Tetrahedron 65 (2009) 6682–6695

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Scandium triflate-catalyzed intramolecular Friedel–Crafts acylation with Meldrum's acids: insight into the mechanism

Eric Fillion *, Dan Fishlock †

Department of Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada

ARTICLE INFO

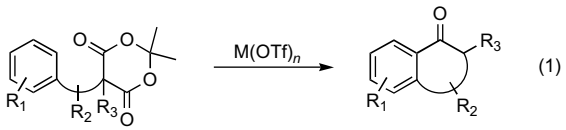
Article history:
Received 30 March 2009
Received in revised form 21 May 2009
Accepted 21 May 2009
Available online 28 May 2009

ABSTRACT

The intramolecular Friedel–Crafts acylation of arenes with Meldrum's acid derivatives catalyzed by $Sc(OTf)_3$ was reported as a mild and general entry into functionalized 1-indanones. Mechanistic investigations were undertaken to determine the rate-determining step in the acylation sequence using Meldrum's acid, as well as to examine the role of the Lewis acid catalyst. Enolizable Meldrum's acid derivatives react via an acyl ketene intermediate under thermal conditions, while quaternized Meldrum's acid derivatives are thermally stable and only act as effective Friedel–Crafts acylating agents in the presence of a Lewis acid catalyst. The acylation was postulated to proceed through direct acylation of a Lewis acid-activated carbonyl. In the catalytic Friedel–Crafts acylation of Meldrum's acids, triflic acid appeared to be the active catalytic species, with $Sc(OTf)_3$ serving as a very mild and convenient reagent for its delivery.

1. Introduction

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (**1**) and its derivatives have established synthetic utility as acylating agents for heteroatomic nucleophiles.[1] However, the high acidity of Meldrum's acid and its propensity to enolize in the presence of Brønsted bases have precluded carbon–carbon forming processes through the addition of carbon nucleophiles.[2] Based on the premise that neutral non-basic π-nucleophiles would add to Meldrum's acid derivatives in the presence of a Lewis acid to activate the carbonyls, our group has demonstrated that Meldrum's acids are powerful acylating agents in metal triflate-catalyzed intramolecular Friedel–Crafts reactions (Eq. 1).[3–6]



(1)

The acylation method has been applied to the synthesis of a variety of benzocyclic ketones and represents the first practical application of the addition of π-nucleophiles to Meldrum's acids under mild and catalytic reaction conditions. We have exploited the unique reactivity of Meldrum's acid in a multiple carbon–carbon forming process to complete the first total synthesis of taiwaniaquinol B.[7,8] In order to broaden the scope of the Friedel–Crafts acylation with Meldrum's acid derivatives and improve its efficiency, a clear understanding of the reaction mechanism is needed.

Over the years, the unique reactivity of Meldrum's acid with heteronucleophiles has prompted a number of mechanistic studies. 1,3-Dioxane-4,6-dione ring cleavage by hydrolysis under neutral, acidic, and basic conditions has been investigated thoroughly. Hydrolysis of 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**), 2,2,5,-trimethyl-1,3-dioxane-4,6-dione (**2**), and 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**3**) with dilute hydrochloric acid results in the formation of malonic acid, 2-methyl and 2,2-dimethyl derivatives, respectively, in addition to an equimolar amount of acetone.[9] Pihlaja and Seilo thoroughly studied the kinetics and mechanisms of this transformation.[10] It was concluded that two reactions, one uncatalyzed and the other catalyzed, were taking place concurrently, the catalyzed reaction being predominant. The acid-catalyzed hydrolysis was determined to proceed through an $A_{Ac}2$ mechanism, which involves attack of water on the protonated carbonyl group. Similarly, a bimolecular acyl–oxygen fission pathway, initiated by attack of a water molecule at the unactivated carbonyl group, was proposed for the uncatalyzed reaction. Notably, the reaction is autocatalytic when starting with a neutral solution owing to the acidity of the resulting malonic acid.

On the contrary, Meldrum's acid (**1**) and its 5-methyl derivative **2** are inert to hydrolysis in alkaline solution due the formation of the corresponding enolate anions, consequently reducing the electrophilicity of the carbonyl toward hydroxide ion.[11] Non-enolizable analog **3**, however, react instantaneously with 2 equiv of

* Corresponding author. Tel.: +1 519 888 4567 x32470; fax: +1 519 746 0435.
E-mail address: efillion@uwaterloo.ca (E. Fillion).
† Current address: Roche Palo Alto LLC, Technical Sciences—Chemical Synthesis, 3431 Hillview Ave, Palo Alto, CA 94304, USA.

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doi:10.1016/j.tet.2009.05.058

aqueous NaOH, while titration with a methanol solution of KOH furnishes the potassium salt of methyl 2,2-dimethylmalonate.[12] Hydrolytic decomposition studies were found to be in agreement with a $B_{Ac}2$ mechanism, in which ring opening is rate-determining following formation of the tetrahedral intermediate.[13]

An alternative ring-opening mode, which is exclusive to enolizable Meldrum's acids, has also been explored thoroughly. In this context, enolizable Meldrum's acid refers to a Meldrum's acid derivative with at least one proton at carbon 5, while non-enolizable derivatives contain no acidic proton at the 5-position. Upon treatment with excess diazomethane, Meldrum's acid (**1**) and 5-alkyl derivatives undergo ring cleavage at room temperature to form acetone and methyl malonate or 2-substituted methyl malonates, respectively.[14] As first described by Zav'yalov, reaction of **1** and 1,5-dioxaspiro[5.5]undecane-2,4-dione (**4**) with diazomethane in undistilled Et_2O lead to dimethylmalonate in addition to acetone or cyclohexanone. 6-Methoxy-1,3-dioxin-4-ones **5** and **6** were postulated as intermediates. Carrying out the reaction of **1** with diazomethane in distilled Et_2O allowed for the detection by IR and UV spectroscopy of 6-methoxy-4*H*-1,3-dioxin-4-one (**5**). Polansky and co-workers reinvestigated this transformation by reacting 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**), 2,2-diphenyl-1,3-dioxane-4,6-dione (**7**), and 2-phenyl-1,3-dioxane-4,6-dione (**8**) with diazomethane in the presence of MeOH or EtOH.[15] Dimethyl malonate or ethyl methyl malonate was generated, respectively, plus acetone, benzophenone or benzaldehyde. Unsymmetrical malonate formation was explained by attack of the EtOH molecule at the carbonyl group of 6-methoxy-1,3-dioxin-4-ones **5**, **9**, and **10** with concurrent ring opening.

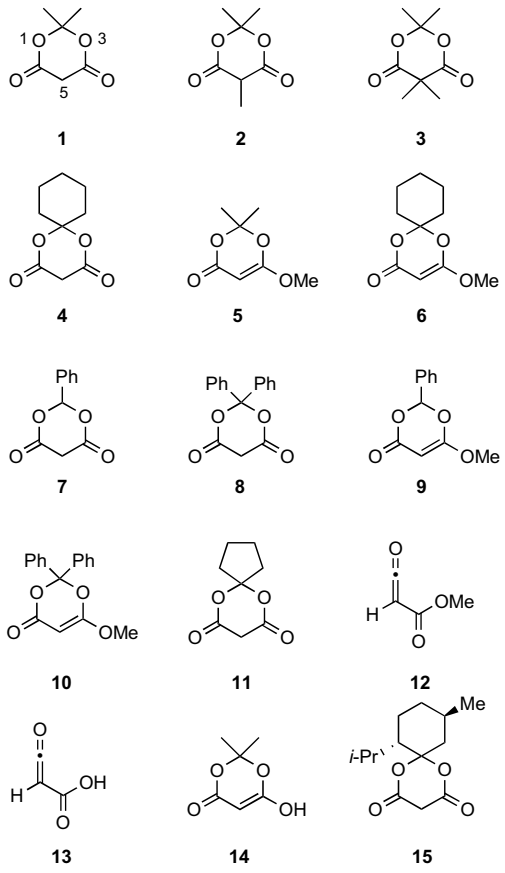


Figure 1. Meldrum's acid derivatives and reactive intermediates.

Ziegler and co-workers further illustrated the anomalous reactivity of Meldrum's acid and its derivatives.[16] Thermolysis of **1** in the presence of cyclopentanone and cyclohexanone resulted in the formation of 2-spirocycloalkane-1,3-dioxane-4,6-diones **11** and **4**, respectively, through substitution of the isopropylidene fragment in the 1,3-dioxane ring. Similar reactivity was observed for compound **2**. A mechanism was put forward in which acylation of the enol of cyclohexanone and cyclopentane by Meldrum's acid is followed by ring closure of the resulting carboxylic acid onto the vinyl ether intermediate.

Based on Zav'yalov's and Polansky's observations, Matoba and Yamazaki reported high-yielding alcoholysis and aminolysis of **1**.[17] Monomethyl malonate derivatives were obtained by reacting Meldrum's acid (**1**) with diazomethane in alcohols or piperidine. The authors' major contribution is the suggestion that 6-methoxy-2,2-dimethyl-1,3-dioxin-4-one (**5**) undergoes cycloreversion at room temperature to produce ketene methyl ester (**12**), the key electrophilic species. Then, acyl ketene condensation with alcohols or piperidine furnishes malonate derivatives. Sato and co-workers further confirmed the Matoba and Yamazaki proposal by preparing a series of 6-methoxy- and 6-siloxy-1,3-dioxin-4-ones and studying their reactivity.[18,19] Infrared spectroscopy revealed facile cycloreversion and acyl ketene formation, which were further trapped with alcohols. The retro hetero-Diels–Alder of 6-methoxy- and 6-siloxy-1,3-dioxin-4-ones is rate-determining step as deduced from the comparable rates of reactivity of *t*-BuOH and EtOH.[20]

Neutral hydrolysis and alcoholysis of Meldrum's acid (**1**) and 5-alkyl derivatives to the corresponding malonic acids and carboxylic acid derivatives under thermal conditions, occasionally accompanied by loss of CO_2, is a well-established synthetic protocol.[21,22] Sato and co-workers studied the alcoholysis of **1**, and demonstrated its high susceptibility to nucleophilic reagents at 80–110 °C.[18] The authors concluded that the high temperature promoted the formation of acyl ketene **13**, generated through cycloreversion of tautomeric 6-hydroxydioxinone **14**. Reacting **1** with L-menthone in refluxing toluene to furnish Meldrum's acid **15** was further evidence of the formation of ketene **13**, which acted as a diene in a hetero-Diels–Alder reaction. Of note, the [4+2] heterocycloaddition was performed under a slight vacuum to remove the acetone by-product. The need to remove acetone is suggestive of a reversible retro hetero-Diels–Alder step.

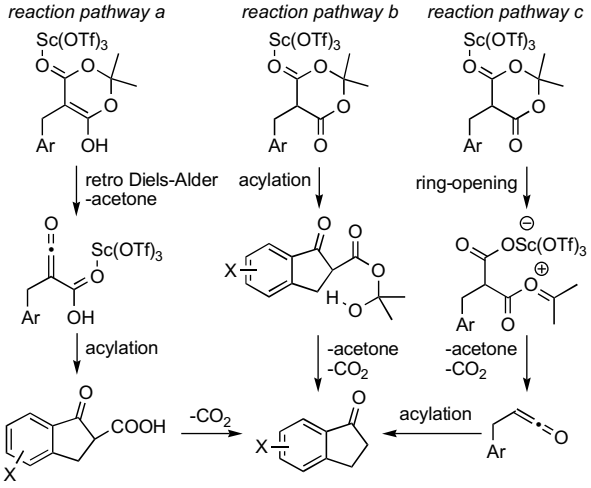
A large body of literature has been published on the flash vacuum pyrolysis of Meldrum's acid derivatives.[23] Meldrum initially observed the thermal instability of 2,2-dimethyl-1,3-dioxin-4,6-dione (**1**) above its melting point (97 °C) at atmospheric pressure; the resulting liquid turning yellow and then brown with carbon dioxide evolution and resinous product formation.[11] Ott revisited Meldrum's observations on the pyrolysis of **1**, under partial vacuum, and reported the generation of acetone, carbon dioxide, acetic acid, and trace amount of carbon suboxide.[24] The group of Brown investigated the flash vacuum pyrolysis of **1** at 430 °C, to furnish ketene, acetone, and carbone dioxide as established by infrared spectroscopy.[25] Brown and co-workers proposed three fragmentation mechanisms involving either a fully concerted reaction, or an initial partial charge separation to form a zwitterionic species. From the latter, a concerted reaction would lead to ketene, or expulsion of acetone to form a four-membered cyclic anhydride, which would then fragment into ketene and carbon dioxide.

Ott also studied the pyrolysis of 2,2,5,5-tetramethyl-1,3-dioxan-4,6-dione (**3**) to dimethylketene, carbone dioxide, and acetone.[24] The Brown group confirmed that excellent yield of dimethylketene could be obtained via flash vacuum pyrolysis of (**3**) at 520 °C.[26]

In stark contrast with the large number of experimental studies, theoretical investigations on the reactivity of Meldrum's acid are scarce.[27] Recently, Pinkerton and co-workers established a correlation between chemical bonding and structure–reactivity in Meldrum's acid by combining electron density obtained from X-ray diffraction data and theoretical electron density calculations.[28]

At the outset of these studies, little information on the interaction of Meldrum's acid with Lewis acids was available.[29] A single Lewis acid-catalyzed acylation procedure with Meldrum's acid had been described in the literature prior to our work. Rigo and co-workers reported the reaction of silylated nucleophiles (amines, alcohols, and lactams) with Meldrum's acid at room temperature as a high-yielding entry into malonic silyl esters.[30] Lewis acid was required exclusively for electron-deficient and hindered nucleophiles and no mechanism was put forward to explain the enhanced reactivity of Meldrum's acid under these conditions.

Derived from the studies described above, Scheme 1 summarizes three plausible reaction pathways for the Lewis acid-catalyzed intramolecular Friedel–Crafts acylation of benzyl Meldrum's acids, leading to 1-indanones. In all three processes, the metal triflate initially engages in coordination with one of the Meldrum's acid carbonyl and triggers the acylation process.



Scheme 1. Proposed reaction pathways.

In reaction pathway a, which applies exclusively to enolizable Meldrum's acid derivatives, the Lewis acid induces tautomerization of the benzyl Meldrum's acid derivative to the corresponding 6-hydroxydioxinone that cycloreverts to furnish an acyl ketene intermediate.[31] Acyl ketene arylation generates a 1-indanone-2-carboxylic acid that further decarboxylates to give the observed 1-indanone. Activation of the acyl ketene via Lewis acid coordination with either the C=O bond of the ketene moiety or the carboxyl group potentially enhances its electrophilicity.

The Meldrum's acid could participate directly in the acylation process as depicted in Scheme 1 (reaction pathway b). In this mechanism, the Lewis acid-activated carbonyl is attacked by the tethered π-nucleophile. Following acylation, subsequent loss of acetone and CO_2 provides the indanone.

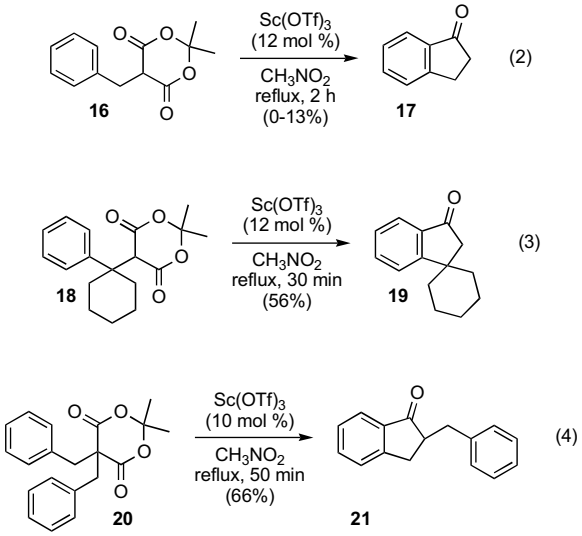
It was also postulated that, analogously to flash vacuum pyrolysis, upon activation by a Lewis acid a concerted or stepwise ring opening reaction generates a ketene with concomitant formation of acetone and CO_2 (Scheme 1, reaction pathway c). Arylation of the ketene, which may be activated by the Lewis acid, completes the catalytic cycle.

In order to make this methodology as synthetically useful as possible, and to enable its expanded application to more complex systems, a thorough understanding is necessary. In this manuscript, we present detailed mechanistic studies to validate or refute any of the three proposed mechanistic pathways depicted in Scheme 1 for enolizable and non-enolizable Meldrum's acids, and gain insights on the factors that influence the Friedel–Crafts acylation process.

2. Results and discussion

2.1. Nature of the Friedel–Crafts acylation precursor versus cyclization efficiency

In the course of investigating the scope of the Lewis acid-catalyzed intramolecular Friedel–Crafts acylation with Meldrum's acid, a reactivity divergence was observed for substrates **16**, **18**, and **20** (Eqs. 1–3).[4] Benzyl Meldrum's acid (**16**) did not provide 1-indanone (**17**) when refluxed for 2 h in CH_3NO_2 in the presence of a catalytic quantity of $Sc(OTf)_3$, but gave exclusively decomposition of the starting material (Eq. 2). Slow addition of the substrate via syringe pump to a solution of the catalyst gave a low 13% yield of **17**. Increasing substitution at the benzylic position affected the acylation and indanone **19** was obtained in 56% yield after 30 min (Eq. 3). Despite the steric hindrance of the neopentylic carbonyl groups, dibenzyl Meldrum's acid (**20**) was an effective substrate and gave access to 2-benzyl-1-indanone (**21**) in good yield (Eq. 4).

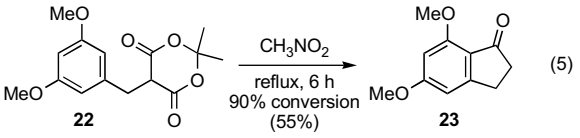


This series of acylation reactions showed that, while π-nucleophilicity remains constant, varying substitution at the benzylic position of the π-nucleophile or the 5-position of Meldrum's acid had a major impact on the carbon–carbon bond-forming process. This difference in reactivity was an incentive to examine the acylation mechanism thoroughly and to pinpoint the substituents' role in the catalytic Friedel–Crafts acylation with Meldrum's acids.

2.2. Determination of the rate-determining step for the acylation with enolizable Meldrum's acids under thermal conditions—competition studies on decomposition of benzyl Meldrum's acid derivatives 16 and 22

Our investigations began with monosubstituted Meldrum's acid derivatives, which are able to undergo enolization. It was initially determined that Meldrum's acids monosubstituted at carbon 5 (Fig. 1 for numbering) are thermally unstable and sufficiently reactive to participate in the acylation process and be transformed to 1-indanones without the requirement of a Lewis acid catalyst if they contain sufficiently electron-rich nucleophiles (Eqs. 5–7). Considering 5-(3,5-dimethoxybenzyl) Meldrum's acid (**22**), its direct thermal conversion to 1-indanone **23** proceeded smoothly with excellent conversion of starting material (90% conversion was attained after 6 h at reflux in CH_3NO_2 as determined by ^1H NMR of the crude reaction mixture), but only in a modest 55% isolated yield

after flash chromatography (Eq. 5). The cyclization of analogous *gem*-dimethyl substrate **24** was about four times slower (26.5 h compared with 6 h when no benzylic substituents were present) but was less prone to side reactions, and 5,7-dimethoxy-3,3-dimethyl-1-indanone (**25**) was isolated in 92% yield at 93% conversion (99% yield based on starting material recovery). Similarly to the Lewis acid-catalyzed reaction (Eq. 2), the thermal cyclization of **16** was unsuccessful (Eq. 7).



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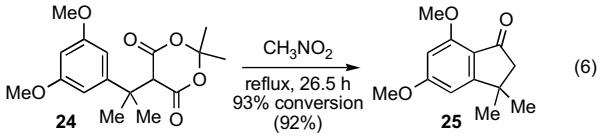

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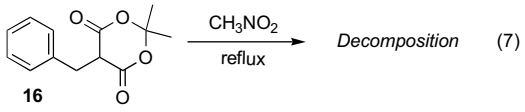

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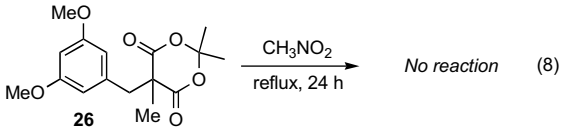
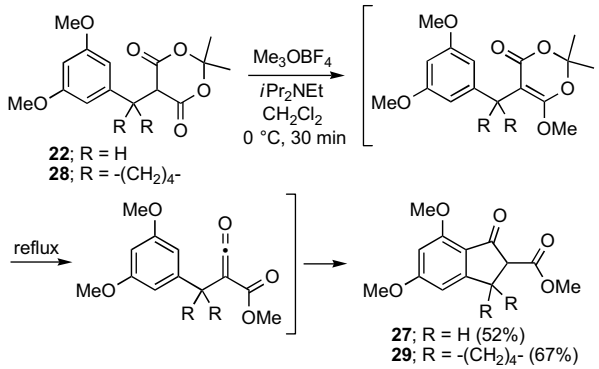


(8)

If formation of the carbon–carbon bond was rate-determining, the Thorpe–Ingold effect would have operated and substrate **24** would have reacted at a faster rate than **22**.[32,33] Therefore, the rate-determining step for the thermal acylation must be the formation of a transient reactive intermediate, either an acyl ketene (Scheme 1, pathway a), or a ketene (Scheme 1, pathway c). As illustrated in Eq. 8, non-enolizable Meldrum's acid **26** was inert when refluxed in nitromethane for 24 h; no decomposition was observed and the substrate was quantitatively recovered. This result suggests that pathway b (Scheme 1) is not operational under thermal conditions.

Ketenes have rarely been exploited as electrophiles in intramolecular Friedel–Crafts acylations,[34] and no precedent on Friedel–Crafts acylation with acyl ketenes was found in the literature. Investigation of reaction pathway a (Scheme 1) proceeded by methylation of Meldrum's acid **22** with Meerwein's salt to produce an α-oxoketene intermediate via cycloreversion of the resulting 6-methoxydioxinone (Scheme 2). Intramolecular arylation of the acyl ketene intermediate was anticipated to produce a β-keto ester incapable of decarboxylation. Gratifyingly, 1-indanone-2-methyl ester (**27**) was formed in 52% yield demonstrating the electrophilic character of acyl ketenes in Friedel–Crafts acylation reactions. Similarly, disubstituted substrate **28** gave 1-indanone **29**.

Additional mechanistic insights supporting pathway a were obtained by the competing reactions of **16** and **22** (Eqs. 5 and 7). It was expected that if nucleophilic attack of the π-nucleophile onto the Meldrum's acid carbonyls (σ-complex formation) or acylation of the acyl ketene was rate-determining, the consumption of the starting materials would be substantially different (Fig. 2). On the contrary, if the tautomerization of the Meldrum's acid or the retro



Scheme 2. Synthesis of acyl-1-indanones via intramolecular Friedel–Crafts acylation with acyl ketenes.

hetero-Diels–Alder reaction controls the rate of the reaction, then the overall starting material consumption rate would be unaffected by the π-nucleophilicity of the arene.

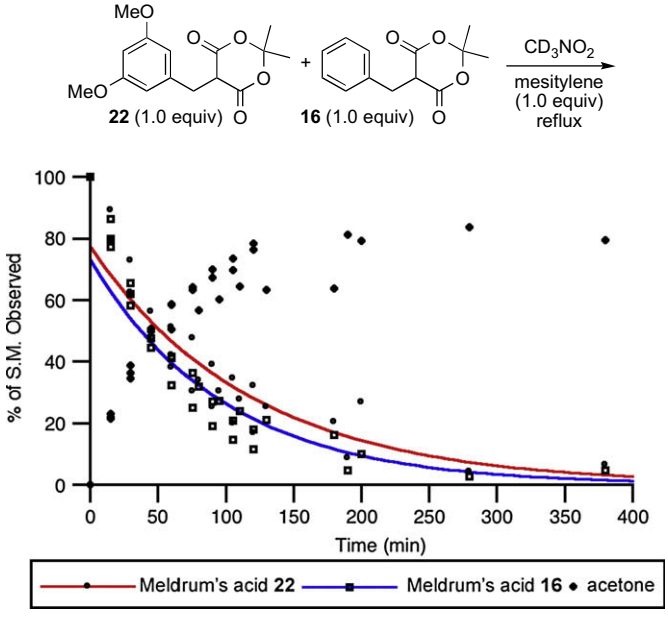
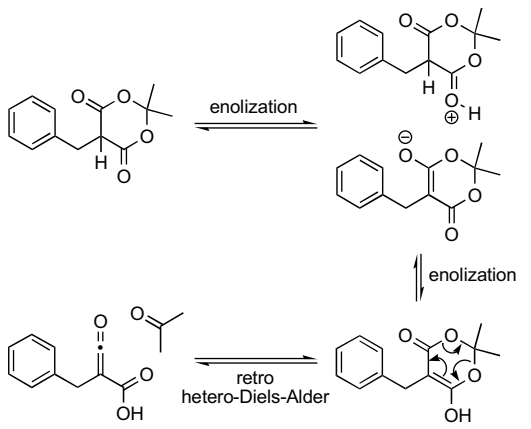


Figure 2. Comparative relative consumption of enolizable substrates **16** and **22** under thermal conditions.

The acquisition of kinetic data was problematic for enolizable Meldrum's acid derivatives. GC or GC–MS data could not be acquired since thermal decomposition of the substrates occurred in the inlet port and on the column. Proton nuclear magnetic resonance data of crude reaction mixtures was complex, and it was difficult to observe the 1-indanone products from starting materials and by-products. It was possible, however, to monitor substrate disappearance by observing the hydrogen at the 5-position of Meldrum's acids and the benzylic protons. An equimolar amount of **16** and **22** was placed in a sealed NMR tube and dissolved in CD_3NO_2. The mixture was heated at 100 °C and the percent consumption monitored by ^1H NMR based on mesitylene, an internal standard.

As shown in Figure 2, the rate of consumption for 3,5-dimethoxybenzyl substrate **22** was slightly faster than for **16**, but this apparent rate difference was very small with respect to the relative nucleophilicity of the competitors. Decomposition was a first order process.[35] Therefore, the rate-determining step for both substrates was the same, and since the nucleophilicity of **22** is about ten thousand orders of magnitude that of **16**,[36] this step cannot be the acylation of the acyl ketene intermediate or Meldrum's acid.

Since the rate of decay is equal for each substrate and independent of π-nucleophilicity, the rate-determining step must either be within the enolization or the retro hetero-Diels–Alder (Scheme 3). The rate of each of these steps would then be the same for both substrates, assuming that the pK_a of the α-protons are nearly identical.



Scheme 3. Plausible rate-determining steps of Meldrum's acids thermal decomposition.

If enolization of Meldrum's acid was rate-determining, then a primary kinetic isotope effect should exist if the proton at the 5-carbon of Meldrum's acid was replaced with deuterium. Using the 3,5-dimethoxybenzyl Meldrum's acid substrate **22** and deuterated analog 5-d_1-**22**, the rate equation for production of acetone from each substrate by thermal decomposition was determined by ^{1}H NMR observations in a sealed tube (Fig. 3a and b). The plot of ln(conversion) versus time was linear in both cases (Fig. 3c and d), indicating their apparent first order nature, and the rate equation was extracted from the linear best-fit trend line.

From the data presented in Figure 3, k_H is 20.3×10^{-3} s^{-1} and k_D is 18.4×10^{-3} s^{-1}, giving an isotope effect k_H/k_D of 1.10. For mechanisms in which the C–H bond is broken in the rate-determining step, deuterium isotope effects of about five in acid- and base-catalyzed processes would be expected.[37] Therefore, in the thermal decomposition of Meldrum's acid derivatives to product acyl ketene and acetone, the rate-determining step does not involve a C–H (or C–D) bond breaking process at the 5-carbon, and thus enolization of the substrate is not rate-determining.

Our experimental data is consistent with Sato's observations on the mechanism of Meldrum's acid ring opening by alcohols.[18] As stated earlier, Sato's group established that the rate of alcoholysis of Meldrum's acid and 5-alkyl derivatives is independent of the nucleophilicity of the alcohol. Morever, Sato mentioned the need to remove acetone while trapping the ketene via Diels–Alder reaction, which is suggestive of a reversible retro hetero-Diels–Alder step.

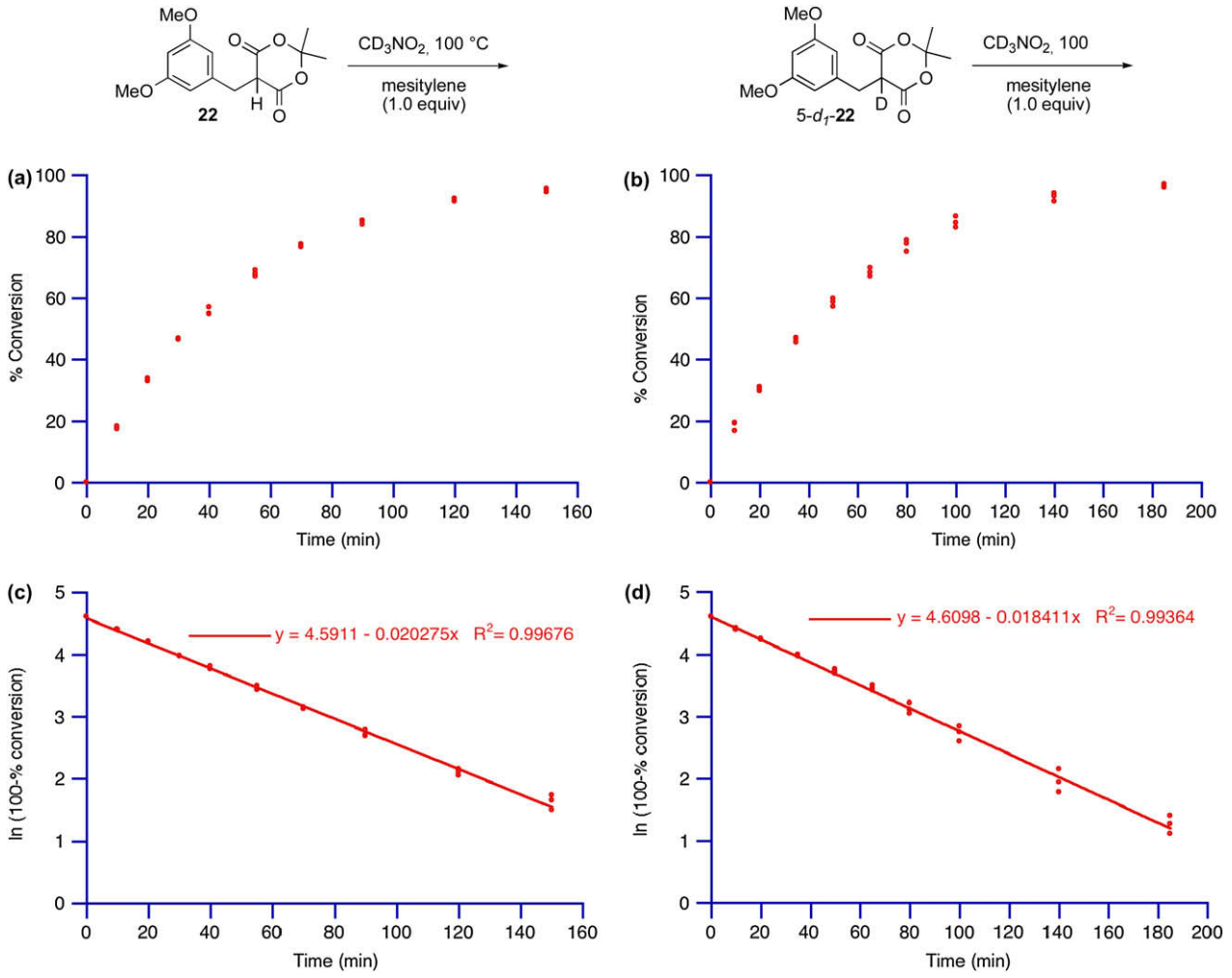


Figure 3. Effect of deuterium substitution on rate constant—evaluation of isotope effect. (a) Acetone production from 5H-substrate **22** (3.2 h). (b) Acetone production from 5D-substrate 5-d_1-**22** (3.2 h). (c) Natural logarithm (ln) of proton data. (d) Natural logarithm (ln) of deuterium data.

In the course of the Friedel–Crafts reaction, no trace of [4+2] cycloaddition product was ever observed between arylketone product and residual Meldrum's acid substrate. Nonetheless, the increasing presence of acetone in the reaction might slow the rate of progress as the cycloreversion equilibrium is shifted to the left. This would only be an issue if the retro hetero-Diels–Alder reaction was in fact the rate-limiting step.[38] If the rate-determining step for the thermal decomposition of benzyl Meldrum's acid derivatives was the retro hetero-Diels–Alder reaction, then an increase in initial acetone concentration should decrease the rate of substrate decomposition, since this step is in equilibrium.

Sealed NMR tube experiments conducted with 3,5-dimethoxybenzyl Meldrum's acid (**22**) in the presence of different initial amounts of acetone (4 mol equiv and 20 mol equiv) were conducted, and the consumption of Meldrum's acid starting material was determined by integration. The results are presented in Figure 4. Indeed, the addition of acetone did affect the rate of substrate decomposition and thus acyl ketene formation, but the effect was relatively small. Even with the addition of 20 mol equiv of acetone, the half-life of the reaction only doubled from about 30 min to about 60 min. Of note, this experiment was conducted in a sealed tube in which the acetone is trapped, although some portion would exist as a vapor in the headspace of the NMR tube at elevated temperature.[39]

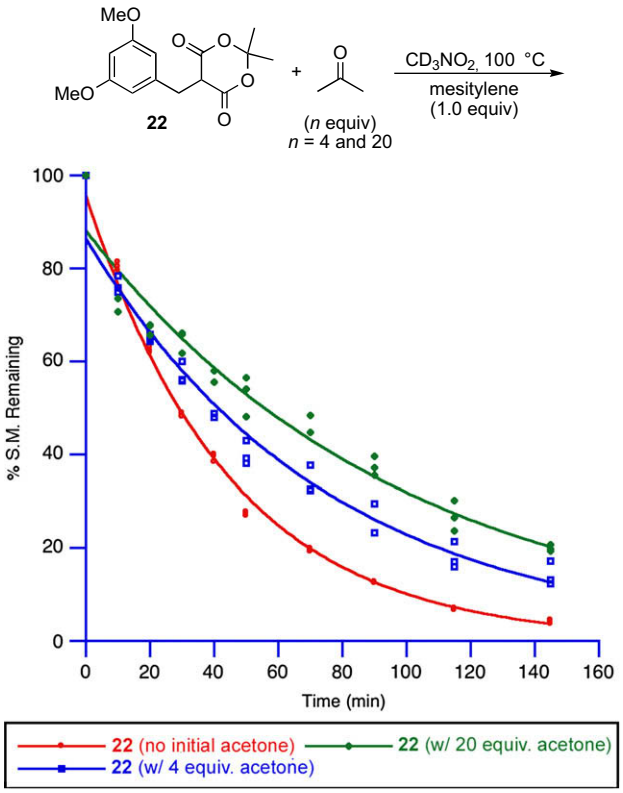
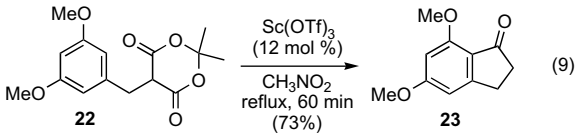


Figure 4. Effect of acetone concentration on substrate decomposition.

For the thermal decomposition of enolizable benzyl Meldrum's acids, the rate-determining step appears to be the retro hetero-Diels–Alder reaction of the tautomerized Meldrum's acid. Increasing the number of benzylic substituents decreases the rate of the retro hetero-Diels–Alder reaction, but results in a more stable acyl ketene species that is less prone to side reactions and leads to an increased yield of the corresponding 1-indanone product.[40] Formation of a ketene intermediate under mild reaction conditions (pathway c, Scheme 1) was discarded; experimental evidence will be provided and discussed in the next section.

2.3. $Sc(OTf)_3$-catalyzed intramolecular Friedel–Crafts acylation of enolizable Meldrum's acid derivatives

We have previously demonstrated that carrying out the Friedel–Crafts acylation reaction with enolizable Meldrum's acids in the presence of a Lewis acid catalyst significantly accelerates the reaction, and that side reactions are minimized.[4] It was found that while $Sc(OTf)_3$ did greatly accelerate the rate of reaction (from 6 h to 1 h for **22**), the yield increase was actually modest, from 55% to 73% using 12 mol % of catalyst (Eq. 9 vs Eq. 5). This result demanded an explanation of the role of $Sc(OTf)_3$ in the Friedel–Crafts acylation process.



(9)

The sealed-tube NMR experiments performed for the thermal acylation using **16** and **22** were repeated, but now using 10 mol % and 30 mol % of $Sc(OTf)_3$. The temperature was decreased to 85 °C since the reaction was considerably faster with catalyst, and acquisition of the initial data points was difficult. The data is depicted in Figure 5. The results clearly demonstrate a significant impact of the catalyst in the initial few minutes of the reaction, and more π-nucleophilic substrate **22** was consumed about twice as quickly as **16**. This suggests that the addition of $Sc(OTf)_3$ catalyst causes the rate-determining step to be nucleophile dependent, and therefore must be the acylation step itself. After this initial divergence, however, the rates of consumption of the remaining material appear to be very similar, implying consumption or destruction of the catalyst and or product inhibition,[41] either by acetone and/or 1-indanone and reversion of the reaction to thermal decomposition described in the previous section.

It has been reported that lanthanide triflates could significantly catalyze the enol formation of 1,3-dicarbonyl compounds.[42] While this is indeed likely with Meldrum's acid, the enolization step is not rate-determining for this acylation reaction, so accelerating this step would not have an impact on the overall rate, as observed with the Lewis acid-catalyzed reaction. In addition, there would also not be a preference for one substrate over another.

Consequently, the direct effect of $Sc(OTf)_3$ on the reactivity of acyl ketenes was examined to determine if the Lewis acid catalyst affects this potential reactive species. The reactivity of known acyl ketene **30**, a stable and easily isolable compound, in intermolecular Friedel–Crafts acylation was investigated. This ketene is unlikely to undergo intramolecular Friedel–Crafts acylation due to the formation of a four-carbon arylketone.

Acyl ketene **30** was refluxed with the electron-rich π-nucleophile 1,3-dimethoxybenzene in CH_3NO_2. In the absence of a catalyst, no product was observed. Ketene **30** was thermally unstable and decomposed, giving an unidentifiable complex mixture by analysis of the crude ^1H NMR spectra (Eq. 10). However, in the presence of a catalytic amount of $Sc(OTf)_3$, arylketone **31** was isolated in 51% yield (Eq. 11). Therefore, in the intermolecular acylation case, the acyl ketene is insufficiently electrophilic for Friedel–Crafts acylation, but when $Sc(OTf)_3$ is used, the acylation proceeded in good isolated yield. Similarly, intermolecular acylation of 5-phenyl Meldrum's acid **32** with 1,3-dimethyoxybenzene also failed in the absence of catalyst (Eq. 12). The catalyzed version did, however, give product **33** in 34% yield (Eq. 13), which supports acyl ketene activation by Lewis acid as key in the carbon–carbon bond-forming events.

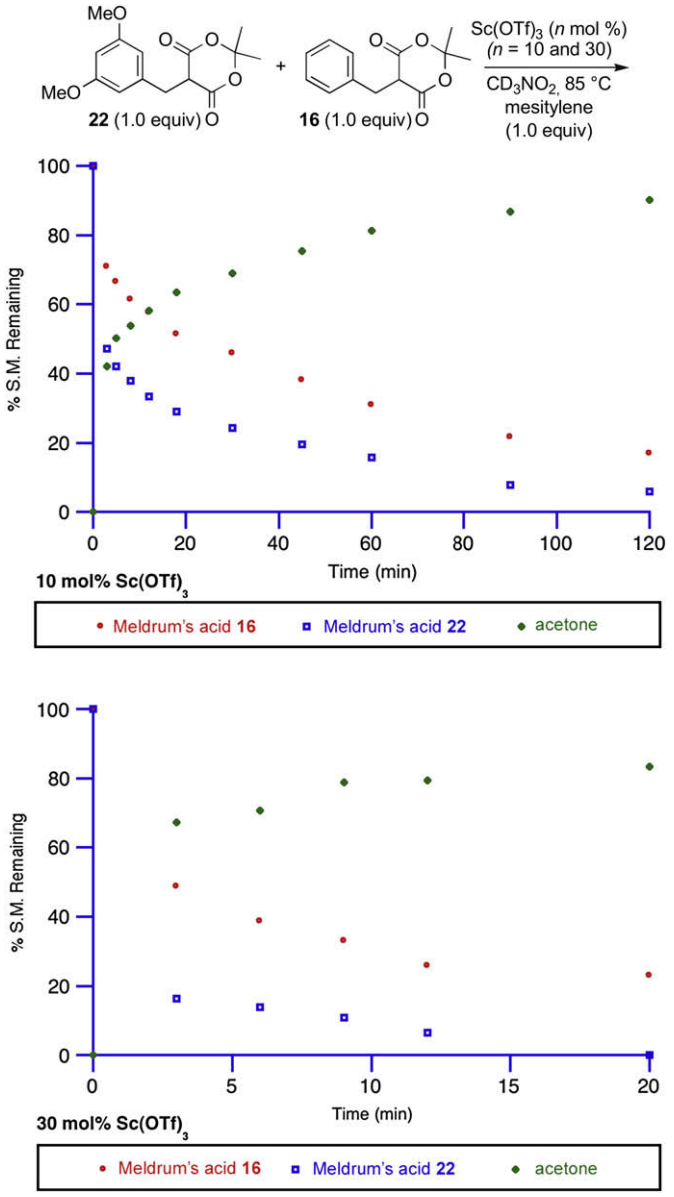
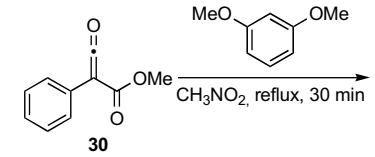
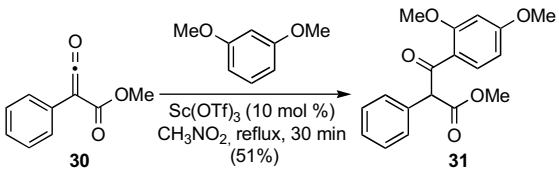


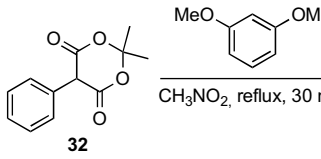
Figure 5. Comparative decomposition of substrates **16** and **22** under catalytic conditions.



(10)



(11)



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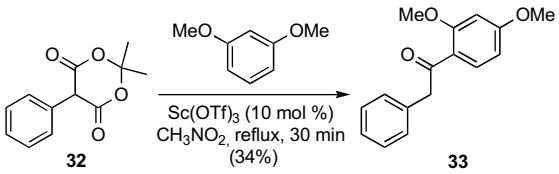


(13)

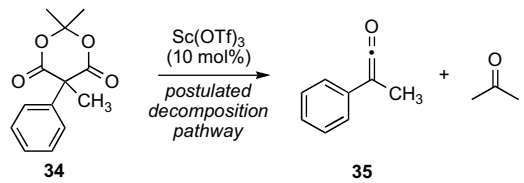
For the Lewis acid-catalyzed Friedel–Crafts acylation, the mechanism for the enolizable substrates is complicated by the continued presence of the thermal pathway that was discussed earlier (pathway a, Scheme 1). Under strict thermal conditions, the rate-determining step is the retro hetero-Diels–Alder reaction step, but in the presence of $Sc(OTf)_3$, alternative reaction pathways appear to predominate the initial stage of the reaction, which could perhaps relate to pathways b and c as illustrated in Scheme 1. This underlying thermal instability of the substrates is a possible contributor to the lower yields generally observed for enolizable substrates. The Lewis acid-catalyzed acylation was therefore better studied with the thermally stable quaternized Meldrum's acids, which will be presented in the next section.

2.4. Quaternized Meldrum's acid derivatives in the catalytic intramolecular Friedel–Crafts acylation reaction

One distinct advantage of the quaternized Meldrum's derivatives is their thermal stability in the absence of Lewis acid catalyst (Eq. 8). This feature greatly simplifies their analysis since it eliminates the underlying background reaction due to the retro hetero-Diels–Alder reaction observed in the enolizable cases, and allows for the direct monitoring of reaction progress by gas chromatography.

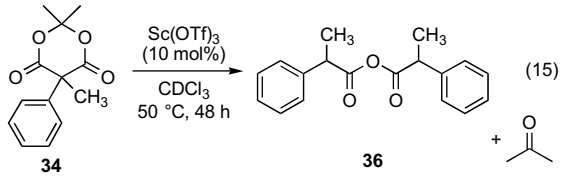
As depicted in Scheme 1, two out of the three proposed mechanisms do not proceed through tautomerization of Meldrum's acid, namely direct acylation (pathway b) and ketene formation (pathway c), and might be operational for the Friedel–Crafts acylation with quaternized Meldrum's acids.

We then set out to study if the Friedel–Crafts acylation proceeded through the intermediacy of a ketene when a quaternized Meldrum's acid was treated with a Lewis acid. It was postulated that the Lewis acid-catalyzed decomposition of 5-methyl-5-phenyl Meldrum's acid (**34**) would lead to methyl phenylketene (**35**), a known stable compound (Eq. 14).[43]

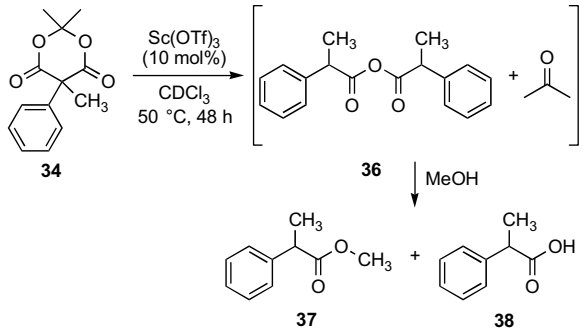


(14)

5-Methyl-5-phenyl Meldrum's acid (**34**) was then heated with a catalytic amount of $Sc(OTf)_3$ in dry deuterated chloroform in a sealed NMR tube and the ^1H and ^{13}C NMR spectra acquired at regular time intervals. The species that quantitatively arose as illustrated in Eq. 15 is anhydride **36** as a 1:1 mixture of diastereoisomers. After 48 h, complete and clean conversion to **36** had occurred, with the production of acetone.



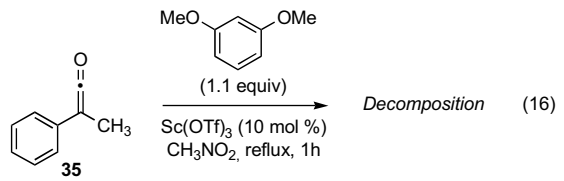
After unsealing the NMR tube and treatment of the reaction mixture with excess methanol, GC–MS analysis revealed methyl hydratropate (**37**) and 2-phenyl propanoic acid (**38**) (Scheme 4).



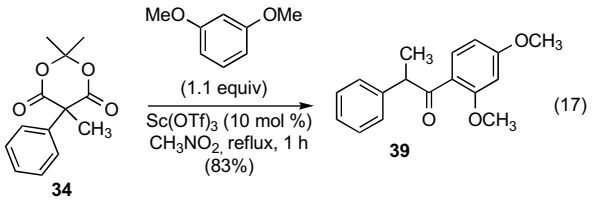
Scheme 4. Reaction of proposed anhydride **36** with methanol.

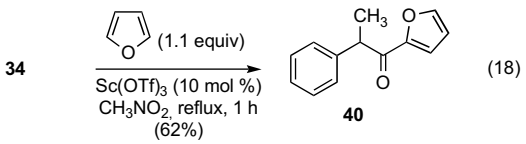
The formation of anhydride **36** is difficult to rationalize considering the strictly anhydrous reaction conditions. The scandium catalyst was pre-dried under high vacuum and handled in a glove box under nitrogen, and the chloroform-d_1 was distilled from CaH_2 and stored in a Schlenk tube. Theoretically, one molecule of **34** could act as a nucleophile and attack another Lewis acid-activated molecule of **34**. A series of decarboxylations, followed by hydrolysis, would produce **36**. However, a molecule of water is required for the conversion to the observed anhydride **36**, which suggests that H_2O is still associated with $Sc(OTf)_3$ despite the extreme measures taken to dry the catalyst.

In spite of this unusual observation, phenyl methyl Meldrum's acid did not provide ketene **35** as judged by ^1H NMR. To confirm that phenyl methylketene **35** was not forming transiently and transforming into anhydride **36**, it was treated under the same conditions, but after 2 h, complete decomposition had occurred with no recognizable peaks by ^1H or ^{13}C NMR. Since direct observation methods were unsuccessful, indirect methods were attempted. Methyl phenylketene **35** was combined with 1,3-dimethoxybenzene in CH_3NO_2 and a catalytic quantity of $Sc(OTf)_3$. After refluxing for 1 h, complete decomposition of the starting material was observed, and none of the desired product was detected (Eq. 16). It is conceivable that under these conditions the ketene undergoes predominantly side reactions compared with the analogous acyl ketene **30** that was successfully acylated under similar conditions above (Eq. 11).



The failure of ketene **35** to undergo Friedel–Crafts acylation under these conditions is in stark contrast to the intermolecular reactivity of **34** under the same reaction conditions (Eqs. 17 and 18). Both 3,5-dimethoxybenzene and furan served as effective intermolecular π-nucleophiles, providing the arylketones **39** and **40** in 83% and 62% yields, respectively.

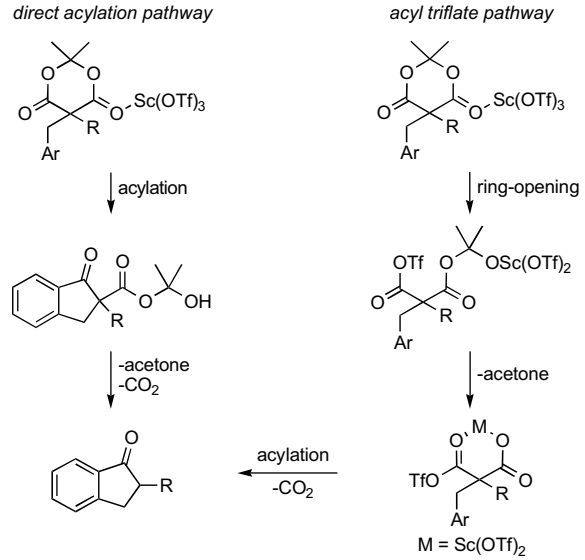




The above results strongly suggest that a ketene or Lewis acid-activated ketene is not the reactive species in the acylation reaction with quaternized Meldrum's acids, and that the direct acylation mechanism likely is operational (Scheme 1, reaction pathway b). In the next section, studies on the direct activation mechanism will be disclosed.

2.5. Study of the direct acylation mechanism through comparison of Lewis acid reaction profiles

Insights into the mechanism of activation of Meldrum's acid by Lewis acids were obtained by comparing the reaction profiles for different Lewis acids in the Friedel–Crafts acylation with quaternized Meldrum's acids. As illustrated in Scheme 5, the direct acylation was postulated to proceed either through direct acylation of a Lewis acid-activated carbonyl, or via the formation of a triflic anhydride reactive intermediate in the case of metal triflate catalysts, followed by acylation.



Scheme 5. Proposed mechanisms of Friedel–Crafts acylation with quaternized Meldrum's acids.

These mechanisms were proposed based on the observations reported for the intermolecular Friedel–Crafts acylation of arenes catalyzed by $Bi(OTf)_3$ and $Bi(NTf_2)_3$. It was found that benzoyl chloride undergoes exchange with $Bi(OTf)_3$ and $Bi(NTf_2)_3$ to produce acyl trifluoromethanesulfonate and acyl bis(trifluoromethanesulfonyl)amide intermediates, respectively, while benzoic anhydride was directly activated by the metal center.

These two mechanisms may also be operational for Meldrum's acid electrophiles.[44]

The reaction profiles for a number of Lewis and Brønsted acids in the intramolecular Friedel–Crafts acylation with quaternized Meldrum's acid was then determined, using (3,5-dimethoxybenzyl)-5-methyl Meldrum's acid (**26**) to produce 1-indanone **41** (Fig. 6).[45] The data presented is remarkable in that all the Lewis acids displayed extremely similar reaction profiles. All of the reactions were

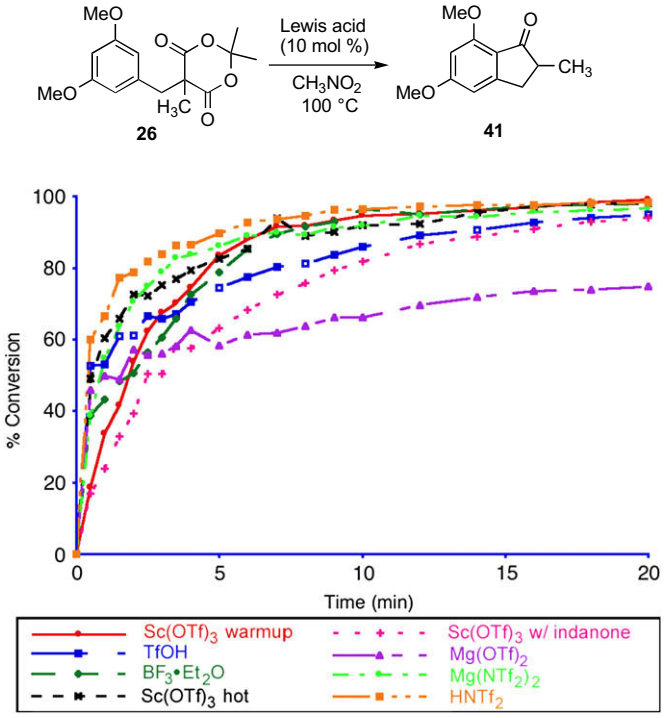
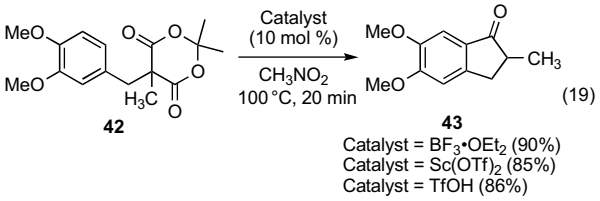


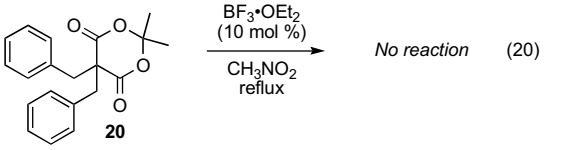
Figure 6. Relative reaction progress for different Lewis and Brønsted acids. In all cases, 10 mol % catalyst was used. Point to point line connections are provided solely for the purpose of clarity.

very fast, with the bulk of substrate conversion occurring within the first 5 min of the reaction.

In addition, some useful details that can influence the application of this methodology in practical synthetic applications can be gleaned from this data. Scandium triflate was utilized for three different experiments. [$Sc(OTf)_3$ (warmup)] allowed the reaction solution to warm up to 100 °C in the presence of catalyst, and so the initial 2 min show a much slower progress than when then catalyst was added to a preheated solution of substrate [$Sc(OTf)_3$ (hot)]. It is clearly advantageous, therefore, to add catalyst to a preheated solution of quaternized derivative. The final scandium experiment [$Sc(OTf)_3$ w/ind] examined the catalyst inhibition by benzocyclic ketone produced in the reaction. 1-Indanone was used as a conveniently available surrogate for indanone product **41** without complicating the GC analysis (a distinct new peak was produced). While this reaction still proceeded rapidly and with near complete conversion within 20 min, the initial rate was much slower than all of the other conditions examined. Clearly the Lewis acid was partially sequestered by the 1-indanone (and likely acetone as well) that was produced in the course of the reaction. This experiment with 1-indanone (4 equiv) was an extreme demonstration of this phenomenon.[46]

The most profound observation was in the comparison between magnesium triflate $Mg(OTf)_2$ and magnesium bistriflamide $Mg(NTf_2)_2$.[47,48] In this controlled experiment at precisely 100 °C, it was found that $Mg(OTf)_2$ provided the lowest overall conversion of the Lewis acids examined, even though it rapidly converted about half of the substrate within a minute of the reaction beginning. On the other hand, $Mg(NTf_2)_2$ was amongst the best catalysts examined, being comparable to $Sc(OTf)_3$. In general, metal triflamides are considered to be more Lewis acidic than their triflate counterparts.[44,49,50] This data with the magnesium-based catalysts is especially revealing when one considers the possible mechanisms of acylation in Scheme 5. If the *acyl triflate pathway* was followed, then $Mg(NTf_2)_2$ would produce an acyl bis(trifluoromethanesulfonyl)amide species which, as an acylating agent, would be less powerful than the acyl triflate formed with $Mg(OTf)_2$ based on the leaving group ability of TfO^- versus Tf_2N^-.[51] This would result in a faster reaction with $Mg(OTf)_2$ assuming that acylation is the rate-determining step, not Meldrum's acid ring opening, which was not observed in this reaction. Therefore, these results support the *direct acylation pathway* in Scheme 5 since the acylation rates correlate with the Lewis acidity of the catalysts.





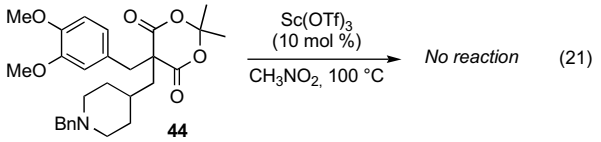
Insights into the direct acylation mechanism were further obtained with $BF_3 \cdot Et_2O$. In addition to **26**, it was observed that $BF_3 \cdot Et_2O$ was effective in promoting the Friedel–Crafts acylation of less electron-rich Meldrum's acid **42** to provide, under catalytic conditions, indanone **43** in 90% yield (Eq. 19). On the other hand, dibenzyl Meldrum's acid derivatives **20** was inert to $BF_3 \cdot Et_2O$ (Eq. 20). These observations suggested that the direct acylation mechanism (Scheme 5) is operational in the intramolecular Friedel–Crafts acylation with Meldrum's acids. To the best of our knowledge, there is no report of acid fluoride formation from acid chlorides and anhydrides using $BF_3 \cdot OEt_2$. Moreover, if an acyl fluoride was to form, Meldrum's acid substrate **20** would be observed to decompose if the strength of the nucleophilic portion was insufficient for a productive Friedel–Crafts acylation. Analysis of the ^1H NMR of the crude reaction mixture showed no reaction, and **20** quantitatively recovered when treated with $BF_3 \cdot Et_2O$ (Eq. 20).

In this section, it was proposed that the acylation of quaternized Meldrum's acid derivatives could occur either via an activated carboxylic acid derivative or by direct acylation of a Lewis acid-activated carbonyl of Meldrum's acid itself. The adoption of the direct acylation pathway as a functional mechanism is consistent with the observations presented, and at a synthetic level, provides an operationally useful model for reaction design and product prediction.

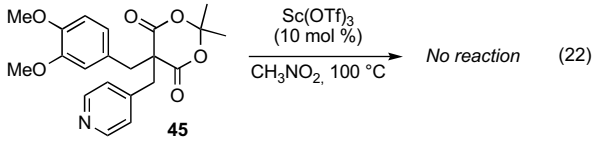
2.6. Catalyst inhibition by amine bases

The role of metal triflate catalysts in the acylation of alcohols with benzoic anhydride has been studied.[52] It was revealed that the acylation is actually promoted by TfOH, which is the true catalytic species, when the reaction is catalyzed by metal triflates. It was

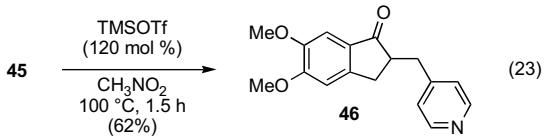
proposed that an acyl triflate intermediate is formed from the acylating agent and the metal triflate, and upon acylation, triflic acid is produced, which then assumes the role of active catalyst. Catalyst inhibition could be obtained by addition of various proportions of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), a hindered organic base that is known to not interact with metal catalysts.[53] $Sc(OTf)_3$ as a source of TfOH was postulated in other transformations.[54] Of note, the efficiency (Eq. 19) and reactivity



(21)



(22)



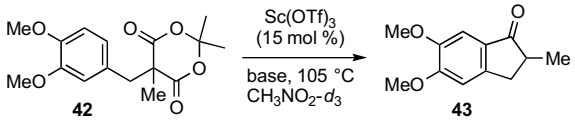
(23)

profile (Fig. 6) of TfOH in the catalytic intramolecular Friedel–Crafts acylation was identical to $Sc(OTf)_3$.

When substrates **44** and **45** were submitted to the standard reaction conditions, no trace of indanone was obtained and the starting material was quantitatively recovered (Eqs. 21 and 22). A superstoichiometric amount of Lewis acid was necessary for the reaction to proceed and yield **46** (Eq. 23). These observations suggested that $Sc(OTf)_3$ was either deactivated by the amino groups, or that the amino groups scavenged TfOH, the true catalytic species.

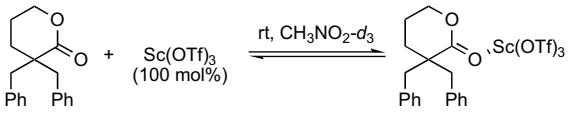
The apparent inhibition of catalytic activity by sp^2- and sp^3-hybridized nitrogen in these quarternarized Meldrum's acids was further examined by intermolecular competition experiments with substrate **42** to provide **43**. Running the same reaction with various proportions of pyridine or 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) revealed that low amounts of pyridine were tolerated, but a threshold was reached such that no substrate conversion was obtained (Table 1). The experiment was performed in a sealed NMR

Table 1
Catalytic acylation of **42** in the presence of amine



Entry	Amine	Loading (mol %)	Time (h)	Conversion (%)
1	Pyridine	0	1	100
2	Pyridine	15	1	100
3	Pyridine	30	1	55
4	Pyridine	45	1	0
5	Pyridine	100	1	0
6	DTBMP	15	2	100
7	DTBMP	30	1	50
8	DTBMP	30	2	75
9	DTBMP	45	18	0

Table 2
Effect of DTBMP on $Sc(OTf)_3$ Lewis acidity



Mixture	δ C=O (ppm)	$\Delta\delta$	δ $^{19}F_3C$ (ppm)
α,α-Dibenzyl-δ-valerolactone (**47**)	176.8	—	—
$Sc(OTf)_3$	—	—	−78.0
47+$Sc(OTf)_3$	190.5 (s)	13.7	−78.2
47+TfOH	190.8 (s)	14.0	−79.2
47+$Sc(OTf)_3$+DTBMP (1 equiv)	178.6 (vb)	1.8	−78.8
47+$Sc(OTf)_3$+DTBMP (2 equiv)	176.9 (b)	0.1	−79.3
47+$Sc(OTf)_3$+DTBMP (3 equiv)	176.9 (s)	0.1	−79.3

b=broad; s=sharp; vb=very broad.

tube containing an internal standard (mesitylene) and the reaction heated at 105 °C. After a fixed time interval (1 or 2 h) the reaction was observed by ^1H NMR to determine the substrate conversion by integration.

It was demonstrated that a ratio of 3:1 base/Lewis acid deactivated the catalyst sufficiently and no trace of product was formed. These results are virtually identical to the results obtained by Markó in a comparable experiment examining the acylation of alcohols catalyzed by metal triflates, and also correlated with the results obtained with Meldrum's acids **44** and **45**.

The Lewis acidity of $Sc(OTf)_3$ in the presence of DTBMP was directly assessed using α,α-dibenzyl-δ-valerolactone **47**, a mimic of quaternized Meldrum's acid since the latter decomposes in the presence of a Lewis acid. An equimolar amount of catalyst and substrate were combined in a sealed NMR tube and the chemical shift of the lactone carbonyl examined.[55,56] With increased loading of DTBMP, the downfield shift was diminished, and essentially disappeared with 2 equiv of DTBMP (Table 2), as evidenced by the chemical shift of the lactone carbonyl. The ^{19}F NMR also indicated that upon combination with increasing amounts of DTBMP, the triflate moiety was more like that of a free triflate anion than in its scandium complex state.

Scandium triflate has been reported to be a water-tolerant Lewis acid but no systematic work has yet been done to shed light on the nature of the catalytic species and mechanism of the reactions.[57] It was proposed that $Sc(OTf)_3$ increased the proticity of MeOH, and behaves as a protic acid in the presence of MeOH.[54c,d] A similar mechanism has been postulated for $Yb(OTf)_3$ and water.[54a,58]

Based on the results discussed above, it appears as though $Sc(OTf)_3$ is practically challenging to obtain in a truly anhydrous form. Consequently, in the catalytic Friedel–Crafts acylation of Meldrum's acids, TfOH is the active catalytic species, with metal triflates acting as a very mild and convenient method for its delivery.

3. Summary

Benzyl Meldrum's acid derivatives are potent acylating agent in the intramolecular Friedel–Crafts acylation. Under thermal conditions, without catalyst, monosubstituted Meldrum's acids enolize, then undergo a rate-limiting retro hetero-Diels–Alder reaction to form an acyl ketene intermediate that reacts intramolecularly with π-nucleophiles, and, upon decarboxylation, an arylketone is formed.

For both quaternized and enolizable Meldrum's acid derivatives, the addition of a Lewis acid is capable of activating the Meldrum's acid carbonyls. This complex is either attacked directly, or undergoes a ligand transfer from the Lewis acid to generate an activated carboxylic acid derivative. Enolizable Meldrum's acids can still enolize and undergo retro hetero-Diels–Alder to generate an acyl ketene intermediate, which can interact

with the Lewis acid in this dichotomous manner. Quaternized derivatives, in their Lewis acid-activated form, immediately undergo acylation without the possibility of enolization (and further decomposition), resulting in faster and high-yielding reactions to generate 2-substituted 1-indanones. Quaternized derivatives are quite poorly Lewis basic, such that the addition of even small quantities of a Lewis base inhibits catalyst activity for this class of substrates. This is particularly true for $Sc(OTf)_3$, which appears to behave as a TfOH delivery device based on the results presented here.

4. Experimental section

4.1. General

All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. Nitromethane was distilled from CaH_2. Scandium triflate was dried under high vacuum (0.5 mmHg) for 2 h at 180 °C and stored in a dry-box. Unless indicated otherwise, all other reagents were used as received from commercial sources. ^1H NMR spectra were referenced to residual ^1H shift in $CDCl_3$ (7.24 ppm). $CDCl_3$ (77.0 ppm) was used as the internal reference for ^{13}C NMR spectra. Reactions were monitored by thin-layer chromatography (TLC) on commercial silica pre-coated plates with a particle size of 60 Å. Developed plates were viewed by UV lamp (254 nm), and with *p*-anisaldehyde stain. Flash chromatography was performed using 230–400 mesh silica gel. Melting points are uncorrected. High resolution mass spectra were run at the University of Waterloo with a source temperature of 200 °C, mass resolution of 9000, and electron energy of 70 eV. The synthesis of Meldrum's acids **16**, **18**, **20**, **22**, **24**, **26**, **28**, **42**, **44**, and **45** was previously described in the literature.[4a]

4.2. Lewis acid-catalyzed intramolecular Friedel–Crafts acylation with Meldrum's acid derivatives

4.2.1. General procedure

Reactions were typically performed on 200 mg of substrate. In a flame-dried round-bottomed flask equipped with a magnetic stir bar, a reflux condenser and under inert atmosphere, was placed the substrate and $Sc(OTf)_3$ (10 mol %) (or other solid catalyst; liquid catalysts were administered to a solution of the substrate in CH_3NO_2). Distilled CH_3NO_2 was added in one portion by syringe, and the resulting suspension immediately placed into an oil bath preheated to 100 °C. The reaction mixture was maintained at this temperature and monitored by TLC until complete consumption of starting material was observed. The reaction mixture was then concentrated under vacuum and directly subjected to flash chromatography, using a small quantity of CH_2Cl_2 to assist column loading. The catalytic Friedel–Crafts acylation of **16**, **18**, **20**, **22**, **26**, **42**, and **45** was previously described in the literature.[4a]

4.3. Thermal intramolecular Friedel–Crafts acylation with Meldrum's acid derivatives

4.3.1. General procedure

Reactions were typically performed on 200 mg of substrate. In a flame-dried round-bottomed flask equipped with a magnetic stir bar, a reflux condenser and under inert atmosphere, was placed the substrate and distilled CH_3NO_2. The resulting suspension was placed into an oil bath preheated to 100 °C. The reaction mixture was maintained at this temperature and monitored by TLC until complete consumption of starting material was observed. The reaction mixture was then concentrated under vacuum and directly subjected to flash chromatography, using a small quantity of CH_2Cl_2 to assist column loading. The thermal Friedel–Crafts acylation of **22** was previously reported. This procedure was applied to Meldrum's acids **16**, **24**, and **26**.

4.4. Thermal intramolecular Friedel–Crafts acylation with acyl ketenes

4.4.1. 5,7-Dimethoxy-1-indanone-2-carboxylic acid methyl ester (*27*)

Meldrum's acid derivative **22** (100 mg, 0.34 mmol) and trimethyloxonium tetrafluoroborate (Meerwein's salt) (70 mg, 0.47 mmol) were combined in a round-bottomed flask equipped with a reflux condenser, magnetic stir bar and a rubber septum under a dry nitrogen atmosphere. At 0 °C, CH_2Cl_2 (5 mL) was added via syringe with stirring, followed by diisopropylethylamine (65 μL, 0.38 mmol). The resulting suspension was stirred for 30 min at 0 °C and then heated at reflux for 1.5 h, at which time no starting material was observed by TLC. The crude reaction mixture was quenched with aqueous 10% HCl then diluted with additional CH_2Cl_2. The layers were partitioned and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic fractions were dried over $MgSO_4$, then filtered and concentrated. The yellow oil was purified by flash chromatography (2:1 EtOAc/Hex) on silica gel to provide 4 mg (52%) of the desired β-keto ester **27** as an oil that solidified on standing. Mp 103–104 °C; lit. 104–105 °C (EtOAc/Et_2O); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.48 (1H, br s), 6.28 (1H, br s), 3.88 (3H, s), 3.86 (3H, s), 3.74 (3H, s), 3.66 (1H, dd, J=8.2, 3.8 Hz), 3.41 (1H, dd, J=17.2, 3.4 Hz), 3.20 (1H, dd, J=17.3, 8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.1, 170.0, 167.6, 160.0, 158.8, 117.6, 101.6, 97.8, 55.8, 53.7, 52.7, 30.2. HRMS (EI): m/z calcd for $C_{13}H_{14}O_5$ (M^+) 250.0841, found 250.0839.

4.4.2. Methyl 4′,6′-dimethoxy-3′-oxo-2′,3′-dihydrospiro-[cyclohexane-1,1′-indene]-2′-carboxylate (*29*)

Meldrum's acid derivative **28** (200 mg, 0.55 mmol) and trimethyloxonium tetrafluoroborate (Meerwein's salt) (114 mg, 0.77 mmol) were combined in a round-bottomed flask equipped with a reflux condenser, magnetic stir bar and a rubber septum under a dry nitrogen atmosphere. At 0 °C, CH_2Cl_2 (5 mL) was added via syringe with stirring, followed by diisopropylethylamine (0.13 mL, 0.75 mmol). The resulting suspension was stirred for 30 min at 0 °C then heated at reflux for 1 h. An additional portion of Meerwein's salt (114 mg, 0.77 mmol) was added and the reflux continued for an additional 30 min. The crude reaction mixture was quenched with aqueous 10% HCl then diluted with additional CH_2Cl_2. The layers were partitioned and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic fractions were dried over $MgSO_4$, then filtered and concentrated. The yellow oil was purified by flash chromatography (1:1 Hex/EtOAc) on silica gel to provide the desired β-keto ester **29** as 112 mg (67%) of white solid. Mp 168–170 °C (Et_2O); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.46 (1H, d, J=1.7 Hz), 6.28 (1H, d, J=1.6 Hz), 3.88 (6H, s), 3.67 (3H, s), 3.56 (1H, s), 2.04–2.09 (1H, m), 1.77–1.16 (9H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.0, 170.0, 168.3, 167.4, 159.6, 116.6, 99.4, 97.4, 64.1, 55.8, 55.7, 52.0, 46.6, 41.8, 31.9, 25.3, 23.6, 22.7; HRMS (EI): m/z calcd for $C_{18}H_{22}O_5$ (M^+): 318.1467, found: 318.1470.

4.5. Thermal intramolecular Friedel–Crafts acylation with enolizable substrates

4.5.1. Competition experiments (Fig. 2)

5-(3,5-Dimethoxybenzyl) Meldrum's acid (**22**) (10 mg, 0.034 mmol) and 5-benzyl Meldrum's acid (**16**) (8.0 mg, 0.034 mmol) were placed in a sealable Schlenk NMR tube, to which was added 4.7 μL of mesitylene and CD_3NO_2 (0.5 mL). The tube was sealed under a dry nitrogen atmosphere, then the t=0 data acquired on a 300 MHz NMR. Integration of the mesitylene peak was defined as nine protons, and integrations of the two benzylic

protons of the two substrates were recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 °C. At the given time points, the tube was removed and placed in an ice/water bath for 1 min, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This experiment was performed in triplicate. Time in minutes; 'benzyl', 'dimethoxy', and 'acetone' are the standardized integration values for each signal in each run; %benzyl, %dimethoxy, and %acetone=100(value$_t$/value$_0$) for each experiment.

4.6. Consumption of enolizable Meldrum's acid derivative under thermal conditions

4.6.1. Determination of rate constant (k_H) (Fig. 3)

5-(3,5-Dimethoxybenzyl) Meldrum's acid (**22**) (10.0 mg, 0.034 mmol) was placed in a sealable Schlenk NMR tube, to which was added 5 μL of mesitylene and CD_3NO_2 (0.5 mL). The tube was sealed under a dry nitrogen atmosphere, then the t=0 data acquired on a 300 MHz NMR. Integration of the mesitylene peak was defined as nine protons, and integration of the Meldrum's methyl peak (three protons) farthest upfield was recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 °C. At the given time points, the tube was removed and placed in an ice/water bath for 1 min, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This reaction was performed in triplicate. Time in minutes; 'acetone' and 'methyl' are the standardized integration values for the acetone and Meldrum's acid methyl signal in each run; %conv=100(acetone/(acetone+methyl)) for each experiment; ln plot=ln(100−%conv).

4.7. Consumption of deuterium labeled enolizable Meldrum's acid derivative under thermal conditions

4.7.1. Determination of rate constant (k_D) (Fig. 3)

5-(3,5-Dimethoxybenzyl)-5-deutero Meldrum's acid (5-d_1-**22**) (>95% incorporation) (10.0 mg, 0.034 mmol) was placed in a sealable Schlenk NMR tube, to which was added 5 μL of mesitylene and CD_3NO_2 (0.5 mL). The tube was sealed under a dry nitrogen atmosphere, then the t=0 data acquired on a 300 MHz NMR. Integration of the mesitylene peak was defined as nine protons, and integration of the Meldrum's methyl peak (three protons) farthest upfield was recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 °C. At the given time points, the tube was removed and placed in an ice/water bath for 1 min, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This reaction was performed in triplicate. Time in minutes; 'acetone' and 'methyl' are the standardized integration values for each signal in each run; %conv=100(acetone/(acetone+methyl)) for each experiment; ln plot=ln(100−%conv).

4.8. Relative effect of initial acetone concentration on reaction rate (Fig. 4)

5-(3,5-Dimethoxybenzyl) Meldrum's acid (**22**) (10.0 mg, 0.034 mmol) was placed in a sealable Schlenk NMR tube, to which was added 5 μl of mesitylene and CD_3NO_2 (0.5 mL). Acetone (10 μL or 50 μL) was added to the tube, which was then sealed under a dry nitrogen atmosphere, and the t=0 data acquired on a 300 MHz NMR. Integration of the mesitylene methyl peak was defined as nine protons, and integration of the Meldrum's methyl peak farthest upfield was recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 °C. At the given time points, the tube was removed and placed in an ice/water bath for 1 min, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This experiment was repeated in triplicate (for each acetone amount). Acetone-free data was used from the kinetics experiment above. Time in minutes; 'methyl' is the standardized integration value for that signal in each run; % S.M.=100(methyl$_t$/methyl$_0$) for each experiment.

4.9. Catalytic intramolecular Friedel–Crafts acylation with enolizable substrates

4.9.1. Competition experiment (Fig. 5)

5-(3,5-Dimethoxybenzyl) Meldrum's acid (**22**) (10 mg, 0.034 mmol) and 5-benzyl Meldrum's acid (**16**) (8 mg, 0.034 mmol) were placed in a sealable Schlenk NMR tube containing $Sc(OTf)_3$ (2 mg, 0.1 equiv) or (6 mg, 0.3 equiv), to which was added 4.7 μL of mesitylene and CD_3NO_2 (0.6 mL). The tube was sealed under a dry nitrogen atmosphere, then the t=0 data acquired on a 300 MHz NMR. Integration of the mesitylene methyl peak was defined as nine protons, and integrations of the two benzylic protons of the two substrates were recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 85 °C. At the given time points, the tube was removed and placed in an ice/water bath for 1 min, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. Time in minutes; 'benzyl', 'dimethoxy', and 'acetone' are the standardized integration values for each signal in each run; %benzyl, %dimethoxy, and %acetone=100(value$_t$/value$_0$) for each experiment.

4.10. Intermolecular Friedel–Crafts acylation with acyl ketenes, ketenes, and Meldrum's acid derivatives

4.10.1. 3-Oxo-2-phenyl-acrylic acid methyl ester (*30*)

Phenyl Meldrum's acid[59] **32** (337 mg, 1.53 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to −70 °C in a Schlenk tube under a dry argon atmosphere. An excess of dry ethereal diazomethane solution (generated under ethanol free conditions) was added and the reaction mixture stirred at this temperature for 30 min. The reaction mixture was then maintained at a temperature between −50 and −40 °C as the solvent was removed under high vacuum (0.3 Torr) with vigorous stirring. The resulting yellow oil was warmed to room temperature under vacuum and then purged with argon. The acyl ketene **30** was obtained as 195 mg of yellow oil (72%) and used immediately without purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (5H, m), 3.81 (3H, s); IR ($CDCl_3$, liquid cell) ketene 2130, ester 1721 cm^{-1}.

4.10.2. Methyl 3-(2,4-dimethoxyphenyl)-3-oxo-2-phenylpropanoate (*31*)

To solution of 1,3-dimethoxybenzene (76 mg, 0.55 mmol) in dry CH_3NO_2 (1 mL) was added dry $Sc(OTf)_3$ (27 mg, 0.055 mmol), and the resulting suspension brought to reflux in an oil bath under argon atmosphere. A solution of acyl ketene **30** (97 mg, 0.55 mmol) in CH_3NO_2 (1 mL) was added in one portion to the refluxing reaction mixture via syringe. After 30 min, the reaction mixture was cooled and concentrated by rotary evaporation, and then purified by flash chromatography (4:1 Hex/EtOAc) to provide 88 mg (51%) of **31** as a pale yellow oil. If the reaction was performed in the absence of $Sc(OTf)_3$ then no product or starting material was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, d, J=8.8 Hz), 7.24–7.30 (5H, m),

6.50 (1H, dd, J=8.8, 2.1 Hz), 6.37 (1H, d, J=2.1 Hz), 5.64 (1H, s), 3.83 (3H, s), 3.81 (3H, s), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 170.1, 165.1, 160.4, 133.9, 133.8, 129.7, 128.3, 127.6, 119.5, 105.7, 198.1, 64.1, 55.5, 55.2, 52.3; IR (NaCl) ester 1734, ketone 1668 cm^{-1}; EI m/z (rel int.) 314 (3), 179 (4), 166 (10), 165 (100); HRMS (EI) calcd for $C_{18}H_{18}O_5$: 314.1154, found 314.1159.

4.10.3. 1-(1,4-Dimethoxyphenyl)-2-phenyl-1-ethanone (**33**)

A solution of 1,3-dimethoxybenzene (140 mg, 1.01 mmol) and $Sc(OTf)_3$ (50 mg, 0.10 mmol) in dry CH_3NO_2 (5 mL) was brought to reflux under a dry nitrogen atmosphere. 5-Phenyl Meldrum's acid (**32**) (223 mg, 1.01 mmol) was added in one portion and the reaction mixture refluxed for 30 min. The dark brown mixture was cooled, concentrated, and then purified by flash chromatography (4:1 Hex/EtOAc) to provide 88 mg (34%) of **33** as a pale yellow oil. If the reaction was performed in the absence of $Sc(OTf)_3$ then no product or starting material was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, d, J=8.7 Hz), 7.27–7.19 (5H, m), 6.5 (1H, dd, J=8.7, 2.1 Hz), 6.43 (1H, d, J=2.1 Hz), 4.26 (2H, s), 3.87 (3H, s), 3.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 164.5, 160.6, 135.7, 133.1, 129.6, 128.2, 126.4, 120.8, 105.2, 98.3, 55.5, 55.4, 50.0; IR (NaCl) C=O 1665 cm^{-1}; EI m/z (rel int.) 256 (1), 179 (3), 166 (10), 165 (100); HRMS (EI) calcd for $C_{16}H_{16}O_3$: 256.1099, found 256.1106.

4.10.4. 1-(2,4-Dimethoxyphenyl)-2-phenyl-1-propanone (**39**)

To a refluxing solution of 1,3-dimethoxybenzene (128 mg, 0.93 mmol) and 5-methyl-5-phenyl Meldrum's acid[60] (**34**) (200 mg, 0.85 mmol) in CH_3NO_2 (5 mL) under nitrogen was added $Sc(OTf)_3$ (42 mg, 0.09 mmol). The reaction mixture was allowed to stir for 1 h and then cooled and concentrated. Purification by flash chromatography (5:1 Hex/EtOAc) provided 191 mg (83%) of **39** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, J=8.7 Hz), 7.25–7.11 (5H, m), 6.43 (1H, dd, J=8.7, 2.2 Hz), 6.34 (1H, d, J=2.2 Hz), 4.75 (1H, q, J=6.9 Hz), 3.79 (3H, s), 3.78 (3H, s), 1.46 (3H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 159.8, 142.0, 132.9, 128.2, 128.0, 126.3, 121.2, 105.0, 98.2, 55.3, 55.2, 51.1, 19.2; IR (NaCl) C=O 1663 cm^{-1}; EI m/z (rel int.) 270 (<1), 179 (8), 166 (10), 165 (100), 122 (7), 77 (6); HRMS (EI) calcd for $C_{17}H_{18}O_3$: 270.1256, found 270.1258.

4.10.5. 1-(2-Furyl)-2-phenyl-1-propanone (**40**)

In a Schlenk tube containing 5-methyl-5-phenyl Meldrum's acid (**34**) (200 mg, 0.85 mmol) and $Sc(OTf)_3$ (42 mg, 0.09 mmol) in CH_3NO_2 (5 mL) under nitrogen was added furan (64 mg, 0.94 mmol). The Schlenk tube was sealed and immediately placed in an oil bath at 105 °C for 1 h. The resulting black reaction mixture was cooled and concentrated, and then purified by flash chromatography (5:1 Hex/EtOAc) to provide 106 mg (62%) of **40** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, dd, J=0.8, 0.8 Hz), 7.50–7.15 (5H, m), 7.12 (1H, br d, J=3.6 Hz), 6.43 (1H, dd, J=3.6, 1.6 Hz) 4.47 (1H, q, J=7.0 Hz), 1.50 (3H, d, J=7.0 Hz); $CDCl_3$ (75 MHz, $CDCl_3$) δ 189.4, 152.2, 146.3, 140.8, 128.8, 127.9, 127.0, 117.8, 112.2, 47.9, 18.3; IR (NaCl) C=O 1674 cm^{-1}; EI m/z (rel int.) 200 (41), 105 (100), 95 (61), 77 (18); HRMS (EI) calcd for $C_{13}H_{12}O_2$: 200.0837, found 200.0840.

4.11. Relative reaction progressions for various Lewis Acids in the intramolecular Friedel–Crafts acylation of quaternized Meldrum's acid derivatives (Fig. 6)

A 0.095 M stock solution containing of 5-(3,5-dimethoxybenzyl)-5-methyl Meldrum's acid (**26**) (2.94 g, 9.55 mmol) in CH_3NO_2 (100 mL) was prepared. In a glove box, the solid catalyst was weighed into a dry screwcap vial. A dry two-necked round-bottomed flask equipped with a reflux condenser and a stir bar was placed into an oil bath preheated to 100 °C under a dry nitrogen atmosphere, and the 5 mL of the stock solution was added via syringe. After 5 min, the t=0 sample was taken. For the liquid catalysts [(TfOH 5 μL, 10 mol %), $BF_3{\cdot}OEt_2$ (9 μL, 10 mol %)], the catalyst was added by microsyringe and timing of the reaction immediately begun. For solid catalysts [$Sc(OTf)_3$ (25 mg, 10 mol %), $Mg(OTf)_2$ (16 mg, 10 mol %), $Mg(NTf_2)_2$ (27 mg, 10 mol %)] the solid was added rapidly through the available neck of the round-bottomed flask and then the flask immediately resealed and timing begun.

Three experiments were performed using scandium triflate. One is as described above, but in another the catalyst was added to the flask first, before the stock solution was added. In this experiment the solution needed to warm up to the oil bath temperature while being exposed to catalyst. In the third experiment the stock solution was used to dissolve 1-indanone (252 mg, 400 mol %), and the catalyst added after the initial warming period.

Samples were taken every 30 s for the first 4 min, then every minute for the next 6 min, then every 2 min for the next 10 min, for a total reaction time of 20 min. This distribution ensured a large sampling rate at the beginning of the reaction. At each time point, 100 μL aliquots were withdrawn using a clean and dry disposable syringe, and immediately injected into 10 μL of distilled Et_3N in 100 μL of methylene chloride. At end of experiment, each sample was filtered through a short plug of silica gel and eluted with ethyl acetate. The samples were then run on a gas chromatograph equipped with a flame ionization detector, with a temperature gradient of 50 °C for 3 min, then 50 to 270 °C over 10 min. The indanone product peak eluted at 11.7 min, and the Meldrum's acid derivative starting material at 12.9 min. In the following tables of raw data, the 'time' column is the reaction time elapsed in minutes, the 'product' column is the integration value for 1-indanone, 'sm' is the Meldrum's acid derivative **68**, and the '%conv'=100×'prod'/('prod'+'sm').

Acknowledgements

This work was supported by Boehringer Ingelheim (Canada) Ltd., AstraZeneca Canada Inc., the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Foundation for Innovation, the Ontario Innovation Trust, and the University of Waterloo. D.F. thanks the Government of Ontario for a fellowship (OGSST). The authors thank Professor Monicá Barra, University of Waterloo, for helpful discussions.

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