Development of New Domino Reactions

of Alkylidene Meldrum's Acids Involving Friedel-Crafts Chemistry

and

Catalytic Conjugate Allylation of Alkylidene Meldrum's Acids

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of my thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Alkylidene Meldrum's acids are very reactive acceptors in conjugate additions, and are known to be significantly more electrophilic than other α,β-unsaturated carbonyl electrophiles. They also offer advantages in terms of ease of preparation, purification and storage. Despite this, they are relatively underused in organic synthesis, and have been treated as something of a curiousity in the literature. The goal of my research was to demonstrate the utility of these molecules in new reactions that are not readily available to other electrophiles.

To facilitate this work, new conditions for the Knoevenagel condensation of aldehydes with Meldrum's acid were developed. This allowed access to a broader range of monosubstituted alkylidenes than was previously possible from any single method.

In a reaction that exploits the acylating ability of Meldrum's acid, a domino addition of phenols to alkylidene Meldrum's acids was developed. Here, $Yb(OTf)_3$ catalyzed the addition of a phenol to the alkylidene as well as acylation through activation of the electrophile. The unique properties of these acceptors permitted synthesis of 3,4-dihydrocoumarins and coumarins through *C*-alkylation/*O*-acylation, and also 4-chromanones and chromones through *O*-alkylation/*C*-acylation. The predictable and general reversal of chemoselectivity is dependent on the number of substituents on the alkylidene.

The same properties that make alkylidene Meldrum's acids strong electrophiles also make them excellent dienophiles. A one-pot Diels-Alder/Friedel-Crafts process was used as an entry into the 6-5-6-tricyclic skeleton of a family of natural products that have been of interest in our group. The modular nature of the reaction allowed structural variation at nearly every position around both 6-membered rings. An attempted extension of this work into the synthesis of ergot alkaloids provided insight into the factors affecting Friedel-Crafts acylation of 4-substituted indoles. These results provided a highly regioselective entry into 4,5-fused indole ring systems.

The electrophilicity of alkylidene Meldrum's acids was combined with Lewis acid activation for development of a mild conjugate allylation reaction. The use of allyltriphenyltin as nucleophile for addition to monosubstituted alkylidenes avoided many of the practical disadvantages of working with trialkylstannanes. By employing such a relatively weak allylating agent, functional group compatibility was maximized to include groups susceptible to nucleophilic allylation. Additions to chiral, non-racemic alkylidenes were highly diastereoselective. It was also shown that functionalized all-carbon quaternary stereocentres can be formed by this process.

francophonie which was a real pleasure for me. Seb's constant good spirits and enthusiasm, and the hospitality he and Val showed to me meant a lot. I still have not had a better meal in Waterloo than confit au canard and foie (not to mention the wine and pastis) at their house. Jarkko Heikkinen was another great friend and colleague, whose work ethic and positive attitude were inspiring. Someday I will repay him the favour and bury *his* car in snow in the middle of a freezing parking lot. Alex Zorzitto, who first worked with me as an undergrad, has been incredibly fun to work with. He introduced me to the orange club, and I have also admired his well-rounded approach to graduate student life. His company on my walks to get coffee in the morning is also an appreciated daily ritual.

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I started graduate studies with an amazing group of fellow students. I thank Laura Ingram, Alla Darwish, and Jarrod Johnson for their friendship, support, and help over these last five years. Julie Goll has been around since those days as well, and she was as good a friend and coworker as she was a boss, even if she did make me hand in my labs on time. Thanks too for a lot of breaks. Of all the people I have worked with, Ash Wilsily deserves special mention. He and I started at nearly the same time, and over five years I have learned to respect him immensely. I have never worked with a more dedicated, hard-working, curious, honest, or trustworthy person. His example has pushed me to be a better chemist, and his friendship has made working in the group a constant pleasure. He is especially fun to work with now that he plays better music than the "Little Shop of Horrors" soundtrack. Our trip to Philadelphia and New York for the ACS meeting was one of the highlights of my grad studies, and Ash's unflagging enthusiasm and energy were a big part of the reason for that. I know he will go on to be an incredibly successful chemist, and I wish him all the best as he moves on from UW.

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List of Abbreviations

Ac	acetyl
app	apparent
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	2,2′-dihydroxy-1,1′-binaphthyl
Bn	benzyl
Br	broad
Bu	butyl
calc'd	calculated
cat	catalytic
d	doublet
DA	Diels-Alder
dba	dibenzylidene acetone
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (dimethyl propylene urea)
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
E^+	electrophile
ee	enantiomeric excess
EI	electron impact
Et	ethyl
equiv	equivalents
EWG	electron withdrawing group
FC	Friedel-Crafts
h	hour
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz

*i*Pr	*iso*-propyl
IR	infrared
J	spin coupling constant
JMOD	J-modulated ^{13}C-decoupled NMR
m	multiplet
m	*meta*
M	metal or molarity (moles/litre)
*m*CPBA	*meta*-chloro-perbenzoic acid
Me	methyl
Meldrum's acid	2,2-dimethyl-1,3-dioxane-4,6-dione
min	minute
mL	millilitre
mmol	millimole
mol	mole
M.p.	melting point
m/z	mass/charge
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
*n*Pr	*normal*-propyl
Ns	nosyl (*para*-nitrobenzenesulfonyl)
Nu$^-$	nucleophile
o	ortho
o-tol	*ortho*-toluyl (2-methylphenyl)
OTf	triflate (trifluoromethanesulfonate)
p	para
Ph	phenyl
Piv	pivaloyl (trimethylacetyl)
*p*K$_a$	-log of acid dissociation constant
PPA	polyphosphoric acid
ppm	parts per million
py	pyridine
q	quartet
quant	quantitative
rt	room temperature
s	singlet

t	triplet
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyl-diphenylsilyl
*t*Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl (*para*-toluenesulfonyl)
UV	ultraviolet
wt	weight

List of Schemes

Chapter 1. Properties and Preparation of Alkylidene Meldrum's Acids

1.1. Structure and Reactivity of Meldrum's Acid

Historically, the development of reactions involving Meldrum's acid (**1.1**) was impeded by the original incorrect assignment of its structure by Meldrum, who believed it to be β-lactonic acid **1.2** (Scheme 1.1).[1] Based on the corresponding condensation of diethyl malonate with acetone in acetic anhydride (which was known at the time to give dimethyl isopropylidenemalonate[2]), Meldrum expected to form isopropylidene malonic acid so it is perhaps not surprising that he assigned a structure based on reaction of the malonic acid methylene group. Further complicating the issue was the mono-acidity of the product, which convinced Meldrum that he had formed a carboxylic acid. The β-lactonic acid model was further reinforced in the literature by incorrect assignments of such structures to the condensation of other ketones with malonic acids under the same conditions used by Meldrum.[3] In the absence of spectroscopic methods for structure determination or a mechanistic approach to chemical reactions, the proposed structure **1.2** stood until 1948.
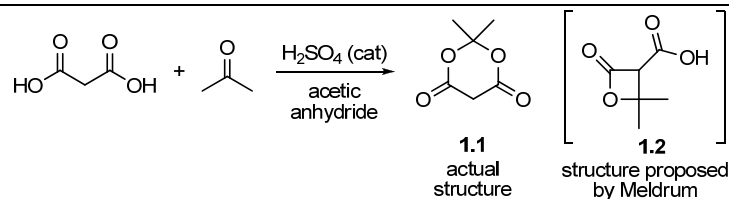
Scheme 1.1. Original synthesis of Meldrum's acid

Davidson and Bernhard reassigned the structure of Meldrum's acid to **1.1** upon examination of its reactions with both nucleophiles and electrophiles.[4] They rationalized the mono-acidity of Meldrum's acid based on comparison to dimedone, although they incorrectly believed the high acidity stemmed from its enol form.[5] Despite this reassignment, the β-lactonic acid derivation was not immediately discarded, as the condensation of benzaldehyde with malonic acid under Meldrum's conditions was incorrectly proposed to give 2-oxo-4-phenyloxetane-3-carboxylic acid in 1954[6]; the correct structure, 2-phenyl-1,3-dioxane-4,6-dione, was later determined by IR

spectroscopy.[7] From the mid-1950's onward only the proper structure of Meldrum's acid is described in the literature, but any remaining ambiguity was eliminated by publication of its crystal structure in 1985.[8]

Meldrum's acid is distinguished from other 1,3-dicarbonyl compounds in two main ways: it is extremely acidic and also highly electrophilic. In terms of acidity, the pK_a of Meldrum's acid in water is 4.83-4.93[9] while in DMSO it is 7.3.[10] Compared to other 1,3-dicarbonyl compounds, Meldrum's acid's acidity is anomalous (Figure 1.1[11]), and many theories have been put forward to explain this. Although the exact explanation is still a matter of debate, it appears as though a combination of the cyclic structure, the (E) geometry of the ester[12], and favourable orbital overlap[13] all contribute to the unusually low pK_a.

| pKa | 7.3 | 8.4 | 11.1 | 16.4 | 11.2 | 15.1 |
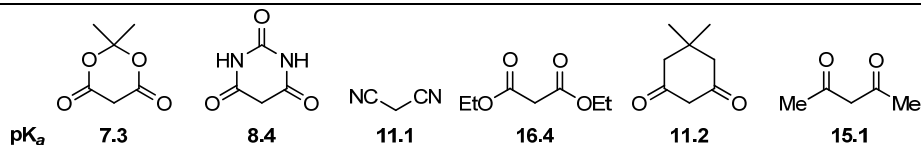
Figure 1.1. pK_a of some common carbon acids in H_2O

The second important chemical property of Meldrum's acid is its electrophilicity, which is in some ways linked to its acidity. For example, alkaline hydrolysis of diethyl malonate occurs readily at 0 °C to give ethyl hydrogen malonate[14], while Meldrum's acid is not hydrolyzed under similar conditions as deprotonation occurs instead.[15] However, Meldrum's acid derivatives lacking acidic protons, such as 5,5-dimethyl Meldrum's acid, are hydrolyzed instantaneously by NaOH solution, yielding the malonic half-esters and acetone.[9] While the acidity of Meldrum's acid precludes the use of strongly basic nucleophiles, Seila[9] demonstrated that protic acid-catalyzed hydrolysis was possible, which is an important observation in the context of the work presented in this thesis.

The unique structure of Meldrum's acid allows another pathway for nucleophilic addition (Scheme 1.2a). As first suggested by Matoba[16], and confirmed in later studies by Sato[17], Meldrum's acid reacts with diazomethane to give dioxinone **1.3**, which undergoes a retro hetero-Diels-Alder to yield acetone and acylketene **1.4**. The highly reactive **1.4** is then the active electrophile, and trapping by alcohols or amines leads to the ester or amide products **1.5**. Importantly, Sato further demonstrated that thermal decomposition of

Meldrum's acid between 80-110 °C also gives an acylketene. This makes Meldrum's acid the reagent of choice for acylations of hindered nucleophiles, as shown in the recent total synthesis of (+)-angelmarin (Scheme 1.2b).[18]
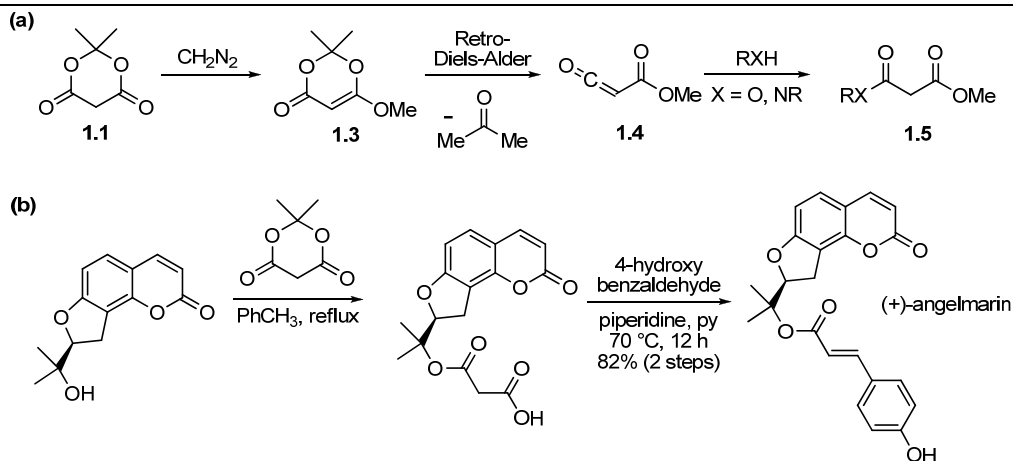
Scheme 1.2. (a) Decomposition of Meldrum's acid to an acylketene. (b) Acylation of 3° alcohols

Due in part to it's relative stability, the conjugate base of Meldrum's acid is a poor nucleophile. For example, the anion of Meldrum's acid is ~10^3 time less reactive than that of the structurally related dimedone anion, and nearly 10^6 times less nucleophilic than the anion of diethyl malonate.[19] Nevertheless, it will attack reactive electrophiles under mild basic conditions, although issues of mono- vs dialkylation can arise. Reaction with excess alkyl iodide or benzyl bromide[20] or aryliodonium salt[21] gives symmetrical 5,5-disubstituted Meldrum's acid derivatives (Scheme 1.3a). Selective preparation of monosubstituted Meldrum's acids is best accomplished by in situ reductive alkylation, while further reaction of these can give the unsymmetrical disubstituted versions (Scheme 1.3b).[22]
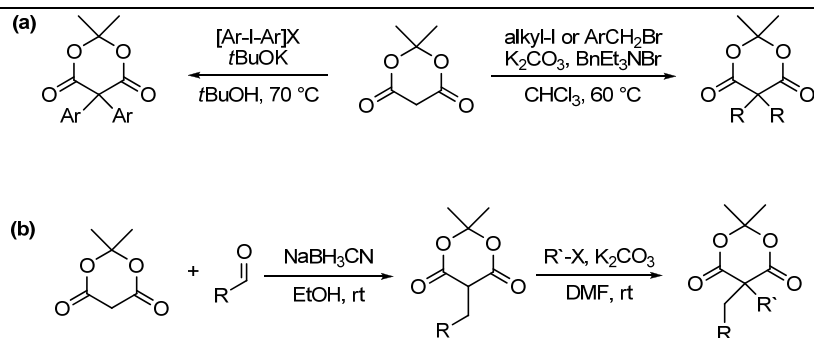
Scheme 1.3. Synthesis of Meldrum's acid derivatives by reactions with electrophiles

The electrophilicity of Meldrum's acid, coupled with its simple and versatile derivatization, makes it a very attractive reagent for organic synthesis. From a practical point of view, it should be pointed that these derivatives are typically crystalline solids that can be purified by recrystallization and are bench stable in air at room temperature, which makes them easy to work with. Still, the unique reactivity of Meldrum's acid derivatives has in some ways been treated as a curiosity, and systematic investigations of new reactions involving these molecules have not been undertaken. As will be shown in the next section, our group has demonstrated new catalytic C-C bond forming reactions of Meldrum's acid which take advantage of its special characteristics.

1.1.2. Friedel-Crafts Acylations of Meldrum's Acid Derivatives

As mentioned above, the acidity of Meldrum's acid and its derivatives can complicate addition of basic nucleophiles. This has limited the development of new C-C bond forming reactions involving attack of a carbon nucleophile on the carbonyls of Meldrum's acid (as opposed to C-C bonds formed by nucleophilic attack of Meldrum's acid C-5). 5,5-Disubstituted Meldrum's acids, which are non-acidic, pose less of a problem, and yet have still been used very infrequently for this reaction. For example, additions of hard organometallic nucleophiles have only been reported twice. An intramolecular reaction of an allyllithium, which involves an interesting bond migration, was demonstrated by Thebtaranonth.[23] In the synthesis of δ-damascone, allyllithium added to Meldrum's acid **1.6** to give a mixture of **1.7** and **1.8**; heating in mild acid

effected decarboxylation and alkene isomerization to yield the natural product (Scheme 1.4).[24]
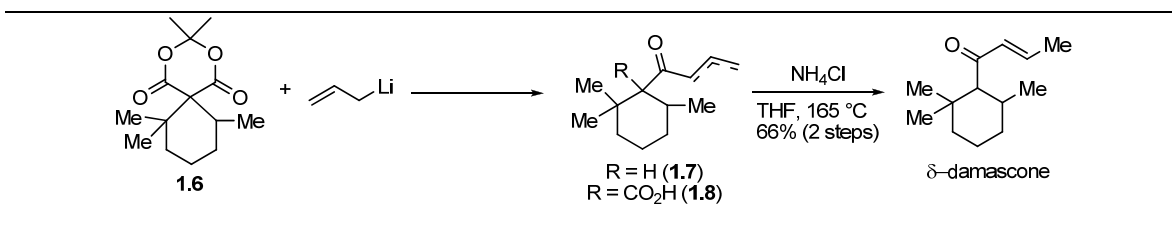
Scheme 1.4. Synthesis of δ-damascone

Our group proposed that neutral π-nucleophilic arenes would react with Meldrum's acid derivatives in the presence of a Lewis acid without the risk of deprotonation as they are non-basic; this would therefore be a new type of Friedel-Crafts acylation. Despite their ubiquitous use for activation of carbonyl compounds, there were nearly no reports of the use of Lewis acids in 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 (Scheme 1.5), who did not speculate on the role of the Lewis acid.[25]
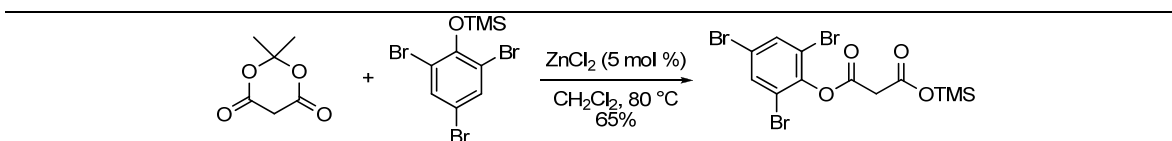
Scheme 1.5. $ZnCl_2$-catalyzed addition of phenols to Meldrum's acid

In work undertaken by Dan Fishlock, our group demonstrated that the intramolecular acylation of a variety of arenes could be accomplished by the $Sc(OTf)_3$-catalyzed reaction of Meldrum's acid derivatives.[22,26] In contrast to more traditional Friedel-Crafts acylations which often produce stoichiometric amounts of halogenated metal waste, the by-products of this reaction are acetone and CO_2. The easy functionalization of Meldrum's acid allowed for a wide range of substitution patterns on both the arene and at the benzylic positions (representative examples are shown in Scheme 1.6). Particularly interesting was the validation of the hypothesis that non-basic carbon nucleophiles would not be affected by the acidity of Meldrum's acid. In fact, the reaction occurred readily with mono- and disubstituted Meldrum's acids. Also, by

varying the tether length between the 5-position of Meldrum's acid and the arene, it was possible to form indanones, tetralones, and benzosuberones.
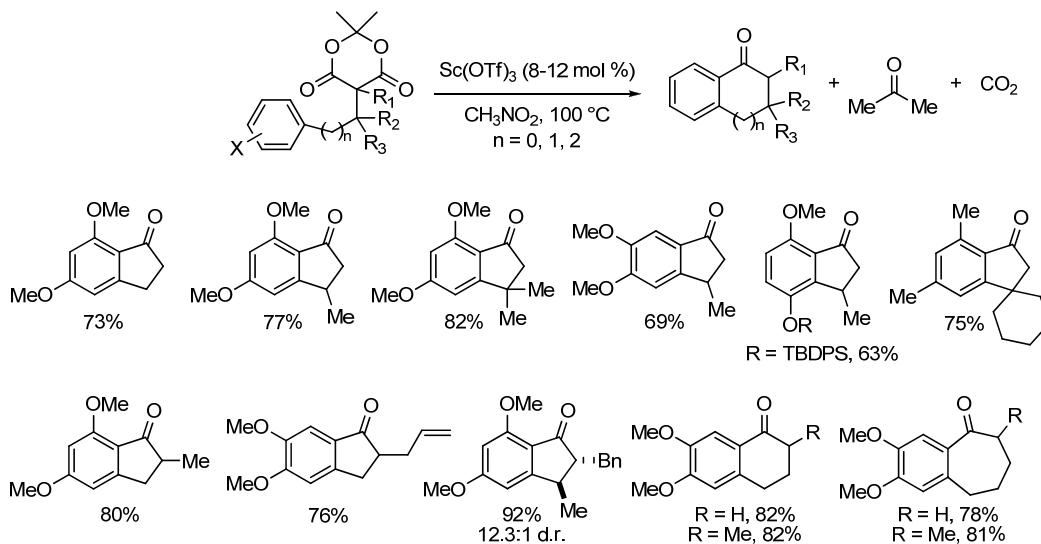
Scheme 1.6. Friedel-Crafts acylation of Meldrum's acid derivatives

A few salient observations that have a bearing on later work presented herein deserve further mention. First, it was found that a basic nitrogen (sp^3 and sp^2 hybridized) inhibited Lewis acid catalysis, such that no reaction occurred with less than a full equivalent of catalyst. However, addition of excess acid did allow cyclization to occur (Scheme 1.7). This suggests that the carbonyls of Meldrum's acid are poorly Lewis basic and are unable to compete effectively with the nitrogen atom for complexation to the Lewis acid. Second, competition studies determined the rate of ring closure to be 6-membered > 7-membered > 5-membered so that tetralones formed faster than benzosuberones, and both were faster than formation of indanones.

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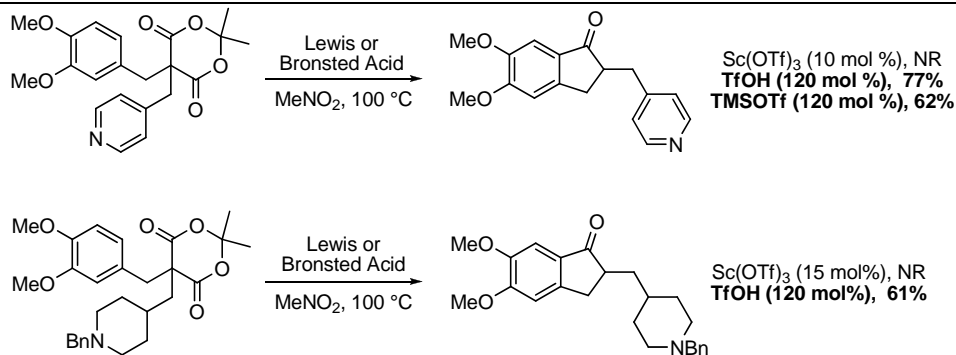
Scheme 1.7. Catalyst deactivation by Lewis basic substituents

On the basis of extensive kinetic studies, the probable mechanism of this reaction was determined.[27] The most important finding of these studies was that the mechanism diverges depending on the Meldrum's acid substitution. That is, mono-substituted Meldrum's acids (which can enolize, hereafter called enolizable Meldrum's acids) and disubstituted Meldrum's acids (hereafter called non-enolizable Meldrum's acids) go through two different pathways based on their ability to enolize or not (Scheme 1.8). In accord with Sato's findings, enolizable Meldrum's acids undergo a retro hetero-Diels-Alder reaction to give an acyl ketene which appears to be the active acylating agent. Attack of the arene, followed by protonation and decarboxylation then leads to the indanone. Non-enolizable Meldrum's acids are most likely attacked directly by the arene after Lewis acid complexation. Loss of acetone then feeds into the same decarboxylation pathway as for the enolizable substrates. In the case of enolizable Meldrum's acids, a background uncatalyzed process is available due to the thermal retro hetero-Diels-Alder, and the acylation can still occur without Lewis acid although in diminished yields. Non-enolizable Meldrum's acids are thermally stable, and there is no acylation unless Lewis acid is added.
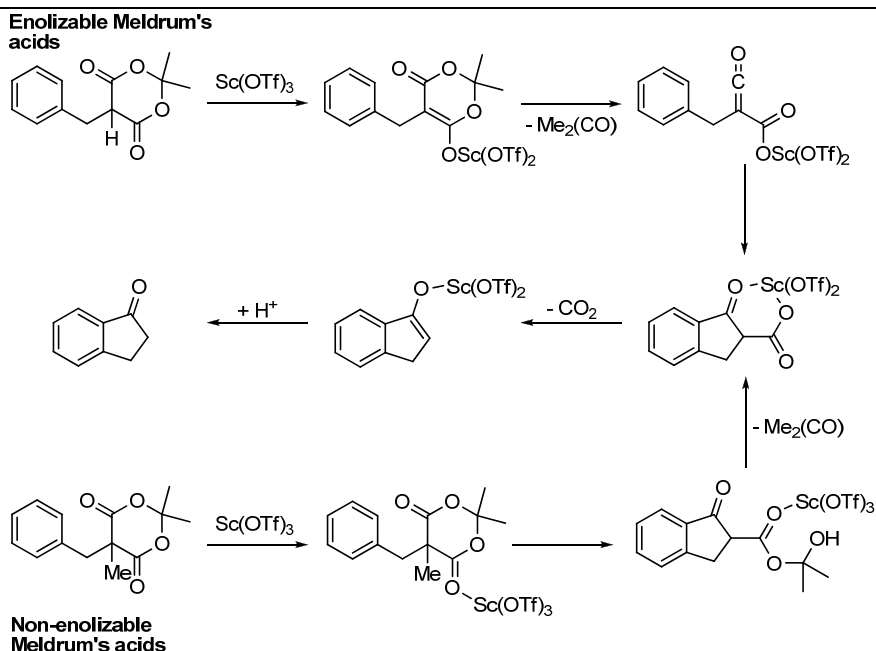
Scheme 1.8. Proposed mechanism for Friedel-Crafts acylation of Meldrum's acid derivatives

Having established that Meldrum's acids are powerful and versatile acylating agents in Lewis-acid catalyzed processes, we have explored further reactions that exploit this reactivity. It is at this point that my work in the group began, and the general concept we developed is illustrated in Scheme 1.9. It was thought that alkylidene Meldrum's acids **1.9** could react with some functionality (FG) in such a way that the alkene would be effectively reduced, leading to a molecule of the type **1.10**. This would then permit the Meldrum's acid moiety to react as an acylating agent based on the chemistry presented above. Depending on which reactant had the most nucleophilic arene, it was thought that the reaction could diverge to give different products **1.11** or **1.12**. Furthermore, catalysis of each step in the sequence by the same Lewis acid would allow mild reaction conditions and expand functional group compatibility.
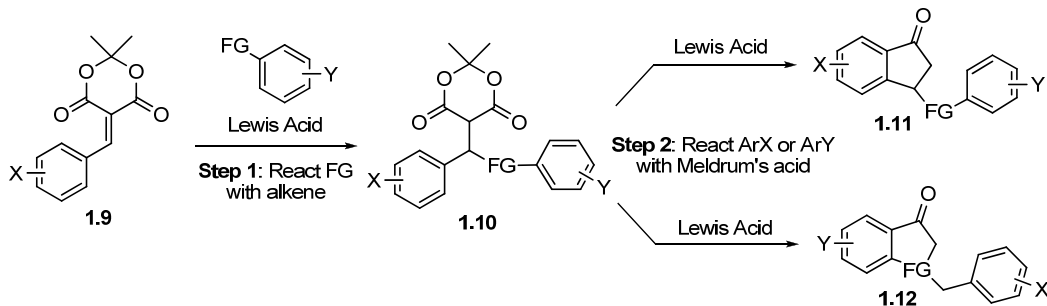
Scheme 1.9. Proposed domino sequence for reaction of alkylidene Meldrum's acids

Before discussing the successful applications of the domino sequence just described, a thorough examination of the nature and synthesis of alkylidene Meldrum's acids is required. As demonstrated in the sections below, these molecules have unique properties which make them ideal reagents for a variety of transformations.

1.3 Properties of Alkylidene Meldrum's Acids

The conjugated 5-alkenyl derivatives of Meldrum's acid (alkylidene Meldrum's acids) share many of the physical properties of the substituted Meldrum's acids described above. That is, they are typically solids that can be purified by recrystallization and are often bench stable in air over long periods of time. For ease of description, they will herein be classified, based on the number of substituents on the alkene, into monosubstituted and disubstituted alkylidenes (Figure 1.2).

Figure 1.2. Structure of alkylidene Meldrum's acids

From the time of their first synthesis[28], the characteristic of alkylidene Meldrum's acids that has attracted the most interest from chemists is their electrophilicity. These highly reactive molecules were termed "neutral organic Lewis acids" due to their rapid (10^{-6} sec) addition of NaOH to give the anionic addition product **1.13** (Scheme 1.10a).[29]

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By contrast, the corresponding addition of even "naked" oxyanions to alkylidene malonates is significantly slower (Scheme 1.10b).[30]
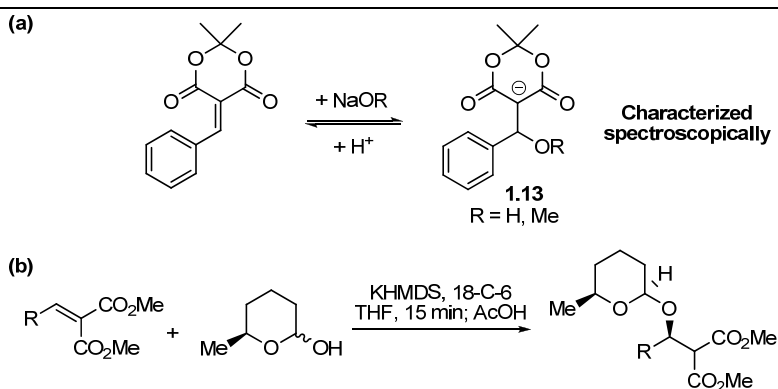
Scheme 1.10. Addition of oxyanions to alkylidene Meldrum's acids and malonates

Pinpointing the exact cause for the reactivity of alkylidene Meldrum's acids towards nucleophiles is difficult, since as described by Bernasconi and Rappoport it involves "an unusually complex interplay of factors".[31] For example, they have found that there is no correlation between the carbon acidity of the acceptor groups and the rate of nucleophilic addition of $HOCH_2CH_2S^-$ (Scheme 1.11). They suggest this is due to a combination of the varying steric hindrance around the electrophilic carbon and differences in structural modifications necessary to stabilize the developing negative charge.[32] Nevertheless, the alkylidene Meldrum's acid was the most electrophilic of the groups studied. On the other hand, in these cases the pK_a does correlate with the relative equilibrium constants for the reaction, which highlights the differences between electrophilicity (kinetic) and Lewis acidity (thermodynamic).
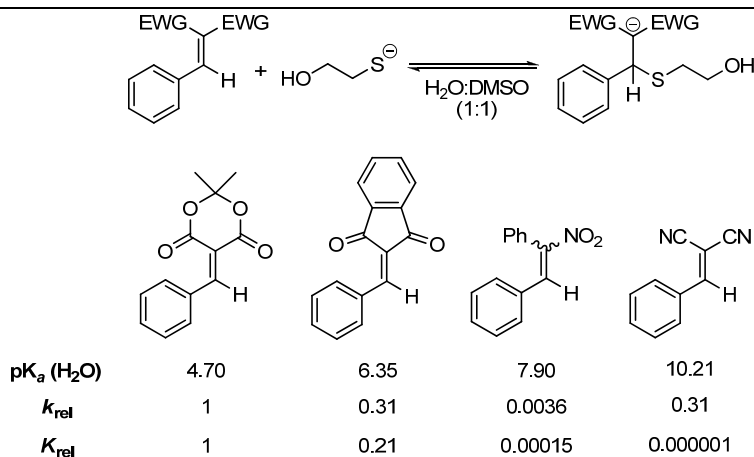
Scheme 1.11. Comparison of reactivity for various activated alkenes

Mayr has also studied the reactivity of alkylidene Meldrum's acids in the context of quantifying electrophilicity.[33] His scale is based on measurement of the rates of addition of stabilized carbanions to the alkylidenes, and representative examples are shown in Figure 1.3 for comparison (the scale is logarithmic, and the more negative values are least electrophilic).[34] Mayr's results follow the same trend as those obtained by Bernasconi and Rappoport, in that alkylidene Meldrum's acids are slightly more electrophilic than alkylidene malononitriles, but the most interesting comparison is the huge difference in reactivity between alkylidene Meldrum's acids and alkylidene malonates. This is further evidence for the unique properties of Meldrum's acid compared to other ester-containing functional groups.

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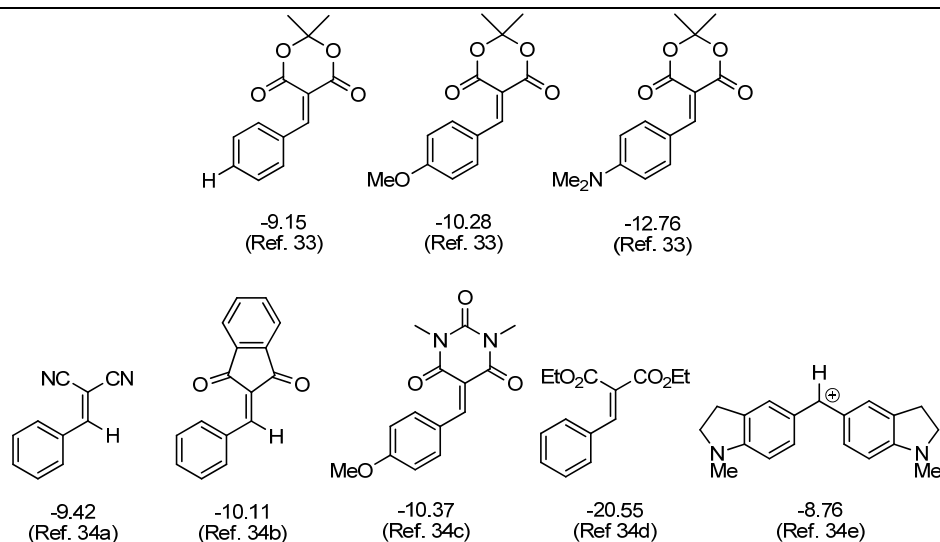
Figure 1.3. Absolute electrophilicities of alkylidene Meldrum's acids

The reactions of alkylidene Meldrum's acids with protic nucleophiles have also been studied kinetically by both Bernasconi[35] and Mayr.[33] They have both noted that the addition of amines is faster than one would suppose based purely on the nucleophilicity of the nitrogen atom. In fact, since Mayr has quantified absolutely both the nucleophilicity of amines and the electrophilicity of the alkylidenes, it was determined that additions of amines are ~100 times faster than predicted. This has been attributed to a stabilizing interaction between the N-H and the developing negative charge on the Meldrum's acid moiety.[35,36] Three possible transition states have been put forward to rationalize this (Scheme 1.12): a four-centred transfer from N to C-5 (**1.14**), a six-membered transfer from N to Meldrum's acid O (**1.15**), or, for reactions in water, a solvent assisted transfer to C-5 (**1.16**). Interestingly, the interactions in **1.14** and **1.16** are akin to the unusual C-H---X hydrogen bonds which have been studied in our group.[37]
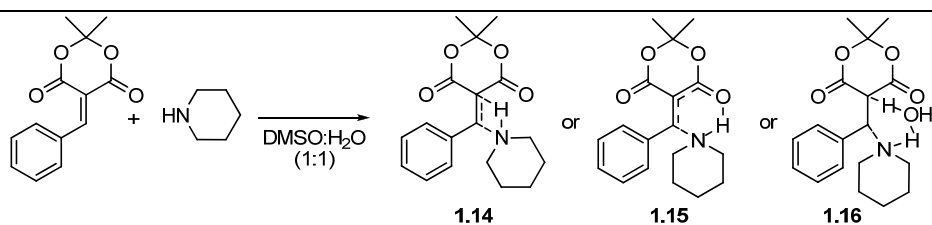
Scheme 1.12. Proposed transition states for addition of amines to alkylidene Meldrum's acids

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Examination of the crystal structure of alkylidene Meldrum's acids lends some clues to the origin of their high electrophilicity. Figure 1.4 shows the X-ray crystal structure of disubstituted alkylidene **1.17** as a representative example.[38] It shows that the Meldrum's acid group has adopted a boat conformation that is typical of such molecules.[39] In this conformation, conjugation of the alkene with both carbonyl groups is maximized within the constraints imposed by steric hindrance and ring strain. This is been proposed as a key contributor to the electrophilicity of alkylidene Meldrum's acids as little structural variation is required to provide optimal stabilization of the developing negative charge during nucleophilic addition.[40]
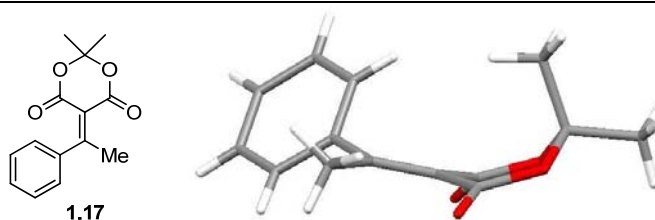
Figure 1.4. X-Ray crystal structure of a disubstituted alkylidene Meldrum's acid

By contrast, Bernasconi has suggested that benzylideneacetylacetone, as a representative acyclic acceptor, has a preferred conformation (in the solid state) where one of the carbonyl groups is nearly perpendicular to the plane of the alkene (C1-O1 dihedral angle of 92.9°, Figure 1.5). In the ground state of the molecule only one carbonyl group is aligned properly to fully activate the olefin (C1-O2 dihedral angle of 6.4°).[41] Therefore the reactive species is one of the four higher energy conformers shown in Figure 1.5, all of which are expected to have significant steric hindrance. Consequently this raises the energy of the transition state for addition of nucleophiles to these acceptors relative to alkylidene Meldrum's acids, where the cyclic structure enforces an optimal alignment.
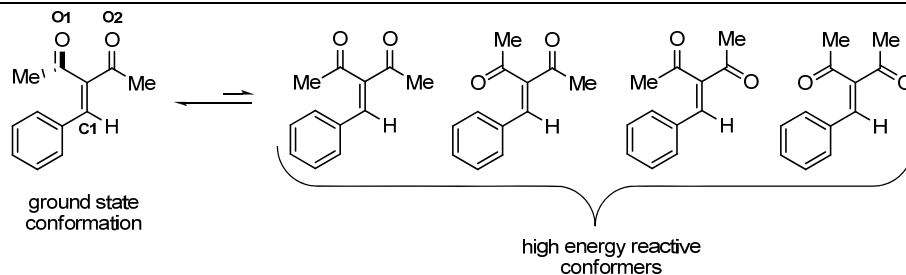
Figure 1.5. Conformations of benzylidene acetylacetone

The structures most resembling alkylidene Meldrum's acids in gross structure are the activated Cu(II) complexes of alkylidene malonates (**1.18**), for which an X-ray structure has been obtained.[42] Dual coordination of both carbonyl groups to the metal centre enforces a 6-membered ring structure, which adopts a boat conformation just as in alkylidene Meldrum's acids, and imposes proper orbital overlap with the alkene. Combining this conformation with the electron-withdrawing and LUMO-lowering nature of the bis-cationic Lewis acid, it is not surprising that these complexes are highly reactive electrophiles in the enantioselective addition of silylketenethioacetals.[43] Also, in at least a superficial manner, alkylidene Meldrum's acids share a resemblance to **1.18** in charge distribution, where the acetal carbon of Meldrum's acid serves in place of the more strongly activating copper ion (Figure 1.6).
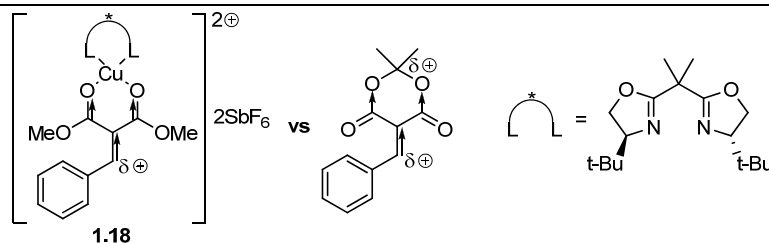
Figure 1.6. Comparison of Lewis-acid activatived malonates to alkylidene Meldrum's acids

Having discussed the unique properties of alkylidene Meldrum's acids, a look at the manner in which they are made is required. As will be shown, the same electrophilicity that makes them attractive synthetic reagents can also cause problems for those attempting to prepare them.

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1.4 Preparation of Alkylidene Meldrum's Acids

The typical bond disconnection for synthesis of alkylidene Meldrum's acids is across the alkene, so that the precursors for disubstituted alkylidenes are Meldrum's acid and ketones. The reaction that has found the widest use in our group is the $TiCl_4$-mediated Knoevenagel condensation reported by Brown,[44] which we have found to be applicable to a large range of ketones (Scheme 1.13).[45] Specific conditions for the condensation of Meldrum's acid with acetone[46] or cyclohexanones[47] are also available.
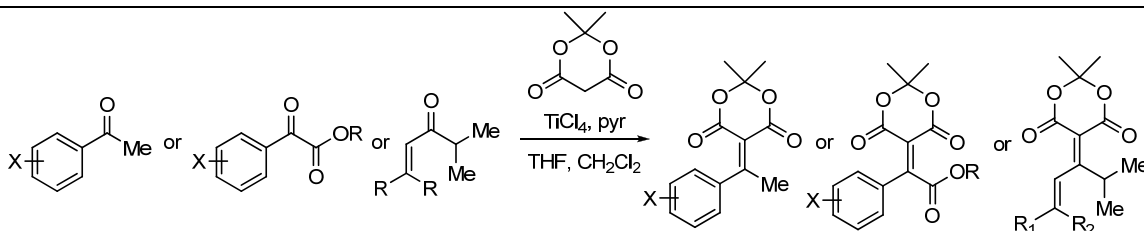
Scheme 1.13. Synthesis of disubstituted alkylidene Meldrum's acids

Although it is perhaps counterintuitive, the condensation of aldehydes with Meldrum's acid is actually more difficult in some ways than the reaction with ketones. The reason is that the monosubstituted alkylidenes are much better electrophiles than their disubstituted counterparts.[31] This means that even poor nucleophiles, such as Meldrum's acid itself, will react with the newly formed alkene over the course of the reaction (Scheme 1.14) to give the bis-Meldrum's acids **1.19**. This unfortunate tendency toward Michael addition has been noted from the earliest syntheses of these molecules[7,28] and presents a challenge during their preparation. In addition to lowering the overall yield of alkylidene, we have found that Michael adducts **1.19** are often difficult to separate from the desired products. Furthermore, there is seemingly no way to predict which alkylidenes are prone to Michael addition under a certain set of conditions, which can then necessitate a random screening of known protocols.
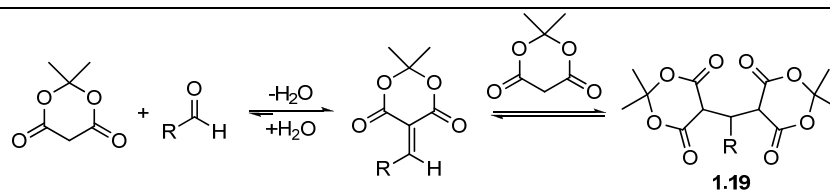
Scheme 1.14. Formation and Michael additions of monosubstituted alkylidene Meldrum's acids

The capricious nature of the Knoevenagel condensation has led to the development of alternative procedures for the synthesis of monosubstituted alkylidenes. One method that avoids the use of aldehydes altogether is the preparation of the dimethylaminomethylene Meldrum's acid **1.21** by reaction of Meldrum's acid with dimethylformamidedimethylacetal (**1.20**). This stable solid reacts with organometallic nucleophiles such as Grignard reagents by addition/elimination to give the monosubstituted alkylidenes (Scheme 1.15).[48] The intermediate anion is stabilized by six-membered ring chelate **1.22** that prevents premature elimination of dimethylamide. In this way, there is no alkylidene formed until after acidic workup and so double addition of the nucleophile is not a problem. For certain alkylidenes, especially ethylidene **1.23**, this is the method of choice in our group.
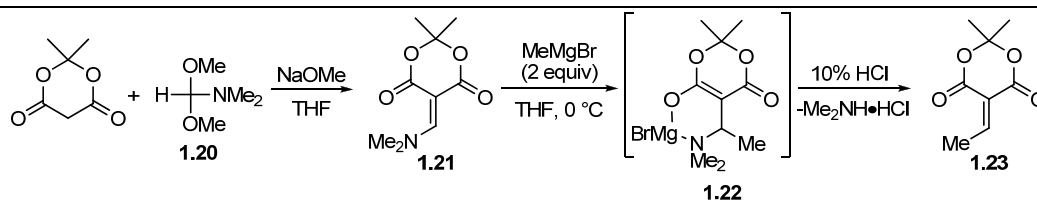
Scheme 1.15. Synthesis of monosubstituted alkylidenes by addition/elimination

A second strategy relies on Knoevenagel condensation to form the alkylidene, but is based on interception of the electrophile with a heteroatomic nucleophile rather than Meldrum's acid. The first report of this approach used methoxide as the nucleophile, where treatment with aqueous acid regenerates the alkylidene (Scheme 1.16a).[49] The main drawback of this method was that it was only demonstrated for condensation with more volatile aliphatic aldehydes, since the aldehyde is used as cosolvent and removed by vacuum distillation. A more practical alternative is the use of pyrrolidine[50] or thiols[51] to

give the neutral addition products. The amine adducts require addition of stoichiometric protic acid to catalyze the elimination and sequester the nitrogen lone pair. The thiol adducts **1.24** are particularly useful as they are isolable solids and are stable in this state for months. However, they eliminate thiophenol spontaneously in solution, so that the liberated alkylidene can be reacted in-situ (a representative example is shown in Scheme 1.16b).
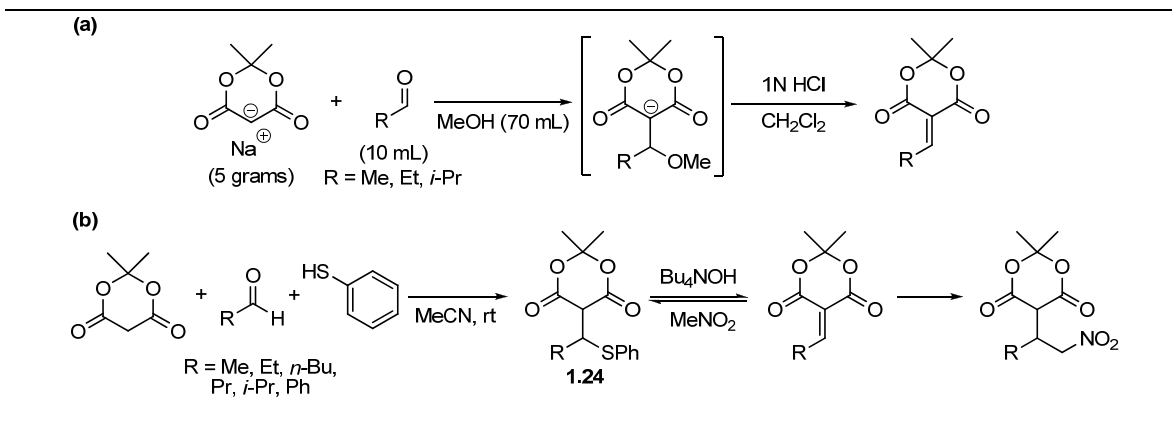
Scheme 1.16. Nucleophilic trapping of alkylidene Meldrum's acids

While both of the above strategies are adequate to overcome some of the limitations of direct Knoevenagel condensation of Meldrum's acid with aldehydes, neither are ideal in terms of developing a research program around the use of monosubstituted alkylidenes. The addition/elimination protocol requires the use of Grignard reagents, which precludes formation of alkylidenes containing functional groups incompatible with these strong nucleophiles. Although the amine or thiol addition sequence would likely be applicable to a broader range of functionalized aldehydes, the main problem with this approach is the stoichiometric release of the heteroatomic nucleophile during generation of the alkylidene. Especially in light of the known sequestration of Lewis acids by amines in the Friedel-Crafts acylation reactions of Meldrum's acids derivatives mentioned above, these methods appeared to not be feasible.

It was clear that in terms of maximizing the number of possible monosubstituted alkylidenes and producing them in isolable forms without by-products, that Knoevenagel condensation with aldehydes was the most direct route. We therefore turned our attention to the discovery of conditions for this reaction that would minimize the amount of

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Michael adduct formed in order to facilitate product isolation and increase the yield of alkylidene. The impetus for this was our inability to form alkylidene **1.28** by condensation of benzaldehyde and Meldrum's acid, where we invariably isolated the Michael adduct **1.29** instead (see Scheme 1.18 below). Since **1.28** was the alkylidene most commonly used in our group for optimization of new reactions, it was frustrating to not have a simple, scalable route to this useful starting material.

A starting point for the discovery of a solution to this problem was literature precedent for the formation of methylene Meldrum's acid **1.27** from the bis-adduct **1.25**.[52] It was found that while decomposition of **1.25** to **1.27** and Meldrum's acid did not occur, addition of an equivalent of formaldehyde resulted in liberation of two equivalents of **1.27**. A mechanism involving formation of the aldol intermediate **1.26**, which facilitates the retro-Michael reaction, was proposed to explain this observation (Scheme 1.17).
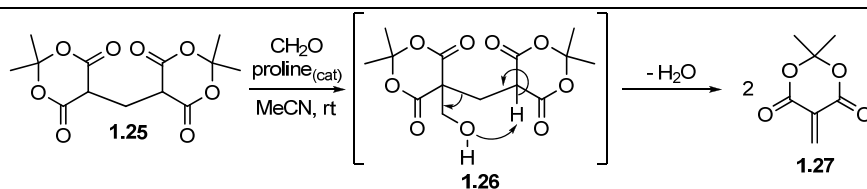
Scheme 1.17. Alkylidene Meldrum's acids by decomposition of Michael adducts

In the cases of attempted formation of **1.28** where large amounts of **1.29** were isolated instead, we noted that the Michael adduct was insoluble in many common solvents (for example, it is difficult to dissolve **1.29** in CDCl$_3$ for the purposes of NMR). It therefore seemed plausible that precipitation of **1.29** from solution during the reactions was preventing the retro-Michael addition since this process requires a second equivalent of benzaldehyde. It was thought that judicious choice of solvent, and the presence of an amino acid to catalyze both processes, could lead to preferential formation of **1.28**.

It was found that the use of benzene as solvent with a catalytic amount of pyrrolidinium acetate led to formation of **1.28** with minimal formation of **1.29**.[53] Scheme 1.18 shows a comparison of these conditions with reported methods for condensation of aldehydes and Meldrum's acid. The uncatalyzed aqueous reaction developed by Bigi (Conditions A)[54], who did not describe the use of benzaldehyde, gave a 7:93 ratio of

1.28:**1.29**. More disappointingly, a method reported to give a 69% yield of **1.28** (Conditions B)[55], actually gave **1.29** as the major product. Under the conditions we discovered (Conditions C), the alkylidene **1.28** was produced in 97:3 ratio with **1.29**. Importantly, the low amount of **1.29** in the crude mixture meant that it could be removed by recrystallization from MeOH, and **1.28** was isolated in 85% yield.
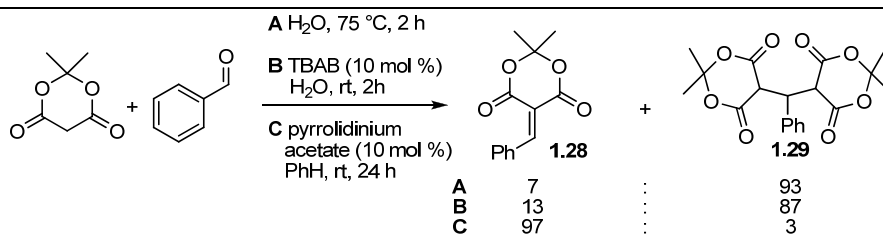
Scheme 1.18. Comparison of Knoevenagel condensations

These conditions have proven general, and they have been used within our group for the synthesis of a large range of alkylidene Meldrum's acids (Scheme 1.19). Condensations with methoxy-substituted benzaldehydes to give the electron-rich alkylidenes **1.30-1.33**, which are useful for Friedel-Crafts acylation studies, worked well for all substitution patterns. Electron-neutral alkyl groups (**1.34**), and electron-withdrawing groups (**1.35-1.37**) are also well-tolerated. In the case of the cyano-substituted **1.35** the reaction temperature was raised to 80 °C because significant amounts of Michael adduct formed at lower temperatures. Halogenated benzaldehydes, which are known to be prone to Michael addition of Meldrum's acid[54], condense cleanly under these conditions and the condensation is general across halogens and positions on the ring (**1.38-1.41**). For other oxygen-containing aldehydes, the condensation is tolerant of free hydroxyl groups (**1.42**), silyl ethers (**1.43**), esters (**1.44**), and furan (**1.45**). Both 2-naphthaldehyde and the more sterically hindered 1-naphthaldehyde condense cleanly and in good yield (**1.46** and **1.47**, respectively). Aliphatic aldehydes can be used, with the caveat that they be unsaturated (**1.48**) or branched (**1.49**). Attempted condensation with acetaldehyde provided a complex mixture even when the reaction was conducted at 0° C. Electron-rich heteroaromatic aldehydes such as thiophene (**1.50**) and *N*-protected indoles (**1.51** and **1.52**) and pyrroles (**1.53**) also work well.

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Overall, these Knoevenagel condensation conditions have been applied to the largest variety of aldehydes of any reported reactions known in the literature.[56] Importantly for us, the reaction can be scaled up easily and we have used it to prepare up to 13 grams of **1.28** at a time.[57] With ready and reliable access to alkylidene Meldrum's acids, our research on new reactions of these molecules was greatly facilitated. My contributions to this work are described in the succeeding chapters.

1.30 88%	**1.31** 88%	**1.32** 84%	**1.33** 85%
1.34 77%	**1.35** 81%	**1.36** 68%	**1.37** 71%
1.38 72%	**1.39** 60%	**1.40** 84%	**1.41** 76%
1.42 48%	**1.43** 63%	**1.44** 56%	**1.45** 76%
1.46 89%	**1.47** 92%	**1.48** 84%	**1.49** 78%
1.50 86%	**1.51** 82%	**1.52** 92%	**1.53** 79%
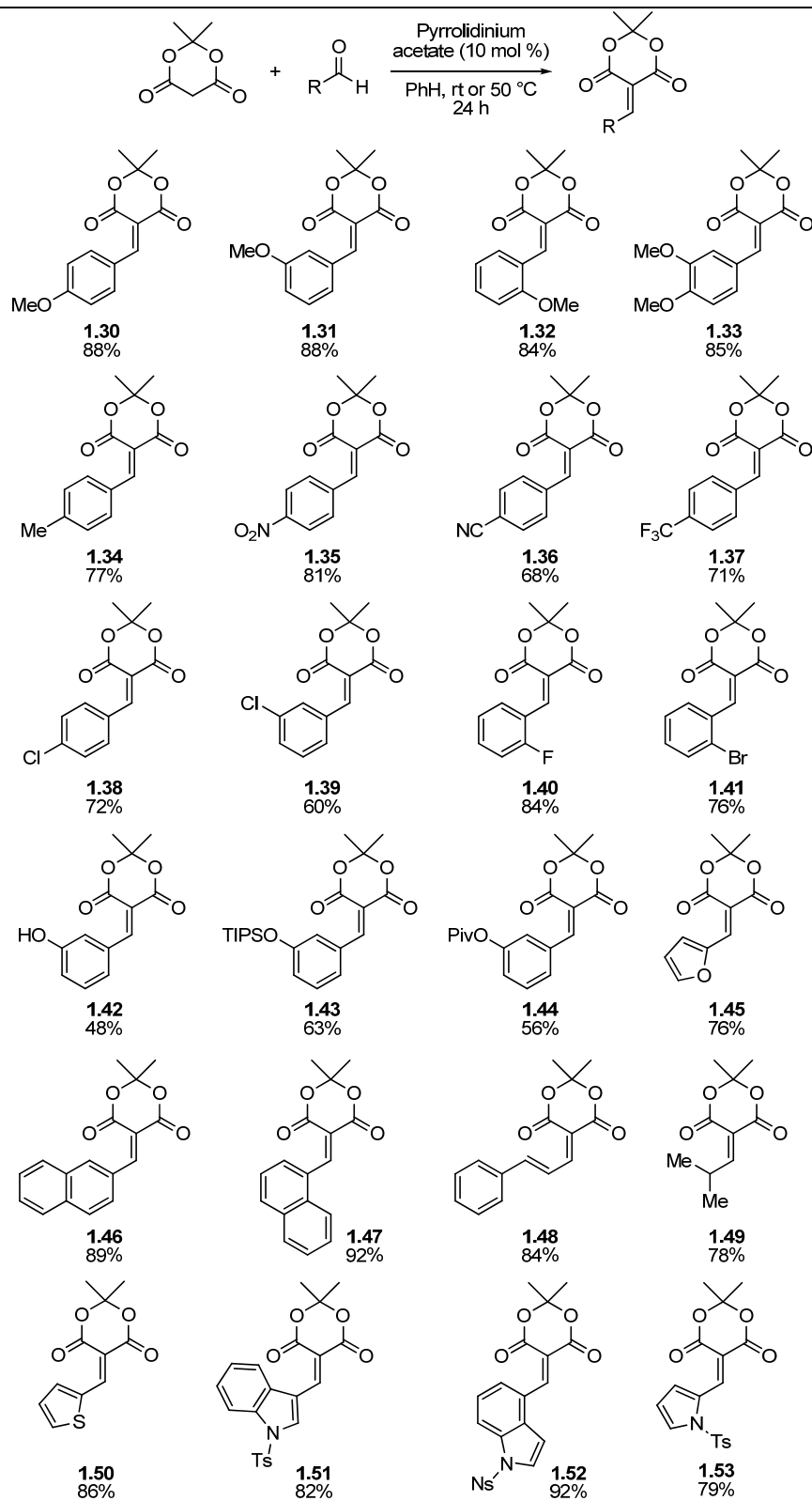
Scheme 1.19. General conditions for condensation of aldehydes with Meldrum's acid

1.5. Experimental Section

General Considerations: Condensations were performed in clean, air-dried glassware without special precautions to avoid air or moisture other than sealing tightly with a plastic cap. Benzene was distilled from Na/benzophenone ketyl before use. Pyrrolidinium acetate solution in benzene was formed by addition of AcOH (1.0 equiv) to a solution of pyrrolidine (1.0 equiv) in benzene and used immediately (pyrrolidinium acetate precipitates upon storage). Reactions above room temperature were performed in preheated oil baths.

Characterization: Melting points are uncorrected. ^{1}H NMR spectra were referenced to residual CHCl$_3$ (7.24 ppm); ^{13}C NMR spectra were referenced to CDCl$_3$ (77.0 ppm). ^{13}C NMR hydrogen multiplicities were determined by JMOD or combined DEPT-90 and DEPT-135 experiments. Chemical shifts are reported in units of parts per million (ppm, δ). High resolution mass spectra were obtained at the University of Waterloo Mass Spectrometry Facility.

General procedure for condensation of aldehydes with Meldrum's acid: Meldrum's acid (1.1 equiv) and the aldehyde (1.0 equiv) were dissolved in benzene (0.2 M relative to aldehyde). To this was added pyrrolidinium acetate solution (0.1 equiv) and the reaction was stirred at the indicated temperature. After 24 h, the flask was cooled to rt if not there already and concentrated by rotary evaporation. The resulting residue was purified by recrystallization from MeOH unless indicated otherwise.

Unless indicated otherwise, condensations were performed using 1.0 mmol aldehyde and 1.1 mmol Meldrum's acid (156 mg). Characterization data for previously unreported alkylidenes or for those not fully characterized in the literature are provided.
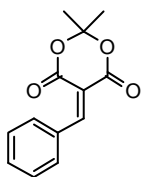
5-Benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (1.28): Prepared by condensation of benzaldehyde with Meldrum's acid at rt and isolated as an off-white solid (197 mg, 85% yield). ^{1}H NMR spectral data matched those

reported.[56d]
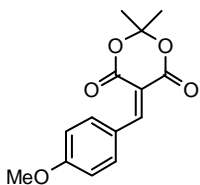
5-(4-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.30): Prepared by condensation of 4-methoxybenzaldehyde with Meldrum's acid at rt and isolated as a yellow solid (230 mg, 88% yield). M.p. 125-126 °C [lit. m.p.[58] 122-124 °C]; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.36 (s, 1H), 8.21 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 164.6 (C), 164.0 (C), 160.4 (C), 157.9 (C), 137.6 (CH), 124.7 (C), 114.3 (CH), 110.8 (C), 104.1 (C), 55.6 (CH$_3$), 27.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{14}$H$_{14}$O$_5$ (M$^+$): 262.0841 Found: 262.0841.
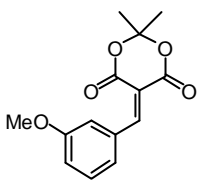
5-(3-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.31): Prepared by condensation of 3-methoxybenzaldehyde with Meldrum's acid at rt and isolated as an off-white solid (229 mg, 88% yield). M.p. 86-88 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.36 (s, 1H), 7.78 (t, J = 3.9 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.12-7.08 (m, 1H), 3.84 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.1 (C), 159.6 (C), 159.3 (C), 157.8 (CH), 132.7 (C), 129.5 (CH), 126.8 (CH), 120.4 (CH), 117.0 (CH), 114.8 (C), 104.4 (CH), 55.3 (CH$_3$), 27.4 (CH$_3$); HRMS(EI) m/z calcd for C$_{14}$H$_{14}$O$_5$ (M$^+$): 262.0841 Found: 262.0847.

5-(2-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.32): Prepared by condensation of 2-methoxybenzaldehyde with Meldrum's acid at rt and isolated as a yellow solid (221 mg, 84% yield). ^{1}H NMR spectral data matched those reported.[217]
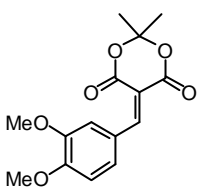
5-(3,4-Dimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.33): Prepared from 3,4-dimethoxybenzaldehyde with Meldrum's acid at rt and isolated as a bright yellow powder (248 mg, 85% yield). Performing this reaction on a 10 mmol scale (relative to aldehyde), **1.33** was formed in 92% yield (2.68 g). M.p. 156-158 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.34 (s, 1H), 8.28 (d, J = 2.0 Hz, 1H), 7.63 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H),

3.97 (s, 3H), 3.94 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 164.1 (C), 160.6 (C), 158.2 (CH), 154.7 (C), 148.7 (C), 132.6 (CH), 125.0 (C), 115.6 (CH), 110.6 (C), 110.5 (CH), 104.1 (C), 56.1 (CH$_3$), 55.9 (CH$_3$), 27.4 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{15}$H$_{16}$O$_6$ (M$^+$): 292.0947 Found: 292.0940.

2,2-Dimethyl-5-(4-methylbenzylidene)-1,3-dioxane-4,6-dione (1.34): Prepared by condensation of 4-methylbenzaldehyde with Meldrum's acid at 50 °C in concentrated benzene solution (0.5M relative to aldehyde) and isolated as white solid (190 mg, 77% yield). ^{1}H NMR spectral data matched those reported.[56d]
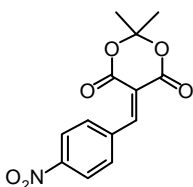
2,2-Dimethyl-5-(4-nitrobenzylidene)-1,3-dioxane-4,6-dione (1.35): Prepared by condensation of 4-nitrobenzaldehyde with Meldrum's acid at 50 °C and isolated as a white solid (224 mg, 81% yield). ^{1}H NMR spectral data matched those reported.[56d]
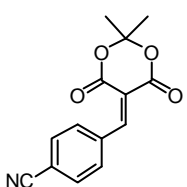
4-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)benzonitrile (1.36): Prepared by condensation of 4-cyanobenzaldehyde with Meldrum's acid at 80 °C and isolated as a white solid (175 mg, 68% yield). ^{1}H NMR spectral data matched those reported.[217]
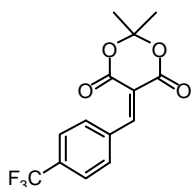
2,2-Dimethyl-5-(4-(trifluoromethyl)benzylidene)-1,3-dioxane-4,6-dione (1.37): Prepared by condensation of 4-trifluoromethylbenzaldehyde with Meldrum's acid at 50 °C and isolated as a white solid (212 mg, 71% yield). ^{1}H NMR spectral data matched those reported.[208]
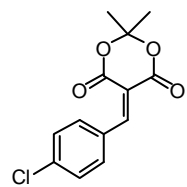
5-(4-Chlorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.38): Prepared by condensation of 4-chlorobenzaldehyde with Meldrum's acid at 50 °C and isolated as a white solid (192 mg, 72% yield). M.p. 157-158 °C [lit m.p.[59] 161-162 °C]; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.35 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 1.79 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.0 (C), 159.6 (C), 156.4 (CH), 140.1 (C), 134.9 (CH), 130.0 (C), 129.1 (CH),

115.0 (C), 104.7 (C), 27.6 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{13}$H$_{11}$ClO$_4$ (M$^+$): 266.0346 Found: 266.0353.
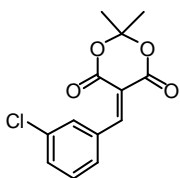
5-(3-chlorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.39): Prepared by condensation of 3-chlorobenzaldehyde with Meldrum's acid at 50 °C and isolated as a white solid (160 mg, 60% yield). M.p. 115-116 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.32 (s, 1H), 8.02 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 1.79 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 162.7 (C), 159.3 (C), 156.0 (CH), 134.6 (C), 133.2 (C), 133.1 (CH), 132.5 (CH), 131.3 (CH), 129.8 (CH), 116.2 (C), 104.7 (C), 27.6 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{13}$H$_{11}$ClO$_4$ (M$^+$): 266.0346 Found: 266.0341.
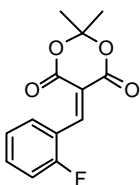
5-(2-Fluorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.40): Prepared by condensation of 2-fluorobenzaldehyde (1.24 g, 1.5 mL, 10.0 mmol) with Meldrum's acid at 50 °C. Purified by recrystallization from MeOH and isolated as a white powder (2.32 g, 93% yield). M.p. 140-141 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.49 (s, 1H), 7.93 (t, *J* = 7.5 Hz, 1H), 7.50 (q, *J* = 7.0 Hz, 1H), 7.24-7.20 (m, 1H, overlaps with CHCl$_3$), 7.13 (t, *J* = 7.1 Hz, 1H), 1.81 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 162.3 (C), 161.5 (d, *J* = 254.7 Hz, C), 159.4 (C), 149.2 (d, *J* = 4.0 Hz, CH), 134.7 (d, *J* = 9.3 Hz, CH), 132.1 (CH), 124.3 (d, *J* = 9.3 Hz, CH), 120.6 (d, *J* = 11.4 Hz, C), 117.9 (C), 115.9 (d, *J* = 22.0 Hz, CH), 104.9 (C), 27.6 (2X CH$_3$); HRMS(EI) *m/z* calcd for C$_{13}$H$_{11}$FO$_4$ (M$^+$): 250.0641 Found: 250.0647.
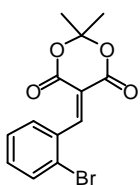
5-(2-Bromobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.41): Prepared by condensation of 2-bromobenzaldehyde with Meldrum's acid at 50 °C and isolated as a white solid (236 mg, 76% yield). ^{1}H NMR spectral data matched those reported.[60]
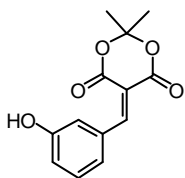
5-(3-Hydroxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.42): Prepared by condensation of 3-hydroxybenzaldehyde (1.22 g, 10.0 mmol) with Meldrum's acid at 50 °C and isolated as a pale yellow solid (1.19 g, 48% yield). ^{1}H NMR spectral data matched those

reported.[56b]
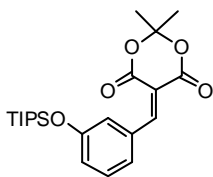
2,2-Dimethyl-5-(3-(triisopropylsilyloxy)benzylidene)-1,3-dioxane-4,6-dione (1.43): Prepared by condensation of 3-(triisopropylsilyloxy)benzaldehyde[61] (4.75 g, 16.4 mmol) with Meldrum's acid at 50 °C. Purified by flash column chromatography eluting with 4:1 hexanes:EtOAc and isolated as a yellow oil (2.48 g, 63% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 8.33 (s, 1H), 7.65 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.07 (dd, J = 8.1 Hz, 1.9 Hz, 1H), 1.78 (s, 6H), 1.27 (app sextet, J = 7.3 Hz, 3H), 1.09 (d, J = 7.2 Hz, 18 H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.4 (C), 159.6 (C), 158.0 (CH), 156. 2 (C), 132.9 (C), 129.7 (CH), 127.0 (CH), 125.7 (CH), 124.3 (CH), 114.7 (C), 104.5 (C), 27.6 (2X CH$_3$), 17.9 (2X CH$_3$), 12.6 (C); HRMS(EI) m/z calcd for C$_{22}$H$_{32}$O$_5$Si (M[+]): 404.2019 Found: 404.2017.
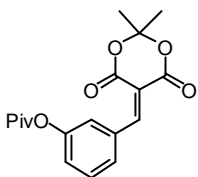
3-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)phenyl pivalate (1.44)[62]: Prepared by condensation of 3-(Pivaloyloxy)-benzaldehyde[63] (3.1 g, 15.0 mmol) with Meldrum's acid at 50 °C and isolated as an off-white solid (2.8 g, 56% yield). M.p. 86 - 90 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 8.36 (s, 1H), 7.86–7.83 (m, 2H), 7.47 (t, J = 8.2 Hz, 1H), 7.25 (d, J = 9.1 Hz, 1H), 1.78 (s, 6H), 1.33 (s, 9H); ^{13}C NMR (75MHz, CDCl$_3$) 176.8 (C), 163.0 (C), 159.4 (C), 156.6 (CH), 151.0 (C), 132.8 (C), 131.1 (CH), 129.5 (CH), 126.8 (CH), 126.0 (CH), 115.5 (C), 104.6 (C), 39.0 (C), 27.5 (CH$_3$), 27.0 (CH$_3$); HRMS (ESI) m/z calcd for C$_{18}$H$_{20}$O$_6$ (M[+]): 332.1260. Found: 332.1271.
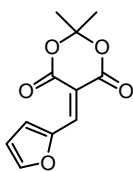
5-(Furan-2-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.45): Prepared by condensation of furfural (freshly distilled) with Meldrum's acid at 50 °C and isolated as a dark purple solid (169 mg, 76% yield). ^{1}H NMR spectral data matched those reported.[56d]
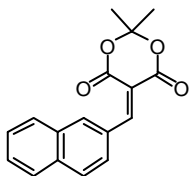
2,2-Dimethyl-5-(naphthalen-2-ylmethylene)-1,3-dioxane-4,6-dione (1.46): Prepared by condensation of 2-naphthaldehyde with Meldrum's acid at 50 °C and isolated as a white solid (251 mg, 89% yield).[197a]
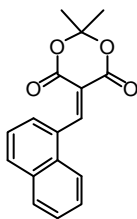
2,2-dimethyl-5-(naphthalen-1-ylmethylene)-1,3-dioxane-4,6-dione (1.47): Prepared by condensation of 1-naphthaldehyde with Meldrum's acid at 50 °C and isolated as a white solid (260 mg, 92% yield). ^{1}H NMR spectral data matched those reported.[64]
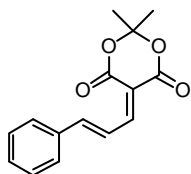
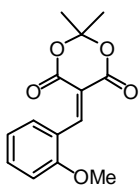**(*E*)-2,2-Dimethyl-5-(3-phenylallylidene)-1,3-dioxane-4,6-dione (1.48):** Prepared by condensation of (*E*)-cinnamaldehyde with Meldrum's acid at 50 °C and isolated as a yellow solid (215 mg, 84% yield). ^{1}H NMR spectral data matched those reported.[197a]

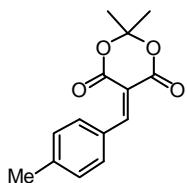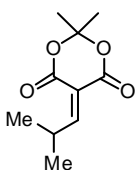**2,2-Dimethyl-5-(2-methylpropylidene)-1,3-dioxane-4,6-dione (1.49):** Prepared by condensation of isobutyraldehyde with Meldrum's acid at 50 °C and isolated as a white solid (169 mg, 76% yield). ^{1}H NMR spectral data matched those reported.[60]
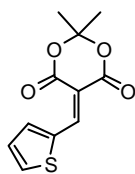
2,2-Dimethyl-5-(thiophen-2-ylmethylene)-1,3-dioxane-4,6-dione (1.50): Prepared by condensation of thiophene-2-carboxaldehyde (freshly distilled, 2.3 mL, 25.0 mmol) with Meldrum's acid at 50 °C and isolated as a beige powder (5.1 g, 86% yield). M.p. 196-197 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.65 (s, 1H), 8.00 (d, *J* = 4.9 Hz, 1H), 7.88 (d, *J* = 3.6 Hz, 1H), 7.27-7.25 (m, 1H, overlaps with CDCl$_3$), 1.76 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.3 (C), 160.9 (C), 149.0 (CH), 144.8 (CH), 141.7 (CH), 136.3 (C), 128.2 (CH), 106.0 (C), 104.5 (C), 27.4 (2X CH$_3$); HRMS(EI) *m/z* calcd for C$_{11}$H$_{10}$O$_4$S (M$^+$): 238.0300 Found: 283.0295.
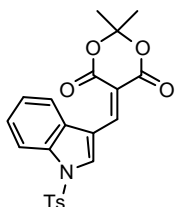
2,2-Dimethyl-5-((1-tosyl-1*H*-indol-3-yl)methylene)-1,3-dioxane-4,6-dione (1.51): Prepared by condensation of 1-tosyl-1*H*-indole-3-carbaldehyde[65] (2.6 g, 8.7 mmol) with Meldrum's acid at rt and isolated as a yellow powder (3.0 g, 82% yield). M.p. 167-168 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 9.60 (s, 1H), 8.72 (s, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.44-7.36 (m, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.36 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.5 (C), 160.8 (C), 146.2 (C), 145.6 (CH), 137.2 (CH), 134.2 (C), 130.3 (CH), 127.3 (CH), 125.9 (CH), 124.6 (CH), 118.6

(CH), 114.3 (C), 113.7 (CH), 110.7 (C), 104.5 (C), 27.5 (2X CH$_3$), 21.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{22}$H$_{19}$NO$_6$S (M$^+$): 425.0933 Found: 425.0930.
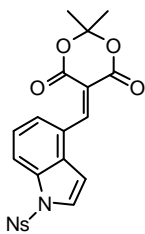
2,2-Dimethyl-5-((1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)methylene)-1,3-dioxane-4,6-dione (1.52): Prepared by condensation of *N*-Ns-indole-4-carboxaldehyde[66] (12.6 g, 38.1 mmol) with Meldrum's acid at rt. After stirring 24 h, an addition 100 mL of benzene was added to dilute the thick suspension, and stirring continued another 24 h at which point the reaction was treated as the others. Isolated as a bright yellow solid (15.9 g, 92% yield). M.p. 204-205 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.72 (s, 1H), 8.30-8.27 (m, 2H), 8.19 (d, J = 7.9 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.06-8.03 (m, 2H), 7.71 (d, J = 3.7 Hz, 1H), 7.43 (t, J = 8.1 Hz, 1H), 6.91 (d, J = 3.8 Hz, 1H), 1.80 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 162.8 (C), 159.5 (C), 153.1 (CH), 150.8 (C), 142.9 (C), 134.6 (C), 132.7 (C), 128.1 (CH), 128.0 (CH), 127.7 (CH), 125.0 (CH), 124.9 (C), 124.7 (CH), 118.0 (CH), 115.8 (C), 108.3 (CH), 104.8 (C), 27.7 (CH$_3$); HRMS(EI) m/z calcd for C$_{21}$H$_{16}$N$_2$O$_8$S (M$^+$): 456.0627 Found: 456.0630.
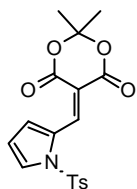
2,2-Dimethyl-5-((1-tosyl-1H-pyrrol-2-yl)methylene)-1,3-dioxane-4,6-dione (1.53): Prepared by condensation of 1-tosyl-1*H*-pyrrole-2-carbaldehyde[63] (2.3 g, 9.2 mmol) with Meldrum's acid at 50 °C and isolated as a brown powder (2.7 g, 79% yield). M.p. 151-152 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.99 (s, 1H), 8.37 (d, J = 3.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.52 (br s, 1H), 2.39 (s, 3H), 1.70 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.6 (C), 160.1 (C), 146.3 (C), 140.7 (CH), 134.9 (C), 132.1 (CH), 131.0 (CH), 130.4 (2X CH), 128.3 (C), 127.5 (2X CH), 113.9 (CH), 108.0 (C), 104.2 (C), 27.4 (2X CH$_3$), 21.7 (CH$_3$); HRMS(EI) m/z calcd for C$_{18}$H$_{17}$NO$_6$S (M$^+$): 375.0777 Found: 375.0777.

Chapter 2. Reactions of Alkylidene Meldrum's Acids with Phenols

2.1. Synthesis of 3,4-Dihydrocoumarins, Coumarins, Chromanones, and Chromones

The first reaction based on the concept outlined in Scheme 1.9 was that between alkylidene Meldrum's acids and phenols. As shown in Scheme 2.1, this conjugate addition/acylation protocol could proceed by two possibly competing mechanisms. *C*-alkylation by Friedel-Crafts conjugate addition followed by *O*-acylation would give 3,4-dihydrocoumarins, while the opposite reaction (*O*-alkylation/*C*-acylation) would give chromanones. Additionally, it was thought that methoxy-substituted alkylidenes would undergo loss of methanol following addition to give the unsaturated versions of these molecules, coumarins and chromones, respectively.
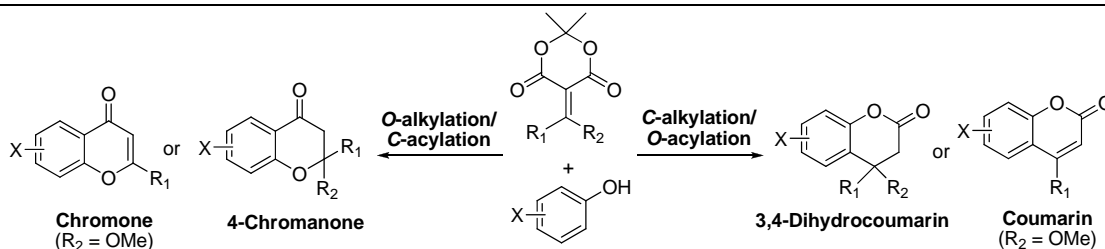
Scheme 2.1. Proposed reactions of alkylidene Meldrum's acids with phenols

All four of these compound classes are present in widespread families of natural products[67], and many of these have found use as medicinal agents owing primarily to their anti-oxidant capabilities.[68] Considering the huge number of known members of these groups, there are a correspondingly large number of means for their preparation[69], which prevents a full overview of these methods in this chapter. However, the most common methods to access each class, as well as examples pertinent to the work presented herein are described below.

The classic method of coumarin synthesis is the Pechmann condensation, which was first reported in 1884.[70] This involves the reaction of β-ketoesters with phenols under acid catalysis to first give a cinnamic ester **2.1** by Friedel-Crafts alkylation. Subsequent transesterification forms the required lactone. This also provides a straightforward route

to 3,4-dihydrocoumarins, as they have commonly been prepared by hydrogenation of coumarins (Scheme 2.2).
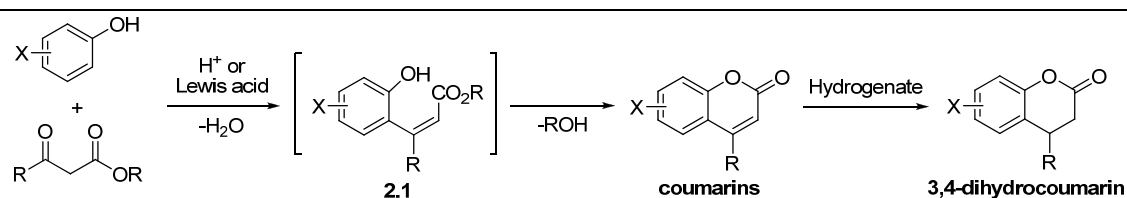
Scheme 2.2. Synthesis of coumarins by Pechmann condensation

The most common means of preparing 4-chromanones is the intramolecular cyclization of *o*-hydroxychalcones **2.2**, which can be prepared in a variety of methods. The most direct route is domino Claisen condensation/cyclization between hydroxy-acetophenones and non-enolizable aldehydes (a representative example is shown in Scheme 2.3a).[71] Although this is a convenient method, its main drawback is that **2.2** and **2.3** are in equilibrium under typical conditions, leading to mixtures of products that must be separated after the reaction. This is especially problematic for syntheses of chiral 4-chromanones where the equilibrium leads to racemization, and therefore alternative procedures are required (Scheme 2.3b).[72] In this case, chiral 4-chromanone **(S)-2.3** was formed without loss of enantiopurity and with only minor amounts of chalcone **2.2**.
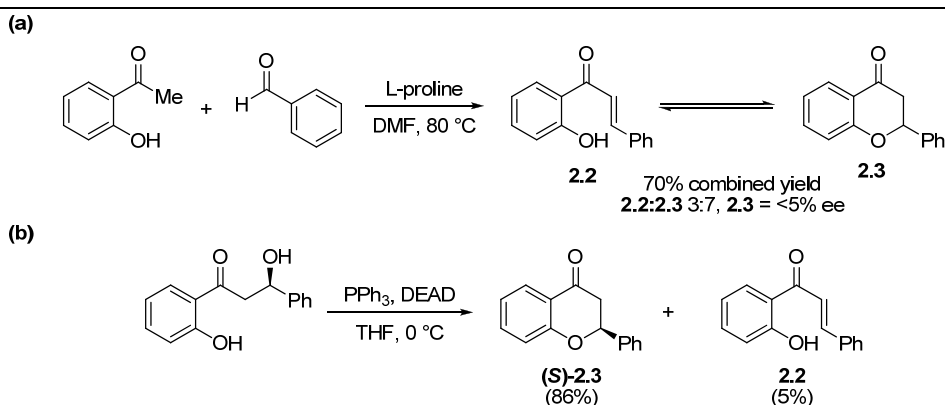
Scheme 2.3. Common preparations of 4-chromanones

The most general means to prepare chromones is the Allan-Robinson reaction, which also uses *o*-hydroxyacetophenone derivatives as starting material.[73] Phenol acylation, followed by Knoevenagel condensation of the resulting ester **2.4** gives

chromone **2.6** (Scheme 2.4, Route A). An alternative procedure which has been reported to be higher yielding is to rearrange ester **2.4** to ketone **2.5**, followed by cyclization under acidic conditions (Scheme 2.4, Route B).[74]
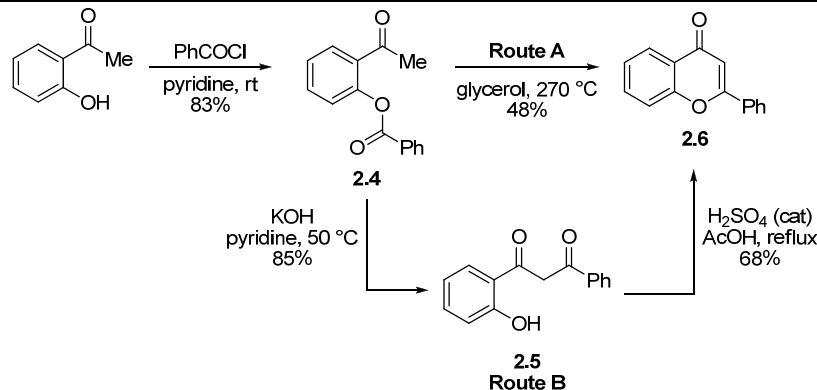
Scheme 2.4. Synthesis of chromones from *o*-hydroxyacetophenone

More in the vein of our proposed reaction, recently many 3,4-dihydrocoumarin and coumarin syntheses have been reported involving reaction of phenols with α,β-unsaturated carbonyl compounds. An interesting example was reported by Fujiwara, who described the reaction of cinnamates and phenols giving 3,4-dihydrocoumarins in the presence of palladium in trifluoroacetic acid (TFA).[75] A representative presumed catalytic cycle is shown in Scheme 2.5a. Acid-catalyzed esterification of phenol **2.7** with acrylate **2.8** yields **2.9**, which then reacts with Pd(II) to give the palladated intermediate **2.10**. Intramolecular carbopalladation (migratory insertion) followed by protonation of the resulting alkenyl palladium regenerates the catalyst and give 3,4-dihydrocoumarin **2.11**. However, this mechanism was later refuted by Tunge, who demonstrated that the reaction proceeds equally well in the absence of Pd(II) salts. This was shown by the nearly equal rates of conversion to 3,4-dihydrocoumarin **2.14** from phenol **2.12** and cinnamic acid **2.13** (Scheme 2.5b).[76] A large number of 3,4-dihydrocoumarins could thus be prepared strictly by TFA catalysis.

31
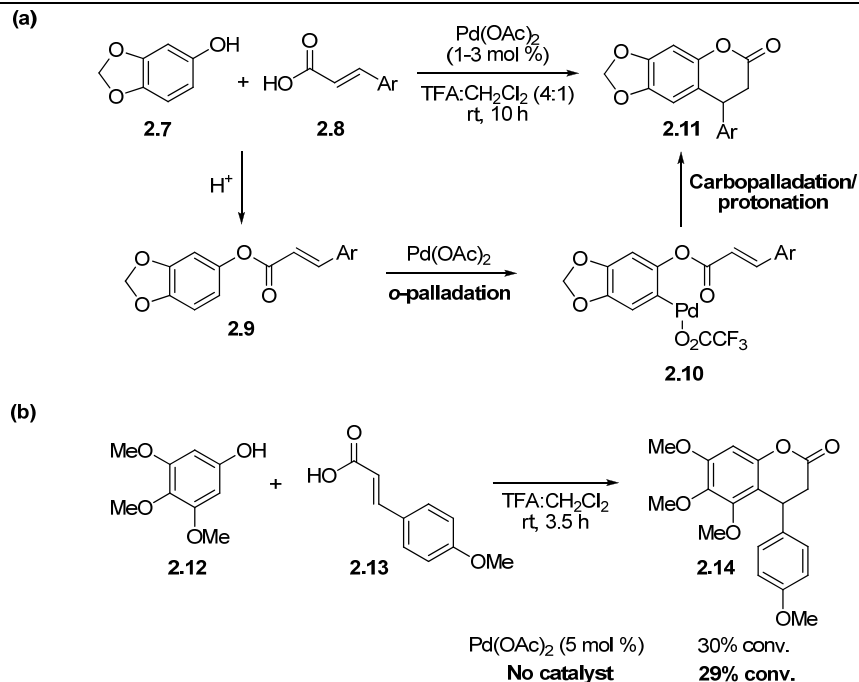
Scheme 2.5. Synthesis of 3,4-dihydrocoumarins by reaction of cinnamic acids and phenols

Since these reactions involve *C*-alkylation/*O*-acylation to form 3,4-dihydrocoumarins, a simple oxidation state change in the electrophile should give coumarins. A Pd-catalyzed reaction of phenols and alkynoates was reported by Trost, who showed that Pd(0) is the catalytic species (Scheme 2.6a).[77] Fujiwara also applied his conditions to the reaction of phenols with propiolic acid which also gives coumarins (Scheme 2.6b).[78] However, in light of Tunge`s later findings, the Pd-catalysis of this reaction is doubtful.
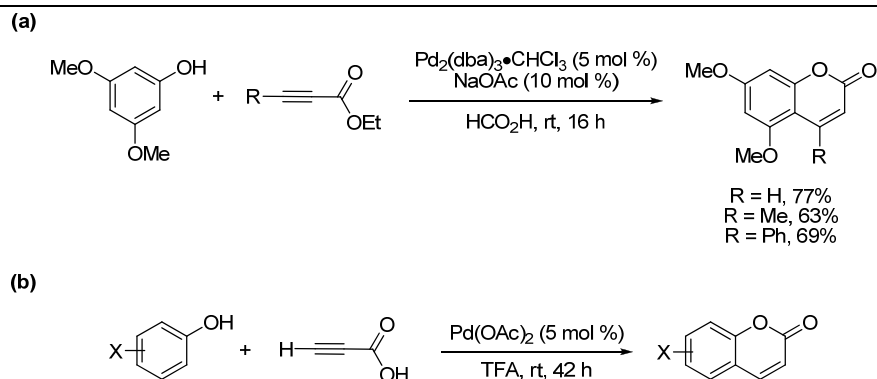
Scheme 2.6. Synthesis of coumarins from alkynes and phenols

In terms of preparing these molecules from Meldrum's acid derivatives, 3-carboxycoumarins **2.17** have been the primary targets (Scheme 2.7a).[79] This involves the condensation of *o*-hydroxy-benzaldehydes or ketones **2.15** with Meldrum's acid to presumably give the alkylidene **2.16** as an intermediate. Subsequent attack of the phenol opens up the Meldrum's acid to give coumarin **2.17**, where the presence of the alkene makes decarboxylation much more difficult than in saturated malonic half-esters.[80] A variant of this reaction starting from *o*-methoxybenzylidene Meldrum's acids **2.18** was reported by Tapia, who reported the demethylative cyclization of these molecules in concentrated H_2SO_4 (Scheme 2.7b).[81]
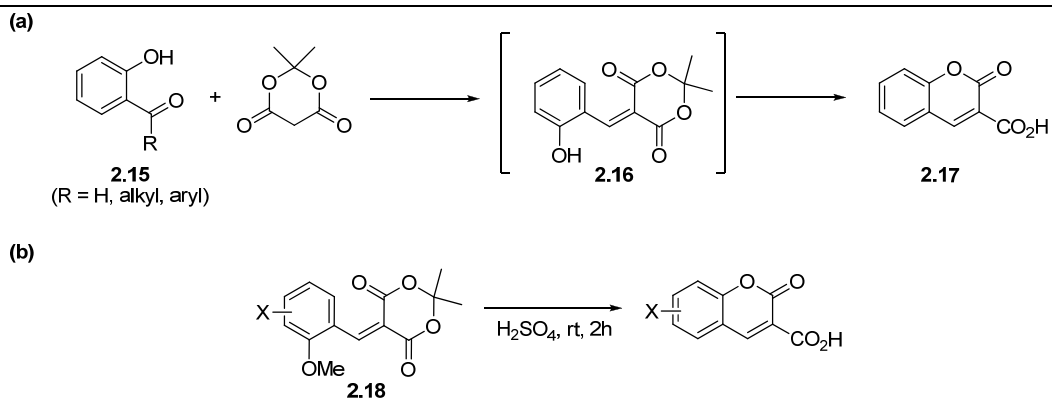
Scheme 2.7. Syntheses of 3-carboxycoumarins from Meldrum's acid derivatives

A reaction similar to that which we proposed was reported by Nair, who reacted phloroglucinol (1,3,5-trihydroxybenzene, **2.19**) with alkylidene Meldrum's acids formed in-situ under basic conditions (Scheme 2.8a).[82] However, the reaction only worked with this very electron-rich nucleophile and so was of limited scope for preparing dihydrocoumarins **2.20**. A related process is the synthesis of dihydroquinolones **2.22** from the reaction of imines **2.21** and Meldrum's acid (Scheme 2.8b). Here, group transfer between the imine and Meldrum's acid gives 2-aminonaphthalene and an alkylidene, which then react by *C*-alkylation/*N*-acylation to give dihydroquinolones **2.22**.
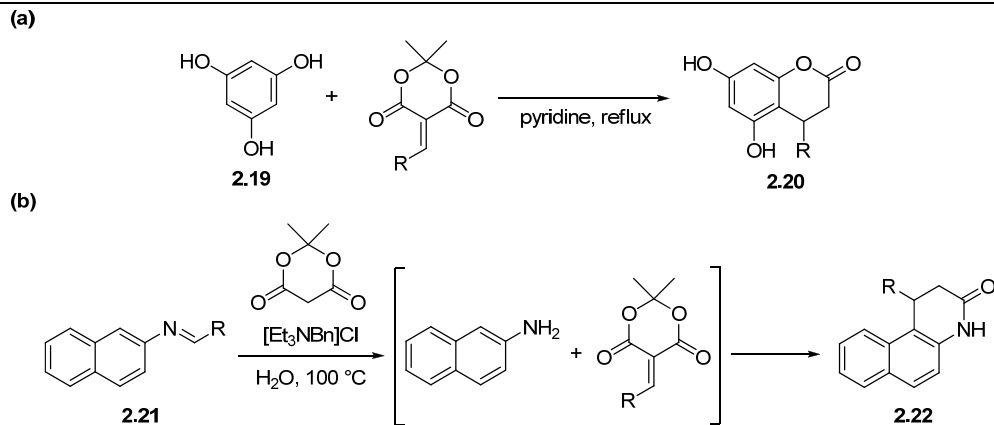
Scheme 2.8. Reaction of alkylidene Meldrum's acids with phloroglucinol and 2-amino-naphthalene

Based on this literature precedent, we were confident that our proposed reaction was possible. More importantly, it was thought that Lewis acid activation of the alkylidenes would broaden the scope of compatible nucleophiles compared to the basic conditions employed by Nair. Our successes in this area are described in the following section.

2.2. Yb(OTf)$_3$-Catalyzed Additions of Phenols to Alkylidene Meldrum's Acids.

The initial reaction studied was the addition of 3,5-dimethoxyphenol (**2.23**) with disubstituted alkylidene **2.24** in nitromethane.[83] Under Sc(OTf)$_3$-catalysis, we were very pleased to isolate a cyclized product, which we initially assigned 3,4-dihydrocoumarin structure **2.26**, in 55% yield. By changing catalysts to Yb(OTf)$_3$, the yield increased to 80%, while Mg(OTf)$_2$ gave no desired product.[84] More interestingly, analysis of the ^{13}C NMR spectrum revealed the presence of a ketone in the product rather than a lactone. On this basis the structure was reassigned to 4-chromanone **2.25**, which is the product of *O*-alkylation/*C*-acylation (Scheme 2.9). This result was surprising based on the literature precedent, but having access to a different reaction pathway was exciting.
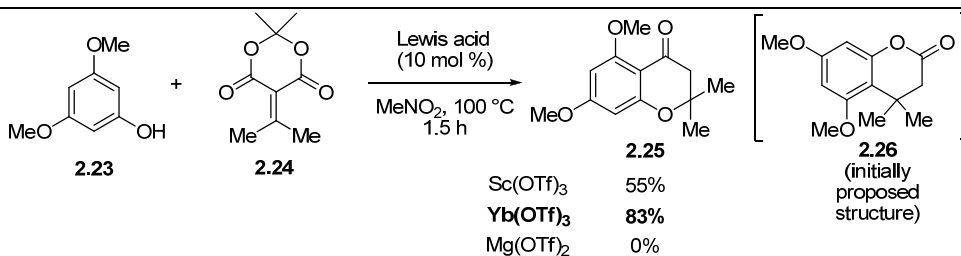
Scheme 2.9. Synthesis of 4-chromanone **2.25**

Attempts to use other, less reactive phenols in this reaction were unfortunately unsuccessful (Scheme 2.10a). In most cases, the reaction gave decomposition of the alkylidene and recovery of the phenol, although in some cases trace amounts of what were believed to be malonic half-ester **2.27** were detected. However, use of other disubstituted alkylidenes **2.28** and **2.29** was tolerated with phenol **2.23**, leading to 4-chromanones **2.30** and **2.31**, respectively (Scheme 2.10b).
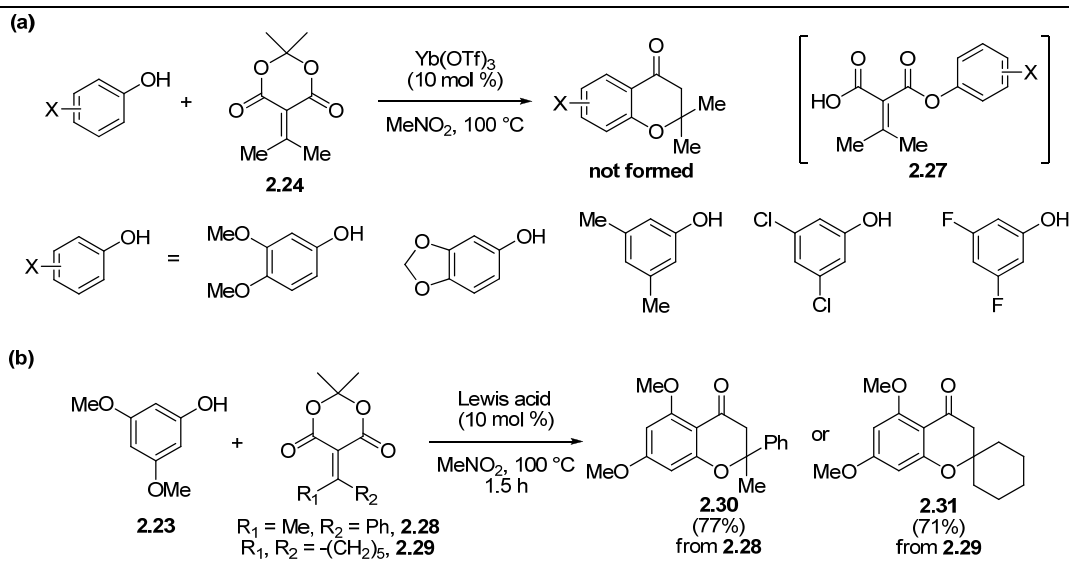
Scheme 2.10. Reactions of alkylidenes **2.24** and **2.28-2.29** with other phenols

It was thought the low reactivity of phenols other than **2.23** was due to the steric hindrance around the electrophilic carbon in the disubstituted alkylidenes, and that by switching to monosubstituted alkylidenes more nucleophiles would be compatible. Surprisingly, a test using electron-rich **2.23** and alkylidene **2.32** gave 3,4-dihydrocoumarin **2.37** as the sole product, which put the reaction back in line with those shown in Scheme 2.8. This *C*-alkylation/*O*-acylation pathway was general across a range of alkylidene Meldrum's acids, and in no case were 4-chromanones observed. Also, we

were correct in thinking that other phenols would react with monosubstituted alkylidenes, and 3,4-dihydrocoumarins **2.42-2.45** were prepared (Scheme 2.11). One reaction of note is that while 3-methoxyphenol gave none of the expected product **2.46**, 2-methyl-3-methoxyphenol gave **2.45**, although in lower yield compared to the other phenols used. The reason for this difference in reactivity is not clear, but could be due to the increased π-nucleophilicity stemming from the methyl group.
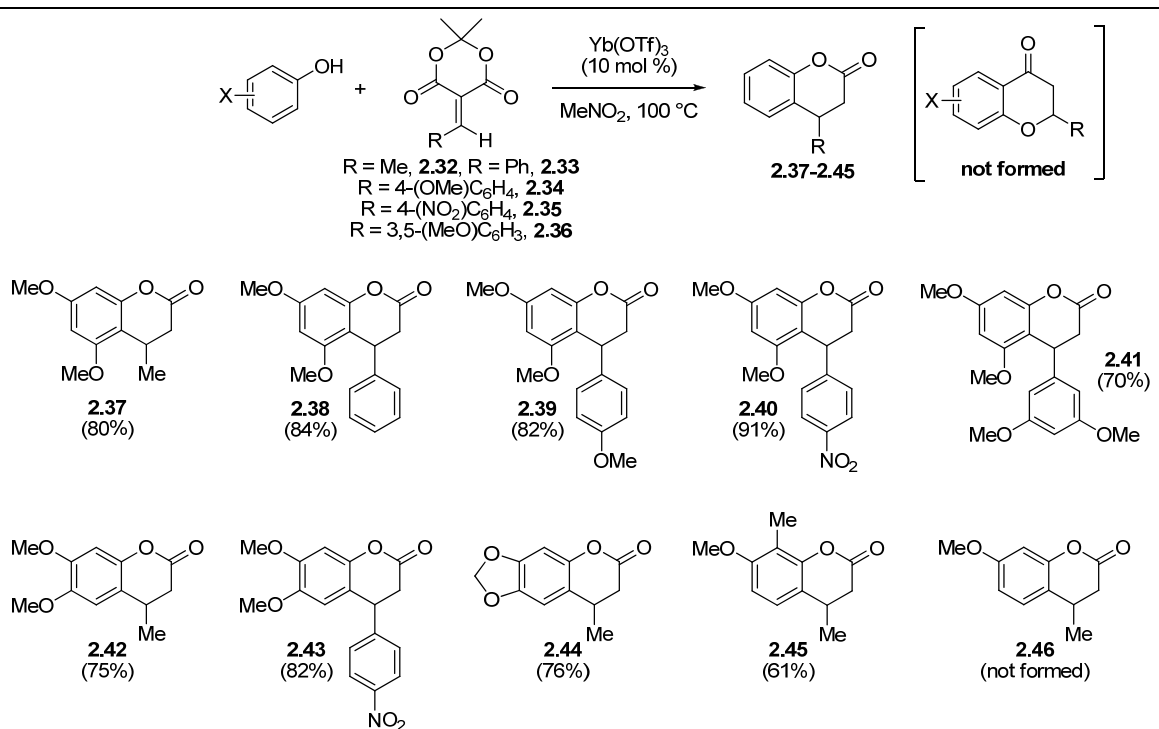
Scheme 2.11. Synthesis of 3,4-dihydrocoumarins from monosubstituted alkylidenes

The complete chemoselectivity reversal between mono- and disubstituted alkylidenes is intriguing. However, direct comparison between the above examples with literature precedent is difficult, as few reactions of phenols with β,β-disubstituted, α,β-unsaturated carbonyls have been reported. Furthermore, the known reactions proceed through different pathways, but unfortunately none of the papers discuss or rationalize their results. In a reaction where the chemoselectivity is the same as our own, addition of phloroglucinol (**2.19**) with β,β-dimethylacrylate **2.47** in neat BF$_3$•OEt$_2$ proceeds by *O*-alkylation/*C*-acylation to give 4-chromanone **2.48** (Scheme 2.12a).[85] However, the reaction of the same electrophile **2.47** with 3,5-dimethoxybenzene (**2.23**)[86] or less

reactive phenols **2.49**[87] gave products of *C*-alkylation/*O*-acylation, 3,4-dihydrocoumarins **2.26** and **2.50-2.51**, respectively (Scheme 2.12b). This is the same pathway as for reactions of phenols with less-hindered acceptors, such as in Scheme 2.5 above.
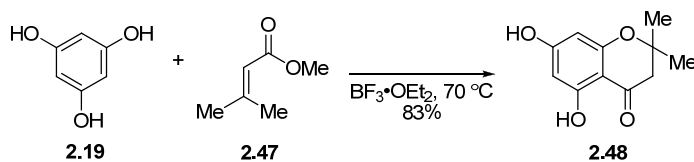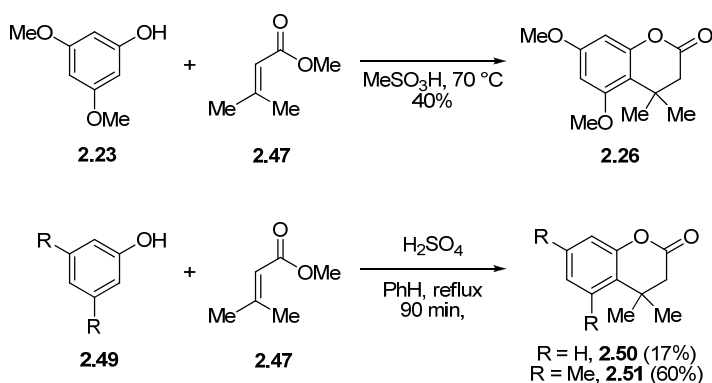
Scheme 2.12. Divergent reactivity in addition of phenols to acrylate **2.47**

Considering that all three reactions employ the same electrophile, and that **2.19** and **2.23** are likely of nearly equivalent π-nucleophilicity, the divergent chemoselectivity is difficult to attribute to an obvious difference in reactivity. In terms of conditions, all three take place at nearly the same temperature using an excess of Lewis acid. One difference is the use of $BF_3 \cdot OEt_2$ for preparation of **2.48**, while the other reactions used protic acid. In any event, these results demonstrate that predicting the course of additions of phenols to enoates is potentially complicated. With regards to the divergence between mono- and disubstituted alkylidenes, a conclusive explanation cannot be made in the absence of mechanistic details, especially the order of bond formation. Synthetically speaking at least, the fact that the reversal is complete and general provides a means of predicting the expected product based on alkylidene substitution.

Continuing these reactions, we turned to methoxysubstituted alkylidene **2.52**[88] as a means to prepare coumarins by combining the alkylation/acylation reaction with elimination of methanol. Under the previously optimized conditions, addition of the same

phenols as for the synthesis of dihydrocoumarins was successful (Scheme 2.13). Again, chemoselectivity was complete and no chromone products were detected. These results were also my first total syntheses, as **2.53** (citropten), **2.54** (scoparone), and **2.55** (ayapin) are all natural products.
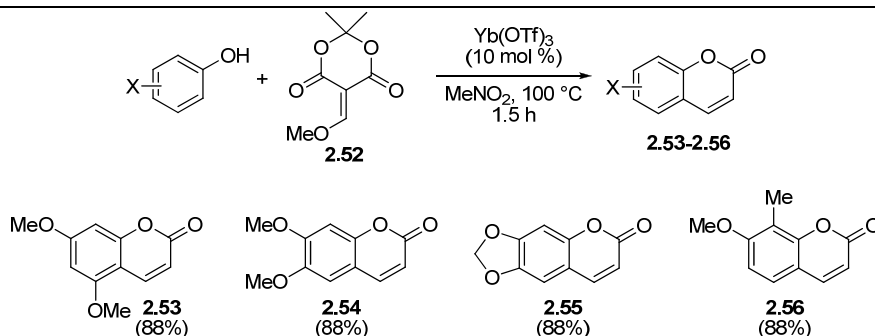
Scheme 2.13. Synthesis of coumarins by reaction of phenols with alkylidene **2.52**

While addition to disubstituted alkylidenes was limited to 3,5-dimethoxyphenol when both substituents were alkyl or aryl, switching to methoxy alkylidene **2.57**[89] allowed other nucleophiles to be used. The reaction proceeded with complete selectivity to give chromones **2.58** and **2.59** from phenols **2.23** and **2.7**, respectively (Scheme 2.14). Replacement of the methyl group in **2.57** with a phenyl ring as a route to flavones was unfortunately unsuccessful as no addition took place using either phenol.
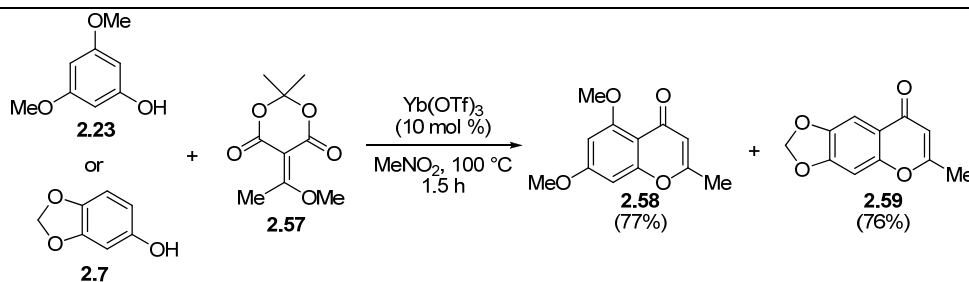
Scheme 2.14. Synthesis of chromones by reaction of phenols with alkylidene **2.57**

While Yb(OTf)$_3$ is an excellent catalyst for these reactions, it does have practical drawbacks stemming primarily from the need to keep it anhydrous by storage in a glove-box. As a more practical alternative for ease of use, it was found that the reaction also took place in the presence of excess TFA. As shown in Scheme 2.15a, the synthesis of 3,4-dihydrocoumarins, coumarins, 4-chromanones, and chromones was possible in this

manner, with chemoselectivity being identical to the previous reactions. More importantly, TFA-promoted reactions were just or nearly as effective at producing the desired compounds as Yb(OTf)$_3$ (yields in italics are the corresponding results from Yb(OTf)$_3$ catalysis). Additionally, with excess acid, Lewis basic nitrogen-containing 3-dimethylaminophenol could be used, whereas with catalytic Yb(OTf)$_3$ no reaction occurred. Dimethylamino products **2.60** and **2.61** were formed from alkylidenes **2.32** and **2.52**, respectively (Scheme 2.15b); 7-aminocoumarins are particularly interesting as they have found widespread use as fluorescent markers for bioassays.[90]
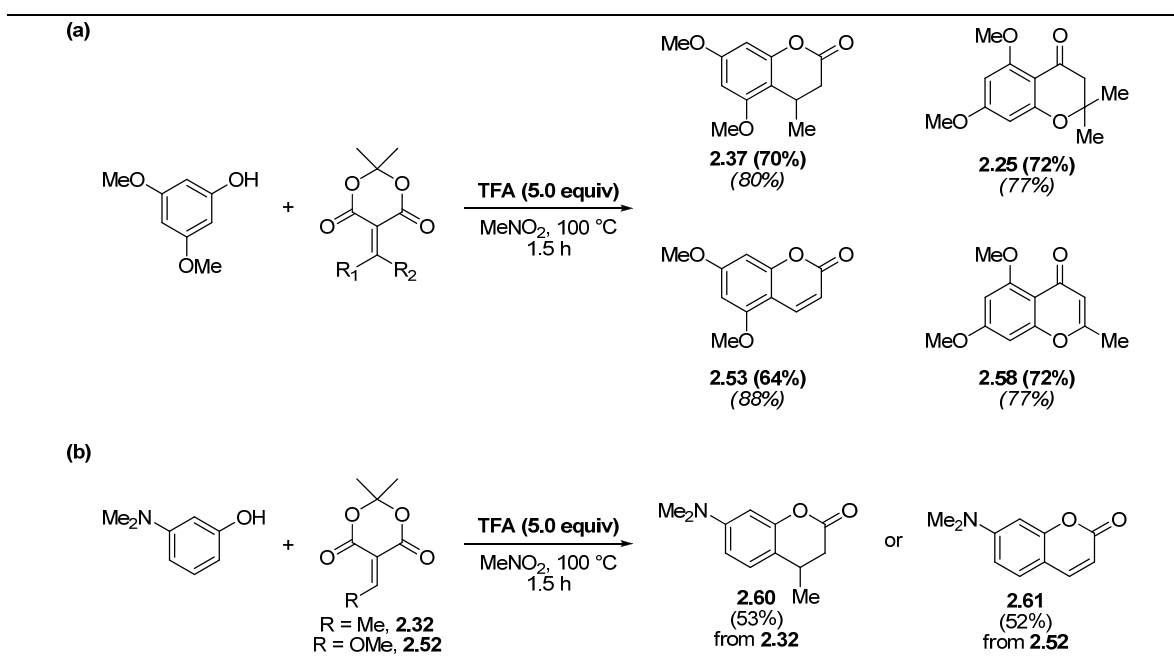
Scheme 2.15. Use of excess TFA to prepare coumarin and chromone derivatives

One very surprising result observed during these studies was the reaction of brominated phenol **2.62**[91] with alkylidene **2.32**, which was expected to give coumarin **2.63**. However, under Yb(OTf)$_3$-catalysis in MeNO$_2$ the only observed product was debrominated coumarin **2.53** (Scheme 2.16a). This unexpected loss of bromine was rationalized based on the known reversible addition of metal triflates to electron-rich arenes.[92] Although it was not clear at which stage of the overall reaction debromination occurs[93], a general mechanism for this process was proposed (Scheme 2.16b). Addition of the Lewis acid at the brominated position of phenol **2.62** would give σ-complex **2.64**. Subsequent removal of the now electrophilic bromine atom by the *aci* tautomer of

nitromethane (**2.65**) would form Yb-substituted **2.67** and bromonitromethane (**2.66**). The equivalent of triflic acid generated by these reactions could then protonate **2.67** to reform Yb(OTf)$_3$ and give reduced phenol **2.23**, which would then yield coumarin **2.53** through reaction with alkylidene **2.32**.
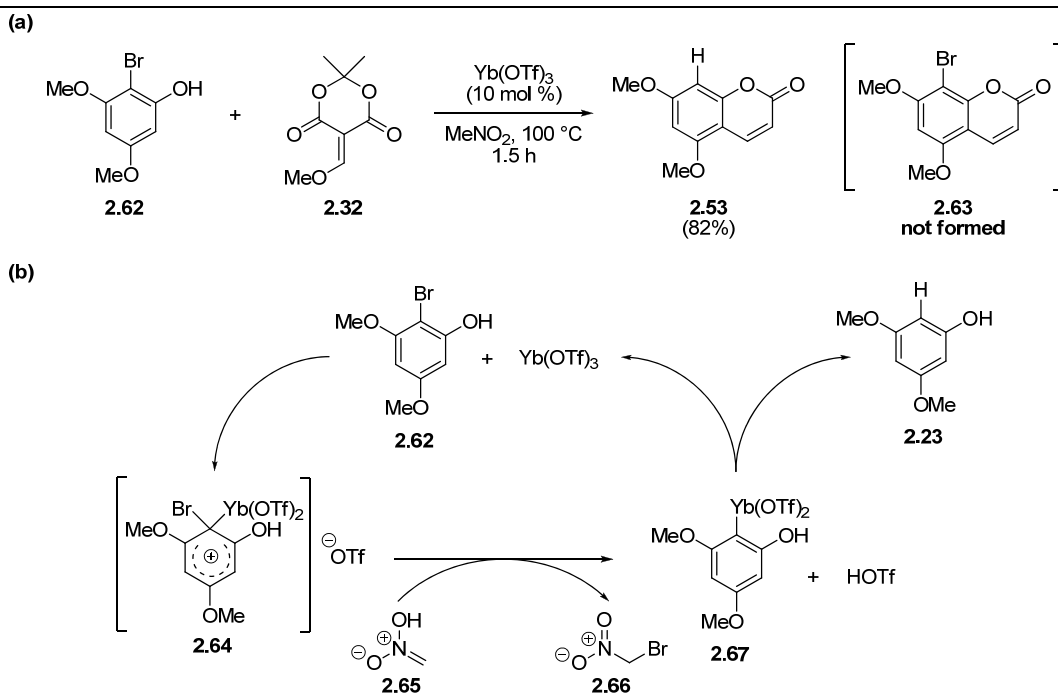
Scheme 2.16. Yb(OTf)$_3$-catalyzed debromination of phenol **2.62**

Based on this mechanism, use of a non-nucleophilic solvent should prevent debromination and allow formation of coumarin **2.63**. By switching to 1,2-dichloroethane (DCE) as solvent, **2.63** was formed as the major product, with a small amount of debrominated **2.53** formed as well (Scheme 2.17a). The results of a separate experiment in DCE to determine the role of Yb(OTf)$_3$ gave an even more unexpected outcome than strict debromination. The 3-bromocoumarin **2.68** was isolated as the only brominated product, along with a nearly equimolar amount of debrominated **2.53** when Yb(OTf)$_3$ was replaced with TfOH. The exact mechanism for this process is unknown, but it likely involves nucleophilic attack of a malonic acid intermediate formed during decomposition of Meldrum's acid (see Scheme 1.8). The intermolecular attack of a nucleophilic malonic acid on an activated intermediate similar to **2.64** would account for migration of the

40

bromine atom and formation of **2.68**. However, it does not explain why none of the "normal" brominated coumarin **2.63** was observed under these conditions.
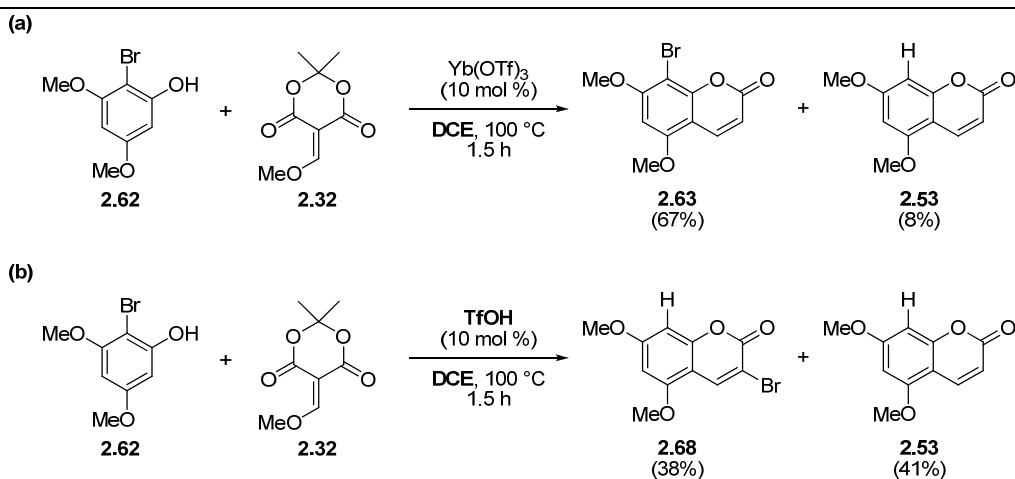
Scheme 2.17. Synthesis of brominated coumarins **2.63** and **2.68**

This section demonstrated the use of alkylidene Meldrum's acids as versatile electrophiles for preparation of a range of benzene-fused heterocycles. These reactions take advantage of the unique electrophilicity of the alkylidenes along with the acylating ability of Meldrum's acid. As the formation of brominated coumarin **2.68** attests, reactions of Meldrum's acid derivatives can provide access to pathways no other carbonyl acceptor can duplicate easily. It should also be noted that the complete switch in chemoselectivity between mono- and disubstituted alkylidenes is seemingly unprecedented in additions of this kind, and more importantly avoids issues of predictability such as were shown in Scheme 2.12. From a practical standpoint, use of TFA to promote these reactions provides a convenient alternative to the use of more expensive and harder to handle Yb(OTf)$_3$.

2.3. Experimental Section

General Considerations: All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. Nitromethane was distilled from CaH$_2$ and stored in a Schlenk flask under nitrogen. Dry dichloroethane was obtained from an MBraun solvent purification system. Ytterbium triflate was obtained from commercial sources as the trihydrate, dried at 180 °C under vacuum (0.2 mmHg) and stored in a glove-box.

Trifluoroacetic acid and trifluoromethanesulfonic acid were distilled and stored in Schlenk flasks under nitrogen.

Characterization: Melting points are uncorrected. ^{1}H NMR spectra were referenced to residual CHCl$_3$ (7.24 ppm); ^{13}C NMR spectra were referenced to CDCl$_3$ (77.0 ppm). ^{13}C NMR hydrogen multiplicities were not determined. Chemical shifts are reported in units of parts per million (ppm, δ). High resolution mass spectra were obtained at the University of Waterloo Mass Spectrometry Facility.

Preparation of Alkylidene Meldrum's Acids:

Alkylidenes not previously described in the preceeding chapter or in the literature were prepared by the method of Bigi.[54]
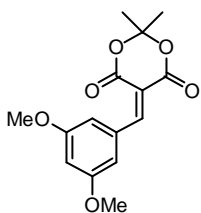
5-[(3,5-Dimethoxybenzylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (2.36): Prepared from 3,5-dimethoxybenzaldehyde and isolated as a yellow powder by Method A. M.p. 156-158 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.31(s, 1H), 7.26 (d, $J = 2.2$ Hz, 2H), 6.66 (t, $J = 2.2$ Hz, 1H), 3.82 (s, 6H), 1.78 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.3, 160.5, 159.6, 157.9, 133.1, 115.1, 111.2, 106.7, 104.5, 55.5, 27.5; HRMS(EI) m/z calcd for C$_{15}$H$_{16}$O$_6$ (M$^+$): 292.0947 Found: 292.0939.

General Method A: Yb(OTf)$_3$-catalyzed reaction of phenols with alkylidene Meldrum's Acids: To a resealable, oven-dried Schlenk flask cooled under nitrogen was added Yb(OTf)$_3$ (0.1 equiv) in a glove-box. Outside of the box, phenol (100 mg, 1.0 equiv) and alkylidene Meldrum's acid (1.5 equiv) were added to the Schlenk tube and the residue was washed into the flask with MeNO$_2$ (0.4 M relative to phenol). The flask was placed in an oil bath at 100 °C and the mixture was allowed to stir until the reaction was complete as monitored by TLC. The flask was removed from the bath and allowed to cool; the contents were rinsed into a separatory funnel with EtOAc. The organic layer was washed water (2X), brine (1X), dried over MgSO$_4$, filtered, and the solvent removed by rotary distillation under reduced pressure. The products were purified by silica gel

chromatography using 1:2 EtOAc:petroleum ether (B.p 35-60 °C) unless stated otherwise.

General Method B: TFA promoted reaction of phenols with alkylidene Meldrum's acids: An oven-dried Schlenk flask cooled under nitrogen was charged with phenol (100 mg, 1.0 equiv) and Meldrum's acid alkylidene (1.5 equiv). TFA (5 equiv) was added to the chamber, and washed into the flask with MeNO$_2$ (0.4M relative to phenol). The remainder of the procedure was identical to Method A, excepting the addition of a saturated NaHCO$_3$ solution wash of the organic phase before using water and brine.

Synthesis of 4-Chromanones 2.25 and 2.30-2.31:
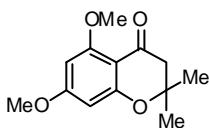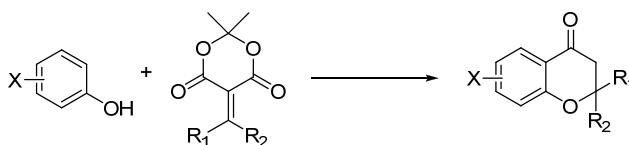
5,7-Dimethoxy-2,2-dimethyl-4-chromanone (2.25): Prepared by reaction of 3,5-dimethoxyphenol (**2.23**) with alkylidene **2.24**.[46] Isolated as a white powder in 83% yield by Methods A and B. M.p 108-109 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.00 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.61 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 189.7, 165.9, 163.4, 161.8, 105.1, 93.7, 92.3, 78.8, 56.0, 55.4, 50.0, 26.4. HRMS(EI) m/z calcd for C$_{11}$H$_{10}$O$_4$ (M$^+$): 236.2676. Found: 236.1046.
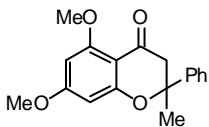
5,7-Dimethoxy-2-methyl-2-phenyl-4-chromanone (2.30): Prepared by the reaction of 3,4-dimethoxyphenol (**2.23**) and alkylidene **2.28**.[44] Isolated as a pale yellow powder in 77% yield by Method A. M.p 127-128 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.45-7.41 (m, 2H), 7.34-7.24 (m, 3H), 6.21 (d, J = 2.3 Hz, 1H), 6.01 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.22 (d, J = 16.1 Hz, 1H), 3.03 (d, J = 16.1 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 188.8, 165.9, 163.4, 161.9, 128.5, 127.5, 124.9, 106.0, 93.9, 92.5, 82.0, 56.0, 55.5, 49.1, 29.6; HRMS(EI) m/z calcd for C$_{18}$H$_{18}$O$_4$ (M$^+$): 298.1205. Found: 298.1208.
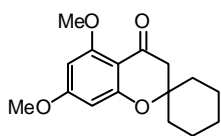
5,7-Dimethoxy-(2,2)-(pentamethylene)-4-chromanone (2.31): Prepared by the reaction of 3,4-dimethoxyphenol (**2.23**) and alkylidene **2.29**.[47] Isolated as a yellow powder in 74% yield by Method A. M.p. 93-95 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.07 (d, J = 2.2 Hz, 1H), 6.02 (d, J = 2.2Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.63 (s, 2H), 1.98-1.92 (m, 2H), 1.75-1.31 (m, 8H); ^{13}C NMR (CDCl$_3$, 75 MHz) 189.8, 165.8, 163.0, 161.8, 105.5, 93.7, 92.2, 79.6, 56.0, 55.4, 49.0, 34.6, 25.2, 21.5; HRMS(EI) m/z calcd for C$_{16}$H$_{24}$O$_4$ (M$^+$): 276.1362. Found: 276.1365.

Synthesis of 3,4-Dihydrocoumarins 2.37-2.45 and 2.60:
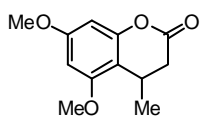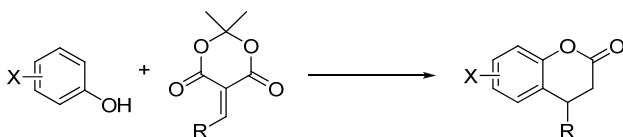
3,4-Dihydro-5,7-dimethoxy-4-methylcoumarin (2.37): Prepared by the reaction of 3,5-dimethoxyphenol (**2.23**) and alkylidene **2.32**.[94] Isolated as an off-white powder in 80% yield by Method A, and in 70% yield by Method B. M.p. 119-120 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.23(d, J = 2.2Hz, 1H), 6.20 (d, J = 2.2 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.41-3.33 (m, 1H), 2.73 (dd, J = 15.8 Hz, 6.0Hz, 1H), 2.65 (d, J = 15.8 Hz, 2.4Hz, 1H) 1.14, (d, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.4, 160.0, 157.0, 152.3, 108.7, 94.8, 93.9, 55.6, 55.5, 36.4, 24.1, 19.9; HRMS(EI) m/z calcd for C$_{12}$H$_{14}$O$_4$ (M$^+$): 222.0892 Found: 222.0898.
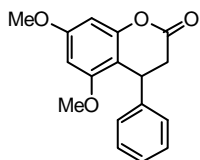
3,4-Dihydro-5,7-dimethoxy-4-phenylcoumarin (2.38): Prepared by the reaction of 3,5-dimethoxyphenol (**2.23**) and alkylidene **2.33**. Isolated as a white powder in 84% yield by Method A. M.p. 111-112 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.27-7.18 (m, 3H), 7.08 (d, J = 7.1 Hz, 2H), 6.31 (d, J = 1.9 Hz, 1H), 6.25 (d, J = 2.0 Hz, 1H), 4.53, (t, J = 4.4 Hz, 1H), 3.80 (s, 3H), 3.73, (s, 3H), 2.98 (d, J = 4.5 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 167.6, 160.6, 157.4, 153.1, 141.5, 128.8, 127.0, 126.7, 106.0, 95.0, 93.9, 55.7, 55.5, 37.0, 34.4; HRMS m/z calcd for C$_{17}$H$_{16}$O$_4$ (M$^+$): 284.1049. Found: 284.1050.
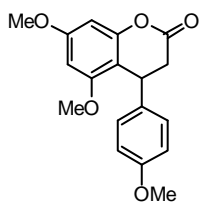
3,4-Dihydro-5,7-dimethoxy-4-(4-methoxyphenyl)coumarin (2.39): Prepared by the reaction of 3,5-dimethoxyphenol (**2.23**) and alkylidene **2.34**. Isolated as a yellow powder in 82% yield by Method A. M.p. 129-130 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.00 (d, J = 8.1 Hz, 2H) 6.77 (d, J = 8.0 Hz, 2H), 6.29 (s, 1H), 6.25 (s, 1H), 4.49 (t, J = 4.2 Hz, 1H), 3.79 (s, 3H), 3.72, (s, 6H), 2.95 (d, J = 4.3 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 167.7, 160.5, 158.5, 157.3, 152.9, 133.5, 127.7, 114.1, 106.2, 95.0, 93.8, 55.7, 55.4, 55.1, 37.4, 33.8; HRMS(EI) m/z calcd for C$_{18}$H$_{18}$O$_5$ (M$^+$): 314.1154. Found: 314.1150.
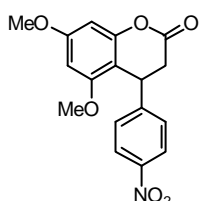
3,4-Dihydro-5,7-dimethoxy-4-(4-nitrophenyl)coumarin (2.40): Prepared by the reaction of 3,5-dimethoxyphenol (**2.23**) and alkylidene **2.35**. Isolated as an off-white powder in 91% yield by Method A. M.p. 169-170 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.11 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 6.32 (d, J = 2.0 Hz, 1H), 6.27 (d, J = 2.0 Hz, 1H), 4.62 (app d, J = 5.2 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.07 (dd, J = 16.0 Hz, 6.9 Hz, 1H), 2.97 (dd, J = 14.0 Hz, 2.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 166.8, 161.2, 157.3, 153.0, 149.0, 147.1, 127.8, 124.1, 104.4, 95.3, 94.1, 55.8, 55.6, 36.4, 34.5; HRMS(EI) m/z calcd for C$_{17}$H$_{15}$NO$_6$ (M$^+$): 329.0899. Found: 329.0900.
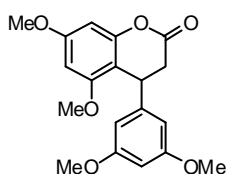
3,4-Dihydro-5,7-dimethoxy-4-(3,5-dimethoxyphenyl)coumarin (2.41): Prepared by the reaction of 3,5-dimethoxyphenol (**2.23**) and alkylidene **2.36**. Isolated as a white powder in 70% yield by Method A. M.p. 118-119 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.29 (m, 2H), 6.24 (m, 3H), 4.46 (dd, J = 2.9 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.71 (s, 6H), 2.96 (t, J = 3.0 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 167.5, 161.0, 160.7, 157.4, 153.1, 144.0, 105.7, 105.0, 98.6, 95.1, 93.9, 55.7, 55.5, 55.2, 37.0, 34.6; HRMS m/z calcd for C$_{19}$H$_{20}$O$_6$ (M$^+$): 344.1260. Found: 344.1260.
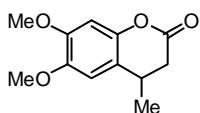
3,4-Dihydro-6,7-dimethoxy-4-methylcoumarin (2.42): Prepared by the reaction of 3,4-dimethoxyphenol and alkylidene **2.32**. Isolated as an off-white powder in 75% yield by Method A. M.p. 65-66 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.63 (s, 1H), 6.54 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.07-3.00 (app sextet, J = 6.6

Hz, 1H), 2.75 (dd, J = 15.7 Hz, 5.5 Hz, 1H), 2.48 (dd, J = 15.8 Hz, 2.9 Hz, 1H), 1.24 (d, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.3, 148.6, 145.7, 144.8, 118.6, 109.1, 101.1, 56.3, 56.0, 36.8, 29.1, 20.0; HRMS m/z calcd for C$_{12}$H$_{14}$O$_4$ (M$^+$): 222.0892. Found: 222.0898.
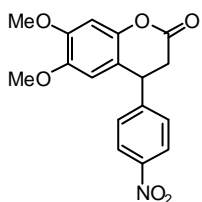
3,4-Dihydro-6,7-dimethoxy-4-(4-nitrophenyl)coumarin   (2.43): Prepared by the reaction of 3,4-dimethoxyphenol and alkylidene **2.35**. Isolated as an off-white powder in 82% yield by Method A. M.p. 150-151 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.18 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 6.71 (s, 1H), 6.42 (s, 1H), 4.37 (t, J = 6.0 Hz, 1H), 3.12 (dd, J = 15.8 Hz, 6.4 Hz, 1H), 2.96 (dd, J = 15.8 Hz, 5.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 166.4, 149.7, 148.1, 147.3, 146.1, 145.5, 128.5, 124.3, 114.1, 110.2, 101.4, 56.3, 56.1, 40.4, 37.0; HRMS(EI) m/z calcd for C$_{17}$H$_{15}$NO$_6$ (M$^+$): 329.0899. Found: 329.0902.
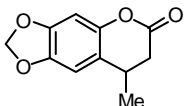
3,4-Dihydro-6,7-methylenedioxy-4-methylcoumarin (2.44): Prepared by the reaction of 3,4-methylenedioxyphenol (**2.7**) and alkylidene **2.32**. Isolated as an off-white powder in 76% yield by Method A. M.p 95-96 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.64 (s, 1H), 6.57 (s, 1H), 5.94 (s, 2H), 3.14-3.03 (sextet, J = 6.6Hz, 1H), 2.81 (dd, J = 15.8 Hz, 5.6 Hz, 1H), 2.54 (dd, J = 15.8 Hz, 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.2, 146.9, 145.5, 144.2, 120.0, 105.6, 101.5, 99.0, 36.6, 29.3, 19.9; HRMS(EI) m/z calcd for C$_{11}$H$_{10}$O$_4$ (M$^+$): 206.0579. Found: 206.0580.
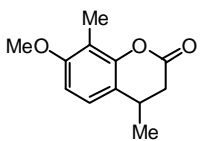
3,4-Dihydro-7-methoxy-4,8-dimethylcoumarin (2.45): Prepared by the reaction of 3-methoxy-2-methylphenol and alkylidene **2.32**. Isolated as grey crystals in 61% yield by Method A. M.p. 71-72 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.97 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H), 3.14-3.03 (app sextet, J = 6.7 Hz, 1H), 2.77 (dd, J = 15.6 Hz, 5.3 Hz, 1H), 2.50 (dd, J = 15.6 Hz, 7.3 Hz, 1H), 2.15 (s, 3H), 1.27 (d, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) 168.6, 157.5, 149.8, 123.2, 120.1, 114.9, 106.0, 55.7, 37.0, 29.2, 20.0, 8.3; HRMS(EI) m/z calcd for C$_{12}$H$_{14}$O$_3$ (M$^+$): 206.0943. Found: 206.0943.
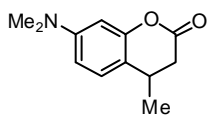
3,4-Dihydro-7-(dimethylamino)-4-methylcoumarin (2.60): Prepared by the reaction of 3-dimethylaminophenol and alkylidene **2.32**. Isolated as a red oil in 53% yield by Method B. ^{1}H NMR (CDCl$_3$, 300 MHz) 7.04 (d, J = 8.5 Hz, 1H), 6.46, (dd, J = 8.5 Hz, 2.6 Hz, 1H), 6.39 (d, J = 2.6 Hz, 1H) 3.14-3.01 (app sextet, J = 6.7 Hz, 1H), 2.91 (s, 6H), 2.79 (dd, J = 15.7 Hz, 5.4 Hz, 1H), 2.50 (dd, J = 15.7 Hz, 7.6 Hz), 1.27 (d, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.8, 152.0, 150.7, 126.6, 115.0, 108.5, 100.5, 40.3, 37.4, 28.4, 20.0; HRMS m/z calcd for C$_{12}$H$_{15}$NO$_2$ (M$^+$): 205.1103. Found: 205.1104.

Synthesis of Coumarins 2.53-2.56 and 2.61:
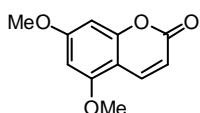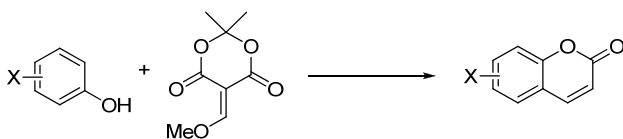
5,7-Dimethoxycoumarin (2.53)[95]**:** Prepared by the reaction of 3,5-dimethoxyphenol (**2.23**) and alkylidene **2.52**. Isolated as a pale yellow powder in 88% yield by Method A, and in 64% yield by Method B. M.p. 143-144 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.94 (d, J = 9.7 Hz, 1H), 6.39 (d, J = 2.0 Hz, 1H), 6.26 (d, J = 2.0 Hz, 1H), 6.13 (d, J = 9.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.6, 161.4, 156.9, 156.7, 138.6, 110.8, 103.9, 94.7, 92.7, 55.8, 55.7.
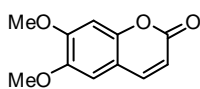
6,7-Dimethoxycoumarin (2.54)[96]**:** Prepared by the reaction of 3,4-dimethoxyphenol and alkylidene **2.52**. Isolated as a pale yellow powder in 84% yield by Method A. M.p. 144-146 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.60 (d, J = 9.5 Hz, 1H), 6.83 (s, 1H), 6.82, (s, 1H) 6.27 (d, J = 9.4 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 161.4, 152.7, 149.9, 146.3, 143.3, 113.4, 111.4, 107.9, 99.9, 56.3 (2C).
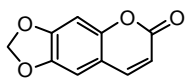
6,7-Methylenedioxycoumarin (2.55)[95]**:** Prepared by the reaction of 3,4-methylenedioxyphenol (**2.7**) and alkylidene **2.52**. Isolated as a yellow

powder in 72% yield by Method A. M.p. 222-223 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.55 (d, J = 9.5 Hz, 1H), 6.80 (s, 2H), 6.25 (d, J = 9.5 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 161.2, 151.3, 144.9, 143.4 (2C), 113.4, 112.7, 105.0, 102.3, 98.4.
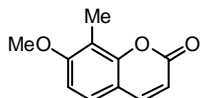
7-Methoxy-8-methylcoumarin (2.56): Prepared by the reaction of 3-methoxy-2-methylphenol and alkylidene **2.52**. Isolated as a beige powder in 31% yield by Method A. M.p. 128-130 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.61 (d, J = 9.4 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.22 (d, J = 9.5 Hz, 1H), 3.90 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 161.2, 160.5, 153.1, 143.8 (2C), 125.8, 114.7, 112.7, 106.9, 56.0, 7.9. HRMS m/z calcd for C$_{11}$H$_{10}$O$_3$ (M$^+$): 190.0630. Found: 190.0634.
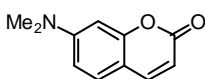
7-(Dimethylamino)coumarin (2.61): Prepared by the reaction of 3-dimethylaminophenol with alkylidene **2.52**. Isolated as a red-purple powder in 52% yield by Method A. M.p. 159-160 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.54, (d, J = 9.3 Hz, 1H), 7.25 (d, J = 2.8 Hz, 1H), 6.61 (dd, J = 8.7 Hz, 2.3 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.06 (d, J = 9.3 Hz, 1H), 3.04 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 162.1, 156.3, 152.9, 143.7, 128.5, 109.8, 109.0, 108.8, 98.1, 40.2; HRMS m/z calcd for C$_{11}$H$_{11}$NO$_2$ (M$^+$): 189.0790. Found: 189.0790.

**Synthesis of Chromones 2.58 and 2.59:**
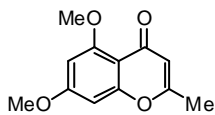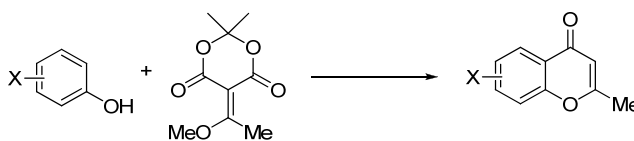
5,7-Dimethoxy-2-methylchromone (2.58)[97]: Prepared by the reaction of 3,5-dimethoxyphenol (**2.23**) with alkylidene **2.57**. Isolated as a white powder in 77% yield by Method A, and in 72% yield by Method B. M.p 166-168 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.42 (s, 1H), 6.27 (s, 1H), 5.94 (s, 1H), 3.83 (s, 6H), 2.51 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 162.7, 161.1, 159.1, 156.9, 154.5, 111.3, 104.8, 95.4, 93.3, 55.7 (2C), 24.2.
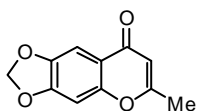
6,7-Methylenedioxy-2-methylchromone (2.59): Prepared by the reaction of 3,4-methylenedioxyphenol (**2.7**) with alkylidene **2.57**. Isolated as a yellow powder in 76% yield. M.p 161-162 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.94 (s, 1H), 6.81 (s, 1H), 6.15 (s, 1H), 6.05 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 161.4, 152.5, 151.0, 150.6, 145.0, 113.9, 102.4, 102.2, 98.5, 19.3. HRMS(EI) *m/z* calcd for C$_{11}$H$_8$O$_4$ (M$^+$): 204.0423. Found: 204.0416.

Reactions of Brominated Phenol 2.62 with alkylidene 2.32:
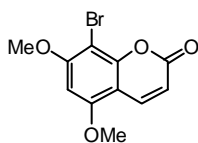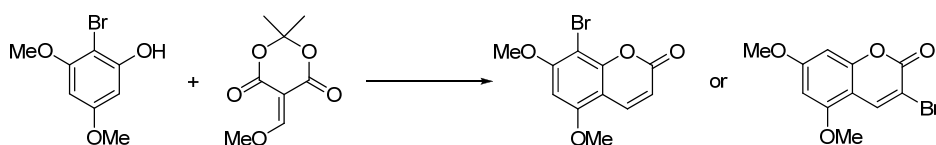
8-Bromo-5,7-dimethoxycoumarin (2.63)[95]: Isolated as a yellow powder in 67% yield by Method A, using DCE as solvent instead of MeNO$_2$. M.p. 226-227 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.93 (d, *J* = 9.7 Hz, 1H), 6.33 (s, 1H), 6.15 (d, *J* = 9.7 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 160.3, 159.6, 156.2, 152.7, 138.2, 111.5, 104.6, 91.0, 90.6, 56.6, 56.0. HRMS *m/z* calcd for C$_{11}$H$_9$BrO$_4$ (M$^+$): 283.9684. Found: 283.9684.
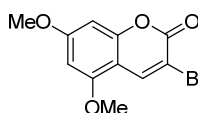
3-Bromo-5,7-dimethoxycoumarin (2.68): A stock solution of TfOH (2 µl/100 µL) in DCE was prepared in a flame-dried flask under nitrogen. A Schlenk tube was charged with phenol **2.62** (100 mg, 1.0 equiv) and alkylidene Meldrum's acid (1.5 equiv). TfOH solution (0.1 equiv) was added to the chamber and washed into the flask with DCE (0.4 M relative to phenol). The reaction mixture was worked up as in Method A, and the product was isolated as a white solid in 38% after purification by flash column chromatography using 1:4 EtOAc:petroleum ether (B.p 35-60 °C). M.p. 188-189 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.31 (s, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 6.28 (s, *J* = 2.1 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.9, 157.6, 156.2, 155.8, 140.0, 105.5, 104.5, 95.2, 92.6, 56.0, 55.8. IR (CH$_2$Cl$_2$) 1731 cm^{-1}; HRMS *m/z* calcd for C$_{11}$H$_9$BrO$_4$ (M$^+$): 283.9684. Found: 283.9688.

Chapter 3. Diels-Alder/Friedel-Crafts Acylation of Alkylidene Meldrum's Acids and Investigations into the Regioselectivity of Friedel-Crafts Acylations of 4-Substituted Indoles

3.1. Taiwaniaquinol B and Related Natural Products

The taiwaniaquinoids are a family of nor-diterpenoids possessing a common carbon skeleton that have attracted considerable interest from the synthetic community (Figure 3.1).[98] The reason for this is the unique 6-5-6 tricyclic framework containing an oxygenated aromatic ring fused to a cyclopentane. Other common structural features are the angular benzylic methyl and the gem-dimethyl group on the cyclohexane portion of the molecules.
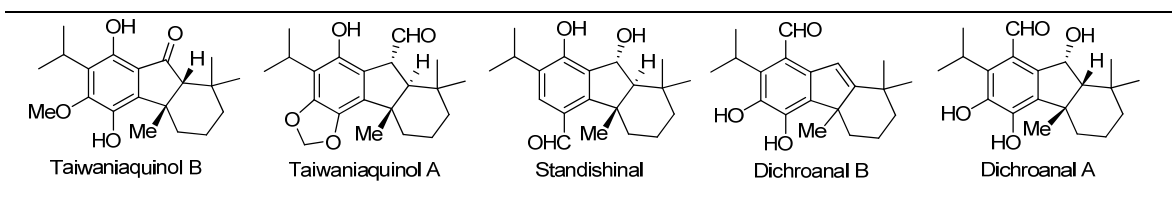
Figure 3.1. Taiwanaiquinoid natural products

The indanone-based framework of taiwaniaquinol B attracted our attention as a testing ground for the intramolecular Friedel-Crafts acylation of Meldrum's acid derivatives. In particular, it was thought that since enolizable Meldrum's acids decompose via a β-keto carboxylic acid this intermediate could participate in an intramolecular α-*tert*-alkylation to form the cyclohexane ring. Furthermore, introduction of the angular methyl group would be facilitated by the electrophilicity of disubstituted alkylidene Meldrum's acids to form the congested all-carbon quaternary centre. This strategy was successfully employed by Dan Fishlock in the first total synthesis of (±)-taiwaniaquinol B in 2005 (Scheme 3.1).[99]
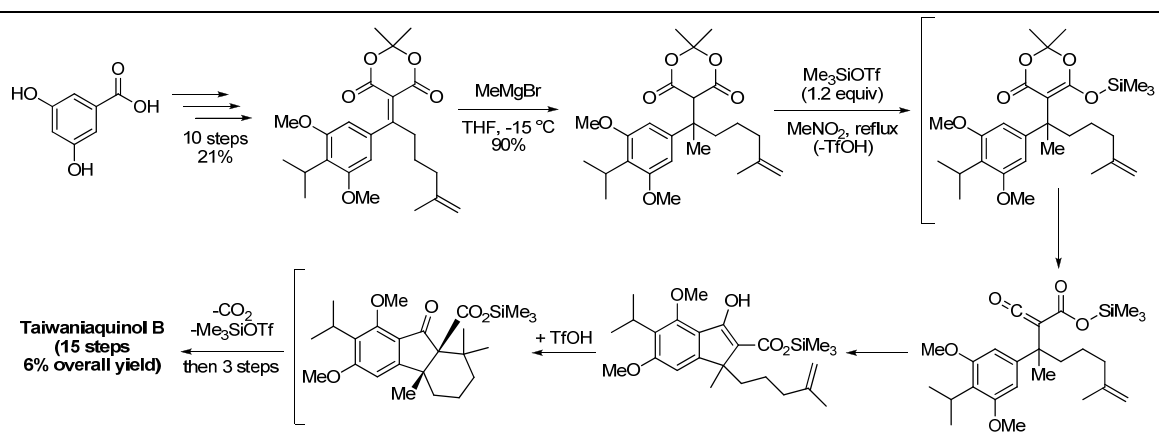
Scheme 3.1. Synthesis of taiwaniaquinol B from a Meldrum's acid derivative

As mentioned, the unique architecture of these molecules has led to a range of approaches to their synthesis. The remainder of this section will outline syntheses of this carbon framework reliant on cationic functionalization of an arene to form one or more of the key C-C bonds, as these relate directly to the research I carried out. Other methods to prepare these compounds have included intramolecular Heck reactions[100], sequential Robinson annulations[101], and electrocyclizations.[102]

Reactions proceeding via Friedel-Crafts alkylation as a general route to 6-5-6 tricycles not directed toward the total synthesis of taiwaniaquinoids have been reported. Banerjee's interest in this skeleton extends back 30 years before the isolation of the taiwaniaquinoids, and he published protic acid-catalyzed cyclizations of cyclohexanols as a route toward gibberellins in 1966 (Scheme 3.2a).[103] A very similar reaction was discovered by Balme, and led to molecules bearing the entire carbon framework of dichroanal B (Scheme 3.2b).[104] A variation of the Balme's process was employed in a recent synthesis of oxidized derivatives of taiwaniaquinols, which are themselves natural products (Scheme 3.2c).[105]

(a)

(b)

E = CO₂Me

(c)

Taiwaniaquinone H
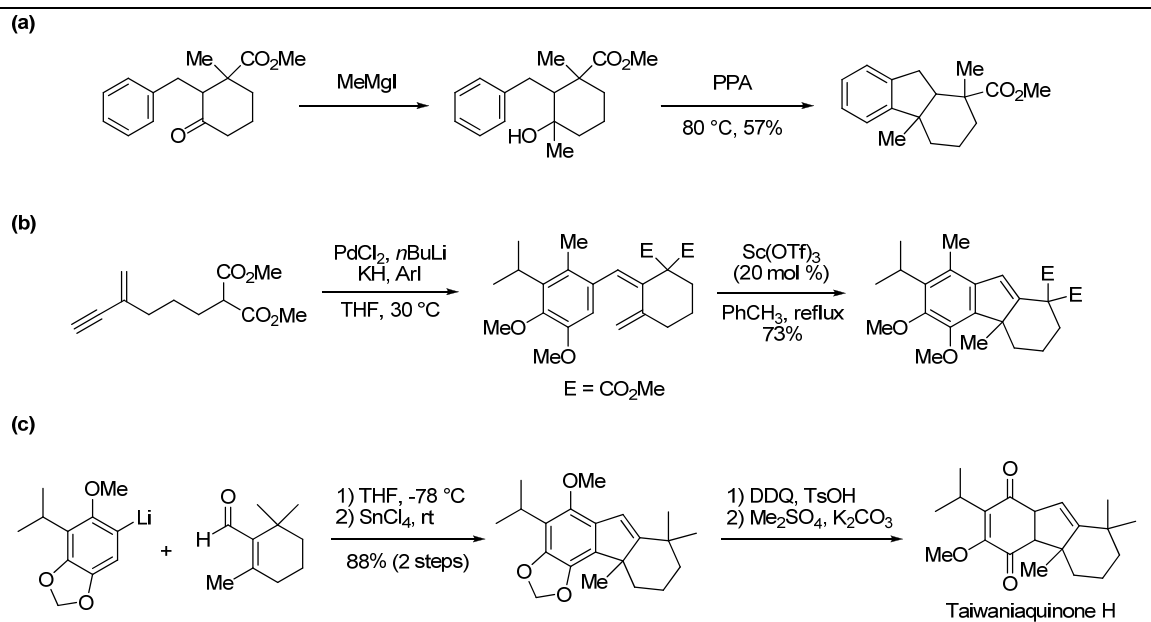
Scheme 3.2. Intramolecular Friedel-Crafts alkylations yielding 6-5-6 tricycles

An interesting cyclization involving a non-traditional activation of the Navarov cyclization was reported by Trauner. In this reaction, triflation of a ketone produces a cationic intermediate that participates in a 4π-electrocyclization to form the benzylic quaternary centre and a vinyl triflate. The triflate serves as a useful handle to introduce additional functional groups allowing the synthesis of taiwaniaquinol D (Scheme 3.3).
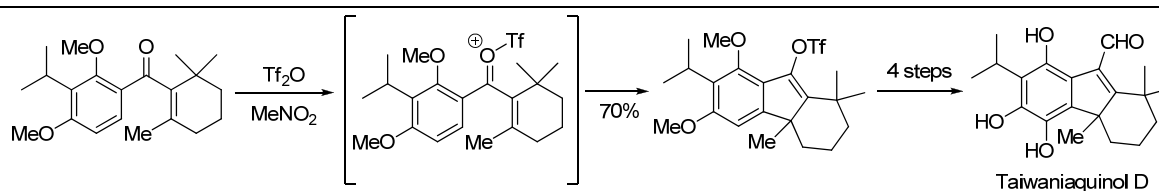
Taiwaniaquinol D

Scheme 3.3. Synthesis of taiwaniaquinol D by Nazarov cyclization

Employing a strategy similar to our own, there have been two other reports of domino reactions for the preparation of these 6-5-6 tricycles. In a low yielding process, Chiu showed that two C-C bonds could be formed in a Me₃SiOTf-promoted biscyclization en route to taiwaniaquinol B (Scheme 3.4a).[106] However, in this case a higher yielding but less efficient strategy was sequential formation of the cyclohexane followed by formation of the indanone. In the other report, a related and very streamlined approach allowing three C-C bonds to be formed in a single operation leading to the core

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of diachroanone was employed (Scheme 3.4b).[107] Here, Friedel-Crafts acylation of geranic acid and two carbocationic ring closures give the 6-5-6 tricycle, which was elaborated in three steps to intercept a molecule en route to the natural product.[101]
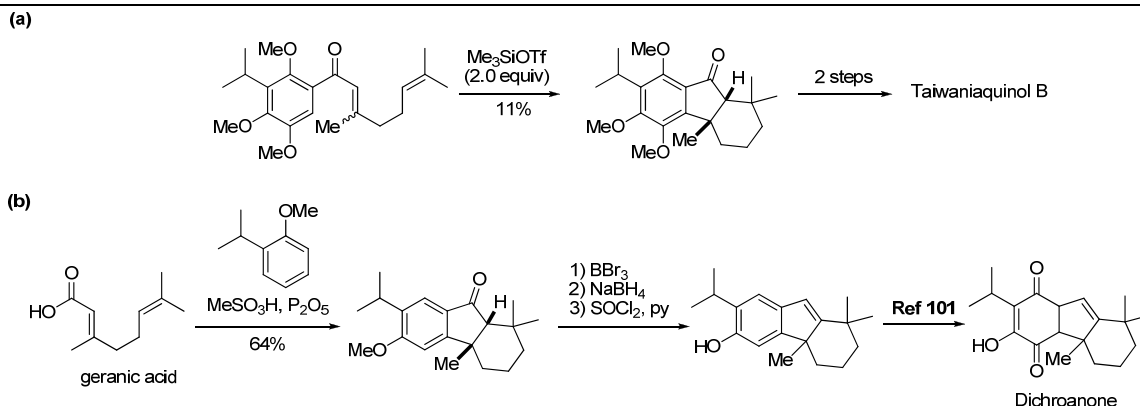
Scheme 3.4. Domino C-C bond forming reactions to form 6-5-6 tricyclic natural products

Our group's interest in the taiwainiaquinoids combined with our domino sequence for exploiting the electrophilicity of alkylidene Meldrum's acids (Scheme 1.9) led us to propose the reaction in Scheme 3.5. By performing a Lewis acid-catalyzed Diels-Alder reaction of the alkylidene **3.1** an adduct **3.2** would form, which would be poised for intramolecular Friedel-Crafts acylation to give **3.3**. Tetrahydrofluorenone **3.3** possesses the unique 6-5-6 tricyclic skeleton of these natural products, and the modular nature of the reaction would allow variation of substituents and substitution patterns on the six-membered rings.
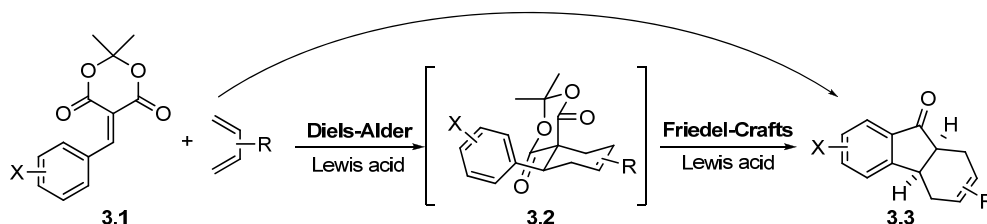
Scheme 3.5. Proposed Diels-Alder/Friedel-Crafts acylation for synthesis of 6-5-6 tricycles

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This strategy relies on the facile Diels-Alder reactions of alkylidene Meldrum's acids. An examination of the literature precedent for these cycloadditions is presented in the following section.

3.2 Diels-Alder Reactions of Alkylidene Meldrum's Acids

Alkylidene Meldrum's acids have been reported to act as both heterodiene and dienophile in [4+2] cycloadditions. As a heterodiene, the concerted[108] intramolecular reaction with electron-rich alkenes has been most prominent, as in the total synthesis of kainic acid (Scheme 3.6a).[109] Another variant of this process is the formal Michael addition of silyl enol ethers to alkylidenes which proceeds by intermolecular hetero-Diels-Alder followed by acidic cleavage of the intermediate dioxinone (Scheme 3.6b).[110] However, the focus of this section will be on reactions where the alkylidene acts as a dienophile, as this is the reactivity relevant to our group's work.
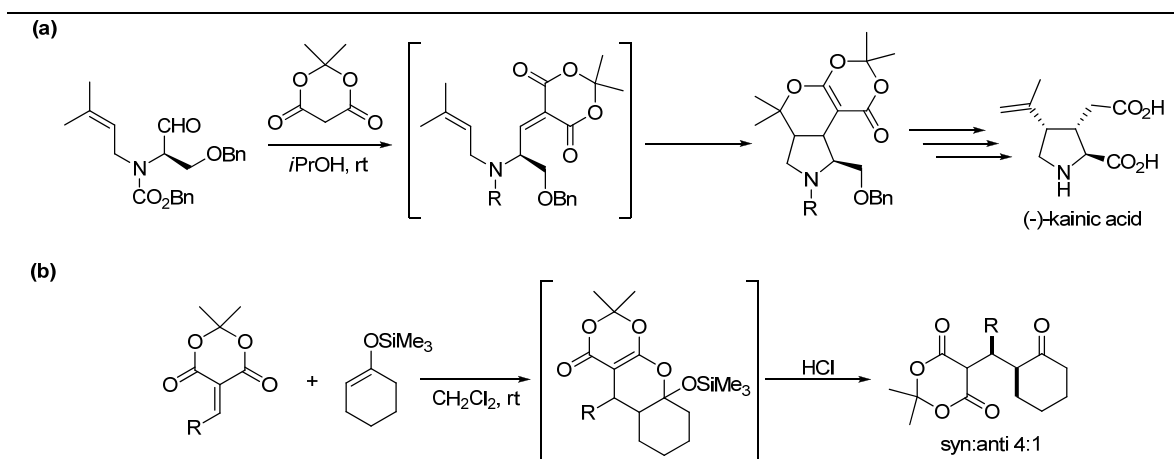
Scheme 3.6. Hetero-Diels-Alder reaction of an alkylidene Meldrum's acids toward kainic acid

Polansky first studied the thermal Diels-Alder reactivity of alkylidene Meldrum's acids, and noted that their dienophilicity was similar to their reactivity toward nucleophiles. For example, the reaction of alkylidene **3.4** with 2,3-dimethylbutadiene (**3.5**) occurred at 70 °C to give adduct **3.6** (Scheme 3.7a). In contrast, the corresponding reaction of alkylidene malonates requires temperatures of 170-180 °C.[111] The most reactive alkylidene is methylene Meldrum's acid **3.8**, which cannot be isolated directly

and must be formed in situ.[112] As shown in Scheme 3.7b, elimination of pyridine from zwitterion **3.7** with acid results in a rapid Diels-Alder reaction with cyclohexadiene to give **3.9**.[113] Notably, there are no reports of Diels-Alder reactions of mono- or disubstituted alkylidenes with cyclic dienes (and our own experiences attempting such reactions suggest they are highly disfavoured) which attests to the reactivity of **3.8**.
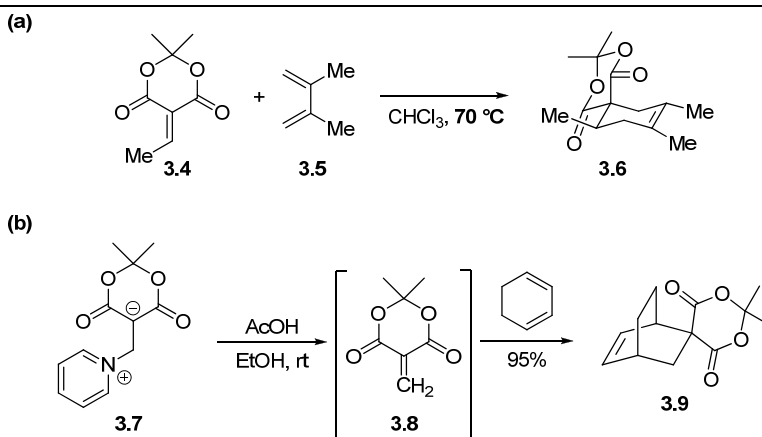
Scheme 3.7. Alkylidene Meldrum's acids as reactive dienophiles

The Diels-Alder reaction of **3.8** features prominently in the synthesis of the spirocyclic core of gymnodimine (Scheme 3.8).[114] Here, **3.8** is generated from **3.7** and reacts with chiral diene **3.10** in excellent regioselectivity but with poor stereoinduction to give a separable mixture of diastereomers **3.11** and **3.12**. Continuing the sequence with **3.12**, manipulation of the Meldrum's acid introduced the cyclic imine.
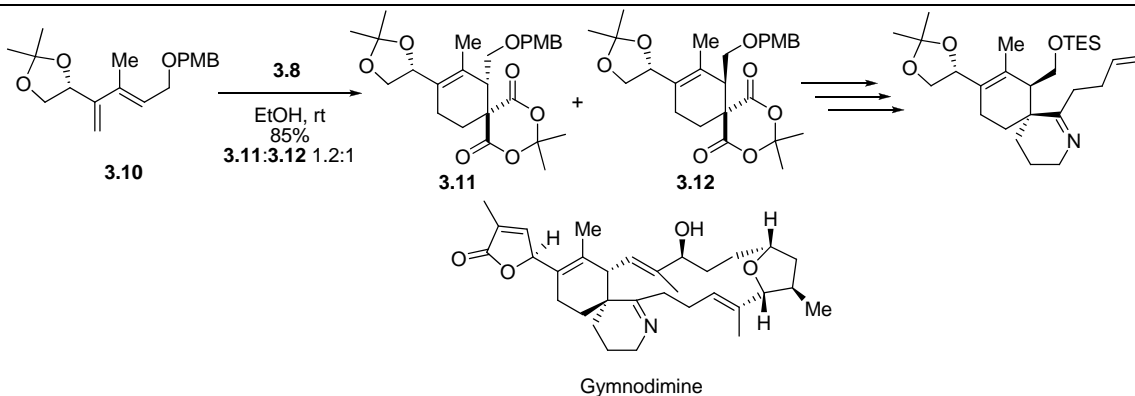
Scheme 3.8. Use of alkylidene **3.8** toward gymnodimine

Other routes toward natural products involving Diels-Alder reactions of alkylidene Meldrum's acids include aphidicolins[115], δ-damascone[24], and quassimarin. The quassimarin route is particularly interesting as it involves the reaction of a mono-substituted alkylidene where endo-exo selectivity is an issue while the others use symmetrical disubstituted alkylidenes. In this synthetic route, alkylidene **3.13** was reacted with **3.14** to give the diastereomeric products **3.15** and **3.16** in a 2:5 ratio. The major Diels-Alder adduct **3.16** was epoxidized stereoselectively to yield **3.17** and ring opening of the Meldrum's acid gave lactone **3.18** as a model of the highly oxygenated and stereochemically complex core of the natural product (Scheme 3.9).[116]
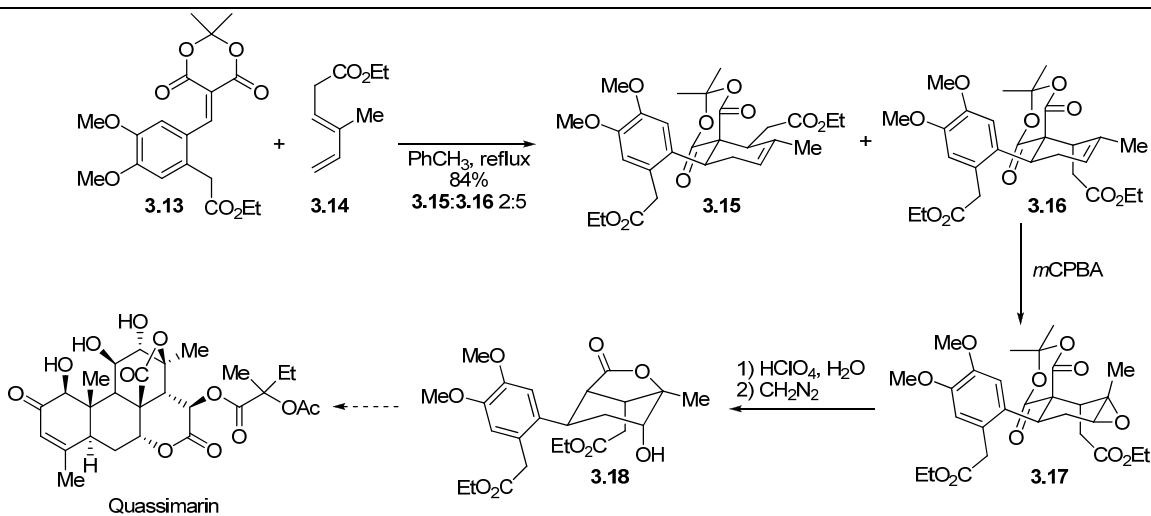
Scheme 3.9. Diels-Alder reaction of a monosubstituted alkylidene Meldrum's acid toward quassimarin

There is a single example of a Lewis acid catalyzed Diels-Alder reaction of a monosubstituted alkylidene. Corey demonstrated the use of the activated chiral oxazaborolidium complex **3.20** for the reaction of alkylidene **3.4** with non-racemic diene **3.19** (Scheme 3.10a).[117] Although the exact source of the stereoinduction is not clear, the combination of catalyst and diene chirality along with the structure of the alkylidene induces a 4:1 ratio of diastereomers in favour of **3.21**. By contrast, enal dieneophiles such as **3.22** produce the opposite configuration at the marked stereocentre using the same catalyst and diene to give **3.23** as the major product (Scheme 3.10b).
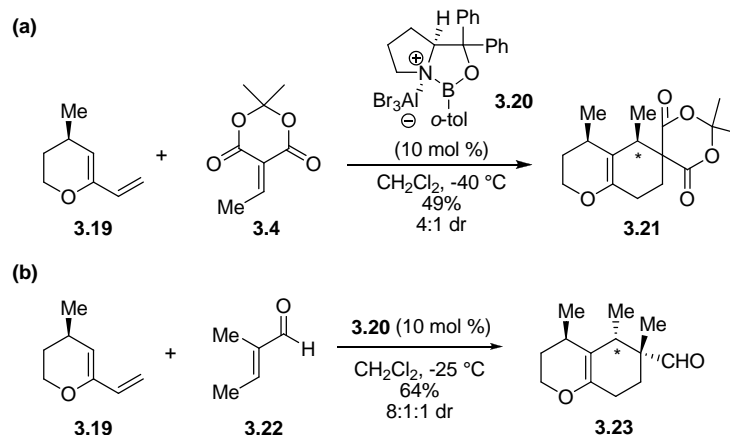
Scheme 3.10. Diastereoselective Lewis acid-catalyzed Diels-Alder reaction of alkylidene **3.4**

Another catalytic Diels-Alder reaction of alkylidene Meldrum's acid was reported by Barbas under proline catalysis.[118] Here, in-situ formation of an enone and an alkylidene by Wittig reaction and Knoevenagel condensation, respectively, yields the Diels-Alder reactants. Addition of proline to the enone gives an unsaturated enamine/activated diene **3.24** which reacts with the alkylidene. Hydrolysis of the resulting enamine **3.25** gives cyclohexanone **3.26** in >100:1 dr (Scheme 3.11). The fully concerted nature of this process has not been demonstrated conclusively, and the authors permit that it may be a double Michael reaction. Since the enone and alkylidene are both formed from the same aldehyde in a multi-component fashion, the resulting product **3.26** is achiral. An enantioselective variant of this reaction was later reported by preforming the enone, and is discussed further in Chapter 4.
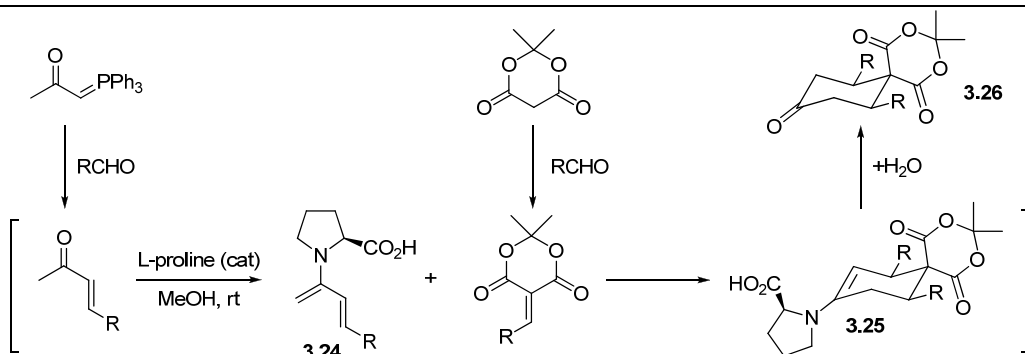
Scheme 3.11. Proline-catalyzed Diels-Alder reactions of monosubstituted alkylidenes

The only other example of the use of Lewis acids to promote Diels-Alder reactions of dienophiles derived from Meldrum's acid did not employ an alkylidene, but rather oxime **3.27** (Scheme 3.12).[119] Treatment with a diene and two equivalents of Me$_2$AlCl resulted in formation of adducts **3.28** as unstable intermediates. Oxidation/elimination of the crude reaction mixture using NCS and sodium methoxide under mild conditions yielded substituted pyridines. The advantage of using oxime **3.27** is that related reactions with oximes derived from malononitrile proceed with poor regioselectivity, leading to mixtures of substituted pyridines.[120]
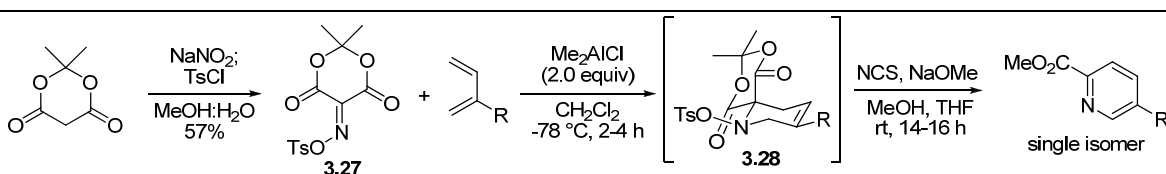
Scheme 3.12. Synthesis of pyridines by Lewis acid-catalyzed Diels-Alder reactions of **3.27**

The use of heteroatomic dienophiles based on Meldrum's acid has also found use in synthetic routes toward natural products. Spino described thione **3.30** as a highly reactive dienophile in cycloadditions with diene **3.29** (Scheme 3.13).[121] In this case, the reaction proceeded in very high regioselectivity to give adduct **3.31** as the major product. The initially attempted reaction used malonate derived thione **3.32**, which proceeded with opposite and lesser regioselectivity relative to **3.30**, yielding **3.33** as the major product. This result again highlights the unique properties of Meldrum's acid compared with more common activating groups.
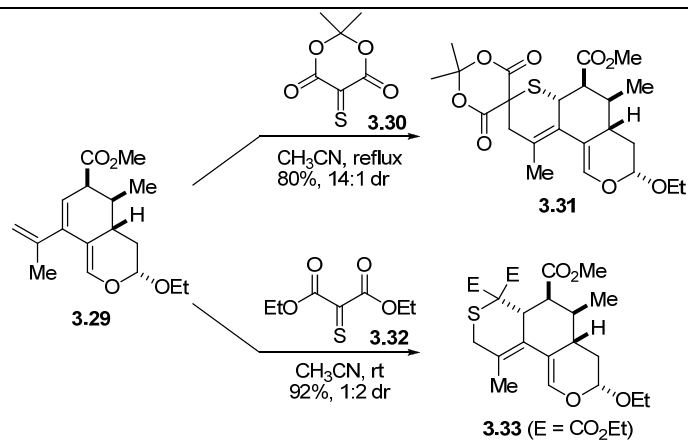
Scheme 3.13. Regioselectivity in Diels-Alder reactions of activated thiones.

The above reactions have demonstrated the variety of reactions and structural frameworks accessible by Diels-Alder reactions with alkylidene Meldrum's acid dienophiles. Our successful application of this process as route to the tricyclic skeleton of the taiwaniaquinoids is described in the next section.

3.3. Diels-Alder/Friedel-Crafts Acylation of Alkylidene Meldrum's Acids

As Shown in Scheme 3.5 above, we had planned a Lewis acid-catalyzed domino process to combine the alkylidene's dienophilicity with the acylating ability of Meldrum's acid. However, at the time we began these investigations, there were no reports of Lewis acid-catalyzed Diels-Alder reactions involving alkylidene Meldrum's acids. The reason for this became apparent after a few months of effort primarily by the undergraduate student, Sylvia Hogg, assisting me with this project. Despite extensive screening of Lewis and Bronsted acids (BF$_3$•OEt$_2$, Me$_3$SiOTf, TiCl$_4$, Sc(OTf)$_3$, Cu(OTf)$_2$, Mg(OTf)$_2$, TfOH, TFA) at various catalyst loadings, solvents of different polarities (MeNO$_2$, PhCH$_3$, CH$_2$Cl$_2$, THF, no solvent), and temperatures from -78 °C to boiling, no Diels-Alder reaction occurred regardless of the diene employed. Since in most cases the alkylidene remained unreacted while the diene appeared to be fully consumed, it seemed likely that cationic polymerization of the electron-rich dienes was the preferred reaction under these conditions (Scheme 3.14).
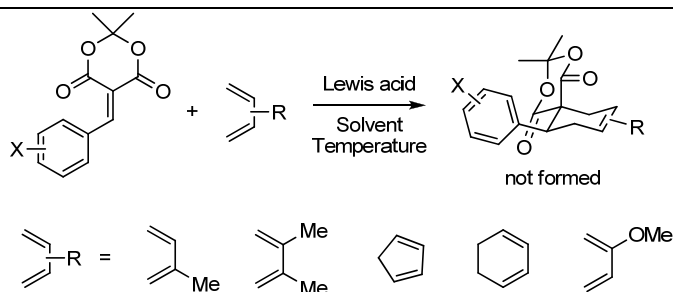
Scheme 3.14. Attempted Lewis acid-catalyzed Diels-Alder reactions of alkylidene Meldrum's acids

Concurrent with these studies, examination of conditions suitable for the Friedel-Crafts acylation proved more fruitful.[122] Diels-Alder adduct **3.36** was produced by the thermal reaction of alkylidene **3.34** with butadiene sulfone (**3.35**) as a convenient source of 1,3-butadiene. In contrast to the attempted Lewis acid-catalyzed Diels-Alder reactions, cycloaddition of **3.34** and **3.35** was facile, and led to **3.36** as the sole product of a very clean process. Moreover, Friedel-Crafts acylation of **3.36** was catalyzed by Sc(OTf)$_3$, TfOH, or Me$_3$SiOTf to give tetrahydrofluorenone **3.37** as a single diastereomer in varying yields (Scheme 3.15). This suggested that at least the Friedel-Crafts acylation portion of the reaction would not be problematic; unfortunately it was quickly found that more difficulties lay ahead.
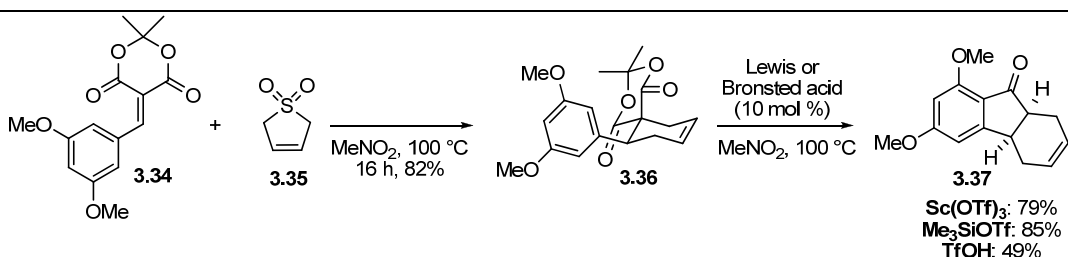
Scheme 3.15. Lewis acid-catalyzed synthesis of **3.37**

When the conditions that had been successful for conversion of **3.36** to **3.37** were applied to the Diels-Alder adduct (**3.38**) of the reaction of **3.34** and 2,3-dimethylbutadiene (**3.5**), the crude reaction mixture was unidentifiable by ^{1}H NMR. The only certain thing was that there was none of the expected product **3.39**. Although we were unsure of the exact process taking place, it was believed that the substantially more electron-rich alkene[34f] in **3.38** relative to **3.36** was contributing to the decomposition

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pathway. Therefore, attempts to produce **3.39** were made with various triflate-based Lewis acids in the hopes that a more suitable catalyst could be found (Scheme 3.16a). While some were not catalytically competent (Mg(OTf)$_2$), and others gave crude reaction mixtures where traces of **3.39** were apparent by ^{1}H NMR (Zn(OTf)$_2$, Sn(OTf)$_2$), the majority of catalysts (Sc(OTf)$_3$, Cu(OTf)$_2$, Me$_3$SiOTf, TfOH) led only to degradation. For instance, Cu(OTf)$_2$ caused full conversion of the starting material **3.38** to an unidentifiable mixture within one minute at 100 °C in MeNO$_2$. Fortunately, it was found that catalytic amounts of BF$_3$•OEt$_2$ produced a much cleaner reaction, and **3.39** was isolated in 53% yield. Further screening found that 1,2-dichloroethane (DCE) as solvent gave the cleanest crude product, and that performing the acylation at 100 °C in sealed tube was preferable to reflux conditions solely for the purpose of quicker reaction times. Under these optimized conditions, **3.39** was produced in 91% yield from **3.38** in 30 minutes using 10 mol % BF$_3$•OEt$_2$ (Scheme 3.16b).
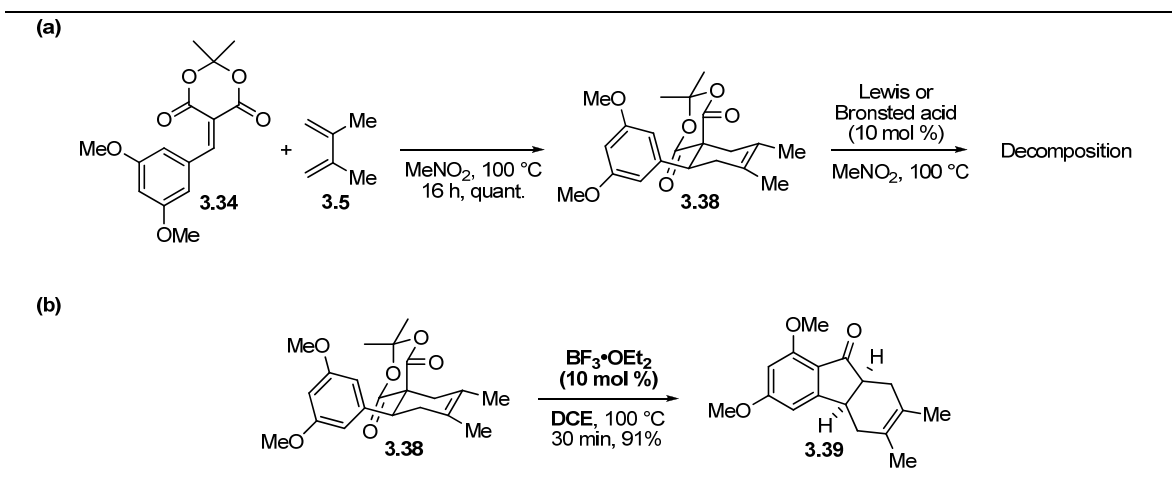
Scheme 3.16. BF$_3$•OEt$_2$-Catalyzed Friedel-Crafts acylation of Diels-Alder adduct **3.38**

At this point, it had also become apparent that Lewis acid catalysis of the Diels-Alder reaction was unfeasible, especially considering that to develop a true domino sequence the cycloaddition would need to be catalyzed by BF$_3$•OEt$_2$ in order to accommodate the limitations of the Friedel-Crafts step. A revised strategy was devised that made use of the fact that the thermal Diels-Alder reaction was very clean and did not require a large excess of diene that could potentially complicate the Lewis acid-catalyzed Friedel-Crafts acylation. Therefore, addition of a catalytic amount of BF$_3$•OEt$_2$ to the

reaction mixture following the thermal Diels-Alder should give a one-pot synthesis of the desired tetrahydrofluorenones. This turned out to be the case, and the procedure was to react the monosubstituted alkylidenes and 1.1 equivalents of the diene dissolved in DCE at 100 °C in a sealed Schlenk tube for 16 hours to ensure complete conversion. After cooling the solution to rt to avoid venting the superheated solvent, a catalytic amount of $BF_3 \cdot OEt_2$ was added and the tube placed back at 100 °C for 30 minutes to effect the Friedel-Crafts acylation.

In this manner, a number of different methoxy-substituted alkylidene Meldrum's acids were successfully converted into tetrahydrofluorenones (Scheme 3.17). Notably, the one-pot reaction leading to **3.39** gave nearly the same yield (86%) as performing each step separately (91%). More importantly, the one-pot synthesis of **3.37** (using 5.0 equiv of **3.35** as diene source) proceeded in 84% yield, while the combined yield for the individual steps gave a maximum of 70% yield. The Diels-Alder reaction using isoprene was very regioselective, and **3.40** was isolated as a >20:1 mixture of regioisomers. Other alkylidenes containing electron-rich arenes gave tetrahydrofluorenones **3.41-3.43**; **3.43** was produced as a ~2:1 mixture of separable regioisomers.
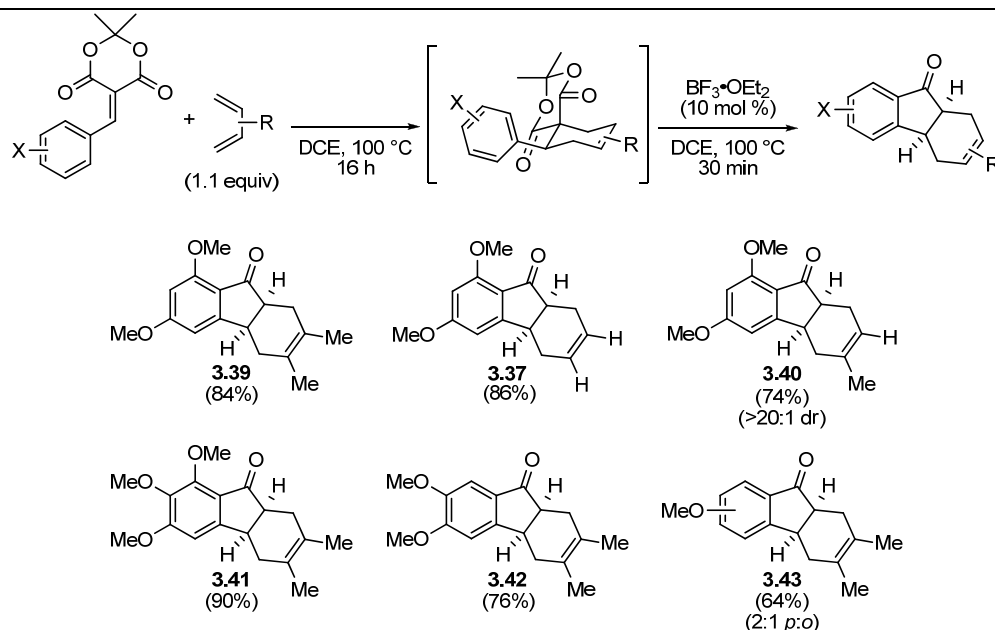
Scheme 3.17. One-pot synthesis of tetrahydrofluorenones **3.39-3.43**

Although this reaction worked well when the arene was strongly activated or not sterically hindered (ie no ortho substitutent), it was found that alkylidenes bearing less electron-rich arenes gave poor results in the Diels-Alder/Friedel-Crafts process. This was most likely due to the decreased π-nucleophilicity of the aromatic ring, which allowed competing reactions involving the now more nucleophilic cycloalkene. In order to facilitate the Friedel-Crafts acylations of less reactive arenes we turned to a diene that would give a relatively non-nucleophilic Diels-Alder adduct. The planned reaction was cycloaddition using ortho-quinodimethane (**3.45**, generated from sultine **3.44**[123]) which would produce a benzene ring in the adduct that would not interfere with the Friedel-Crafts step. However, under the sealed-tube conditions employed, the Diels-Alder reaction was not the most productive pathway; rather, a chelotropic process yielded the sulfone **3.46**. This led to low yields of the desired product **3.47** as most of the starting alkylidene remained unreacted (Scheme 3.18a). Since **3.46** is the product of the chelotropic reaction between **3.45** and SO_2, it was thought that performing the reaction in an open vessel under reflux conditions would allow the gas to escape and minimize formation of **3.46**. This was the case, and **3.48** was formed in 87% yield (with a longer reaction time for the Friedel-Crafts acylation to make up for the lower temperature, Scheme 3.18b).
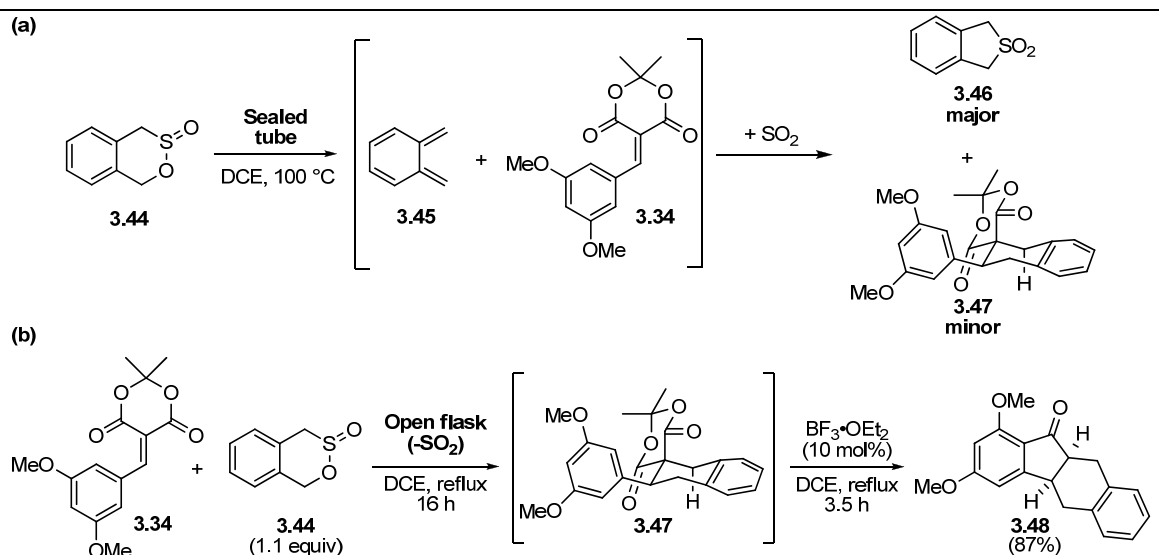
Scheme 3.18. Optimization of reactions using sultine **3.44**

With suitable conditions for this reaction, Diels-Alder/Friedel-Crafts acylations of alkylidenes containing less reactive arenes was feasible (Scheme 3.19.). Benzotetrahydrofluorenones **3.49-3.51** all contain aromatic rings less π-nucleophilic than **3.39**, and were poor substrates for reactions with 2,3-dimethylbutadiene. However, by essentially eliminating reactions stemming from the presence of another nucleophilic alkene these were all now compatible with the Lewis acid-catalyzed step.
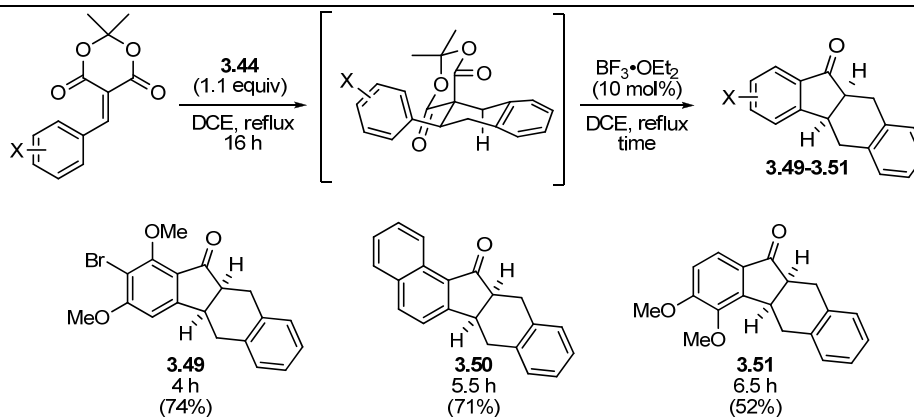
Scheme 3.19. Synthesis of benzotetrahydrofluorenones **3.49-3.51**

An interesting observation was made during the Diel-Alder/Friedel-Crafts acylation of **3.34** using (*E*)-1-phenylbutadiene **3.52**. This was the first reaction we had attempted that would give endo/exo diastereomers in the Diels-Alder step[124]; diastereoselectivity was low and led to a ~2:1 mixture of **3.53**:**3.54**.[125] Surprisingly though, only the exo isomer **3.53** underwent Friedel-Crafts acylation leading to **3.55** while the remaining endo isomer **3.54** was recovered (Scheme 3.20).

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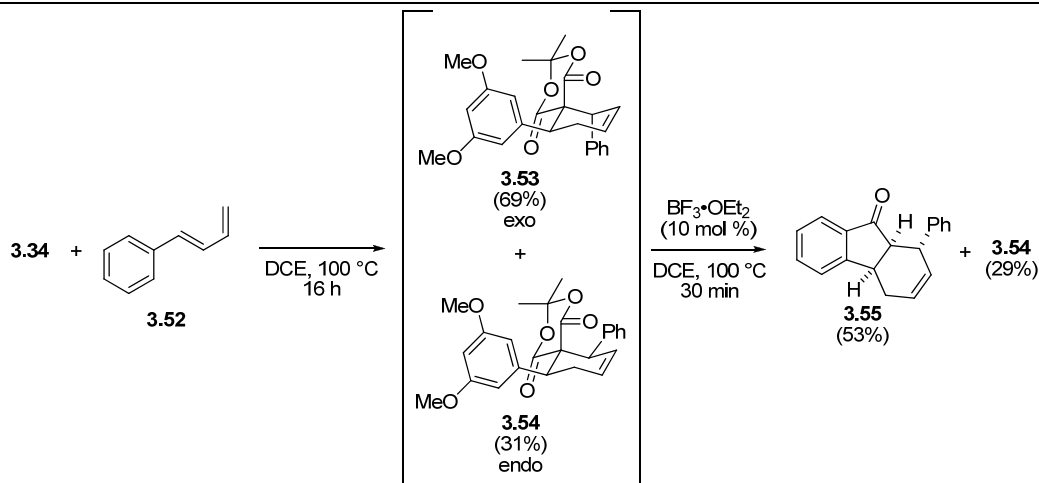
Scheme 3.20. Diels-Alder/Friedel-Crafts acylation using 1-phenylbutadiene **3.52**

On the other hand, reaction of **3.34** with (*E*)-1-methylbutadiene gave a similar endo:exo ratio, but now both **3.57** and **3.58** reacted to give diastereomeric tetrahydrofluorenones **3.59** and **3.60**. The fact that a small amount of the minor endo isomer **3.58** was isolated after addition of BF$_3$•OEt$_2$ suggested that this adduct reacted more slowly than exo **3.57** in the Friedel-Crafts acylation (Scheme 3.21).
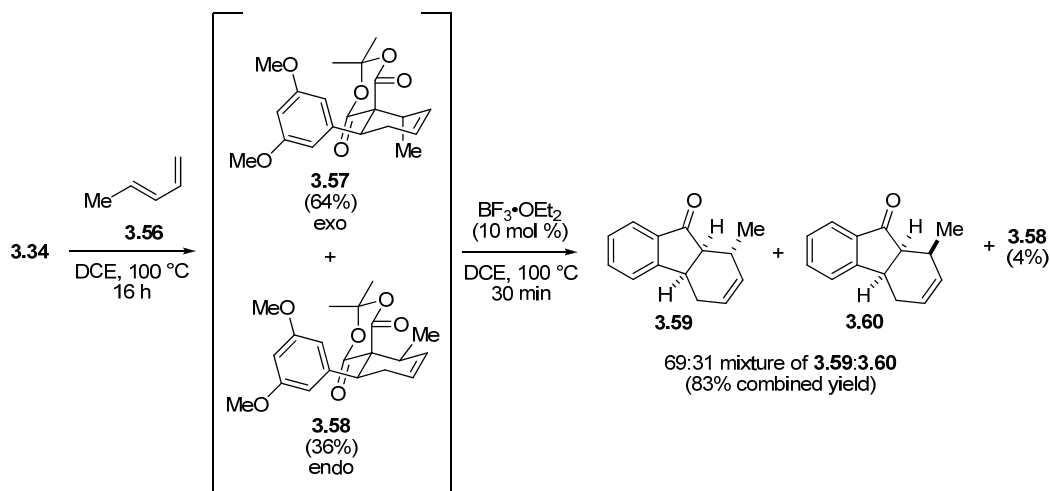
Scheme 3.21. Diels-Alder/Friedel-Crafts acylation using 1-methylbutadiene **3.56**

The reason for the unreactivity of the endo isomer **3.54** became clear upon examination of its crystal structure (which also validated the structural assignment of

these isomers based on NMR spectroscopy). In the solid state, the aromatic rings of **3.54** flank the Meldrum's acid carbonyls in a fairly crowded arrangement. By contrast, the structure of **3.53** has the phenyl ring in a pseudoaxial position which leaves one carbonyl exposed (Figure 3.2). Assuming that complexation of BF$_3$•OEt$_2$ is required to activate Meldrum's acid for attack of the arene, the shielded carbonyls in **3.54** likely account for its failure to undergo acylation. A similar argument can be made to rationalize the slow reactivity of **3.58** relative to **3.57**, while the smaller size of methyl vs phenyl explains why **3.58** can react where **3.54** does not.

endo adduct **3.54**   exo adduct **3.53**
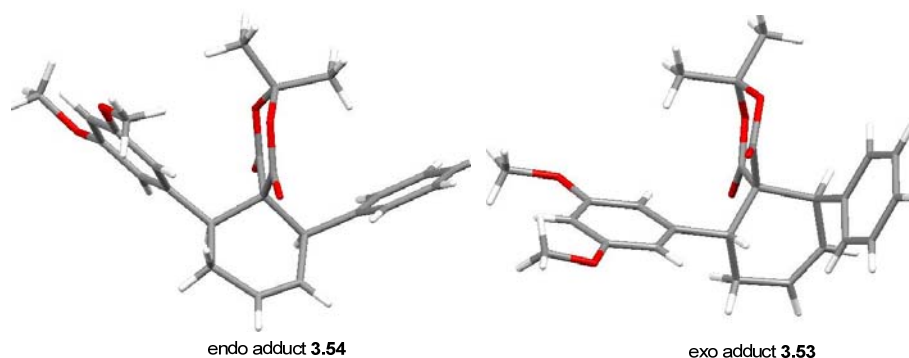
Figure 3.2. X-ray structures of Diels-Alder adducts **3.54** and **3.53**

The reactions with diene **3.52** led us to realize that by moving the electron-rich arene from the dienophile to the diene, tetrahydrofluorenones with the alkene in a different position would be formed. As shown in Scheme 3.22, reaction of benzylidene Meldrum's acids with dienes **3.61** and **3.62**[126] gave Diels-Alder adducts in roughly the same dr as the reaction of **3.34** and **3.52**. Addition of BF$_3$•OEt$_2$ again led to Friedel-Crafts acylation of the exo adduct to give tetrahydrofluorenones **3.63-3.66** and recovery of the corresponding endo adducts **3.67-3.70**. A test of the Friedel-Crafts acylation of endo adduct **3.67** suggested that conversion to a non-isolated product with ^{1}H NMR spectra similar to **3.63-3.66** was slow. For instance, with BF$_3$•OEt$_2$ (10 mol %) as catalyst, **3.67** was ~50% converted to this product after 8 h at 100 °C. This low reactivity explains why none of the diastereomers of **3.63-3.66** were isolated from these reactions.
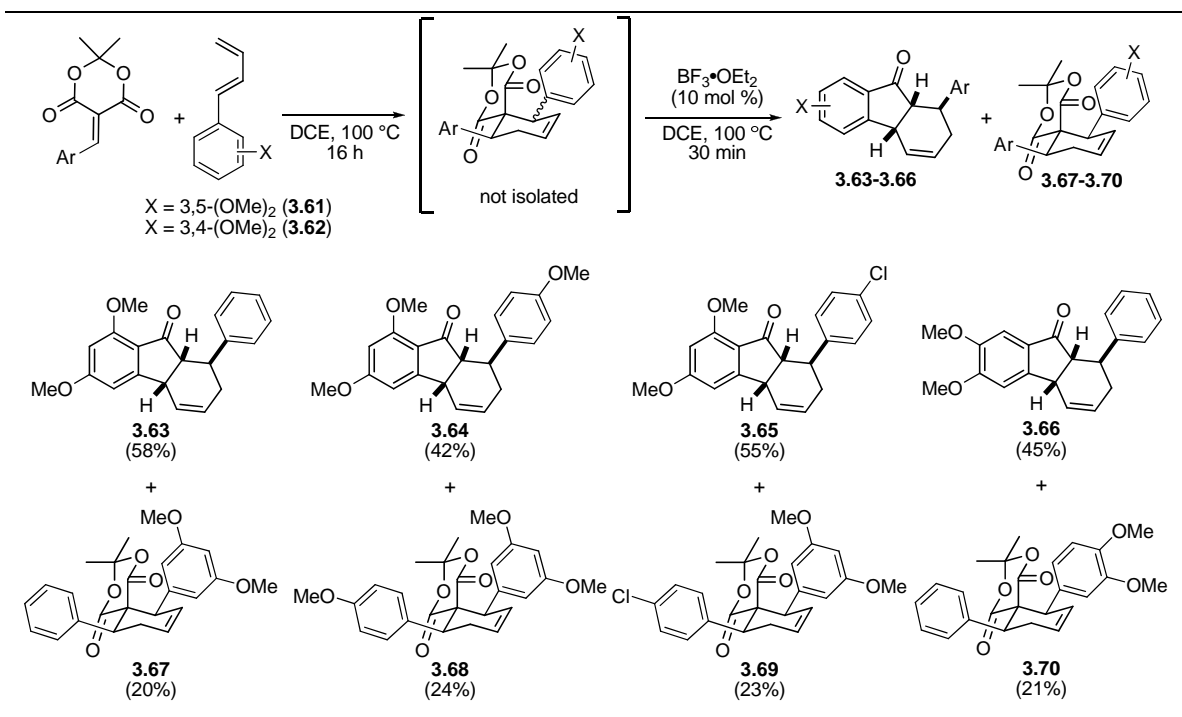
Scheme 3.22. "Reverse" Diels-Alder/Friedel-Crafts reactions

The final set of reactions in this project involved preparation of tetrahydrofluorenones bearing the gem-dimethyl group common to the taiwaniaquinoids (see Figure 3.1 above). Attempts to introduce this group through reaction of alkylidenes with 1,1-dimethylbutadiene **3.71** were unsuccessful, and led only to recovery of the starting alkylidene (Scheme 3.23a). This follows the general trend observed for Diels-Alder reactions with alkylidene Meldrum's acids in that terminal (*Z*) substituents are not tolerated (i.e. no reaction with cyclic dienes such as cyclopentadiene). On the other hand, use of the "reverse" Diels-Alder/Friedel-Crafts reaction where the electron-rich arene is on the diene was more fruitful. As shown in Scheme 3.23b, the Diels-Alder reactions of **3.61** and **3.62** with disubstituted alkylidene **3.72** led to gem-dimethyltetrahydrofluorenones **3.73** and **3.74**, respectively. Diene **3.62**, in which the diene is conjugated with one of the aromatic methoxy groups, was more reactive and gave a higher yield of **3.74** than **3.61** gave of **3.73**.

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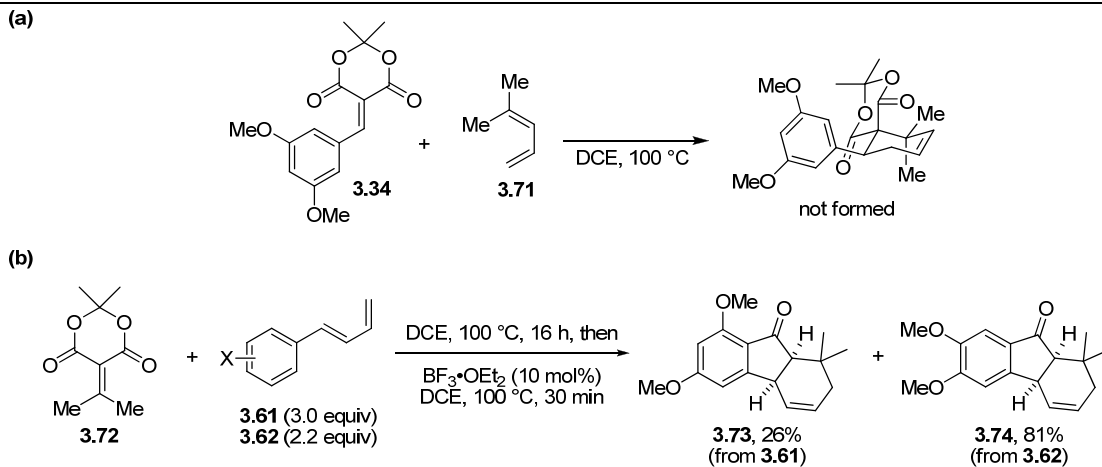
Scheme 3.23. Synthesis of gem-dimethyl tetrahydrofluorenones.

Having demonstrated that the Diels-Alder/Friedel-Crafts protocol is an efficient means for the construction of polycyclic compounds containing aromatic rings, we thought to exploit this method for reactions with heteroaromatic systems. Specifically, we targeted the ergot alkaloid family as being accessible through this route. The lessons learned through an attempted synthesis of festuclavine are presented in the following section.

3.4. Regioselective Friedel-Crafts Acylations of 4-Substituted Indoles

The ergot alkaloids are an immense family of natural product alkaloids most commonly isolated from fungus of the species *Claviceps*, which are parasites of rye and related grasses. Aside from the historical, medicinal, and recreational interest in members of this family, they have attracted considerable interest from synthetic chemists due to the interesting architecture and the variety of substituents and stereochemistries around the tetracyclic framework.[127] The basic skeleton is that of ergoline (**3.75**), and common features are the 3,4-disubstituted indole fused to a 6-6 bicyclic framework of varying oxidation state (Figure 3.3).
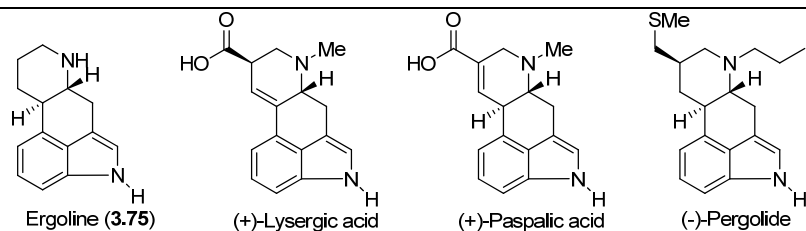
Figure 3.3. Representative members of the ergot alkaloids

We targeted festuclavine (**3.80**) as accessible via our Diels-Alder/Friedel-Crafts acylation reaction. Based on the proposed synthesis in Scheme 3.24, regioselective Diels-Alder reaction of a suitably protected 4-indolyl alkylidene Meldrum's acid **3.76** with the chiral hydrazine-derived diene **3.77**[128] would give adduct **3.78**. This would introduce the first of the two required six-membered rings; the second would be formed by Friedel-Crafts acylation of **3.78**. We were confident that acylation would take place on the 3-position of indole, as opposed to the adjacent 5-position, due to it being the most nucleophilic[129], as well as the already determined preference for 6-membered ring formation in Friedel-Crafts acylations using Meldrum's acids.[26] From tetracycle **3.79**, a flexible sequence of reductions and deprotections would give festuclavine in a short total synthesis.
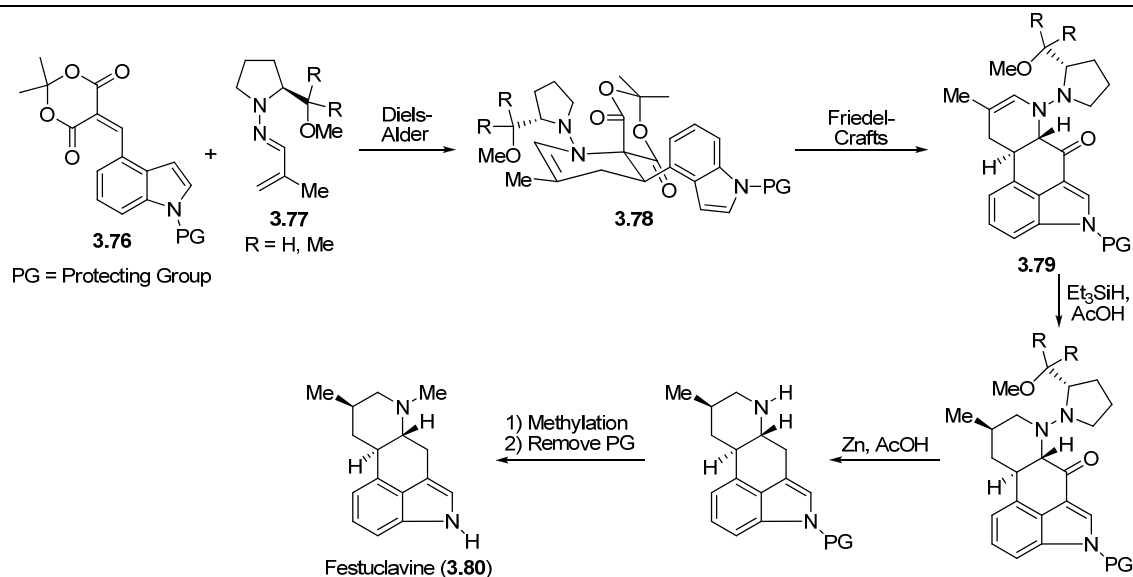
Scheme 3.24. Proposed synthesis of festuclavine

While festuclavine has been prepared by semi-synthesis[130], no total synthesis of this particular ergot alkaloid has been reported. However, the synthesis of a diastereomer of festuclavine, costaclavine (**3.81**), is illustrative of the most common general strategy for preparation of these molecules (Scheme 3.25a). Here, the synthesis starts from a 3,4-disubstituted indoline (serving as a less reactive surrogate of indoles)[131], and a Pummerer-induced cycloaddition is used to form the two non-aromatic six-membered rings.[132] While a huge number of different reactions have been used to form these two rings, the key disconnections typically proceed from intermediates where the indole substituents are already in place. In cases where they do not, the indole bond formations nearly always involves cyclizations of a 3-position tethered group onto the 4-position. For example, ketone **3.83** is an important intermediate in a number of ergot alkaloid syntheses.[133] It is most conveniently prepared by Friedel-Crafts acylation of a 3-substituted indole; in this case the regioselectivity was controlled by introduction of a bulky protecting group which limits cyclization at the more nucleophilic 2-position which leads to **3.82** (Scheme 3.25b).
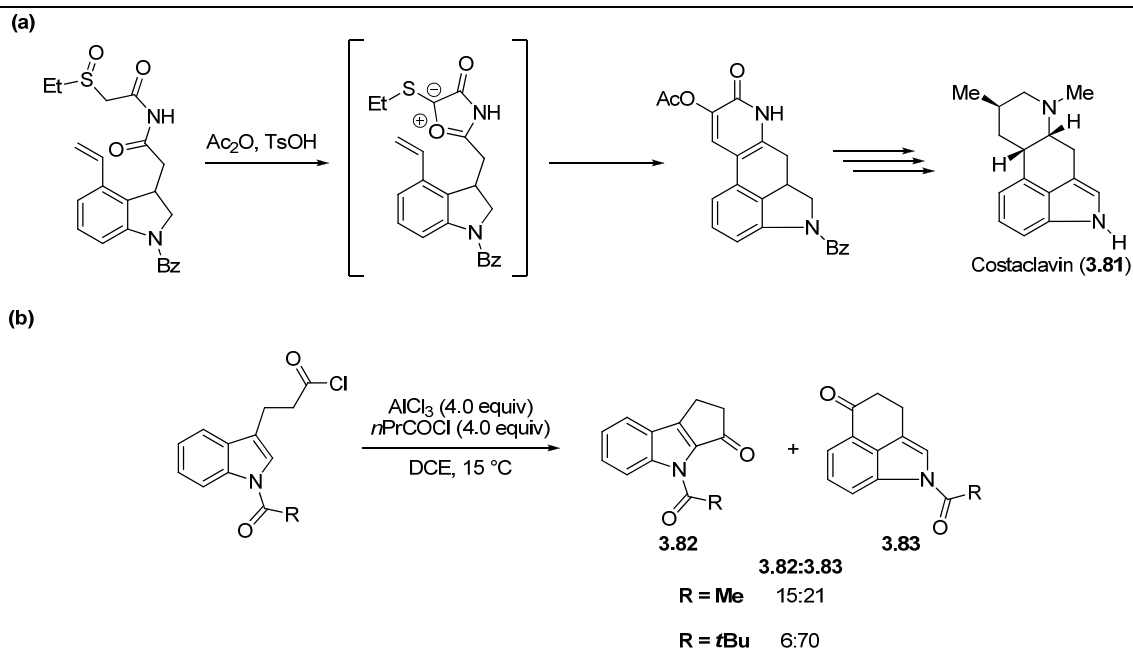
Scheme 3.25. Common strategies for synthesis of key ergot ring systems

On the other hand, very few syntheses of ergot alkaloids proceed by ring formation from a tethered electrophile on a 4-substituted indole. In the only example of this reaction among the syntheses of lysergic acid, anionic alkylation of an N-H indole on

a tethered aldehyde produced the final six-membered ring in a very efficient route (Scheme 3.26a).[134] This process can be seen as analogous to attack of a metalloenamine on a carbonyl group. In an example more relevant to our proposed transformation, a cationic alkylation of a 4-substituted indole was reported as a route toward the hapalindole skeleton. In this case, treatment of ketone **3.84** with $BF_3 \cdot OEt_2$ led to preferential reaction at the 3-position to give **3.85** as the major product, with only a small amount of the regioisomer **3.86** (Scheme 3.26b).[135]
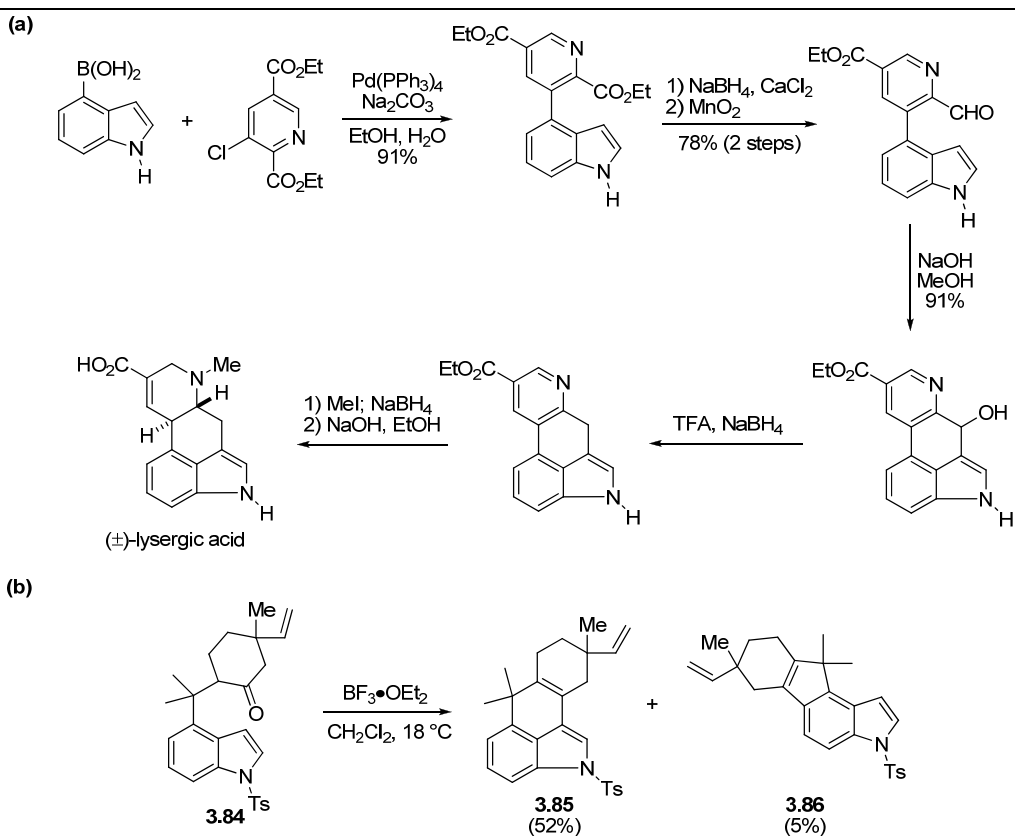
Scheme 3.26. Indole alkylations from tethered 4-position electrophiles

In terms of Friedel-Crafts acylations of 4-substituted indoles, there are only two literature examples of a 4 → 3-position cyclization, both of which employ N-H indoles. In one, the polyphosphoric acid induced reaction of a tethered carboxylic acid **3.87** forms a six-membered ring to the 3-position to give ketone **3.88** (Scheme 3.27a).[136] In this case, regioselectivity was not an issue as the 5-position was blocked by an activating methoxy group. However, in the other example, a $POCl_3$-activated amide (**3.89**) cyclizes

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exclusively at the 3-position to yield **3.90** as a single regioisomer, despite the 5-position being available (Scheme 3.27b).[137]
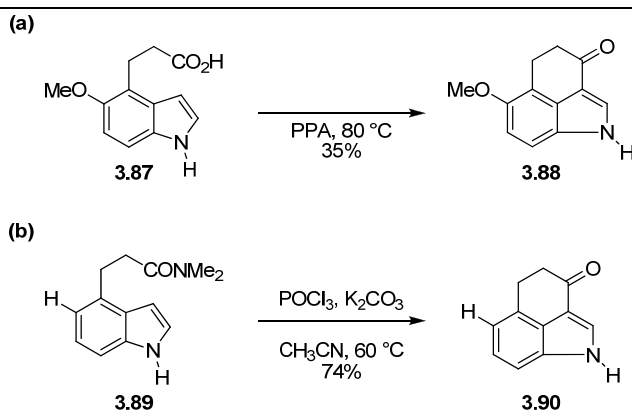
Scheme 3.27. Friedel-Crafts 3-acylation of 4-substituted indoles

Our work in this area began with identification of a suitable *N*-protecting group for the indole that would be compatible with alkylidene formation.[138] The alkylidene's high electrophilicity coupled with the π-nucleophilicity of indole makes reaction of the two extremely facile and uncatalyzed Friedel-Crafts alkylations between these two have been used frequently.[139] As well, the known ability of sp^3- and sp^2-hybridized nitrogen atoms to sequester Lewis acids in catalyzed Friedel-Crafts reactions of Meldrum's acid derivatives suggested that any protecting group would have to limit the heteratom's nucleophilicity. After some experimentation, it was found that the *p*-nitrobenzenesulfonyl (Ns) group served both these purposes, and a high yielding entry into 4-substituted indolyl alkylidene **3.93** was developed (Scheme 3.28). The synthesis started from commercially available indole-4-carboxaldehyde (**3.91**).[140] An advantage of the Ns group is that NsCl is significantly more reactive than the more traditional *p*-toluenesulfonyl (Ts) chloride, and the *N*-Ns was installed under very mild conditions. Condensation of protected indole **3.92** with Meldrum's acid under the conditions developed in our group then gave **3.93**; 16.9 g of **3.93** were prepared in a single batch, providing ample material for further studies. Diels-Alder reaction with the diene derived from sultine **3.44** gave adduct **3.94** as a model substrate to test the Friedel-Crafts acylation.

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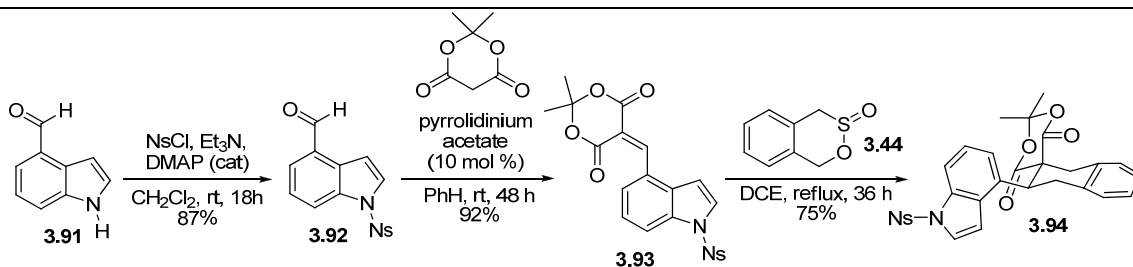
Scheme 3.28. Preparation of *N*-Ns indolyl Diels-Alder adduct **3.94** as a model substrate

When adduct **3.94** was treated with catalytic BF$_3$•OEt$_2$, none of the desired 3-position cyclization product **3.95** was observed. Disappointingly, the result of this Friedel-Crafts acylation was the 4,5-disubstituted indole **3.96** as the sole regioisomer (Scheme 3.29). This result was surprising in light of the successful cyclization of other electrophiles in a 4 → 3 manner shown above, even for the relatively deactivated *N*-Ts indole **3.84**. In addition, we had thought that the native nucleophilicity of the indole 3-position combined with the preference for six-membered ring formation in Friedel-Crafts acylation of Meldrum's acid derivatives would favour the desired outcome. This discouraging result led us into investigate the reason for this unexpected regioselectivity in the hopes of developing an alternate route to festuclavine.
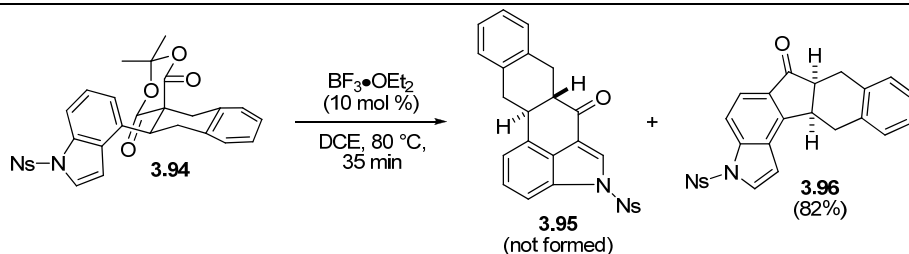
Scheme 3.29. Unexpected regioselectivity in Friedel-Crafts acylation of **3.94**

We initially explored the possibility that the ring structure in adduct **3.94** was favouring orientation of the indole in such a way that the electrophilic carbon was forced to overlap preferentially with the 5-position rather than the 3-position. Acyclic 4-indolyl substituted Meldrum's acids derivatives were then prepared in order to test this theory. Conjugate reduction of **3.93** with sodium cyanoborohydride gave enolizable Meldrum's acid **3.97**, which was then alkylated with various electrophiles to give non-enolizable **3.98-3.100** (Scheme 3.30).

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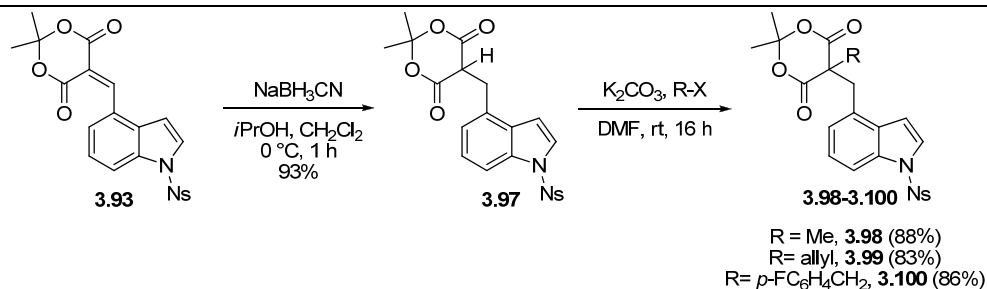
Scheme 3.30. Preparation of acyclic 4-indolyl Meldrum's acid derivatives

Because the active acylating agent should be different for enolizable and non-enolizable Meldrum's acid (see Scheme 1.8), the use of **3.97** versus **3.98-3.100** would also test whether the regioselectivity was affected by the nature of the electrophile. However, when enolizable **3.97**, which should form acyl ketene **3.101** as the intermediate electrophile, was reacted with catalytic BF$_3$•OEt$_2$, cyclization again occurred only at the 5-position to give **3.102** (Scheme 3.31a). Unfortunately, the same regioselectivity was obtained for **3.98-3.100** to give 4,5-disubstituted indoles **3.104-3.106** (Scheme 3.32b). These acylations should occur through direct attack on Lewis acid-activated intermediate **3.103**, the same mechanism as for acylation of cyclic adduct **3.94**.
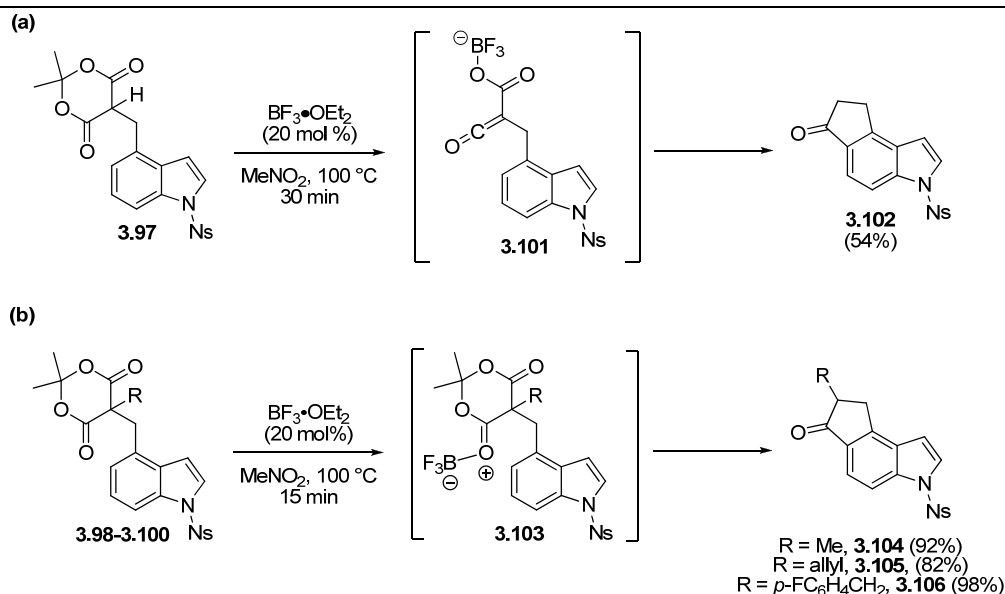
Scheme 3.31. Friedel-Crafts acylations of acyclic Meldrum's acid derivatives

These results suggested that conformation and the nature of the electrophile were not the primary determinants of regioselectivity in Friedel-Crafts acylation of 4-substituted indoles. It seemed therefore reasonable that the most likely cause of the unexpected regioselectivity was the highly electron-withdrawing Ns group. While this protecting group had allowed formation of **3.93** by reducing the π-nucleophilicity of the indole ring and preventing attack on the alkylidene, for the purposes of Friedel-Crafts acylation a more electron-rich arene was clearly desirable. In fact, the only literature example of a 4 → 5 cyclization of a 4-substituted indole is one where the "enamine" portion of the indole is deactivated by an ester group (Scheme 3.32a).[141] It was hoped that Meldrum's acids **3.107** or **3.108**, where the Ns group was removed by treatment with thioglycolic acid, would therefore undergo acylation at the 3-position. Upon treatment with excess Me₃SiOTf, which was shown to be effective for arenes bearing Lewis basic nitrogens, **3.107** and **3.108** led only to decomposition and no products of Friedel-Crafts acylation to either the 3- or 5-position could be isolated (Scheme 3.32b).
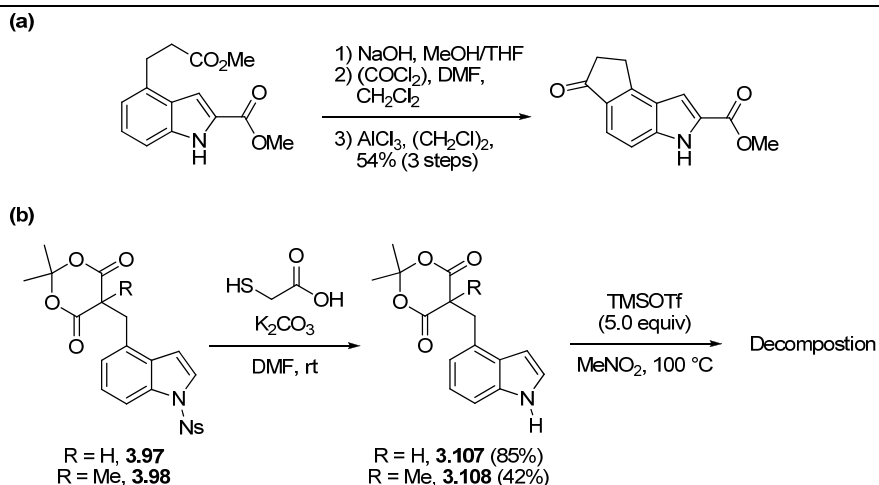
Scheme 3.32. Attempted Friedel-Crafts acylations of *N*-H indoles **3.107-3.108**

The decomposition of **3.107** and **3.108** under the Friedel-Crafts conditions meant no information on the regioselectivity of these reactions could be gathered. We therefore devised an alternate strategy to determine whether the 3- or 5-positions in *N*-Ns indoles was the most nucleophilic. It was thought than an *intermolecular* Friedel-Crafts acylation of indole **3.109** with Meldrum's acid **3.110** would distinguish the most nucleophilic position by eliminating (as far as possible) any steric or conformational bias that might

exist in the tethered, intramolecular substrates (Scheme 3.33). While this reaction did not occur using a catalytic amount of BF$_3$•OEt$_2$, use of a slight excess gave 3-substituted indole **3.111** in 76% yield as the sole product. To ensure that the excess Lewis acid was not playing a role, a reaction using Yb(OTf)$_3$ (10 mol %) was also performed; again, **3.111** was the only product although in lower isolated yield.[142] This suggested that while the 3-position in *N*-Ns indoles is the most electronically activated, the relative difference in nucleophilicity between the 3- and 5-positions in the 4-substituted indoles such as **3.94** was insufficient to overcome the ring strain inherent in forming the six-membered ring to bridge the 3- and 4-positions.
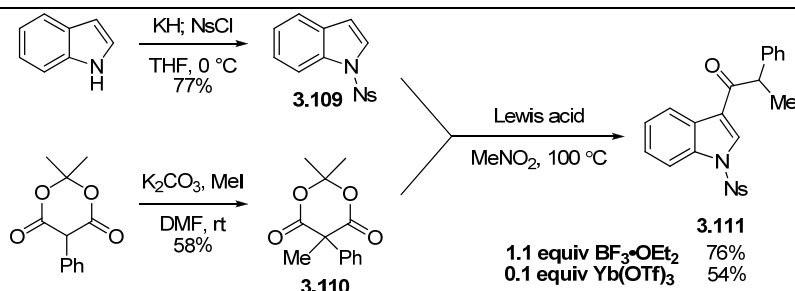
Scheme 3.33. Intermolecular Friedel-Crafts acylation of *N*-Ns indole **3.109**

At this point in the work, the total synthesis of festuclavine was appearing more and more distant. For instance, the Diels-Alder reaction using chiral dienes **3.77** had not yet been investigated. Furthermore, the failure of the *N*-Ns-substituted indoles in the Friedel-Crafts step but the requirement for this group in order to prepare the precursors suggested protecting group manipulations that would lengthen the total sequence to an extent that would make it uncompetitive with the modern standards for ergot alkaloid syntheses. We therefore changed our focus to a broader understanding of the intramolecular Friedel-Crafts acylations of 4-substituted indoles.

All of the above reactions involved Meldrum's acid derivatives with a 2-carbon tether between the indole and the electrophilic carbon, leading to possible formation of 5- or 6-membered rings depending on the regioselectivity. To see if a longer tether would change the regioselectivity, we prepared *N*-Ts indoles **3.114** and **3.115** containing an extra methylene group between the indole and Meldrum's acid (Scheme 3.34a).[143] This was accomplished from known nitrile **3.112**[144], which was hydrolyzed to acid **3.113**

before performing reductive homologation with Meldrum's acid according to the published procedure.[145] A portion of the Meldrum's acid **3.114** thus obtained was methylated, giving **3.115**, to allow reactions of enolizable and non-enolizable Meldrum's acids. Friedel-Crafts acylation of both **3.114** and **3.115** under Yb(OTf)$_3$-catalysis led to exclusive formation of the 4,5-disubstituted indoles **3.116** and **3.117**, with no trace of the regioisomeric product. This reaction provides an entry into the 4,5-fused cyclohexanone backbone of the natural product lolicine A, which has been prepared only one other time.[146]
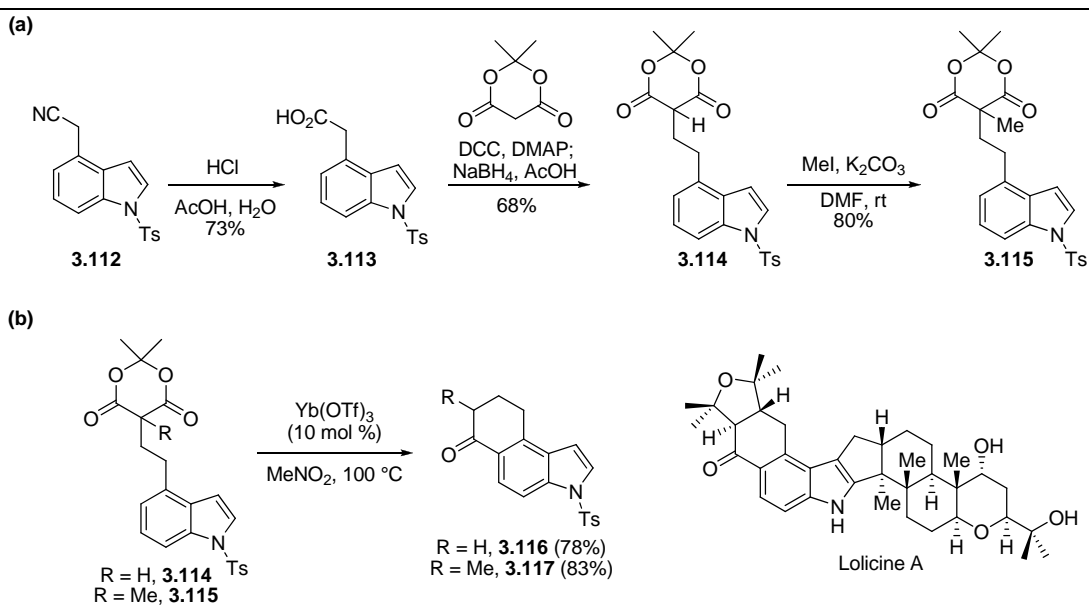
Scheme 3.34. Preparation and Friedel-Crafts acylations of extended tether 4-indolyl Meldrum's acids

In order to determine the effect of various protecting groups on the outcome of the acylation, we realized the Meldrum's acid derivatives would not be suitable due to the difficulties that would be presented for their preparation. We therefore turned to carboxylic acids, which would be easier to prepare with different protecting groups and could be acylated by conventional means through formation of the acid chlorides. The sulfonyl-protected **3.121** and **3.122** were prepared by olefination of indole-4-carboxaldehyde **3.91** followed by hydrogenation of the crude reaction product to give the ester **3.118**. Reaction with either TsCl or NsCl gave the protected products **3.119** and **3.120**, which were then converted into the acids **3.121** and **3.122** by acid or base

hydrolysis, respectively (Scheme 3.35a). A shorter alternate route was used to prepare the carbonyl-protected **3.124** and **3.125**, where olefination of **3.91** followed by protection and hydrogenation/hydrogenolysis of **3.123** gave the acids (Scheme 3.35b). Formation of the acid chlorides using oxalyl chloride, followed by immediate treatment with AlCl$_3$ in DCE gave the cyclized products **3.104** and **3.126-3.128** as single regioisomers (Scheme 3.35c). The possible 3-position regioisomer was not detected for any of these reactions.
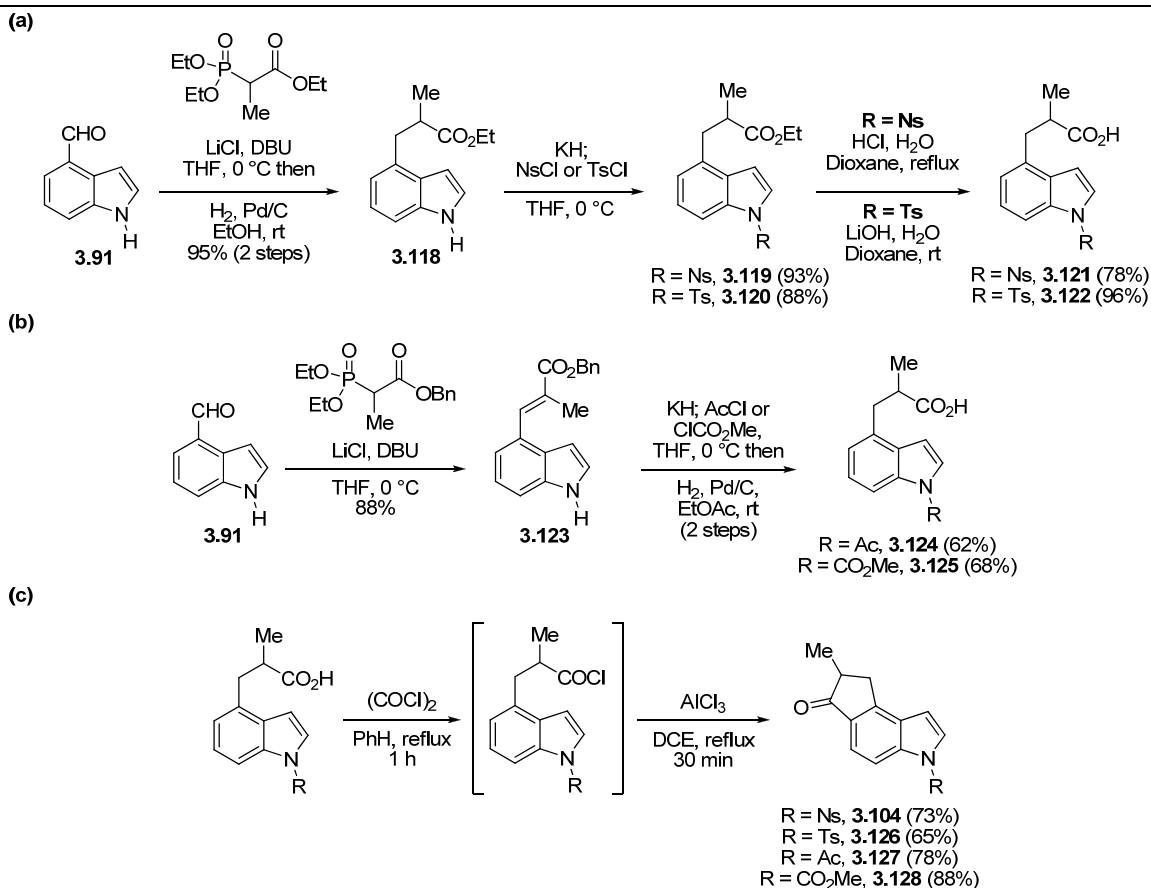
Scheme 3.35. Preparation and Friedel-Crafts acylation of 4-indolyl propionic acids

Comparing these results to the successful 4 → 3 cyclization of *N*-H indoles shown in Scheme 3.27a and 3.27b, it seems most likely that the electron-withdrawing protecting groups are the reason for the reversed regioselectivity observed in the above reactions. This presents an obstacle to the preparation of ergot alkaloids through Friedel-Crafts acylations of 4-substituted indoles as many of these protocols require the use of reagents or electrophiles that are incompatible with the high π-nucleophilicity of *N*-H indoles.[147] While the failure to achieve anything close to the total synthesis of festuclavine was

disappointing, the insights gained into the reactivity of 4-substituted indoles was interesting. Considering the ubiquity of the indole nucleus in natural products and medicinal compounds, the availability of a rather general and highly stereoselective methods for the preparation of 4,5-disubstituted indole-fused ring systems is potentially useful.

3.5. Experimental Section

Part 1. Diels-Alder/Friedel-Crafts Acylation of Alkylidene Meldrum's Acids

General Considerations: All reactions were carried out under a dry N_2 atmosphere in flame-dried round bottom flasks or oven-dried Schlenk glassware. $MeNO_2$ was distilled from CaH_2 and stored under N_2 in a Schlenk flask. Dichloroethane was dried and purified from a solvent system by the published procedure.[222] $BF_3 \cdot OEt_2$ was distilled under vacuum from CaH_2 through a 15 cm Vigreux column before use. All other commercial reagents were used as received without further purification. Reactions were monitored using commercial TLC plates visualized under UV light and developed with cerium molybdate (Hanessian's stain). Flash chromatography was performed using 230-400 mesh silica gel.

Characterization: Melting points are uncorrected. ^1H and ^{13}C NMR spectra for all compounds were obtained in $CDCl_3$ at 300 MHz and 75 MHz, respectively. ^1H NMR spectra were referenced to residual $CHCl_3$ (7.24 ppm); ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm). ^{13}C NMR hydrogen multiplicity was determined by a JMOD experiment for compounds **S3.1-S3.2**; all others were determined from DEPT-90 and DEPT-135 experiments. Chemical shifts are reported in parts per million (ppm, δ). High resolution mass spectra were obtained at the University of Waterloo Mass Spectrometry Facility.

Preparation of Alkylidene Meldrum's Acids:

Alkylidene Meldrum's acids were prepared from Knoevenagel condensation of substituted benzaldehydes with Meldrum's acid in water.[54] All products were

recrystallized from MeOH. Characterization data for alkylidenes not previously referred to in the preceeding chapters are presented below.
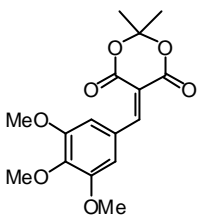
5-(3,4,5-Trimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (S3.1): Prepared from 3,4,5-trimethoxybenzaldehyde and isolated as a pale yellow powder. M.p. 155-156 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.30 (s, 1H), 7.59 (s, 2H), 3.96 (s, 3H), 3.89 (s, 6H), 1.77 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.8 (C), 160.2 (C), 158.0 (CH), 152.6 (C), 143.8 (C), 126.6 (C), 112.5 (CH), 112.4 (C), 104.3 (C), 61.1 (CH$_3$), 56.2 (CH$_3$), 27.4 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{16}$H$_{18}$O$_7$ (M$^+$): 322.1053 Found: 322.1045.
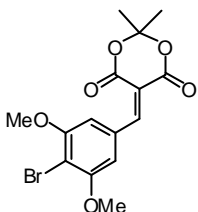
5-(4-Bromo-3,5-dimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (S3.2): Prepared from 4-bromo-3,5-dimethoxybenzaldehyde[148] and isolated as a yellow powder by Method A. M.p. 187-189 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.32 (s, 1H), 7.46 (s, 2H), 3.94 (s, 6H), 1.79 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 163.3 (C), 159.8 (C), 157.3 (CH), 157.0 (C), 131.3 (C), 114.8 (CH), 110.1 (C), 108.5 (C), 104.6 (C) 55.6 (CH$_3$), 27.5 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{15}$H$_{15}$^{79}BrO$_6$ (M$^+$): 370.0052 Found: 370.0041.
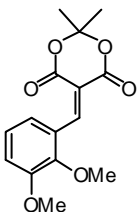
5-(2,3-Dimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (S3.3): Prepared from 2,3-dimethoxybenzaldehyde and isolated as a bright yellow powder by. M.p. 104-105 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.67 (s, 1H), 7.48-7.44 (m, 1H), 7.10-7.04 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 1.79 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 162.8 (C), 159.6 (C), 153.1 (CH), 152.3 (C), 149.7 (C), 126.3(C), 123.5 (CH), 123.0 (CH), 117.0 (CH), 116.4 (C), 104.5 (C), 61.8 (CH$_3$), 55.9 (CH$_3$), 27.6 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{15}$H$_{16}$O$_6$ (M$^+$): 292.0947 Found: 292.0939.

Synthesis of Diels-Alder Adduct 3.36 and Friedel-Crafts Acylation to 3.37:
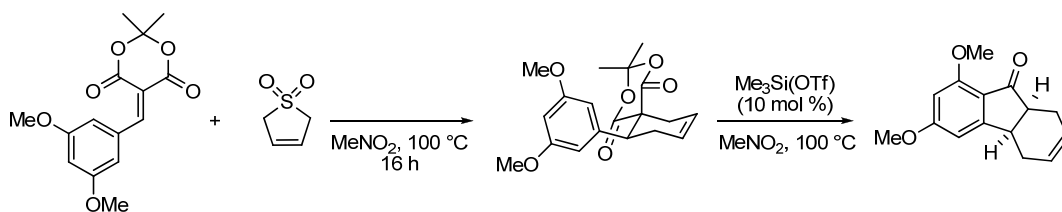
11-(3,5-Dimethoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (3.36): An oven-dried Schlenk tube cooled under N_2 was charged with alkylidene Meldrum's acid **3.34** (2.0 g, 6.8 mmol, 1 equiv), butadiene sulfone (8.0 g, 68 mmol, 10 equiv), and $MeNO_2$ (34 mL, 0.2 M). The tube was heated in an oil bath at 100 °C for 16 hours, cooled to rt, poured into saturated $NaHCO_3$ solution and stirred until bubbling ceased. This was extracted with EtOAc (2X), and the combined organic layers were washed with water (1X) and brine (1X), dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography eluting with 3:17 EtOAc:hexanes and isolated as a white solid (1.9 g, 82% yield). M.p. 118-119 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.34 (m, 3H), 6.01-5.96 (m, 1H), 5.74-5.69 (m, 1H), 3.72 (s, 6H), 3.47 (dd, J = 11.7 Hz, 5.1 Hz, 1H), 2.99-2.83 (m, 2H), 2.48 (dd, J = 17.9 Hz, 4.6 Hz, 1H), 2.34 (dt, J = 17.8 Hz, 4.7 Hz, 1H), 1.58 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 170.7 (C), 166.9 (C), 160.8 (C), 141.5 (C), 127.0 (CH), 121.0 (C), 106.7 (CH), 104.9 (C), 100.2 (CH), 55.3 (CH$_3$), 52.5 (C), 46.3 (CH), 34.8 (CH$_2$), 29.8 (CH$_3$), 28.8 (CH$_2$), 27.9 (CH$_3$); HRMS(EI) m/z calcd for C$_{19}$H$_{22}$O$_6$ (M$^+$): 346.1416 Found: 346.1420.
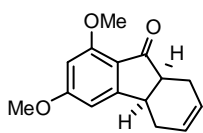
(4bR*,8aS*)-4b,5,8,8a-Tetrahydro-1,3-dimethoxyfluoren-9-one (3.37): An oven-dried Schlenk tube cooled under N_2 was charged with cycloadduct **3.36** (100 mg, 0.29 mmol, 1.0 equiv). A solution of TMSOTf in $MeNO_2$ (0.1 equiv/100 µl) was washed into the tube with $MeNO_2$ (2.8 mL) and the tube was sealed and heated to 100 °C for 2.5 hours. Once the reaction had cooled to rt, the contents were rinsed into a separatory funnel with EtOAc and washed with water (1X) followed by brine (1X). The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash chromatography eluting with 1:2 EtOAc:hexanes to a clear, colourless oil (60 mg, 85% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 6.46 (d, J = 1.1 Hz, 1H), 6.25 (d, J = 1.6 Hz, 1H), 5.85-5.80 (m, 1H), 5.73-5.68 (m, 1H),

3.85 (s, 3H), 3.84 (s, 3H), 3.46 (dt, J = 12.3 Hz, 7.4 Hz, 1H), 3.46 (dt, J = 12.2 Hz, 7.9 Hz, 1H), 2.52-2.42 (m, 2H), 2.33-2.29 (m, 1H), 2.17 (dt, J =15.3 Hz, 5.1 Hz, 1H) ; ^{13}C NMR (CDCl$_3$, 75 MHz) 204.7 (C), 167.1 (C), 163.7 (C), 158.8 (C), 128.5 (CH), 126.9 (CH), 119.6 (C), 100.5 (CH), 97.3 (CH), 55.66 (CH$_3$) 55.63 (CH$_3$), 46.8 (CH), 37.6 (CH), 28.5 (CH$_2$), 24.5 (CH$_2$); HRMS(EI) m/z calcd for C$_{15}$H$_{16}$O$_3$ (M$^+$): 244.1099 Found: 244.1102.

Synthesis of Diels-Alder Adduct 3.38 and Friedel-Crafts Acylation to 3.39:
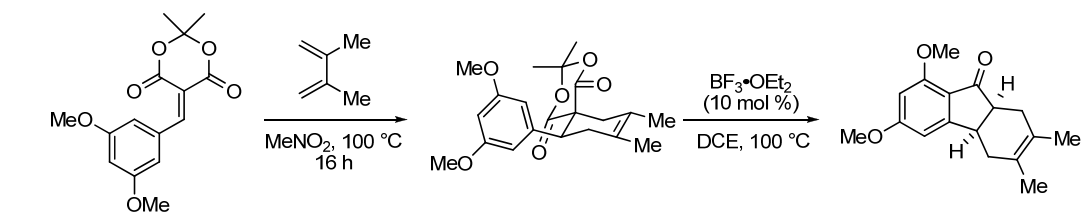
 11-(3,5-Dimethoxyphenyl)-3,3,8,9-tetramethyl-2,4-dioxaspiro-[5.5]undec-8-ene-1,5-dione (3.38): An oven-dried Schlenk tube cooled under N$_2$ was charged with alkylidene Meldrum's acid **3.34** (200 mg, 0.68 mmol, 1 equiv) and 2,3-dimethylbutadiene (42 μL, 0.75 mmol, 1.1 equiv) was added to the top chamber via syringe and washed into the tube with MeNO$_2$ (3.4 mL, 0.2 M). The tube was heated in an oil bath at 100 °C for 16 hours, cooled to rt, and the contents transferred into a round bottom flask with EtOAc. The solvent was removed by rotary evaporation, and the product **6b** isolated as a white solid (254 mg, quant. yield). M.p. 129-130 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.35 (d, J = 2.1 Hz, 2H), 6.32 (t, J = 2.1 Hz, 1H), 3.72 (s, 6H), 3.48 (dd, J = 12.0 Hz, 5.4 Hz, 1H), 2.94-2.89 (m, 2H), 2.29 (d, J = 17.4 Hz, 1H), 2.15 (dd, J = 17.4 Hz, 5.3 Hz, 1H), 1.73 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 171.1 (C), 167.0 (C), 160.9 (C), 141.7 (C), 126.2 (C), 119.8 (C), 106.7 (CH), 104.8 (C), 100.2 (CH), 55.4 (CH$_3$), 53.9 (C), 47.0 (CH), 40.8 (CH$_2$), 35.0 (CH$_2$), 29.8 (CH$_3$), 28.0 (CH$_3$), 19.0 (CH$_3$), 18.3 (CH$_3$); HRMS(EI) m/z calcd for C$_{21}$H$_{26}$O$_6$ (M$^+$): 374.1729 Found: 374.1725.
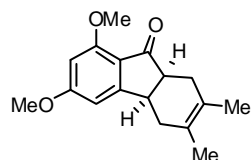
 (4aR*,9aS*)-1,4,4a,9a-Tetrahydro-6,8-dimethoxy-2,3-dimethylfluoren-9-one (3.39): An oven-dried Schlenk tube cooled

under N_2 was charged with cycloadduct **3.38** (100 mg, 0.27 mmol, 1.0 equiv). A solution of $BF_3 \cdot OEt_2$ in DCE (0.1 equiv/100 µl) was washed into the tube with DCE (2.6 mL, 0.1 M) and the tube was sealed and heated to 100 °C for 30 minutes. The contents were rinsed into a separatory funnel with CH_2Cl_2 and washed with brine (1X). The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash chromatography 1:2 EtOAc:hexanes to yield the product as a white solid (67 mg, 91% yield). ^1H NMR (CDCl$_3$, 300 MHz) 6.46 (d, J = 1.1 Hz, 1H), 6.25 (d, J = 1.6 Hz, 1H), 5.85-5.80 (m, 1H), 5.73-5.68 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.46 (dt, J = 12.3 Hz, 7.4 Hz, 1H), 3.46 (dt, J = 12.2 Hz, 7.9 Hz, 1H), 2.52-2.42 (m, 2H), 2.33-2.29 (m, 1H), 2.17 (dt, J =15.3 Hz, 5.1 Hz, 1H) ; ^{13}C NMR (CDCl$_3$, 75 MHz) 204.7 (C), 167.1 (C), 163.7 (C), 158.8 (C), 128.5 (CH), 126.9 (CH), 119.6 (C), 100.5 (CH), 97.3 (CH), 55.66 (CH$_3$) 55.63 (CH$_3$), 46.8 (CH), 37.6 (CH), 28.5 (CH$_2$), 24.5 (CH$_2$); HRMS(EI) *m/z* calcd for $C_{15}H_{16}O_3$ (M$^+$): 244.1099 Found: 244.1102.

One-Pot Synthesis of Tetrahydrofluorenones 3.37 and 3.39-3.43:
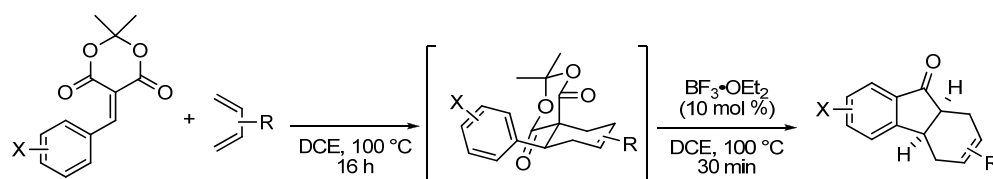
General Procedure A: An oven-dried Schlenk tube cooled under N_2 was charged with Meldrum's acid alkylidene (200 mg, 1.0 equiv) and the diene (1.1 equiv) was washed into the tube with DCE (0.2 M relative to the alkylidene). The tube was sealed, heated in an oil bath at 100 °C for 16 h, and removed from the bath to cool to rt. A 50 µL aliquot was removed and concentrated to determine conversion and endo:exo ratio (where applicable) of the Diels-Alder reaction by ^1H NMR. A solution of $BF_3 \cdot OEt_2$ in DCE (0.1 equiv/100 µL) was washed into the tube with sufficient DCE to bring the total concentration to 0.15 M. The tube was reheated to 100 °C for 30 min, cooled to rt, and the contents transferred into a separatory funnel with CH_2Cl_2 *(Caution: A small amount of pressure builds up in the tube during the FC acylation as CO_2 is evolved)*. The organic phase was washed with

brine (1X), dried over MgSO$_4$, filtered, and concentrated. Purification by flash chromatography eluting with EtOAc:hexanes solvent mixtures yielded the product.
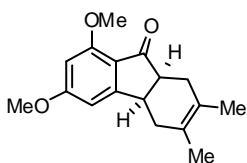
(4aR*,9aS*)-1,4,4a,9a-Tetrahydro-6,8-dimethoxy-2,3-dimethylfluoren-9-one (3.39): Prepared by reaction of alkylidene **3.34** and 2,3-dimethylbutadiene. Isolated as a yellow oil by flash chromatography eluting with 1:4 EtOAc:hexanes in 86% yield. The oil solidified upon two weeks storage at rt in air, with no change in the NMR spectra. Spectral data were identical to those obtained above.
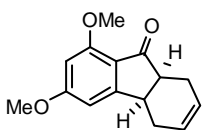
(4bR*,8aS*)-4b,5,8,8a-Tetrahydro-1,3-dimethoxyfluoren-9-one (3.37): Prepared by reaction of alkylidene **3.34** with butadiene sulfone (5.0 equiv). Isolated as a clear, colourless oil by flash chromatography eluting with 3:7 EtOAc:hexanes in 84% yield. Spectral data were identical to those obtained above.
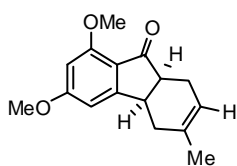
(4aR*,9aS*)-1,4,4a,9a-Tetrahydro-6,8-dimethoxy-3-methyl-fluoren-9-one (3.40): Prepared by reaction of alkylidene **3.34** and isoprene. By analysis of the crude NMR after the DA reaction, the adduct was formed as 9:1 mixture of regioisomers. After the FC reaction, only the major product could be isolated by flash chromatography eluting with 1:9 to 1:4 EtOAc:hexanes as a yellow oil in 74% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 6.47 (d, J = 1.3 Hz, 1H), 6.25 (d, J = 1.7 Hz, 1H), 5.46 (dd, J = 5.7 Hz, 4.2 Hz, 1H), 3.84 (s, 6H), 3.47 (dd, J = 7.3 Hz, 4.8 Hz, 1H), 2.76 (dt, J = 4.5 Hz, 2.9 Hz, 1H), 2.46-2.36 (m, 2H), 2.27-2.18 (m, 1H), 2.09 (dd, J = 14.9 Hz, 4.6 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 205.1 (C), 167.0 (C), 163.6 (C), 158.8 (C), 135.1 (C), 121.0 (CH), 119.8 (C), 100.4 (CH), 97.2 (CH), 55.7 (2X CH$_3$), 46.8 (CH), 38.0 (CH), 33.7 (CH$_2$), 25.1 (CH$_2$), 23.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{16}$H$_{18}$O$_3$ (M$^+$): 258.1256 Found: 258.1255.
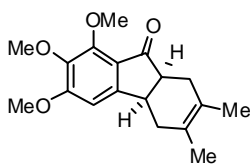
4aR*,9aS*)-1,4,4a,9a-Tetrahydro-6,7,8-trimethoxy-2,3-dimethylfluoren-9-one (3.41): Prepared by reaction of alkylidene

S3.1 with 2,3-dimethylbutadiene. Isolated by flash chromatography eluting with 1:4 EtOAc:hexanes as a clear, colourless oil in 90% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 6.65 (s, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.81 (s, 3H), 3.42 (dd, J = 7.3 Hz, 4.8 Hz, 1H), 2.76 (dt, J = 7.5 Hz, 4.9 Hz, 1H), 2.47 (dd, J = 14.6 Hz, 6.7 Hz, 1H), 2.32 (**A**BX, J = 14.8 Hz, 4.7 Hz, 1H), 2.23 (A**B**X, J = 14.9 Hz, 7.1 Hz, 1H), 2.05 (dd, J = 14.6, 4.7 Hz, 1H), 1.61 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 205.1 (C), 159.6 (C), 156.6 (C), 150.8 (C), 140.5 (C), 127.3 (C), 125.8 (C), 123.3 (C), 102.2 (CH), 61.8 (CH$_3$), 61.3 (CH$_3$), 56.2 (CH$_3$), 47.7 (CH), 38.2 (CH), 35.8 (CH$_2$), 31.6 (CH$_2$), 19.4 (CH$_3$), 19.2 (CH$_3$); HRMS(EI) m/z calcd for C$_{18}$H$_{22}$O$_4$ (M$^+$): 302.1518 Found: 302.1512.
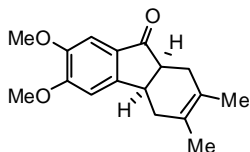
(4aR*,9aS*)-1,4,4a,9a-Tetrahydro-6,7-dimethoxy-2,3-dimethyl-fluoren-9-one (3.42): Prepared by reaction of alkylidene **1.33** with 2,3-dimethylbutadiene. Isolated by flash chromatography eluting with 1:4 EtOAc:hexanes as a white solid in 76% yield. M.p. 102-104 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.09 (s, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.49 (dt, J = 7.0 Hz, 4.6 Hz, 1H), 2.80 (dt, J = 7.1 Hz, 4.8 Hz, 1H), 2.47 (dd, J = 14.3 Hz, 6.7 Hz, 1H), 2.34 (**A**BX, J = 14.8 Hz, 4.9 Hz, 1H), 2.27 (A**B**X, J = 14.8 Hz, 6.7 Hz, 1H), 2.09 (dd, J = 14.5 Hz, 4.4 Hz, 1H), 1.61 (s, 3H), 1.48 (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 207.9 (C), 155.5 (C), 153.7 (C), 149.4 (C), 130.5 (C), 127.3 (C), 125.9 (C), 106.0 (CH), 103.6 (CH), 56.2 (CH$_3$), 56.0 (CH$_3$), 47.4 (CH), 38.3 (CH), 35.6 (CH$_2$), 31.7 (CH$_2$), 19.5 (CH$_3$), 19.2 (CH$_3$); HRMS(EI) m/z calcd for C$_{17}$H$_{20}$O$_3$ (M$^+$): 272.1412 Found: 272.1409.
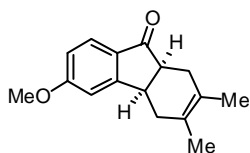
(4aR*,9aS*)-1,4,4a,9a-Tetrahydro-6-methoxy-2,3-dimethyl-fluoren-9-one (*para*-3.43): Prepared by reaction of alkylidene **1.33** with 2,3-dimethylbutadiene and formed as the major regioisomer of a 67:33 mixture. Isolated as the first product to elute from flash chromatography eluting with 1:4 EtOAc:hexanes as a white solid in 46% yield. M.p. 116-118 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) 7.60 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 6.85 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 3.86 (s, 3H), 3.50 (dd, J = 7.3 Hz, 4.4 Hz, 1H), 2.80 (dt, J = 7.5 Hz, 4.8 Hz, 1H), 2.47 (dd, J = 14.5 Hz, 6.8 Hz, 1H), 2.33 (**A**BX, J = 14.8 Hz, 4.5 Hz, 1H), 2.27 (A**B**X, J = 14.8 Hz, 7.2 Hz, 1H), 2.10 (dd, J = 14.7 Hz, 4.5 Hz), 1.60 (s, 3H), 1.49 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) 207.4 (C), 165.2 (C), 161.4 (C), 130.9 (C), 127.2 (C),

125.9 (C), 124.8 (CH), 115.1 (CH), 108.4 (CH), 55.5 (CH$_3$), 47.3 (CH), 38.5 (CH), 35.5 (CH$_2$), 31.5 (CH$_2$), 19.4 (CH$_3$), 19.1 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{16}$H$_{18}$O$_2$ (M$^+$): 242.1307 Found: 242.1309.
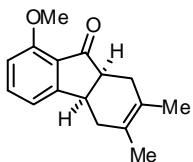
(4a*R**,9a*S**)-1,4,4a,9a-Tetrahydro-8-methoxy-2,3-dimethylfluoren-9-one (*ortho*-3.43): Prepared by reaction of alkylidene **1.33** with 2,3-dimethylbutadiene and formed as the minor product of a 67:33 mixture. Isolated as the second product to elute flash chromatography eluting with 1:4 EtOAc:hexanes as a yellow wax in 18% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) 7.49 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 3.50 (dt, *J* = 7.3 Hz, 4.7 Hz, 1H), 2.78 (dt, *J* = 7.5 Hz, 4.5 Hz, 1H), 2.46 (dd, *J* = 14.7 Hz, 6.8 Hz, 1H), 2.36 (**A**BX, *J* = 14.8 Hz, 4.3 Hz, 1H), 2.26 (A**B**X, *J* = 14.8 Hz, 7.2 Hz, 1H), 2.10 (dd, *J* = 14.6 Hz, 4.3 Hz), 1.61 (s, 3H), 1.47 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) 207.0 (C), 161.4 (C), 157.4 (C), 136.3 (CH), 127.3 (C), 125.8 (C), 125.7 (CH), 117.0 (CH), 108.7 (CH), 55.7 (CH$_3$), 47.4 (CH), 38.1 (CH), 35.6 (CH$_2$), 31.6 (CH$_2$), 19.4 (CH$_3$), 19.2 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{16}$H$_{18}$O$_2$ (M$^+$): 242.1307 Found: 242.1309.

One-Pot Synthesis of Benzotetrahydrofluorenones 3.48-3.51:
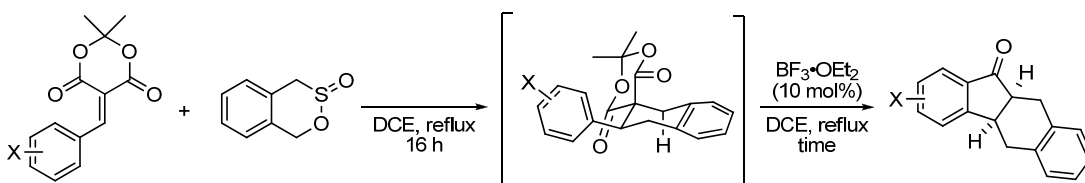
General Procedure B: A flame-dried round bottom flask equipped with a condenser under N$_2$ with an outlet for SO$_2$ was charged with Meldrum's acid alkylidene (200 mg, 1.0 equiv). Sultine **3.44** (1.1 equiv) was weighed into a vial, and rinsed into the flask with DCE (0.2 M relative to the alkylidene). The contents were heated to reflux for 16 hours and cooled to rt before removing a 50 µL aliquot to check the reaction progress by ^{1}H NMR. A solution of BF$_3$•OEt$_2$ in DCE (0.1 equiv/100 µL) was added to the flask, as well as enough DCE to bring the total volume to 0.15 M. The reaction was heated to reflux for

the indicated times and then cooled to rt. The remainder of the procedure is identical to A.
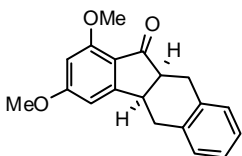
(4b*S**,10a*R**)-1,3-Dimethoxy-5,10,10a,11-tetrahydro-4b*H*-benzo[*b*]-fluoren-11-one (3.48): Prepared from alkylidene **3.34** with FC acylation running for 3.5 hours. Isolated by flash chromatography eluting with 1:4 EtOAc:hexanes as a white powder in 87% yield. M.p. 183-185 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.14-7.01 (m, 4H), 6.55 (s, 1H), 6.20 (d, J = 1.3Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.60 (q, J = 6.7 Hz, 1H), 3.15 (dd, J = 14.3 Hz, 6.5 Hz, 1H), 3.05-2.84 (m, 3H), 2.73 (dd, J = 14.3 Hz, 6.6 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 204.0 (C), 167.2 (C), 162.8 (C), 159.1 (C), 137.2 (C), 136.8 (C), 127.6 (CH), 127.2 (CH), 126.6 (CH), 126.3 (CH), 119.6 (C), 100.6 (CH), 97.4 (CH), 55.68 (CH$_3$), 55.66 (CH$_3$), 47.6 (CH), 38.7 (CH), 34.4 (CH$_2$), 30.6 (CH$_2$); HRMS(EI) *m/z* calcd for C$_{19}$H$_{18}$O$_3$ (M$^+$): 294.1256 Found: 294.1255.
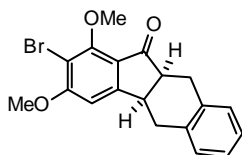
(4b*S**,10a*R**)-2-Bromo-1,3-dimethoxy-5,10,10a,11-tetrahydro-4b*H*-benzo[*b*]fluoren-11-one (3.49): Prepared by reaction of alkylidene **S3.2** with FC acylation running for 4.0 hours. Isolated by flash chromatography eluting with 1:4 EtOAc:hexanes as a white powder in 74% yield. M.p. 181-182 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.13-6.99 (m, 4H), 6.77 (s, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 3.67 (q, J = 6.6 Hz, 1H), 3.19 (dd, J = 14.3 Hz, 6.5 Hz, 1H), 3.09-2.90 (m, 3H), 2.76 (dd, J = 14.3 Hz, 6.1 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 202.9 (C), 162.4 (C), 160.6 (C), 156.1 (C), 136.8 (C), 136.4 (C), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.6 (CH), 123.5 (C), 106.6 (CH), 102.8 (CH), 61.9 (CH$_3$), 56.8 (CH$_3$), 47.7 (CH), 38.9 (CH), 34.5 (CH$_2$), 30.8 (CH$_2$); HRMS(EI) *m/z* calcd for C$_{19}$H$_{17}$^{79}BrO$_3$ (M$^+$): 372.0361 Found: 372.0355.
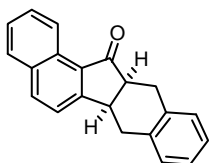
(6b*S**,12a*R**)-7,12,12a,13-Tetrahydro-6b*H*-dibenzo[*a,h*]fluoren-13-one (3.50): Prepared by reaction of alkylidene **1.46** with FC acylation running for 5.5 hours. Isolated by flash chromatography eluting with 1:9 EtOAc:hexanes as a white powder in 71% yield. M.p. 155-156 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 9.08 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.84 (d, J

= 8.1 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 1.0 Hz, 1H), 7.53-7.48 (m, 1H), 7.17 (d, J = 6.8 Hz, 1H), 7.10-7.01 (m, 3H), 3.86 (q, J = 6.6 Hz, 1H), 3.29 (dd, J = 14.4 Hz, 6.6 Hz, 1H), 3.21-3.02 (m, 3H), 2.89 (dd, J = 14.4 Hz, 6.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 208.6 (C), 160.5 (C), 136.9 (C), 136.7 (C), 136.2 (CH), 131.4 (C), 129.0 (C), 129.0 (CH), 128.9 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 124.2 (CH), 122.5 (CH), 47.5 (CH), 39.0 (CH), 34.1 (CH$_2$), 30.8 (CH$_2$); HRMS(EI) m/z calcd for C$_{21}$H$_{16}$O (M$^+$): 284.1201 Found: 284.1203.
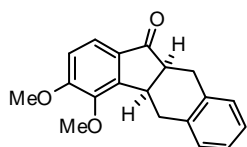
(4bS*,10aR*)-3,4-Dimethoxy-5,10,10a,11-tetrahydro-4bH-benzo[b]-fluoren-11-one (3.51): Prepared by reaction of alkylidene **S3.3** and sultine **3.44** (2.0 equiv) with FC acylation running for 6.5 hours. Isolated by flash chromatography eluting with 1:9 EtOAc:hexanes as a white powder in 52% yield. M.p. 133-135 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.40 (d, J = 8.4 Hz, 1H), 7.16-7.06 (m, 4H), 6.91 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.83 (q, J = 7.0 Hz, 1H), 3.27 (dd, J = 14.3 Hz, 6.5 Hz, 1H), 3.10-2.84 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) 206.7 (C), 158.1 (C), 149.9 (C), 145.8 (C), 137.5 (C), 137.0 (C), 131.2 (C), 127.45 (CH), 127.35 (CH), 126.5 (CH), 126.4 (CH), 120.1 (CH), 112.7 (CH), 60.5 (CH$_3$), 56.1 (CH$_3$), 47.5 (CH), 37.2 (CH), 32.9 (CH$_2$), 30.5 (CH$_2$); HRMS(EI) m/z calcd for C$_{19}$H$_{18}$O$_3$ (M$^+$): 294.1256 Found: 294.1256.

Synthesis of Diels-Alder adducts 3.53 and 3.54 and Tetrahydrofluorenone 3.55:
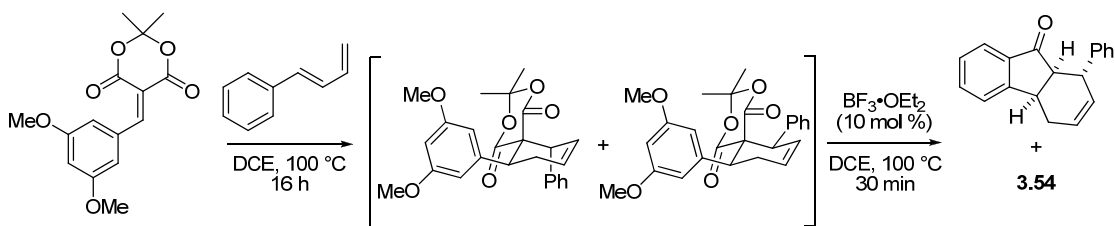
To confirm the stereochemistry of **3.53** and **3.54**, a large-scale Diels-Alder reaction was performed in order to isolate each product. Crystallization of each by slow evaporation of a saturated EtOH solution gave crystals suitable for X-ray analysis. X-Ray data tables can be found at the conclusion of this section.
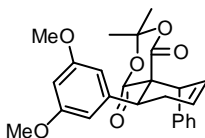
(7S*,11S*)-11-(3,5-Dimethoxyphenyl)-3,3-dimethyl-7-phenyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (3.53): An oven-dried Schlenk flask cooled under N_2 was charged with alkylidene **3.34** (3.06 g, 105 mmol, 1.0 equiv). (*E*)-1-phenylbutadiene **3.52**[149] (1.5 g, 115 mmol, 1.1 equiv) was added to the chamber and washed into the flask with DCE (52 mL, 0.2 M). The flask was sealed, heated to 100 °C for 16 hours, then cooled to rt. The solution was rinsed into a flask with EtOAc and concentrated by rotary evaporation. The residue was purified by flash chromatography eluting with 1:4 EtOAc:hexanes, with **3.53** eluting second to give a white solid. M.p. 148-150 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.32-7.23 (m, 5H), 6.45 (d, *J* = 2.2 Hz, 2H), 6.30 (d, *J* = 2.2 Hz, 1H), 6.26-6.20 (m, 1H), 5.81 (dt, *J* = 10.2 Hz, 2.0 Hz, 1H), 3.98 (app d, *J* = 2.0 Hz, 1H), 3.70 (s, 6H), 3.56 (dd, *J* = 9.5 Hz, 6.3 Hz, 1H), 3.01-2.90 (m, 1H), 2.65-2.55 (m, 1H), 1.49 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 167.7 (C), 166.3 (C), 160.7 (C), 142.7 (C), 138.6 (C), 130.0 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 125.0 (CH), 107.6 (CH), 104.9 (C), 99.9 (CH), 59.7 (C), 55.3 (CH$_3$), 48.9 (CH), 41.8 (CH), 30.0 (CH$_2$), 29.3 (CH$_3$), 28.8 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{25}$H$_{26}$O$_6$ (M$^+$): 422.1729 Found: 422.1716.
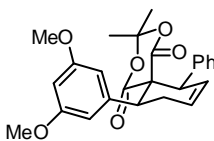
(7R*,11S*)-11-(3,5-Dimethoxyphenyl)-3,3-dimethyl-7-phenyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (3.54): Prepared from the above reaction as the first product to elute and isolated as white solid. M.p. 167-169 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.31-7.18 (m, 5H), 6.40 (d, *J* = 2.2 Hz, 2H), 6.33 (d, *J* = 2.2 Hz, 1H), 6.15-6.11 (m, 1H), 5.81 (dd, *J* = 10.2 Hz, 2.0 Hz, 1H), 4.50 (br s, 1H), 3.83-3.72 (m, 1H), 3.72 (s, 6H), 3.06-2.95 (m, 1H), 2.47 (dt, *J* = 18.3 Hz, 5.2 Hz, 1H), 0.76 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 169.5 (C), 163.8 (C), 160.9 (C), 141.2 (C), 138.8 (C), 129.5 (CH), 128.8 (CH), 128.02 (CH), 127.98 (CH), 126.3 (CH), 106.8 (CH), 105.5 (C), 100.4 (CH), 59.8 (C), 55.3 (CH$_3$), 50.7 (CH), 47.8 (CH), 29.4 (CH$_2$), 28.6 (CH$_3$), 28.5 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{25}$H$_{26}$O$_6$ (M$^+$): 422.1729 Found: 422.1736.

The stereochemistry of the two adducts was assigned based on the following data: a) NOESY correlations detailed in Table 3.1 and b) the strong anisotropic shielding of the

Meldrum's acid methyl signals in the endo adduct (0.76 and 0.58 ppm) vs that found in the exo adduct (1.49 and 1.15 ppm)
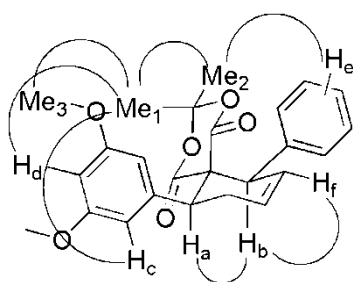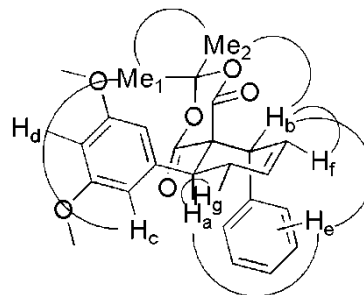
Endo adduct **3.54**		Exo adduct **3.53**	
Proton (δ)	nOe w/ proton (δ)	Proton (δ)	nOe w/ proton (δ)
H_b (4.50)	H_a (3.83-3.72), H_e (7.31-7.18), H_f (5.81)	H_a (3.56)	H_c (6.45), H_e (7.32-7.23), H_g (2.65-2.55)
Me_1 (0.76)	H_c (6.33), H_d (6.33), Me_2 (0.58), Me_3 (3.72)	H_b (3.98)	H_e (7.32-7.23), H_f (5.81), Me_2 (1.49)
Me_2 (0.58)	H_e (7.31-7.18), Me_1 (0.76)	Me_1 (1.15)	H_c (6.45), Me_2 (1.50)
		Me_2 (1.49)	H_b (3.98), Me_1 (1.15)

Table 3.1. NOESY correlations of endo adduct **3.54** and exo adduct **3.53** relevant to the assignment of relative stereochemistry
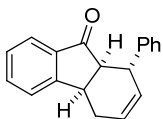
(1R*,4aR*,9aR*)-1,4,4a,9a-Tetrahydro-6,8-dimethoxy-1-phenylfluoren-9-one (3.55): Prepared by reaction of alkylidene **3.34** and diene **3.52** according to General Procedure A. Purification by flash chromatography eluting with 1:4 EtOAc:hexanes gave endo adduct **3.54** as the first product to elute in 29% yield (^{1}H NMR matched that reported above). The fluorenone **3.55** eluted second, and was isolated as a clear, colourless oil in 53% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 7.37-7.27 (m, 4H), 7.22-7.19 (m, 1H), 6.48 (d, J = 1.5 Hz, 1H), 6.29 (d, J = 1.8 Hz, 1H), 6.00-5.94 (m, 1H), 5.89-5.84 (m, 1H), 4.05 (br s, 1H), 3.88-3.80 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.49 (dd, J = 13.6 Hz, 7.8 Hz, 1H), 3.00 (dd, J = 7.8 Hz, 3.2 Hz, 1H), 2.63-2.55 (m, 1H), 2.09 (dt, J = 14.7 Hz, 4.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 202.4 (C), 167.0 (C), 163.4 (C), 159.0 (C), 144.5 (C), 130.9 (CH), 128.4 (CH), 127.7 (CH), 126.3 (CH), 125.9 (CH), 118.1 (C), 100.6 (CH), 97.4 (CH), 55.6 (CH$_3$), 54.9 (CH), 40.0 (CH), 36.5 (CH), 29.4 (CH$_2$); HRMS(EI) m/z calcd for C$_{21}$H$_{20}$O$_3$ (M$^+$): 320.1412 Found: 320.1416.

Synthesis of Endo Adduct 3.58 and Tetrahydrofluorenones 3.59 and 3.60:
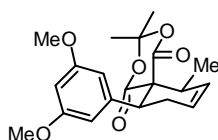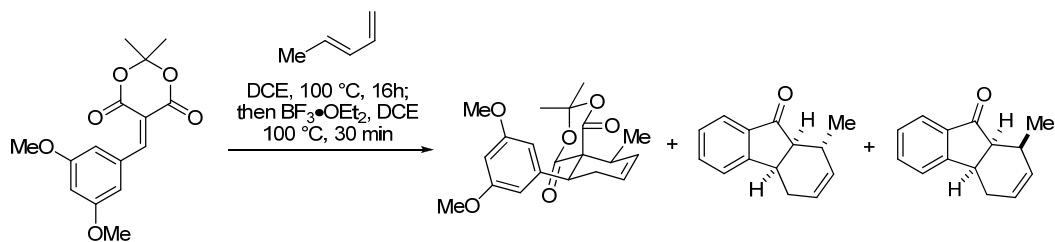
(7S*,11S*)-11-(3,5-Dimethoxyphenyl)-3,3,7-trimethyl-2,4-dioxaspiro-[5.5]undec-8-ene-1,5-dione (3.58): Prepared by reaction of alkylidene **3.34** with (*E*)-1,3-pentadiene **3.56** according to General Procedure A. Adduct **3.58** eluted first by flash chromatography eluting with 3:17 EtOAc:hexanes, and was isolated as a white powder in 4% yield. M.p. 209-211 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.39 (d, *J* = 2.2 Hz, 2H), 6.32 (t, *J* = 2.2 Hz, 1H), 5.96-5.90 (m, 1H), 5.48 (dd, *J* = 10.2 Hz, 2.1 Hz, 1H), 3.73 (s, 6H), 3.59 (dd, *J* = 11.8 Hz, 5.6 Hz, 1H), 3.23 (br s, 1H), 2.95-2.85 (m, 1H), 2.35 (dt, *J* = 18.2 Hz, 5.3 Hz, 1H), 1.56 (s, 3H), 1.07 (d, *J* = 7.4 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 170.3 (C), 164.5 (C), 161.0 (C), 142.0 (C), 127.7 (CH), 126.4 (CH), 107.1 (CH), 105.7 (C), 100.3 (CH), 58.7 (C), 55.4 (CH$_3$), 46.2 (CH), 41.0 (CH), 29.6 (CH$_3$), 29.2 (CH$_2$), 28.9 (CH$_3$), 16.9 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{20}$H$_{24}$O$_6$ (M$^+$): 360.1573 Found: 360.1583.

Increasing the polarity of the mobile phase to 1:4 EtOAc:hexanes and continued elution yielded a large number of mixed fractions containing both **3.59** and **3.60** ratio which were combined to give a 83% yield as 69:31 mixture in favour of **3.59**.
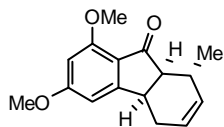
(1R*,4aR*,9aS*)-1,4,4a,9a-tetrahydro-6,8-dimethoxy-1-methylfluoren-9-one (3.59): Repurification of the above mixture by flash column chromatography gave the major product **3.59** as a white solid in 39% yield. M.p. 63-64 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.46 (d, *J* = 0.9 Hz, 1H), 6.27 (s, 1H), 5.73 (br s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.38 (dd, *J* = 14.9 Hz, 7.4 Hz, 1H), 2.70-2.58 (m, 1H), 2.54-2.41 (m, 1H), 1.94-1.87 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 204.0 (C), 167.0 (C), 163.4 (C), 159.1 (C), 135.1 (CH), 125.5 (CH), 118.8 (C), 100.5 (CH), 97.4 (CH), 55.70 (CH$_3$), 55.66 (CH$_3$), 54.2 (CH),

37.7 (CH), 30.5 (CH), 28.9 (CH$_2$), 20.5 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{16}$H$_{18}$O$_3$ (M$^+$): 258.1256 Found: 258.1265.
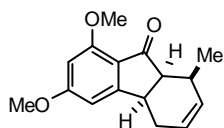
(1S*,4aR*,9aS*)-1,4,4a,9a-tetrahydro-6,8-dimethoxy-1-methyl-fluoren-9-one (3.60): Isolated as the first product to elute from the above column as a white powder in 14% yield. M.p. 140-142 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.44 (s, 1H), 6.29 (s, 1H), 5.74 (dt, *J* = 9.8 Hz, 2.6 Hz, 1H), 5.58 (br d, *J* = 10.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.98-2.89 (m, 1H), 2.69-2.57 (m, 2H), 2.26-2.16 (m, 1H), 2.06 (dd, *J* = 10.6 Hz, 9.6 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 201.4 (C), 166.5 (C), 158.9 (C), 157.8 (C), 136.1 (CH), 125.1 (CH), 118.6 (C), 99.7 (CH), 97.2 (CH), 59.1 (CH), 55.7 (CH$_3$), 41.0 (CH), 32.7 (CH), 29.0 (CH$_2$), 19.4 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{16}$H$_{18}$O$_3$ (M$^+$): 258.1256 Found: 258.1255.

Preparation of Arylbutadienes 3.61 and 3.62:
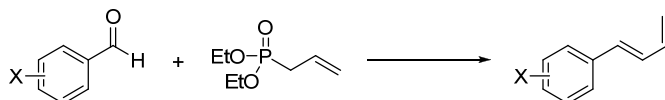
(*E*)-1-Aryl-1,3-butadienes were prepared from the appropriate benzaldehyde and diethylallylphosphonate according to the procedure of Wang and West.[128] They were stored in a fridge in the dark for up to two weeks.
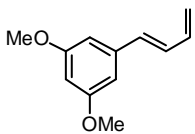
5-((*E*)-Buta-1,3-dienyl)-1,3-dimethoxybenzene (3.61): Prepared from 3,5-dimethoxybenzaldehyde and isolated as a clear, colourless oil in 33% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 6.75 (dd, *J* = 15.5 Hz, 10.5 Hz, 1H), 6.55 (brs, 2H), 6.51 (brs, 1H), 6.45-6.35 (m, 2H), 5.33 (d, *J* = 16.8 Hz, 1H), 5.17 (d, *J* = 9.7 Hz, 1H), 3.79 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) 160.9 (C), 139.1 (C), 137.0 (CH), 132.8 (CH), 130.1 (CH), 117.9 (CH), 104.4 (CH), 100.0 (CH), 55.3 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{12}$H$_{14}$O$_2$ (M$^+$): 190.0994 Found: 190.1000.
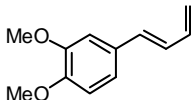
4-((*E*)-Buta-1,3-dienyl)-1,2-dimethoxybenzene (3.62): Prepared from 3,4-dimethoxybenzaldehyde and isolated as a clear, colourless oil in

23% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 6.94 (s, 1H), 6.93 (overlapping d, 1H, J = 8.2 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.66 (dd, J = 15.5 Hz, 10.2 Hz, 1H), 6.53-6.40 (m, 2H), 5.28 (d, J = 16.9 Hz, 1H), 5.11 (d, J = 9.8 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 149.0 (C), 148.8 (C), 137.2 (CH), 132.6 (CH), 130.1 (C), 127.8 (CH), 119.8 (CH), 116.6 (CH$_2$), 111.0 (CH), 108.5 (CH), 55.8 (CH$_3$), 55.7 (CH$_3$); HRMS(EI) m/z calcd for C$_{12}$H$_{14}$O$_2$ (M$^+$): 190.0994 Found: 190.0987.

Synthesis of Tetrahydrofluorenones 3.63-3.66 and Endo Adducts 3.67-3.70:
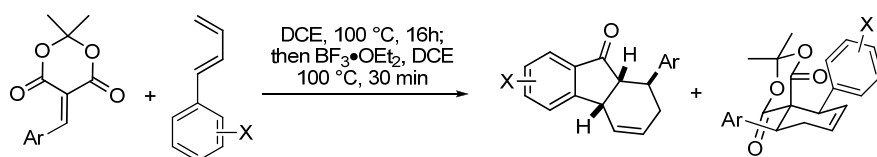
General Procedure C: The reactions were performed and worked up according to General Procedure A. Separation of the two products was achieved by flash chromatography eluting with 1:9 EtOAc:hexanes to elute the unreacted endo DA adduct. The polarity of the mobile phase was increased to 1:4 EtOAc:hexanes and elution continued to isolate the fluorenone product.
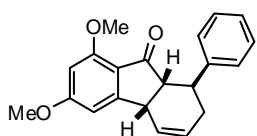
(1S*,4aS*,9aR*)-1,2-Dihydro-6,8-dimethoxy-1-phenyl-4aH-fluoren-9(9aH)-one (3.63): Prepared by reaction of alkylidene **1.29** with diene **3.61**; the Diels:Alder reaction gave an exo:endo ratio of 66:34. Isolated as a yellow oil in 58% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 7.35-7.16 (m, 5H), 6.52 (d, J = 1.4 Hz, 1H), 6.30 (d, J = 1.7 Hz, 1H), 5.94 (br d, J = 10.0 Hz, 1H), 5.81-5.74 (m, 1H), 3.88-3.87 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.62 (dd, J = 9.5 Hz, 4.0 Hz), 3.09-3.00 (dd, J = 6.1 Hz, 4.3 Hz, 1H), 2.34 (m, 1H), 2.21 (br d, J = 17.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 201.8 (C), 167.0 (C), 161.0 (C), 159.4 (C), 145.2 (C), 128.3 (CH), 127.8 (CH), 127.7 (CH), 126.4 (CH), 126.0 (CH), 117.0 (C), 100.9 (CH), 97.6 (CH), 55.8 (CH$_3$), 55.7 (CH$_3$), 53.4 (CH), 38.7 (CH), 37.7 (CH), 28.3 (CH$_2$); HRMS(EI) m/z calcd for C$_{21}$H$_{20}$O$_3$ (M$^+$): 320.1412 Found: 320.1410.
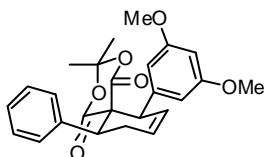
(7R*,11S*)-7-(3,5-Dimethoxyphenyl)-3,3-dimethyl-11-phenyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (3.67): Isolated as a white powder in 20% yield. M.p. 145-146 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.31-7.22 (m, 5H), 6.38 (d, J = 2.2 Hz, 2H), 6.33 (t, J = 2.2 Hz, 1H), 6.17-6.12 (m, 1H), 5.83 (dd, J =10.3 Hz, 1.7 Hz, 1H), 4.48 (brs, 1H), 3.79 (dd, J = 11.7 Hz, 5.5 Hz, 2H), 3.72 (s, 6H), 3.09-3.00 (m, 1H), 2.46 (dt, J = 18.3 Hz, 5.2 Hz), 0.71 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 169.6 (C), 163.9 (C), 160.9 (C), 141.1 (C), 138.8 (C), 128.9 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 126.3 (CH), 107.2 (CH), 105.5 (C), 100.6 (CH), 59.9 (C), 55.4 (CH$_3$), 50.3 (CH), 47.7 (CH), 29.1 (CH$_2$), 28.7 (CH$_3$), 28.2 (CH$_3$); HRMS(EI) m/z calcd for C$_{25}$H$_{26}$O$_6$ (M$^+$): 422.1729 Found: 422.1734.
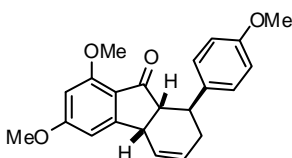
(1S*,4aS*,9aR*)-1,2-Dihydro-6,8-dimethoxy-1-(4-methoxyphenyl)-4aH-fluoren-9(9aH)-one (3.64): Prepared by the reaction of alkylidene **1.30** with diene **3.61**; the Diels-Alder reaction gave an exo:endo ratio of 69:31. Isolated as a yellow oil in 53% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 7.24 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.52 (d, J = 1.1 Hz, 1H), 6.29 (d, J = 1.7 Hz, 1H), 5.94 (br d, J = 9.9 Hz 1H), 5.81-5.75 (m, 1H), 3.88-3.80 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3,77 (s, 3H), 3.53 (dd, J = 9.6 Hz, 4.5 Hz, 1H), 3.04 (dd, J = 6.3 Hz, 4.7 Hz, 1H), 2.34-2.28 (m, 1H), 2.24 (br d, J = 18.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 201.9 (C), 167.0 (C), 161.0 (C), 159.4 (C), 157.8 (C), 137.2 (C), 128.6 (CH), 127.6 (CH), 126.6 (CH), 117.1 (C), 113.6 (CH), 100.9 (CH), 97.5 (CH), 55.8 (CH$_3$), 55.7 (CH$_3$), 55.2 (CH$_3$), 53.6 (CH), 38.7 (CH), 37.1 (CH), 28.7 (CH$_2$); HRMS(EI) m/z calcd for C$_{22}$H$_{22}$O$_4$ (M$^+$): 350.1518 Found: 350.1519.
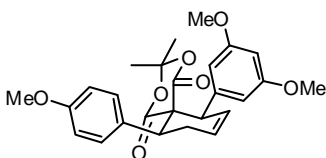
(7R*,11S*)-7-(3,5-Dimethoxyphenyl)-11-(4-methoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (3.68): Isolated as a white powder in 24% yield. M.p. 147-149 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.14 (d, J = 8.7 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.37 (d, J = 2.2 Hz, 2H), 6.32 (t, J = 2.2 Hz, 1H), 6.15-6.10 (m, 1H), 5.81 (dd, J =10.2 Hz, 1.8 Hz, 1H), 4.46 (br s, 1H), 3.77-3.72 (m, 1H), 3.74 (s, 3H), 3.72 (s, 6H), 3.03-2.94 (m, 1H), 2.42 (dt, J = 18.4 Hz, 5.2 Hz, 1H) 0.71 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 169.8 (C), 164.1 (C), 161.0 (C), 159.4 (C), 141.2 (C), 130.9 (C),

130.0 (CH), 128.1 (CH), 126.3 (CH), 114.1 (CH), 107.2 (CH), 105.5 (C), 100.6 (CH), 60.1 (C), 55.4 (CH$_3$), 55.2 (CH$_3$), 50.4 (CH), 47.0 (CH), 29.4 (CH$_2$), 28.8 (CH$_3$), 28.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{26}$H$_{28}$O$_7$ (M$^+$): 452.1835 Found: 452.1845.
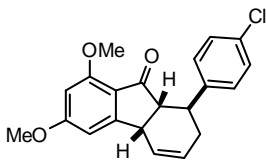
(1S*,4aS*,9aR*)-1-(4-Chlorophenyl)-1,2-dihydro-6,8-dimethoxy-4aH-fluoren-9(9aH)-one (3.65): Prepared by the reaction of alkylidene **1.38** with diene **3.61**; the Diels-Alder reaction gave an exo:endo ratio of 64:36. Isolated as a yellow oil in 51% yield. ^{1}H NMR (CDCl$_3$, 300 MHz)7.24 (s, 4H), 6.51 (d, J = 1.4 Hz, 1H), 6.29 (d, J = 1.8 Hz, 1H), 5.96 (br d, J = 10.0 Hz, 1H), 5.80-5.75 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82-3.81 (m, 1H), 3.50 (dd, J = 9.9 Hz, 4.7 Hz, 1H), 3.04 (dd, J = 6.2 Hz, 5.5 Hz, 1H), 2.29 (m, 1H), 2.19 (br d, J = 17.5 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 201.4 (C), 167.1 (C), 160.8 (C), 159.4 (C), 143.5 (C), 131.7 (C), 129.0 (CH), 128.3 (CH), 127.7 (CH), 126.2 (CH), 116.8 (C), 100.9 (CH), 97.5 (CH), 55.7 (CH$_3$), 53.2 (CH), 38.5 (CH), 37.5 (CH), 28.5 (CH$_2$); HRMS(EI) m/z calcd for C$_{21}$H$_{19}$ClO$_3$ (M$^+$): 354.1023 Found: 354.1023.
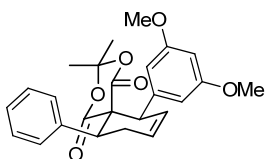
(7R*,11S*)-11-(4-Chlorophenyl)-7-(3,5-dimethoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (3.69): Isolated as a white powder in 24% yield. M.P. 161-163 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.26 (d, J = 8.5 Hz, 2H), 7.16 (d, J =8.5 Hz, 2H), 6.36 (d, J = 2.2 Hz, 2H), 6.33 (t, J = 2.2 Hz, 1H), 6.15-6.08 (m, 1H), 5.82 (dd, J =10.3 Hz, 2.0 Hz, 1H), 4.54 (brs, 1H), 3.79-3.72 (m, 1H), 3.72 (s, 6H), 3.09-2.91 (m, 1H), 2.42 (dt, J = 18.4 Hz, 5.3 Hz) 0.74 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 169.4 (C), 163.8 (C), 140.9 (C), 137.3 (C), 134.0 (C), 130.3 (CH), 128.9 (CH), 127.7 (CH), 126.4 (CH), 107.2 (CH), 105.6 (C), 100.6 (CH), 59.7 (C), 55.4 (CH$_3$), 50.3 (CH), 47.3 (CH), 29.2 (CH$_2$), 28.7 (CH$_3$), 28.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{25}$H$_{25}$ClO$_6$ (M$^+$): 456.1340 Found: 456.1338.
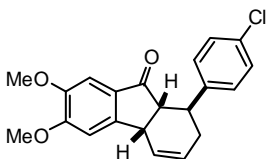
(1S*,4aS*,9aR*)-1,2-Dihydro-6,7-dimethoxy-1-phenyl-4aH-fluoren-9(9aH)-one (3.66): Prepared by the reaction alkylidene **1.29** with diene **3.62**; the Diels-Alder reaction gave an exo:endo ratio of 65:35. The initially isolated product was contaminated with ~10% of endo adduct

3.70. Repurification by flash chromatography eluting with 1:19 acetone:toluene gave the pure product as a yellow oil in 45% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 7.32-7.20 (m, 5H), 7.17 (s, 1H), 6.92 (s, 1H), 6.05 (dd, J = 10.0 Hz, 1.8 Hz, 1H), 5.84-5.79 (m, 1H), 3.97-3.89 (br s, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.44 (dd, J = 10.6 Hz, 5.3 Hz, 1H), 3.12 (t, J = 6.0 Hz, 1H), 2.27 (t, J = 4.4 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 204.7 (C), 155.6 (C), 151.3 (C), 149.6 (C), 144.8 (C), 128.4 (CH), 127.8 (CH), 127.7 (CH), 126.5 (CH), 126.3 (CH), 106.3 (CH), 104.7 (CH), 56.3 (CH$_3$), 56.1 (CH$_3$), 53.2 (CH), 39.0 (CH), 38.7 (CH), 29.2 (CH$_2$); HRMS(EI) m/z calcd for C$_{21}$H$_{20}$O$_3$ (M$^+$): 320.1412 Found: 320.1410.
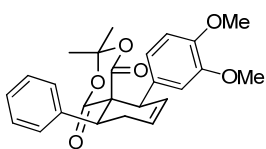
(7R*,11S*)-7-(3,4-Dimethoxyphenyl)-3,3-dimethyl-11-phenyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (3.70): Isolated as a white solid in 21% yield. M.P. 160-162 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.30-7.21 (m, 5H), 7.13-7.09 (m, 1H), 6.76 (s, 2H), 6.73 (s, 1H), 6.17-6.11 (m, 1H), 5.82 (dd, J =10.2 Hz, 2.0 Hz, 1H), 4.49 (br s, 1H), 3.83-3.76 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.09-2.97 (m, 1H), 2.46 (dt, J = 18.3 Hz, 5.2 Hz), 0.65 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 169.8 (C), 164.1 (C), 149.1 (C), 148.7 (C), 138.9 (C), 131.3 (C), 128.92 (CH), 128.87 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 126.7 (CH), 121.8 (C), 112.3 (CH), 111.1 (C), 105.5 (CH), 60.3 (C), 55.9 (CH$_3$), 49.9 (CH), 47.6 (CH), 29.1 (CH$_2$), 28.9 (CH$_3$), 28.2 (CH$_3$); HRMS(EI) m/z calcd for C$_{25}$H$_{26}$O$_6$ (M$^+$): 422.1729 Found: 422.1721.

Synthesis of gem-Dimethyl Tetrahydrofluorenones 3.73 and 3.74:
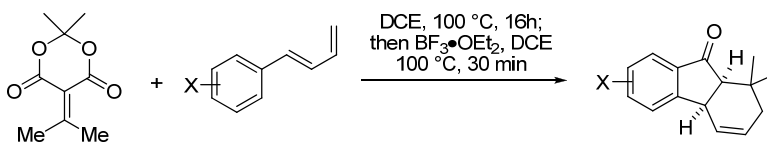
General Procedure D: An oven-dried Schlenk tube cooled under N$_2$ was charged with 5-(1-methylethylidene) Meldrum's acid **3.72**[46] (100 mg, 0.54 mmol, 1.0 equiv). The arylbutadiene (X equiv) was weighed into a vial, then transferred into the tube with DCE (0.4 M). The tube was sealed and heated to 100 °C for 16 hours, then cooled to rt. A 50 µL aliquot was removed to check conversion by ^{1}H NMR, then a solution of BF$_3$•OEt$_2$ in DCE (0.1 equiv/100 µL) was washed into the tube with sufficient DCE to bring the

concentration to 0.15 M. The reaction was reheated to 100 °C for 30 minutes, cooled to rt., and worked up as in Procedure A. Flash chromatography eluting with 1:9 to 1:4 EtOAc:hexanes afforded a yellow powder, which was recrystallized from Et$_2$O to remove coloured impurities.
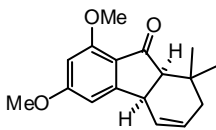
(4a*R**,9a*R**)-1,2-Dihydro-6,8-dimethoxy-1,1-dimethyl-4a*H*-fluoren-9(9a*H*)-one (3.73): Prepared using diene **3.61** (3.0 equiv); the Diels-Alder reaction proceeded to 79% completion. Isolated as a white solid in 26% yield. M.p. 164-166 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 6.55 (s, 1H), 6.31 (s, 1H), 6.00 (br d, J = 10.0 Hz, 1H), 5.79-5.75 (m, 1H), 3.913 (s, 3H), 3.908 (s, 3H), 3.76 (br s, 1H), 2.61 (d, J = 7.0 Hz, 1H), 1.93 (app t, J = 1.8 Hz, 2H), 1.25 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 203.3 (C), 166.8 (C), 160.3 (C), 159.1 (C), 126.7 (CH), 125.7 (CH), 118.8 (C), 99.9 (CH), 97.3 (CH), 56.6 (CH$_3$), 55.73 (CH$_3$), 55.70 (CH$_3$), 39.5 (CH), 38.6 (CH$_2$), 32.4 (C), 29.0 (CH$_3$), 24.3 (CH$_3$); HRMS(EI) m/z calcd for C$_{17}$H$_{20}$O$_3$ (M$^+$): 272.1412 Found: 272.1407.
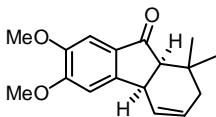
(4a*R**,9a*R**)-1,2-Dihydro-6,7-dimethoxy-1,1-dimethyl-4a*H*-fluoren-9(9a*H*)-one (3.74): Prepared using diene **3.62** (2.2 equiv); the Diels-Alder reaction proceeded to 89% completion. Isolated as a white solid in 81% yield. M.p. 138-140 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.11 (s, 1H), 6.91 (s, 1H), 6.02 (br d, J = 9.9 Hz, 1H), 5.78-5.71 (m, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.78 (br s, 1H), 2.61 (d, J = 6.7 Hz, 1H), 1.93 (**A**BX, J = 16.9 Hz, 2.6 Hz, 1H), 1.84 (A**B**X, J = 16.9 Hz, 4.9 Hz, 1H) 1.24 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 206.0 (C), 155.3 (C), 150.4 (C), 149.3 (C), 129.5 (C), 126.4 (CH), 125.9 (CH), 105.5 (CH), 104.0 (CH), 56.2 (CH$_3$), 56.0 (CH$_3$), 39.2 (CH), 38.8 (CH$_2$), 32.5 (C), 29.1 (CH$_3$), 24.1 (CH$_3$); HRMS(EI) m/z calcd for C$_{17}$H$_{20}$O$_3$ (M$^+$): 272.1412 Found: 272.1404.
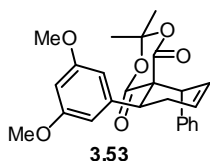
X-Ray Crystal Diffraction Data for exo adduct 3.53

3.53

Table 1. Crystal data and structure refinement for $C_{25}H_{26}O_6$

Empirical formula	$C_{25}H_{26}O_6$
Formula weight	422.46
Temperature	180(1) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 9.8323(5)$ Å, $b = 14.6015(7)$Å, $c = 15.7652(8)$Å
	$\alpha = 93.625(1)°$, $\beta = 97.552(1)°$, $\gamma = 107.306(1)°$
Volume	2129.59(18) Å^3
Z, Calculated density	4, 1.318 g/cm^3
Absorption coefficient	0.094 mm^{-1}
F(000)	896
Crystal size	0.32 x 0.21 x 0.08 mm
Theta range for data collection	1.86 to 30.10 °
Limiting indices	-13<=h<=13, -20<=k<=20, -21<=l<=22
Reflections collected / unique	15393 / 11634 [$R_{(int)} = 0.0320$]
Completeness to $\theta = 30.10$	92.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11634 / 0 / 562
Goodness-of-fit on F^2	1.308
Final R indices [$I>2\sigma(I)$]	R1 = 0.0548, wR2 = 0.0780
R indices (all data)	R1 = 0.0823, wR2 = 0.0814
Extinction coefficient	0.0078(4)
Largest diff. peak and hole	0.402 and -0.382 e. Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C$_{25}$H$_{26}$O$_6$

	x	y	z	U(eq)
O(1)	-1230(1)	3547(1)	2489(1)	37(1)
C(2)	234(2)	4126(1)	2756(1)	37(1)
O(3)	1101(1)	3551(1)	3074(1)	40(1)
C(4)	945(2)	2666(1)	2680(1)	29(1)
C(5)	-560(1)	2083(1)	2232(1)	24(1)
C(6)	-1499(2)	2705(1)	1978(1)	27(1)
C(7)	824(2)	4614(1)	2012(1)	56(1)
C(8)	244(2)	4818(1)	3503(1)	56(1)
O(9)	1950(1)	2366(1)	2780(1)	37(1)
O(10)	-2529(1)	2460(1)	1425(1)	34(1)
C(11)	-598(2)	1372(1)	1451(1)	27(1)
C(12)	187(2)	638(1)	1682(1)	36(1)
C(13)	-57(2)	274(1)	2528(1)	34(1)
C(14)	-676(2)	651(1)	3090(1)	31(1)
C(15)	-1251(1)	1483(1)	2968(1)	25(1)
C(16)	-144(2)	1831(1)	658(1)	28(1)
C(17)	-1038(2)	1493(1)	-122(1)	31(1)
C(18)	-656(2)	1873(1)	-868(1)	30(1)
C(19)	619(2)	2610(1)	-856(1)	30(1)
C(20)	1503(2)	2951(1)	-74(1)	32(1)
C(21)	1144(2)	2561(1)	673(1)	33(1)
O(22)	-1624(1)	1480(1)	-1600(1)	42(1)
C(23)	-1425(2)	1945(1)	-2359(1)	41(1)
O(24)	2779(1)	3686(1)	23(1)	45(1)
C(25)	3178(2)	4129(1)	-726(1)	41(1)
C(26)	-2892(1)	1156(1)	2810(1)	26(1)
C(27)	-3672(2)	317(1)	2283(1)	32(1)
C(28)	-5161(2)	19(1)	2144(1)	40(1)
C(29)	-5886(2)	559(1)	2522(1)	44(1)
C(30)	-5136(2)	1398(1)	3039(1)	43(1)
C(31)	-3643(2)	1692(1)	3188(1)	35(1)
C(33)	5688(2)	4802(1)	3208(1)	49(1)
C(35)	5047(2)	6180(1)	3788(1)	37(1)
C(36)	6511(1)	6870(1)	3690(1)	27(1)
C(37)	7331(2)	6409(1)	3140(1)	30(1)
O(32)	7115(3)	5465(2)	3316(2)	36(1)
O(34)	4915(3)	5300(2)	3844(2)	39(1)
C(38)	5818(6)	4034(4)	3754(3)	61(1)
C(39)	4836(5)	4581(3)	2422(3)	51(1)
O(32A)	6914(2)	5451(1)	2858(1)	36(1)
O(34A)	4657(2)	5235(1)	3312(1)	39(1)
C(38A)	6245(4)	4368(3)	3942(2)	61(1)
C(39A)	5033(3)	4034(2)	2382(2)	51(1)
O(40)	4137(1)	6410(1)	4087(1)	48(1)

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O(41)	8312(1)	6855(1)	2814(1)	35(1)
C(42)	6389(2)	7791(1)	3292(1)	28(1)
C(43)	5661(2)	8367(1)	3826(1)	37(1)
C(44)	6141(2)	8423(1)	4769(1)	39(1)
C(45)	6894(2)	7897(1)	5120(1)	38(1)
C(46)	7414(2)	7181(1)	4634(1)	32(1)
C(47)	5722(2)	7632(1)	2353(1)	26(1)
C(48)	6512(2)	8109(1)	1764(1)	27(1)
C(49)	5888(2)	8053(1)	914(1)	30(1)
C(50)	4476(2)	7474(1)	624(1)	31(1)
C(51)	3721(2)	6968(1)	1213(1)	32(1)
C(52)	4311(2)	7059(1)	2072(1)	32(1)
O(53)	6739(1)	8614(1)	407(1)	43(1)
C(54)	6143(2)	8602(1)	-468(1)	55(1)
O(55)	2332(1)	6370(1)	1010(1)	46(1)
C(56)	1697(2)	6186(1)	130(1)	46(1)
C(57)	9036(2)	7569(1)	4645(1)	32(1)
C(58)	9715(2)	8541(1)	4599(1)	37(1)
C(59)	11186(2)	8883(1)	4599(1)	50(1)
C(60)	11991(2)	8265(2)	4651(1)	58(1)
C(61)	11344(2)	7304(2)	4695(1)	56(1)
C(62)	9868(2)	6959(1)	4697(1)	44(1)

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Table 3. Hydrogen coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C$_{25}$H$_{26}$O$_6$

	x	y	z	U(eq)
H(7X)	1815	4992	2191	84
H(7Y)	274	5026	1818	84
H(7Z)	761	4135	1550	84
H(8X)	-192	4464	3942	84
H(8Y)	-289	5242	3315	84
H(8Z)	1221	5191	3731	84
H(11)	-1615	992	1282	33
H(12X)	-138	96	1237	43
H(12Y)	1213	936	1694	43
H(13)	247	-250	2669	41
H(14)	-763	377	3604	37
H(15)	-936	1914	3507	30
H(17)	-1906	1005	-145	37
H(19)	872	2868	-1358	36
H(21)	1770	2789	1189	39
H(23X)	-1373	2610	-2244	61
H(23Y)	-2221	1631	-2806	61
H(23Z)	-545	1910	-2539	61
H(25X)	3330	3665	-1131	62
H(25Y)	4050	4659	-568	62
H(25Z)	2421	4362	-982	62
H(27)	-3185	-50	2020	38
H(28)	-5671	-548	1794	48
H(29)	-6889	358	2429	53
H(30)	-5631	1769	3288	52
H(31)	-3139	2255	3546	42
H(38U)	6255	4319	4329	92
H(38V)	6407	3692	3523	92
H(38W)	4877	3594	3765	92
H(39U)	3907	4150	2472	76
H(39V)	5277	4278	2027	76
H(39W)	4724	5162	2211	76
H(38X)	6708	4862	4411	92
H(38Y)	6929	4070	3772	92
H(38Z)	5460	3892	4121	92
H(39X)	4219	3534	2504	76
H(39Y)	5754	3757	2236	76
H(39Z)	4732	4348	1909	76
H(42)	7383	8209	3317	33
H(43X)	5874	9015	3656	45
H(43Y)	4624	8067	3700	45
H(44)	5894	8856	5130	46
H(45)	7122	7973	5717	46
H(46)	7231	6602	4938	38
H(48)	7473	8472	1939	33

H(50)	4057	7430	53	38
H(52)	3760	6735	2461	38
H(54X)	5884	7959	-752	83
H(54Y)	6844	9030	-749	83
H(54Z)	5301	8809	-493	83
H(56X)	1655	6779	-84	70
H(56Y)	739	5743	73	70
H(56Z)	2268	5911	-194	70
H(58)	9175	8967	4567	45
H(59)	11628	9535	4564	60
H(60)	12982	8499	4657	70
H(61)	11892	6883	4723	68
H(62)	9434	6306	4733	52

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Table 4. Bond lengths [Å] and angles [°] for C₂₅H₂₆O₆

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O(1)-C(6)	1.3629(16)
O(1)-C(2)	1.4267(17)
C(2)-O(3)	1.4328(18)
C(2)-C(8)	1.500(2)
C(2)-C(7)	1.503(2)
O(3)-C(4)	1.3541(17)
C(4)-O(9)	1.1911(16)
C(4)-C(5)	1.5207(18)
C(5)-C(6)	1.5119(19)
C(5)-C(11)	1.5484(18)
C(5)-C(15)	1.5992(18)
C(6)-O(10)	1.1942(15)
C(11)-C(16)	1.5119(19)
C(11)-C(12)	1.5305(19)
C(12)-C(13)	1.489(2)
C(13)-C(14)	1.3172(19)
C(14)-C(15)	1.4983(19)
C(15)-C(26)	1.5215(18)
C(16)-C(17)	1.3825(18)
C(16)-C(21)	1.3879(18)
C(17)-C(18)	1.3808(19)
C(18)-O(22)	1.3668(16)
C(18)-C(19)	1.3856(18)
C(19)-C(20)	1.3803(18)
C(20)-O(24)	1.3697(16)
C(20)-C(21)	1.3815(19)
O(22)-C(23)	1.4203(17)
O(24)-C(25)	1.4258(17)
C(26)-C(31)	1.3828(19)
C(26)-C(27)	1.3874(18)
C(27)-C(28)	1.3805(19)
C(28)-C(29)	1.368(2)
C(29)-C(30)	1.374(2)
C(30)-C(31)	1.385(2)
C(33)-C(39)	1.364(4)
C(33)-O(34A)	1.366(2)
C(33)-O(32)	1.430(3)
C(33)-C(38A)	1.473(4)
C(33)-C(38)	1.481(6)
C(33)-O(32A)	1.490(2)
C(33)-C(39A)	1.591(3)
C(33)-O(34)	1.595(3)
C(35)-O(40)	1.1851(18)
C(35)-O(34)	1.263(3)
C(35)-O(34A)	1.447(2)
C(35)-C(36)	1.525(2)
C(36)-C(37)	1.5127(19)
C(36)-C(42)	1.5495(19)
C(36)-C(46)	1.5916(18)
C(37)-O(41)	1.1921(16)
C(37)-O(32A)	1.361(2)

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C(37)-O(32)              1.382(3)
C(42)-C(47)              1.5124(18)
C(42)-C(43)              1.5344(19)
C(43)-C(44)              1.4886(19)
C(44)-C(45)              1.316(2)
C(45)-C(46)              1.504(2)
C(46)-C(57)              1.5229(19)
C(47)-C(48)              1.3787(18)
C(47)-C(52)              1.3868(18)
C(48)-C(49)              1.3845(18)
C(49)-O(53)              1.3645(17)
C(49)-C(50)              1.3910(19)
C(50)-C(51)              1.3776(19)
C(51)-O(55)              1.3683(16)
C(51)-C(52)              1.3834(18)
O(53)-C(54)              1.4235(17)
O(55)-C(56)              1.4184(17)
C(57)-C(62)              1.377(2)
C(57)-C(58)              1.388(2)
C(58)-C(59)              1.382(2)
C(59)-C(60)              1.365(2)
C(60)-C(61)              1.369(3)
C(61)-C(62)              1.388(2)


C(6)-O(1)-C(2)           118.32(12)
O(1)-C(2)-O(3)           110.83(12)
O(1)-C(2)-C(8)           106.72(13)
O(3)-C(2)-C(8)           106.35(13)
O(1)-C(2)-C(7)           109.82(13)
O(3)-C(2)-C(7)           109.52(14)
C(8)-C(2)-C(7)           113.54(14)
C(4)-O(3)-C(2)           121.72(11)
O(9)-C(4)-O(3)           117.96(13)
O(9)-C(4)-C(5)           124.71(14)
O(3)-C(4)-C(5)           116.89(13)
C(6)-C(5)-C(4)           112.98(12)
C(6)-C(5)-C(11)          109.91(11)
C(4)-C(5)-C(11)          114.76(12)
C(6)-C(5)-C(15)          106.18(11)
C(4)-C(5)-C(15)          103.33(10)
C(11)-C(5)-C(15)         109.06(11)
O(10)-C(6)-O(1)          118.95(14)
O(10)-C(6)-C(5)          124.28(13)
O(1)-C(6)-C(5)           116.28(12)
C(16)-C(11)-C(12)        111.16(12)
C(16)-C(11)-C(5)         115.45(12)
C(12)-C(11)-C(5)         113.11(11)
C(13)-C(12)-C(11)        113.07(12)
C(14)-C(13)-C(12)        123.96(14)
C(13)-C(14)-C(15)        125.44(14)
C(14)-C(15)-C(26)        111.55(11)
C(14)-C(15)-C(5)         110.40(11)
C(26)-C(15)-C(5)         113.12(11)
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C(17)-C(16)-C(21)          118.37(14)
C(17)-C(16)-C(11)          118.48(13)
C(21)-C(16)-C(11)          123.13(12)
C(18)-C(17)-C(16)          120.71(14)
O(22)-C(18)-C(17)          115.42(13)
O(22)-C(18)-C(19)          123.42(13)
C(17)-C(18)-C(19)          121.15(13)
C(20)-C(19)-C(18)          117.94(14)
O(24)-C(20)-C(19)          123.34(14)
O(24)-C(20)-C(21)          115.38(13)
C(19)-C(20)-C(21)          121.28(14)
C(20)-C(21)-C(16)          120.53(13)
C(18)-O(22)-C(23)          118.18(11)
C(20)-O(24)-C(25)          117.46(11)
C(31)-C(26)-C(27)          118.42(13)
C(31)-C(26)-C(15)          120.62(13)
C(27)-C(26)-C(15)          120.96(13)
C(28)-C(27)-C(26)          120.83(15)
C(29)-C(28)-C(27)          119.99(15)
C(28)-C(29)-C(30)          120.16(15)
C(29)-C(30)-C(31)          119.99(15)
C(26)-C(31)-C(30)          120.60(14)
C(39)-C(33)-O(34A)          77.3(2)
C(39)-C(33)-O(32)          120.7(3)
O(34A)-C(33)-O(32)         113.49(17)
C(39)-C(33)-C(38A)         143.0(3)
O(34A)-C(33)-C(38A)        118.4(2)
O(32)-C(33)-C(38A)          85.4(2)
C(39)-C(33)-C(38)          120.9(3)
O(34A)-C(33)-C(38)         118.7(3)
O(32)-C(33)-C(38)          104.5(3)
C(38A)-C(33)-C(38)          22.4(3)
C(39)-C(33)-O(32A)          92.2(2)
O(34A)-C(33)-O(32A)        111.36(15)
O(32)-C(33)-O(32A)          28.52(11)
C(38A)-C(33)-O(32A)        109.75(19)
C(38)-C(33)-O(32A)         124.1(3)
C(39)-C(33)-C(39A)          33.4(2)
O(34A)-C(33)-C(39A)        105.54(18)
O(32)-C(33)-C(39A)         122.1(2)
C(38A)-C(33)-C(39A)        111.7(2)
C(38)-C(33)-C(39A)          91.3(2)
O(32A)-C(33)-C(39A)         98.16(17)
C(39)-C(33)-O(34)          107.8(3)
O(34A)-C(33)-O(34)          31.50(11)
O(32)-C(33)-O(34)          103.01(18)
C(38A)-C(33)-O(34)          88.8(2)
C(38)-C(33)-O(34)           95.6(3)
O(32A)-C(33)-O(34)         116.90(16)
C(39A)-C(33)-O(34)         130.79(19)
O(40)-C(35)-O(34)          111.47(19)
O(40)-C(35)-O(34A)         118.18(15)
O(34)-C(35)-O(34A)          34.99(13)
O(40)-C(35)-C(36)          124.88(15)
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O(34)-C(35)-C(36)          119.26(19)
O(34A)-C(35)-C(36)         115.55(15)
C(37)-C(36)-C(35)          112.73(12)
C(37)-C(36)-C(42)          107.50(11)
C(35)-C(36)-C(42)          112.59(12)
C(37)-C(36)-C(46)          108.91(11)
C(35)-C(36)-C(46)          106.58(12)
C(42)-C(36)-C(46)          108.42(11)
O(41)-C(37)-O(32A)         111.52(15)
O(41)-C(37)-O(32)          123.75(18)
O(32A)-C(37)-O(32)          30.50(12)
O(41)-C(37)-C(36)          123.68(13)
O(32A)-C(37)-C(36)         124.17(14)
O(32)-C(37)-C(36)          109.20(16)
C(37)-O(32)-C(33)          120.3(2)
C(35)-O(34)-C(33)          116.8(2)
C(37)-O(32A)-C(33)         117.51(16)
C(33)-O(34A)-C(35)         120.35(16)
C(47)-C(42)-C(43)          111.04(12)
C(47)-C(42)-C(36)          114.95(11)
C(43)-C(42)-C(36)          112.77(12)
C(44)-C(43)-C(42)          112.84(13)
C(45)-C(44)-C(43)          123.79(14)
C(44)-C(45)-C(46)          125.20(14)
C(45)-C(46)-C(57)          110.66(12)
C(45)-C(46)-C(36)          110.68(12)
C(57)-C(46)-C(36)          113.53(11)
C(48)-C(47)-C(52)          118.83(13)
C(48)-C(47)-C(42)          119.16(12)
C(52)-C(47)-C(42)          121.93(13)
C(47)-C(48)-C(49)          120.62(13)
O(53)-C(49)-C(48)          115.29(13)
O(53)-C(49)-C(50)          123.76(13)
C(48)-C(49)-C(50)          120.93(13)
C(51)-C(50)-C(49)          117.73(13)
O(55)-C(51)-C(50)          123.59(13)
O(55)-C(51)-C(52)          114.65(13)
C(50)-C(51)-C(52)          121.71(14)
C(51)-C(52)-C(47)          120.03(13)
C(49)-O(53)-C(54)          117.80(12)
C(51)-O(55)-C(56)          117.65(12)
C(62)-C(57)-C(58)          118.23(14)
C(62)-C(57)-C(46)          120.53(15)
C(58)-C(57)-C(46)          121.24(14)
C(59)-C(58)-C(57)          120.73(17)
C(60)-C(59)-C(58)          120.10(18)
C(59)-C(60)-C(61)          120.18(17)
C(60)-C(61)-C(62)          119.86(18)
C(57)-C(62)-C(61)          120.89(17)
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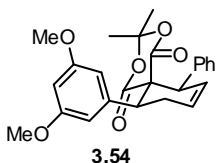
 X-Ray Crystal Diffraction Data for endo adduct 3.54

Table 1. Crystal data and structure refinement for $C_{25}H_{26}O_6$

Empirical formula	$C_{25}H_{26}O_6$
Formula weight	422.46
Temperature	180(1) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.8685(3) A, b = 9.8291(3) A, c = 13.5654(5) A
	α = 97.767(1) °, β = 107.642(1) °, γ = 101.452(1) °
Volume	1080.02(6) Å^3
Z, Calculated density	2, 1.299 g/cm^3
Absorption coefficient	0.092 mm^{-1}
F(000)	448
Crystal size	0.32 x 0.23 x 0.23 mm
Theta range for data collection	1.61 to 30.03 °
Limiting indices	-12<=h<=12, -13<=k<=11, -19<=l<=19
Reflections collected / unique	8900 / 6007 [$R_{(int)}$ = 0.0221]
Completeness to θ = 30.03	95.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6007 / 0 / 285
Goodness-of-fit on F^2	1.983
Final R indices [I>2σ(I)]	R1 = 0.0424, wR2 = 0.0987
R indices (all data)	R1 = 0.0476, wR2 = 0.0997
Extinction coefficient	0.066(3)
Largest diff. peak and hole	0.297 and -0.254 e. Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C$_{25}$H$_{26}$O$_6$

	x	y	z	U(eq)
O(1)	1307(1)	3825(1)	2578(1)	29(1)
C(2)	2504(1)	4022(1)	3607(1)	26(1)
O(3)	4045(1)	4921(1)	3696(1)	30(1)
C(4)	4185(1)	6018(1)	3201(1)	22(1)
C(5)	2777(1)	6023(1)	2232(1)	21(1)
C(6)	1228(1)	4867(1)	2028(1)	23(1)
C(7)	2805(2)	2586(1)	3718(1)	36(1)
C(8)	1896(2)	4673(1)	4436(1)	36(1)
O(9)	5477(1)	6879(1)	3518(1)	32(1)
O(10)	−33(1)	4778(1)	1335(1)	31(1)
C(11)	3287(1)	5734(1)	1214(1)	23(1)
C(12)	4784(1)	6868(1)	1278(1)	29(1)
C(13)	4688(1)	8337(1)	1664(1)	31(1)
C(14)	3622(1)	8609(1)	2115(1)	30(1)
C(15)	2336(1)	7489(1)	2272(1)	25(1)
C(16)	3440(1)	4229(1)	969(1)	22(1)
C(17)	4814(1)	3820(1)	1552(1)	23(1)
C(18)	4860(1)	2417(1)	1343(1)	25(1)
C(19)	3582(1)	1402(1)	556(1)	27(1)
C(20)	2247(1)	1824(1)	−21(1)	27(1)
C(21)	2174(1)	3235(1)	186(1)	26(1)
O(22)	6129(1)	1905(1)	1876(1)	35(1)
C(23)	7489(1)	2897(1)	2663(1)	39(1)
O(24)	924(1)	935(1)	−811(1)	38(1)
C(25)	922(2)	−531(1)	−1026(1)	46(1)
C(26)	1877(1)	7927(1)	3239(1)	26(1)
C(27)	3052(1)	8594(1)	4217(1)	33(1)
C(28)	2592(2)	8956(1)	5093(1)	39(1)
C(29)	953(2)	8659(1)	4989(1)	40(1)
C(30)	−227(2)	8003(1)	4023(1)	41(1)
C(31)	231(1)	7645(1)	3149(1)	34(1)

Table 3. Hydrogen coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C$_{25}$H$_{26}$O$_6$

	x	y	z	U(eq)
H(7X)	3200	2233	3156	54
H(7Y)	1783	1923	3659	54
H(7Z)	3628	2666	4409	54
H(8X)	2705	4792	5139	53
H(8Y)	858	4049	4394	53
H(8Z)	1728	5600	4314	53
H(11)	2362	5825	606	27
H(12X)	5776	6685	1761	35
H(12Y)	4890	6800	568	35
H(13)	5433	9115	1580	37
H(14)	3671	9576	2357	36
H(15)	1324	7346	1647	30
H(17)	5701	4499	2084	28
H(19)	3629	440	421	32
H(21)	1248	3513	−214	31
H(23X)	7942	3643	2344	59
H(23Y)	8329	2411	2965	59
H(23Z)	7136	3323	3223	59
H(25X)	1849	−627	−1255	69
H(25Y)	−101	−1063	−1586	69
H(25Z)	1015	−908	−383	69
H(27)	4178	8804	4290	39
H(28)	3402	9407	5760	47
H(29)	639	8907	5586	48
H(30)	−1351	7797	3955	49
H(31)	−586	7203	2483	41

Table 4. Bond lengths [Å] and angles [°] for C$_{25}$H$_{26}$O$_6$

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O(1)-C(6)	1.3481(12)
O(1)-C(2)	1.4351(12)
C(2)-O(3)	1.4334(12)
C(2)-C(7)	1.5067(15)
C(2)-C(8)	1.5082(15)
O(3)-C(4)	1.3502(12)
C(4)-O(9)	1.1972(11)
C(4)-C(5)	1.5152(13)
C(5)-C(6)	1.5226(13)
C(5)-C(15)	1.5644(13)
C(5)-C(11)	1.5862(12)
C(6)-O(10)	1.2004(11)
C(11)-C(16)	1.5134(13)
C(11)-C(12)	1.5263(14)
C(12)-C(13)	1.4956(14)
C(13)-C(14)	1.3218(14)
C(14)-C(15)	1.5069(14)
C(15)-C(26)	1.5207(13)
C(16)-C(21)	1.3802(14)
C(16)-C(17)	1.4025(13)
C(17)-C(18)	1.3807(14)
C(18)-O(22)	1.3685(12)
C(18)-C(19)	1.3962(14)
C(19)-C(20)	1.3815(15)
C(20)-O(24)	1.3657(12)
C(20)-C(21)	1.3960(14)
O(22)-C(23)	1.4205(13)
O(24)-C(25)	1.4307(14)
C(26)-C(27)	1.3895(15)
C(26)-C(31)	1.3945(15)
C(27)-C(28)	1.3931(15)
C(28)-C(29)	1.3835(17)
C(29)-C(30)	1.3780(18)
C(30)-C(31)	1.3897(16)
C(6)-O(1)-C(2)	122.36(8)
O(3)-C(2)-O(1)	111.83(7)
O(3)-C(2)-C(7)	106.00(9)
O(1)-C(2)-C(7)	106.30(8)
O(3)-C(2)-C(8)	109.05(9)
O(1)-C(2)-C(8)	109.53(9)
C(7)-C(2)-C(8)	114.13(9)
C(4)-O(3)-C(2)	123.33(8)
O(9)-C(4)-O(3)	116.90(9)
O(9)-C(4)-C(5)	123.98(9)
O(3)-C(4)-C(5)	118.89(8)
C(4)-C(5)-C(6)	114.04(8)
C(4)-C(5)-C(15)	112.40(8)
C(6)-C(5)-C(15)	108.57(8)
C(4)-C(5)-C(11)	109.05(7)

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C(6)-C(5)-C(11)          105.61(7)
C(15)-C(5)-C(11)         106.71(7)
O(10)-C(6)-O(1)          118.16(9)
O(10)-C(6)-C(5)          122.70(9)
O(1)-C(6)-C(5)           118.85(8)
C(16)-C(11)-C(12)        114.01(8)
C(16)-C(11)-C(5)         111.90(7)
C(12)-C(11)-C(5)         111.66(8)
C(13)-C(12)-C(11)        112.58(8)
C(14)-C(13)-C(12)        123.46(9)
C(13)-C(14)-C(15)        124.36(10)
C(14)-C(15)-C(26)        114.23(8)
C(14)-C(15)-C(5)         111.84(8)
C(26)-C(15)-C(5)         112.32(8)
C(21)-C(16)-C(17)        119.75(9)
C(21)-C(16)-C(11)        119.10(9)
C(17)-C(16)-C(11)        121.10(9)
C(18)-C(17)-C(16)        119.17(9)
O(22)-C(18)-C(17)        123.79(9)
O(22)-C(18)-C(19)        114.67(9)
C(17)-C(18)-C(19)        121.54(9)
C(20)-C(19)-C(18)        118.67(9)
O(24)-C(20)-C(19)        124.25(9)
O(24)-C(20)-C(21)        115.23(9)
C(19)-C(20)-C(21)        120.52(9)
C(16)-C(21)-C(20)        120.35(9)
C(18)-O(22)-C(23)        117.24(8)
C(20)-O(24)-C(25)        117.10(9)
C(27)-C(26)-C(31)        118.71(10)
C(27)-C(26)-C(15)        121.99(9)
C(31)-C(26)-C(15)        119.29(10)
C(26)-C(27)-C(28)        120.54(11)
C(29)-C(28)-C(27)        119.86(11)
C(30)-C(29)-C(28)        120.29(10)
C(29)-C(30)-C(31)        119.85(11)
C(30)-C(31)-C(26)        120.73(11)
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Part 2. Investigations of the Friedel-Crafts Acylation of 4-Substituted Indoles

General Considerations: All reactions were performed in flame- or oven-dried glassware under a nitrogen atmosphere unless indicated otherwise. 1,2-Dichloroethane, THF, toluene and CH_2Cl_2 were dried and purified from a solvent system by the published procedure.[222] $MeNO_2$ and DMF were distilled over CaH_2 and stored in Schlenk flasks under N_2. Benzene (over Na/benzophenone), Et_3N (over CaH_2), and $BF_3•OEt_2$ (over CaH_2, through a 15 cm Vigreux column) were freshly distilled before use. Lithium chloride (ACS Reagent grade, ≥99%) was opened and stored in a glovebox. $Yb(OTf)_3$ was purchased as the hydrate, dried by heating at 180 °C under high vacuum for 8 h, and stored in a glovebox. All other reagents and solvents were used as received. Reactions were monitored by thin-layer chromatography and visualized by UV and/or staining with ceric ammonium molybdate followed by warming with a heat gun. Flash chromatography was performed using 230-400 mesh silica gel.

Characterization: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 300 MHz and 75 MHz, respectively. Proton spectra were calibrated to residual $CHCl_3$ (7.24 ppm); carbon spectra were calibrated to $CDCl_3$ (77.0 ppm). Carbon multiplicities (C, CH, CH_2, CH_3) were determined by combined DEPT 90/135 experiments. Chemical shifts are reported in parts per million (ppm, δ). High resolution mass spectrometry was performed at the University of Waterloo Mass Spectrometry facility.

Synthesis of (*N*-Ns-4-indolyl) Alkylidene Meldrum's Acid 3.93:
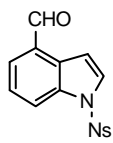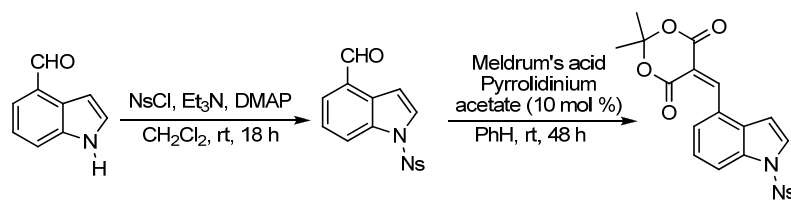
 1-(4-Nitrophenylsulfonyl)-*1H*-indole-4-carbaldehyde (**3.92**): Indole-4-carboxaldehyde (**3.91**, 6.0 g, 41.2 mmol, 1.0 equiv) and DMAP (400 mg, 3.3 mmol, 8 mol %) were dissolved in CH_2Cl_2 (80 mL) at rt. Et_3N (8.4 mL, 62.0

mmol, 1.5 equiv) was added via syringe and the solution stirred 10 min. In a separate flask, 4-nitrophenylsulfonyl chloride (NsCl, 10.0 g, 45.2 mmol, 1.1 equiv) was dissolved in CH_2Cl_2 (80 mL), and then added to the solution of indole via syringe over 5 min. The reaction was stirred at rt for 18 h, and then quenched by addition of 5% HCl (200 mL). The contents of the flask were poured into a separatory funnel and layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL), and the combined organic phases were dried over $MgSO_4$, then filtered through a pad of silica gel and concentrated. The resulting beige powder was dried under high vacuum to a constant weight to give **3.92** (11.8 g, 87% yield). The solid darkens to a red colour upon storage at rt in air with no change in spectral purity. M.p. 155-157 °C; ^1H NMR (CDCl$_3$, 300 MHz) 10.16 (s, 1H), 8.27 (d, J = 8.8 Hz, 2H), 8.26-2.24 (m, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.76-7.71 (m, 2H), 7.56-7.49 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 191.9 (CH), 150.7 (C), 143.0 (C), 135.4 (C), 130.1 (CH), 129.08 (C), 129.04 (C), 129.00 (CH), 128.1 (CH), 125.0 (CH), 124.7 (CH), 118.9 (CH), 110.0 (CH); HRMS(EI) m/z calcd for $C_{15}H_{10}N_2O_5S$ (M$^+$): 330.0310 Found: 330.0303.
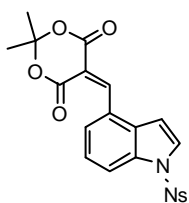
2,2-Dimethyl-5-((1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)methylene)-1,3-dioxane-4,6-dione (3.93): Preparation of this compound is described in Chapter 1 (Compound **1.52**).

Synthesis of Diels-Alder Adduct 3.94 and Friedel-Crafts Acylation Product 3.96:
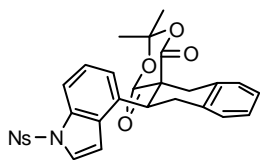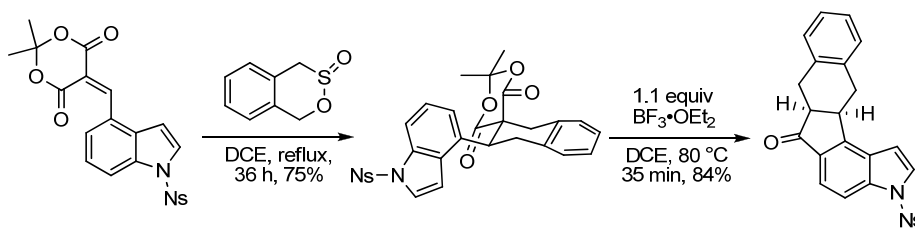
2,2-Dimethyl-3'-(1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)-3',4'-dihydro-1'*H*-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (3.94): Alkylidene Meldrum's acid **3.93** (456 mg, 1.0 mmol, 1.0 equiv) was dissolved in DCE (2 mL) in a flask equipped with an oven-dried, water-

cooled condenser. A solution of sultine **3.44** (200 mg, 1.2 mmol, 1.2 equiv) in DCE (3 mL) was added, and the reaction heated to reflux for 18 h, at which point the reaction was 66% complete as determined by ^{1}H NMR. An additional amount of **3.44** (200 mg, 1.2 mmol, 1.2 equiv) was added, and heating continued for 18 h. The reaction was cooled to rt, concentrated, and the residue purified by flash column chromatography eluting with 7:1 PhCH$_3$:Et$_2$O to yield the product as a yellow solid (422 mg, 75% yield). M.p. 146-148 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.26-8.23 (m, 2H), 8.00 (d, J = 8.9 Hz, 2H), 7.92 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 3.8 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1), 7.24-7.09 (m, 5H), 6.82 (d, J = 3.8 Hz, 1H), 4.09 (dd, J = 5.0 Hz, 12.9 Hz, 1H), 3.76 (d, J = 16.6 Hz, 1H), 3.69-3.64 (m, 1H), 3.26 (d, J = 17.0 Hz, 1H), 3.00 (dd, J = 16.9 Hz, 5.0 Hz, 1H), 1.57 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 170.2 (C), 167.0 (C), 150.6 (C), 143.2 (C), 135.2 (C), 134.8 (C), 132.6 (C), 131.1 (C), 130.7 (C), 128.3 (CH), 128.03 (CH), 127.98 (CH), 126.5 (CH), 126.4 (CH), 126.2 (CH), 125.4 (CH), 124.4 (CH), 122.6 (CH), 113.0 (CH), 109.3 (CH), 105.0 (C), 52.7 (C), 44.0 (CH), 38.0 (CH$_2$), 33.2 (CH$_2$), 30.2 (CH$_3$), 27.4 (CH$_3$); HRMS(EI) m/z calcd for C$_{29}$H$_{24}$N$_2$O$_8$S (M$^+$): 560.1253 Found: 560.1254
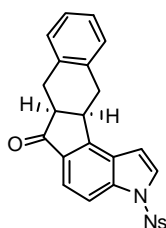
4,5-Disubstituted Indole 3.96: Adduct **3.94** (113 mg, 0.2 mmol, 1.0 equiv) was dissolved in DCE (0.8 mL) in an oven-dried Schlenk tube cooled under nitrogen. BF$_3$•OEt$_2$ (28 μL, 0.22 mmol, 1.1 equiv) was rinsed into the tube with DCE (0.5 mL), the tube sealed tightly and heated at 80 °C in a temperature controlled oil bath for 35 min. The reaction was cooled to rt, rinsed into a round-bottom flask with CH$_2$Cl$_2$ and concentrated. The residue was purified by flash column chromatography eluting with 2:1 hexanes:EtOAc, followed by trituration of the resulting yellow solid with Et$_2$O to give the product as a white solid (77 mg, 84% yield). M.p. 236-237 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.29 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 3.6 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.16-6.99 (m, 4H), 6.92 (d, J = 7.1 Hz, 1H), 3.96 (dd, J = 13.4 Hz, 6.6 Hz, 1H), 3.29 (dd, J = 14.2 Hz, 6.6 Hz, 1H), 3.14-3.05 (m, 2H), 2.94 (dd, J = 16.9 Hz, 9.4 Hz, 1H), 2.84 (dd, J = 14.2 Hz, 6.6 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 206.9 (C), 152.4 (C), 150.9 (C), 143.0 (C), 138.3 (C), 136.8 (C), 133.5 (C), 128.2 (CH), 127.6 (CH), 127.5 (C), 127.2 (CH), 126.9 (CH), 126.5 (CH), 124.7 (CH), 120.3 (CH), 113.3 (CH), 108.4 (CH),

47.3 (CH), 38.6 (CH), 33.8 (CH$_2$), 30.4 (CH$_2$); HRMS(EI) m/z calcd for C$_{25}$H$_{18}$N$_2$O$_5$S (M$^+$): 458.0936 Found: 458.0933.

Synthesis of Acyclic 4-Indolyl Meldrum's acids 3.97-3.100:
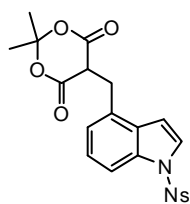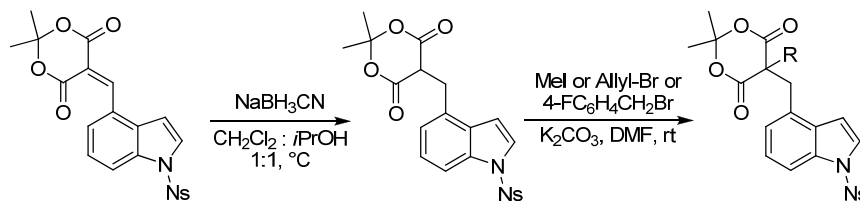
2,2-Dimethyl-5-((1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)methyl)-1,3-dioxane-4,6-dione (3.97): Alkylidene Meldrum's acid **3.93** (1.37 g, 3.0 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$ (50 mL) and *i*PrOH (50 mL) at rt and cooled to 0 °C. Sodium cyanoborohydride (282 mg, 4.5 mmol, 1.5 equiv) was added in portions, and the reaction stirred for 1 h until complete by TLC. The solution was concentrated by rotary evaporation, and the residue stirred with 10% HCl (100 mL) and CH$_2$Cl$_2$ (100 mL) for 30 min, then poured into a separatory funnel and the layers separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (2X 50 mL). The combined organic phases were washed with 10% HCl (1X 50 mL), distilled water (1X 50 mL), and brine (1X 50 mL), dried over MgSO$_4$, filtered, and concentrated. The product **3.97** was obtained as a pale yellow solid (1.3 g, 93% yield). M.p. 150-153 °C (dec); ^{1}H NMR (CDCl$_3$, 300 MHz) 8.23 (d, J = 8.9 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 7.87 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 3.8 Hz, 1H), 7.30-7.24 (m, 1H, overlaps with CHCl$_3$), 6.90 (d, J = 3.7 Hz, 1H), 3.72-3.64 (m, 3H), 1.68 (s, 3H), 1.52 (s, 3H, overlaps with H$_2$O); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.2 (C), 150.7 (C), 143.3 (C), 134.8 (C), 131.3 (C), 130.4 (C), 128.1 (CH), 126.0 (C), 125.4 (CH), 124.8 (CH), 124.5 (CH), 112.3 (CH), 108.8 (CH), 105.3 (C), 47.5 (CH), 28.9 (CH$_2$), 28.4 (CH$_3$), 26.94 (CH$_3$); HRMS(EI) m/z calcd for C$_{21}$H$_{18}$N$_2$O$_8$S (M$^+$): 458.0784 Found: 458.0783.

General procedure for alkylation of Meldrum's acid 3.97: Meldrum's acid derivative **3.97** (458 mg, 1.0 mmol, 1.0 equiv) was dissolved in DMF (2.5 mL) and K$_2$CO$_3$ (210 mg, 1.5 mmol, 1.5 equiv) was added at rt. The electrophile was added neat to the resulting

solution and stirring was continued for 16 h. The contents were poured into distilled water (25 mL) in a separatory funnel, and the aqueous phase extracted with CH_2Cl_2 (3X 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography yielded the alkylated products.
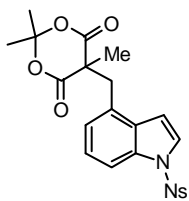
2,2,5-Trimethyl-5-((1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)methyl)-1,3-dioxane-4,6-dione (3.98): Prepared using MeI (0.32 mL, 5.0 mmol, 5.0 equiv) and chromatographed eluting with 4:1 hexanes:EtOAc to yield a pale yellow solid (415 mg, 88% yield). M.p. 163-164 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.22 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.3 Hz, 1H), 7.26-7.21 (m, 1H overlaps with CHCl$_3$), 7.10 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 3.8 Hz, 1H), 3.51 (s, 2H), 1.76 (s, 3H), 1.51 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 169.7 (C), 150.6 (C), 143.2 (C), 134.9 (C), 130.8 (C), 128.7 (C), 128.0 (CH), 126.2 (CH), 126.0 (CH), 125.4 (CH), 124.4 (CH), 113.0 (CH), 109.8 (CH), 105.1 (C), 51.2 (C), 42.0 (CH$_2$), 29.4 (CH$_3$), 27.9 (CH$_3$), 25.8 (CH$_3$); HRMS(EI) m/z calcd for $C_{22}H_{20}N_2O_8S$ (M$^+$): 472.0940 Found: 472.0947.
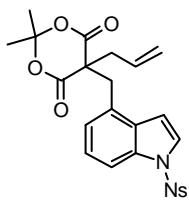
5-Allyl-2,2-dimethyl-5-((1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)methyl)-1,3-dioxane-4,6-dione (3.99): Prepared using freshly distilled allyl bromide (0.1 mL, 1.2 mmol, 1.2 equiv) and chromatographed eluting with 4:1 hexanes:EtOAc to yield a pale yellow solid (412 mg, 83%). M.p. 183-184 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.24-8.21 (m, 2H), 8.01-7.97 (m, 2H), 7.88 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 3.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H, overlaps with CHCl$_3$), 7.11 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 3.5 Hz, 1H), 5.72-5.58 (m ,1H), 5.09 (dd, J = 17.1 Hz, 1.1 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 3.51 (s, 2H), 2.90 (d, J = 7.5 Hz, 2H), 1.43 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.3 (C), 150.6 (C), 143.1 (C), 134.8 (C), 130.8 (C), 130.4 (CH), 128.5 (C), 128.0 (CH), 126.3 (CH), 126.2 (CH), 125.4 (CH), 124.4 (CH), 121.7 (CH$_2$), 113.0 (CH), 109.7 (CH), 105.7 (C), 55.9 (C), 44.1 (CH$_2$), 41.0 (CH$_2$), 29.7 (CH$_3$), 28.3 (CH$_3$); HRMS(EI) m/z calcd for $C_{24}H_{22}N_2O_8S$ (M$^+$): 498.1097 Found: 498.1096.
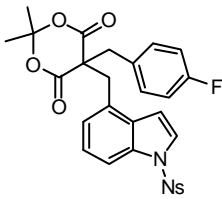
5-(4-Fluorobenzyl)-2,2-dimethyl-5-((1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)methyl)-1,3-dioxane-4,6-dione (5d):Prepared using 4-fluorobenzyl bromide (227 mg, 1.2 mmol, 1.2 equiv) and chromatographed eluting with 17:3 hexanes:EtOAc to yield a pale yellow solid (490 mg, 86%). M.p. 206-207 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.22 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 3.8 Hz, 1H), 7.28-7.24 (m, 1H, overlaps with CHCl$_3$), 7.17-7.12 (m, 3H), 6.95 (app t, J = 3.8 Hz, 2H), 6.88 (d, J = 3.7 Hz, 1H), 3.63 (s, 2H), 3.45 (s, 2H), 0.63 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.1 (C), 162.4 (d, J = 245.6 Hz, CF), 150.9 (C), 143.1 (C), 134.9 (C), 131.9 (d, J = 8.0 Hz, CH), 130.8 (C), 130.4 (d, J = 3.4 Hz, C), 128.1 (C), 128.0 (CH), 126.3 (CH), 126.1 (CH), 125.5 (CH), 124.4 (CH), 115.7 (d, J = 21.2 Hz, CH), 113.1 (CH), 109.7 (CH), 105.8 (C), 59.0 (C), 43.9 (CH$_2$), 41.9 (CH$_2$), 28.8 (CH$_3$), 28.2 (CH$_3$); HRMS(EI) m/z calcd for C$_{28}$H$_{23}$FN$_2$O$_8$S (M$^+$): 566.1159 Found: 566.1151.

Synthesis of 4,5-Disubstituted Indoles 3.102 and 3.104-3.106:
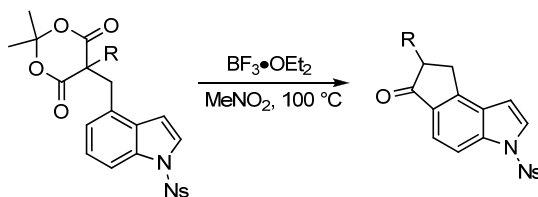
General Procedure for Friedel-Crafts Acylation of 3.97-3.100: An oven-dried Schlenk flask cooled under nitrogen was charged with Meldrum's acid derivative (92 mg, 0.2 mmol, 1.0 equiv) and dissolved in MeNO$_2$ (0.8 mL). BF$_3$•OEt$_2$ (5.0 μL, 0.04 mmol, 0.2 equiv) was added and washed into the flask with MeNO$_2$ (0.5 mL). The flask was sealed tightly, and placed in a temperature controlled oil bath at 100 °C. After 15 min, the flask was removed from the bath and cooled to rt. The contents were rinsed into a round-bottom flask with CH$_2$Cl$_2$ and concentrated. The residue was purified by flash column chromatography eluting with 4:1 hexanes:EtOAc to give the acylated product.
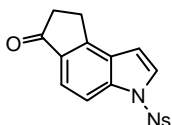
3-(4-Nitrophenylsulfonyl)-7,8-dihydrocyclopenta[e]indol-6(3*H*)-one (3.102): The reaction was run for 30 min, and flash chromatography

performed with 2:1 hexanes:EtOAc. Isolated as a yellow solid (39 mg, 54% yield). M.p. 207-208 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.28 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.9 Hz, 2H), 7.99 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 3.7 Hz, 1H), 6.85 (d, J = 3.7 Hz, 1H), 3.22 (app t, J = 3.7 Hz, 2H), 2.76-2.72 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 205.7 (C), 150.8 (C), 150.3 (C), 143.0 (C), 137.8 (C), 133.4 (C), 128.3 (C), 128.1 (CH), 127.2 (CH), 124.7 (CH), 120.4 (CH), 112.9 (CH), 108.4 (CH), 36.1 (CH$_2$), 24.3 (CH$_2$); HRMS(EI) m/z calcd for C$_{17}$H$_{12}$N$_2$O$_5$S (M$^+$): 356.0467 Found: 356.0468.
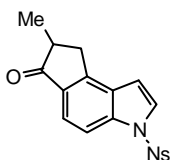
7-Methyl-3-(4-nitrophenylsulfonyl)-7,8-dihydrocyclopenta[e]indol-6(3*H*)-one (3.104): Isolated as an off-white powder (68 mg, 92% yield). M.p. 189-191 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.28 (dd, J = 1.9 Hz, 7.0 Hz, 2H), 8.06 (dd, J = 1.9 Hz, 7.0 Hz, 2H), 7.99 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 3.7, 1H) 6.95 (d, J = 3.6 Hz, 1H), 3.49 (dd, J = 17.4 Hz, 7.6 Hz, 1H), 2.83-2.73 (m, 2H), 1.31 (d, J = 7.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 208.2 (C), 150.9 (C), 148.7 (C), 143.1 (C), 137.9 (C), 132.6 (C), 128.2 (CH), 127.1 (CH), 124.7 (CH), 120.7 (CH), 113.0 (CH), 108.4 (CH), 41.9 (CH), 33.4 (CH$_2$), 16.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{18}$H$_{14}$N$_2$O$_5$S (M$^+$): 370.0623 Found: 370.0631.
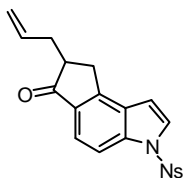
7-Allyl-3-(4-nitrophenylsulfonyl)-7,8-dihydrocyclopenta[e]indol-6(3*H*)-one (3.105): Isolated as yellow powder (65 mg, 82% yield). M.p. 166-167 °C; ^{1}H NMR (CDCl$_3$, 300 MHz)8.29 (d, J = 8.9 Hz, 2H), 8.07 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 3.7 Hz, 1H), 6.84 (d, J = 3.6 Hz, 1H), 5.84-5.71 (m, 1H), 5.09 (dd, J = 17.1 Hz, 1.1 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 3.37 (dd, J = 7.6 Hz, 17.6 Hz, 1H), 2.93 (dd, J = 3.4 Hz, 17.7 Hz, 1H), 2.86-2.66 (m, 2H), 2.29-2.19 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 206.8 (C), 150.8 (C), 149.0 (C), 143.1 (C), 137.9 (C), 135.3 (CH), 132.9 (C), 128.2 (CH), 127.2 (CH), 124.7 (CH), 120.6 (CH), 117.1 (CH$_2$), 113.0 (CH), 108.4 (CH), 46.5 (CH), 35.6 (CH$_2$), 30.5 (CH$_2$); HRMS(EI) m/z calcd for C$_{20}$H$_{16}$N$_2$O$_5$S (M$^+$): 396.0780 Found: 396.0785.
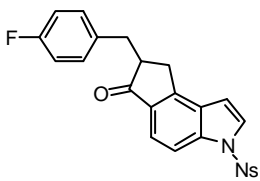
7-(4-Fluorobenzyl)-3-(4-nitrophenylsulfonyl)-7,8-dihydro-cyclopenta-[e]indol-6(3*H*)-one (**3.106**): Isolated as a yellow powder (88 mg, 98% yield). M.p. 192-194 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.28 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 3.7 Hz, 1H), 7.17 (dd, *J* = 5.5 Hz, 8.3 Hz, 2H), 6.95 (app t, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 3.6 Hz, 1H), 3.33 (dd, *J* = 4.5 Hz, 14.3 Hz, 1H), 3.30-3.21 (m, 1H), 3.05-2.97 (m, 1H), 2.87 (dd, *J* = 3.7 Hz, 17.4 Hz, 1H), 2.66 (dd, *J* = 10.1 Hz, 14.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 206.3 (C), 161.6 (d, *J* = 242.9 Hz, CF), 150.9 (C), 148.7 (C), 137.9 (C), 135.0 (d, *J* = 4.0 Hz, C), 132.7 (C), 130.3 (d, *J* = 7.8 Hz, CH), 128.2 (CH), 128.1 (C), 127.2 (CH), 124.7 (CH), 120.6 (CH), 115.34 (d, *J* = 21.0 Hz, CH), 113.1 (CH), 108.3 (CH), 48.8 (CH), 36.1 (CH$_2$), 30.4 (CH$_2$); HRMS(EI) *m/z* calcd for C$_{24}$H$_{17}$FN$_2$O$_5$S (M$^+$): 464.0842 Found: 464.0849.

Synthesis of *N*-H indoles 3.107 and 3.108:
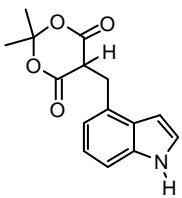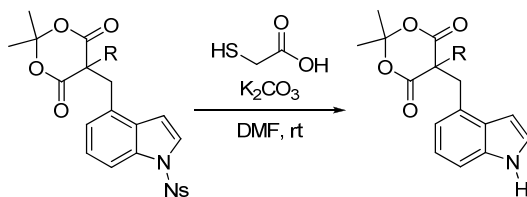
5-((1*H*-Indol-4-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3.107**): Meldrum's acid derivative **3.97** (458 mg, 1.0 mmol, 1.0 equiv) was dissolved in DMF (4 mL) at rt and K$_2$CO$_3$ (750 mg, 6.0 mmol, 6.0 equiv) was added. When bubbling ceased, thioglycolic acid (200 µL, 3.0 mmol, 3.0 equiv) was added; stirring was continued for 16 h, at which point a thick suspension had formed. This was diluted with H$_2$O (20 mL) and poured into a separatory funnel containing 5% HCl (10 mL). The aqeous phase was extracted with Et$_2$O (3X 15 mL), the combined organic phases dried over MgSO$_4$, filtered, and concentrated. The residue was purified by flash column chromatography eluting with a gradient from 9:1 to 4:1 hexanes:EtOAc to yield the product as a yellow wax (221 mg, 85% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 8.23 (br s, 1H), 7.30-7.26 (m, 1H), 7.20 (t, *J* = 2.8 Hz, 1H), 7.12 (dd, *J* = 9.1 Hz, 7.2 Hz, 1H), 7.11 (s, 1H), 6.64 (br s, 1H), 3.88 (t, *J* = 5.0 Hz, 1H), 3.76 (d, *J*

= 5.0 Hz, 2H), 1.67 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.6 (C), 135.8 (C), 129.8 (C), 127.0 (C), 124.3 (CH), 122.1 (CH), 120.6 (CH), 110.2 (CH), 105.2 (C), 100.6 (CH), 47.6 (CH), 29.7 (CH$_2$), 28.5 (CH$_3$), 26.8 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{15}$H$_{15}$NO$_4$ (M$^+$): 273.1001 Found: 273.0998.
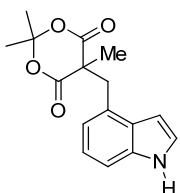
5-((1*H*-Indol-4-yl)methyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione 3.108: Prepared by the same procedure as **3.107**, using Meldrum's acid derivative **3.98** (470 mg, 1.0 mmol, 1.0 equiv) and stirring for 6 h at rt. Isolated by flash column chromatography eluting with 4:1 hexanes:EtOAc to give the indole as a white solid (121 mg, 42% yield). M.p. 195-196 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.14 (br s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H, overlaps with CHCl$_3$), 7.17 (br s, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.65 (br s, 1H), 3.65 (s, 2H), 1.80 (s, 3H), 1.51 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 170.2 (C), 135.9 (C), 127.8 (C), 127.3 (C), 124.4 (CH), 122.0 (CH), 121.6 (CH), 110.6 (CH), 105.2 (C), 101.9 (CH), 42.8 (CH$_2$), 29.5 (CH$_3$), 27.9 (CH$_3$), 26.0 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{16}$H$_{17}$NO$_4$ (M$^+$): 287.1158 Found: 287.1161.

Intermolecular Friedel-Crafts Acylation of *N*-Ns Indole 3.109:
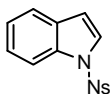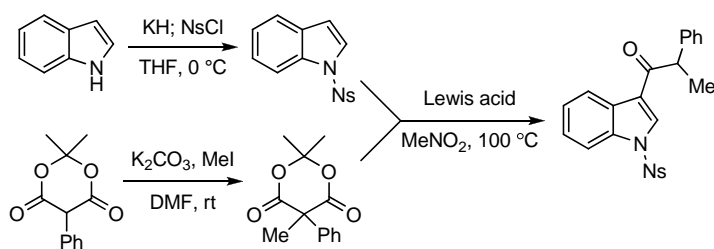
1-(4-Nitrophenylsulfonyl)-*1H*-indole (3.109): KH (240 mg, 6.0 mmol, 1.2 equiv, from 35 wt% suspension in mineral oil washed 3X with pentane) was suspended in THF (20 mL) and cooled to 0 °C. Indole (585 mg, 5.0 mmol, 5.0 equiv) dissolved in THF (10 mL) was added dropwise over 5 min (*Caution: H$_2$ gas evolved. Vent reaction flask)* and stirred at 0 °C for 30 min. A solution of NsCl (1.66 g, 7.5 mmol, 1.5 equiv) in THF (10 mL) was then added dropwise over 2 minute, and stirring continued for 30 min at 0 °C. The reaction was quenched with saturated NH$_4$Cl solution

(15 mL) and poured into a separatory funnel containing H_2O (50 mL). This was extracted with EtOAc (3X 50 mL), the combined organic phases were dried over $MgSO_4$, filtered through a pad of silica, and concentrated to give an orange solid (1.17 g, 77%). M.p. 110-112 °C; ^1H NMR (CDCl$_3$, 300 MHz) 8.25-8.21 (m, 2H), 8.03-7.99 (m, 2H), 7.98-7.95 (m, 1H), 7.54-7.51 (m, 2H), 7.36-7.30 (m, 1H), 7.28-7.21 (m, 1H, overlaps with CHCl$_3$), 6.71-6.69 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 150.6 (C), 143.3 (C), 134.7 (C), 130.9 (C), 128.0 (CH), 126.0 (CH), 125.2 (CH), 124.5 (CH), 124.1 (CH), 121.8 (CH), 113.4 (CH), 110.7 (CH); HRMS(EI) m/z calcd for $C_{14}H_{10}N_2O_4S$ (M$^+$): 302.0361 Found: 302.0370.
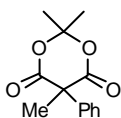
2,2,5-Trimethyl-5-phenyl-1,3-dioxane-4,6-dione (**3.110**): 2,2-Dimethyl-5-phenyl-1,3-dioxane-4,6-dione[150] (1.46 g, 6.6 mmol, 1.0 equiv) was dissolved in DMF (10 mL) at rt. K_2CO_3 (1.80 g, 13.2 mmol, 2.0 equiv) was added with vigorous stirring, followed by methyl iodide (2.0 mL, 33 mmol, 5.0 equiv). The reaction was stirred 18 h at rt, poured into a separatory funnel containing Et_2O (100 mL), and washed with saturated $NaHCO_3$ (1X), H_2O (3X) and brine (1X, 75 mL each), dried over $MgSO_4$, filtered and concentrated. The resulting solid was recrystallized from MeOH to give **3.110** as an off-white solid (950 mg, 58% yield). M.p. 147-149 °C; ^1H NMR (CDCl$_3$, 300 MHz) 7.39-7.32 (m, 5H), 1.84 (s, 3H), 1.70 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 167.4 (C), 137.1 (C), 129.7 (CH), 128.8 (CH), 125.7 (CH), 105.5 (C), 55.5 (C), 29.4 (CH$_3$), 27.2 (CH$_3$), 26.3 (CH$_3$); HRMS(EI) m/z calcd for $C_{13}H_{14}O_4$ (M$^+$): 234.0892 Found: 234.0886.
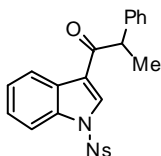
1-(1-(4-Nitrophenylsulfonyl)-*1H*-indol-3-yl)-2-phenylpropan-1-one (**11**): **Reaction w/ BF$_3$•OEt$_2$:** An oven-dried Schlenk tube cooled under N_2 was charged with **3.109** (64 mg, 0.2 mmol, 1.0 equiv), **3.110** (70 mg, 0.3 mmol, 1.5 equiv), and $MeNO_2$ (300 μL). BF$_3$•OEt$_2$ (28 μL, 0.22 mmol, 1.1 equiv) was added, rinsed into the tube with $MeNO_2$ (200 μL), and tube was sealed and heated at 100 °C in a temperature-controlled oilbath for 90 min. The reaction was cooled to rt, the contents rinsed into a round-bottom flask with EtOAc, and concentrated. Purification of the residue by flash column chromatography eluting with 19:1 hexanes:EtOAc gave the product as a yellow solid (66 mg, 76% yield). M.p. 159-161 °C; ^1H NMR (CDCl$_3$, 300

MHz) 8.37-8.34 (m, 1H), 8.15 (d, J = 8.8 Hz, 2H), 7.98 (s, 1H), 7.86-7.83 (m, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.35-7.24 (m, 7H, overlaps with CHCl$_3$), 4.43 (q, J = 6.8 Hz, 1H), 1.54 (d, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 195.8 (C), 150.7 (C), 142.4 (C) 134.6 (C), 132.2 (CH), 129.2 (CH), 128.3 (C), 128.0 (CH), 127.6 (CH), 127.1 (CH), 126.3 (CH), 125.5 (CH), 124.6 (CH), 123.6 (CH), 121.4 (C), 112.9 (CH), 50.5 (C), 18.7 (CH$_3$); HRMS(EI) m/z calcd for C$_{23}$H$_{18}$N$_2$O$_5$S (M$^+$): 434.0936 Found: 434.0930.

Reaction with Yb(OTf)$_3$: An oven-dried Schlenk tube cool under N$_2$ was charged with Yb(OTf)$_3$ (13 mg, 0.02 mmol, 10 mol %) in a glovebox and the tube removed from the box. To it was added **3.109** (64 mg, 0.2 mmol, 1.0 equiv) and **3.110** (70 mg, 0.3 mmol, 1.5 equiv) and MeNO$_2$ (0.5 mL), the tube was sealed tightly and heated at 100 °C in a temperature-controlled oilbath for 30 min. The reaction was worked up and purified in the same manner as for the reaction with BF$_3$•OEt$_2$, giving the product as a yellow solid (47 mg, 54% yield). Spectral data was identical to that obtained using BF$_3$•OEt$_2$.
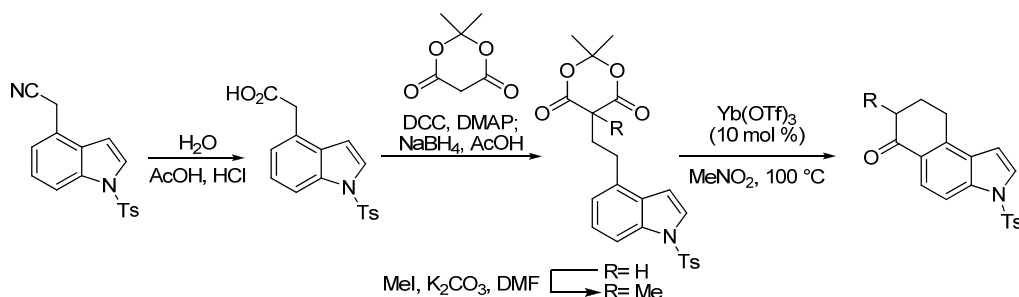
2-(1-Tosyl-*1H*-indol-4-yl)acetic acid (3.113): 2-(1-Tosyl-*1H*-indol-4-yl)acetonitrile (**3.112**, 775 mg, 2.5 mmol) was dissolved in glacial acetic acid (10 mL) at rt. With vigorous stirring, concentrated HCl (7 mL) was added and the resulting solution heated to reflux for 1 h. Distilled water (3 mL) was added to the refluxing reaction through the top of the condenser, and heating continued for 15 h. The solution was cooled, and poured into H$_2$O (50 mL) in a separatory funnel. The reaction flask was rinsed with EtOAc (50 mL), and the rinses added to the funnel and the layers separated. The aqueous phase was extracted 2X with EtOAc (25 mL each), the combined organics were washed with H$_2$O (3X 50 mL) and brine (1X 50 mL), dried over MgSO$_4$, filtered and concentrated. The residue was dissolved in dry benzene (100 mL)

and concentrated (repeated twice) to remove residual acetic acid. After drying on high vacuum to a constant weight, the acid was obtained as a beige solid (600 mg, 73% yield). M.p. 151-152 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.90 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 3.7 Hz, 1H), 7.27-7.24 (m, 1H, overlaps with CHCl$_3$), 7.20 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 3.7 Hz, 1H), 3.79 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 177.0 (C), 145.0 (C), 135.2 (C), 134.7 (C), 130.3 (C), 129.9 (CH), 126.9 (CH), 126.4 (CH), 125.9 (C), 124.7 (CH), 124.3 (CH), 112.8 (CH), 106.9 (CH), 38.5 (CH$_2$), 21.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{17}$H$_{15}$NO$_4$S (M$^+$): 329.0722 Found: 329.0716.
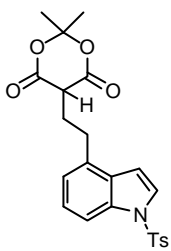
2,2-Dimethyl-5-(2-(1-tosyl-*1H*-indol-4-yl)ethyl)-1,3-dioxane-4,6-dione (3.114):Indoleacetic acid **3.112** (330 mg, 1.0 mmol) was condensed with Meldrum's acid and reduced according the described procedure.[145] Isolated as a white solid (300 mg, 68%) following recrystallization from MeOH. M.p. 153-155 °C (dec); ^{1}H NMR (CDCl$_3$, 300 MHz) 7.84 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 3.6 Hz, 1H), 7.24-7.19 (m, 3H, overlaps with CHCl$_3$), 7.06 (d, J = 7.3 Hz, 1H), 6.83 (d, J = 3.5 Hz, 1H), 3.46 (t, J = 5.0 Hz, 1H), 2.99 (t, J = 7.9 Hz, 2H), 2.42-2.35 (m, 2H), 2.32 (s, 3H), 1.73 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.5 (C), 144.9 (C), 134.8 (C), 133.3 (C), 130.2 (C), 129.9 (CH), 126.8 (CH), 126.2 (CH), 124.8 (CH), 123.2 (CH), 111.9 (CH), 107.1 (CH), 105.0 (C), 45.2 (CH), 29.5 (CH$_2$), 28.4 (CH$_3$), 27.2 (CH$_2$), 26.5 (CH$_3$), 21.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{23}$H$_{23}$NO$_6$S (M$^+$): 441.1246 Found: 441.1248.
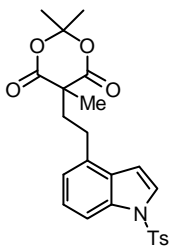
2,2,5-Trimethyl-5-(2-(1-tosyl-*1H*-indol-4-yl)ethyl)-1,3-dioxane-4,6-dione (3.115): Meldrum's acid derivative **3.114** (90 mg, 0.2 mmol, 1.0 equiv) was alkylated with MeI (60 μL, 1.0 mmol, 5.0 equiv), K$_2$CO$_3$ (55 mg, 0.4 mmol, 2.0 equiv) following the general procedure and workup for the preparation of **3.98-3.100**. Chromatographed eluting with 4:1 hexanes:EtOAc to give a white solid (74 mg, 80% yield). M.p. > 250 °C (dec); ^{1}H NMR (CDCl$_3$, 300 MHz) 7.83 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 3.7 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.18 (t, J = 7.9 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.69 (d, J = 3.8 Hz, 1H), 2.71-2.66 (m, 2H), 2.31 (s, 3H), 2.29-2.26 (m, 2H), 1.76 (s, 3H), 1.74 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 170.2 (C), 144.9 (C), 135.3 (C), 134.8 (C),

132.6 (C), 129.8 (CH), 129.7 (C), 126.8 (CH), 126.2 (C), 124.7 (CH), 122.9 (CH), 112.0 (CH), 106.8 (CH), 105.1 (C), 49.5 (C), 41.7 (CH$_2$), 29.8 (CH$_3$), 29.3 (CH$_2$), 28.7 (CH$_3$), 24.4 (CH$_3$), 21.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{24}$H$_{25}$NO$_6$S (M$^+$): 455.1403 Found: 455.1404.

General Procedure for acylation of Meldrum's acids 3.114 and 3.115: An oven-dried Schlenk tube cooled under nitrogen was charged with Yb(OTf)$_3$ (6 mg, 0.01 mmol, 0.1 equiv) and Meldrum's acid derivative (0.1 mmol, 1.0 equiv). To this was added MeNO$_2$ (1.0 mL), the tube was sealed tightly and heated at 100 °C in a temperature controlled oilbath. Upon completion, the tube was cooled to rt, the contents filtered through a short pad of silica gel, the pad washed with CH$_2$Cl$_2$, and the solvent evaporated. The residue was purified by flash column chromatography or recrystallization to give the acylated products
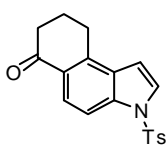
3-Tosyl-8,9-dihydro-3H-benzo[e]indol-6(7H)-one (3.116):Prepared from **3.114** (44 mg), heated for 1.75 h, and purified by recrystallizing from MeOH to give the product as a beige solid (27 mg, 78% yield). M.p. 219-221 °C (dec); ^{1}H NMR (CDCl$_3$, 300 MHz) 8.00 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 3.7 Hz, 1H), 7.22 (d, J = 9.1 Hz, 2H, overlaps with CHCl$_3$), 6.73 (d, J = 3.6 Hz, 1H), 3.07 (t, J = 6.1 Hz, 2H), 2.65 (t, J = 6.5 Hz, 2H), 2.33 (s, 3H), 2.15 (app quint, J = 6.3 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 197.8 (C), 145.4 (C), 138.7 (C), 136.9 (C), 135.1 (C), 130.0 (CH), 128.0 (C), 126.93 (C), 126.90 (CH), 123.8 (CH), 111.8 (CH), 107.4 (CH), 38.8 (CH$_2$), 26.3 (CH$_2$), 22.9 (CH$_2$), 21.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{19}$H$_{17}$NO$_3$S (M$^+$): 339.0929 Found: 339.0926.
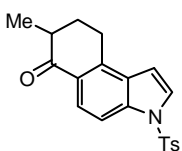
7-Methyl-3-tosyl-8,9-dihydro-3H-benzo[e]indol-6(7H)-one (3.117): Prepared from **3.115** (45 mg), heated for 30 min, and purified by flash chromatography eluting with 9:1 hexanes:EtOAc to give the product as a white solid (29 mg, 83% yield). M.p. 214-216 °C (dec); ^{1}H NMR (CDCl$_3$, 300 MHz) 8.00 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 3.7 Hz, 1H), 7.24-7.21 (m, 2H, overlaps with CHCl$_3$), 6.72 (d, J = 3.6 Hz, 1H), 3.20-2.99 (m, 2H), 2.66-2.54 (m, 1H), 2.33 (s, 3H), 2.24 (dq, J = 4.4 Hz, 13.2

124

Hz, 1H), 1.96-1.83 (m, 1H), 1.25 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 200.2 (C), 145.3 (C), 138.3 (C), 136.8 (C), 135.0 (C), 130.0 (CH), 129.1 (C), 127.3 (C), 126.89 (CH), 126.86 (CH), 124.0 (CH), 111.9 (CH), 107.3 (CH), 42.1 (CH), 30.9 (CH$_2$), 25.6 (CH$_2$), 21.6 (CH$_3$), 15.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{20}$H$_{19}$NO$_3$S (M$^+$): 353.1086 Found: 353.1090.

Synthesis of *N*-Sulfonyl-Protected 4-Indolylpropionic Acids 3.121 and 3.122
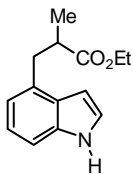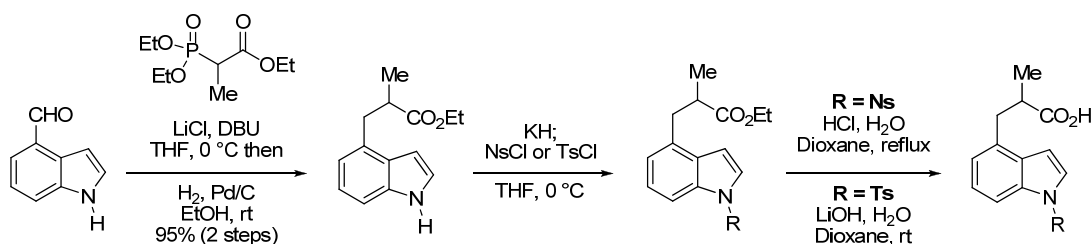
 Ethyl 3-(1*H*-indol-4-yl)-2-methylpropanoate (3.118): In a glovebox, a dry round-bottom flask was charged with LiCl (760 mg, 18 mmol, 3.6 equiv) in THF (20 mL) was added ethyl 2-(diethoxyphosphoryl)propanoate (1.25 mL, 6 mmol, 1.2 equiv) at rt. DBU (2.7 mL, 18 mmol, 3.6 equiv) was added and the reaction was stirred 1 h at rt, at which point a white precipitate had formed. To this was added a solution of indole-4-carboxaldehyde (**3.91**, 725 mg, 5.0 mmol, 1.0 equiv) in THF (20 mL) dropwise over 5 min and stirring was continued for 18 h. The reaction was quenched with 50 mL saturated NH$_4$Cl solution, and poured into 50 mL H$_2$O in a separatory funnel. The aqueous phase was extracted with EtOAc (3X 100 mL), and the combined organic phases dried over MgSO$_4$, filtered and concentrated. The residue was dissolved in reagent grade EtOH (50 mL) and degassed/purged with vacuum/nitrogen three times. 10% palladium on carbon (wt/wt, 70 mg) was added, and the flask was degassed/purged with vacuum/H$_2$ (balloon) three times. The reaction was stirred under an atmosphere of H$_2$ (balloon) for 16 h, then filtered through Celite and concentrated. Purification by flash column chromatography eluting with 17:3 hexanes:EtOAc yielded the ester **3.118** as a pink oil (1.1 g, 95% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 8.15 (br s, 1H), 7.25 (d, $J = 8.3$ Hz, 1H, overlaps with CHCl$_3$), 7.19 (t, $J = 2.8$ Hz, 1H), 7.10 (t, $J = 7.7$ Hz, 1H), 6.90 (d, $J = 7.1$ Hz, 1H), 6.58 (t, $J = 2.1$ Hz, 1H), 4.09 (q, $J = 7.1$ Hz, 2H),

3.34 (app dd, J = 16.6 Hz, 9.5 Hz, 1H), 2.93-2.85 (m, 2H) 1.17 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 176.6 (C), 135.7 (C), 131.7 (C), 127.5 (C), 123.7 (CH), 121.9 (CH), 120.1 (CH), 109.3 (CH), 101.0 (CH), 60.2 (CH$_2$), 40.6 (CH), 37.4 (CH$_2$), 16.9 (CH$_3$), 14.1 (CH$_3$); HRMS(EI) m/z calcd for C$_{14}$H$_{17}$NO$_2$ (M$^+$): 231.1259 Found: 231.1266.

General procedure for preparation of 3.119 and 3.120: KH (44 mg, 1.1 mmol, 1.1 equiv, from 35 wt% suspension in mineral oil washed 3X with pentane) was suspended in THF (5 mL) and cooled to 0 °C. To this was added a solution of ester **3.118** (231 mg, 1.0 mmol, 1.0 equiv) in THF (5 mL) dropwise over three min. After stirring 5 min at 0 °C, a solution of the appropriate electrophile in THF (5 mL) was added. The reaction was stirred 30 min, and quenched by addition of saturated NaHCO$_3$ solution (15 mL), poured into a separatory funnel containing distilled water (50 mL), and the aqueous phase was extracted with EtOAc (3X 50 mL). The combined organic phases dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography eluting with 17:3 hexanes:EtOAc yielded the protected ester.
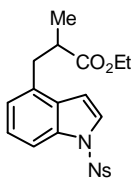
Ethyl 2-methyl-3-(1-(4-nitrophenylsulfonyl)-1H-indol-4-yl)propanoate (3.119): Prepared using 4-nitrophenylsulfonyl chloride (250 mg, 1.2 mmol, 1.2 equiv) and isolated as a yellow oil (385 mg, 93% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 8.26-8.23 (m, 2H), 8.02 (dd, J = 1.9 Hz, 7.0 Hz, 2H), 7.82 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 3.8 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H, overlaps with CHCl$_3$), 7.05 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 3.7 Hz, 1H), 4.00 (d, J = 7.0 Hz, 2H), 3.19 (app dd, J = 13.1 Hz, 6.5 Hz, 1H), 2.84-2.70 (m, 2H), 1.12 (d, J = 6.7 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 175.7 (C), 150.6 (C), 143.3 (C), 134.7 (C), 133.0 (C), 130.3 (C), 128.0 (CH), 125.6 (CH), 125.2 (CH), 124.5 (CH), 124.4 (CH), 111.5 (CH), 108.9 (CH), 60.3 (CH$_2$), 40.8 (CH), 36.6 (CH$_2$), 17.0 (CH$_3$), 14.0 (CH$_3$); HRMS(EI) m/z calcd for C$_{20}$H$_{20}$N$_2$O$_6$S (M$^+$): 416.1042 Found: 416.1034.
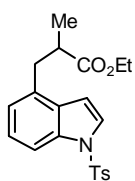
Ethyl 2-methyl-3-(1-(tosyl)-1H-indol-4-yl)propanoate (3.120):Prepared using tosyl chloride (228 mg, 1.2 mmol, 1.2 equiv) and isolated as a colourless oil (340 mg, 88%). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.83 (d, J = 8.3

Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 3.7 Hz, 1H), 7.22-7.17 (t, J = 7.8 Hz, 1H), 7.21-7.18 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 7.3 Hz, 1H), 6.69 (d, J = 3.7 Hz, 1H), 4.02-3.95 (m, 2H), 3.19 (dd, J = 12.7 Hz, 6.0 Hz, 1H), 2.84-2.71 (m, 2H), 2.32 (s, 3H), 1.16 (d, J = 6.7 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 176.0 (C), 144.9 (C), 135.3 (C), 134.7 (C), 132.5 (C), 130.2 (C), 129.8 (CH), 126.8 (CH), 125.9 (CH), 124.5 (CH), 123.6 (CH), 111.7 (CH), 107.2 (CH), 60.3 (CH$_2$), 40.8 (CH), 36.8 (CH$_2$), 21.5 (CH$_3$), 17.0 (CH$_3$), 14.0 (CH$_3$); HRMS(EI) m/z calcd for C$_{21}$H$_{23}$NO$_4$S (M$^+$): 385.1348 Found: 385.1354.
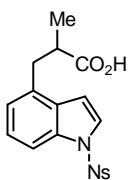
2-Methyl-3-(1-(4-nitrophenylsulfonyl)-*1H*-indol-4-yl)propanoic acid (3.121): Ethyl ester **3.119** (350 mg, 0.84 mmol) was dissolved in dioxane (10 mL) at rt, and H$_2$O (5 mL) was added. The resulting cloudy solution was heated to reflux, and concentrated HCl (1 mL) was added through the condenser. The solution was heated 6 h, and then additional HCl (1 mL) was added. After another 6 h, the reaction was cooled to rt, diluted with H$_2$O (50 mL) and extracted with EtOAc (3X 25 mL). The combined organic phases were washed with H$_2$O (3X 50 mL), dried over MgSO$_4$, filtered, and concentrated. Purification by flash column chromatography eluting with 2:1 hexanes:EtOAc gave the acid as a white solid (254 mg, 78% yield). M.p. 172-173 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.25 (dd, J = 7.0 Hz, 1.8 Hz, 2H), 8.03-8.00 (m, 2H), 7.84 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H, overlaps with CHCl$_3$), 7.07 (d, J = 7.4 Hz, 1H), 6.76 (d, J = 3.8 Hz, 1H), 3.25-3.20 (m, 1H), 2.85-2.74 (m, 2H), 1.14 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 181.5 (C), 150.6 (C), 143.3 (C), 134.7 (C), 132.5 (C), 130.3 (C), 1281. (CH), 125.8 (CH), 125.3 (CH), 124.5 (CH), 124.4 (CH), 111.7 (CH), 108.6 (CH), 40.5 (CH), 36.3 (CH$_2$), 16.8 (CH$_3$); HRMS(EI) m/z calcd for C$_{18}$H$_{16}$N$_2$O$_6$S (M$^+$): 388.0729 Found: 388.0724.
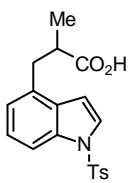
2-Methyl-3-(1-tosyl-*1H*-indol-4-yl)propanoic acid (3.122): Ethyl ester **3.120** (315 mg, 0.82 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (10 mL) at rt, and distilled water (10 mL), followed by LiOH•H$_2$O (140 mg, 3.3 mmol, 4.0 equiv), was added. The solution was stirred for 6 h and acidified (pH 1) by dropwise addition of concentrated HCl. The suspension was extracted with EtOAc (3X 25 mL), and the combined organic layers were washed with H$_2$O (3X 50 mL)

and with brine (1X 50 mL), dried over MgSO$_4$, filtered, and concentrated. Purification by flash chromatography eluting with 2:1 EtOAc:hexanes gave the product as a white solid (280 mg, 96% yield). M.p. 139-141 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.84 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 3.3 Hz, 1H), 7.21 (app t, J = 8.2 Hz, 3H, overlaps with CHCl$_3$), 3.27 (dd, J = 17.0 Hz, 9.4 Hz, 1H), 2.80 (app br d, J = 8.9 Hz, 2H), 2.31 (s, 3H), 1.13 (d, J = 5.8 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 182.4 (C), 144.9 (C), 135.2 (C), 134.7 (C), 132.0 (C), 130.1 (C), 129.8 (C), 126.8 (CH), 126.0 (CH), 124.5 (CH), 123.6 (CH), 111.8 (CH), 106.9 (CH), 40.5 (CH), 36.3 (CH$_2$), 21.6 (CH$_3$), 16.7 (CH$_3$); HRMS(EI) m/z calcd for C$_{19}$H$_{19}$NO$_4$S (M$^+$): 357.1035 Found: 357.1044.

Preparation of HWE reagent S3.5
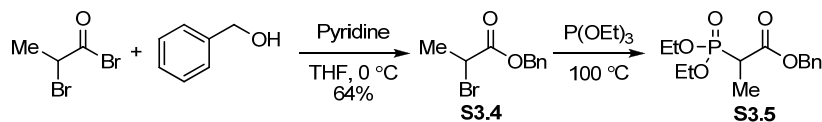
Benzyl 2-bromopropanoate (S3.4): Benzyl alcohol (10.3 mL, 100 mmol, 2.0 equiv) and pyridine (8.0 mL, 100 mmol, 2.0 equiv) were dissolved in THF (100 mL) and cooled to 0 °C. 2-Bromopropionyl bromide (5.2 mL, 50 mmol, 1.0 equiv) was added dropwise over 10 min, during which time a white precipitate formed. The mixture was stirred at 0 °C for 45 min, and then quenched by addition of H$_2$O (100 mL). The solution was poured into a separatory funnel containing ether (100 mL) and the layers separated. The organic phase was washed sequentially with saturated NH$_4$Cl solution (2X 50 mL), distilled water (1X 50 mL), saturated NaHCO$_3$ (1X 50 mL), and brine (1X 50 mL), dried over MgSO$_4$, filtered, and concentrated. Bulb-to-bulb distillation of the residue (0.5 mm Hg, 70 °C) to remove excess benzyl alcohol gave the ester as a clear, colourless oil (7.8 g, 64% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.36-7.31 (m, 5H), 5.19 (s, 2H), 4.39 (q, J = 6.9 Hz, 1H), 1.82 (d, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 170.0 (C), 135.2 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 67.6 (CH$_2$), 40.0 (CH), 21.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{10}$H$_{11}$BrO$_2$ (M$^+$): 241.9942 Found: 241.9946.

Benzyl 2-(diethoxyphosphoryl)propanoate (S3.5): Benzyl ester **S3.4** (7.5 g, 30.9 mmol, 1.0 equiv) and triethyl phosphite (5.5 mL, 32.4 mmol,

1.05 equiv) were mixed in a flask equipped with an air condenser, and heated at 100 °C in a temperature controlled oilbath. After heating for 16 h, an addition amount of triethyl phosphite (5.5 mL, 32.4 mmol, 1.05 equiv) was added and heating continued for 6 h. The reaction was cooled to rt, and bulb-to-bulb distilled (0.5 mm Hg, rt) to remove excess phosphite. Increasing the temperature (0.5 mm Hg, 130 °C) distilled the product as a clear, very pale yellow oil (7.0 g, 75% yield). The product thus obtained is contaminated with 10% **S3.4**, but can be used in subsequent steps without complications. ^{1}H NMR (CDCl$_3$, 300 MHz) 7.38-7.28 (m, 5H), 5.17 (AB q, J = 12.3 Hz, 18.7 Hz, 2H), 4.13-3.98 (m, 2H), 3.06 (dq, J = 7.3 Hz, 23.5 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H).

Synthesis of *N*-Carbonyl-Protected 4-Indolylpropionic Acids 3.124-3.125:
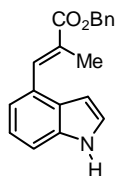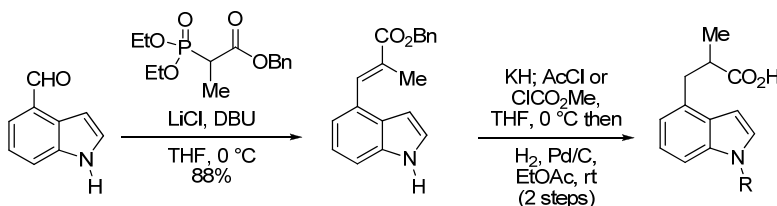
(*E*)-Benzyl 3-(1*H*-indol-4-yl)-2-methylacrylate (3.123): Prepared by the procedure for HWE reaction to yield **3.118**, on the same scale but omitting the subsequent hydrogenation. Purification by flash column chromatography eluting with 4:1 hexanes:EtOAc gave the unsaturated ester as a yellow oil (1.28 g, 88% yield, 10:1 ratio of *E:Z* isomers). Spectral data is of the major isomer only. ^{1}H NMR (CDCl$_3$, 300 MHz) 8.29 (br s, 1H), 8.18 (s, 1H), 7.49-7.36 (m, 6H), 7.29-7.20 (m, 4H, overlaps with CHCl$_3$), 6.63 (t, J = 2.1 Hz, 1H), 5.34 (s, 2H), 2.19 (d, J = 1.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.7 (CH), 137.6 (CH), 136.4 (C), 135.7 (C), 128.5 (CH), 128.3 (C), 128.1 (CH), 128.0 (CH), 127.9 (C), 127.5 (C), 124.6 (CH), 121.6 (CH), 120.6 (CH), 111.4 (CH), 101.5 (CH), 66.5 (CH$_2$), 14.7 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{19}$H$_{17}$NO$_2$ (M$^+$): 291.1259 Found: 291.1258.

General Procedure for protection/reduction of 3.123: KH (washed, 44 mg, 1.1 mmol, 1.1 equiv) was suspended in THF (5 mL) and cooled to 0 °C. To this was added a

solution of ester **3.123** (290 mg, 1.0 mmol, 1.0 equiv) in THF (5 mL) dropwise over three min. After stirring 5 min at 0 °C, the electrophile was added neat via syringe. The reaction was stirred 15 min at 0 °C, removed from the ice bath, stirred 15 min at rt and quenched by addition of saturated NH₄Cl solution (20 mL). This was extracted 3X with EtOAc (20 mL), and the combined organic phases washed with brine (30 mL), dried over MgSO₄, filtered, and concentrated. The residue was dissolved in EtOAc (10 mL), and degassed/purged with water-aspirator vacuum/nitrogen (3X). Pd-C (10 wt%, 40 mg) was added and the flask degassed/purged with vacuum/hydrogen (balloon, 3X), and then stirred at rt under an atmosphere of H₂ (balloon) for 48 h. The reaction was degassed/purged with vacuum/nitrogen (3X), filtered through a pad of Celite, the pad washed with EtOAc (50 mL), and concentrated. Purification by flash column chromatography or recrystallization gave the protected carboxylic acid.
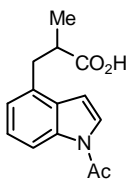
3-(1-Acetyl-*1H*-indol-4-yl)-2-methylpropanoic acid (3.124): Prepared using acetyl chloride (90 µL, 1.3 mmol, 1.3 equiv), and flash chromatography eluting by a gradient from 2:1 to 2:3 hexanes:EtOAc to give the product as a white solid (152 mg, 62% yield). M.p. 118-119 °C; ¹H NMR (CDCl₃, 300 MHz) 8.31 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 3.8 Hz, 1H), 7.27 (t, *J* = 8.8 Hz, 1H, overlaps with CHCl₃), 7.09 (d, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 3.8 Hz, 1H), 3.34 (dd, *J* = 17.0 Hz, 9.5 Hz, 1H), 2.92-2.86 (m, 2H), 2.62 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) 181.8 (C), 168.7 (C), 135.6 (C), 131.4 (C), 129.8 (C), 125.2 (CH), 125.0 (CH), 124.2 (CH), 115.0 (CH), 107.3 (CH), 40.7 (CH), 36.4 (CH₂), 24.0 (CH₃), 16.6 (CH₃); HRMS(EI) *m/z* calcd for C₁₄H₁₅NO₃ (M⁺): 245.1052 Found: 245.1045.
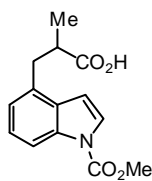
3-(1-(Methoxycarbonyl)-*1H*-indol-4-yl)-2-methylpropanoic acid (3.125): Prepared from methyl chloroformate (100 µL, 1.3 mmol, 1.3 equiv), and recrystallized from acetone to give the product as a white solid (178 mg, 68% yield). M.p. 137-138 °C; ¹H NMR (CDCl₃, 300 MHz) 8.06 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H, overlaps with CHCl₃), 7.06 (d, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 3.7 Hz, 1H), 4.02 (s, 3H), 2.92-2.86 (m ,2H), 1.17 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) 181.9 (C), 151.5 (C), 153.3 (C), 131.5 (C), 129.9 (C), 125.3 (CH), 124.6 (CH), 123.5 (CH), 113.6 (CH), 106.2 (CH),

53.8 (CH$_3$), 40.6 (CH), 36.5 (CH$_2$), 16.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{14}$H$_{15}$NO$_4$ (M$^+$): 261.1001 Found: 261.0997.

Friedel-Crafts Acylation of *N*-Protected 4-Indolylpropionic Acids:
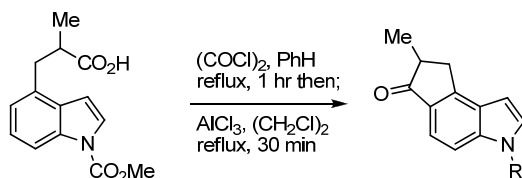
General Procedure for preparation of acid chlorides and AlCl$_3$-catalyzed acylation: Carboxylic acid (0.1 mmol, 1.0 equiv) was dissolved in benzene (1.0 mL) in a flask equipped with an oven-dried, water-cooled condenser. To this was added distilled (COCl)$_2$ (35 μL, 0.4 mmol, 4.0 equiv) at rt, and the solution heated to reflux for 1 hr. The flask was removed from heat, cooled to rt, then concentrated by rotary evaporation. The residue was dissolved in benzene (2 mL) and concentrated, followed by the same procedure with DCE (2X 2 mL). The resulting crude acid chloride was dissolved in DCE (2 mL) at rt, and AlCl$_3$ (40 mg, 0.3 mmol, 3.0 equiv) was added. The suspension was heated to reflux for 30 min, cooled to rt, and quenched with saturated NaHCO$_3$ (10 mL). The reaction was poured into a separatory funnel and the layers separated; the aqueous phase was extracted with CH$_2$Cl$_2$ (3X 5mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated. Purification by flash column chromatography or recrystallization yielded the indanones.
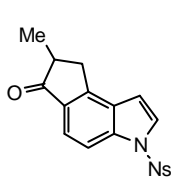
7-Methyl-3-(4-nitrophenylsulfonyl)-7,8-dihydrocyclopenta[e]indol-6(3*H*)-one (3.104): Prepared from **3.121** (39 mg) and purified by flash chromatography eluting with 2:1 hexanes:EtOAc to give the product as a yellow solid (27 mg, 73% yield). Spectral data matched that obtained by BF$_3$•OEt$_2$-catalyzed cyclization of **3.98**.
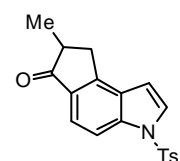
7-Methyl-3-tosyl-6,7-dihydrocyclopenta[e]indol-8(3*H*)-one **(3.126)**: Prepared from **3.122** (36 mg) and purified by recrystallization from 17:3 hexanes:EtOAc to give the product as a white solid (22 mg, 65% yield).

M.p. 188-190 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.98 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 3.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 6.4 Hz, 2H, overlaps with CHCl$_3$), 6.75 (d, J = 3.7 Hz, 1H), 3.48 (dd, J = 17.6 Hz, 7.8 Hz, 1H), 2.82-2.70 (m, 2H), 2.33 (s, 3H), 1.30 (d, J = 7.4 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 208.5 (C), 148.5 (C), 145.5 (C), 138.0 (C), 135.0 (C), 131.8 (C), 130.1 (CH), 127.8 (C), 127.4 (CH), 126.9 (CH), 119.9 (CH), 113.2 (CH), 106.8 (CH), 41.9 (CH), 33.4 (CH$_2$), 21.6 (CH$_3$), 16.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{19}$H$_{17}$NO$_3$S (M$^+$): 339.0929 Found: 339.0932.
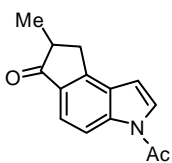
3-Acetyl-7-methyl-6,7-dihydrocyclopenta[e]indol-8(3H)-one (3.127): Prepared from **3.124** (25 mg) and purified by recrystallization from Et$_2$O to give the product as a white solid (18 mg, 78% yield). M.p. 202-204 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.46 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 3.8 Hz, 1H), 6.75 (d, J = 3.7 Hz, 1H), 3.54 (dd, J = 17.1 Hz, 7.4 Hz, 1H), 2.88-2.76 (m, 2H), 2.68 (s, 3H), 1.35 (d, J = 7.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 208.8 (C), 168.8 (C), 147.7 (C), 138.9 (C), 132.0 (C), 127.5 (C), 126.3 (CH), 120.5 (CH), 116.2 (CH), 107.1 (CH), 41.9 (CH), 33.4 (CH$_2$), 24.2 (CH$_3$), 16.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{14}$H$_{13}$NO$_2$ (M$^+$): 227.0946 Found: 227.0945.
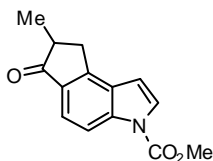
Methyl 7-methyl-8-oxo-7,8-dihydrocyclopenta[e]indole-3(6H)-carboxylate (3.128): Prepared from **3.125** (26 mg) and recrystallized from Et$_2$O to give the product as a white solid (21 mg, 88% yield). M.p. 133-134 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 8.21 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 3.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 3.7 Hz, 1H), 4.07 (s, 3H), 3.54 (dd, J = 17.1 Hz, 7.4 Hz, 1H), 2.88-2.77 (m, 2H), 1.35 (d, J = 7.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 208.8 (C), 151.2 (C), 148.1 (C), 138.7 (C), 131.6 (C), 127.6 (C), 126.7 (CH), 120.0 (CH), 114.9 (CH), 106.2 (CH), 54.2 (CH$_3$), 42.0 (CH), 33.4 (CH$_2$), 16.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{14}$H$_{13}$NO$_3$ (M$^+$): 243.0895 Found: 243.0904.

Chapter 4. Catalytic Conjugate Allylation of Alkylidene Meldrum's Acids

4.1 Nucleophilic Allylating Agents: General Considerations

The allyl group (CH$_2$CH=CH$_2$) is an extremely versatile synthon that is one of the fundamental building blocks of modern organic synthesis. Consequently, various means for its introduction via formation of a new C-C bond have been developed. Broadly speaking, they can be subdivided into electrophilic, neutral, and nucleophilic allylations, and each of these have been studied extensively. Electrophilic allylations such as the venerable S$_N$2′ reaction or the Tsuji-Trost reaction[151] (Scheme 4.1a) take advantage of the more reactive nature of allylic leaving groups. What could be considered a neutral allylation is the Alder-ene sigmatropic rearrangement, which is the most atom-economical means of allyl addition (Scheme 4.1b).[152] The third method, nucleophilic allylation using an allylorganometallic, is perhaps the most widely used reaction of the three (Scheme 4.1c). The synthetic utility of the allyl group lies in the versatility of the alkene, which can be used in various transformations such as oxidations, reductions, metathesis, hydrometallation *etc* (Scheme 4.1d).
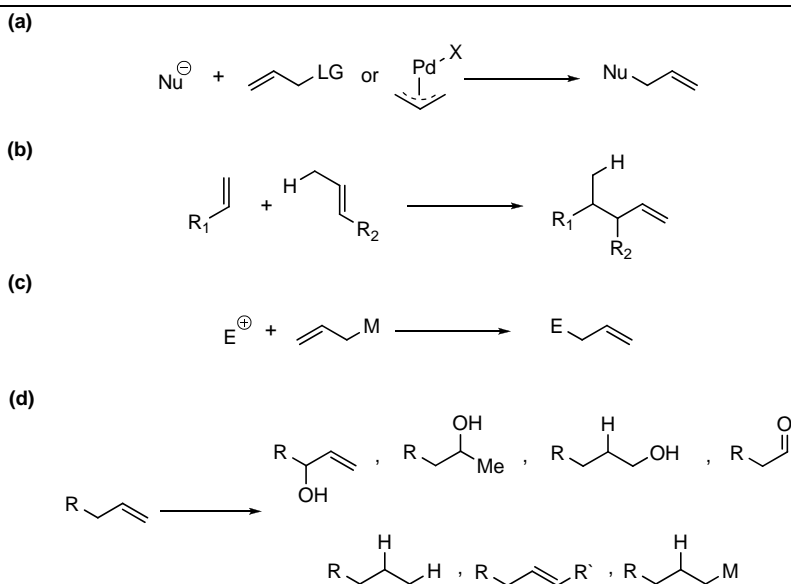
Scheme 4.1. Introduction and transformations of allyl groups

As mentioned, the addition of an allylorganometallic to an electrophile is an extremely useful C-C bond forming reaction that has found widespread use. One reason for the ubiquity of this process is the incredible array of known allyl-metals, which spans nearly every group of the periodic table, such that a suitable nucleophile can be found for nearly any desired electrophile.[153] The reaction that has attracted the most attention historically is the allylation of carbonyls, especially in terms of acting as a complement to the aldol reaction.[154] In this regard, the development of nucleophilic allylation was advanced significantly in the late 1970's and early 1980's when nucleophilic crotylation was studied extensively as a route to polypropionate natural products (Scheme 4.2). Investigations into the stereochemical course of these reactions by correlation of the geometry (*E* or *Z*) of the crotyl-metal reagent with the resulting diastereoselection (syn or anti) of the addition led to a realization that different mechanistic pathways were available. Subsequently, allylation reactions were classified into three types, which are dependant largely on the metal and the reaction conditions (especially the presence of catalysts).[155]
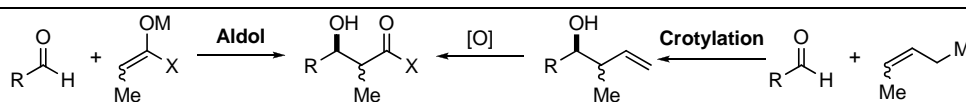
Scheme 4.2. Comparison of aldol and crotylation methods for synthesis of propionates

The Type I allylations are those where the allyl-metal reagent has a fixed, stable alkene geometry, and the syn:anti ratio of the products corresponds with the *E:Z* ratio of the nucleophile. The most commonly used Type I allylation is addition of allylboronates, and in fact it was Hoffmann's observation that (*Z*)-butenyl boronates add to aldehydes to give syn products that provided the stimulus for further studies in this area.[156] Therefore, as shown in Scheme 4.3a, the allylation is diastereoselective, and (*E*) alkene geometry leads to anti products, while the (*Z*)-alkene gives syn products. The allylations reactions which have the most bearing on the work presented in this chapter are the Type II, which are the reactions of (most commonly) allylsilicon and allyltin reagents with carbonyls, typically under Lewis acid catalysis. In these reactions, both the (*E*) and (*Z*) isomers lead predominantly to the syn products, with varying but often very high levels of selectivity

(Scheme 4.3b).[157] The advantage of Type II allylations is eliminating the need for highly stereoselective syntheses of the allylmetals. Type III allylations are those where either the (*E*) or (*Z*) allyl nucleophile gives predominantly the anti product (Scheme 4.3c). This is due to equilibration of the alkene to the more stable (*E*) geometry through allylic transposition before addition to the carbonyl.[158]
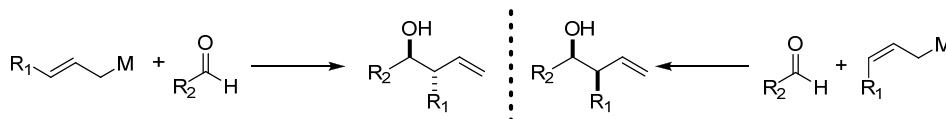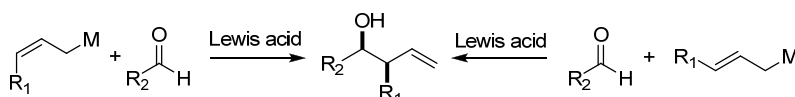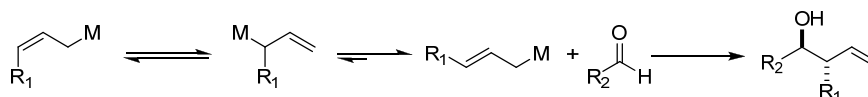
Scheme 4.3. Types I, II, and III in allylation of carbonyl compounds

The stereoselectivity of Type I and III reactions is rationalized by the formation of a six-membered ring transition state through the interaction of the carbonyl oxygen with the metal. Assuming a pseudoequatorial arrangement for the largest group on the carbonyl, the (*Z*) alkenes have their groups pseudoaxial while the (*E*) alkene is pseudoequatorial.[159] This then leads to the syn and anti addition products, respectively (Scheme 4.4a). Two possible mechanisms are proposed to account for the stereoconvergence of Type II, both of which assume an open (ie non-cyclic) transition state. Yamamoto suggested that the nucleophile approaches the carbonyl in an antiperiplanar orientation, where gauche interactions are minimized by placing the vinyl substituent near the aldehyde proton. Since the methylene carbon bearing the metal is not close to the reaction centre, its relative position is unimportant (Scheme 4.4b).[160] On the other hand, Denmark proposed that a synclinal orientation is optimal on the basis of intramolecular allylations on a system with constrained rotation (Scheme 4.4c).[161] While this model appears to cause more steric interactions than the antiperiplanar approach, it is

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proposed that favourable Coulombic interactions and secondary orbital overlap assist in stabilizing this approach.
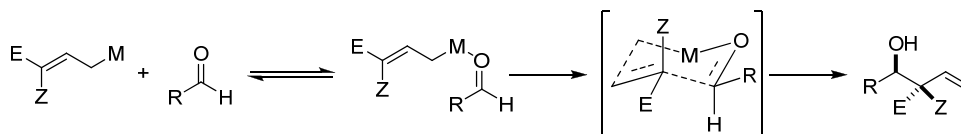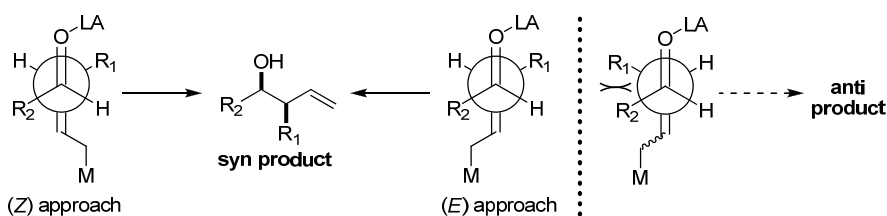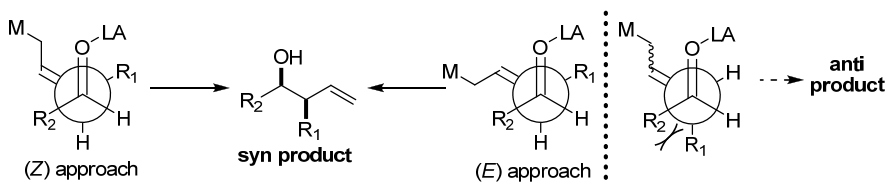
Scheme 4.4. Mechanisms of Types I and III and Type II allylations

Aside from the stereochemical issues of the mechanism, Type II allylations differ from Types I and III in that they are stepwise processes which involve the formation of a carbocation upon initial attack of the electrophile (Figure 4.1). The carbocation is stabilized by a hyperconjugative interaction with the adjacent C-M bond[162]; subsequent loss of the metal group regenerates the double bond. Consequently, the nucleophilicity of the allylating agent increases with the stability of the carbocation and is dependent on both the metal and the alkene substitution. As shown in Figure 4.1, the general trend is that allylsilanes are poorer nucleophiles than allylstannanes (with the substituents on the metal playing a role), and that addition of a methyl group at the 2-position has a strong influence on reactivity (the scale is logarithmic and the larger numbers are the most nucleophilic).[163]
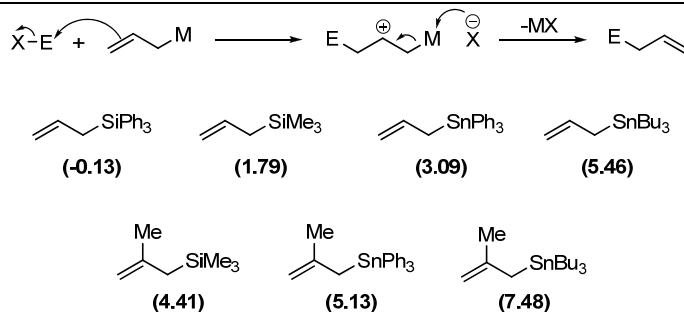
Figure 4.1. Mechanism of allylation and nucleophilicity of Type II allylation agents

The importance of Type II allylations to the work presented in this thesis is that they are not reliant on complexation to the electrophile in order to effect allyl transfer. In the next chapter, the significance of this in terms of extending the reactions of allyl nucleophiles to conjugate addition will be explored.

4.2 Lewis Acid-Activated Conjugate Allylations

While the precomplexation of the metal in allylnucleophiles to the carbonyl oxygen provides an incredibly useful organization of the reactants in Type I and III allylations, the resulting preference for 1,2-addition makes these allylations unsuitable for selective 1,4-conjugate additions. For example, cuprates are often used as soft nucleophiles which preferentially undergo 1,4-addition to α,β-unsaturated carbonyl compounds.[164] However, the intervention of a six-membered ring transition state in the case of reactions using allylcuprates can cause this selectivity to be lost. As shown in Scheme 4.5a, reaction of the unsaturated ester **4.1** with the reagent formed from allylMgBr and CuBr•DMS leads to predominant formation of the 1,2-addition product **4.2** and only a small amount of the conjugate addition product **4.3**.[165] In contrast, addition of non-allylcuprates to the same electrophile leads to exclusive formation of the 1,4-product **4.4** (Scheme 4.5b).[166]

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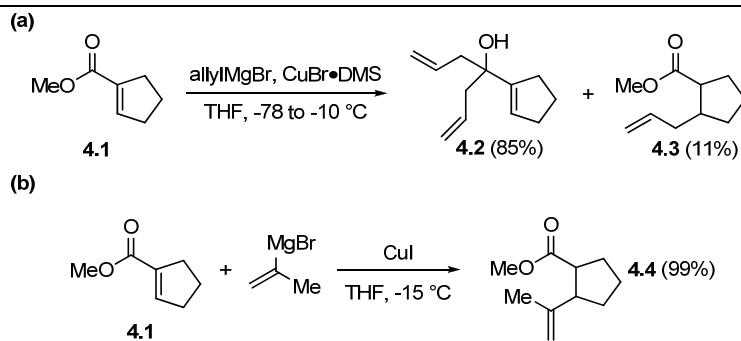
Scheme 4.5. Comparison of cuprates in selective additions

While Type I and III allylations can still occur in a conjugate fashion, they must do so through the formation of an eight-membered ring. This has been proposed for the anti-selective addition of crotylborane **4.5** to ethylidene malonate **4.6**, through the intermediate crown formations **4.7** and **4.8** (Scheme 4.6).[167] In **4.7**, which leads to the anti product **4.9**, steric interactions between the two adjacent methyl groups are minimized. However, in the conformation **4.8** leading to the minor syn product **4.10**, these two methyl groups are gauche. It should be pointed out that this is made possible for malonate acceptors by their relatively high conjugate electrophilicity compared to mono-activated α,β-unsaturated esters such as **4.1**. For instance, even hard nucleophiles such as allylMgBr and (allyl)$_2$Zn undergo selective 1,4-addition to alkylidene malonates.[168]
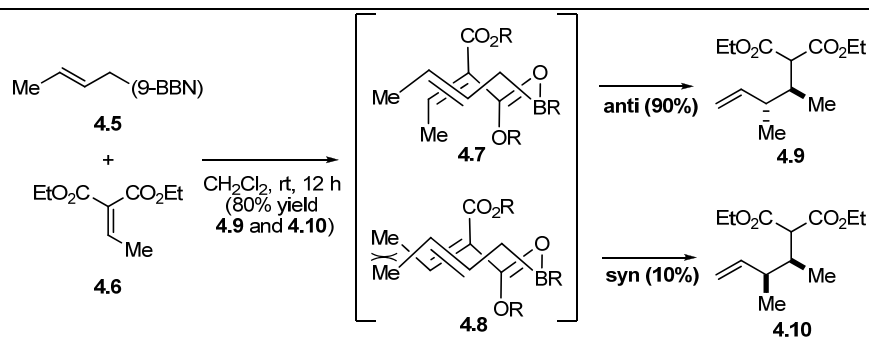
Scheme 4.6. Conjugate addition in Type I allylations

In terms of developing a more general and selective 1,4-conjugate allylation, nucleophiles capable of Type II reactions are the reagents of choice. This is because they do not rely on complexation of the metal to the carbonyl as a precondition for adding, but

rather react through open transition states. Further, use of a stoichiometric amount of strong Lewis acid minimizes any possible 1,2-addition through a Type I process by effectively removing the oxygen lone pair while at the same time activating the electrophile. This was first put into practice by Sukurai and Hosomi (after whom the reaction has been named), who showed that allylsilanes[169] and allylstannanes[170] add selectively to Lewis acid-activated α,β-unsaturated ketones (Scheme 4.7a and 4.7b, respectively). One interesting observation was that unsaturated esters do not react with allylsilanes under the conditions used, yet relatively deactivated β,β-disubstituted enones do. Subsequently, the Sakurai-Hosomi reaction of allylsilanes has been used extensively[171] and only recent examples of interest will be presented. The corresponding reaction of allylstannanes has found far less use, but representative precedent from the literature will be shown.
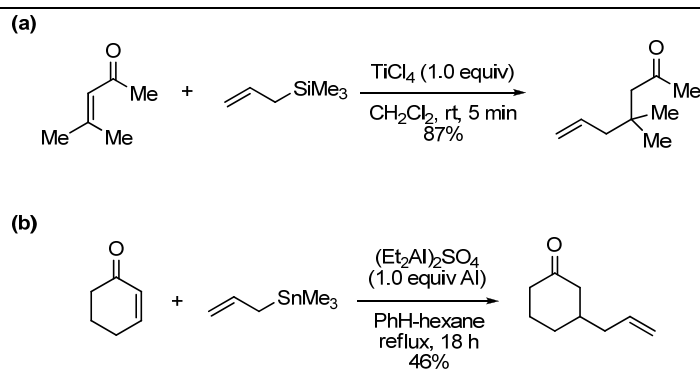
Scheme 4.7. Reactions of allylsilanes and allylstannanes reported by Sakurai and Hosomi

As mentioned above, an advantage of allylation reactions is that the allyl group can be reacted further. Considering this, Coates has developed an interesting Sakurai allylation-Prins cyclization reaction that makes dual use of TiCl$_4$ (Scheme 4.8a).[172] Here, a Sakurai reaction introduces the allyl group which upon protonation gives the ketone **4.11** as the major diastereomer. The alkene is now aligned perfectly for an intramolecular Prins reaction that yields the decalin **4.12** with high selectivity. It should be pointed out that the Prins reaction cannot occur during the initial TiCl$_4$-promoted allylation as the ketone is protected as a Ti-enolate. However, the fact that Sakurai allylation leads to an enolate intermediate can be valuable, as in the reaction shown in Scheme 4.8b.[173] In this case, intramolecular allylation of **4.13** gives the enolate **4.14** as a stable intermediate;

addition of an aldehyde gives the aldol product **4.15** as a single diastereomer after chromatography.
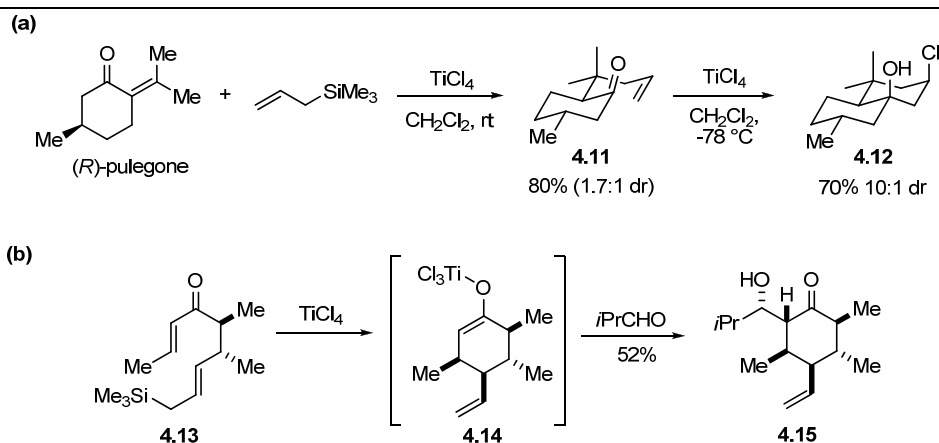
Scheme 4.8. Sakurai reactions in the synthesis of complex products

One interesting complication can arise from the formation of a Ti-enolate during these allylations. Since the reaction proceeds in a stepwise manner that results in the formation of a silyl-stabilized carbocation (Figure 4.1 above), the presence in a single molecule of a nucleophile and electrophile can lead to intramolecular cyclization. This is primarily the case when allylSi(*i*-Pr)$_3$ is used as the allylating agent rather than allylSiMe$_3$. Presumably this arises from a slower attack of chloride ion on silicon for the bulkier silane, which allows competitive addition of the enolate to give silylcyclopentane **4.17** rather than allylation product **4.16** (Scheme 4.9a).[174] However, in certain situations where the presence of significant steric hindrance impedes chloride addition, trimethylsilanes can also be prone to a formal [2 + 2] process that yields cyclobutanes (Scheme 4.9b).[175]
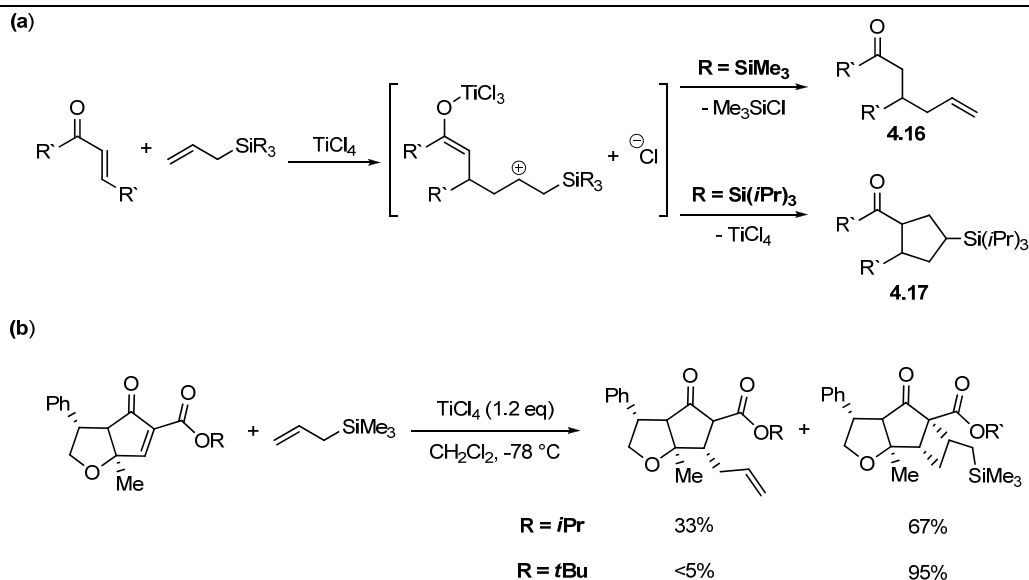
Scheme 4.9. Competitive cyclobutane formation during Sakurai allylations

Conjugate allylation using allylstannanes as initially reported by Sakurai employed the trimethyltin nucleophile, which is generally not desirable due to the volatility and toxicity of this moiety. The preferable reagents are allytributylstannanes, which have been used for both inter- and intramolecular conjugate additions. While these are stronger nucleophiles than the corresponding allylsilanes, they have been used far less frequently for Sakurai reactions perhaps owing to the relative toxicity of the tin group and the more tedious removal of the tributyltin residues. A second reason may be that under the strongly Lewis acidic conditions of the Sakurai reaction, relative differences in nucleophilicity become less of a factor.

A third reason may be the ability of allylstannanes to participate in 1,2-addition to unsaturated ketones. For example, addition of tetraallyltin[176] (Scheme 4.10a) or allylSnBu$_3$[177] (Scheme 4.10b) to enones both proceed exclusively at the carbonyl carbon. This difference in reactivity relative to allylsilanes can be understood in terms of a hard/soft mismatch. In cases where 1,2-addition does occur on unsaturated carbonyls, the overall product of conjugate addition can still be formed. As shown in Scheme 4.10c, addition of allylstannanes to *o*-quinone **4.18** gives an initial homoallylic alcohol, which undergoes [3,3] sigmatropic rearrangement (oxy-Cope) to give the product of a net conjugate addition.[178]
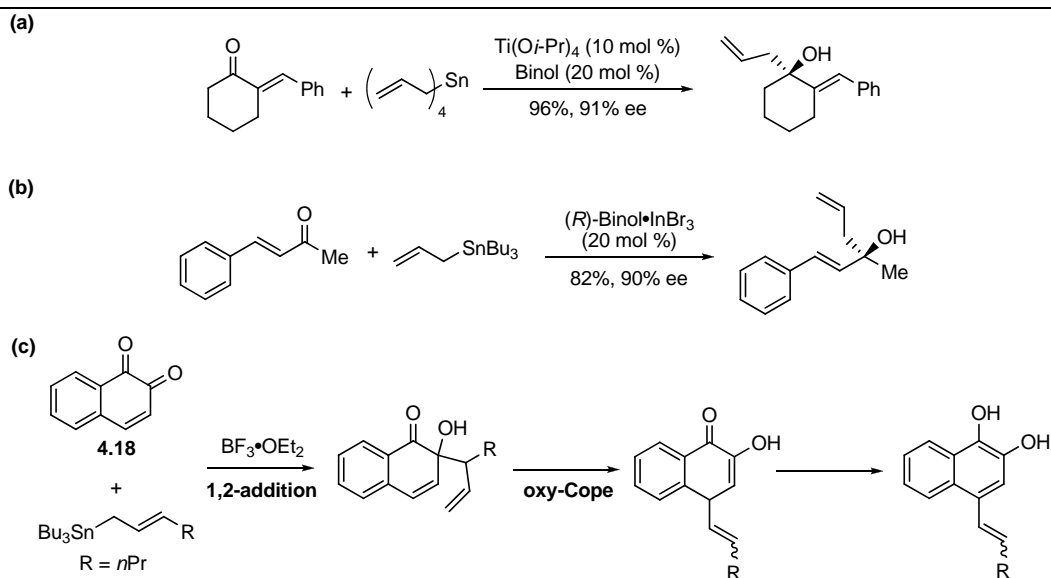
Scheme 4.10. Examples of 1,2-addition of allylstannanes to unsaturated carbonyls

Nevertheless, for some conjugate acceptors allylstannanes react strictly by 1,4-addition in the presence of a Lewis acid. For instance, switching from enones to enoates decreases the electrophilicity of the carbonyl carbon and makes these molecules resistant to 1,2-addition. In that regard, Yamamoto demonstrated that allylstannanes add in a highly anti selective fashion to alkylidene malonates (Scheme 4.11a).[167] Notably, this addition is nearly as selective as that using allylboranes which proceeds through a closed transition state (Scheme 4.6 above). In the same vein, conjugate allylation of the chiral acceptor **4.19** proceeds exclusively by 1,4-addition to give the product **4.20** in high diastereoselectivity (Scheme 4.11b). Alternatively, by performing additions to unsaturated ketones intramolecularly the chemoselectivity becomes less of an issue as ring strain and rates of ring closure predominate to give exclusively 1,4-addition (Scheme 4.11c).[179]
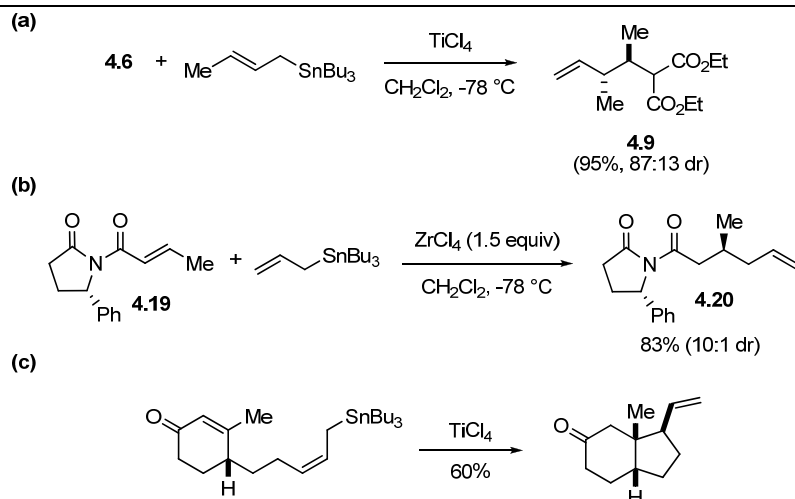
Scheme 4.11. Selective conjugate allylation using allylstannanes

The common feature of all of these conjugate additions, whether they be inter- or intramolecular or with allylsilane or stannane nucleophiles, is the use of a full equivalent or more of Lewis acid.[180] This is striking considering the advances made in catalytic conjugate additions of other organometallic nucleophiles[181], and in the development of catalytic 1,2-allylations.[182] Notably, for both of those reactions the primary modern focus is on development of catalytic *enantioselective* reactions, which makes the area of conjugate allylations seem particularly anachronistic. However, recent work on catalytic conjugate allylations is hopefully a sign of "catch up" to other areas. This work, along with our investigations in the field, will be presented in the following sections.

4.3. Catalytic Conjugate Allylations

One of, if not the first catalytic conjugate allylation methods did not employ any metal catalyst at all. This was the fluoride anion-activation of allylsilanes, which was initially proposed to form a naked allyl anion as the active nucleophile and was unselective for 1,2- vs 1,4-addition under the conditions employed (THF, reflux).[183] Subsequent reinvestigation of the reaction by Majetich showed that the use of polar solvents with added HMPA allowed a broader range of electrophiles to be used relative to the Sakurai reaction.[184] However, additions to enones were less selective than the Lewis acid induced allylations (Scheme 4.12a). They also proposed that the active species was a

pentacoordinate silicate rather than an allyl anion. This reaction has proven successful in more complicated systems and is still prevalent in modern synthesis, as demonstrated by its use in the total synthesis of aburatubolactam A (Scheme 4.12b).[185]
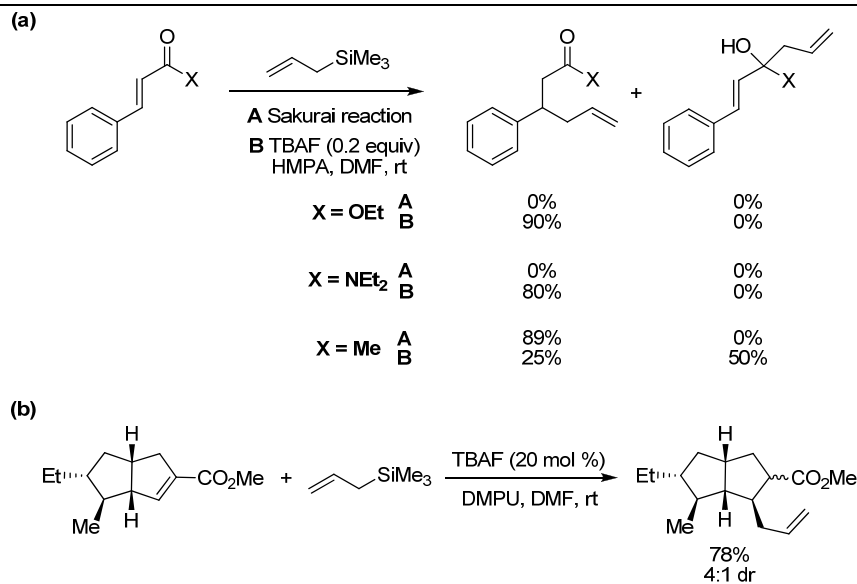
Scheme 4.12. TBAF-Catalyzed conjugate allylations

Recently, a resurgence of interest in catalytic conjugate allylations has seen the publication of numerous reports of this reaction. Jarvo has shown that allylboronates combine with a Pd-NHC complex **4.21** to generate a *nucleophilic* Pd(II)-allyl reagent.[186] This reagent adds in a conjugate fashion to α,β-unsaturated *N*-acyl pyrroles under very mild conditions (Scheme 4.13a).[187] Extension of this work to other acceptors however has not been as successful, as competing electrophilic allylation can occur. For example, despite using an optimized catalyst **4.22**, Pd-catalyzed allylation of alkylidene malononitriles still gave mixtures of monoallylated **4.23** and diallylated **4.24** (Scheme 4.13b).[188] This example highlights the main flaw in this catalyst system, which is that Pd(II)-allyl complexes are typically electrophilic. While the unique electron-donating properties of the NHC ligands help produce *umpolung* of the Pd-allyl complex, the fact remains that the nature of conjugate addition necessitates formation of enolates or their equivalents which may pose a complication for some catalytic systems such as this one.

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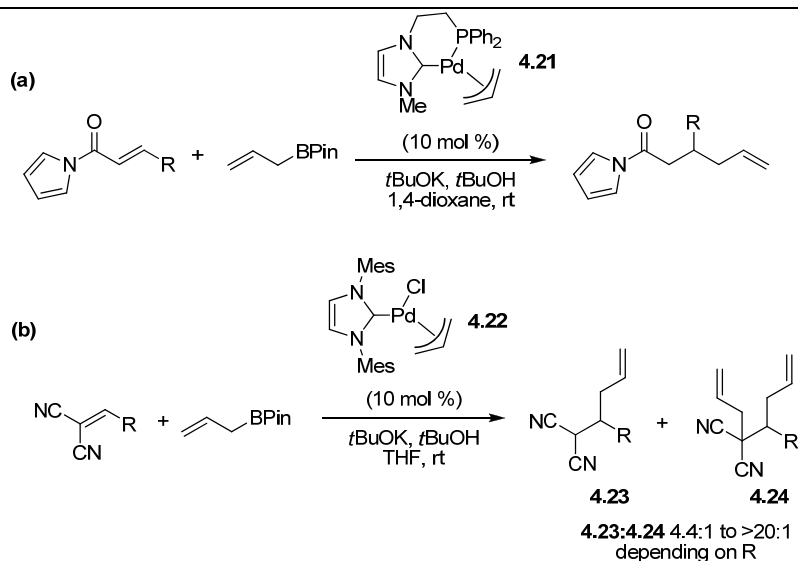
Scheme 4.13. Pd(II)-catalyzed conjugate allylations

Another transition metal-catalyzed conjugate allylation was reported by Morken, who demonstrated that a nickel complex catalyzes the addition of allylboronates to benzylidene acetone derivatives.[189] This reaction proceeds by a unique mechanism, where the styryl unit serves as an auxiliary to allow facile oxidative addition of the Ni complex. Subsequent transfer of the allyl group from B to Ni and reductive elimination forms a boron enolate and regenerates the catalyst along with the styryl group (Scheme 4.14a). The regioselectivity varies, but with PCy_3 as ligand addition occurs at the non-phenyl substituted β-position. Most significantly, replacement of PCy_3 with the TADDOL-derived phosphoramidite **4.25** yielded the first catalytic, enantioselective conjugate allylation (Scheme 4.14b). Interestingly, **4.25** favoured addition to the aryl-substituted β`-position, and a pentyl chain was employed as a dummy group. The regioselectivity was typically good, while the ee was invariably >90%.[190]
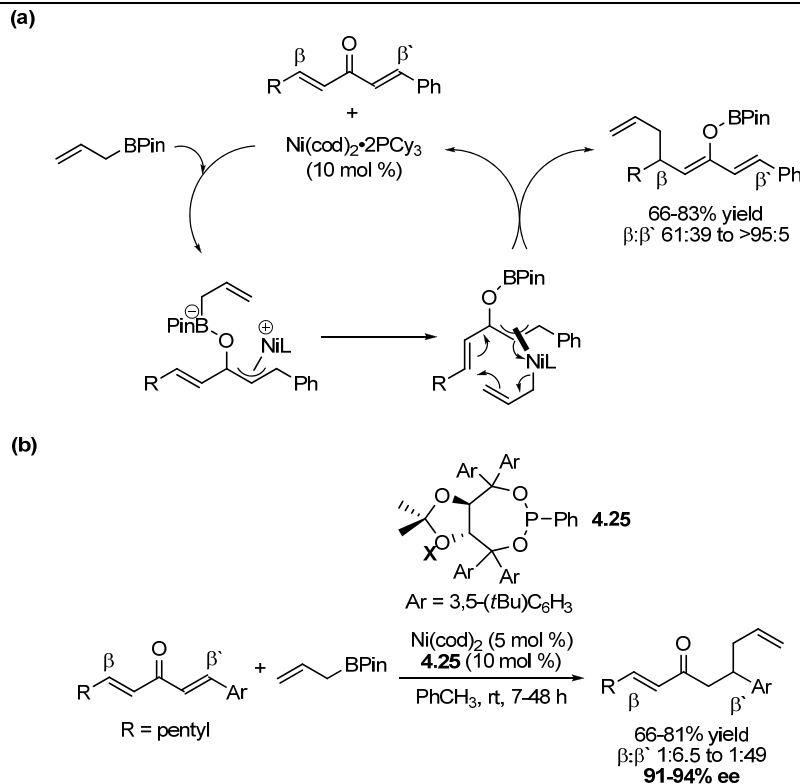
Scheme 4.14. Ni-catalyzed enantioselective conjugate allylation

A step towards a catalytic Sakurai allylation was reported in 2001, when it was found that $InCl_3$ is a competent activator of unsaturated ketones for addition of allylsilanes.[191] Based on spectroscopic evidence, it was proposed that the reason traditional Sakurai allylations require an equivalent of, for example, $TiCl_4$, is that the resulting Ti-enolate is relatively stable. Therefore, transmetallation with the stoichiometric amount of R_3MCl generated by the addition is disfavoured (Scheme 4.15a). By switching to a weaker Lewis acid such as $InCl_3$ they believed that catalytic conjugate addition would be feasible. Unfortunately, while the reaction was catalytic in $InCl_3$ it still required addition of five equivalents of Me_3SiCl (which did not catalyze the addition) as an additive. The authors proposed that the additional Me_3SiCl served to speed up turnover, which was prohibitively slow based solely on the small amount of silyl chloride bi-product present as a result of the addition. Nevertheless, these conditions employ far milder and easier to handle Lewis acids than traditional Sakurai allylations.
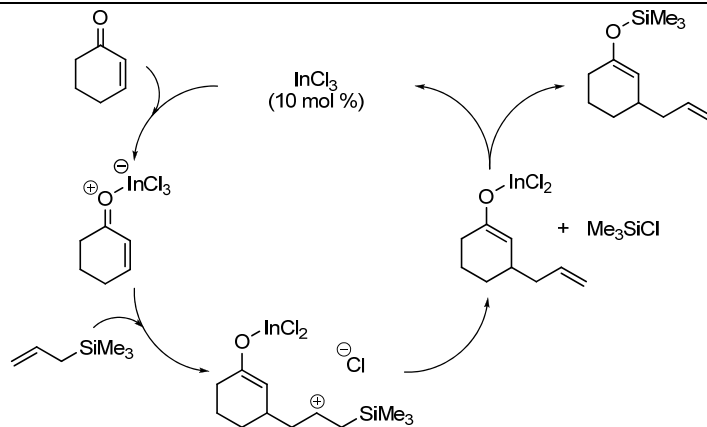
Scheme 4.15. InCl$_3$-catalyzed Sakurai allylation

A substantial contribution to catalytic Sakurai reactions was reported by Snapper, who used a copper-bisoxazoline complex to effect enantioselective conjugate allylation of β-ketoesters (Scheme 4.16).[192] This method not only provided just the second example of enantioselective conjugate allylation, but was also the first (to the best of my knowledge) to employ a catalytic amount of Lewis acid. This most likely results from the use of Cu(OTf)$_2$ rather than a Lewis acid with a less labile counter-ion such as chloride (ex. TiCl$_4$). Therefore, the initial addition produces a Cu-enolate and Me$_3$SiOTf, which has been shown to transmetallate significantly faster than Me$_3$SiCl in Lewis acid-catalyzed reactions where catalyst turnover is an issue.[193] Enantioselectivities were high (>90% ee) for optimized acceptors, but proved very sensitive to structural variations away from the electrophilic carbon. The main drawback of this system is the use of cyclic, unsymmetrical electrophiles, which produce mixtures of diastereomers upon protonation of the intermediate enolate.

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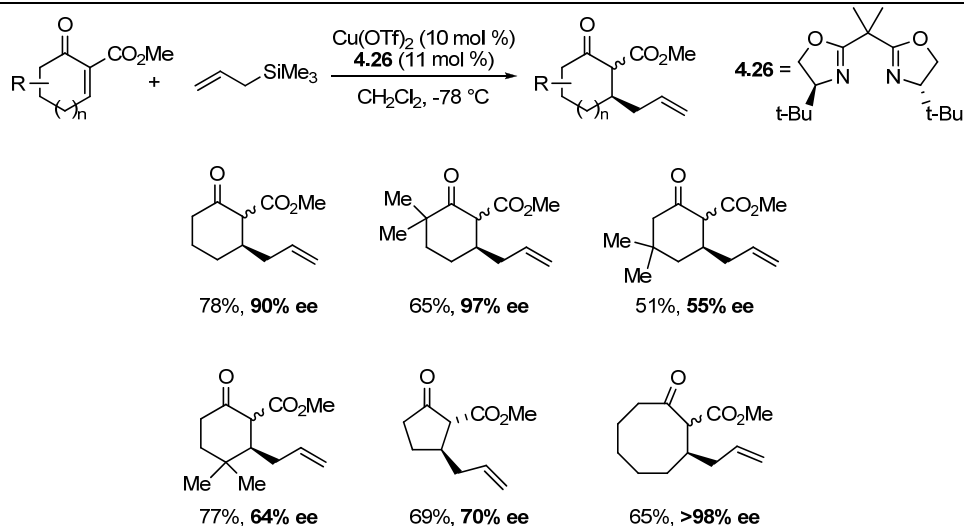
Scheme 4.16. Catalytic enantioselective Sakurai reactions

The above examples were the only means available for catalytic conjugate allylation prior to our investigations. Our work on the use of alkylidene Meldrum's acids in catalytic Sakurai reactions is presented below.

4.4 Sc(OTf)$_3$-Catalyzed Conjugate Allylation of Alkylidene Meldrum's Acids

One aspect of catalytic conjugate allylation chemistry that attracted our attention was the fact that no single method is general for all classes of α,β-unsaturated carbonyl compounds. For instance, TBAF activation of silanes works poorly for enones, while the Sakurai reaction is ineffective for enoates. Neither method is applicable to enals, as 1,2-addition is the preferred mode of allylation for these reactive electrophiles.[194] Therefore, allylation of electrophiles which can serve as convenient surrogates of enones, enals, enoates etc would provide an alternative to the use of various nucleophiles and catalysts for each substrate. In this regard, the allylation of N-acyl pyrroles reported by Jarvo is relevant as these molecules have the same reactivity as Weinreb amides.[195]

We thought that conjugate allylation of alkylidene Meldrum's acids would be ideal in terms of developing a catalytic method using a versatile electrophile. For one thing, the alkylidenes are extremely resistant to 1,2-addition, as even very hard alkyllithium nucleophiles add preferentially to the β-position.[196] Also, in line with the catalytic Sakurai conditions reported by Snapper and our own work on Lewis acid

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activation of Meldrum's acid, metal triflates would be competent catalysts. Further, the ease of preparation and increased electrophilicity of the alkylidene would allow formation of both tertiary and quaternary carbon centres. Most importantly in terms of electrophile surrogacy, the Meldrum's acid moiety can be transformed in a single step into either aldehydes[197], ketones[22,26,138], esters, or amides.[198]

There is limited literature precedent for Sakurai allylations of alkylidene Meldrum's acids. Roush reported a $BF_3 \cdot OEt_2$-promoted addition of allylSnBu$_3$ to a chiral Fe(CO)$_3$-complexed conjugated alkylidene which proceeded with perfect diastereoselectivity (Scheme 4.17a). A very similar reaction also using allylSnBu$_3$ but promoted by LiClO$_4$ in THF was reported by Paley.[199] A sole intramolecular example using a tethered allylsilane to give a trans cyclopentane was reported by Tietze (Scheme 4.17b).[200] In all of these cases, a stoichiometric amount of Lewis acid was used.
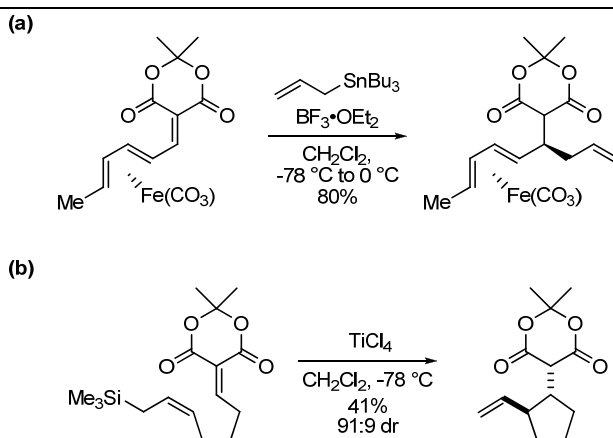
Scheme 4.17. Inter- and intramolecular Sakurai reactions of alkylidene Meldrum's acids

We began our investigations by examining the addition allylSiMe$_3$ to benzylidene Meldrum's acid **4.27**.[201] While this nucleophile added cleanly under conventional stoichiometric Sakurai conditions to give **4.28** (Scheme 4.18a), use of a catalytic amount (10 mol %) of TiCl$_4$ resulted in no addition even at room temperature. Variation of the Lewis acid to TiF$_4$, BF$_3 \cdot OEt_2$, SnCl$_4$, Me$_3$SiOTf, and Sc(OTf)$_3$ produced the same result. This suggested that the allylsilane was insufficiently nucleophilic to react with the alkylidene unless activated by a full equivalent of Lewis acid. We therefore turned to allylSnBu$_3$, which is significantly more reactive than allylSiMe$_3$ (see Figure 1 above).

Now, the better nucleophile added without catalyst to the alkylidene, giving 98% conversion to the allylated product after 1 h at room temperature. This rapid addition seemingly eliminated the need for a catalyst, as addition of Sc(OTf)$_3$ produced an identical outcome to the uncatalyzed process (Scheme 4.18b). Interestingly, addition of catalytic TiCl$_4$ was detrimental to the reaction and caused decreased conversion. The lack of signals in the ^{1}H NMR attributable to the excess allylstannane in this case suggested that the Lewis acid was promoting decomposition of the nucleophile.
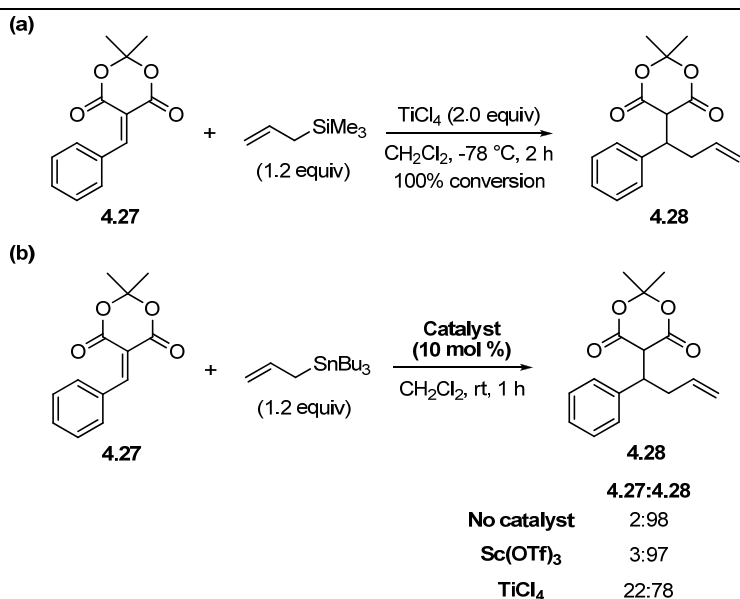
Scheme 4.18. Conjugate allylations of **4.27** using allylSiMe$_3$ and allylSnBu$_3$

Use of allylSnBu$_3$ as nucleophile did provide a very mild method of performing conjugate allylations, but its main drawback was purification of the desired product from the tributyltin residues. We therefore turned to allylSnPh$_3$, which is of intermediate nucleophilicity to the trimethylsilyl and tributylstannyl groups. More importantly, the reagent itself is a stable solid and the triphenyltin residues are much more easily removed.[202] Reaction of this nucleophile with benzylidene **4.27** without a catalyst showed a much slower background process than with allylSnBu$_3$. Gratifyingly, addition of a catalytic amount of Sc(OTf)$_3$ resulted in significant improvement in the rate of reaction (Scheme 4.19). Moreover the addition was incredibly clean, and the only observed

species in the ^{1}H NMR of the crude reaction mixture were the starting material, the product, and the remaining tin-containing molecules.
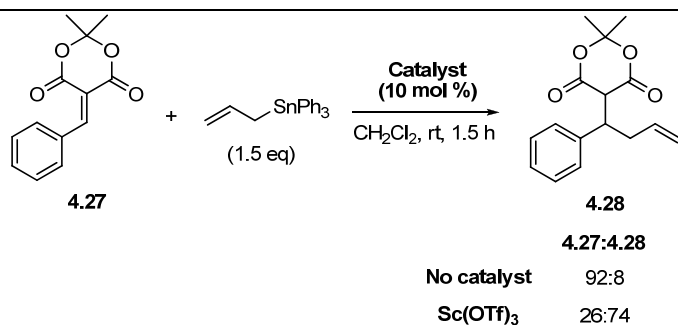
Scheme 4.19. Sc(OTf)$_3$-catalyzed addition of allylSnPh$_3$ to benzylidene **4.27**

The addition required very little optimization, and it was quickly found that extending the reaction time with lower catalyst loading gave complete conversion of the alkylidene. A slight excess of allylSnPh$_3$ (1.3 equiv) was needed to ensure the reaction went to completion. With these conditions, allylation of a large range of alkylidene was performed on a synthetically useful 1.0 mmol scale (Scheme 4.20). The majority of alkylidenes were allylated at room temperature using 5 mol % of Sc(OTf)$_3$, although for some acceptors minor variations of the conditions were required. For electron rich alkylidenes or those which were insoluble in CH$_2$Cl$_2$ at room temperature (**4.32** and **4.33**, respectively), an alternative was to run the reactions at 50 °C in 1,2-dichloroethane (DCE). As opposed to higher temperature, other electron-rich alkylidenes, such as those bearing heteroaromatics (**4.38-4.40**), or sterically hindered acceptors (**4.37** and **4.43**) reacted to completion by increasing the catalyst loading and running the reaction for longer times. It should be pointed out that at no time were products of 1,2-addition observed for any alkylidenes.

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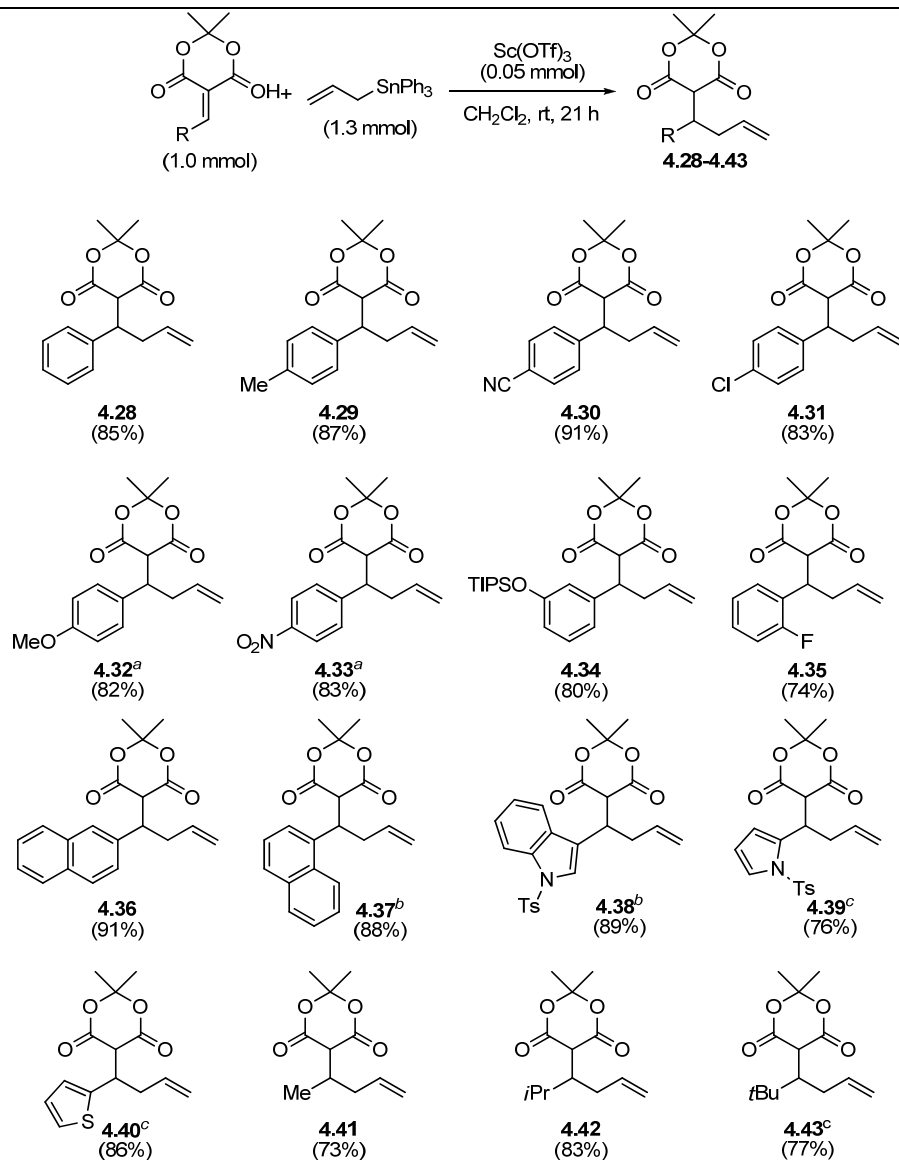
Scheme 4.20. Conjugate allylation of monosubstituted alkylidene Meldrum's acids. [a] Reaction performed in DCE at 50 °C. [b] Sc(OTf)$_3$ loading was 0.1 mmol. [c] Sc(OTf)$_3$ loading was 0.1 mmol and reaction time 36 h.

Allylation of known chiral, non-racemic alkylidene **4.44**[203] proceeded to full conversion without hydrolysis of the acetal.[204] Analysis of the crude reaction mixture suggested that the addition was highly (>20:1) diastereoselective, but unfortunately an analytically pure sample of the allylated product **4.45** could not be obtained. Compound **4.45** decomposed on silica gel, and other methods of purification (i.e. recrystallization, extraction, and Florisil chromatography) could not remove the remaining triphenyltin residues. However, treatment of the crude reaction mixture with acidic methanol effected

deprotection of the acetal, lactonization, and Fischer esterification to give the chiral lactone **4.46**. This product could be isolated cleanly by silica gel chromatography, and was found to be a single diastereomer by ^{1}H NMR (Scheme 4.21a). A similar result was obtained for the reaction of alkylidene **4.47**, although the diastereoselectivity of the allylation could not be determined as the presence of non-resolvable rotamers made the ^{1}H NMR spectrum of **4.48** inconclusive. However, treatment of **4.48** with acidic methanol removed the acetal while leaving the carbamate untouched, allowing cyclization to the lactone **4.49** (Scheme 4.21b). This was formed as 19:1 mixture of diastereomers, suggesting that the allylation proceeded with nearly the same diastereoselection as the addition to **4.44**. The relative stereochemistry of **4.46** and **4.49** was assigned by analysis of the proton coupling constants, and corresponds with that obtained for the known additions of indoles to these alkylidenes.[205]
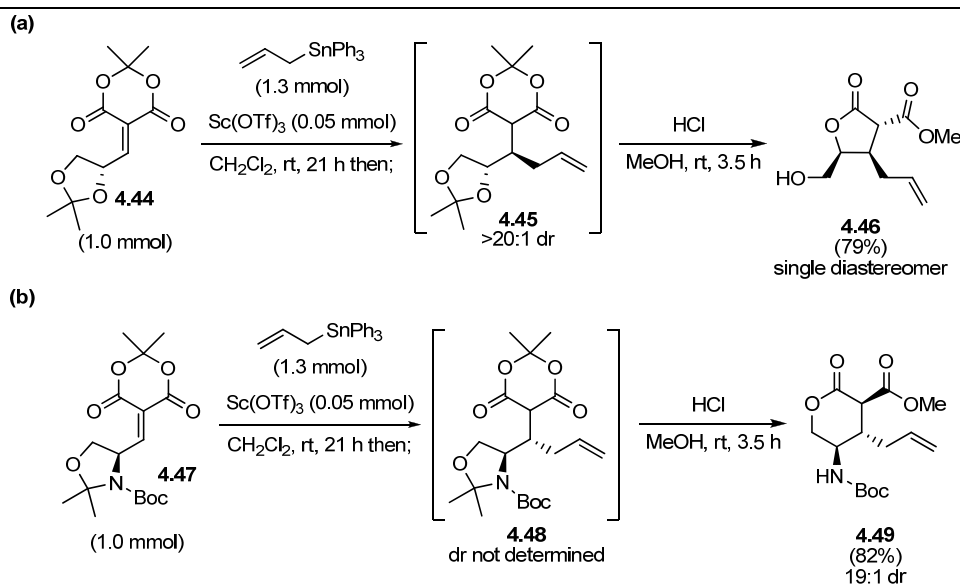
Scheme 4.21. Diastereoselective allylation of non-racemic alkylidene Meldrum's acids

When this conjugate allylation was attempted with disubstituted alkylidenes **4.50** and **4.51** no reaction occurred, and increasing the reaction temperature had no effect (Scheme 4.22a). We therefore returned to the more nucleophilic allylSnBu$_3$, and found that it added to the activated acceptor **4.51** at room temperature but not to the less reactive alkylidene **4.50**. The conversion of the addition to **4.51** was further improved by performing the reaction in DCE at 50 °C (Scheme 4.22b). Allylation occurred exclusively

at the alkene carbon activated by the Meldrum's acid and not that of the ester, and no 1,2-addition at either carbonyl group was observed.
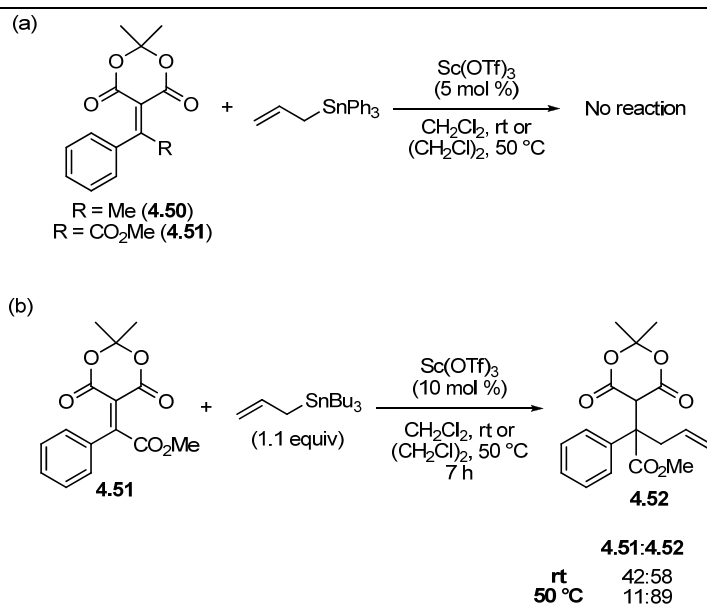
Scheme 4.22. AllylSnBu$_3$ as nucleophile for conjugate allylation of disubstituted alkylidenes

By increasing the amount of allylSnBu$_3$ and extending the reaction time, catalyst loading was reduced to 5 mol %. These optimized conditions were applied to various disubstituted alkylidene Meldrum's acids (Scheme 4.23). Not only was substitution of the aryl ring possible (**4.52-4.55**) but also variation of the ester group (**4.56**).
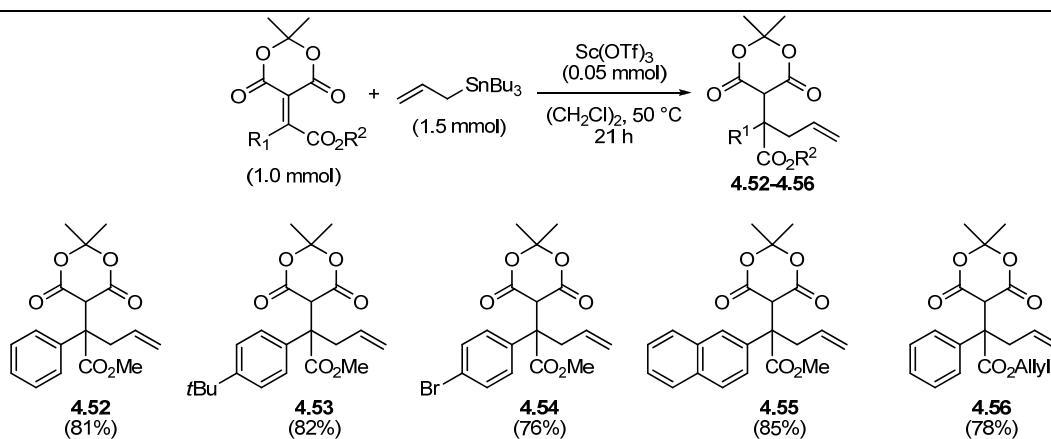
Scheme 4.23. Conjugate allylation of disubstituted alkylidene Meldrum's acids

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An interesting result that highlights the chemoselectivity of this process was made by a competition experiment. Here, equal amounts of 2-naphthyl alkylidene **4.57**, 2-naphthaldehyde (**4.58**), and allylSnPh$_3$ were combined with a catalytic amount of Sc(OTf)$_3$ (Scheme 4.24a, yields are versus an internal standard of mesitylene). It was found that allylation occured exclusively to alkylidene **4.57** to give **4.36**, and none of the known homoallylic alcohol **4.59**[206] was found in the ^{1}H NMR of the crude reaction mixture. The lower yield of **4.36** relative to the reaction performed in Scheme 4.20 can be explained by the use of stoichiometric allylSnPh$_3$ as opposed to the 1.3 equivalents used in the standard conditions. Considering that aldehyde **4.58** is allylated in a Sc(OTf)$_3$-catalyzed reaction with allylSnPh$_3$ (Scheme 4.24b, yield relative to internal standard of mesitylene), we attributed the chemoselectivity to the superior electrophilicity of alkylidene Meldrum's acids.
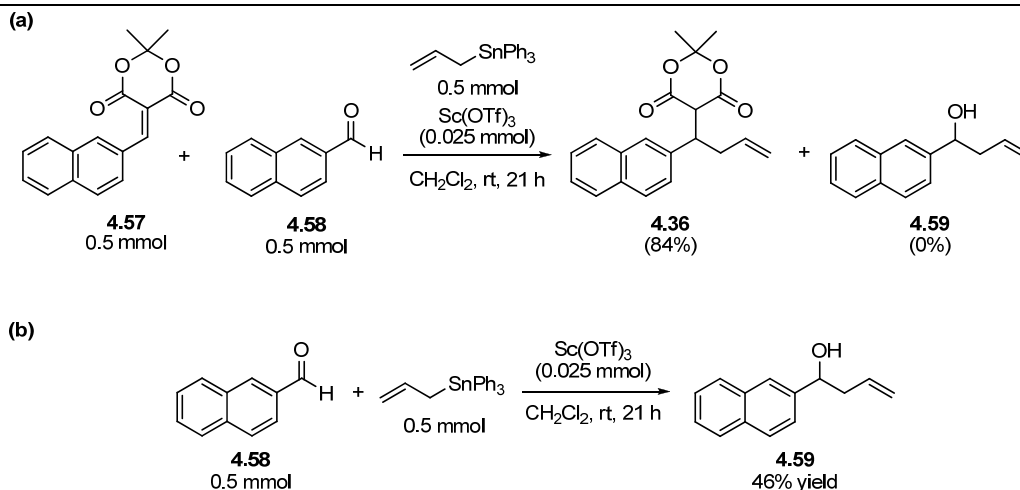
Scheme 4.24. Chemoselectivity in the allylation of monosubstituted alkylidenes

As mentioned above, one advantage of using alkylidene Meldrum's acids as the electrophile in conjugate allylations is the synthetic versatility of the Meldrum's acid group (Scheme 4.25). For example, electrophilic allylation of the 5-position can be performed by reacting the product of nucleophilic allylation with allyl bromide under mild basic conditions to give **4.60**. Reactions of the Meldrum's acid carbonyls can also be performed, as in the ring opening with methanol to form the ester **4.61**. Notably, because the conjugate allylation reactions are very clean and the majority of the tin byproducts are

removed by filtration during the work-up, these reactions could be performed directly on the crude **4.28** before chromatography.
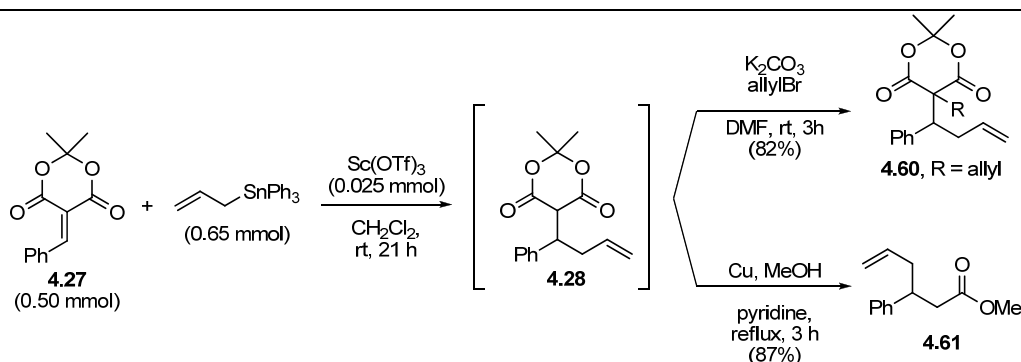
Scheme 4.25. Transformations of allylated Meldrum's acids

The above reactions demonstrated that alkylidene Meldrum's acids are ideal electrophiles for catalytic conjugate allylation. The utility of this reaction lies in the mildness of its conditions, the range of its functional group compatibility, the diastereoselectivity of its additions to non-racemic alkylidenes, and its ability to form both tertiary and quaternary stereocentres. However, in order to bring this reaction fully up to the level of modern organic chemistry a catalytic *enantioselective* variant must be developed. Our initial forays into this area are presented in the final section below.

4.5. Catalytic, Enantioselective Conjugate Allylation of Alkylidene Meldrum's Acids

Despite the great potential of alkylidene Meldrum's acids as electrophiles for additions of a broad range of nucleophiles, there are surprisingly few catalytic enantioselective reactions employing these substrates. In fact, aside from the contributions of my colleague Ash Wilsily, there are only three other examples reported in the literature. Barbas described an enantioselective Diels-Alder reaction of alkylidene Meldrum's acids formed in situ with α,β-unsaturated ketones in 2003 (Scheme 4.26a).[207] That same year, Carreira published the addition of Et$_2$Zn to monosubstituted alkylidenes in the presence of a Cu-phosphoramidite complex (Scheme 4.26b).[208] Later, Carreira's group reported an extremely efficient Cu-catalyzed addition of terminal alkynes to

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monosubstituted alkylidenes that was performed in water without the use of preformed alkynyl organometallics (Scheme 4.26c).[209] We hoped to add conjugate allylation to this list.
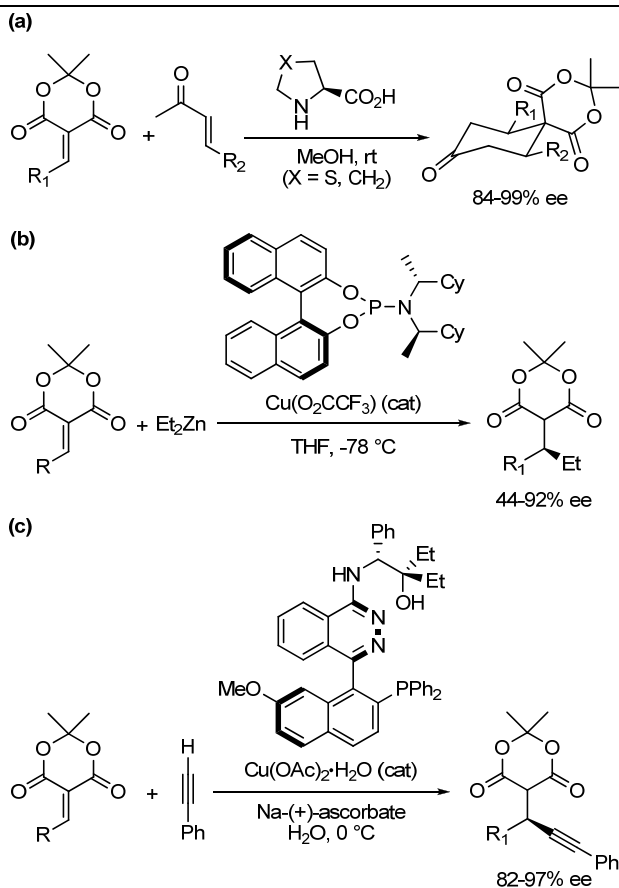
Scheme 4.26. Catalytic enantioselective conjugate additions to alkylidene Meldrum's acids

The obvious place to start this investigation was the use of chiral Lewis acid complexes for the addition of allylSnPh$_3$ with benzylidene **4.27** (Scheme 4.27).[210] Attempts with Sc(OTf)$_3$-pybox **4.62** yielded only a low conversion to racemic product, which suggested that the decreased Lewis acidity of the metal due to ligand binding was inhibiting the catalytic process. Another problem with complex **4.62** is that it relies on two-point binding to properly organize the electrophile in the optimal orientation for shielding of one face of the alkene.[211] Therefore, we attempted the reaction with Lewis acid complexes known to proceed through a one-point binding mode. The BINOL-TiCl$_2$

complex **4.63** initially reported by Mikami[212] led to no reaction but switching to the TiF$_2$ derivative **4.64**, which is known to be more reactive[213], did lead to product formation. Unfortunately, the reaction was not clean and gave equal amounts of an unidentified side product and more to the point gave racemic **4.28**. Multiple attempts with a variety of neutral and cationic metal-salen complexes, which catalyze the hetero-Diels-Alder reaction of carbonyl compounds through one-point binding[214], gave either no reaction with the neutral complex **4.65** or a racemate with the cationic **4.66**.[215]
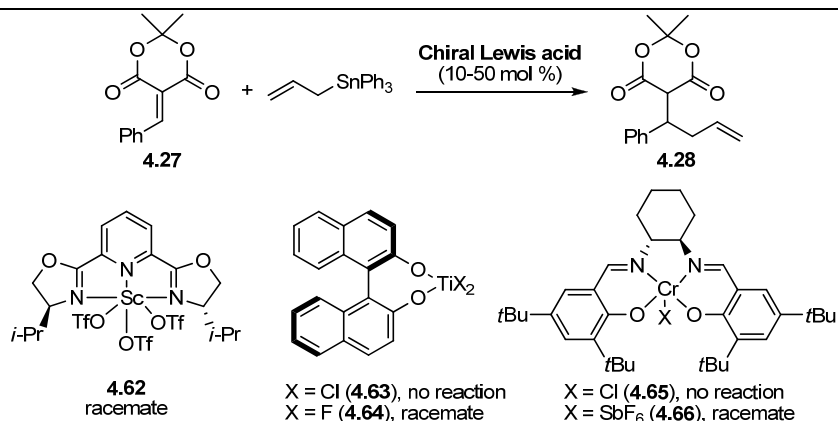
Scheme 4.27. Attempted enantioselective allylation of **4.27** with chiral Lewis acid complexes

A possible explanation for the failure of these reactions to generate non-racemic products is due to the distance between the electrophilic carbon centre and the Lewis acid complex. As shown in Figure 4.2, there are four possible binding modes for a Lewis acid on alkylidene Meldrum's acids (**4.67-4.70**). Complexes **4.67** and **4.68**, where the metal is on the lone-pair anti to the ester oxygen, have significant steric interactions between the alkene groups and the Lewis acid. The most likely complexes are **4.69** or **4.70** where the Lewis acid is very remote relative to the site of addition. This would prevent relay of the chiral environment from the ligand to the alkene, leading to racemic products.

4.67 **4.68** **4.69** **4.70**
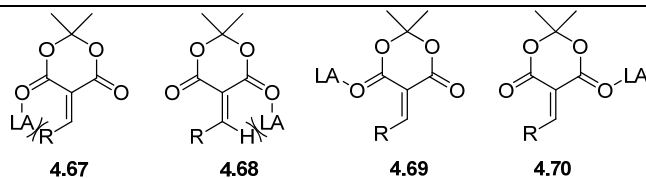
Figure 4.2. Possible configurations of an alkylidene Meldrum's acid-Lewis acid complex

   Having had no success with enantioselective allylations proceeding via formation of a chiral electrophile, we thought that generating a chiral allylorganometallic might lead to more success. Examination of the known enantioselective additions to alkylidene Meldrum's acids suggests that this is more feasible, as all of these involve formation of chiral nucleophiles. Inspiration came from work being carried out by Alex Zorzitto in our group concurrent with our investigations on catalytic allylations. He found that a Rh(I)-phosphine complex catalyzed the additions of terminal alkynes to alkylidene Meldrum's acids in very high enantioselectivity (Scheme 4.28a).[216] Further, previous work by my former co-workers Sébastien Carret, Lauren Mercier, and Vincent Trépanier had demonstrated mild Sn-Rh transmetallation using alkenylstannanes to generate racemic nucleophiles that add to alkylidenes under mild reaction conditions (Scheme 4.28b).[217] We thought that by combining these two ideas, Rh(I) complexes could transmetallate with allylSnPh3 to form an active, chiral allylating agent under catalytic conditions (Scheme 4.28c).

159
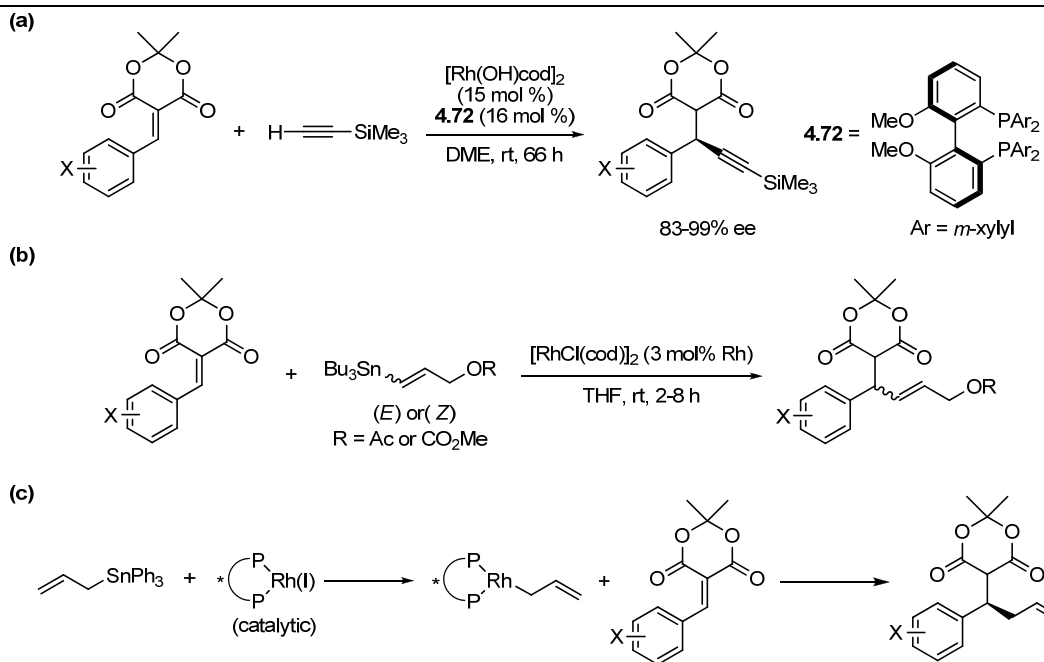
Scheme 4.28. Rh-catalyzed conjugate additions to alkylidene Meldrum's acid and proposed enantioselective conjugate allylation

Typically, Rh-allyl complexes are formed from Rh(I) oxidative additions into allylic ethers or esters to form electrophilic Rh(III)-allyl species.[218] However, recent reports on nucleophilic allylation have demonstrated that transition metals commonly used to form high valence electrophilic π-allyls can form allyl nucleophiles when these metals are in lower oxidation states.[219] Therefore, the proposed mechanism seemed reasonable in terms of generating an active allylating agent, although to the best of my knowledge there are no examples of Rh-Sn transmetallation involving $SnPh_3$ or allylstannanes.

Initial results on the addition of allylSnPh$_3$ to benzylidene **4.27** catalyzed by a Rh(I)-*S*-BINAP complex in 1,2-dimethoxyethane (DME)[220] showed a rate acceleration relative to having no catalyst, which was encouraging (Scheme 4.29). In that regard, it was found that cationic (BF$_4$ counter-ion) complexes gave higher conversion than the neutral Rh chloride. More importantly, the reaction proceeded in low but reproducible enantioselectivity, which validated our hypothesis that chiral nucleophiles would be more selective than using chiral Lewis acid complexes.[221]

160
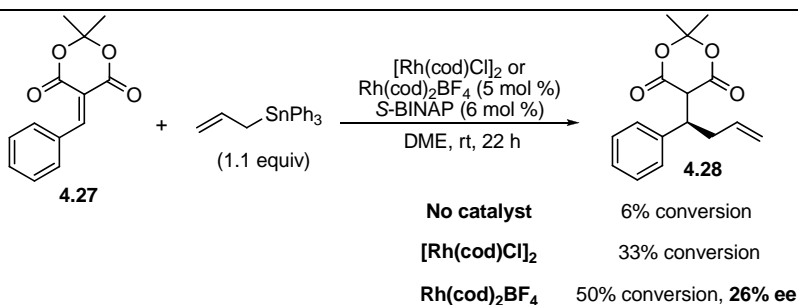
Scheme 4.29. Initial results for catalytic enantioselective conjugate allylation

In order to increase enantioselectivity, we turned to variation of the ligand framework to find an optimal complex (Scheme 4.30). Modified BINAP ligands **4.71** and **4.72** gave slightly higher enantioselectivity than the parent complex, while the conversion was higher for the less sterically hindered **4.71**. Similar results were obtained with the BIPHEP-based ligands **4.73** and **4.74**. Electron-rich ligand **4.75** gave very low conversion (ee not determined) and consumed all of the allylSnPh$_3$, while the bulkyl trialkylphosphine Tangphos (**4.76**) gave no conversion. Phosphoramidite ligand **4.77**, which works well for Cu-catalyzed additions of diorganozinc reagents to alkylidene Meldrum's acids, produced racemic material. The ligand that gave the best conversion with relatively similar enantioselectivity to the other complexes was *R*,*S*-Josiphos (**4.78**), which gave 97% conversion and -26% ee.
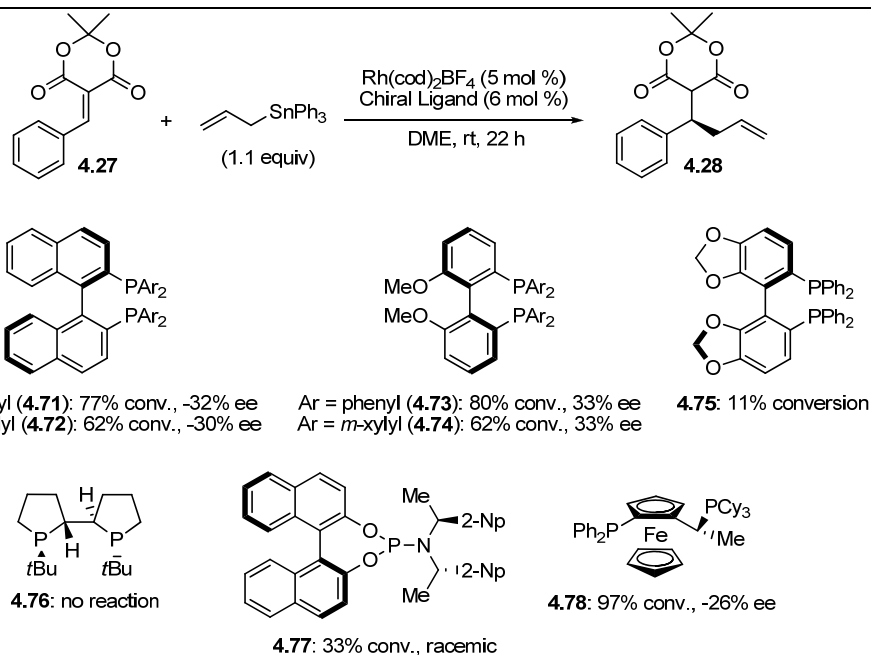
Scheme 4.30. Ligand variations for enantioselective conjugate allylation of **4.27**

The reason we were pleased with the result using *R,S*-Josiphos was that this is the ligand class for which there is the largest number of commercially available derivatives. A variety of these ligands were screened in the hopes that we could find one that would provide higher enantioselectivity while maintaining the good conversion and clean reaction profile of the parent **4.78** (Scheme 4.31). Bulkier ligand **4.79** led to lower conversions but slightly higher selectivity. Reversing the positions of the PPh$_2$ and PCy$_2$ groups relative to **4.78** as in ligand **4.80** gave excellent conversion but similar low ee. Ligand **4.81** with two PCy$_2$ gave the same results as Josiphos. Variation of the aryl ring as in **4.82** and **4.83** showed that the conversion was sensitive to the electronic properties of those rings, but in the case of **4.82** the enantioselectivity was not affected. The consistently low ee of these reactions (mid-20's to 33%) was disappointing, and so we turned to structurally related ligands Mandyphos (**4.84**) and Walphos (**4.85**), but unfortunately these both gave no reaction. Also, reactions with Josiphos (**4.78**) were attempted at lower temperatures (0 °C and -15 °C, not shown) in an attempt to increase the selectivity but these gave no conversion to the desired product **4.28** although the allylSnPh$_3$ was consumed.

162
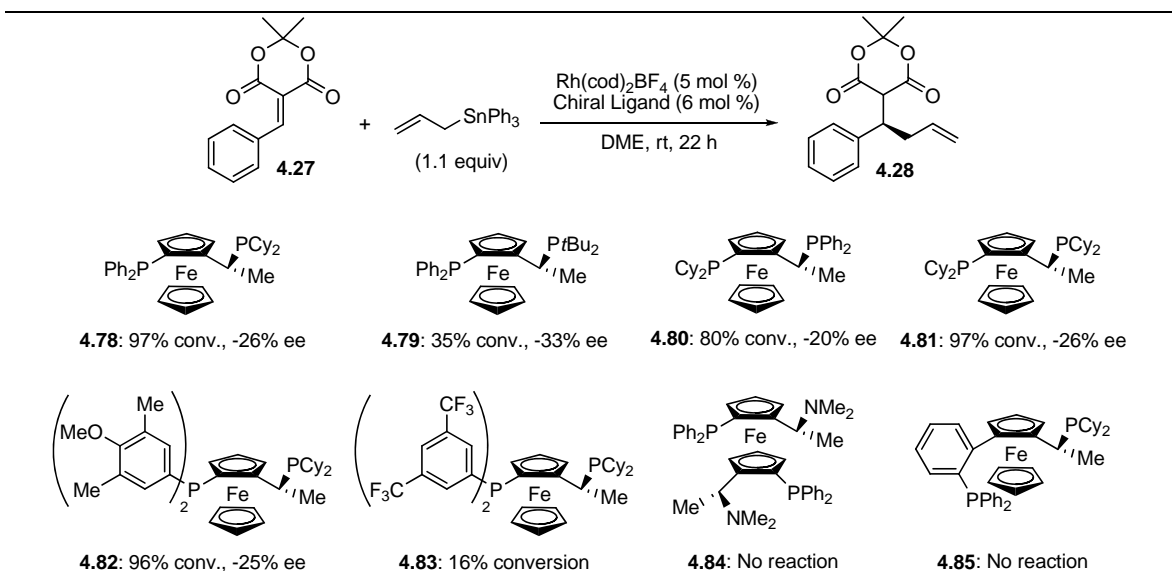
Scheme 4.31. Enantioselective conjugate allylation using ferrocene-based ligands

These preliminary results on enantioselective conjugate allylation are a first step toward a challenging transformation. With the huge array of known chiral bisphosphine ligands available for Rh, it is possible that a complex which catalyzes this reaction in high enantioselectivity can be found. Alternatively, if this reaction is proceeding by formation of a chiral Rh(I)-allyl complex, this may represent a new method for catalytic enantioselective allylations of other acceptors, either in 1,2- or 1,4-additions. Spectroscopic investigations into the reaction of allylSnPh$_3$ with cationic Rh complexes may provide some evidence for this process, although the ability of some of these complexes to decompose the nucleophile in reactions with **4.27** where no addition took place may make identification of the supposed intermediate difficult. In any event, further investigations in this area are left to future members of the Fillion group, as the above results mark the end of this thesis.

4.6. Experimental Section

General: All reactions were performed in flame- or oven-dried glassware under a nitrogen atmosphere unless indicated otherwise. CH$_2$Cl$_2$ was dried by distilling over CaH$_2$ or obtained from a solvent purification system based on the published procedure.[222] 1,2-Dichloroethane was obtained from a solvent purification system based on the

published procedure.[1] DMF and pyridine were distilled from over CaH_2 and stored in Schlenk flasks under argon. MeOH was heated to reflux over Mg powder overnight and then distilled, and stored over 3 Å molecular sieves. DME was distilled from Na/benzophenone ketyl, degassed by three cycles of freeze/pump/thaw and stored in a glovebox. Commercial $Sc(OTf)_3$ was dried by heating at 180 °C under high vacuum for 8 h, and stored in a glovebox under nitrogen. Unless indicated otherwise, all other reagents were used as received from commercial sources. Reactions were monitored by thin-layer chromatography and visualized by UV quenching and/or staining with I_2 in silica gel.[223] Flash chromatography was performed using 230-400 mesh silica gel.

Characterization: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra for all compounds except the ^{1}H NMR spectra of **4.46**, **4.47**, and **4.49** were obtained in $CDCl_3$ or C_6D_6 at 300 MHz and 75 MHz, respectively. ^{1}H NMR spectra for **4.46**, **4.47**, and **4.49** were recorded at 500 MHz. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual $CHCl_3$ (7.24 ppm) or C_6HD_5 (7.15 ppm); carbon spectra were calibrated to $CDCl_3$ (77.0 ppm) or C_6D_6 (128.0 ppm). Carbon multiplicities (C, CH, CH_2, CH_3) were determined by combined DEPT 90/135 experiments. High resolution mass spectrometry was performed at the University of Waterloo Mass Spectrometry facility.

Preparation of alkylidene Meldrum's acids:
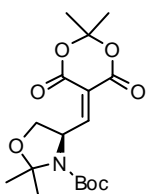
(*R*)-tert-Butyl 4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)-2,2-dimethyloxazolidine-3-carboxylate (4.47): Prepared by condensation of (*S*)-Garner's aldehyde[224] (2.29 g, 10.0 mmol) at 50 °C for 3.5 h using the method discussed in Chapter 1.[53] Purified by flash column chromatography eluting with 2:1 hexanes:EtOAc and isolated as a white solid (2.13 g, 60% yield). The alkylidene is a ~4:5 mixture of rotamers at rt based on integration of the peaks at 7.99 ppm and 7.84 ppm (^{1}H NMR, C_6D_6) which coalesce at 60 °C. Proton NMR data at both temperatures are provided; ^{13}C NMR data at rt contains extra peaks due to the rotamers, all of which are listed. M.p. 91-92 °C; ^{1}H NMR (C_6D_6, 300 MHz, rt, some peaks integrate for non-integer values due to the presence of rotamers) 7.99 (d, *J* = 7.9 Hz, 0.37 H), 7.84

(d, J = 8.6 Hz, 0.49H), 5.62-5.52 (m, 1H), 4.12-4.00 (m, 1H), 3.55-3.50 (m, 1H), 1.65 (s, 1.44H), 1.50 (s, 1.53H), 1.42-1.40 (m, 2.17H), 1.30-1.27 (m, 12.09H), 1.17-1.48 (m, 4.27H); (C_6D_6, 300 MHz, 60 °C) 7.88 (br s, 1H), 5.55-5.54 (br m, 1H), 4.10 (t, J = 8.2 Hz, 1H), 3.55 (dd, J = 9.4 Hz, 3.9 Hz, 1H), 1.54-1.09 (m, 21H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.8, 166.1, 161.5, 159.9, 159.7, 152.3, 151.3, 118.6, 105.6, 105.3, 95.4, 94.5, 81.1, 80.8, 68.1, 67.2, 57.2, 57.0, 28.3, 27.9, 27.8, 27.6, 27.5, 27.2, 26.3, 24.8, 23.7; HRMS(EI) m/z calcd for $C_{14}H_{19}NO_6$ (M$^+$ - acetone): 297.1212 Found: 297.1218.
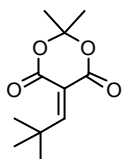
5-(2,2-Dimethylpropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (S4.1): Prepared by addition of tBuMgCl (2.0 equiv) to 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.65 g, 25.0 mmol), followed by acidic workup. Purified by recrystallization from MeOH and isolated as a white powder (3.4 g, 65% yield). M.p. 59-60 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.80 (s, 1H), 1.72 (s, 6H), 1.32 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) 175.0 (CH), 165.1 (C), 158.9 (CH), 118.5 (C), 104.4 (C), 35.2 (C), 28.7 (3X CH$_3$), 27.4 (2X CH$_3$); HRMS(EI) m/z calcd for $C_{10}H_{13}O_4$ (M$^+$ - methyl): 197.0814 Found: 197.0818.

Alkylidenes used for the synthesis of **4.53-4.56** were generously donated by Ash Wilsily. Their preparation of these alkylidenes has been described previously.[45b] Aside from **4.51**, their structures are shown below:
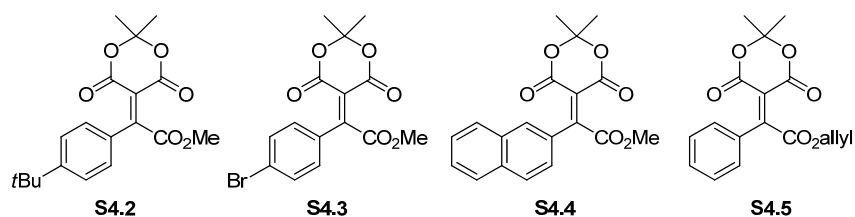
General Procedure A: Synthesis of allylated Meldrum's acids 4.28-4.43:
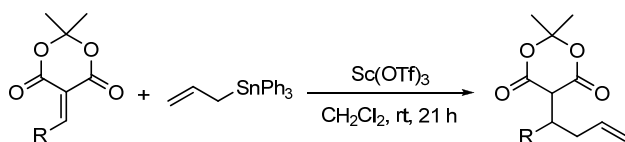
A flame-dried flask was transferred into a glove-box and charged with Sc(OTf)$_3$ (24.6 mg, 0.05 mmol, 0.05 equiv) and removed from the glove-box. The alkylidene (1.00 mmol, 1.0 equiv) and allyltriphenyltin (508 mg, 1.30 mmol, 1.3 equiv) were added to the flask, the solids dissolved in CH$_2$Cl$_2$ (5.0 mL) and the flask sealed securely with a plastic cap. The reaction was stirred for 21 h at room temperature, and 10% HCl (10 mL) was added to the flask. The contents were poured into a separatory funnel, the flask was rinsed with CH$_2$Cl$_2$ (2X 10 mL), and the funnel was shaken vigorously for 2-3 minutes to fully protonate the intermediate tin enolate. The organic layer was drained into an Erlenmeyer flask that could be capped tightly, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2X 10 mL). NaF (~140 mg) and H$_2$O (2mL) was added to the combined organic layers in the Erlenmeyer flask. The flask was capped tightly and shaken vigorously; this resulted in the formation of a white precipitate. The contents were filtered through a pad of Celite$^®$ to remove the precipitate, and the filtrate was dried over MgSO$_4$, filtered, and concentrated. After analysis of the crude reaction mixture by ^{1}H NMR, the residue was dissolved in CH$_2$Cl$_2$ and concentrated onto a small amount of silica gel. This was loaded to the top of a packed silica gel column and the products isolated by flash column chromatography using the indicated solvent gradient.
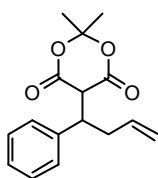
2,2-Dimethyl-5-(1-phenylbut-3-enyl)-1,3-dioxane-4,6-dione (**4.28**): Prepared from alkylidene **4.27** and isolated as a clear, colourless oil by flash chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (234 mg, 85% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.32-7.22 (m, 5H), 5.82-5.75 (m, 1H), 5.23 (d, J = 16.9 Hz, 1H), 5.12 (d, J = 10.1 Hz, 1H), 3.89-3.83 (m, 1H), 3.77 (d, J = 2.9 Hz, 1H), 3.06 (dt, J = 14.1 Hz, 9.2 Hz, 1H), 2.76 (dt, J = 13.8 Hz, 6.2 Hz, 1H), 1.61 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.9 (C), 165.4 (C), 139.5 (C), 135.7 (CH), 128.8 (2X CH), 128.6 (2X CH), 127.6 (CH), 118.6 (CH$_2$), 105.3 (C), 49.3 (CH), 45.1 (CH), 36.4 (CH$_2$), 28.1 (CH$_3$), 28.0 (CH$_3$); HRMS(EI) m/z calcd for C$_{13}$H$_{12}$O$_3$ (M$^+$ - acetone): 216.0786 Found: 216.0780.
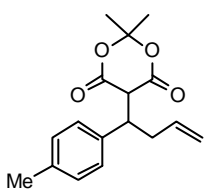
2,2-Dimethyl-5-(1-p-tolylbut-3-enyl)-1,3-dioxane-4,6-dione (**4.29**): Prepared from alkylidene **1.34** and isolated as clear, colourless oil by

flash column chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (251 mg, 87% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.19 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 5.85-5.72 (m, 1H), 5.22 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 3.86-3.79 (m, 1H), 3.75 (d, J = 2.8 Hz, 1H), 3.03 (dt, J = 14.0 Hz, 9.1 Hz, 1H), 2.78-2.70 (m, 1H), 2.28 (s, 3H), 1.61 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 166.0 (C), 164.6 (C), 137.3 (C), 136.5 (C), 135.9 (CH), 129.3 (2X CH), 128.7 (2X CH), 118.4 (CH$_2$), 105.3 (C), 49.5 (CH), 44.8 (CH), 36.5 (CH$_2$), 28.1 (CH$_3$), 28.0 (CH$_3$), 20.9 (CH$_3$); HRMS(EI) m/z calcd for C$_{17}$H$_{20}$O$_4$ (M$^+$): 288.1362 Found: 288.1368.
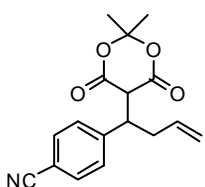
4-(1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)but-3-enyl) benzonitrile (4.30): Prepared from alkylidene **1.36** and isolated as a white solid by flash chromatography eluting with 19:1 toluene:acetone (271 mg, 91% yield). M.p. 89-90 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.58 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 5.82-5.68 (m, 1H), 5.21 (dd, J = 17.1 Hz, 0.8 Hz, 1H), 5.14 (d, J = 10.2 Hz, 1H), 3.99-3.92 (m, 1H), 3.80 (d, J = 2.8 Hz, 1H), 3.01 (dt, J = 14.0 Hz, 9.1 Hz, 1H), 2.81-2.72 (m, 1H), 1.68 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.0 (C), 164.1 (C), 145.1 (C), 135.1 (CH), 132.2 (2X CH), 130.1 (2X CH), 119.3 (CH$_2$), 118.6 (C), 111.5 (C), 105.2 (C), 49.2 (CH), 43.8 (CH), 36.0 (CH$_2$), 28.1 (CH$_3$), 27.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{14}$H$_{14}$NO$_3$ (M$^+$ - acetone): 241.0739 Found: 241.0741.
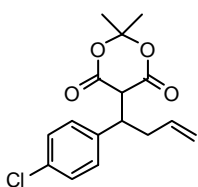
5-(1-(4-Chlorophenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.31): Prepared from alkylidene **1.38** and isolated as a white solid by flash column chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (262 mg, 85% yield). M.p. 52-53 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.30-7.23 (m, 4H, overlaps with CHCl$_3$), 5.83-5.70 (m, 1H), 5.21 (d, J = 17.0 Hz, 1H), 5.13 (d, J = 10.0 Hz, 1H), 3.89-3.83 (m, 1H), 3.76 (d, J = 2.8 Hz, 1H), 3.01 (dt, J = 14.1 Hz, 9.1 Hz, 1H), 2.78 -2.69 (m, 1H), 1.64 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.6 (C), 164.4 (C), 138.0 (C), 135.5 (CH), 133.5 (C), 130.5 (2X CH), 128.7 (2X CH), 118.8 (CH$_2$), 105.2 (C), 49.4 (CH), 44.0 (CH), 36.4 (CH$_2$), 28.1 (CH$_3$) 27.9 (CH$_3$); HRMS(EI) m/z calcd for C$_{13}$H$_{11}$ClO$_3$ (M$^+$ - acetone): 250.0397 Found: 250.0397.
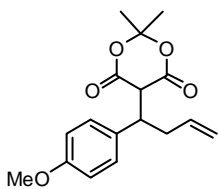
5-(1-(4-Methoxyphenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane
(4.32): Prepared from alkylidene **1.30** by the general procedure, except using DCE as solvent and heating at 50 °C for 21 h instead of rt. Isolated as yellow oil by flash column chromatography eluting with a gradient from 9:1 to 4:1 hexanes:EtOAc (250 mg, 84% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.22-7.20 (m, 2H, overlaps with CHCl$_3$), 6.83-6.80 (m, 2H), 5.80-5.75 (m, 1H), 5.22 (dd, J = 17.1 Hz, 0.9 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 3.85-3.78 (m, 1H), 3.75 (s, 3H), 3.75-3.74 (m, 1H, overlaps with signal at 3.75 ppm), 3.03 (dt, J = 14.1 Hz, 9.1 Hz, 1H), 2.77-2.69 (m, 1H), 1.61 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 166.2 (C), 164.6 (C), 159.0 (C), 135.9 (CH), 131.5 (C), 130.0 (2X CH), 118.5 (CH$_2$), 113.9 (2X CH), 105.3 (C), 55.2 (CH$_3$), 49.5 (CH), 44.5 (CH), 36.8 (CH$_2$), 28.2 (CH$_3$), 28.1 (CH$_3$); HRMS(EI) m/z calcd for C$_{17}$H$_{20}$O$_5$ (M$^+$): 304.1311 Found: 304.1316.

2,2-Dimethyl-5-(1-(4-nitrophenyl)but-3-enyl)-1,3-dioxane-4,6-dione (4.33): Prepared from alkylidene **1.35** by the general procedure, except using DCE as solvent and heating at 50 °C for 21 h instead of rt. Isolated as a yellow oil that solidified into a wax upon cold storage by flash column chromatography eluting with a gradient from 17:3 to 4:1 hexanes:EtOAc (265 mg, 83% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 8.14 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 5.83-5.69 (m, 1H), 5.21 (dd, J = 17.1 Hz, 1.1 Hz, 1H), 5.15 (d, J = 10.2 Hz, 1H), 4.05-3.99 (m, 1H), 3.82 (d, J = 2.8 Hz, 1H), 3.03 (dt, J = 14.0 Hz, 9.0 Hz, 1H), 2.84-2.75 (m, 1H), 1.69 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 164.9 (C), 164.0 (C), 147.3 (C), 147.1 (C), 135.0 (CH), 130.4 (2X CH), 123.6 (2X CH), 119.4 (CH$_2$), 105.2 (C), 49.3 (CH), 43.4 (CH), 36.1 (CH$_2$), 28.1 (CH$_3$), 27.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{13}$H$_{11}$NO$_5$ (M$^+$ - acetone): 261.0637 Found: 261.0637

**2,2-Dimethyl-5-(1-(3-(triisopropylsilyloxy)phenyl)but-3-enyl)-1,3-dioxane-4,6-dione (4.34):** Prepared from alkylidene **1.43** and isolated as a clear, colourless oil by flash column chromatography eluting with 9:1 hexanes:EtOAc (355 mg, 80% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.11 (t, J = 7.8 Hz, 1H), 6.86-6.82 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H),

5.86-5.72 (m, 1H), 5.22 (d, J = 17.0 Hz, 1H), 5.12 (d, J = 10.1 Hz, 1H), 3.82-3.76 (m, 1H), 3.74 (d, J = 2.8 Hz, 1H), 3.02 (dt, J = 14.1 Hz, 9.1 Hz, 1H), 2.77-2.68 (m, 1H), 1.61 (s, 3H), 1.28-1.16 (m, 1H, overlaps with signal at 1.20 ppm), 1.20 (s, 3H, overlaps with multiplet at 1.28-1.16 ppm), 1.07 (d, J = 7.1 Hz, 18 H); ^{13}C NMR (CDCl$_3$, 75 MHz) 166.0 (C), 164.6 (C), 156.2 (C), 140.9 (C), 135.8 (CH), 129.5 (CH), 121.5 (CH), 120.2 (CH), 119.2 (CH), 118.6 (CH$_2$), 105.2 (C), 49.2 (CH), 45.1 (CH), 36.6 (CH$_2$), 28.2 (2X CH$_3$), 17.9 (6X CH$_3$), 12.6 (3X CH); HRMS(EI) m/z calcd for C$_{25}$H$_{38}$O$_5$Si (M$^+$): 446.2489 Found: 446.2498.
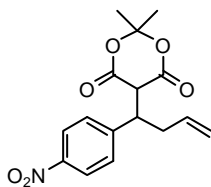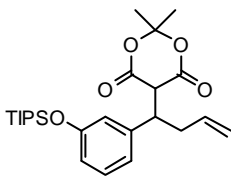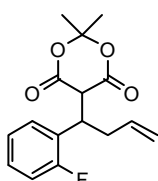
5-(1-(2-Fluorophenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.35): Prepared from alkylidene **1.40** and isolated as a white solid by flash column chromatography eluting with 9:1 to 17:3 hexanes:EtOAc (217 mg, 74% yield). M.p. 63-64 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.51 (t, J = 7.5 Hz, 1H), 7.25-7.19 (m, 1H, overlaps with CHCl$_3$), 7.12 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 9.4 Hz, 1H), 5.82-5.68 (m, 1H), 5.15 (d, J = 16.9 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 4.28 (td, J = 8.0 Hz, 2.5 Hz, 1H), 3.76 (d, J = 2.6 Hz, 1H), 2.86-2.70 (m, 2H), 1.67 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 164.8 (C), 164.3 (C), 160.6 (d, J = 244.1 Hz, C), 135.3 (CH), 130.1 (d, J = 3.7 Hz, CH), 128.8 (d, J = 8.6, CH), 127.2 (d, J = 13.4 Hz, C), 124.2 (d, J = 3.4 Hz, CH), 118.5 (CH$_2$), 115.3 (d, J = 22.6 Hz, CH), 105.1 (C), 49.1 (d, J = 1.1 Hz, CH), 36.0 (d, J = 2.3 Hz, CH), 34.5 (CH$_2$), 28.2 (CH$_3$), 27.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{13}$H$_{11}$FO$_3$ (M$^+$ - acetone): 234.0692 Found: 234.0690.
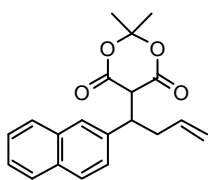
2,2-Dimethyl-5-(1-(naphthalen-2-yl)but-3-enyl)-1,3-dioxane-4,6-dione (4.36): Prepared from alkylidene **4.57** and isolated as a yellow oil that became a waxy solid upon freezer storage by flash column chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (294 mg, 91% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) 7.82-7.71 (m, 4H), 7.48-7.41 (m, 3H), 5.90-5.76 (m, 1H), 5.26 (d, J = 17.1 Hz, 1H), 5.13 (d, J = 10.2 Hz, 1H), 4.09-4.03 (m, 1H), 3.85 (d, J = 2.9 Hz, 1H), 3.16 (dt, J = 14.1 Hz, 9.2 Hz, 1H), 2.92-2.83 (m, 1H), 1.61 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.9 (C), 164.7 (C), 137.0 (C), 135.8 (CH), 133.2 (C), 132.7 (C), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 126.7 (CH), 126.1 (CH), 126.0 (CH), 118.7 (CH$_2$), 105.3 (C), 49.5

(CH), 45.0 (CH), 36.6 (CH$_2$), 28.05 (CH$_3$), 28.01 (CH$_3$) ; HRMS(EI) m/z calcd for C$_{20}$H$_{20}$O$_4$ (M$^+$): 324.1362 Found: 324.1357.
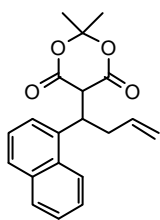
2,2-Dimethyl-5-(1-(naphthalen-1-yl)but-3-enyl)-1,3-dioxane-4,6-dione (4.37): Prepared from alkylidene **1.47** by the general procedure using 10 mol % Sc(OTf)$_3$ (49.2 mg). Isolated as a yellow oil by flash column chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (287 mg, 88% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 8.15 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 7.1 Hz, 1H), 7.59-7.54 (m, 1H), 7.51-7.48 (m, 2H), 5.90-5.76 (m, 1H), 5.21 (d, J = 16.9 Hz, 1H), 5.08 (d, J = 10.1 Hz, 1H), 4.88 (app t, J = 7.3 Hz, 1H), 3.79 (d, J = 1.9 Hz, 1H), 3.03 (dt, J = 14.0 Hz, 8.9 Hz, 1H), 2.90-2.82 (m, 1H), 1.57 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.9 (C), 164.2 (C), 136.1 (C), 135.7 (CH), 133.9 (C), 131.2 (C), 129.3 (CH), 128.0 (CH), 126.9 (CH), 126.4 (CH), 125.6 (CH), 125.4 (CH), 122.1 (CH), 118.5 (CH$_2$), 105.0 (C), 49.4 (CH), 38.0 (CH), 35.0 (CH$_2$), 28.0 (CH$_3$), 27.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{20}$H$_{20}$O$_4$ (M$^+$): 324.1362 Found: 324.1366.
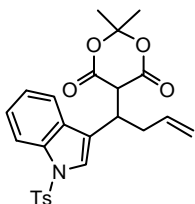
2,2-Dimethyl-5-(1-(1-tosyl-1H-indol-3-yl)but-3-enyl)-1,3-dioxane-4,6-dione (4.38): Prepared from alkylidene **1.51** according to the general procedure using 10 mol % Sc(OTf)$_3$ (49.2 mg). Isolated as a yellow solid by flash column chromatography eluting with a gradient from 17:3 to 4:1 to 2:1 hexanes:EtOAc. M.p. 62-63 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.95 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 7.9 Hz, 2), 7.62 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.31-7.17 (m, 4H, overlaps with CHCl$_3$), 5.82-5.69 (m, 1H), 5.19 (d, J = 17.1 Hz, 1H), 5.09 (d, J = 10.1 Hz, 1H), 4.16 (app t, J = 8.1 Hz, 1H), 3.74 (s, 1H), 2.99-2.89 (m, 1H), 2.81-2.72 (m, 1H), 2.30 (s, 3H), 1.61 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.0 (C), 164.9 (C), 144.8 (C), 135.4 (CH), 135.1 (C), 134.6 (C), 130.2 (C), 129.8 (2X CH), 126.9 (2X CH), 125.9 (CH), 124.9 (CH), 123.4 (CH), 121.5 (CH), 119.5 (CH), 118.8 (CH$_2$), 113.7 (CH), 105.0 (C), 48.4 (CH), 36.6 (CH$_2$), 35.0 (CH), 27.9 (CH$_3$), 27.7 (CH$_3$), 21.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{25}$H$_{25}$NO$_6$S (M$^+$): 467.1403 Found: 467.1393.
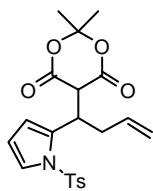
2,2-Dimethyl-5-(1-(1-tosyl-1H-pyrrol-2-yl)but-3-enyl)-1,3-dioxane-4,6-dione (4.39): Prepared from alkylidene **1.53** according to the general procedure using 15 mol % Sc(OTf)$_3$ (73.8 mg) and running the reaction for 36 h. Isolated as a yellow solid by flash chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc. (317 mg, 76% yield). M.p. 113-114 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.71 (d, J = 8.3 Hz, 2H), 7.37-7.29 (m, 3H), 6.46 (br s, 1H), 6.26 (t, J = 3.4 Hz, 1H), 5.28-5.14 (m, 1H), 4.78 (d, J = 17.1 Hz, 1H), 4.69 (d, J = 10.1 Hz, 1H), 4.24 (d, J = 2.0 Hz, 1H), 4.07-4.02 (m, 1H), 2.66-2.56 (m, 1H), 2.40 (s, 3H), 2.35-2.28 (m, 1H), 1.75 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 164.6 (C), 163.1 (C), 145.2 (C), 135.7 (C), 135.1 (CH), 133.0 (C), 130.1 (2X CH), 127.1 (2X CH), 122.5 (CH), 117.4 (CH$_2$), 116.3 (CH), 111.4 (CH), 104.7 (C), 50.2 (CH), 34.3 (CH), 33.9 (CH$_2$), 28.4 (CH$_3$), 26.3 (CH$_3$), 21.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{18}$H$_{18}$NO$_6$S (M$^+$ - allyl): 376.0855 Found: 376.0850.
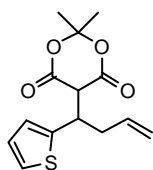
2,2-Dimethyl-5-(1-(thiophen-2-yl)but-3-enyl)-1,3-dioxane-4,6-dione (4.40): Prepared from alkylidene **1.50** according to the general procedure using 15 mol % Sc(OTf)$_3$ (73.8 mg) and running the reaction for 36 h. Isolated as a white solid by flash chromatography eluting with 19:1 toluene:acetone (240 mg, 86% yield). M.p. 70-71 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.16 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 6.98 (d, J = 3.3 Hz, 1H), 6.91 (dd, J = 5.0 Hz, 3.6 Hz, 1H), 5.86-5.72 (m, 1H), 5.22 (d, J = 17.1 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 4.21-4.15 (m, 1H), 3.80 (d, J = 2.6 Hz, 1H), 3.03 (dt, J = 14.0 Hz, 9.3 Hz, 1H), 2.86-2.78 (m, 1H), 1.67 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.6 (C), 164.2 (C), 142.2 (C), 135.4 (CH), 126.7 (2X CH), 124.8 (CH), 119.0 (CH$_2$), 105.3 (C), 49.5 (CH), 39.9 (CH), 38.2 (CH$_2$), 28.2 (CH$_3$), 27.7 (CH$_3$); HRMS(EI) m/z calcd for C$_{11}$H$_{11}$O$_4$S (M$^+$ - allyl): 239.0378 Found: 239.0376.
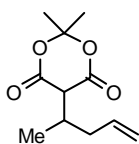
2,2-Dimethyl-5-(pent-4-en-2-yl)-1,3-dioxane-4,6-dione (4.41): Prepared from alkylidene **1.23** and isolated as a white solid by flash chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (151 mg, 72% yield). M.P. 60-61 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 5.81-5.67 (m, 1H), 5.09 (d, J = 17.3 Hz, 1H), 5.06 (d, J = 9.6 Hz, 1H), 3.50 (d, J = 2.4 Hz, 1H), 2.71-2.62 (m, 1H), 2.51-2.41

(m, 1H), 2.33-2.26 (m, 1H), 1.72 (s, 6H), 1.10 (d, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 165.6 (C), 164.5 (C), 136.5 (CH), 117.8 (CH$_2$), 104.6 (C), 48.8 (CH), 38.1 (CH$_2$), 33.3 (CH), 28.2 (CH$_3$), 27.2 (CH$_3$), 16.5 (CH$_3$); HRMS(EI) m/z calcd for C$_8$H$_{10}$O$_4$ (M$^+$ - allyl): 171.0657 Found: 171.0654.
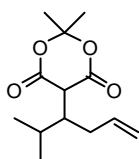
2,2-Dimethyl-5-(2-methylhex-5-en-3-yl)-1,3-dioxane-4,6-dione **(4.43):** Prepared from alkylidene **1.49** and isolated as a clear, colourless oil by flash column chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (211 mg, 83% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 5.80-5.67 (m, 1H), 5.10-5.04 (m, 2H), 3.56 (d, J = 1.4 Hz, 1H), 2.51-2.32 (m, 3H), 2.03-1.99 (m, 1H), 1.71 (s, 3H), 1.70 (s, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 166.1 (C), 165.7 (C), 137.3 (CH), 118.2 (CH$_2$), 104.6 (C), 45.6 (CH), 45.1 (CH), 35.1 (CH$_2$), 29.8 (CH), 28.1 (CH$_3$), 27.3 (CH$_3$), 21.6 (CH$_3$), 21.2 (CH$_3$); HRMS(EI) m/z calcd for C$_{10}$H$_{13}$O$_4$ (M$^+$ - i-Pr): 197.0814 Found: 197.0820.
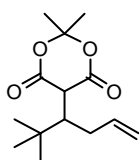
5-(2,2-Dimethylhex-5-en-3-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione **(2p):** Prepared from alkylidene **S4.1** by the general procedure using 15 mol% Sc(OTf)$_3$ (73.8 mg, 0.15 mmol) and running the reaction for 36 h. Isolated as a clear, colourless oil by flash column chromatography eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc (196 mg, 77% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 5.67-5.56 (m, 1H), 5.06-5.00 (m, 2H), 3.45 (d, J = 1.0 Hz, 1H), 2.79-2.74 (m, 1H), 2.62-2.50 (m, 1H), 2.40-2.34 (m, 1H), 1.70 (s, 6H), 1.00 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) 167.0 (C), 164.9 (C), 136.9 (CH), 118.7 (CH$_2$), 104.2 (C), 47.9 (CH), 44.7 (CH), 33.5 (C), 31.4 (CH$_2$), 29.0 (3X CH$_3$), 28.0 (CH$_3$), 27.3 (CH$_3$). Due to unusual fragmentation, HRMS data could not be obtained for this compound.

General Procedure B: Synthesis of chiral lactones 4.46 and 4.49:

X = (S)-O, (R)-NBoc
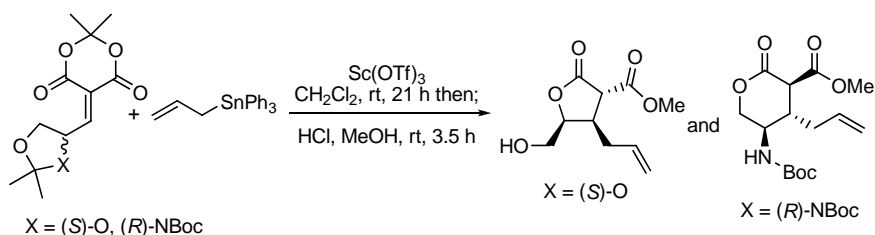
The allylation was performed as General Procedure A. After 21 h, the solvent was removed by rotary evaporation. After checking reaction conversion by ^{1}H NMR, the residue was dissolved in MeOH (reagent grade, 10 mL) at rt, and concentrated HCl (10 drops) was added. The reaction was stirred at rt for 3.5 h, concentrated by rotary evaporation, and the residue dissolved in 40 mL CH_2Cl_2. Treatment of the solution with NaF and H_2O as for the preparation of **4.28-4.43**, filtration through Celite, drying over $MgSO_4$, filtration, and concentrating gave the crude lactone. Purification was achieved by flash column chromatography eluting with a gradient from 4:1 to 2:1 hexanes:EtOAc to give lactones contaminated with a small amount of tin residues. Repurification by flash chromatography eluting with 2:1 hexanes:EtOAc yielded the pure lactones.
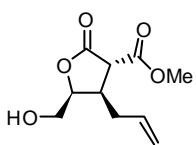
(3S,4R,5S)-Methyl 4-allyl-5-(hydroxymethyl)-2-oxo-tetrahydrofuran -3-carboxylate (4.46): Prepared from alkylidene **4.44** and isolated as clear colourless oil that solidified upon freezer storage (167 mg, 79% yield). M.p. 55-56 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) 5.75-5.67 (m, 1H), 5.13 (dd, J = 17.1 Hz, 1.3 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.61 (dt, J = 8.0 Hz, 2.5 Hz, 1H), 3.95 (**A**BXX`, $J$ = 12.5 Hz, 5.8 Hz, 2.6 Hz, 1H), 3.84 (A**B**XX`, J = 12.5 Hz, 5.1 Hz, 2.6 Hz, 1H), 3.77 (s, 3H), 3.63 (d, J = 11.2 Hz, 1H), 3.26-3.20 (m, 1H), 2.45-2.33 (m, 2H), 1.76 (t, J = 5.5 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 172.5 (C), 168.6 (C), 134.6 (CH), 117.6 (CH$_2$), 80.9 (CH), 61.3 (CH$_2$), 52.9 (CH$_3$), 52.0 (CH), 41.4 (CH), 32.8 (CH$_2$); HRMS(EI) m/z calcd for C$_{10}$H$_{14}$O$_5$ (M$^+$): 214.0841 Found: 214.0838.
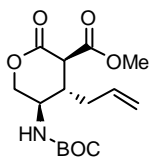
(3R,4S,5R)-Methyl 4-allyl-5-(tert-butoxycarbonylamino)-2-oxotetrahydro-2H-pyran-3-carboxylate (4.49): Prepared from alkylidene **4.47** and isolated as a clear, colourless oil (256 mg, 82% yield). ^{1}H NMR (CDCl$_3$, 500 MHz) 5.74-5.66 (m, 1H), 5.17-5.12 (m, 2H), 4.83 (br m, 1H), 4.26 (dd, J = 11.7 Hz, 3.7 Hz, 1H), 4.15 (br dd, J = 11.2 Hz, 4.9 Hz, 1H), 3.87 (br s, 1H), 3.79 (s, 3H), 3.39 (d, J = 8.4 Hz, 1H), 2.44-2.39 (m, 1H), 2.27 (t, J = 6.6 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.8 (C), 167.7 (C), 154.9 (C), 132.6 (CH), 119.7 (CH$_2$), 80.2 (C), 69.5 (CH$_2$), 53.0 (CH$_3$), 50.6 (CH), 48.0 (CH), 40.1 (CH), 37.1 (CH$_2$), 28.2 (3X CH$_3$); HRMS(EI) m/z calcd for C$_{11}$H$_{15}$NO$_6$ (M$^+$ - isobutene): 257.0899 Found: 257.0895.

The diasteromeric ratio was determined to be 19:1 by the relative integration of the doublet at 3.39 ppm (1.00H) to the doublet at 3.33 ppm (0.07H).

General Procedure C: Synthesis of allylated Meldrum's acids 4.52-4.56:
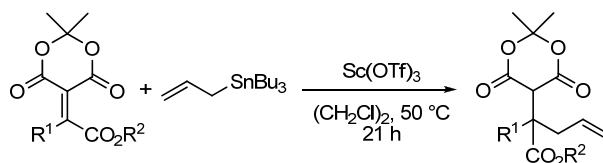
In a glove-box, a flask was charged with Sc(OTf)$_3$ (24.6 mg, 0.05 mmol, 0.05 equiv) and the flask was removed from the box. The alkylidene (1.0 mmol, 1.0 equiv) was added the flask and the solids dissolved in (CH$_2$Cl)$_2$ (5 mL). Allyltributyltin (465 μL, 1.5 mmol, 1.5 equiv) was added, the flask was sealed tightly with a plastic cap, and then placed in an oil bath preheated to 50 °C. After stirring for 21 h, the reaction was removed from the bath to cool to rt, diluted with CH$_2$Cl$_2$ (15 mL), and shaken in a separatory funnel with 10% HCl (10 mL) for 2-3 minutes. The layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (3X 5mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated. After checking the crude reaction mixture by ^{1}H NMR, the residue was dissolved in CH$_2$Cl$_2$ and evaporated onto a small amount of silica gel which was then loaded onto the top of a packed silica gel column. Elution with the indicated solvent gradient gave the product contaminated with Bu$_3$SnX, which was removed by a second elution through silica gel in the same manner as the first.
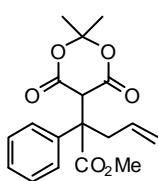
Methyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenylpent-4-enoate (4.52): Prepared from alkylidene **4.51** and isolated as a white solid by flash column chromatography eluting with a gradient from 17:3 to 4:1 to 2:1 hexanes:EtOAc (270 mg, 81% yield). M.p. 119-120 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.44 (d, J = 7.6 Hz, 2H), 7.35-7.26 (m, 3H), 5.92-5.78 (m, 1H), 5.08 (d, J = 18.1 Hz, 1H), 5.06 (d, J = 9.6 Hz, 1H), 4.70 (s, 1H), 3.70 (s, 3H), 3.46 (dd, J = 14.1 Hz, 6.6 Hz, 1H), 3.14 (dd, J = 14.2 Hz, 8.7 Hz, 1H), 1.83 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 172.7 (C), 163.3 (C), 162.8 (C), 138.0 (C), 134.3 (CH), 128.3 (2X CH), 127.5 (CH), 127.2 (2X CH), 119.4 (CH$_2$), 104.6 (C), 54.3 (C), 52.8 (CH$_3$), 51.3

(CH), 38.7 (CH$_2$), 28.5 (CH$_3$), 26.5 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{18}$H$_{20}$O$_6$ (M$^+$): 332.1260 Found: 332.1257.

Methyl 2-(4-tert-butylphenyl)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)pent-4-enoate (4.53): Prepared from alkylidene **S4.2** and isolated as a white solid by flash column chromatography eluting with a gradient from 9:1 to 17:3 to 4:1 hexanes:EtOAc (319 mg, 82% yield). M.p. 113-114 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.36-7.29 (m, 4H), 5.88-5.77 (m, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 5.07 (d, *J* = 18.8 Hz, 1H), 4.69 (s, 1H), 3.70 (s, 3H), 3.45 (dd, *J* = 14.1 Hz, 6.4 Hz, 1H), 3.12 (dd, *J* = 14.1 Hz, 9.0 Hz, 1H), 1.81 (s, 3H), 1.61 (s, 3H), 1.28 (s, 9H) ; ^{13}C NMR (CDCl$_3$, 75 MHz) 172.8 (C), 163.4 (C), 162.9 (C), 150.2 (C), 134.8 (C), 134.5 (CH), 127.0 (2X CH), 125.2 (2X CH), 119.2 (CH$_2$), 104.6 (C), 54.2 (C), 52.8 (CH$_3$), 51.5 (CH), 39.0 (CH$_2$), 34.4 (C), 31.2 (3X CH$_3$), 28.5 (CH$_3$), 26.6 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{21}$H$_{25}$O$_6$ (M$^+$ - methyl): 373.1651 Found: 373.1660.

Methyl 2-(4-bromophenyl)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)pent-4-enoate (4.54): Prepared from **S4.3** and isolated as a white solid by flash chromatography eluting with a gradient from 19:1 to 9:1 toluene:acetone (312 mg, 76% yield). M.p. 125-126 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.44 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 5.86-5.72 (m, 1H), 5.09 (d, *J* = 17.0 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.63 (s, 1H), 3.71 (s, 3H), 3.42 (dd, *J* = 14.3 Hz, 6.5 Hz, 1H), 3.11 (dd, *J* = 14.2 Hz, 8.6 Hz, 1H), 1.82 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 172.3 (C), 163.0 (C), 162.8 (C), 136.8 (C), 133.7 (CH), 131.3 (2X CH), 129.6 (2X CH), 121.8 (C), 119.8 (CH$_2$), 104.8 (C), 54.2 (C) 52.9 (CH$_3$), 51.5 (CH), 38.9 (CH$_2$), 28.4 (CH$_3$), 26.4 (CH$_3$); HRMS(EI) *m/z* calcd for C$_{18}$H$_{19}$BrO$_6$ (M$^+$ - methyl): 410.0365 Found: 410.0356.
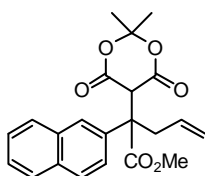
Methyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-(naphthalen-2-yl)pent-4-enoate (4.55): Prepared from alkylidene **S4.4** and isolated as a white solid by flash column chromatography eluting with a gradient from 4:1 to 2:1 hexanes:EtOAc (324 mg, 85% yield). M.p. 138-139 °C (dec); ^{1}H NMR (CDCl$_3$, 300 MHz) 7.90 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 3H), 7.58 (d, *J* = 8.8

Hz, 1H), 7.47 (br s, 2H), 5.91 (sextet, J = 8.4 Hz, 1H), 5.15-5.07 (m, 2H), 4.82 (s, 1H), 3.71 (s, 3H), 3.58 (dd, J = 14.2, 1H), 3.27 (dd, J = 13.8 Hz, 8.7 Hz, 1H), 1.86 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 172.7 (C), 164.4 (C), 162.8 (C), 135.4 (C), 134.4 (CH), 133.0 (C), 132.4 (C), 128.4 (CH), 127.8 (CH), 127.3 (CH), 126.6 (CH), 126.6 (CH), 126.2 (CH), 125.1 (CH), 119.5 (CH$_2$), 104.7 (C), 54.6 (C), 52.9 (CH$_3$), 51.3 (CH), 38.8 (CH$_2$) 28.5 (CH$_3$), 26.6 (CH$_3$); HRMS(EI) m/z calcd for C$_{22}$H$_{22}$O$_6$ (M$^+$): 382.1416 Found: 382.1411.

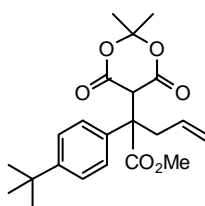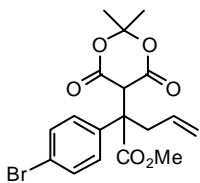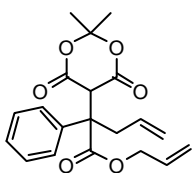**Allyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenylpent-4-enoate (4.56):** Prepared from alkylidene **S4.5** and isolated as a white solid by flash chromatography eluting with a gradient from 4:1 to 2:1 hexanes:EtOAc (279 mg, 78% yield). M.p. 74-76 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.45 (d, J = 7.7 Hz, 2H), 7.35-7.25 (m, 3H), 5.93-5.76 (m, 2H), 5.16 (d, J = 17.1 Hz, 1H), 5.15 (d, J = 10.5 Hz, 1H), 5.09 (d, J = 17.5 Hz, 1H), 5.07 (d, J = 9.7 Hz, 1H), 4.72 (s, 1H), 4.65 (dd, J = 13.3, 5.6 Hz), 4.57 (dd, J = 13.3 Hz, 5.7 Hz, 1H), 3.46 (dd, J = 14.2 Hz, 6.7 Hz, 1H), 3.18 (dd, J = 14.3 Hz, 8.5 Hz, 1H), 1.82 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 171.9 (C), 163.3 (C), 162.8 (C), 138.0 (C), 134.3 (CH), 131.6 (CH), 128.3 (2X CH), 127.5 (CH), 127.2 (2X CH), 119.5 (CH$_2$), 118.3 (CH$_2$), 104.6 (C), 66.3 (CH$_2$), 54.4 (C), 51.3 (CH), 38.6 (CH$_2$), 28.5 (CH$_3$), 26.5 (CH$_3$); HRMS(EI) m/z calcd for C$_{20}$H$_{22}$O$_6$ (M$^+$): 358.1416 Found: 358.1408.

Competition Experiment: Allylation of alkylidene 4.57 vs 2-napthaldehyde (4.58):

5.87-5.82 (m, 0.84H)
84% yield

8.69 (s, 0.16H)
16% yield

10.16 (s, 1.00H)
100% yield
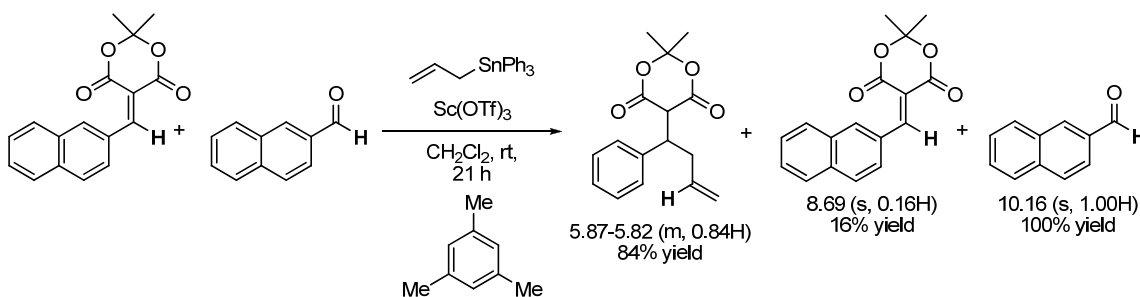
In a glove-box, a flame-dried flask was charged with Sc(OTf)$_3$ (12.3 mg, 0.025 mmol, 0.05 equiv). Outside of the box, alkylidene **4.57** (141 mg, 0.50 mmol, 1.0 equiv), 2-naphthaldehyde (78 mg, 0.50 mmol, 1.0 equiv) and allylSnPh$_3$ (196 mg, 0.50 mmol, 1.0

equiv) was added to the flask. The solids were dissolved by addition of CH_2Cl_2 (2.36 mL) at rt, and then mesitylene (140 µL, 1.00 mmol, 2.0 equiv) was added, bringing the total volume to 2.5 mL (0.2 M). The reaction was stirred at rt for 21 h, quenched by addition of 10% HCl (2.5 mL) and transferred into a separatory funnel using CH_2Cl_2 (3 rinses, 20 mL total) to transfer the contents. The funnel was shaken vigorously for 2 min to ensure full protonation of all species, and the organic layer drained off. The aqueous layer was extracted with CH_2Cl_2 (3X 5 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation using water aspirator suction in a room temperature water bath. Reaction conversion was determined by ^{1}H NMR integration of signals of unambiguous origin (protons in bold in above scheme) against a calibrated internal standard of mesitylene (ArCH_3, 2.29 ppm, s, 18.0H).

Based on the integrations obtained and the lack of peaks attributable to the product of 1,2-allylation (see below), addition occurred exclusively on alkylidene **4.57**. The NMR yields for each compound are indicated in the above scheme.

Control Experiment- Allylation of 2-napthaldehyde:
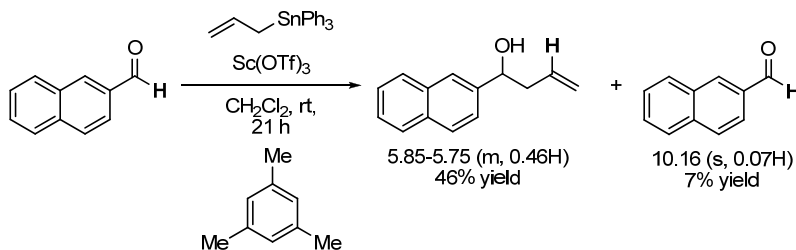
To determine whether allylSnPh$_3$ reacts with 2-naphthaldehyde under Sc(OTf)$_3$ catalysis, the same procedure as for the competition experiment was performed, omitting alkylidene **2i**. The reaction was quenched after 40 h, and the conversion determined by ^{1}H NMR integration of the indicated protons relative to the calibrated internal standard of mesitylene (ArCH_3, 2.29 ppm, s, 18.0H). While the reaction did not proceed cleanly, the unidentified side products did not prevent unambiguous determination of the signals from the homoallylic alcohol product. The NMR yields of each product are indicated in the above scheme.

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Transformations of allylated Meldrum's acid 4.28:
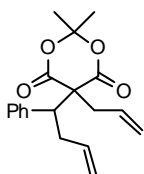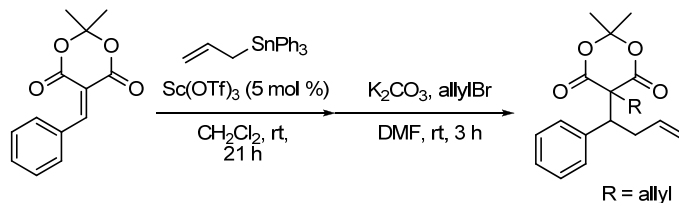
5-Allyl-2,2-dimethyl-5-(1-phenylbut-3-enyl)-1,3-dioxane-4,6-dione (4.60): Alkylidene **4.27** was allylated according to General Procedure A on 0.50 mmol scale. The crude **4.28** thus obtained was dissolved in DMF (2.5 mL), anhydrous K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) and freshly distilled allyl bromide (65 µL, 0.75 mmol, 1.5 equiv) was added and the flask was stopped with a plastic cap. After stirring 3 h at rt, the reaction was diluted with ether (30 mL) and poured into a separatory funnel. The organic phase was washed with H_2O (2X 15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography eluting with 9:1 hexanes:EtOAc gave the product as a waxy white solid (128 mg, 82% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.30-7.19 (m, 3H, overlaps with CHCl$_3$), 7.14 (d, J = 7.0 Hz, 2H), 5.74-5.60 (m, 1H), 5.49-5.35 (m, 1H), 5.24 (d, J = 17.1 Hz, 1H), 5.17 (d, J = 10.1 Hz, 1H), 4.97 (d, J = 17.0 Hz, 1H), 4.85 (d, J = 10.3 Hz, 1H), 3.43 (dd, J = 11.6 Hz, 4.4 Hz, 1H), 3.07 (dd, J = 12.6 Hz, 7.7 Hz, 1H), 2.97-2.71 (m, 3H), 1.49 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 168.4 (C), 167.2 (C), 137.8 (C), 135.4 (CH), 131.3 (CH), 129.6 (CH), 128.7 (2X CH), 127.9 (2X CH), 121.7 (CH$_2$), 117.1 (CH$_2$), 106.0 (C), 60.1 (C), 53.2 (CH), 40.6 (CH$_2$), 33.0 (CH$_2$), 30.7 (CH$_3$), 27.8 (CH$_3$); HRMS(EI) m/z calcd for $C_{16}H_{16}O_3$ (M$^+$ - acetone): 256.1099 Found: 256.1100.

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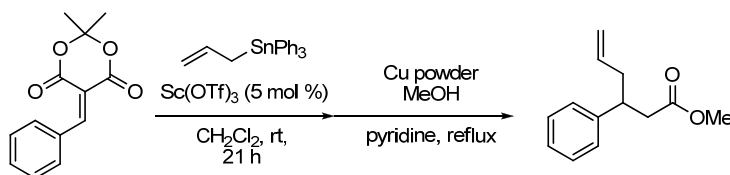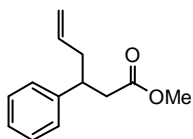
Methyl 3-phenylhex-5-enoate (4.61): Alkylidene **4.27** was allylated according to General Procedure A on 0.50 mmol scale. The crude **4.28** thus obtained was dissolved in 4:1 (v/v) pyridine:MeOH (5 mL), Cu powder (6.4 mg, 0.1 mmol, 0.2 equiv) was added, and the flask was capped with a water-cooled reflux condenser and purged with nitrogen. The reaction was heated to reflux for 3 h, cooled to rt, and a small amount of silica gel was added before concentrating dry by rotary evaporation. The silica gel was loaded onto the top of a silica gel column packed with 19:1 hexanes:EtOAc, and the product was eluted with 19:1 hexanes:EtOAc to give the product as a clear, colourless oil (89 mg, 87% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) 7.30-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.71-5.57 (m, 1H), 5.01-4.93 (m, 2H), 3.56 (s, 3H), 3.20 (pentet, J = 7.5 Hz, 1H), 2.68 (**ABX**, J = 15.4 Hz, 6.7 Hz, 1H), 2.55 (**ABX**, J = 15.5 Hz, 8.3 Hz, 1H), 2.40-2.35 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) 172.7 (C), 143.6 (C), 135.9 (CH), 128.4 (2X CH), 127.3 (2X CH), 126.5 (CH), 116.8 (CH$_2$), 51.4 (CH$_3$), 41.7 (CH), 40.6 (CH$_2$), 40.4 (CH$_2$); HRMS(EI) m/z calcd for C$_{13}$H$_{16}$O$_2$ (M$^+$): 204.1150 Found: 204.1147.

General Reaction D: Rh-catalyzed Enantioselective synthesis of alkylidene 4.28
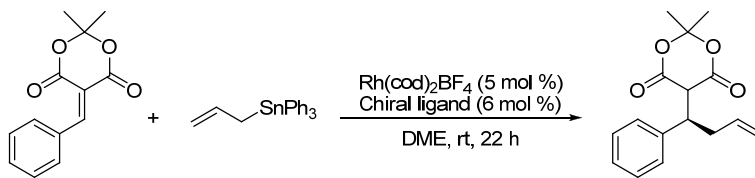
An oven-dried vial was taken into a glovebox, and to it were added the Rh catalyst (2.0 mg, 0.005 mmol, 0.05 equiv) and the chiral ligand (0.006 mmol, 0.06 equiv). These were dissolved in DME (0.5 mL) and stirred in the glovebox for 30 min to form the chiral complex. Still in the box, alkylidene **4.27** (26 mg, 0.1 mmol, 1.0 equiv) and allylSnPh$_3$ (43 mg, 0.11 mmol, 1.1 equiv) were added to the vial, and the contents rinsed down with additional DME (0.5 mL). The vial was capped tightly and removed from the box to stir for 22 h at rt. The reactions were worked up as in General Procedure A but omitting the NaF removal of the tin residue. The product obtained from flash column chromatography on silica gel eluting with a gradient from 9:1 to 17:3 hexanes:EtOAc was analyzed by HPLC to determine the enantioselectivity. A Chiralcel AD-H column was used, eluting

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with 1% isopropanol in hexane at a rate of 1 mL/min. Retention times are: 1st peak @ 14.8 min, 2nd peak @ 16.1 min. Products where the first peak was larger than the second are shown as positive ee, and vice-versa. Results are shown in Scheme 4.30.

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