on how the tropylium ion activates the diketone substrates for these C-C cleavage reactions, we carried out a series of mechanistic studies on substrate **2a**. ¹H and ¹³C NMR spectra of mixtures of substrate **2a** and tropylium salt **1** (1 : 1 or 10 : 1 ratios) revealed clear evidence



Scheme 4 Proposed mechanism.

that tropylium ion coordinates to substrate **2a**,¹⁶ presumably *via* the diketone complex form **9** or the enol complex form **9'** (Scheme 4, top). The progress of the tropylium-promoted reactions between **2a** and water or methanol was also monitored by NMR spectroscopy; unfortunately the crude mixtures were too messy for any useful mechanistic insights to be deduced. The enolization of substrate **2a** (to **2a'**) and its subsequent reaction intermediates also contributed to the complication of spectroscopic signals. Indeed, when we treated substrate **2a** with deuterated water and methanol, the level of deuteration on products **4aD/4bD** indicated that uncontrolled enolization occurred during these reactions (Scheme 4, bottom).¹⁶ Changes in reaction temperatures and reaction times led to different deuterium contents in **4aD/4bD**.

Based on these studies and prior knowledge in this field, we propose that the *retro*-Claisen reaction occurs through the mechanistic pathways depicted in Scheme 4 (top). Again, enolization could happen for intermediates **10–13** during the course of reaction. We cannot rule out the possibility that tropylium ion can coordinate to the alcohol/water reagent itself to generate a strong Brønsted acid (**14**), which can in turn facilitate the *retro*-Claisen reaction. However, comparative reactions with strong Brønsted acid such as HBF₄ or TfOH (see Table 1, entries 19–22) showed much lower efficiency than the tropylium-promoted protocol, even at longer reaction times. Therefore, we believe that the hidden Brønsted acid catalytic pathway, if indeed exists, is not the predominant process to mediate the *retro*-Claisen reaction.

In conclusion, we have developed a new convenient method for C–C bond cleavage of 1,3-diketone compounds using tropylium tetrafluoroborate as an organic Lewis acid promoter. A wide range of carboxylic acid, ester and amide products were efficiently obtained in batch or flow using this approach with water, alcohols and amines, respectively. Replacement of these solvolytic reagents with mercaptans led to the formation of a range of new alkenyl thioethers.

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Conflicts of interest

There are no conflicts to declare.

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- See the ESI† for more details.
- Diketone **2b** predominantly formed enamine adducts with amine substrates, see the ESI† page S18 for more details. Diketone **2c** only formed enamine adducts with primary amines.
- Reactions between acyclic 1,3-diketone substrates (dibenzoylmethane, benzoylacetone and 1-benzoyl-3,3,3-trifluoroacetone) and mercaptans (cyclohexyl thiol and benzyl thiol) did not work, giving mainly starting materials back and a mixture of unidentifiable minor products.
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