ACCOUNTS
of chemical research

Meldrum's Acids and 5-Alkylidene Meldrum's Acids in Catalytic Carbon–Carbon Bond-Forming Processes

AARON M. DUMAS AND ERIC FILLION*

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

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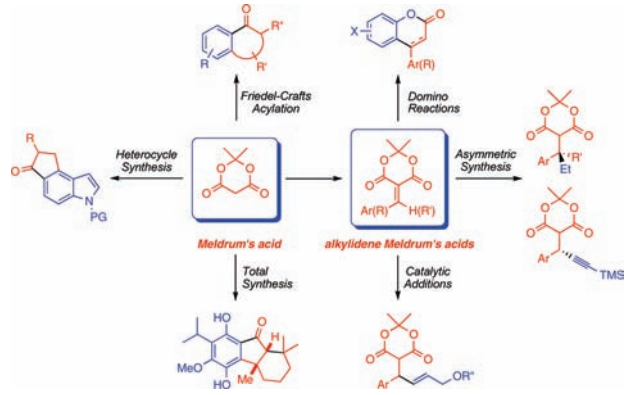
CONSPECTUS

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is a molecule with a unique history, owing to its originally misassigned structure, as well as a unique place among acylating agents, owing to its high acidity and remarkable electrophilicity. In this Account, we outline the work of our group and others toward harnessing the reactivity of Meldrum's acid derivatives in catalytic C–C bond-forming reactions.



Taking advantage of the ability of Meldrum's acid to decompose to CO_2 and acetone following acyl substitution, we have shown that intramolecular Friedel–Crafts acylations can be performed under mild Lewis acidic conditions to yield a variety of benzocyclic ketones. In a further expansion of this method, a domino Friedel–Crafts acylation/α-*tert* alkylation reaction was used to complete the first total synthesis of (±)-taiwaniaquinol B.

The unique characteristics of Meldrum's acid extend to its alkylidene derivatives, which have also proven exceptionally useful for the development of new reactions not readily accessible from other unsaturated carbonyl electrophiles. By combining the electrophilicity and dienophilicity of alkylidene Meldrum's acid with our Friedel–Crafts chemistry, we have demonstrated new domino syntheses of coumarin derivatives and tetrahydrofluorenones by conjugate additions, Diels–Alder cycloadditions, and C–H functionalizations. Additionally, we have used these powerful acceptors to allow conjugate alkenylation with functionalized organostannanes, and conjugate allylation under very mild conditions. We have also shown that these molecules permit the asymmetric formation of all-carbon quaternary stereocenters via enantioselective conjugate additions. These reactions employ dialkylzinc nucleophiles, maximizing functional group compatibility, while the presence of a Meldrum's acid moiety in the product allows a variety of postaddition modifications. A full investigation of this reaction has determined the structural factors of the alkylidene that contribute to optimal enantioselectivity. We have also used these acceptors to form tertiary propargylic stereocenters in very high enantiomeric excess by an extremely mild, Rh(I)-catalyzed addition of TMS-acetylene.

Overall, we demonstrate that Meldrum's acid and its derivatives provide access to a broad range of reactivities that, combined with their ease of handling and preparation, make them ideal electrophiles.

Introduction

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, **1**) and its derivatives are exceedingly versatile reagents in organic synthesis (Figure 1). First synthesized by Meldrum in 1908,[1] the correct structure was elucidated in 1948 by Davidson and Bernhard.[2] The simplicity of its structure, combined with its unique properties and complex reactivity, has made Meldrum's acid a molecule of great synthetic[3] and theoretical interest.[4]

A wide array of synthetic transformations have emerged as a result of the intrinsic electrophilic and

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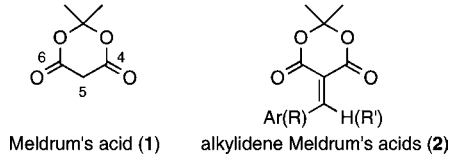
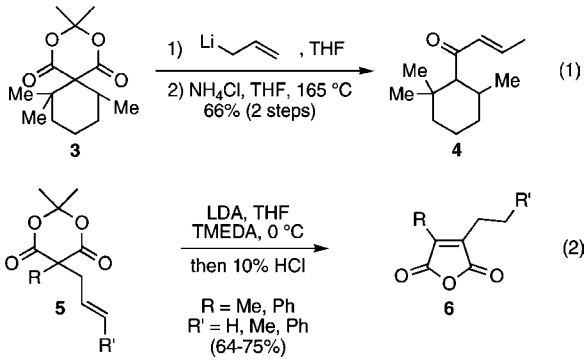


FIGURE 1. Meldrum's acid (**1**) and alkylidene derivatives (**2**)

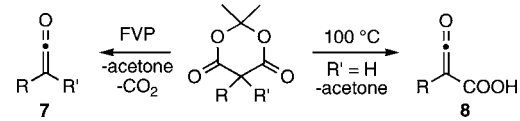
nucleophilic properties of the 1,3-dioxan-4,6-dione core of Meldrum's acid. Derivatives with at least one hydrogen atom at C(5) are enolizable and are ambident nucleophiles, which have been reacted under stoichiometric and catalytic conditions with a variety of electrophiles at either the C(5)-position or the carbonyl oxygens.

On the other hand, the carbonyls of Meldrum's acids, the C(4) and C(6) positions, are highly susceptible to nucleophilic attack. Acyl substitution results in a unique ring-opening reaction with loss of acetone, followed in some cases by decarboxylation. While there is a significant body of literature on various ring-opening strategies by heteronucleophiles, carbon−carbon bond-forming reactions have been overlooked, as a direct consequence of Meldrum's acids' high acidity[5] (pK_a of 4.83−4.93[6] in H_2O) and their propensity to be deprotonated by Brønsted basic carbon nucleophiles.

At the time that we initiated our research program, acylation of carbon nucleophiles with Meldrum's acids was scarcely documented. Nonenolizable Meldrum's acid derivatives (quaternized Meldrum's acids) were reported to react with organolithium reagents, in both inter- and intramolecular fashions. The synthesis of the natural product δ-damascone (**4**) was achieved by addition of allyllithium to Meldrum's acid **3**, followed by decarboxylation and alkene isomerization (eq 1).[7] Maleic anhydrides **6** were prepared from Meldrum's acids **5** (eq 2), where allylic deprotonation induced ring enlargement through nucleophilic attack on the carbonyl and C−C bond cleavage; treatment with acid gave the anhydrides with concomitant alkene migration.[8] While efficient, the narrow scope of these transformations is seemingly not amenable to the development of catalytic carbon−carbon bond-forming methods.

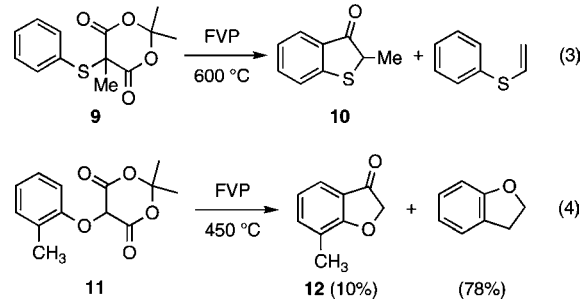


SCHEME 1. Ketene Formation from Meldrum's Acids



It is well established that the thermal instability of Meldrum's acid allows access to highly reactive ketene intermediates. Flash vacuum pyrolysis (FVP) of Meldrum's acids leads to ketenes **7**,[9] while enolizable Meldrum's acids, when heated at 100 °C, undergo retro-hetero-Diels−Alder cycloaddition with loss of acetone to furnish acyl ketenes **8** (Scheme 1).[10]

The ability of Meldrum's acids derivatives to decompose to highly electrophilic ketenes opens up the possibility of forging new C−C bonds from these intermediates. For example, pyrolysis of phenylthioether **9** furnished Friedel−Crafts acylation product **10**, albeit in an undetermined yield, in addition to phenyl vinyl sulfide (eq 3).[11] Similarly, pyrolysis of **11** yielded a Friedel−Crafts acylation byproduct, benzofuran-2(3*H*)-one (**12**), in a modest 10% yield (eq 4).[12] In these cases, the unconventional FVP conditions present a practical limitation in terms of exploiting the unique reactivity of Meldrum's acid derivatives.

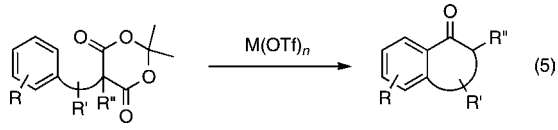


In contrast to the dearth of C−C bond-forming reactions of Meldrum's acid derivatives, alkylidene Meldrum's acids **2** have found relatively extensive use as electrophiles in conjugate additions and as both heterodienes and dienophiles in [4 + 2] cycloadditions. Their anomalously high reactivity led them to be termed "neutral organic acids",[13] and they have subsequently been used extensively in studies on conjugate addition.[14] Similarly, the highly electron-deficient alkene present in **2** is significantly more reactive as a dienophile compared with the analogous alkylidene malonates.[15] However, systematic investigation of new catalytic methods based around these unique molecules has not been fully explored.

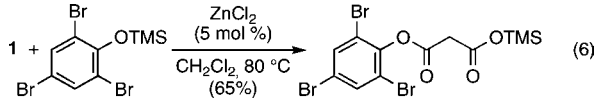
Inspired by the untapped potential of Meldrum's acid derivatives, our group has dedicated a great deal of effort to the design, discovery, and development of novel catalytic C−C bond-forming processes. Meldrum's acid's availability, ease of functionalization, handling, purification (generally by recrys-

tallization), and moisture stability are additional characteristics that were also taken into consideration in the quest to identify ideal electrophilic reagents. In this Account, our efforts in exploiting the electrophilicity of Meldrum's acid derivatives in Lewis acid- and transition metal-catalyzed C−C bond-forming reactions are described.

1-Indanone Synthesis from Benzyl Meldrum's Acids through Metal Triflate-Catalyzed Intramolecular Friedel−Crafts Acylation. Our first studies to determine the viability of adding carbon-based nucleophiles to Meldrum's acid derivatives were carried out by reacting benzyl Meldrum's acids in the presence of a Lewis acid. We postulated that neutral nonbasic π-nucleophilic arenes would react with more electrophilic Lewis acid-activated Meldrum's acid derivatives, eliminating the problems associated with its high acidity, and making the process a new variant of the Friedel−Crafts acylation (eq 5). Although this venerable reaction is the most powerful means of preparing aromatic ketones, it still suffers from significant drawbacks in the context of modern organic synthesis. Typical procedures rely on formation of acid chlorides and the use of stoichiometric amounts of strong Lewis acids, both of which involve the generation of significant quantities of acidic or metallic waste. Aside from the associated safety and environmental concerns, the combination acid chlorides and stoichiometric amounts of strong Lewis acids also poses problems for functional group compatibility and product isolation. We believed that the use of Meldrum's acid as acylating agent would provide a solution to overcome both of these issues simultaneously.

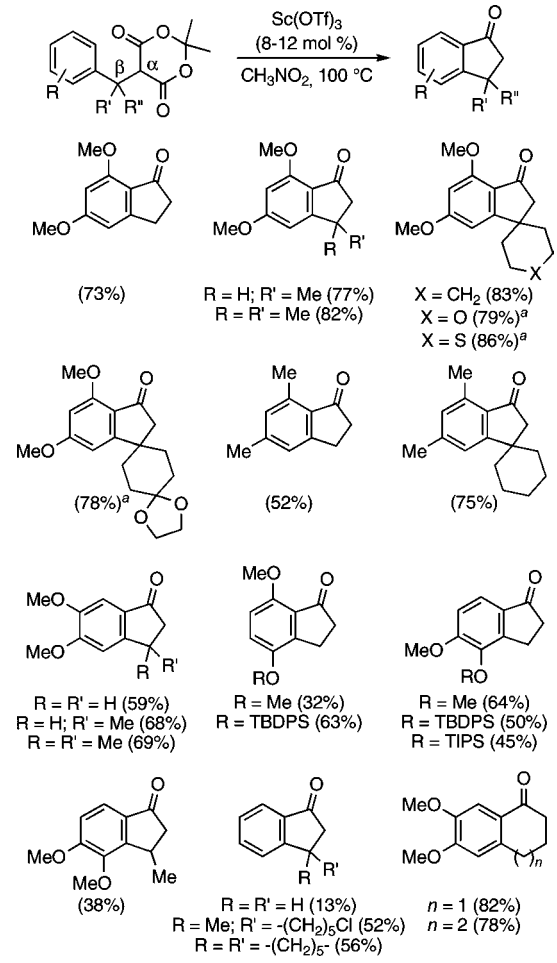


At the outset of studying the Friedel−Crafts acylation with Meldrum's acid, despite their ubiquitous use for activation of carbonyl compounds, there were nearly no reports of the use of Lewis acids in ring-opening reactions of Meldrum's acid. The sole example was the $ZnCl_2$-catalyzed addition of a hindered TMS-protected phenol to Meldrum's acid reported by Rigo and co-workers (eq 6).[16]



Validating our hypotheses, enolizable benzyl Meldrum's acids were acylated upon heating with a catalytic amount of $Sc(OTf)_3$ (Scheme 2).[17] Yields were generally excellent for electron-rich 3,5-dimethoxy-substituted arene nucleophiles, while

SCHEME 2. 1-Indanone Synthesis and Analogues from Enolizable Benzyl Meldrum's Acids[a]

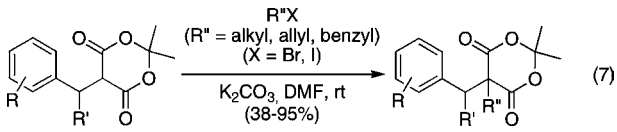


[a] $Yb(OTf)_3$ (7−10 mol %) used as catalyst.

lower but acceptable yields were obtained for less π-nucleophilic benzene rings. A significant gem-dialkyl effect was observed, where increasing substitution at the benzylic position favored cyclization and led to higher yields of acylation product over analogous unsubstituted cases. More importantly, our goal of developing a mild Friedel−Crafts acylation protocol was demonstrated by the compatibility of aryl and alkyl ethers, thio- and silylethers, ketals, and alkyl chlorides over a range of substitution patterns. Larger ring sizes could also be formed, leading to tetralones and benzosuberones. In addition, compared with traditional acylation procedures, the generation of volatile and inert side products (acetone and CO_2) simplified product isolation and purification because stoichiometric amounts of metal waste were not produced.

2-Substituted 1-Indanone Synthesis from Quaternized Benzyl Meldrum's Acids. While the reactions shown in Scheme 2 demonstrated that the acidic Meldrum's acid proton was not necessarily incompatible with the use of carbon nucleophiles, these limited the available substitutions in the

cyclized products. However, another advantage of using Meldrum's acid as an acylating agent is that it can be easily functionalized at C(5) by addition of reactive electrophiles (eq 7).



As shown in Scheme 3, reactions of quaternized benzyl Meldrum's acids gave 2-substituted 1-indanones in excellent yields.[17] Notably, the yields were far less variable with changes in π-nucleophilicity than were the reactions of enolizable Meldrum's acids. Importantly, a variety of groups could be added to C(5) of the starting materials, leading to diverse 2-substituents in the products while demonstrating further functional group compatibility. Reactions yielding 2,3-disubstituted 1-indanones proceeded with high diastereoselectivity, and larger rings sizes could also be accessed.

A few salient observations deserve further mention. For both type of substrates, enolizable and quaternized Meldrum's acids, competition studies determined the rate of carbocyclization to be tetralone > benzosuberone > indanone (Figure 2).[17a]

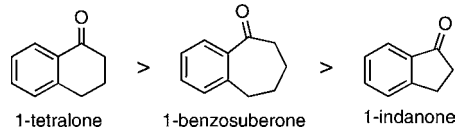
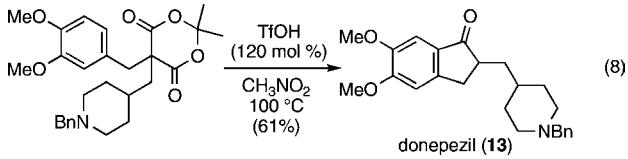
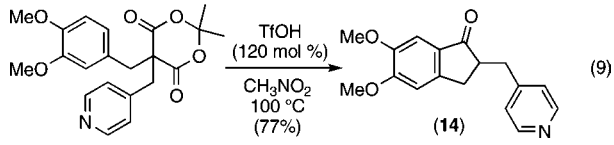


FIGURE 2. Structure of benzocyclic ketones and relative rate of carbocyclization.

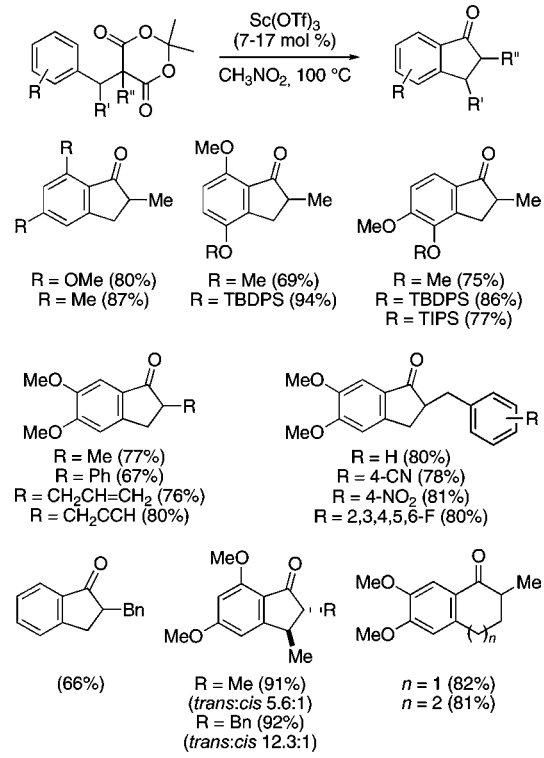
Furthermore, it was found that sp^3- and sp^2-hybridized nitrogen atoms in the substrate inhibited Lewis acid catalysis.[17a] For the Friedel–Crafts cyclization to proceed in the synthesis of the potent acetylcholinesterase inhibitor donepezil (**13**) and pyridine analogue **14**, addition of more than a full equivalent of catalyst (120 mol % of TfOH or TMSOTf) was necessary (eqs 8 and 9).



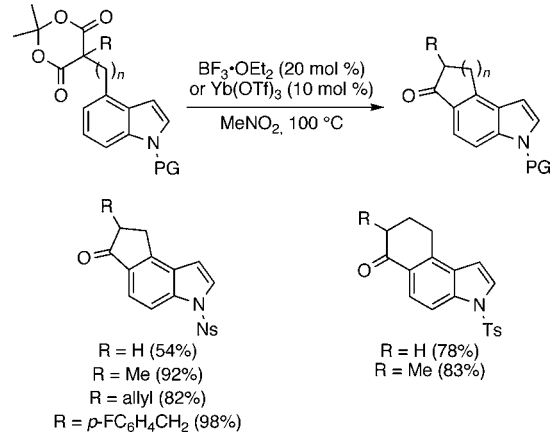


Deactivation of the Lewis acid catalyst was not encountered with nonbasic nitrogen-containing substrates, because the Friedel–Crafts reaction could be performed in acetonitrile.[17] Furthermore, indolyl Meldrum's acids with electron-withdrawing *N*-substituents underwent Friedel–Crafts acylation to give exclusively the *N*-protected 4,5-fused indole ring systems with catalytic amounts of Lewis acid (Scheme 4).[18] The regioselectivity of the cyclization of the 4-substituted indoles to the 5-position was most likely the result of geometrical constraints associated with the indole bicyclic system, because we demonstrated that the indole 3-position is the most nucleophilic toward electrophilic aromatic substitution in an intermolecular acylation of *N*-nosyl indole.

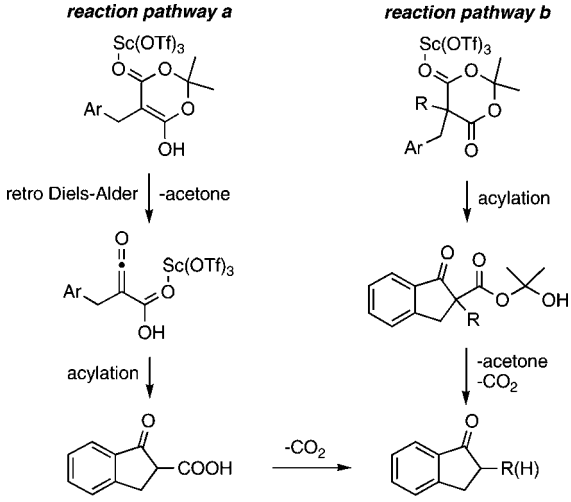
SCHEME 3. 2-Substituted 1-Indanones from Quaternized Benzyl Meldrum's Acids



SCHEME 4. Synthesis of Fused 4,5-Disubstituted Indole Ring Systems by Intramolecular Friedel–Crafts Acylation of 4-Substituted Indoles



SCHEME 5. Proposed Reaction Pathways for Acylation with Quaternized and Enolizable Meldrum's Acids

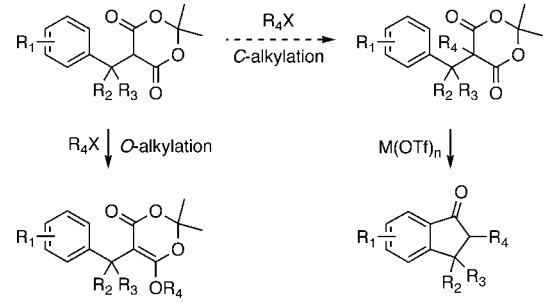


On the basis of extensive kinetic studies, the probable mechanism of these reactions was determined. The most important finding was that the mechanism depends on the Meldrum's acid substitution.[19] Enolizable Meldrum's acids undergo a retro-hetero-Diels–Alder reaction to give an acyl ketene, which appears to be the active acylating agent (Scheme 5, pathway a).[10] Attack of the arene, followed by decarboxylation then leads to the indanone. Nonenolizable Meldrum's acids are most likely attacked directly by the arene after Lewis acid complexation (Scheme 5, pathway b). Loss of acetone then feeds into the same decarboxylation pathway as for the enolizable substrates.

Total Synthesis of (±)-Taiwaniaquinol B via TMSOTf-Mediated Intramolecular Friedel–Crafts Acylation/Carbonyl α-*tert*-Alkylation. Our Friedel–Crafts acylation strategy with Meldrum's acids rapidly assembles 2-substituted, 2,3-disubstituted, and 3,3-disubstituted 1-indanones. However, an inherent limitation of this method is the inability to *C*-alkylate β,β-disubstituted benzyl Meldrum's acids to generate two contiguous all-carbon quaternary centers, *O*-alkylation being favored. Acylation of such precursors would have provided access to 2,3,3-trisubstituted 1-indanones (Scheme 6).

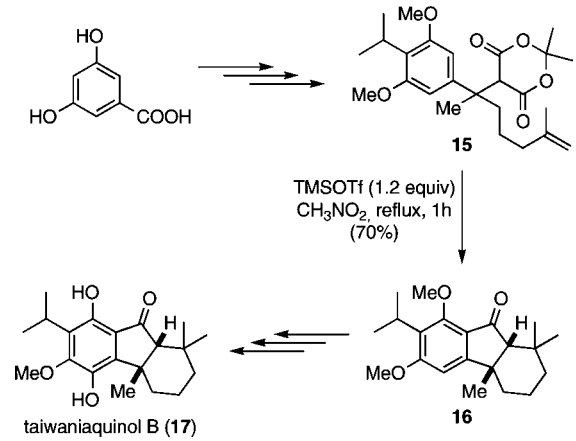
As discussed previously, under specific reaction conditions, the acylation of enolizable benzyl Meldrum's acids occurs via the intermediacy of an acyl ketene that produces a 1-indanone-2-carboxylic acid species, which subsequently decarboxylates (Scheme 5, pathway a). This peculiar reactivity was combined with the established Lewis acid-promoted intramolecular *tert*-alkylation of β-ketoesters with alkenes[20] and prompted us to explore the synthesis of hexahydrofluorenones through intramolecular domino Friedel–Crafts acylation/carbonyl α-*tert*-alkylation reactions.

SCHEME 6. Postulated Synthesis of 2,3,3-Trisubstituted 1-Indanones



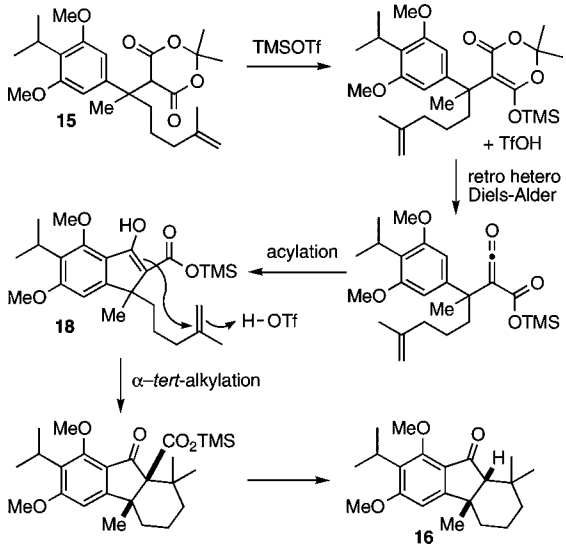
As illustrated in Scheme 7, a stoichiometric amount of TMSOTf promoted the domino dicyclization reaction of Meldrum's acid **15** to tricycle **16** in 70% isolated yield. From the latter, the total synthesis of taiwaniaquinol B (**17**),[21] a member of a small family of diterpenoid natural products displaying aromatase inhibitory activity,[22] was completed.[23]

SCHEME 7. Total Synthesis of Taiwaniaquinol B



A tentative mechanism for the TMSOTf-mediated intramolecular Friedel–Crafts acylation/carbonyl α-*tert*-alkylation domino reaction is depicted in Scheme 8. Treatment of enolizable Meldrum's acid **15** with TMSOTf forms the corresponding 6-siloxy-1,3-dioxin-4-one with release of one equivalent of TfOH. Retro-hetero-Diels–Alder reaction of the thermally unstable dioxinone generates an acyl ketene, which undergoes intramolecular arylation by the electron-rich aromatic to furnish key 1-indanone **18** as its enol form. α-*tert*-Alkylation of **18** with the triflic acid-activated alkene followed by decarboxylation leads to tricycle **16**.

SCHEME 8. Tentative Mechanism for the Domino Friedel–Crafts Acylation/Carbonyl α-*tert*-Alkylation Reaction



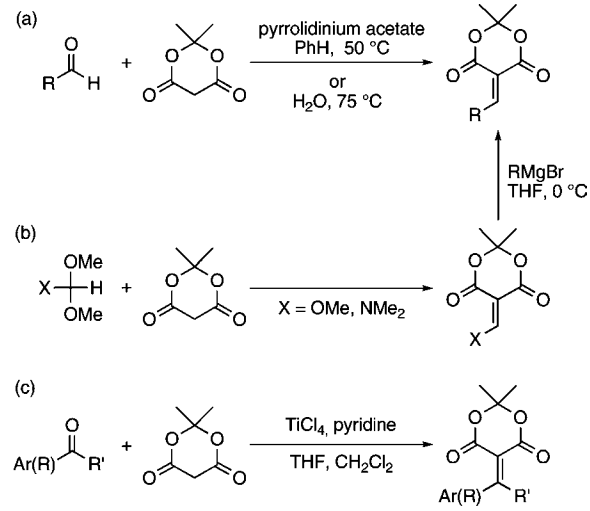
Reactions of 5-Alkylidene Meldrum's Acids

Properties and Preparation of Alkylidene Meldrum's Acids. The conjugated alkylidene derivatives of Meldrum's acid share many of the qualities of the saturated Meldrum's acid derivatives presented above. That is, they are typically crystalline, stable solids that can be prepared on large scale and purified by recrystallization. In terms of reactivity, a quantitative measure of their electrophilicity has recently been reported by Mayr, who found that they are $\sim 10^{11}$ times more reactive than the corresponding diethyl alkylidene malonates.[24]

Alkylidene Meldrum's acids are most easily prepared by the Knoevenagel condensation of Meldrum's acid with aldehydes and ketones. Synthesis of alkylidenes derived from aldehydes can be achieved under a large variety of conditions, but the ones that we have found to be most general and reliable are the pyrrolidinium acetate-catalyzed condensation in benzene[25] and the aqueous reaction reported by Bigi and co-workers (Scheme 9a).[26] For alkylidenes not accessible by these routes, an alternative is the preparation of methoxy- or dimethylaminomethylene Meldrum's acids followed by addition/elimination using organometallic nucleophiles (Scheme 9b).[27] Alkylidenes derived from ketones are nearly always prepared by us using the $TiCl_4$-mediated condensation of ketones with Meldrum's acid (Scheme 9c).[28]

Domino Reactions of Alkylidene Meldrum's Acids Involving Friedel–Crafts Acylations. Expanding on the powerful acylating abilities of Meldrum's acid in Lewis-acid catalyzed Friedel–Crafts reactions, we have developed domino processes that also take advantage of the highly electrophilic character of alkylidene Meldrum's acids. The general

SCHEME 9. Preparation of Alkylidene Meldrum's Acids



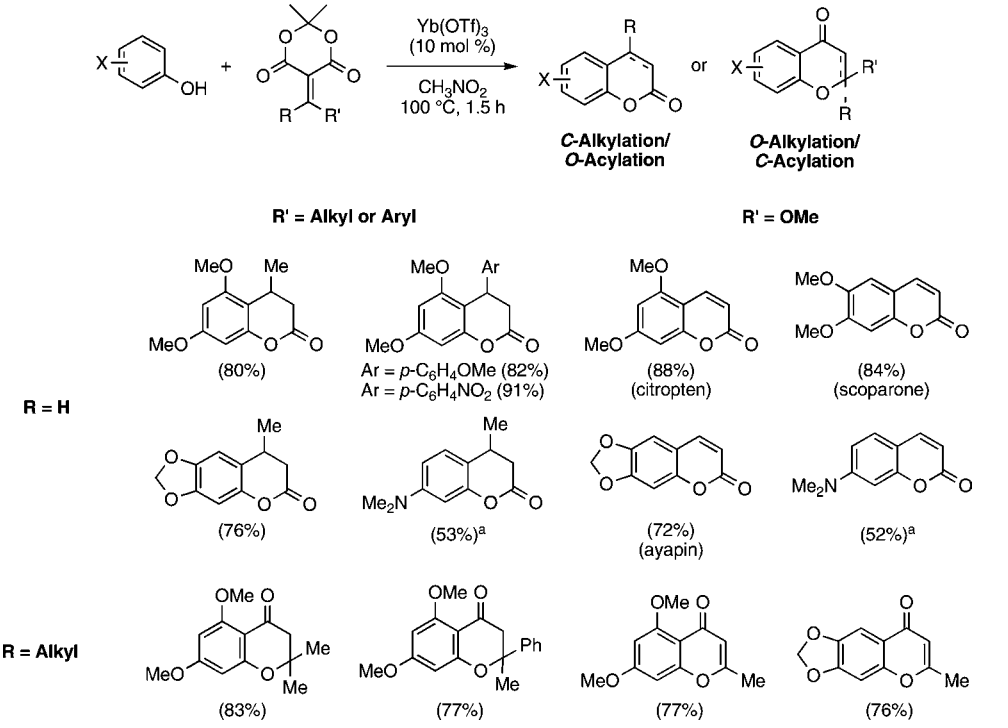
strategy is to use the alkene in a first reaction that either introduces an electron-rich aromatic group or otherwise permits a new reaction of an already present aromatic ring. Upon consumption of the alkene, the Meldrum's acid moiety can then function as the new electrophilic center for Lewis acid-catalyzed acylation.

Reactions with Electron-Rich Phenols. Our first example of this approach was the reaction of electron-rich phenols as bisnucleophiles with alkylidene Meldrum's acids acting as biselectrophiles. A reaction involving the combination of Meldrum's acid, an aldehyde, and phloroglucinol (1,3,5-trihydroxybenzene) in pyridine had been reported but was limited to that very electron-rich nucleophile.[29] We believed that a Lewis acid-catalyzed protocol would be more effective in terms of supporting less-activated phenols while using preformed alkylidenes would broaden the scope of electrophiles.

We found that the $Yb(OTf)_3$-catalyzed reaction of electron-rich phenols with monosubstituted Meldrum's acids proceeded exclusively by *C*-alkylation/*O*-acylation to give 3,4-dihydrocoumarin products.[30] It was further found that methoxy-substituted alkylidene Meldrum's acids undergo loss of methanol to give coumarins, permitting easy access to some naturally occurring compounds. When disubstituted Meldrum's acids were used as electrophiles, a shift in chemoselectivity was observed. Now, the additions occurred exclusively by *O*-alkylation/*C*-acylation to give chromanones and chromones (Scheme 10). This shift is most likely due to the increased steric hindrance around the electrophilic alkene, favoring attack by the more accessible phenol oxygen.

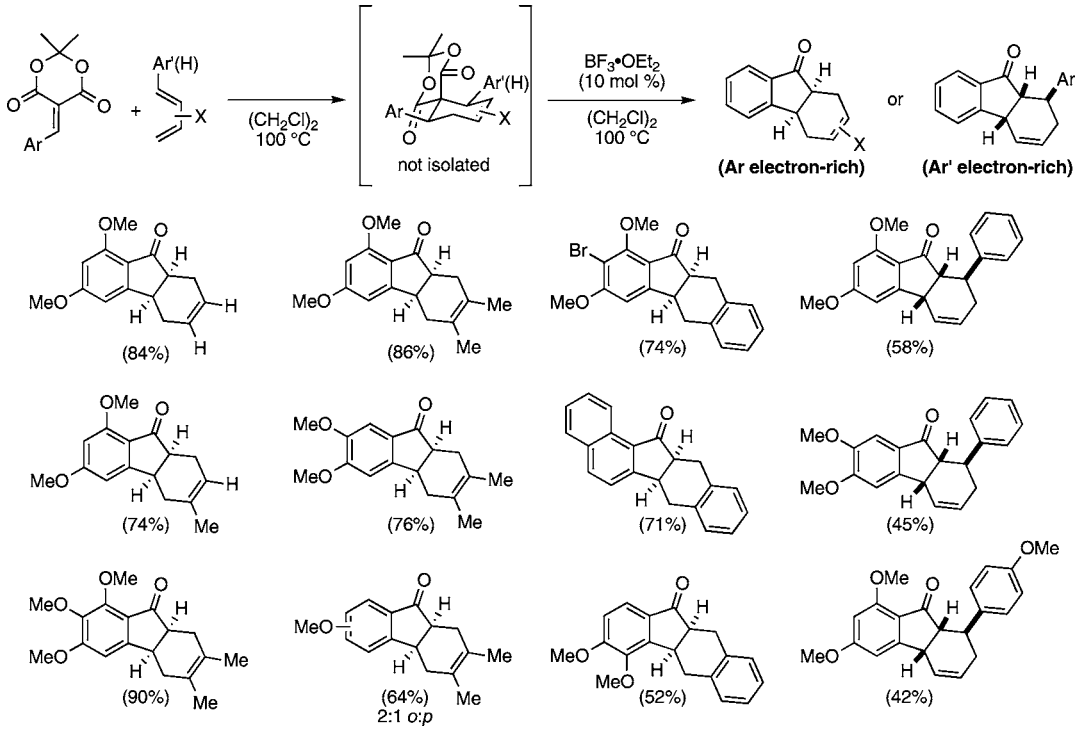
One-Pot Diels–Alder/Friedel–Crafts Acylation. Alkylidene Meldrum's acids participate in Diels–Alder reactions readily, because their electron deficiency makes them highly

SCHEME 10. Synthesis of 3,4-Dihydrocoumarins, Coumarins, Chromanones, and Chromones[a]

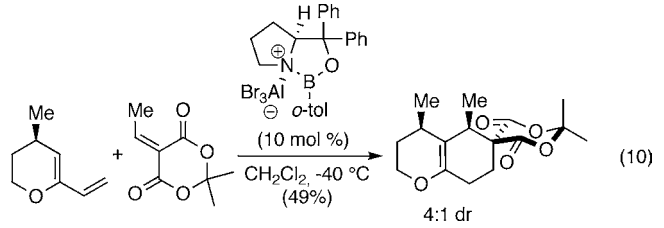


[a] 5.0 equiv TFA used as promoter.

SCHEME 11. Domino Diels–Alder/Friedel–Crafts Acylation Reaction



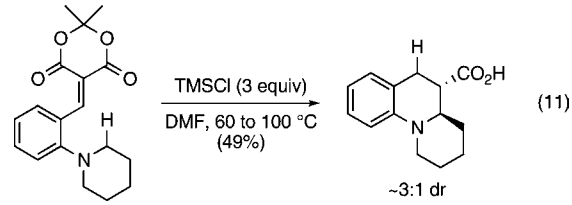
reactive dienophiles. Although they have not been used as often as other α,β-unsaturated carbonyls, their unique steric and electronic properties can be useful. For example, Hicken and Corey reported the chiral Lewis acid-catalyzed Diels–Alder reaction of an enantiopure diene with ethylidene Meldrum's acid (eq 10).[31] Here, the new stereocenter was installed with 4:1 dr, while other dienophiles gave the opposite diastereomer.



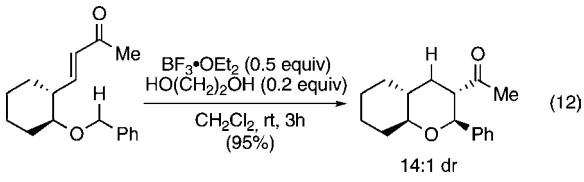
(10)

In our case, we capitalized on the acylating ability of Meldrum's acid to develop a one-pot synthesis of tetrahydrofluorenone derivatives.[32] This procedure involved a thermal Diels–Alder reaction, which gave the cycloadducts in modest diastereoselectivities, ranging from 2.2:1 to 1.8:1 dr, followed by addition of catalytic $BF_3 \cdot OEt_2$ to enable the Friedel–Crafts acylation. In this manner, a variety of substituted tetrahydrofluorenones were obtained (Scheme 11).

Domino Hydride Transfer/Cyclization/Friedel–Crafts Acylation. The electrophilicity of alkylidene Meldrum's acids allows them to react with often inert nucleophiles, including typically stable C–H bonds. Literature precedent for the reaction of Meldrum's acids with 2-aminobenzaldehydes through 1,5-hydride transfer/cyclization (eq 11)[33] caught our attention because there has been a resurgence of interest in this relatively obscure reaction. In particular, Sames and co-workers have reported that a large range of nucleophilic C–H bonds can be transformed under mild Lewis acid catalysis (eq 12).[34]



(11)

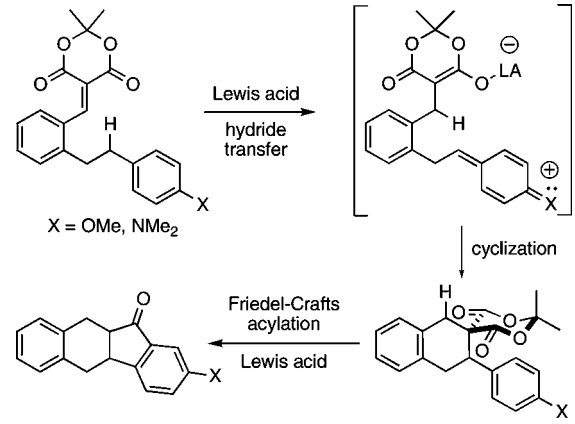


(12)

It seemed likely that alkylidene Meldrum's acids could be used to activate even more unreactive C–H bonds and that the resulting products could undergo a Friedel–Crafts acylation under the Lewis acidic conditions in a sequential or one-pot fashion (Scheme 12).

After optimization of the Lewis acid and solvent, $Sc(OTf)_3$ in toluene was shown to be most effective for both steps. The hydride shift/cyclization occurred at room temperature to give isolable spiro products; alternatively, heating the resulting solution to 100 °C allowed the Friedel–Crafts acylation. It was possible to vary the substituents on each aromatic ring, and also to add a group at the reactive benzylic position to form a crowded all-carbon quaternary center (Scheme 13).[35]

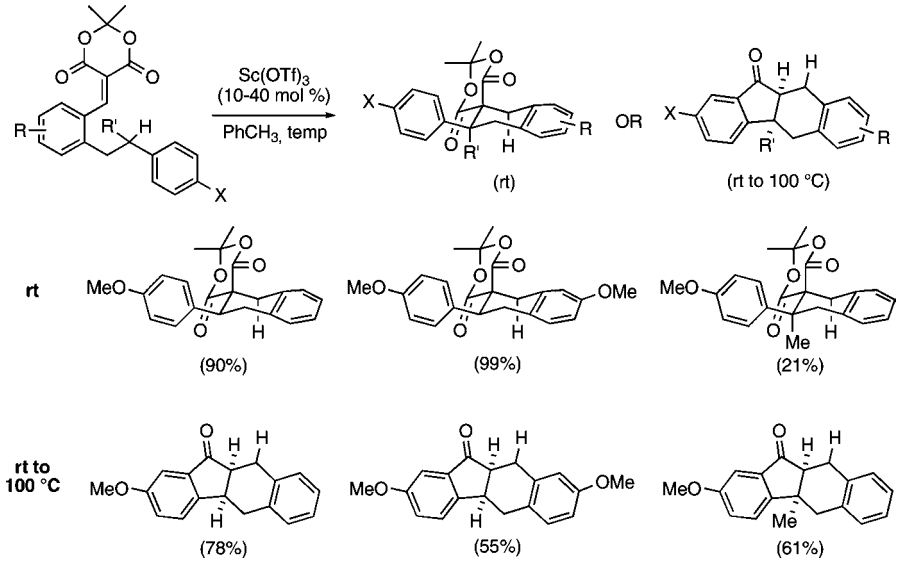
SCHEME 12. Proposed Hydride Transfer/Cyclization/Friedel–Crafts Acylation Reactions



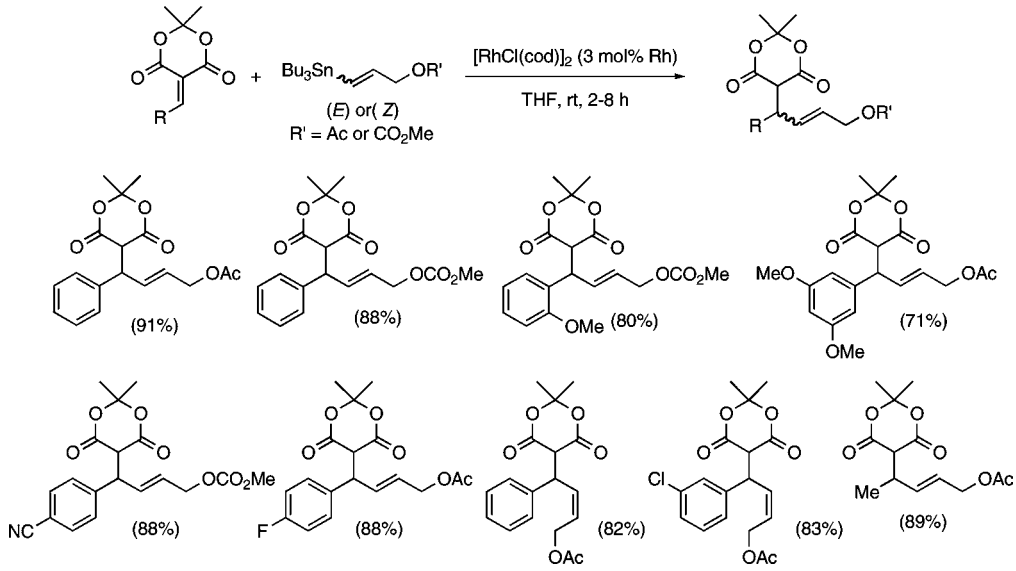
Conjugate Addition of Organotin Nucleophiles. Aside from reactions involving Friedel–Crafts chemistry, we have also used the high electrophilicity of alkylidene Meldrum's acid to facilitate conjugate additions of weak nucleophiles not commonly used in such reactions. Particularly, we have developed new addition reactions of alkenyl and allyl organostannanes because these are easily prepared or commercially available, air and moisture stable, and compatible with many functional groups. The value of using alkylidene Meldrum's acids for these reactions is the range of reactions available to the Meldrum's acid moiety after addition; for example, it can be transformed directly into ketones via our Friedel–Crafts protocols, as well as aldehydes,[36] esters,[3] and amides,[3] making it a versatile surrogate of all the common carbonyl functional groups.

Rh-Catalyzed Vinylation of Alkylidene Meldrum's Acids. While the rhodium-catalyzed addition of alkenylboronic acids to unsaturated acceptors has been studied by many groups since its introduction by Miyaura,[37] the corresponding additions of alkenylstannanes have been essentially ignored.[38] This may be due to the relatively higher reactivity of alkenylboronic acids, and the environmental issues revolving around organotin compounds. However, alkenylstannanes do provide some benefits over alkenylboronic acids in terms of ease of handling and purification, determination of stoichiometry, and functional group compatibility. In addition, the hot aqueous conditions typically employed for additions of alkenylboronic acids may present limitations on the number of available nucleophiles and electrophiles. A goal of our research was to therefore use an alkenylstannane with a sensitive yet orthogonal functionality under anhydrous condi-

SCHEME 13. Benzylic C−H Bond Functionalization Using Alkylidene Meldrum's Acids



SCHEME 14. Addition of Allyl Acetate and Carbonate Units to Alkylidene Meldrum's Acids

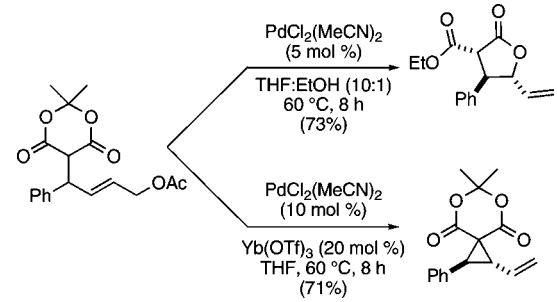


tions and low temperature to showcase the high reactivity of alkylidene Meldrum's acids.

The reaction that we devised was the Rh-catalyzed addition of 3-(tributylstannyl)allyl acetates and carbonates to alkylidene Meldrum's acids.[39] As shown in Scheme 14, addition of the (*E*)- or (*Z*)-alkene occurred at room temperature to give the addition products in good yields. Importantly, the reactions proceeded with complete retention of double bond geometry.

The utility of this reaction lies in the introduction of a highly reactive yet latent electrophile that can be activated by introduction of a catalytic amount of palladium. Highlighting the unique divergent reactivity of Meldrum's acid, it was possible to form two different products from the same intermediate (Scheme 15). Under neutral conditions and in the presence of alcohol to trap an intermediate ketene, Pd(II)-catalyzed cyclization gave a γ-lactone via *O*-alkylation. By removing the alcohol and adding catalytic $Yb(OTf)_3$, cyclization occurred at the Meldrum's acid C(5)

SCHEME 15. Variable Alkylation in Pd(II)-Catalyzed Reactions of Allyl Acetate Meldrum's Acids

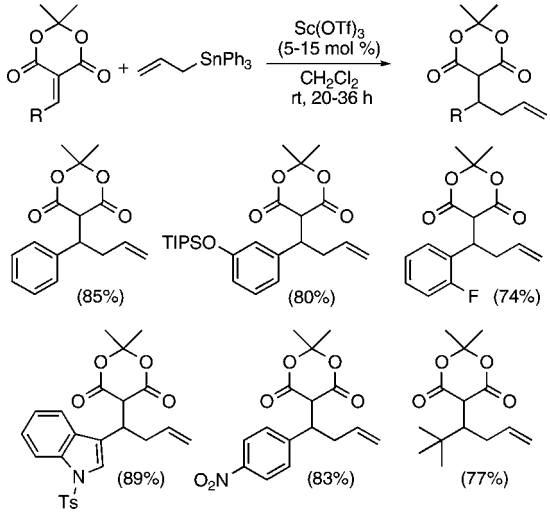


resulting in a vinylcyclopropane as a single diastereomer.[39] Of note, the synthesis of γ-lactones could be carried out sequentially in a single synthetic operation.

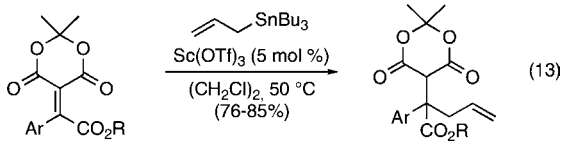
$Sc(OTf)_3$-Catalyzed Conjugate Allylation of Alkylidene Meldrum's Acids. Compared with catalytic nucleophilic allylation of aldehydes and ketones, there are relatively few examples of catalytic conjugate allylations.[40] Because of the high electrophilicity of alkylidene Meldrum's acids and their tendency toward 1,4-addition over competing modes of nucleophilic attack, we believed they would be ideal acceptors for the development of a catalytic conjugate allylation protocol.

It was found that allyltriphenyltin underwent $Sc(OTf)_3$-catalyzed conjugate allylation toward a large variety of monosubstituted alkylidene Meldrum's acids (Scheme 16).[41] Reaction conditions were extremely mild, occurring at room temperature in CH_2Cl_2, and no products of 1,2-addition were detected.

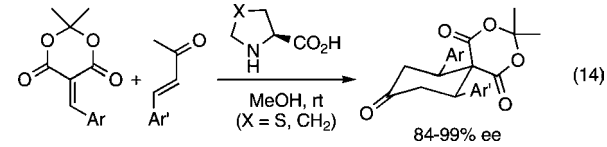
SCHEME 16. Catalytic Conjugate Allylation of Monosubstituted Alkylidene Meldrum's Acids

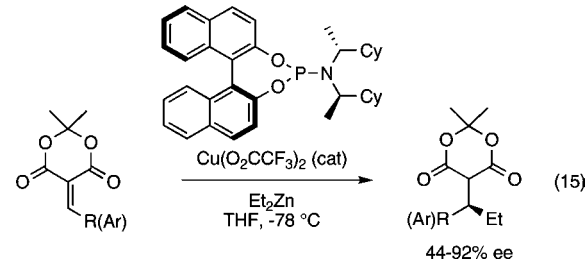


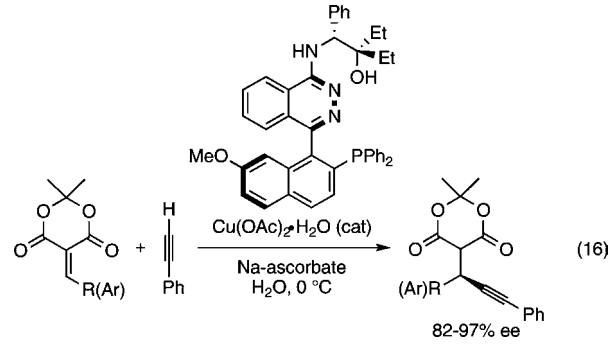
Use of the stronger allylating agent allyltributyltin allowed formation of the more challenging all-carbon quaternary centers via addition to disubstituted alkylidene Meldrum's acids (eq 13). In these cases, the increased steric hindrance around the electrophilic center necessitated a higher reaction temperature.



Enantioselective Addition of Diorganozincs to 1-Arylalkylidene Meldrum's Acids. Despite their participation in a wide array of reactions, alkylidene Meldrum's acids have been employed in very few catalytic, enantioselective transformations. Barbas and co-workers have demonstrated an organocatalytic Diels–Alder reaction of alkylidene Meldrum's acids (formed in situ) to give chiral cyclohexanones (eq 14).[42] Carreira and co-workers have used monosubstituted alkylidenes as acceptors in two different Cu-catalyzed additions: addition of Et_2Zn using a phosphoramidite ligand[43] and of phenylacetylene under very mild aqueous conditions (eqs 15 and 16, respectively).[44] One common feature of these reactions is the use of relatively weak nucleophiles/dienes at or below room temperature, which attests to the alkylidenes' reactivity.



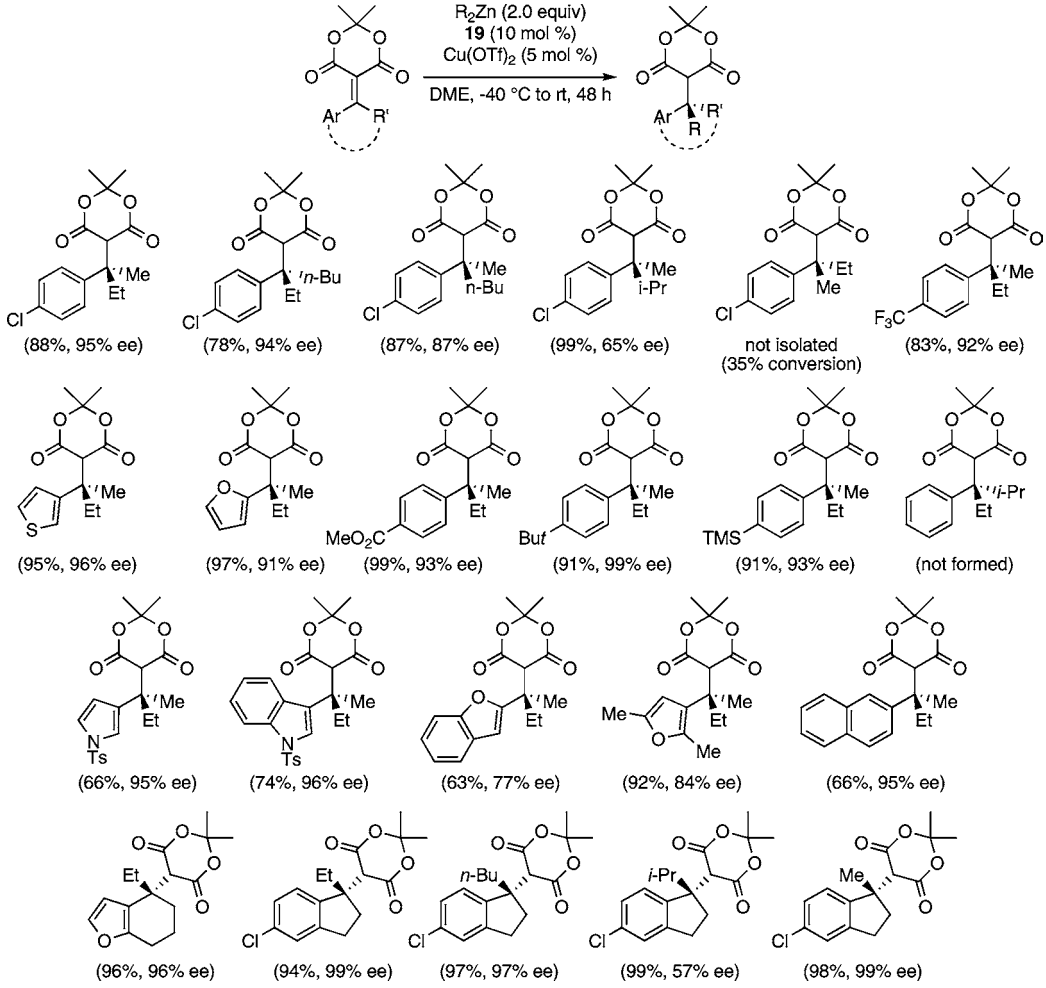




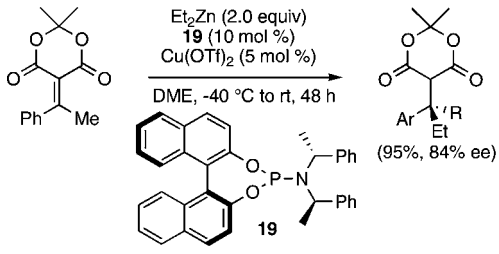
The scarcity of enantioselective reactions of alkylidene Meldrum's acids first caught our attention during the synthesis of taiwaniaquinol B, where the key stereocenter was installed by addition of MeMgBr to a disubstituted alkylidene. In fact, at that time there were no examples of enantioselective conjugate addition to form all-carbon quaternary stereocenters (although this area has developed greatly since then).[45,46] The steric congestion and relative electronic deactivation of the electrophilic carbon makes this a very challenging area of organic synthesis, but one for which we thought the strong activating ability of Meldrum's acid would be ideally suited.

As a starting point to begin our investigations we made the fortuitous decision to examine the Cu-catalyzed addition of dialkylzinc reagents as nucleophiles and the chiral phosphoramidites developed especially by Feringa and co-workers as ligands.[47] Our choice was based on the commercial availability

SCHEME 17. Enantioselective Addition of R_2Zn to Disubstituted Alkylidene Meldrum's Acids



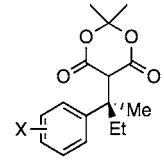
of phosphoramidite ligand **19** and various dialkylzincs, the high functional group tolerance of dialkylzincs relative to other organometallic nucleophiles, and literature precedent for the asymmetric conjugate addition of R_2Zn to alkylidene Meldrum's acids to generate tertiary carbon stereocenters presented above (eq 15). This choice of nucleophile and ligand turned out to work extremely well, and after extensive optimization of solvent and copper source, the reaction shown in eq 17 was developed.[48]



(17)

The addition of R_2Zn was applied to a large range of 1-arylalkylidene Meldrum's acids (Scheme 17). Addition of Et_2Zn was successful for an extremely varied set of substituted benzene rings and hetereoaromatics. Nucleophiles other than diethylzinc could also be used, although Me_2Zn proved problematic (discussed further below). While ortho substituents impeded the reaction (not shown), rotationally restricted alkylidenes derived from cyclic ketones were excellent acceptors and the products were formed in higher enantioselectivity than the acyclic alkylidenes. The higher reactivity of these alkylidenes was reinforced by the reaction of Me_2Zn, which added with excellent conversion and ee.

A trend was observed relating the enantioselectivity to the substitution pattern on the aromatic rings (Figure 3). Regardless of their electronic nature, para substituents increased ee compared with the unsubstituted case (84% ee), while meta groups decreased selectivity. Interestingly, sterically bulky groups provided extremely high ee regardless of the position. Further inves-



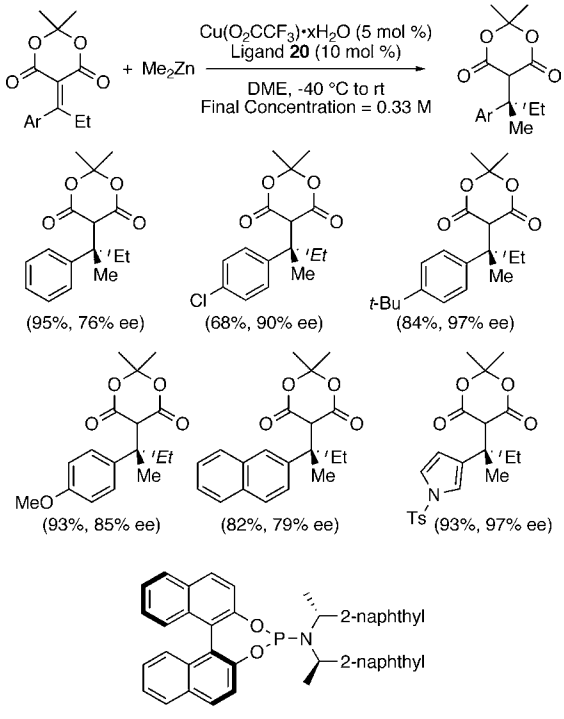
	Para	Meta
X = Me	89% ee	78% ee
X = OBn	93% ee	79% ee
X = Cl	95% ee	74% ee
X = *i*-Pr	**98% ee**	**97% ee**
X = *t*-Bu	**99% ee**	**98% ee**

FIGURE 3. Relationship between selectivity and substitution pattern.

tigation into these results suggests that steric interactions between the para substituent and the large L_2CuEt complex (L = phosphoramidite **19**) result in higher selectivity, while changes in the relative conformation of meta-substituted alkylidenes accounts for the dramatic differences in ee.

The poor result obtained for addition of Me_2Zn to noncyclic alkylidenes was disappointing as methyl-substituted benzylic quaternary stereocenters are by far the most commonly occurring in natural products. We therefore turned our attention to studying this addition in order to increase conversion and determine the enantioselectivity. After examining a range of methyl nucleophiles, different phosphoramidites, and copper sources, an improved protocol was developed.[49] In the end, 2-naphthyl-containing ligand **20** gave the highest enantioselectivity of the eight phosphoramidites tried, while the conversion was boosted significantly by switching Cu source to $Cu(O_2CCF_3)_2 \cdot xH_2O$ and running the reactions at much higher concentration (Scheme 18).

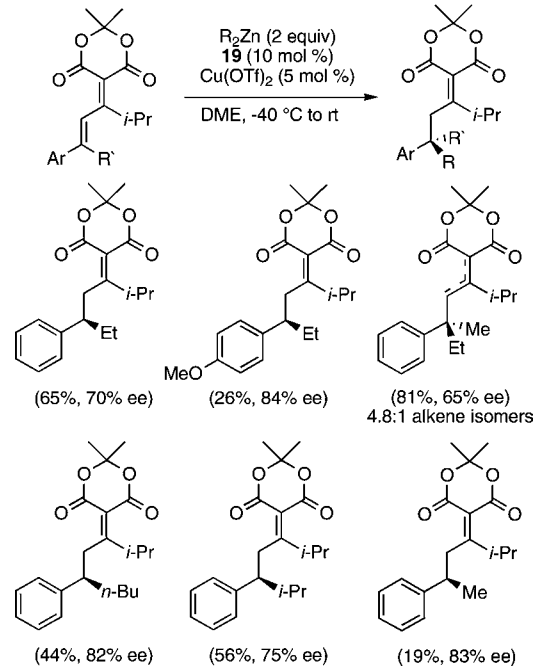
SCHEME 18. Optimized Conditions for Addition of Me_2Zn



20

Enantioselective 1,6-Conjugate Addition. During the above studies, we noticed that sterically crowded alkylidenes bearing an adjacent *i*-Pr group did not undergo the addition reaction. Taking advantage of this observation, we devised vinylalkylidene Meldrum's acids containing an extended conjugated framework in the hopes that these acceptors would participate in enantioselective 1,6-conjugate addition.[50] This

SCHEME 19. Enantioselective 1,6-Conjugate Additions



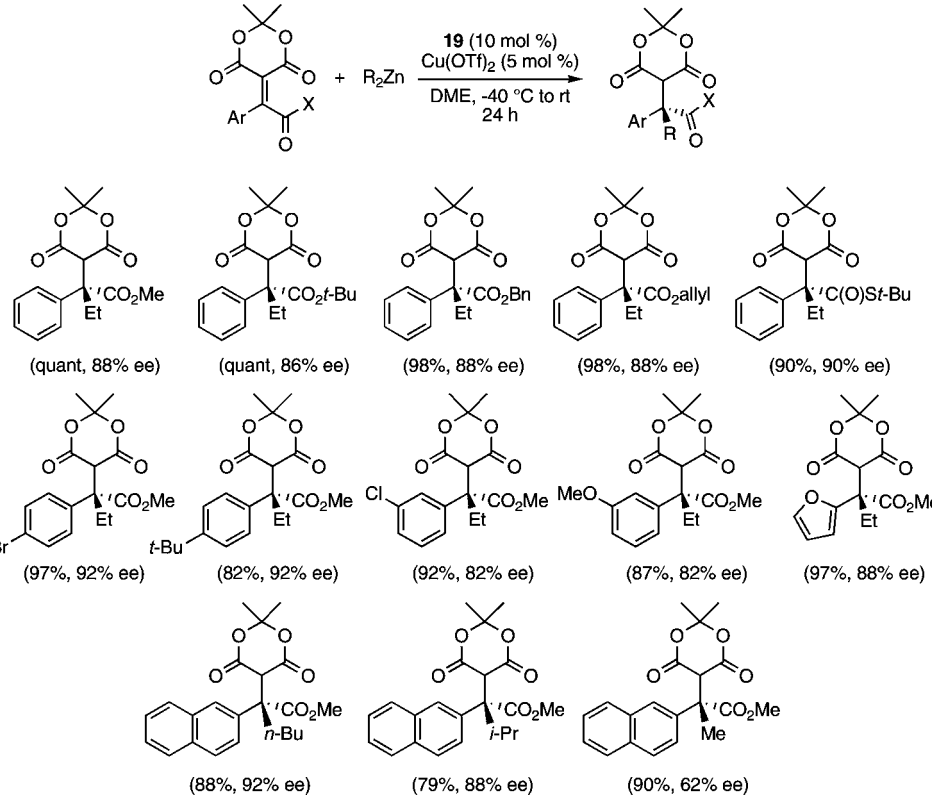
turned out to be the case, and tertiary and quaternary carbon centers could be formed in up to 84% ee (Scheme 19).[51]

Enantioselective Conjugate Addition to Functionalized Alkylidene Meldrum's Acids. The ability to form all-carbon quaternary stereocenters with high enantioselectivity was a breakthrough for us in terms of demonstrating the utility of alkylidene Meldrum's acids. However, one drawback of this method was that the stereocenters were substituted with only one group (the Meldrum's acid) that could be easily transformed in further reactions. To extend the versatility of the products, we thought that replacing the alkyl group on the alkylidene with a carboxylic acid derivative would provide a new synthetic handle,[52] while the unique reactivity of Meldrum's acid would make these two functional groups orthogonal.

The alkylidenes derived from α-ketoesters proved to be highly reactive and the additions occurred with excellent enantioselectivity (Scheme 20).[53] It was possible to vary both the substituents on the aryl ring and the ester portion of the alkylidene, which was an important goal in terms of developing further transformations; various dialkylzincs could also be used.

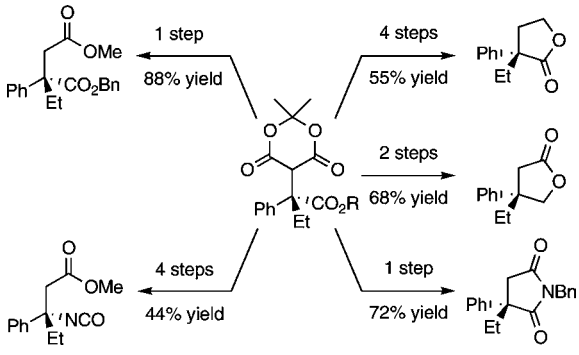
The synthetic utility of these products was demonstrated by various transformations outlined in Scheme 21.[53] From a single functionalized starting material, manipulation of either the Meldrum's acid or ester group was possible, depending on the conditions employed; alternatively, reactions involving both groups could be performed. Again, this versatility is due in

SCHEME 20. Enantioselective Addition to Functionalized Alkylidenes



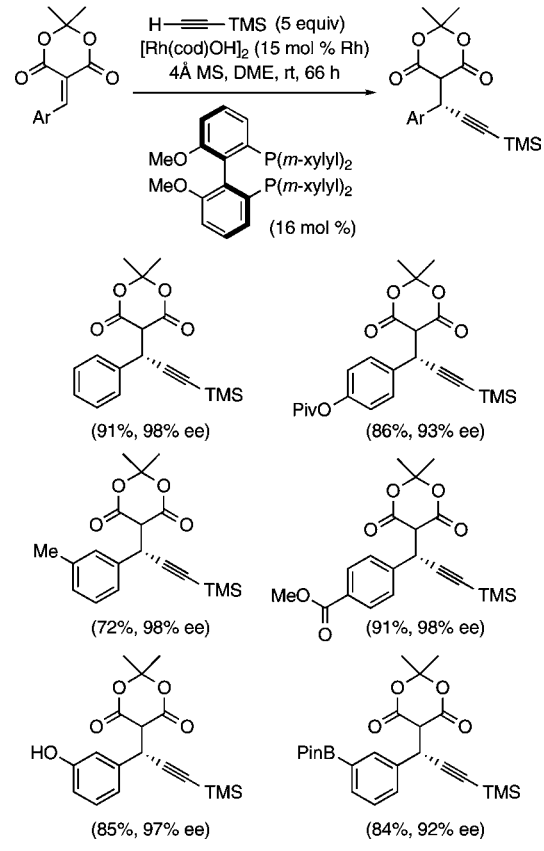
large part to the unique properties of Meldrum's acid compared with other carboxyl functional groups.

SCHEME 21. Transformation of Functionalized Chiral Products



Enantioselective Conjugate Alkynylation of Benzylidene Meldrum's Acids. Expanding on and complementing Carreira's pioneering work (eq 15), we have developed a highly enantioselective Rh(I)-catalyzed addition of TMS-acetylene to benzylidene Meldrum's acids (Scheme 22).[54,55] The mild conditions were remarkably tolerant of reactive functional groups, including acidic phenols and sensitive boronic esters, and the selectivities were uniformally excellent (>90% ee).

SCHEME 22. Asymmetric Alkynylation of Benzylidene Meldrum's Acids



Conclusion

Nearly 100 years since its discovery, Meldrum's acid continues to offer a rich array of reactivities that set it apart from other electrophilic agents. Meldrum's acid is an ideal electrophile for intramolecular Friedel–Crafts acylations. The substrates are easy to prepare and functionalize, the reaction conditions are mild, and functional group compatibility is high. Also, the versatility of alkylidene Meldrum's acids offers a very large platform for the development of new reactions. We are currently developing new enantioselective conjugate additions and have recently begun investigations into C–C bond *cleaving* reactions of Meldrum's acid derivatives that are opening new avenues for further discovery enabled by this fascinating molecule.[56]

We are grateful to the dedicated and enthusiastic co-workers who carried out and intellectually contributed to the research described herein. We also thank the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Foundation for Innovation (CFI), the Ontario Innovation Trust (OIT), the Government of Ontario, AstraZeneca Canada Inc., Boehringer Ingelheim (Canada) Ltd., the Merck Frosst Centre for Therapeutic Research, and the University of Waterloo for financial support. A.M.D. thanks the Government of Ontario for an OGS scholarship and NSERC for a CGS-D scholarship.

BIOGRAPHICAL INFORMATION

Aaron M. Dumas received his B.Sc. (Biopharmaceutical Sciences) from the University of Ottawa, where he conducted undergraduate research with Prof. Alex Fallis. He joined Prof. Eric Fillion's group at the University of Waterloo in 2004 and is exploring new reactions of alkylidene Meldrum's acids. He will begin postdoctoral studies with Prof. Jeffrey Bode in January 2010.

Eric Fillion received his undergraduate degree in biochemistry from the Université de Sherbrooke. After completing his M.Sc. in medicinal chemistry at the Université de Montréal with Prof. Denis Gravel, he began his doctoral studies in 1994 at the University of Toronto under the direction of Prof. Mark Lautens. From 1998 to 2000, he was an NSERC postdoctoral fellow in the laboratories of Prof. Larry E. Overman at the University of California, Irvine. In August 2000, he joined the Department of Chemistry at the University of Waterloo, where he is currently an Associate Professor of Chemistry. His research program centers on the design and development of transition metal- and Lewis acid-promoted carbon–carbon bond-forming methods.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: efillion@uwaterloo.ca.

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