The Conjugate Addition of Novel Nucleophiles and Catalytic Intramolecular Tandem [1,5]-Hydride Shift / Cyclization and Friedel-Crafts Acylation with Alkylidene Meldrum's Acid Derivatives

By

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

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Abstract

Investigations into the conjugate addition of phenols and sp^3-hybridized carbons bound to tin, boron and silicon by transition metal catalysts through novel transmetallation pathways were undertaken with limited success. An intramolecular Lewis acid-catalyzed tandem [1,5]-hydride shift / cyclization and Friedel-Crafts acylation reaction with alkylidene Meldrum's acid derivatives has been accomplished.

The use of metal phenolates as nucleophiles for transition metal catalyzed conjugate addition onto alkylidene Meldrum's acids is explored, and the ambident nucleophilic property of metal phenolates allow for the C-alkylation and O-acylation with alkylidene Meldrum's acids, producing substituted 3,4-dihydrocoumarins in modest yields.

The transmetallation of rhodium complexes with alkyl boron, tin and silicon derivatives and subsequent conjugate addition onto alkylidene Meldrum's acid derivatives is investigated without success.

An intramolecular Lewis acid-catalyzed [1,5]-hydride shift / cyclization reaction promoted by electron-rich aromatic rings is employed with alkylidene Meldrum's acid derivatives to furnish *spiro* Meldrum's acids in excellent yields. These can subsequently be used as electrophiles in the Friedel-Crafts acylation reaction, and a tandem, one-pot variation of this reaction has been accomplished in moderate to good yields. Preliminary investigations into the scope and limitations of this transformation are outlined.

Acknowledgements

It is with heartfelt thanks that I recognize Professor Eric Fillion for the opportunity to pursue my Master's research in his lab. We may not have always agreed with one another, but he has consistently encouraged me to strive harder, think deeper, and grow as a chemist and a person. Thanks are due as well to the members of my committee, Professors Mike Chong and Scott Taylor, who have been generous with their time and resources during my time at Waterloo.

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Finally, for my girlfriend Kathleen, who makes every day better for being here with her, I cannot begin to express my appreciation for everything she has done to help me during my studies here in Waterloo. Thank you.

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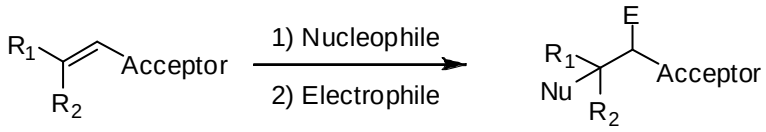
List of Abbreviations

18-C-6: 18-crown-6, 1,4,7,10,13,16-hexaoxacyclooctadecane
acac: acetylacetonato
9-BBN: 9-borabicyclo[3.3.1]nonane
Binap: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
cod: 1,5-cyclooctadiene
Cp*: C_5Me_5
Diox: 1,3-dioxane
DME: dimethoxyethane
DMF: dimethylformamide
DMSO: dimethylsulfoxide
Dppe: diphenylphosphinoethane
Dppf: 1,1'-bis(diphenylphosphino)ferrocene
Dppp: 1,3-bis(diphenylphosphino)propane
d.r. : diastereomeric ratio
ee: enantiomeric excess
GCMS: gas chromatograph / mass spectrometer
Hex: hexanes
MeCN: acetonitrile
MVK: methyl vinyl ketone, 3-buten-2-one
NMR: nuclear magnetic resonance
PCC: pyridinium chlorochromate
pin: pinacol, 2,3-dimethyl-2,3-butanediol
PMB: *p*-methoxybenzyl
TBAB: tetrabutylammonium bromide
TBAF: tetrabutylammonium fluoride
Tf: trifluoromethanesulfonyl
TFA: trifluoroacetic acid
THF: tetrahydrofuran
THP: tetrahydropyran
TMEDA: *N*,*N*,*N*,*N*-tetramethylethane-1,2-diamine
TMS: trimethylsilyl
T.O.F. : Turnover Frequencies
Ts: *p*-toluenesulfonyl

Chapter 1 – Introduction

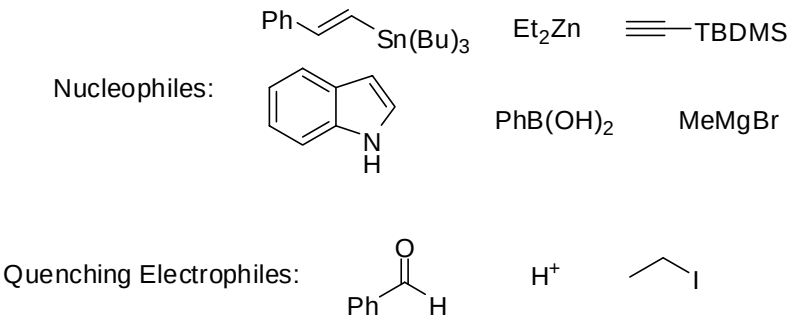
The conjugate addition reaction is one of the more versatile and useful bond-forming reactions in the modern synthetic toolbox (Scheme 1.1).[1] Because of the range of nucleophiles that can be employed, from organometallic reagents of sp, sp^2 and sp^3 hybridization to 1,3-dicarbonyl compounds, aromatic rings to heteroatoms, it has seen an incredible amount of research in recent years (Figure 1.1).[2,3,4,5,6]

Scheme 1.1: Conjugate Addition Reactions



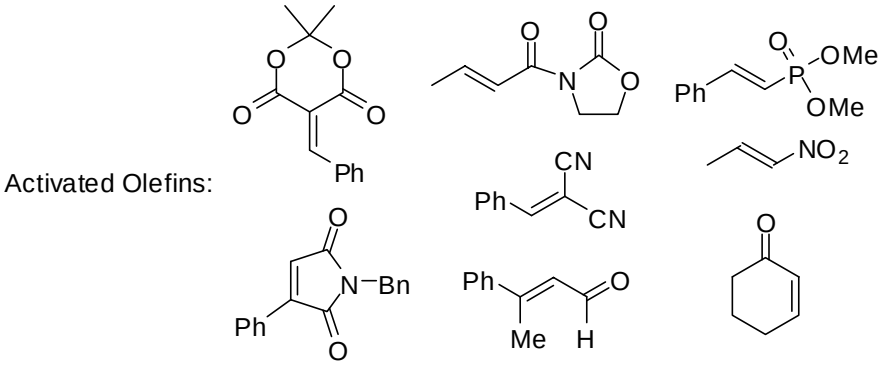
Furthermore, the scope of electrophiles for conjugate addition is similarly broad, with enals, enones, enoates, enamides, nitroolefins, alkenylphosphates, alkenylsulfates and others all proving to be capable acceptors for conjugate addition (Figure 1.2).

Figure 1.1: Commonly Employed Nucleophiles and Quenching Electrophiles for Conjugate Addition



This intense investigation has also lead to the successful development of asymmetric variants for many of these transformations, often in well above 90% ee. Advantageously, after addition, a number of electrophiles can be used to quench the resulting enolate or corresponding stabilized carbanion. These can range from protons to aldehydes or alkyl halides (Figure 1.1).

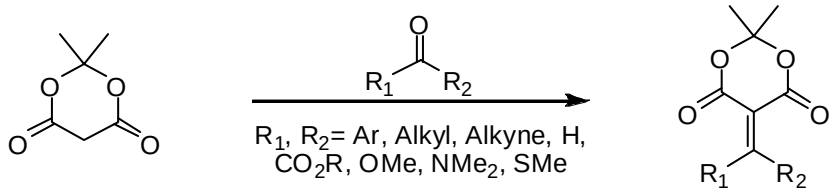
Figure 1.2: Commonly Employed Activated Olefins for Conjugate Addition



One type of acceptor which has been very successfully employed as an electrophile for conjugate addition is alkylidene Meldrum's acids.[7] These olefins are symmetrically doubly activated which serves to both increase their reactivity and eliminates the need for purification of *E/Z* isomers. Alkylidene Meldrum's acids bear higher electrophilic reactivity compared to alkylidene malonic esters, which has been related to the unusually high acidity of the Meldrum's acid,[8] which has a pKa of 4.83, some ten orders of magnitude more acidic than the acyclic malonates, although the acid exists overwhelmingly (>99.5%) in the diketo tautomer rather than the enolic form.[7]

These alkylidenes are synthetically desirable compounds due to their frequently crystalline nature, ease of formation by Knoevenagel condensation with appropriate carbonyl-containing compounds on small and large scales, and simple purification by recrystallization (Scheme 1.2).[9]

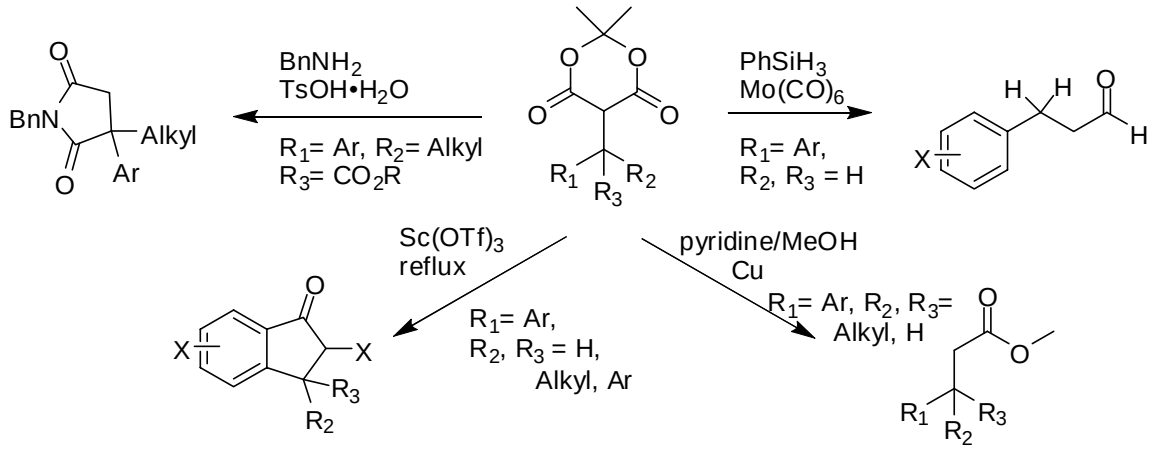
Scheme 1.2: Preparation of Alkylidene Meldrum's Acids by Knoevenagel Condensation



The high synthetic versatility of the alkylidenes is shown in several ways. First, it is an excellent acceptor for conjugate addition of sp and sp^3-hybridized nucleophiles,[10,11] by transition metal catalysis to form tertiary and quaternary all-carbon benzylic stereocentres, as well as functionalized quaternary stereocentres.[12] sp^2-Hybridized nucleophiles have been added by transition metal-catalyzed conjugate addition,[13] as well as by Friedel-Crafts conjugate addition, catalyzed by Lewis acids.[14] The superior electrophilicity of the alkylidenes has enabled the challenging formation of quaternary stereocentres in high yield, as well as smoothly undergoing Rh(I)-catalyzed conjugate addition of vinyltributyltin derivatives at room temperature, as opposed to literature conditions (60 °C).

Secondly, the product of these addition reactions can then be easily transformed into a variety of synthetically useful products including malonates by hydrolysis, mono acids or esters by hydrolysis and decarboxylation, succinimides by treatment with monoalkylated amines and catalytic acid under high reflux, indanones by Friedel-Crafts acylation,[15] β-aryl aldehydes by Mo(0) catalyzed reduction with $PhSiH_3$,[16] and many others (Scheme 1.3). This has resulted in the utilization of Meldrum's acid derivatives in numerous total syntheses, to the degree that a recent review article focused exclusively on this topic.[17]

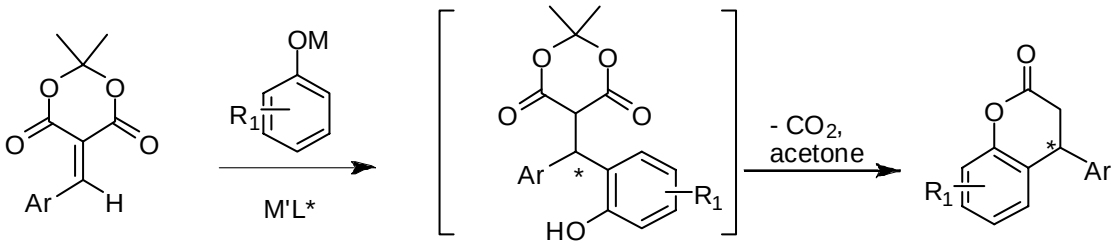
Scheme 1.3: Synthetic Transformations with 5-alkyl Meldrum's Acids



Within the Fillion group, a research program designed to exploit this great reactivity has been undertaken, with the development of catalytic intra- and intermolecular Friedel-Crafts acylation and alkylation reactions,[18] the sequential thermal Diels-Alder, Lewis acid-catalyzed Friedel-Crafts acylation on benzene[19] and indole derivatives,[20] and conjugate addition of alkyl, alkenyl and aryl nucleophiles.[14]

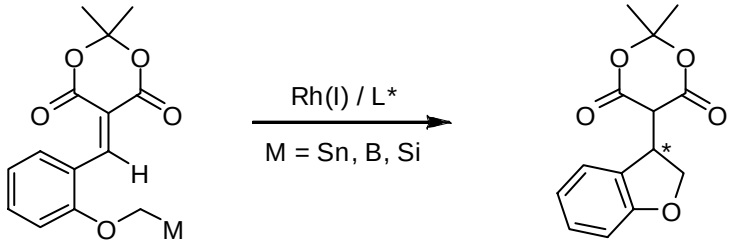
This research aimed to build upon the research successes in conjugate addition through expanding the scope of nucleophiles capable of adding in high yields onto alkylidene Meldrum's acids. The first research project undertaken looked at the addition of metal phenolates by transition metal catalysis, wherein the phenolate attacked in a manner similar to an enolate, generating an organometallic intermediate capable of effecting C-alkylation on the 4-position of the alkylidene. This addition product was then well aligned to undergo O-acylation, which after loss of CO_2 and acetone produced 3,4-dihydrocoumarin derivatives (Scheme 1.4).

Scheme 1.4: Addition of Metal Phenolates onto Alkylidene Meldrum's Acids by C-Alkylation/O-Acylation



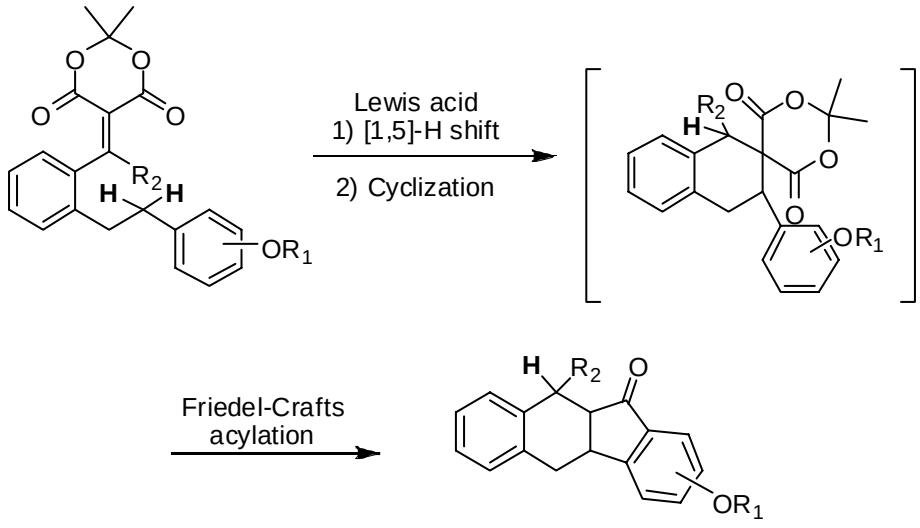
The second research project presented herein examined the feasibility of rhodium(I) catalyzed transmetallation and conjugate addition of air and moisture-stable alkyltin, boron and silicon compounds (Scheme 1.5).

Scheme 1.5: Rh(I) Catalyzed Transmetallation / Conjugate Addition of Alkyltin, Boron and Silicon Compounds



Finally, the third project details approaches towards the sequential one pot Lewis acid-catalyzed [1,5]-hydride shift and Friedel-Crafts acylation of ethylanisole derivatives of benzylidene Meldrum's acid (Scheme 1.6).

Scheme 1.6: Sequential One Pot 1,5-Hydride Shift/ Cyclization and Friedel-Crafts Acylation Reaction



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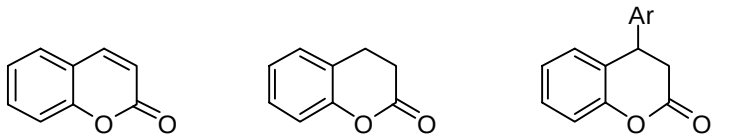
Chapter 2 - The Transition Metal Catalyzed Conjugate Addition of Metal Phenoxides onto Alkylidene Meldrum's Acids

Introduction

The immense list of biologically active natural products which contain aromatic groups provides a phenomenal opportunity for developing synthetic methodologies to introduce aryl groups into compounds. One aromatic-containing natural product backbone is 3,4-dihydrocoumarin, or 1,2-benzodihydropyrone, which has been the target of various synthetic investigations as its derivatives are both natural products and synthetic intermediates and targets of pharmaceutical interest.

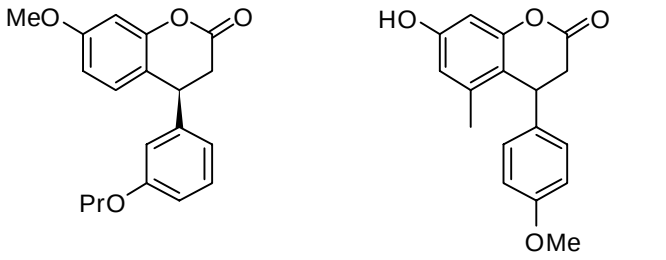
Figure 2.1: The Coumarin and 3,4-Dihydrocoumarin Backbone



coumarin 3,4-dihydrocoumarin 4-aryl-3,4-dihydrocoumarin

Naturally, they are found in extracts of plants of the Leguminosae, Guttiferae, Rubiaceae, and Passifloraceae families[1] and have reported biological activity with variously molluscicidal, piscicidal and batericidal traits,[2,3,4] as well as some activity towards several carcinoma tumour cell lines.[5] Synthetically, their interest includes a chiral dihydrocoumarin used by SmithKline Beecham as a key intermediate in the formation of an endothelin antagonist,[6] as a precursor to tolterodine,[7] a muscarinic receptor antagonist designed to treat overactive bladder,[8] and as a bactericide with in vitro activity against members of the *Tripanosoma* family.

Figure 2.2: Dihydrocoumarins of Biological Utility

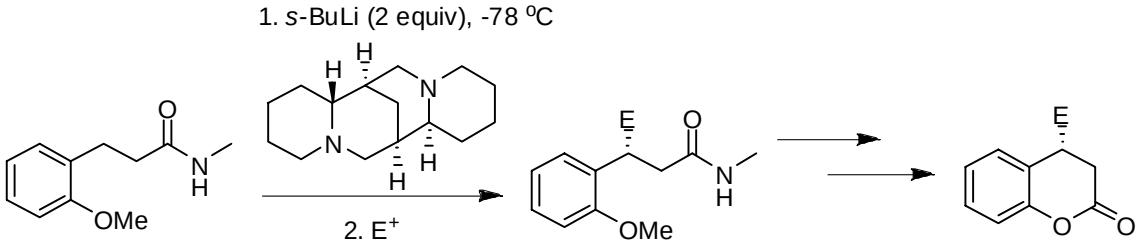


SmithKilne Beecham Intermediate

Bactericidal Dihydrocoumarin Derivative

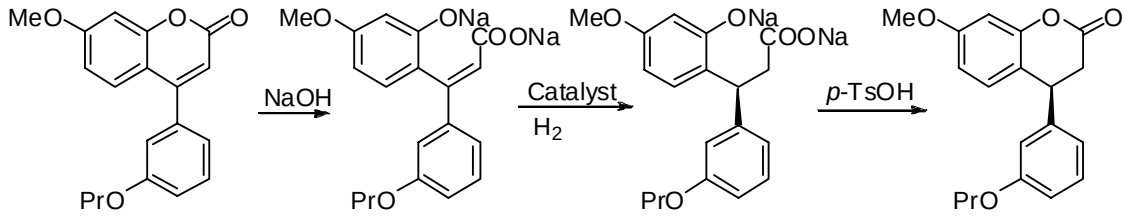
Importantly, while the racemic synthesis of 4-substituted dihydrcoumarins is fairly well established,[9,10,11,12,13] their asymmetric synthesis until recently generally required multiple steps. One chiral preparation involved the asymmetric lithiation of β-arylcarboxamides with *s*-BuLi and (-)-sparteine, followed by quenching with various carbon, silicon and tin-based electrophiles,[14] which then necessitated several more transformations to provide the chiral dihydrocoumarin (Scheme 2.1).

Scheme 2.1: Formation of Chiral 3,4-Dihydrocoumarins from β-phenylcarboxamides



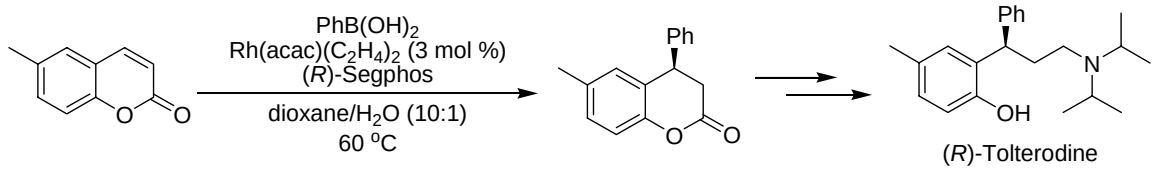
The SmithKline Beecham pathway involved formation of the 4-aryl coumarin backbone, followed by basic hydrolysis of the lactone, asymmetric hydrogenation, and then relactonization to the product (Scheme 2.2).

Scheme 2.2: Formation of Chiral 3,4-Dihydrocoumarins by Lactone Ring-Opening and Asymmetric Reduction



This target and tolterodine are two of many where 4-aryl substitution is a common motif, leading to efforts towards their synthesis.[7,15] Of these, the approach taken by the Hayashi group towards (*R*)-tolterodine is interesting due to its excellent selectivities and high yields for the Rh-catalyzed addition of arylboronic acids onto coumarins (Scheme 2.3)

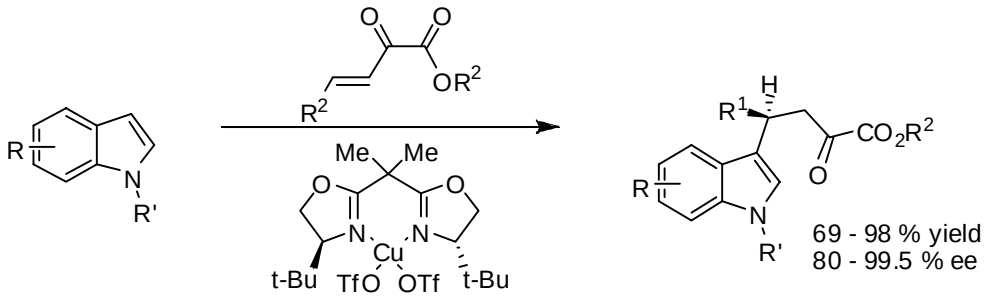
Scheme 2.3: Preparation of (*R*)-Tolterodine by Rh(I)-Catalyzed Conjugate Addition onto a Coumarin Derivative



Synthetically, the pursuit of methods to introduce aromatic groups has proved fruitful, and a number of techniques to form C-C bonds to aryl groups have been developed. Cross coupling with transition metals has provided ways to attach aryl groups onto

alkenyl and aryl (Suzuki coupling, for example)[16], and alkynyl (Sonogashira)[17] substrates with great success. Attaching onto alkyl groups has been shown to proceed efficiently through Friedel-Crafts reaction,[18] or anion-based nucleophilic substitution or addition.[19,20] The Friedel-Crafts alkylation reaction occurs with replacement of a proton on the aromatic ring with a carbon β- to an activating group, promoted by the coordination of a Lewis acid (such as $AlCl_3$ or $TiCl_4$) or Brønsted acid (such as HF, H_2SO_4 and H_3PO_4) onto the activating group, thereby increasing the electrophilicity of the aforementioned carbon. While this reaction can proceed with unactivated or deactivated aryl groups, it most readily undergoes addition with more electron rich rings. In the initial investigations into the enantioselective variant of this reaction,[21] it was only reported that highly electron rich aromatic groups like indoles, 2-methylfuran and 1,3-dimethoxybenzene were successfully alkylated using a chiral Cu(II) catalyst.

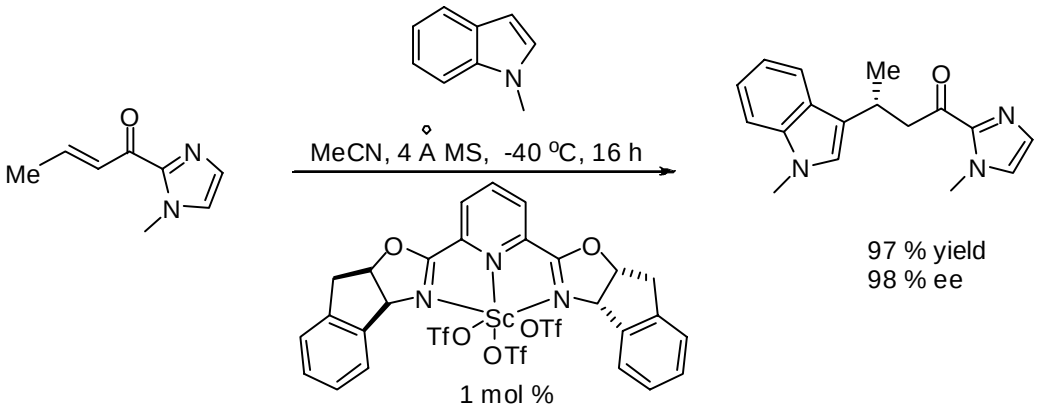
Scheme 2.4: Catalytic Asymmetric Friedel-Crafts Conjugate Addition by Chiral Cu(II) Catalyst



Subsequent publications have now expanded the scope of nucleophiles to also include anilines, pyrroles, anisoles and combinations therein with a variety of chiral Lewis acids such as Sc(III)[22] and Zr(IV).[23] In these examples, the alkene is highly activated, with

among others, β,γ-unsaturated-α-ketoesters, α,β-unsaturated 2-acyl phosphonates and alkylidene malonates proving to be excellent substrates.

Scheme 2.5: Chiral Lewis Acid-Catalyzed Michael Addition of Heterocycles onto Enone Systems

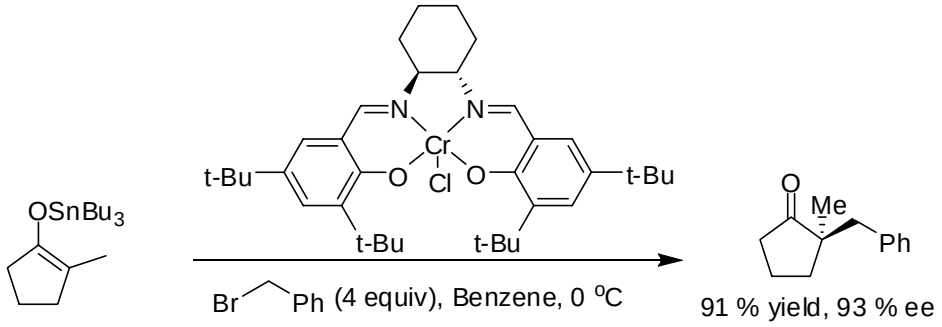


An alternate route for the asymmetric introduction of a carbon nucleophile is the conjugate addition of organometallic reagents catalyzed by chiral transition metal complexes, and this has been successfully examined by many groups using metals such as copper or rhodium.[19,24] These both would require the prefunctionalization of the substrate as an organometallic compound, either in situ or as an isolable intermediate, and two options exist for forming these from phenols. As the desired carbon nucleophile is that which is *ortho* to the hydroxyl, it can be envisaged that this could arise firstly as a C-M compound from generation through lithium-halogen exchange or magnesium insertion into deprotonated 2-halophenols. Alternately, viewing the phenol as an aromaticity-stabilized enol, generation of O-M compounds could through tautomerization provide the same C-M substrate. These could arise from deprotonation with a reactive organometallic

to leave the appropriate phenolic salt, or deprotonation with either an organic or inorganic base and then quenching with a metal halide. Utilizing the second method has seen limited research into employing the carbon as nucleophile, but under the right conditions could effect the desired transformation.

The use of enolates as nucleophiles is in itself well studied, as in the aldol reaction and its many variants.[25] A transition metal catalyzed example of stereoselective attack of an enolate is Jacobsen's alkylation of cyclic[26] and linear[27] tin enolates using a Cr(III)-salen complex. One proposed pathway in this reaction is the loss of $Bu_3Sn(X)$ to form a chiral Cr(III)-enolate, followed by attack onto the alkyl halide (Scheme 2.6).

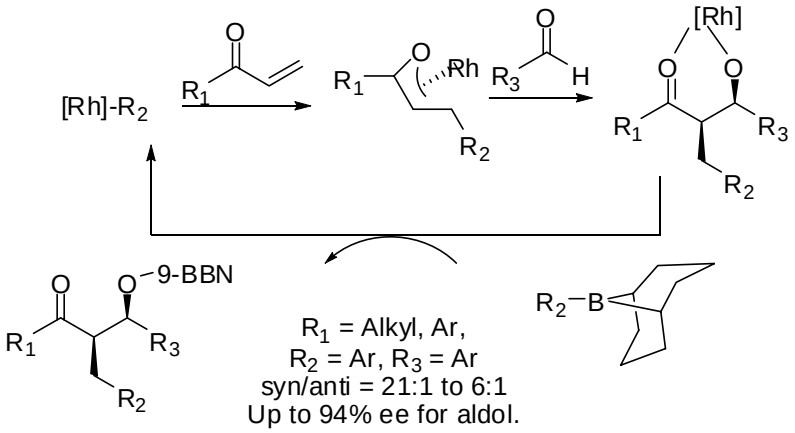
Scheme 2.6: Enantioselective Transition Metal-Catalyzed Alkylation of Tin Enolates



Furthermore, Hayashi has postulated that a chiral (oxa-π-allyl)rhodium intermediate is the catalytically active species in a tandem asymmetric conjugate addition / aldol reaction[28] generated from addition of aryl-9-BBN's onto substituted vinyl esters with chiral Rh(I) complexes. This conclusion stems from the selectivity of the aldol reaction, whereby the (oxa-π-allyl)rhodium complex coordinated with (S)-binap is formed with

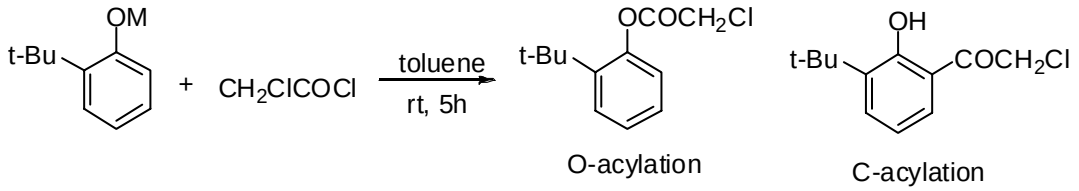
facial selectivity such that the attack proceeds in a selective manner to form the rhodium aldolate product. This produces the second stereocentre in up to 21:1 syn/anti and 94% ee. As a boron enolate intermediate would not form the aldol product with any selectivity, the observed ee's lead to this hypothesis being rejected.

Scheme 2.7: Chiral Rhodium Enolate in Asymmetric Aldol Reaction



As compared to alkyl enolates, the use of metal phenoxides as enolate nucleophiles has limited precident. Because the stabilizing effect of the aromatic system as previously mentioned, the breaking of this aromaticity to form a carbon nucleophile proceeds through a transition state which is higher in energy than the corresponding cyclic, non-aromatic enolate. As a result, it is less energetically favourable to perform the C-addition as compared to O-addition, thus metal phenolates generally provide the product of O-addition, as opposed to that from the ortho carbon (Scheme 2.8).

Scheme 2.8: Metal Phenolate O- and C-Acylation with Chloroacetic Acid Chloride



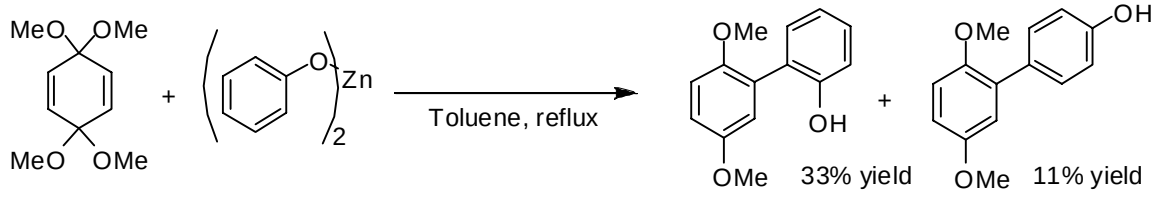
When various metal phenolates were prepared from 2-$^{t}BuC_6H_4OH$ and combined with chloroacetic acid chloride, O-acylation was found to predominate (Table 2.1).[29]

Table 2.1: Cation Effect in the Reaction of Metal 2-tert-butylphenolate with Chloroacetic Acid Chloride

Entry	Metal Ion M	Recovered Phenol, %	O-Acylation	C-Acylation
1	Na	15	100	-
2	MgBr	20	71	29
3	Ti (IV)	85	30	70

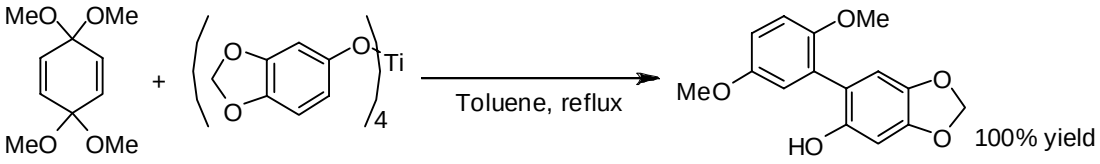
Only in the case of Ti(IV) was C-acylation the major product, and then only in very low yields. In a subsequent study[30] using benzoquinone bis(dimethyl ketal) as an electrophile which is selective such that only C-attack product is isolated. This reaction was not very regioselective for unsubstituted phenol, as mixtures of the *ortho*- and *para*- arylated product were isolated to varying degrees depending on the metal employed. With unsubstituted phenols, Zn-derived phenolates resulted in the highest chemical yield (52%), while still maintaining reasonable regioselectivity (3:1 *o/p*) (Scheme 2.9).

Scheme 2.9: Zn-Phenoxide Arylation with Benzoquinone Ketal



Using substituted phenols immediately served to increase both chemical yield and regioselectivity. In this manner, the metal phenolates derived from Ti and 3,4-methylenedioxyphenol were able to effect the *ortho*-arylation in up to quantitative yields (Scheme 2.10).

Scheme 2.10: Substituted Ti-Phenoxide Arylation with Benzoquinone Ketal

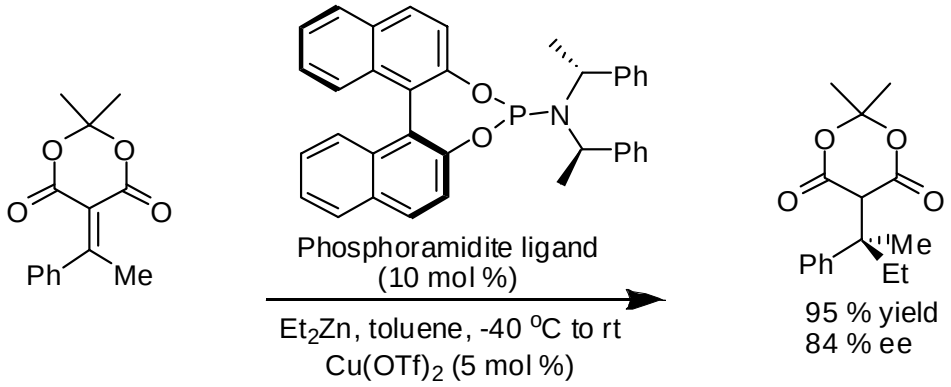


It remained to be seen whether these metal phenolates could attack other electrophiles, specifically activated olefins like alkylidene Meldrum's acids. In order to use metal phenolates for the asymmetric conjugate addition the most synthetically viable approach would be to use chiral ligands on the catalytically active metal centre to induce the selectivity. The two most common metals used as catalysts in conjugate addition reactions are copper and rhodium, with a variety of ligands to promote enantioselectivity known for each in the literature, and both will be addressed in turn herein.

As Sartori has shown that zinc phenolates undergo the C-arylation reaction in moderate yields and regioselectivity, it could be considered as a possible cation for the desired transformation. In the literature, organozinc nucleophiles have been well established as excellent reagents for the Cu-catalyzed conjugate addition reaction because of their facile transmetallation with copper and low background reaction, even with strong electrophiles such as alkylidene Meldrum's acids.[31,32] In addition, phosphoramidite ligands have been

seen to both accelerate the reaction and highly differentiate between the faces of these conjugate addition acceptors, resulting in ee`s in up to 99%.[50]

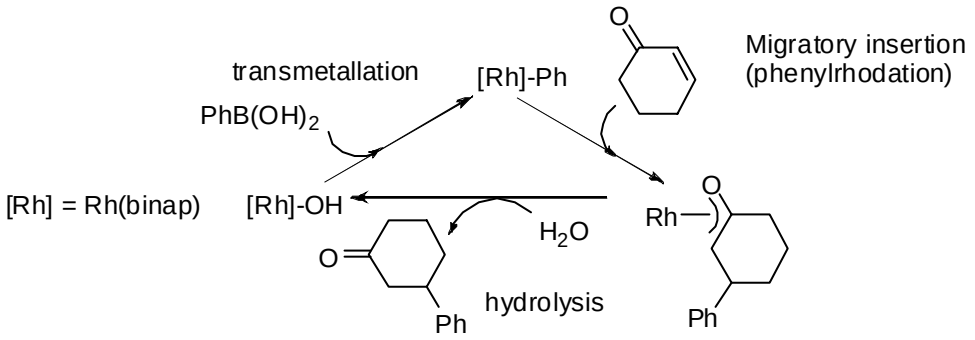
Scheme 2.11: Conjugate Addition of Dialkylzinc Reagents onto Alkylidene Meldrum's Acids via a Chiral Copper catalyst



The second metal which has seen great research in the asymmetric conjugate addition reaction is rhodium, which is most commonly employed with organostannanes[33] and –boranes,[34] although it has also been employed with various silicon based organometallics,[35,36] to great success (generally greater than 90% yields are obtained). The rhodium catalyst in all these systems is proposed to react through transmetallation with the organometallic reagent (almost exclusively sp^2-hybridized carbons, although sp-hybridized carbons are now being added in high yield and selectivity[37]) to produce a much more reactive organorhodium complex, followed by coordination of the activated olefin to the rhodium (Scheme 2.12). Carborhodation gives the new C-C bond and the oxa-π-allyl intermediate, which can as previously discussed be involved in aldol-type

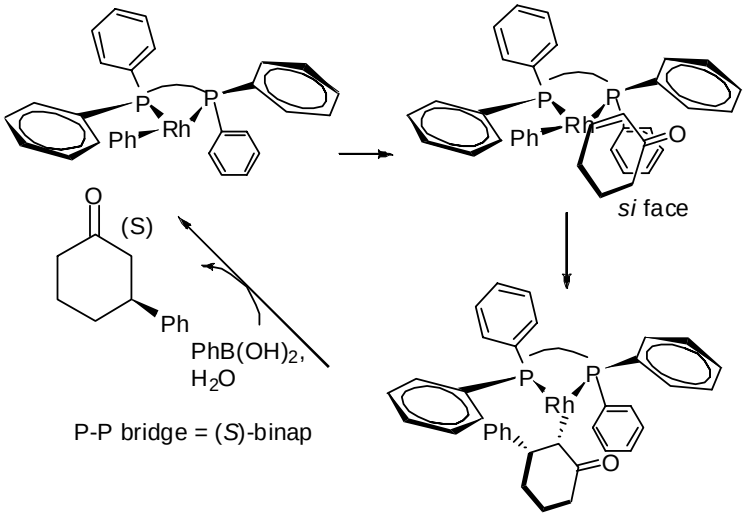
chemistry or have the rhodium catalyst liberated through protonolysis or transmetallation with another equivalent of the organometallic substrate to restart the catalytic cycle.

Scheme 2.12: Catalytic Cycle for the 1,4-Addition of Organoboron Reagents by a Rhodium Catalyst



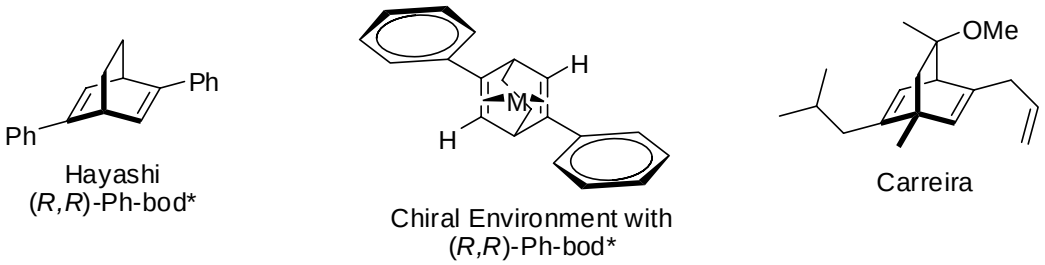
In the addition of organoboron substrates, high facial selectivity is obtained using (*S*)-binap as a chiral ligand, resulting from the constrained environment around the metal centre of complex, as the lowest calculated energy is for coordination of the enone via its *si* face (Scheme 2.13). This provides the stereogenic centre upon arylrhodation, followed by hydrolysis or quenching the enolate with an electrophile to give the final product.

Scheme 2.13: Stereochemical Pathway for Asymmetric Conjugate of $PhB(OH)_2$ by Rh-(*S*)-binap Complex



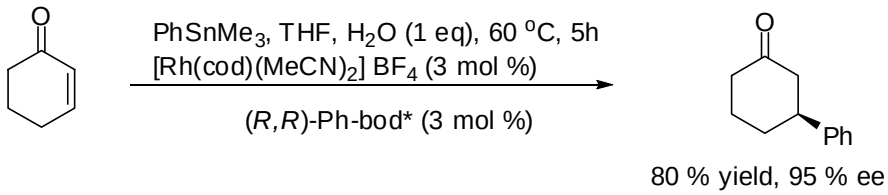
As previously indicated, this system works effectively for alkenyl and arylboron derivatives as well as alkenyl and arylsiloxanes; however it has been observed that phosphine ligands hinder the reaction of the corresponding trialkylstannane reagents.[33] The addition of phenyltrimethyltin to 4-phenylbut-3-en-2-one using the cationic rhodium catalyst $[Rh(cod)(MeCN)_2)]BF_4$ gave 86% yield of the product after 2 h at 60°C, while adding 1.0 equiv PPh_3 lowered that yield to 63%, 2.0 equiv to 15%, and 1.0 equiv of the chelating diphosphine ligand dppp to 48%. Consequentially, the standard chiral ligands, being phosphine-based like binap, were not considered for use in this system, and only racemic products were obtained in all cases. The structure of the rhodium complex is important to the reactivity of the overall system, and it has been noted by Hayashi that diene ligands have a strong accelerating effect on reactions performed with the complexes. As a method of utilizing this observation, both Hayashi[38] and Carreira[39] have disclosed the synthesis of chiral diene ligands for the rhodium catalyzed asymmetric addition reaction (Figure 2.3). These are based upon the rigid [2.2.1]norbornadiene and bicyclo[2.2.2]octa-2,5-diene frameworks and both work to establish chiral environments through steric differences between the protons and substituents (usually bulky, such as ^{i}Bu, Ph, Bn) which are cis to one another on the dienes.

Figure 2.3: Chiral Chelating Diene Ligands for Rhodium Catalyzed 1,4-Addition



When this ligand was exchanged for two ethylene molecules in a rhodium catalyst, this provided a complex which was capable of transmetallating with $PhSnMe_3$ and undergoing conjugate addition onto 2-cyclohexeneone to provide after hydrolysis the product in 80% yield and 95% ee (Scheme 2.14). This is a great improvement, as its inclusion is followed by a note that the equivalent transformation using binap as the ligand gave less than 10% of the addition product.

Scheme 2.14: Enantioselective Conjugate Addition of Organotin Reagents onto Cyclohexenone by $[Rh(cod)(MeCN)_2]BF_4$ / (*R,R*)-Ph-bod*

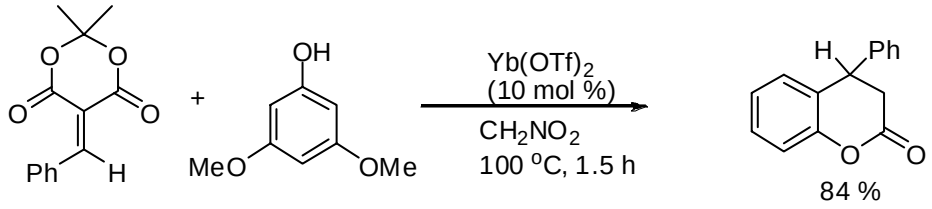


80 % yield, 95 % ee

This is the only known example in the literature of organotin compounds undergoing Rh-catalyzed addition with any selectivity. However, other attempts to effect selectivity in the addition of vinylic tin reagents both inter- and intramolecularly with rhodium complexes based around the Hayashi ligand system onto alkylidene Meldrum`s acids have not produced any enantiomerically enriched products.[40,41] The reasons behind this lack of selectivity, be it a result of the chosen electrophile, the vinylic rather than aryltin, or one of a myriad of other factors is not known.

In both the direct acylation and conjugate addition, the Fillion group has found derivatives of Meldrum's acid to be an excellent electrophile in the intra- and intermolecular Friedel-Crafts reaction.[42,43,44,45,46] Most pertinently, they exploited the biselectrophilicity of the alkylidene Meldrum`s acids in combination with bisnucleophilic electron-rich phenols to undergo sequential C-alkylation, O-acylation or O-alkylation, C-acylation to give coumarin and chromanone derivatives selectively. In the addition of phenols onto monosubstituted alkylidenes to produce coumarins, the strategy worked to produce both 4-alkyl and 4-aryl-3,4-dihydrocoumarin derivatives in good to excellent yields (Scheme 2.15).

Scheme 2.15: Formation of 3,4-Dihydrocoumarins by Friedel-Crafts C-Alkylation / O-Acylation

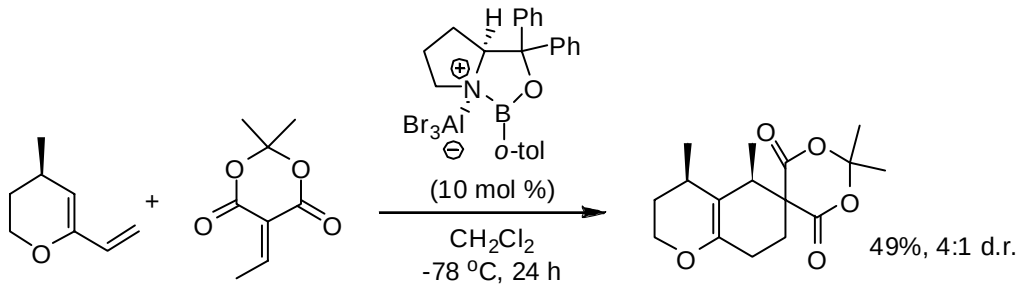


However, this methodology is limited to highly electron rich phenols (3,5-dimethoxy, 3,4-dimethoxy, etc.), and strong Lewis acids ($Yb(OTf)_3$, $Sc(OTf)_3$, etc.) were necessary to afford any product. Furthermore, no selectivity has ever been observed with this methodology when chiral catalysts have been employed.[47]

This lack of success in employing chiral Lewis acid catalysts to effect a selective reaction with alkylidene Meldrum`s acids is seemingly not atypical though, as only one example

is known in the literature, and was diastereo-, not enantioselective.[48] This involved the asymmetric Diels-Alder cycloaddition of ethylidene Meldrum`s Acid with a chiral vinyl dihydropyran, catalyzed by an $AlBr_3$ – activated oxazaborolidine catalyst, albeit in poor yield and only a moderate selectivity of 4:1 dr (Scheme 2.16).

Scheme 2.16: Diastereoselective Diels-Alder Cycloaddition with Ethylidene Meldrum's Acid Catalyzed by a Chiral Lewis Acid



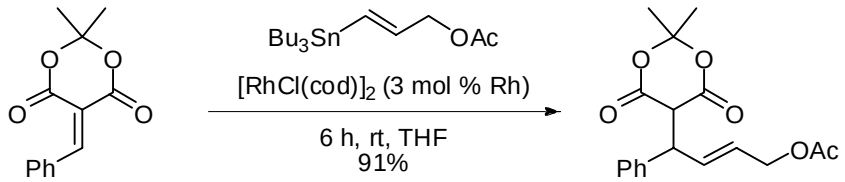
In order to expand upon the published addition of phenols onto alkylidene Meldrum`s acids, several areas of investigation could be pursued. First, the modification of the aromatic ring to one which is not by necessity highly electron rich and secondly accomplishing the addition with a high degree of selectivity would allow for the facile synthesis of chiral pharmaceutical precursors.

Alkylidene Meldrum's acids have also been used as electrophiles in the transition metal catalyzed conjugate addition of organometallic nucleophiles. The addition of alkyl groups to form chiral centres has been published both in the formation of tertiary[49] and quaternary[50] centres in excellent yield and enantioselectivity (up to 99% ee). The quaternary case employed the conditions illustrated in Scheme 2.11. Furthermore, the

addition of aromatic alkynyl groups also proceeds in high yields racemically[51] or enantioselectively in up to 97% ee,[52] and this reaction has since been expanded to other acetylene derivatives.[53] For both these nucleophile classes, copper complexes have proven to be the most successful catalysts.

Finally, addition of sp^2-hybridized nucleophiles onto alkylidene Meldrum`s acids has been reported for both aryl[54] and vinylic[55] substrates. In the first case, 4-methylphenylmagensium bromide added with the aid of a copper catalyst onto the Meldrum`s acid alkylidene derived from acetone in moderate yield. Rhodium-catalyzed conjugate addition with both vinyltributyltin and (tributylstannyl)allyl alcohol derviatives has also been accomplished with alkylidene Meldrum's acids (Scheme 2.17). Importantly, it was demonstrated that the transmetallation and conjugate addition proceeds smoothly at room temperature, in large part due to the superior electrophilicity of the alkylidene stubstrate. There was however, no enantioselectivity achieved in this reaction.

Scheme 2.17: Conjugate Addition of Vinyltributyltin Derivative onto Benzylidene Meldrum's Acid by Rhodium Catalysis

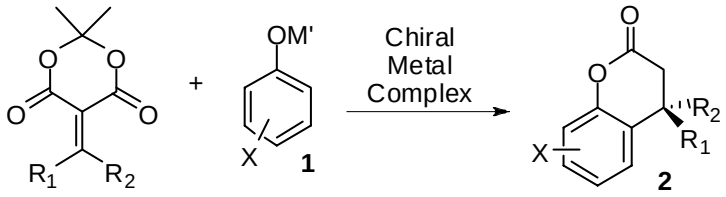


It remained to be seen though whether alkylidene Meldrum's acids could act as electrophiles for the transition metal catalyzed asymmetric conjugate addition of aryl, and more specifically phenolic, nucleophiles.

Results and Discussion:

The objective of this research was to effect and optimize the enantioselective addition of phenols onto alkylidene Meldrums`s acids, to form a new C-C bond from the carbon *ortho* to the hydroxyl, followed by O-acylation of the phenolic OH with one of the carbonyls of the Meldrum`s acid unit, producing enantioenriched substituted dihydroucoumarins (**2**) (Scheme 2.18).

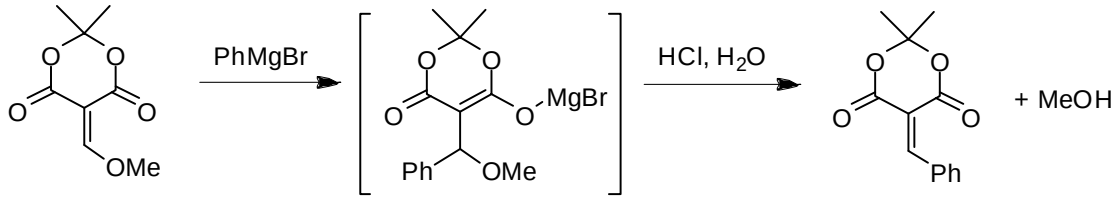
Scheme 2.18: General Reaction Scheme for Chiral Metal-Catalyzed Metal Phenolate Addition



Because of the pharmaceutical importance of this structural motif, in addition to the ease of formation of the starting materials, this methodology would have provided quick access to a host of useful synthetic intermediates in very few steps. Maximizing the yield of this reaction was predicated upon increasing the ratio of attack through the carbon versus through the oxygen of the enolate. The conjugate addition of oxygen-based nucleophiles is not synthetically useful in many cases, as the resulting products can readily eliminate the oxygen-based substituent when treated to acidic workup conditions.

Indeed, this is commonly employed in the formation of alkylidene Meldrum's acids from the methoxy-substituted alkylidene, as acidic workup following addition of an organometallic compound eliminates methanol, to form a differently substituted alkylidene.

Scheme 2.19: Conjugate Addition onto Methoxy-Subsituted Alkylidene Meldrum's Acids



As a result, O-alkylation of the phenol without a Lewis acid strong enough to promote C-acylation would after workup give back the starting alkylidene and hydrolyzed metal phenoxide.

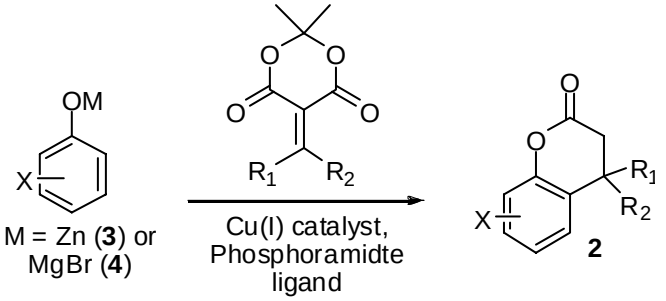
As previously discussed, conjugate addition of phenols could proceed through Lewis acid-promoted Friedel-Crafts alkylation, or by transition metal catalyzed transmetallation with an appropriate metal phenolate, followed by addition via the resulting metal complex. The first route suffers from limited aryl substitution patterns and necessarily high electron density within the ring, as well as a lack of robust chiral catalysts for enantioselective Lewis acid-catalyzed reactions with alkylidene Meldrum's acids. As a result, addition following transmetallation with a chiral transition metal complex, which is known to perform admirably with alkylidene Meldrum's acids, was selected for

investigation. Thus, finding a metal phenoxide which performed C-alkylation with high regioselectivity after transmetallating with a transition metal complex bearing ligands which promoted high facial selectivity was the overall goal.

This research therefore aimed to expand the scope of nucleophiles which can be used for the transition metal catalyzed conjugate addition onto activated alkenes to include metal phenolates. The mild conditions employed to form the metal phenolates, especially compared with preparing some of the traditional nucleophiles for conjugate addition such as alkylzincs or arylstannanes, and the ambident nucleophilicity of the phenol provided an appealing manner to prepare chiral 3,4-dihydrocoumarins. However, this was contingent on finding metal phenolates which preferentially underwent C-alkylation via a chiral transition metal catalyst.

The initial metal phenolates examined were derived from zinc (**3**) and magnesium bromide (**4**), as they have previously shown to attack via the carbon *ortho* to the –OH. However, the intended transformation would employ a copper-phosphoramidite catalyst to effect the addition onto the alkylidene Meldrum`s acids (Scheme 2.20). These were selected for initial investigatiom because of the success these copper complexe have previously had in asymmetric conjugate addition.

Scheme 2.20: General Addition of Zinc / Magnesium Bromide Phenolate by Copper (I) Catalyst

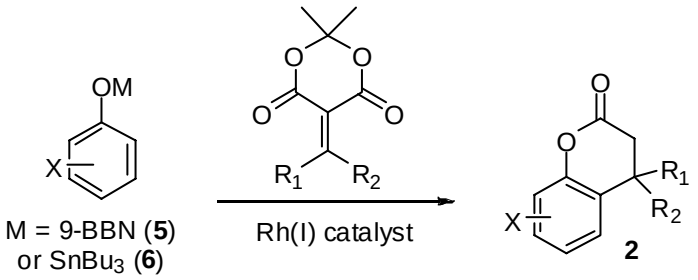


However, in order to take advantage of this, the catalytically active species would have to be the copper phenolate, and no experimental results were readily found in the literature in which a copper phenolate acted as a nucleophile through its *ortho* carbon. While this concept therefore deviates with known literature data, there is an observed increase in reactivity for both sp^3 and sp^2–hybridized organozincs and Grignard reagents in conjugate addition once transmetallated with copper-phosphoramidite catalysts. As a result, it will be investigated if this increase in reactivity could show applicability with zinc or magnesium halide phenoxides as well. Changing the metal source could affect the reactivity of the system through their different Lewis acidity, as it is these which take the place of the copper after addition, to regenerate the $Cu(X)_n$ catalyst, and so changing their reactivity could increase the rate of reaction.

Secondly, rhodium(I) effectively performs the conjugate addition of sp^2-hybridized carbon nucleophiles derived from transmetallation with tin, boron and silicon, with alkylidene Meldrum`s acids effectively employed in the racemic addition reaction with vinyl tin derivatives. Furthermore, it has been postulated that chiral rhodium oxa-π-allyl

complexes undergo nucleophilic attack through the carbon to form enantioenriched products (Scheme 2.21).

Scheme 2.21: General Addition of Boron / Tin Phenolate by Rhodium (I) Catalyst



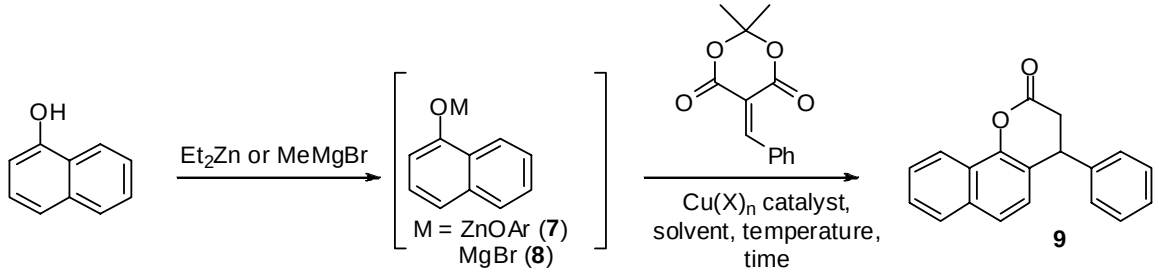
Both tin and boron enolates have been utilized as substrates for the formation of chiral transition metal complexes, with high selectivity observed in these reactions. In no known cases have the enolates been derived from aromatic alcohols though, and this research will establish if these metal phenolates can add in a similar manner to the corresponding non-aromatic substrates.

Because the conjugate addition of phenols as enolates is not known to proceed in the literature, this transformation could encounter a number of problems including low reactivity, low selectivity for C-alkylation, and low facial selectivity. Possible solutions to circumvent this include changing the ligands on the metal centre to modify the electronic nature of the metal, changing the counter ion of the complex or changing the metal on the phenolate to increase reactivity and enantioselectivity.

Results

Benzylidene Meldrum's acid was selected as the electrophile for this reaction and was prepared using the literature methods.[56] Initial investigations centred on zinc and magnesium bromide as the metal phenolates with copper catalysts, and phenol, 1- and 2-naphthol were the phenols selected for examination. The metal phenolate was generated in situ by the addition of 0.5 eq Et_2Zn or 1.0 eq MeMgBr, followed by the addition of the alkylidene and catalyst, and the system tested with several different variables, as illustrated in Table 2.2.

Table 2.2: Conjugate Addition of Zinc / Magnesium Bromide Phenolate onto Benzylidene Meldrum's Acid by Copper Catalyst



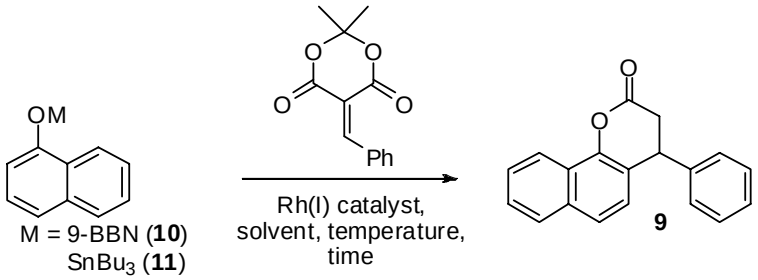
Entry	Aromatic Alcohol	Metal Source	Transition Metal / Catalyst Loading	Time (h)/ Temp °C	Solvent	Yield %
1	1-naphthol	Et_2Zn (**7a**)	None	72/rt	DME	0
2	2-naphthol	Et_2Zn (**7b**)	None	72/rt	DME	0
3	1-naphthol	Et_2Zn (**7a**)	$Cu(OTf)_2$ / 5 mol %	120/rt	DME	0
4	2-naphthol	Et_2Zn (**7b**)	$Cu(OTf)_2$ / 5 mol %	120/rt	DME	0
5	Phenol	Et_2Zn (**7c**)	CuCl / 20 mol %	104/rt	THF	0[a]
6	1-naphthol	Et_2Zn (**7a**)	CuCl / 20 mol %	104/rt	THF	0[a]
7	2-naphthol	Et_2Zn (**7b**)	CuCl / 20 mol %	104/rt	THF	0[a]
8	1-naphthol	MeMgBr (**8a**)	None	24/rt	THF	0
9	1-naphthol	MeMgBr (**8a**)	CuCN / 10 mol %	36/60	THF	Trace
10	1-naphthol	Et_2Zn (**7a**)	$Cu(OTf)_2$ / 5 mol %	120/60	THF	0
11	2-naphthol	Et_2Zn (**7b**)	$Cu(OTf)_2$ / 5 mol %	120/60	THF	0
12	1-naphthol	Et_2Zn (**7a**)	CuCN (5 mol %), Phosphoramidite ligand (10 mol %)	72/60	THF	0
13	1-naphthol	Et_2Zn (**7a**)	Cu(OTf)2 (5 mol %), Phosphoramidite ligand (10 mol %)	72/60	THF	0

[a] Benzylidene Meldrum's acid recovered

In all but one case there was no product formation observed in the crude reaction mixture by ^{1}H NMR, with the alkylidene also generally not remaining. In this study both copper (I) and (II) sources were investigated, with no difference observed. Furthermore, both Mg (II) and Zn(II) derived naphthoxides and phenoxide were generally unreactive, even at elevated reaction temperatures and extended reaction times. Finally, use of the phosphoramidite ligand shown in Scheme 2 did not have any effect on the formation of product **9**, with either copper (I) and (II). In the face of these disappointing results, the use of rhodium catalyst and boron or tin-derived phenolates was thus investigated.

Much like with zinc and magnesium, the boron-based phenolate was generated in situ from 9-BBN (**10**),[57] whereas the tributyltin derivative was prepared independently and purified before use (**11**). Initial investigations with Rh(I) catalysis are outlined in Table 2.3.

Table 2.3: Addition of Boron / Tin Phenolate onto Benzylidene Meldrum's Acid by Rhodium Catalyst



Entry	Aromatic Alcohol	M	Rhodium Source / Catalyst loading	Time (h)/ Temp °C	Solvent	Yield of **9** (%)
1	1-naphthol	$SnBu_3$ (**11a**)	$[RhCl(cod)]_2$ / 4 mol %	52/60	THF	0
2	2-naphthol	$SnBu_3$ (**11b**)	$[RhCl(cod)]_2$ / 4 mol %	52/60	THF	0
3	1-naphthol	9-BBN (**10**)	$[RhCl(cod)]_2$ / 3 mol %	60/rt	THF	0
4	1-naphthol	$SnBu_3$ (**11a**)	$[Rh(cod)(MeCN)_2]BF_4$/ 6 mol %	24/60	PhMe	25
5	1-naphthol	$SnBu_3$ (**11a**)	None	72/rt	THF	0

While initial attempts with both boron and tin phenolates failed to produce any product with the neutral $[RhCl(cod)]_2$ complex, switching to the cationic $[Rh(cod)(MeCN)_2]BF_4$ gave 25% of the anticipated product after 24 h (Figure 2.4). Much like with the neutral complex, a blank reaction without any rhodium added gave no product, and thus the cationic complex was therefore considered necessary for the addition to proceed. Attempts to optimize the reaction were undertaken, as illustrated in Table 2.4 to 2.6.

Table 2.4: Optimization of Solvent

Entry	Tributyl Tin Aryloxide	Ratio of Tin to Meldrum's Acid	Rhodium Source/ Catalyst loading	Time (h)/ Temp (°C)	Solvent	Yield of **9** (%)
1	**11a**	1.1:1	$[Rh(cod)(MeCN)_2]BF_4$/ 6 mol %	72/rt	CH_2Cl_2	28
2	**11a**	1.1:1	$[Rh(cod)(MeCN)_2]BF_4$/ 6 mol %	72/rt	MeCN	17
3	**11a**	1.1:1	$[Rh(cod)(MeCN)_2]BF_4$/ 6 mol %	72/rt	PhMe	14
4	**11a**	1.1:1	$[Rh(cod)(MeCN)_2]BF_4$/ 6 mol %	72/rt	THF	29

Table 2.5: Optimization of Ratio of Tin Phenolate to Benzylidene Meldrum's Acid

Entry	Tributyl Tin Aryloxide	Ratio of Tin to Meldrum's Acid	Rhodium Source/ Catalyst loading	Time (h)/ Temp (°C)	Solvent	Yield of **9** (%)
1	**11a**	1:1	$[Rh(cod)(MeCN)_2]BF_4$/ 8 mol %	72/rt	THF	25
2	**11a**	1.3:1	$[Rh(cod)(MeCN)_2]BF_4$/ 8 mol %	72/rt	THF	30
3	**11a**	1.5:1	$[Rh(cod)(MeCN)_2]BF_4$/ 8 mol %	72/rt	THF	40
4	**11a**	2:1	$[Rh(cod)(MeCN)_2]BF_4$/ 8 mol %	72/rt	THF	43

Table 2.6: Addition of Phosphine Ligands

Entry	Tributyl Tin Aryloxide	Additive	Rhodium Source/ Catalyst loading	Time (h)/ Temp (°C)	Solvent	Yield of **9** (%)
1	**11a**	PPh_3 / 10 mol %	$[Rh(cod)(MeCN)_2]BF_4$/ 8 mol %	72/rt	THF	7[a]
2	**11a**	dppe / 8 mol %	$[Rh(cod)(MeCN)_2]BF_4$/ 8 mol %	72/rt	THF	25[a]

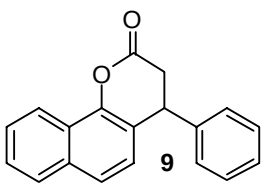
[a] Reaction carried out with 1.5 eq **11a**

Although an improvement from 25 to 43% yield was observed, the best case for this reaction only resulted in modest yields. Increasing the ratio of naphthoxide to alkylidene lead to a increase in yield, however the increases were not proportionate to one another,

and the subsequent addition of greater amounts of tributyltin compounds made the purification of the product progressively more problematic, so that no further additions of equivalents of reagents was pursued. In these cases, although protracted reactions and excesses of reagents were employed, after acidic workup of the reaction mixture there remained alkylidene starting material. It is not known whether this is material which had not reacted, or whether this was as a result of elimination of the product of O-alkylation.

Interestingly, although Oi and Hayashi had independently observed that phosphine ligands greatly decreased the yields from their conjugate addition reactions, using the chelating diphosphine ligand dppe did not show that same dramatic drop, which was the case with 1.25 equiv of PPh_3. However, the addition of the ligand did overall negatively affect the reaction, so while chiral diphosphine ligands could promote enantioselectivity in this reaction, both observed trends and poor reactivity for tin-based nucleophiles in the literature suggest this would not be the case. Alternately, the use of a chiral chelating diene ligand to create the chiral environment to effect selectivity would be still possible, but these ligands rarely show a dramatic increase in the yield of reactions, their electronic properties being already similar to the cyclooctadiene or norbornadiene ligands commonly employed with rhodium, and integrated into the complexes used here.

Figure 2.4: 4-Phenyl-3,4-dihydrobenzocoumarin



9

In order to attempt to improve chemical yields of this reaction, several parameters could be pursued. Firstly, the alkylidene could be modified to see how substituents, both on the aryl ring currently attached to the electrophilic carbon, or in place of the aforementioned ring, impact the yield. Secondly, it remains to been seen what effect electron withdrawing or donating groups on the phenol would have. Finally, the reactivity of the system could have been investigated by changing the metal phenolate to the trimethyl- and triphenyltin versions, but the latter generally shows much lower reactivity, and the former, while typically more reactive, is highly toxic and was thus not pursued for safety reasons.

Conclusions

The racemic synthesis of 4-phenyl-3,4-dihydrobenzocoumarin (**9**) has been accomplished in moderate yield through the conjugate addition of tributyltin-1-naphthoxide (**11a**) onto benzylidene Meldrum's acid using a cationic rhodium catalyst. This marks the first known use of transition metal catalyzed conjugate addition of a metal enolate generated from an aromatic alcohol. Synthetic yields from this reaction have been improved, but still remain low, due to unknown factors. In these reactions it is unclear to what degree O-alkylation interferes with the reaction, and this could be a source of decreased yields, however tin enolates when transmetallated with rhodium can be said to show at least equal regioselectivity for C-alkylation and the corresponding O- attack.

Supporting Information

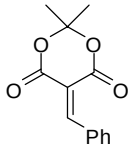
General Methods. All reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. CH_2Cl_2, THF, hexanes, toluene and MeCN were purified using an MBraun Solvent Purification System. DME was distilled from sodium-benzophenone ketyl under nitrogen. Reagents were obtained from commercial sources and used without further purification unless otherwise specified. ^1H NMR spectra were referenced to residual ^1H shift in $CDCl_3$ (7.26 ppm). $CDCl_3$ (77.0 ppm) was used as the internal reference for ^{13}C NMR. Reactions were monitored by thin-layer chromatography on commercially prepared plates with a particle size of 60 Å. Developed plates were viewed by UV lamp (254 nm), and with ceric ammonium molybdate or iodine stain. Flash chromatography was performed using 230-400 mesh silica gel. Melting points are uncorrected. High resolution mass spectra were run by Dr. R. Smith at the University of Waterloo with a source temperature of 200 °C, mass resolution of 9000 and electron energy of 70 eV.

General Procedure A: In Situ formation of Metal Phenoxides and Transition Metal Catalyzed Conjugate Addition onto Benzylidene Meldrum's Acid: The phenol was placed in a dry flask under nitrogen, then dissolved in DME or THF. With stirring at 0 °C, the corresponding organometallic compound (Et_2Zn, MeMgBr or 9-BBN) was added dropwise with a stream of nitrogen to allow for gas generated to escape. Once no more bubbling was observed, benzylidene Meldrum's acid and the transition metal catalyst were added. The flask was sealed and allowed to stir for the times indicated in Table 2.2 and 2.3, at which point the reactions were quenched with HCl (aq) and worked up in the

usual manner (Et_2O extraction, H_2O and Brine wash, dried over $MgSO_4$, filtered) and the solvent was removed.

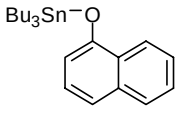
General Procedure B: Conjugate Addition of Tributyltin Phenoxides onto Benzylidene Meldrum's Acid: Benzylidene Meldrum's acid, the corresponding tributyltin phenoxide and rhodium (I) catalyst were added in the glove box to a Schlenk tube, to which the appropriate additive and solvent were added. The tube was sealed, and the mixture stirred and heated for the time indicated in Table 2.3 through 2.6. The reaction was quenched with HCl and heated for 15 minutes at 50 °C to hydrolyze the tin enolate and promote full O-acylation, then worked up in the usual manner. Flash chromatography gave the pure product.

Benzylidene Meldrum's acid (5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione):



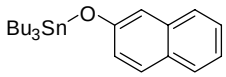
Benzylidene Meldrum's Acid was prepared according to the literature procedure.[43]

Tributyltin-1-naphthoxide (tributyl(naphthalen-1-yloxy)stannane) (11a): [58]



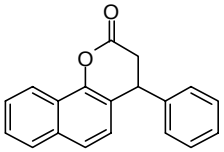
Tributyltin-1-naphtoxide was prepared according to the literature procedure to yield a yellow oil that was stored under inert atmosphere.

Tributyltin-2-naphthoxide (tributyl(naphthalen-2-yloxy)stannane) (11b):[59]



Tributyltin-2-naphthoxide was prepared according to the same procedure as tributyltin-1-naphtoxide to yield a yellow oil that was stored under inert atmosphere.

4-Phenyl-3,4-dihydrobenzocoumarin (9):



Prepared from tributyltin-1-naphthoxide as an off-white solid according to General Procedure B in 43% yield.

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Chapter 3 - The Transmetallation of Alkyl Tin, Boron and Silicon Reagents with Rhodium Complexes and their Conjugate Addition Reactions

Introduction

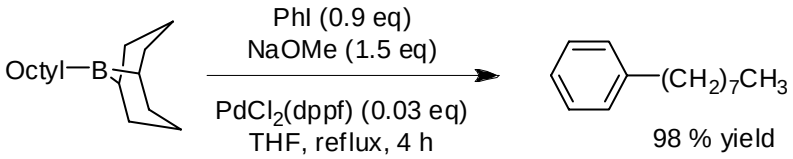
The transition metal catalyzed conjugate addition of carbon-based nucleophiles onto activated olefins has shown itself to be a useful method for the synthesis of complex natural products, and thus has seen extensive research in recent years.[1,2,3] This requires the active species in the reaction to be a metal complex containing the nucleophile, which is generally formed through transmetallation or C-H insertion. The ease with which this complex forms is highly dependent on the hybridization of the carbon nucleophile, as the strength and reactivity of the C-X bond (X = H, metal) is dictated by this orbital hybridization. sp-Hybridized carbons are made into nucleophiles with transition metals both by facile deprotonation with mild or strong bases then transmetallation,[4] or through C-H insertion by the metal catalyst, requiring no prefunctionalization of the carbon.[5] sp^2-Hybridized carbons have seen the most use in conjugate addition reactions as the air and water stable boron,[6] tin[7] or silicon[8] compounds, which easily undergo transmetallation with transition metals to form active complexes thanks to weaker bonds compared with the corresponding sp^3-hybridized carbons to these main group elements. Conversely, sp^3-hybridized carbons form stronger bonds with both protons and main group elements, and thus the carbon must be functionalized with a highly reactive metal such as Li, Mg(II)[9] and Zn(II)[10] in order to easily transmetallate with transition metals for conjugate addition. These organometallic compounds are highly pyrophoric and air and water sensitive, rendering them more difficult to handle compared with sp- and sp^2-hybridezed carbons

which form the complexes used in conjugate addition. As a result, sp^3-hybridized carbon – metal compounds which can easily transmetallate have lower functional group tolerances and are typically generated from the precursors immediately when required. In comparison, in addition to being stable to protic conditions, C-B, C-Sn and C-Si bonds on sp^2 carbons are stable to a variety of chemical transformations, and thus can be installed early in a synthesis and carried through several steps prior to their application in conjugate addition.

The transition metal catalyzed conjugate addition reaction with alkyl groups has employed these reactive compounds despite their synthetic limitations because the transmetallation of the corresponding alkyl boron, tin or silicon compounds with appropriate metal catalysts is energetically challenging. Transformations of these compounds are routinely performed, as boron derivatives on alkyl chains are easily converted to alcohols, amines or olefins in one step,[11] and alkyl(trialkoxy)silicon compounds can be oxidized to alcohols with a mixture of KHF_2, H_2O_2 and Ac_2O, but reactions which first transmetallate to transition metals are much more uncommon.

There are a limited number of reports using alkylboron compounds with transmetallation occurring. One is a variant of the Suzuki coupling where alkylboron compounds show reactivity towards transition metals as either 9-alkyl-9-BBN or trialkylboranes. In the presence of NaOMe, $PdCl_2$(dppf) and PhI, 9-octyl-9-BBN transmetallated and effectively coupled with the Ph group in excellent yield (Scheme 3.1).[12]

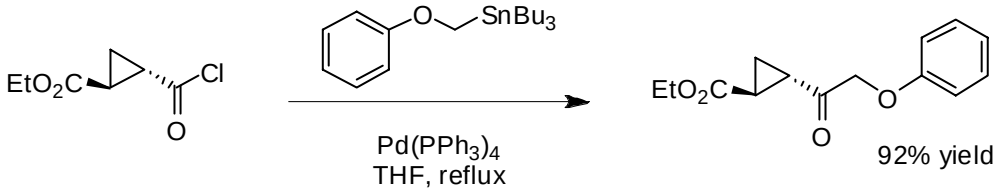
Scheme 3.1: Cross Coupling of 9-Alkyl-9-BBN with PhI by Pd(II)



This methodology has since been applied to numerous substrates with varying success. In 2007 Molander showed that alkyl groups of varying lengths and substitution (-OH, -TMS, -Br) functionalized as the air and moisture stable $-BF_3K$ salt could undergo similar couplings with alkenyl bromides in moderate to excellent yields.[13] Both these reports are important as they demonstrate the ability to transmetallate with alkylboron compounds, and interesting that they have managed to accomplish it with without appreciable β-hydride elimination from the generated alkylpalladium intermediate.

The Stille cross coupling of an organotin with an acid chloride has also been applied to functionalized alkyltin derivatives. While alkyl groups typically resist transmetallation from tin and are subsequently used as unreactive substituents on tin (as the Me_3 or Bu_3 analogues), the CH_2OPh substituent undergoes transmetallation and cross coupling in excellent yields with Pd(0) (Scheme 3.2).[14]

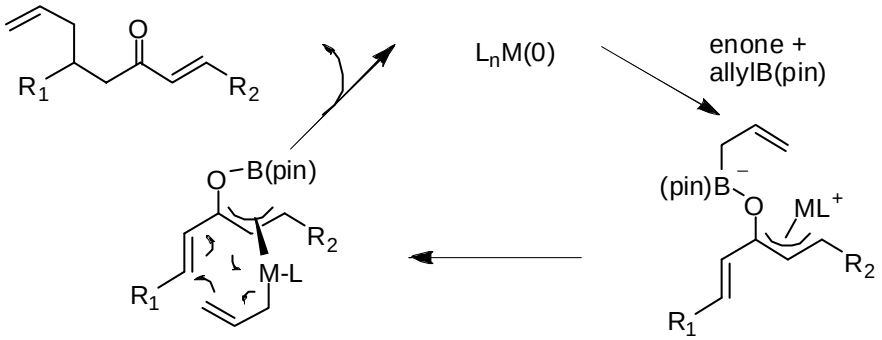
Scheme 3.2: Cross Coupling of Aryloxyalkyl(trialkyl) Tin with Acid Chlorides by Pd(0)



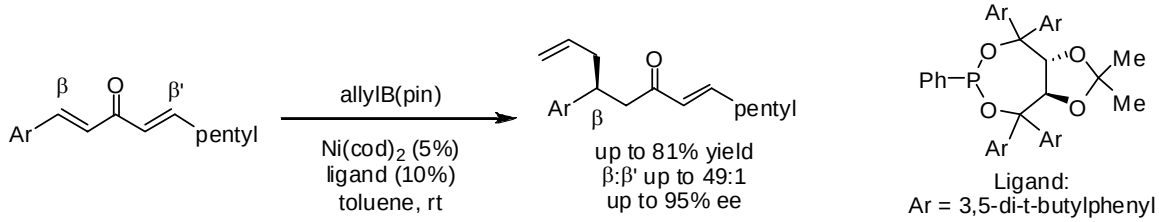
That the starting material also carries no β-hydrogens prevents the alkylpalladium intermediate from decomposing by β-hydride elimination.

Recently Morken has published the Ni- or Pd- catalyzed conjugate allylation of activated enones with allyl pinacol boronate,[15,16] postulated to proceed first by Lewis acid promoted oxidative addition of the metal to the enone and attack by the generated alkoxide onto the boronate (Scheme 3.3). Transmetallation of the allyl group from the "ate" complex to the transition metal, followed by 3,3' reductive elimination gave the addition product as the boron enolate in up to 95% ee (Scheme 3.4)

Scheme 3.3: Mechanistic Rational for Conjugate Allylation of Styryl-activated Enones by Transmetallation



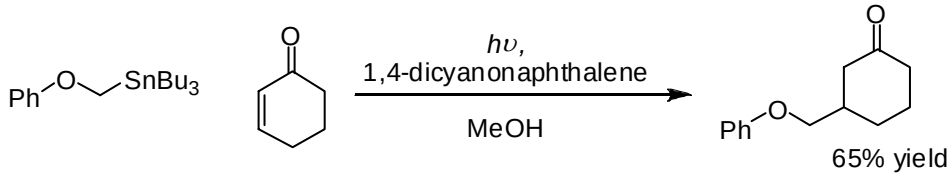
Scheme 3.4: Conjugate Allylation of Styryl-activated Enones by Ni(O)



The Lewis acid-catalyzed version of this conjugate addition is well known, and diastereoselective versions have been reported for allylstannanes,[17] silanes[18] and barium reagents.[19] However, while these addition reactions proceed using chiral transition metals, none proceed via transmetallation, and thus fall outside the scope of this project.

The conjugate addition of alkyltin derivatives has also proceeded without a metal catalyst, by photochemical generation of radical species from α-stannyl ethers of the type seen in Scheme 3.5. The addition onto cyclic and acyclic enones proceeds in variable yields depending on the source of irradiation, sensitizer and aryl group employed.[20] This has also proceeded, albeit less efficiently, with similar substituted oxymethylsilanes.[21] While these reactions do not involve transmetallation and thus are not mechanistically related to this investigation, their synthetic outcome is identical to the intended one here.

Scheme 3.5: Conjugate Addition of Aryloxymethyl(tributyl)tin by Radical Pathway

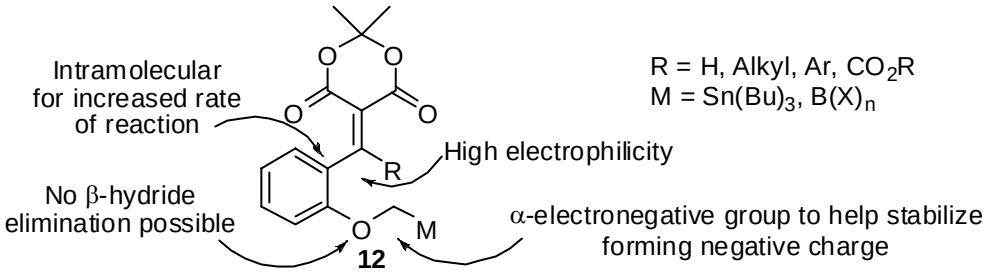


Results and Discussion

This research aimed to examine the ability of Rh(I) complexes to transmetallate with air and water stable alkyltin, boron or silicon compounds and use the C-Rh species generated to perform conjugate addition onto alkylidene Meldrum's acids. This synthetic study focussed upon the intramolecular conjugate addition of these alkylmetal groups based upon the 2-hydroxybenzaldehyde (salicylaldehyde) or 2-hydroxyacetophenone backbone,

such that the nucleophilic methylene group bore an α-oxygen (**12**) (Figure 3.1). This basic structure was selected for several reasons, first being the increase in the rate of reaction for intramolecular processes versus the comparable intermolecular reaction.

Figure 3.1: General Substrate for Transmetallation / Intramolecular Conjugate Addition of Aryloxymethylene Metal Compounds onto Alkylidene Meldrum's Acids



Both the salicylaldehyde- and acetophenone-based alkylidene Meldrum's acids benefits from the high activation of the β-position of the enone system, and although there is a decreased reactivity for disubstituted β-positions, the acetophenone-derived electrophiles have still shown high reactivity in the conjugate addition reaction. This variation in the substrate thus opens the possibility of forming all-carbon quaternary stereocentres. Finally, by placing an electronegative Lewis base α to the methylene, it was thought that this could promote the transmetallation by stabilizing the forming negative charge on the carbon atom.

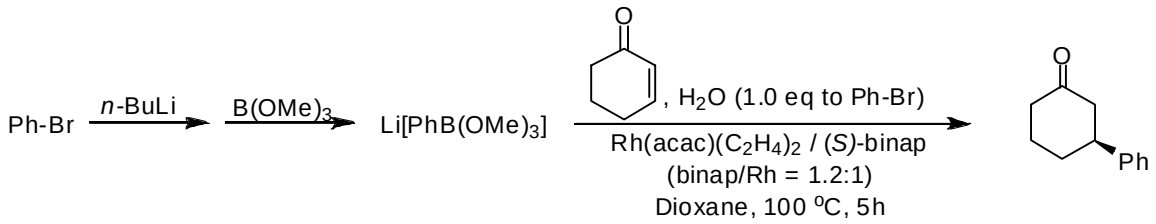
The rhodium-catalyzed conjugate addition of organotin compounds has commonly been performed with trialkyltin compounds at elevated temperatures; however the Fillion group has demonstrated that the superior electrophilicity of alkylidene Meldrum's acids

can allow for high yields to be obtained even at room temperature.[22] In these cases the neutral rhodium catalyst $[RhCl(cod)]_2$ is employed, and although Oi et al. used the cationic complex $[Rh(cod)MeCN]_2BF_4$ in their additions of phenyltrimethyltin onto cyclohexenone, Hayashi has subsequently shown that the in situ formed [RhCl((*R,R*)-Bn-bod*)]$_2$ complex can also cleanly perform the same transformations as Oi with 95% ee.[23]

Organoboron compounds used for conjugate addition come in several structural variations, the boronic acids, esters, lithium organotrialkylborates and potassium organotrifluoroborates. Boronic acids and boroxines ($R_3B_3O_3$, formed by dehydration of three equivalents of boronic acid) are the most commonly employed boron compounds, with a catalyst formed from $[Rh(acac)(C_2H_4)_2]$ and binap in dioxane/water giving excellent yields and ee's generally in excess of 90%.[3]

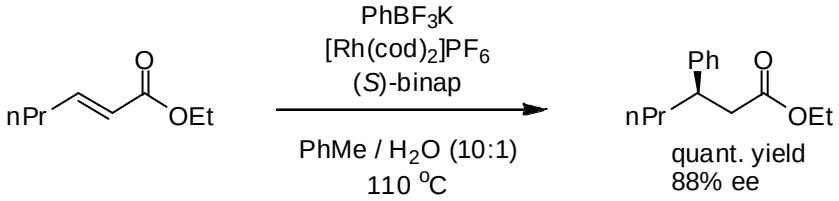
Lithium organotrialkylborates are generated in situ from aryl bromides, butyllithium and trialkoxyborane and show similar or better reactivity to the corresponding boronic acids (Scheme 3.6). These were heralded as an improvement for conjugate addition as the enantioselectivity was excellent even with Rh(I)/(*S*)-binap loading as low as 0.1 mol % and because it avoided the isolation of the boronic acid which can be a tedious procedure. This derives from boronic acids existing as mixtures of the pure $RB(OH)_2$, the boroxine $R_3B_3O_3$ and all the variations between the two, making the exact molecular weight of the compound being used variable.

Scheme 3.6: Lithium Phenyltrimethoxyborate in Conjugate Addition with Rh(I)



Boronic esters eliminate this uncertainty, especially the highly air and water stable pinacol-derived esters. These show relatively comparable reactivity to the boronic acids, and are conveniently formed by esterification of a boronic acid or treating an organolithium or magnesium halide with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (isopropylpinacolboronate), followed by acidic workup. The final type of boron compounds is the potassium organotrifluoroborates, prepared by treatment of boronic acids with aqueous KHF_2.[24] These have seen great success in both 1,2 and 1,4 addition both by the Batey group in racemic fashion[25] and enantioselectively by the Darses group (Scheme 3.7).[26]

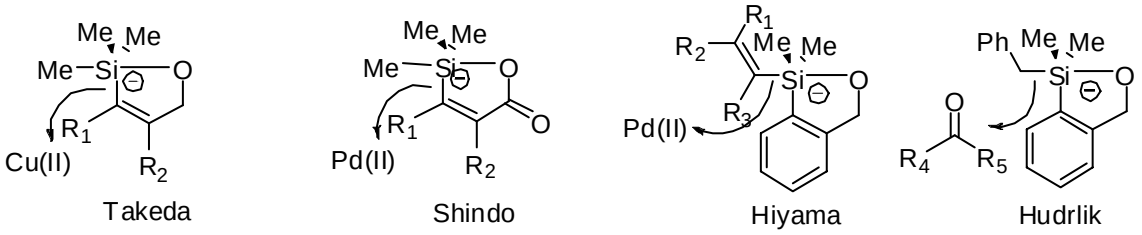
Scheme 3.7: Conjugate Addition of Potassium Phenyltrifluoroborate by Rh(I)



Silicon-based nucleophiles of various types have been developed for Rh(I)-catalyzed conjugate addition, including organotri(alkoxy)silanes,[27] organosilanediols,[28] organochlorosilanes[29] and organo[2-(hydroxymethyl)phenyl]dimethylsilanes.[30] This final example from Hayashi and Hiyama utilizes an internal activating group, the benzyl

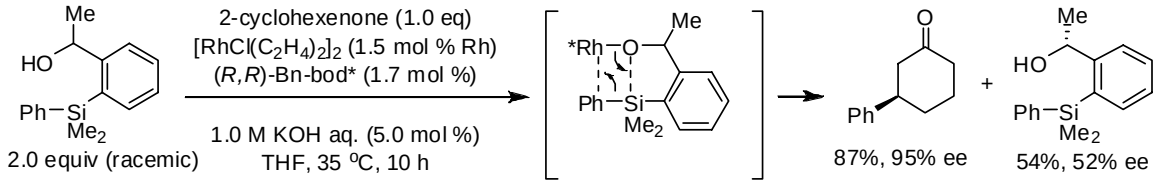
alcohol located *ortho* to the silicon on the aromatic backbone to promote the transmetallation of the aryl or alkenyl group from the chemically stable tetraorganosilicon to the rhodium. This is an extension of work done by Takeda,[31] Shindo[32] and Hiyama[33] with metal catalysts for cross coupling and Hudrlik's work in addition to carbonyl compounds and halides.[34]

Figure 3.2: Previous Work in Silicon Activation by an Internal Activating Group



These reagents have been postulated to proceed either through the pentacoordinate form as illustrated in Figure 3.2, or alternately through a metal alkoxide intermediate. Hayashi proposed the second intermediate for the conjugate addition reaction based on an observed kinetic resolution of a racemic chiral phenylsilane with Rh/(*R,R*)-Bn-bod* (Scheme 3.8). When 2.0 equiv of silane were combined with 1.0 equiv of cyclohexenone, enantiomerically enriched silane was recovered from the reaction mixture along with the addition product. Because of this enrichment, it was proposed that the illustrated rhodium alkoxide is more plausible for the transmetallation step.

Scheme 3.8: Rationalization for Rhodium Alkoxide in Hayashi / Hiyama Silane Conjugate Addition



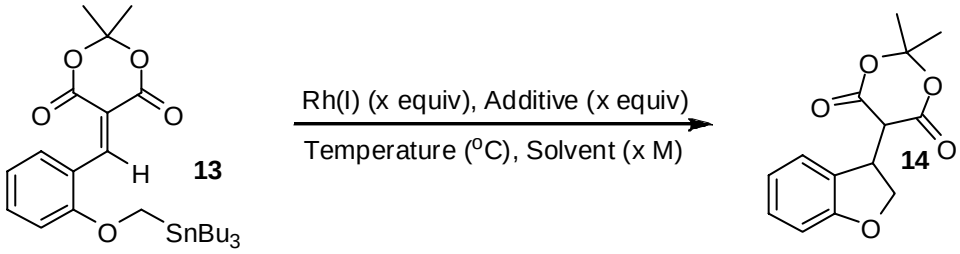
The transmetallation and conjugate addition of aryloxymethylenetin, boron and silicon compounds by rhodium complexes was thus investigated, using these literature examples as a guide.

Results

First to be investigated was the tributyltin derivative, prepared from iodomethyltributyl tin and salicylaldehyde, then condensation with Meldrum's acid in high yield. The yellow oil was then subjected to the conditions outlined in Table 3.1.

Initial attempts to affect the transmetallation under anhydrous conditions (entries 1-4) proved fruitless, so water was incorporated into the reaction mixture (entries 5-12) with the hope that the Lewis bacisity of water or hydroxide would allow it to attack the tin, generating the "ate" complex which would promote the transmetallation.

Table 3.1: Results from Rh(I) Catalyzed Conjugate Addition of Tin Derivatives



Entry	Rh (I) (mol %)	Additive (equiv)	Solvent (M)	Temp (°C)	Yield of **14** (%)
1	$[Rh(cod)Cl]_2$ (0.1)	None	THF (0.05)	rt	0 (SM)
2	$[Rh(cod)(MeCN)_2]BF_4$ (0.1)	None	THF (0.05)	rt	0 (SM)
3	$[Rh(acac)(C_2H_4)_2]$ (0.1)	None	THF (0.05)	rt	0 (SM)
4	$[Rh(cod)OH]_2$ (0.1)	None	THF (0.05)	rt	0 (SM)
5	$[Rh(cod)(MeCN)_2]BF_4$ (0.05)	H_2O (1)	THF (0.1)	80	0[a] (SM)
6	$[Rh(acac)(C_2H_4)_2]$ (0.05)	H_2O (1)	THF (0.1)	80	0[a] (SM)
7	$[Rh(cod)(MeCN)_2]BF_4$ (0.05)	H_2O (1), KOH (0.5)	THF (0.1)	50	0[a] (SM)
8	$[Rh(acac)(C_2H_4)_2]$ (0.05)	H_2O (1), KOH (0.5)	THF (0.1)	50	0[a] (SM)
9	$[Rh(cod)(MeCN)_2]BF_4$ (0.05)	H_2O (1), NaOMe (0.5)	THF (0.1)	50	0[a] (SM)
10	$[Rh(acac)(C_2H_4)_2]$ (0.05)	H_2O (1), NaOMe (0.5)	THF (0.1)	50	0[a] (SM)
11	$[Rh(cod)(MeCN)_2]BF_4$ (0.05)	H_2O (1), K_2CO_3 (0.5)	THF (0.1)	50	0[a] (SM)
12	$[Rh(cod)(MeCN)_2]BF_4$ (0.05)	H_2O (1), $NaHCO_3$ (0.5)	THF (0.1)	50	0[a] (SM)
13	$[Rh(cod)(MeCN)_2]BF_4$ (0.05)	H_2O (1), TBAB (1)	THF (0.1)	50	23[a,b]
14	None	H_2O (1), TBAB (1)	THF (0.1)	50	29[a,b]
15	$[Rh(cod)(MeCN)_2]BF_4$ (0.05)	H_2O (1), CsF (1)	THF (0.1)	50	0[a] (SM)
16	None	H_2O (1), CsF (1)	THF (0.1)	50	0[a] (SM)
17	$[Rh(cod)OH]_2$ (0.03)	Br-BBN (1)	toluene (0.2)	rt to 50	Decomp / trace
18	None	MeLi (1)	Et_2O (0.1)	-78 to rt	0[a] (SM)
19	None	CuCN (0.08), TMSCl (2.5)	THF (0.1)	rt to 50	Decomp/ trace
20	None	MeLi (1) (new bottle)	Et_2O (0.05)	-78 to rt	0[a] (SM)
21	$[Rh(cod)OH]_2$ (0.03)	Br-BBN (1)	toluene (0.2)	-78 to 50	Decomp / trace

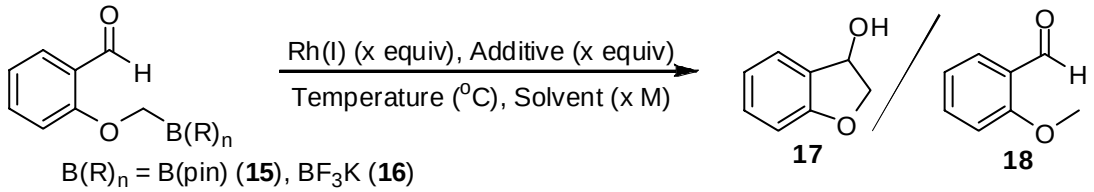
[a] hydrolysis of alkylidene to aldehyde observed to varying amounts. [b] reaction did not go to completion

However, these conditions did not show any product, with the only variation from the starting material being the hydrolysis of up to 50% of the alkylidene to the aldehyde. To promote the formation of the stannate, two halide sources were tried (entries 13-16), and TBAB did result in formation of the desired product **14**, however the rhodium-free reaction went in similar yields. Although it has been illustrated that using an N-spiro chiral ammonium bromide phase transfer catalyst can promote the asymmetric conjugate addition reaction,[35] this fell outside the goals of the project, and was not pursued further.

Finally, in an attempt to promote the transmetallation, several final additives were tried. Firstly, the reaction with Br-BBN did not produce more than a fleeting trace of product by NMR, with the starting material decomposing, both when the reaction was performed at rt and -78 °C. This is an attempt to use the conditions developed by Singleton to generate the 9-alkyl-9-BBN compound[36] which has shown the ability to transmetallate with Pd catalysis. Secondly, the lithium-tin exchange was attempted with two different bottles of MeLi, but the starting material was recovered in both cases, despite the anticipated higher stability of the phenoxyalkyllithium species as compared with MeLi. Finally, the transmetallation with CuCN was attempted using the Falck conditions,[37,38] but only a trace of product was observed by ^{1}H NMR along with decomposition of the starting material.

The second metal selected for investigation was boron, as it is the most highly researched metal used in rhodium-catalyzed conjugate addition of alkenyl and aryl groups, and shows facile transmetallation with sp^2-hybridized carbons with Rh(I), and has been shown to transmetallate with Pd. The synthesis of the starting materials proved much more challenging, and synthetically useful amounts of the B(pinacol) (**15**) and BF_3K (**16**) substrates were obtained, although the attempted condensation with Meldrum's acid did not give any product on anything larger than 0.33 mmol scale. As a result, the transmetallation was investigated with the aldehyde. There are published conditions for the direct addition of $ArBF_3K$ salts onto aldehydes, and these were used as a guide. The results of these reactions are summarized in table 3.2.

Table 3.2: Results from Rh(I) Catalyzed Conjugate Addition of Boron Derivatives



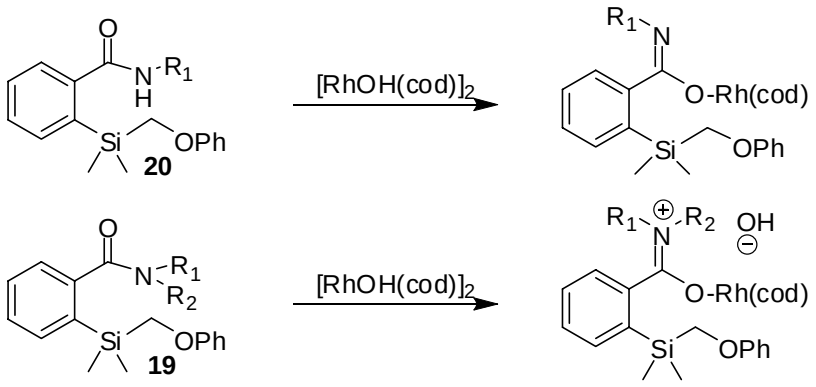
$B(R)_n$ = B(pin) (**15**), BF_3K (**16**)

Entry	$B(R)_n$	Rh (I) (mol %)	Additive (equiv)	Solvent (M)	Temp (°C)	Yield of **17/18** (%)
1	**16**	$[Rh(acac)(C_2H_4)_2]$ (0.03)	PPh_3 (0.06)	DMF/H_2O (1:1), (0.33)	80	0 (SM)
2	**16**	None	None	DMF/H_2O (1:1), (0.33)	80	0 (SM)
3	**16**	$[Rh(cod)_2]BF_4$ (0.03)	PPh_3 (0.06)	PhMe/H_2O (10:1), (0.2)	100	0 (SM)
4	**16**	$[Rh(cod)(MeCN)_2]BF_4$ (0.03)	PPh_3 (0.06)	PhMe/H_2O (10:1), (0.2)	100	0 (SM)
5	**16**	$[Rh(acac)(CO)_2]$ (0.03)	PPh_3 (0.06)	DMF/H_2O (1:1), (0.33)	80	0 (SM)
6	**15**	$[Rh(acac)(C_2H_4)_2]$ (0.03)	(*S*)-binap (0.03), K_2CO_3 (0.5)	Diox/H_2O (9:1), (0.1)	80	0 (SM)
7	**15**	$[Rh(cod)Cl]_2$ (0.03)	(*S*)-binap (0.03), K_2CO_3 (0.5)	Diox/H_2O (9:1), (0.1)	80	0 (SM)
8	**15**	$[Rh(cod)_2]BF_4$ (0.03)	(*S*)-binap (0.03), K_2CO_3 (0.5)	Diox/H_2O (9:1), (0.1)	80	0 (SM)
9	**15**	$[Rh(acac)(C_2H_4)_2]$ (0.03)	(*S*)-binap (0.03), K_2CO_3 (0.5)	Diox/H_2O (9:1), (0.1)	180	Decomp
10	**15**	$[Rh(cod)OH]_2$ (0.03)	(*S*)-binap (0.03), K_2CO_3 (0.5)	Diox/H_2O (9:1), (0.1)	100	Decomp

Despite the use of the optimized conditions of Batey (entry 1), Darses and Genet (entries 3, 5) and Hayashi and Miyaura (entry 6), no reactivity was observed, with starting material being recovered in every instance. To try to force the reaction to proceed, the reaction temperature was increased to 180 °C, at which point decomposition was observed. No anisaldehyde (**18**) was observed either, which would indicate hydrolysis of the organorhodium intermediate, suggesting that no transmetallation had occurred – this being a useful guide as protonolysis of C-Rh bonds occurs appreciably in these reaction conditions, whereas cleavage of the C-B bonds is minimal. With no observed transmetallation, this avenue of research was discontinued.

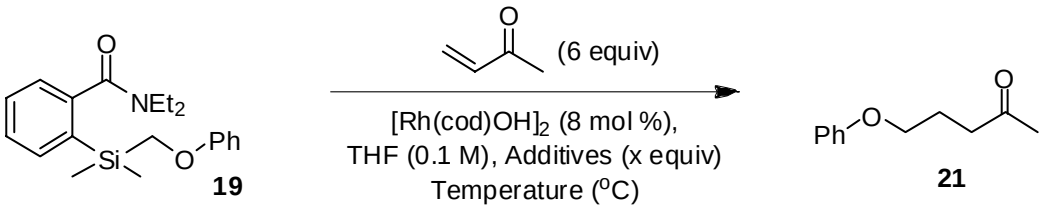
The next approach to promote the transmetallation again utilized the same α-oxyaryl methylene bound now to silicon. However, in order to employ the activating properties of the internal hydroxyl key to the success of Hudrlik, Hiyama, Hayashi and others, it was decided that an external electrophile would be utilized. In addition, an analogue of this compound was prepared having a diethylbenzamide activating group in place of the benzyl alcohol (**19**) in order to probe the ability of carbonyl compounds to promote the transformation. While 2° amide groups (**20**) would be more thermodynamically inclined to perform this activation by forming imidic acids, rather than the charged imminium zwitterionic compound here (Scheme 3.9), their preparation proved highly problematic and no starting material was obtained to test.

Scheme 3.9: 2° and 3° Amides for Silicon Activation with Rh(1) coordination



The diethylbenzamide was subjected to conditions similar to those used by Hiyashi and Hiyama in their publication pertaining to conjugate addition and are summarized in Table 3.3.

Table 3.3: Results from Rh(I) Catalyzed Conjugate Addition of Organosilicon Benzamide Derivative



Entry	Additive (equiv)	Temp (°C)	Yield of **21** (%)
1	None	50 to 120	0 (SM)
2	CsF (1)	50	0 (SM)
3	TBAF (1)	50	0[a]

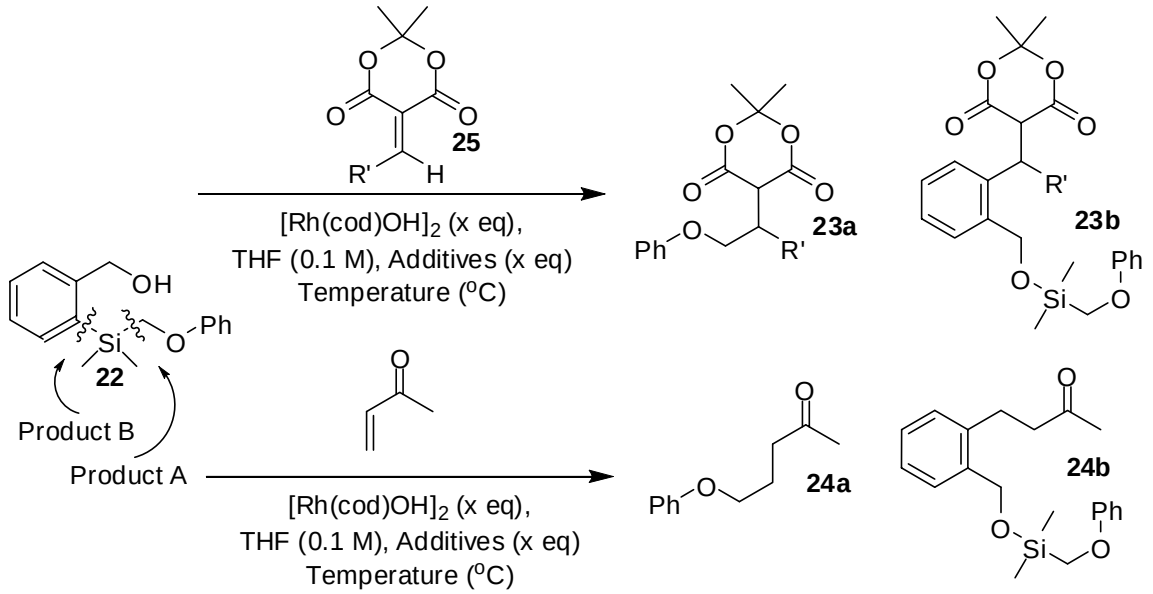
[a] Desilylated diethylbenzamide was the only observable isolated product

The reaction did not show anything but starting materials by TLC after 24 h at 50 °C and increasing the temperature over another 48 hours to 120 °C had no observable effect. In an attempt to promote transmetallation with this substrate, CsF (entry 2) and TBAF (entry 3) were added, which although this negates the effect of the amide promotion, would, thanks to silicon's fluorophilicity, likely form the fluorosilicate and promote a transformation of some type. Unfortunately, CsF had no effect on the starting material and TBAF cleaved exclusively the Ar-Si bond, leaving the C(sp^3)-Si bond intact. As such forcing conditions were required for any reaction to occur with this starting material was not felt to have any more potential in the desired synthetic transformation.

The benzyl alcohol derivative **22** was also examined to see if this substrate, which is expected to form the oxorhodium species as postulated in the Hayashi mechanism is capable of performing the desired transmetallation of the alkyl-silicon bond and

conjugate addition. With a good amount of starting material on hand, the key step was attempted using MVK and alkylidene Meldrum's acids as the electrophile (see table 3.4)

Table 3.4: Results from Rh(I) Catalyzed Conjugate Addition of Organosilicon Benzyl Alcohol Derivative



Entry	Electrophile (equiv)	Rh(I) (equiv)	Additive (equiv)	Temp (°C)	% Yield (prod)
1	MVK (7)	0.1	None	50	20 (**24b**)
2	**25**, R' = Ph (0.5)	0.1	None	50	0 (SM)
3	**25**, R' = Ph (0.5)	0.1	dppe (0.1)	50	0 (SM)
4	**25**, R' = ^{i}Pr (1)	0.09	^{t}BuONa (1)	50	Trace (**23b**)
5	**25**, R' = ^{i}Pr (1)	0.09	K_2CO_3 (1)	50	Trace (**23b**)
6	**25**, R' = ^{i}Pr (1)	0.09	K_2CO_3 (1), 18-C-6 (0.1)	50	0 (SM)

Unfortunately, after workup none of the desired products **24a** (entry 1) was obtained, the benzyl alcohol having bound to the silicon and the Ar-Si bond broke as shown for the Product B arrow, generating an aryl anion which then conceivably as the Ar-Rh species added in a conjugate manner onto MVK to give product **24b**, although only in 20% yield, and the reaction did not go to completion. None of the desired product **24a** was observed

by NMR or GCMS. This is in contrast to the report of Hayashi, wherein none of the benzyl alcohol's C-Si bond was ever reported cleaved through this methodology, but is not unfathomable as this carbon is the standard hybridization to undergo this transmetallation.

Several more reactions were performed with this starting material to get a better idea of its reactivity relative to various electrophiles, and although no product was observed in the addition onto benzylidene Meldrum's acid with or without a chelating diphosphine ligand (entries 2,3), using the isopropyl alkylidene and one equivalent of either a strong (entry 4) or weak (entry 5) base resulted in a trace amount of product **23b** being observed, although too little to isolate cleanly. The alkylidene was mostly consumed in these conditions though, so decomposition of the alkylidene could be competing with the conjugate addition in these conditions, contributing to the low yield. There was still a large amount of the silated benzyl alcohol after the reaction. Interestingly, using a catalytic amount of 18-C-6 (entry 6) to increase the bacicity of the K_2CO_3 lead to no product formation whatsoever, and the starting material was recovered exclusively.

Seeing that none of the desired transformation was occurring, rather the substrate was reacting through a transmetalltion of the Ar-Si bond rather than the alkyl group, this approach was not accomplishing its objectives, and the 2-hydroxymethyl phenylsilane backbone was deemed unsatisfactory for this research.

Conclusions

After numerous reactions to try to promote the transmetallation and conjugate addition of sp^3-hybridized, non-allylic carbon-silicon, boron and tin bonds with rhodium, it can be seen that this reaction is not synthetically useful. The only successes seen in breaking these bonds came through halide activation independent of the transition metal, and only proceeded in poor yields. Internal activation of the carbon with an α-oxygen did not affect the carbon to a sufficient degree as to allow the transmetallation to occur. Activation of the metal by way of an amide did not produce any transmetallation product, as the starting material was recovered, and fluoride activation only cleaved the more energetically favourable Ar-Si bond. When activation by an internal alcohol was investigated, again none of the desired alkyl-Si bond was cleaved, instead the aryl-Si bond cleaved and resulted in the aryl group being added 1,4 onto the electrophiles.

Although alkyl groups have been shown in the literature to transmetallate from boron and tin derivatives with palladium, and despite conscientious design of substrates and use of the highly activated alkylidene Meldrum's acids, the desired conjugate addition with rhodium did not prove to be successful. As compounds of this type have shown the ability to react with Pd(II), this lack of success could be due to the rhodium complexes involved. An alternate method to accomplish this type of transformation would be to do a thorough examination of the Falck Sn – Cu transmetallation, as alkylidene Meldrum's acids are known to react in high yields and enantioselectivities with chiral organocoppers.

Alternately, the Rh(I)-catalyzed conjugate addition reaction could be investigated more thoroughly with alkylidene Meldrum's acid to ascertain if high selectivities can ever be obtained when sp^2-hybridized carbons are employed. In this manner the Hayashi / Hiyama silane-substituted benzyl alcohol could be used for the synthesis in the formation of all-carbon tertiary, and potentially quaternary stereocentres. Because the proposed catalytic cycle relies on the post-addition enolate to deprotonate another equivalent of starting material, and because Meldrum's acid enolates are such poor bases, it would be advisable to oxidize the benzyl alcohol in the starting material to the benzoic acid. This would be similar to the system used by Shindo as shown previously (Figure 3.2), which gave appreciable amounts of product in that reaction. However, it is not known how this oxidation state change would affect the coordination of the rhodium to form the oxorhodium species proposed in their catalytic cycle, or how it would change the transmetallation step. Furthermore, these Ar-M species have not been used in conjugate addition with alkylidene Meldrum's acids for electrophiles, especially not in the formation of quaternary stereocentres, so there remain substantial questions regarding this transformation.

Supporting Information

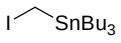
General Methods. All reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. CH_2Cl_2, THF, hexanes, $(CH_2Cl)_2$ and Et_2O were purified using an MBraun Solvent Purification System. Benzene was distilled from sodium-benzophenone keyl under nitrogen. Et_3N was distilled from CaH_2 under nitrogen. DMF was distilled from CaH_2 under nitrogen. Reagents were obtained from commercial sources and used without further purification unless otherwise specified. ^1H NMR spectra were referenced to residual ^1H shift in $CDCl_3$ (7.26 ppm) or acetone-D_6 (2.05) as specified. $CDCl_3$ (77.0 ppm) or acetone-D_6 (206.26 ppm) was used as specified as the internal reference for ^{13}C NMR. Reactions were monitored by thin-layer chromatography on commercially prepared plates with a particle size of 60 Å. Developed plates were viewed by UV lamp (254 nm), and with ceric ammonium molybdate or iodine stain. Flash chromatography was performed using 230-400 mesh silica gel. Melting points are uncorrected. High resolution mass spectra were run by Dr. R. Smith at the University of Waterloo with a source temperature of 200 °C, mass resolution of 9000 and electron energy of 70 eV.

General Procedure A: Alkylation of Salicylaldehyde with Iodomethyl Tin or Boron Compounds:[39] Potassium carbonate (1.1 equiv), salicylaldehyde (1.1 equiv) and DMF (2 M) are added to a dry flask under nitrogen. The appropriate iodomethyl compound is dissolved in DMF (1 M) and added gradually by syringe to the reaction flask. DMF (to make a 0.5 M solution) is added to wash down the flask, then heated at 70°C until the starting material is all consumed. The reaction mixture is poured into a 1:1:2 mixture of hexanes / diethyl ether and water and stirred for 15 minutes. The aqueous phase is

washed 3x with ether, and the combined organic phase is washed 3-5x with water. After drying with $MgSO_4$ and filtering, the product is purified by flash chromatography.

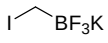
General Procedure B: Alkylation of Phenol with Chloromethyl(dimethyl)Silicon Compounds:[40] Phenol (1.5 equiv) and K_2CO_3 (7.5 equiv) are added to a dry flask with DMSO (0.3 M), sealed and heated at 90 °C with stirring for 1 h, then removed from the heat and cooled to rt. The appropriate chloromethylsilane is dissolved in DMSO (0.5 M) with KI (5.0 equiv) and added to the cooled solution. This mixture is heated at 90 °C for 16 h, then cooled and poured into a large excess of water. The crude product is extracted with EtOAc 3x, washed with water 2x, brine 2x, then dried with $MgSO_4$, filtered and concentrated.

Tributyl(iodomethyl)stannane:[41]



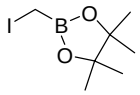
Prepared according to the literature method to yield a clear oil in 84 % yield.

Potassium Iodomethyltrifluoroborate:[42]



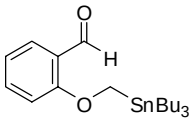
Prepared according to the literature method to yield a white powdery solid in 60 % yield.

2-(Iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:[43]



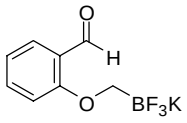
The title compound was prepared as a pale yellow oil in 83% yield.

2-((Tributylstannyl)methoxy)benzaldehyde (25):



Prepared using General Procedure A as a clear colourless oil in 89 % yield after flash chromatography (9:1 Hex/EtOAc, Rf = 0.9). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.47 (s, 1H), 7.81 (dd, *J* = 8, 1.8 Hz, 1H), 7.56 (dt, *J* = 8, 1.8 Hz, 1H), 7.17 (d, *J* = 8 Hz, 1H), 7.00 (t, *J* = 8 Hz, 1H), 4.23 (t, *J* = 7.5 Hz, 2H), 1.53 (m, 6 H), 1.33 (m, 6 H), 1.00 (t, *J* = 8.4 Hz, 6H), 0.89 (t, J = 8.4 Hz, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.8, 164.2, 135.9, 127.9, 124.9, 120.2, 111.8, 58.9, 29.0 ($J_{Sn\text{-}C}$ = 24.2), 27.2 ($J_{Sn\text{-}C}$ = 52.4), 13.7, 9.5 ($J_{Sn\text{-}C}$ = 322.0).

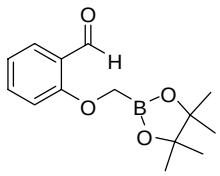
Potassium 2-((trifluoroboryl)methoxy)benzaldehyde (16):



Prepared using a modification of General Procedure A in 92 % yield as a pale white powder. After heating for 25 h, the reaction was quenched with a fivefold excess (relative to DMF) of a 1.5 M solution of KHF_2 in H_20. The water was removed by rotary evaporation and the DMF was removed by high vacuum to leave a brown powder. The powder was extracted with acetone four times, and the product was precipitated out with Et_2O. The combined organic media was filtered to leave the product as a powdery solid. M.p. >250 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 10.32 (s, 1H), 7.69 (dd, *J* = 7.8, 1.2 Hz,

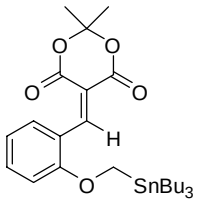
1H), 7.58 (dt, *J* = 8, 1.2 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 6.94 (t, *J* = 7.9 Hz, 1H), 3.29 (q, *J* = Hz, 2H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.3,136.5, 130.7, 125.2, 119.3, 113.7.

2-((4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)methoxy)benzaldehyde (15):



Prepared using General Procedure A as a clear colourless oil in 50 % yield after flash chromatography (CH_2Cl_2 (100 %) then EtOAc (100%), Rf (9:1 Hex/EtOAc) = 0.07). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.56 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.00 (m, 2H), 3.95 (s, 2H), 1.30 (s, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 158.7, 135.8, 128.0, 126.7, 120.5, 112.1, 84.5, 60.4, 24.8, 24.8, 24.6, 24.5.

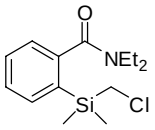
5-(2-((Tributylstannyl)methoxy)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (13):



Prepared by condensation of Meldrum's acid with 2-((tributylstannyl)methoxy)benzaldehyde (**25**) in 82 % yield by the procedure of Curci et al,[44] as a yellow oil after flash chromatography (9:1 Hex/EtOAc, Rf = 0.53). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8 Hz, 1H), 6.96 (t, *J* = 8 Hz, 1H), 4.23 (t, *J* = 7.5 Hz, 2H), 1.79 (s, 6H), 1.53 (m, 6

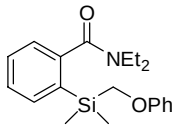
H), 1.33 (m, 6 H), 1.00 (t, J = 8.4 Hz, 6H), 0.89 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.1, 163.1, 162.1, 153.7, 135.4, 132.4, 132.0, 121.1, 120.1, 111.0, 104.2, 59.5, 29.1 (J_{Sn-C} = 24.6), 27.0 (J_{Sn-C} = 52.0), 13.6, 9.5 (J_{Sn-C} = 334.0.

2-((Chloromethyl)dimethylsilyl)-N,N-diethylbenzamide (26):



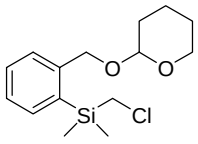
Prepared in 16 % yield from N,N-diethylbenzamide as a yellow oil after flash chromatography (9:1 Hex/EtOAc, Rf = 0.21) using a modification of Snieckus' procedure.[45] TMEDA (1.1 equiv) and THF (2 M) are added into a dry flask, and cooled to -78 °C under nitrogen. s-BuLi (1.1 equiv) was then added dropwise over 10 minutes with stirring, then a solution of the aromatic in 2 M THF was added dropwise over 10 minutes with stirring. The solution was then stirred for 1 h at -78 °C, at which point it was transferred by cannule into a second flask at -78 °C containing a solution of (chloromethyl)dimethylsilyl chloride (1.5 equiv) in THF (1 M) over 1.5 h. The initial flask was washed 2x with THF and transferred. The solution was stirred from -78 °C to rt overnight, then quenched with NH_4Cl saturated solution, extracted with Et_2O, and worked up in the usual manner (wash with water, brine, dry with $MgSO_4$, filter and concentrate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (m, 1H), 7.38 (m, 2H), 7.22 (m, 1H), 3.57 (q, J = 7.2 Hz, 2H), 3.22 (q, J = 7.2 Hz, 2H), 3.08 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H), 0.41 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.1, 143.0, 135.6, 134.2, 129.0, 128.2, 125.7, 43.6, 39.2, 31.1, 13.9, 12.8, -3.5.

N,N-Diethyl-2-(dimethyl(phenoxymethyl)silyl)benzamide (19):



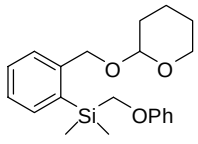
Prepared from 2-((chloromethyl)dimethylsilyl)-N,N-diethylbenzamide (**26**) in 28 % yield as a clear colourless oil after flash chromatography (5:1 Hex/EtOAc, Rf = 0.27) using General Procedure B. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (m, 1H), 7.36 (m, 2H), 7.26 (m, 3H), 6.92 (m, 3H), 4.12 (s, 2H), 3.54 (q, *J* = 7.2 Hz, 2H), 3.19 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 0.42 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 161.3, 142.9, 135.6, 134.7, 129.1, 128.8, 128.1, 125.6, 120.1, 114.1, 60.4, 43.6, 39.2, 13.8, 12.9, -3.5.

(Chloromethyl)dimethyl(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)silane:



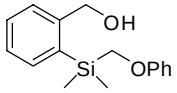
Prepared without purification from 2-(2-bromobenzyloxy)-tetrahydro-2H-pyran according to the procedure of Hayashi.[30]

Dimethyl(phenoxymethyl)(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)silane (27):



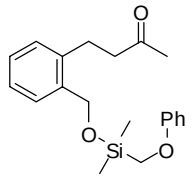
Prepared in 41 % yield over 2 steps from (chloromethyl)dimethyl(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)silane as a clear colourless oil after flash chromatography (19:1 Hex/EtOAc, Rf = 0.51) using General Procedure B. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.30 (m, 3H), 6.94 (m, 3H), 4.88 (d, *J* = 12 Hz, 1H), 4.70 (t, *J* = 3.6 Hz, 1H), 4.62 (d, *J* = 12 Hz, 1H), 3.91 (m, 1H), 3.85 (s, 2H), 3.54 (m, 1H), 1.62 (m, 4H), 0.48 (s, 6 H).

(2-(Dimethyl(phenoxymethyl)silyl)phenyl)methanol (22):



Prepared in 64 % yield from dimethyl(phenoxymethyl)(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)silane (**27**) as a pale yellow oil after flash chromatography (9:1 Hex/EtOAc, Rf = 0.37) by a modification of a procedure of Hayashi. The THP-protected alcohol was added to a flask with 0.02 equiv TsOH and MeOH (0.5 M) and stirred at rt for 16 hours. The MeOH was removed by rotary evaporation and the crude oil was dissolved in EtOAc, washed with saturated sodium bicarbonate solution, water and brine, then dried over $MgSO_4$, filtered and concentrated. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.45 (m, 2H), 7.33 (m, 3H), 6.95 (m, 3H), 4.82 (s, 2H), 3.85 (s, 2H), 2.24 (br, 1H), 0.52 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.0, 146.7, 135.3, 134.9, 130.0, 129.3, 128.5, 127.2, 120.6, 114.1, 65.8, 61.0, -2.7.

4-(2-(Hydroxymethyl)phenyl)butan-2-one, dimethyl(phenoxymethyl)silicon protected (24b):



Prepared in 20 % yield from the conjugate addition onto methyl vinyl ketone by (2-(dimethyl(phenoxymethyl)silyl)phenyl)methanol (**22**) as a clear oil after flash chromatography (9:1 Hex/EtOAc, Rf = 0.24). The aryl silane was added to a flask with THF (0.2 M), $[RhOH(cod)]_2$ (0.045 equiv) under inert atmosphere. A solution of methyl vinyl ketone (7.0 equiv) in THF (0.2 M) was then added and the flask heated at 50 °C for 15 h with stirring. After filtering through a short pad of silica with EtOAc and CH_2Cl_2, the solution was concentrated to yield a bright yellow oil, which was purified by flash chromatography. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, *J* = 7.2 Hz, 1H), 7.30 – 7.13 (m, 5H), 6.92 (m, 3H), 4.82 (s, 2H), 3.82 (s, 2H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.74 (t, *J* = 6.9 Hz, 2H) 2.10 (s, 3H), 0.30 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.0, 139.0, 129.2, 129.0, 128.1, 127.8, 126.2, 120.3, 114.0, 63.5, 59.8, 44.7, 29.8, 26.0, -3.3.

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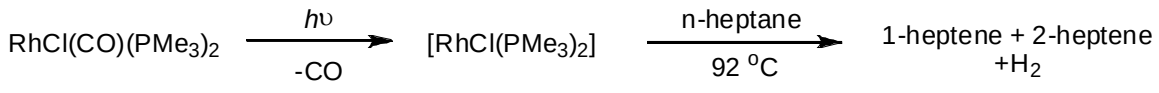
Chapter 4 - The Lewis Acid-Catalyzed Tandem [1,5]-Hydride Shift / Cyclization and Friedel Crafts Acylation with Alkylidene Meldrum's Acids

Introduction

Saturated hydrocarbons present to organic synthetic chemists a distinct challenge: their ubiquity in nature is unquestioned, yet the transformation of their C-C or C-H connections into bonds to other atoms is historically difficult, that is, beyond combustion, gas-phase free radicals, or protonating with "super acids". The low reactivity of these C-H bonds is often attributed to both their high bond energies (typically 90 – 100 kcal/mol) and very low acidity (pKa ~ 45 – 60).[1] The development of methods to selectively activate C-H bonds of sp^3-hybridized carbons thus became an area of great interest for synthetic chemists – biological C-H activation is known,[2] but falls outside the scope of these investigations. The advantage of this type of methodology is immediately evident as it eliminates the need to use more rare or reactive substrates to perform transformations - the formation of a reactive alkyl-transition metal complex from an alkane, rather than from an alkyl halide or main group metal species.

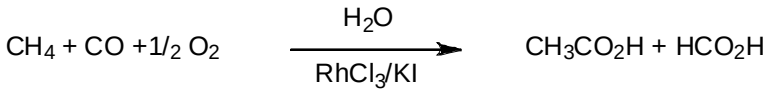
Alkane dehydrogenation is one excellent example of this type of C-H activation, and Tanaka[3] and Saito[4] have both reported the following dehydrogenation of alkanes to the corresponding alkenes by $RhCl(CO)(PMe_3)_2$.

Scheme 4.1: Dehydrogenation of Alkanes by Rh(I) Complex



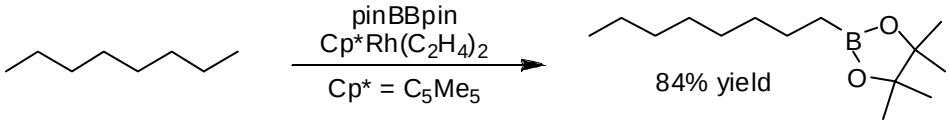
The irradiation of the complex generates the active species which undergoes C-H insertion. β-hydride elimination from the heptyl(hydrido)rhodium species and reductive elimination of $RhCl(PMe_3)_2$ gives the two products with turnover frequencies (T.O.F.) as high as 795 h^{-1} being attained. Subsequent studies have also shown that the alkyl-metal species can add onto various groups including CO in the presence of a reoxidant to yield for example alkyl acids.[5]

Scheme 4.2: C-H Activation and Carbonylation with Rh(III)



Recently, Hartwig has also employed Rh(I) complexes to perform C-H activation/ functionalization with the diboron compound pinBBpin. This process displays excellent turnover numbers as well as regioselectivity in producing terminal alkyl boronic esters.[6]

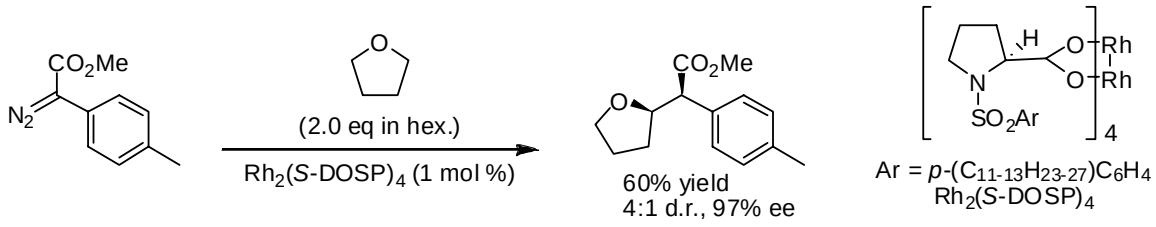
Scheme 4.3: C-H Activation and Boronylation with Rh(I)



The C-H activation of alkyl carbons has been employed on substrates bearing heteroatoms, and these can be divided into two classes: those employing transition metal complexes to perform the insertion, and those which proceed without metal insertion. The first system includes work by Davies, who performed highly regio-, diastereo- and

enantioselective C-H insertion into cyclic amines[7] and ethers[8] using diazo-derived metal carbenoid species to perform the activation.

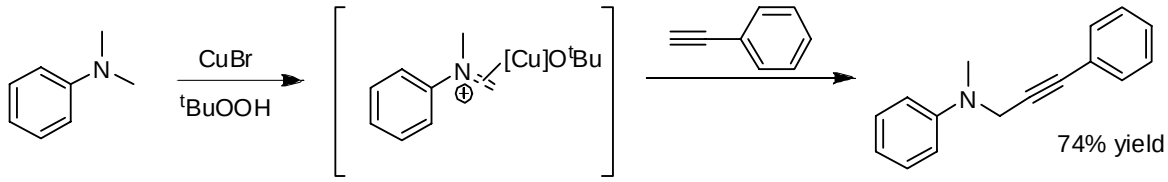
Scheme 4.4: C-H Activation by Rhodium Carbenoid on Tetrahydrofuran



The use of oxygen-substituted cyclopentane resulted in an increase of relative rate from 0.66 to 2700; however these were still ten times less favourable than the C-H insertion into styrenes or Si-H insertion with dialkylaryl silanes. It was postulated that the most reactive C-H bonds would be those which are most able to stabilize a build-up of positive charge during the transition state, although steric effects from the very bulky rhodium carbenoid could trump electronic effects.

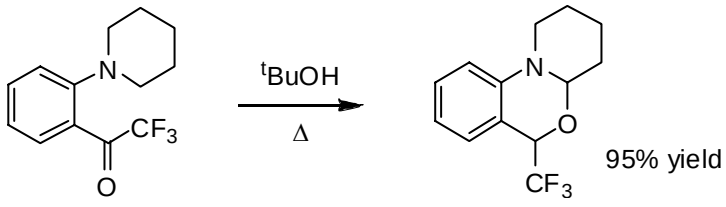
Li has also shown that C-H bonds adjacent to nitrogen atoms can be alkynylated racemically by CuBr,[9] or enantioselectively by CuOTf/(*S*)-Ph-Pybox.[10] This is proposed to proceed through an imine-type intermediate, catalyzed by the copper salt whose coordination promotes its formation, followed by activation of the alkyne and cross-coupling of the two intermediates and regeneration of the copper catalyst. Variations on this concept have been exploited by a number of groups with varying success.

Scheme 4.5: C-H Activation by Cu(I) on Dimethylaniline



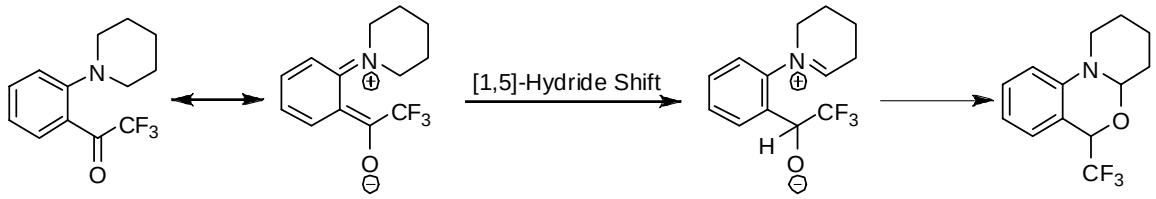
The second approach to C-H activation is one which employs an intramolecular rearrangement via a hydride shift. The [1,5]hydride shift in 1,3-pentanediene has elicited curiosity for over 30 years and continues to be a topic of research.[11] Hydride shifts can occur within both these conjugated carbon systems, as well as from saturated carbons with α-heteroatoms. The heteroatom-mediated homolytic cleavage of the C-H bond to generate a carbocation and a hydride unit has most frequently been observed with amines. Noting that tertiary amines performed this transformation when activated acceptors were present for the hydride lead to the naming of this as the "*tert*-Amino Effect".[12] Early investigations included heating 2-trifluoroacetyl-*N*,*N*-dialkylanilines gave near quantitative yields of a hydride transfer/ cyclization product as a 1:1 mixture of isomers.[13]

Scheme 4.6: 1,5-Hydride Shift / Cyclization with 2-Trifluoroacetyl-*N*,*N*-dialkylanilines



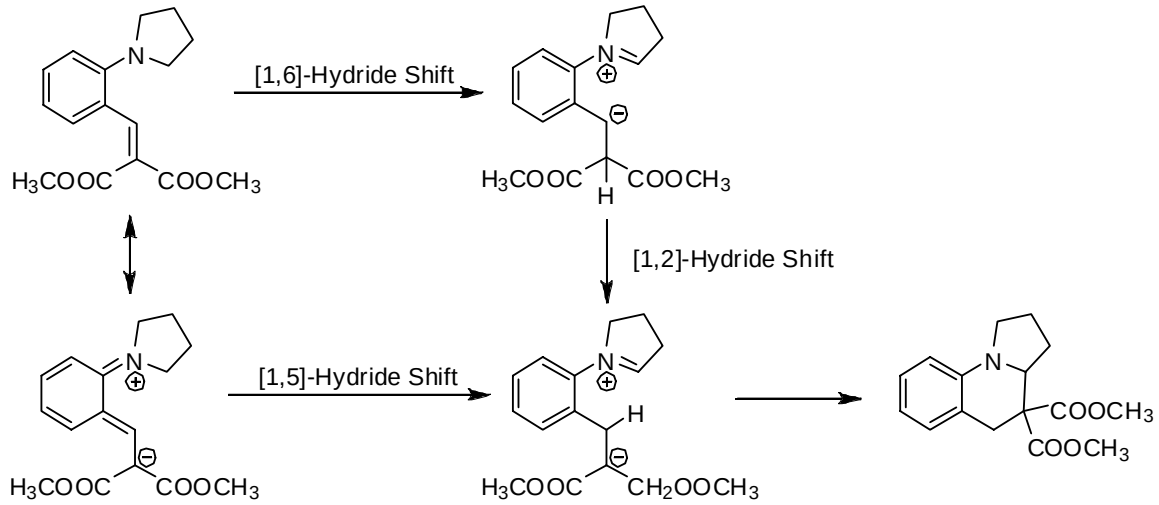
The reaction proceeds via its zwitterionic equilibrium component which promotes a suprafacial [1,5]-hydride shift to yield the iminium alkoxide. Subsequent intramolecular addition of the oxygen to the iminium gives the product (Scheme 4.7).

Scheme 4.7: Mechanism of [1,5]-Hydride Shift/ Cyclization



Running this reaction in ^{t}BuOD lead to no deuterium incorporation, attesting to the intramolecular nature of this hydride transfer. Subsequent studies with this system have furthered the scope of this interesting reaction (Scheme 4.8).

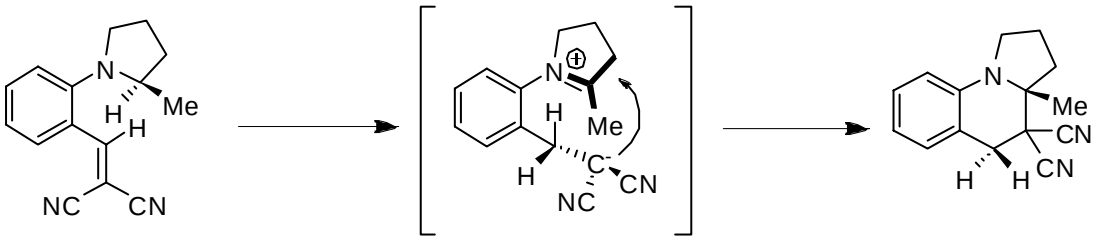
Scheme 4.8: Possible Pathways for the Conjugate Addition/ Cyclization Reaction



First, the conjugate addition of the hydride onto the diester or dicyano olefin proceeds smoothly upon heating in toluene, and the resulting carbanion added effectively onto the iminium to form the cyclised product. These activated systems had been proposed to react via either a sequential [1,6]-, [1,2]-Hydride shift pathway; however the unstabilized nature of the first intermediate of this process as compared with that of the [1,5] H-shift path makes the second pathway more likely.

Reinhoudt then examined the stereochemistry of this transformation with optically pure tertiary amines similar to those employed before (Scheme 4.9).[14]

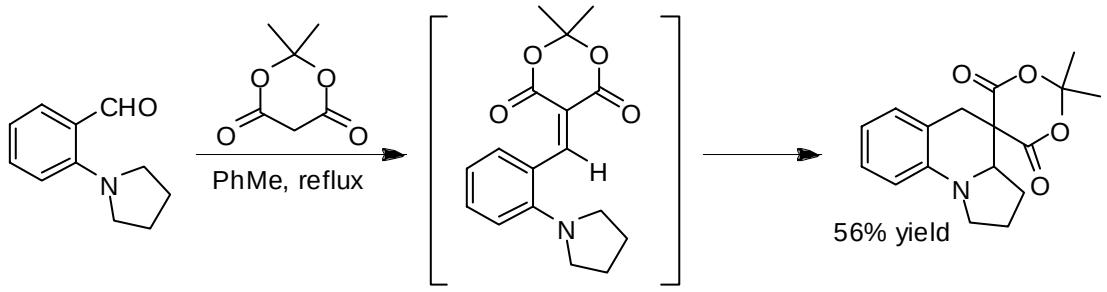
Scheme 4.9: Stereochemistry of the [1,5]-Hydride Shift / Cyclization



This compound smoothly underwent the [1,5]-hydride shift / cyclization to give one regioisomer as a single enantiomer. Thus, the carbanion adds to the iminium double bond exclusively from one side, moreover from the side the migrating hydrogen is transferred, and there is no equilibrium of the dipolar intermediates. This was termed by Reinhoudt to produce the products "*enantiomerically pure with self-reproduction of chirality, without the need of any auxiliary reagent.*" This stereochemical path is thus of great importance, especially as it also allowed for formation of a single diastereomer when the olefinic proton was changed to a methyl group. The transformation also proceeded for other

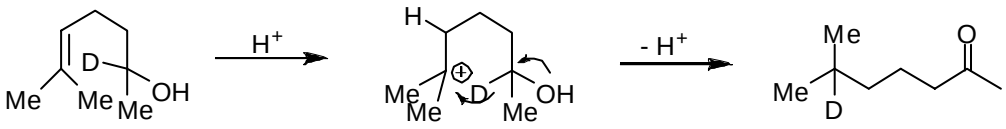
activated olefins, such as ones substituted with cyclohexanedione, barbituric acid derivatives, and Meldrum's acid (Scheme 4.10). Here, the Knoevenagel condensation was performed in refluxing toluene, and produced the hydride shift / cyclization products smoothly, albeit only in moderate yields for the Meldrum's acid derivatives.[15]

Scheme 4.10: Application of the *tert*-Amino Effect with Alkylidene Meldrum's Acid



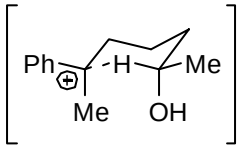
Another route that has been examined is the oxygen-promoted [1,5]-hydride shift, although a key difference is these often require a strong Lewis acid to proceed, as opposed to heating like with amines. In 1963, Colonge and Brunie published the isomerisation of γ-hydroxy olefins to saturated ketones with polyphosphoric acid,[16] and a subsequent deuterium-labelled investigation of this reaction gave >95% deuterated product, verifying the intramolecular hydride shift mechanism (Scheme 4.11).[17]

Scheme 4.11: [1,5]-Hydride Shift Promoted by H^+/Alcohol



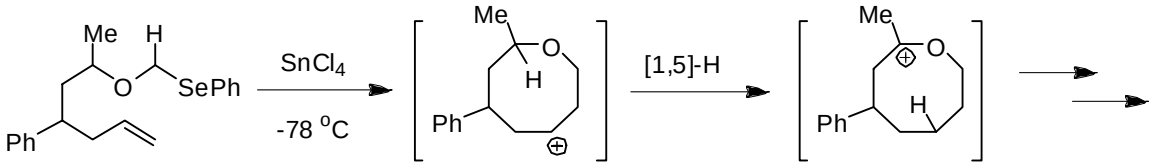
In order to examine this hydride shift and the transition state the reaction could follow, an optically pure derivative of known absolute configuration was prepared; after running the reaction the product was formed with optical purity of 15%. A chair conformation as illustrated in Figure 4.1 conforms to the axial / equatorial steric requirements of the substituents, and gives a product whose absolute configuration matches the observed compound, suggesting that the reaction proceeds via a chair transition state.

Figure 4.1: Proposed 6-Membered Transition State for [1,5]-Hydride Shift of Optically Pure γ-hydroxyolefins



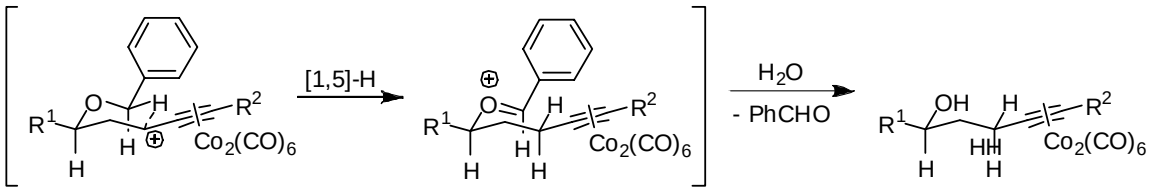
Similarly, this type of oxygen and Lewis acid promoted [1,5]-hydride shift has also proceeded using $SnCl_4$ (the pertinent aspects of this transformation are shown in Scheme 4.12),[18] or by Co(0) coordination with BF_3•OEt_2 with acetylenic monoprotected diols (Scheme 4.13).[19]

Scheme 4.12: $SnCl_4$-Catalyzed [1,5]-Hydride Shift with Oxygen-Stabilized Cation



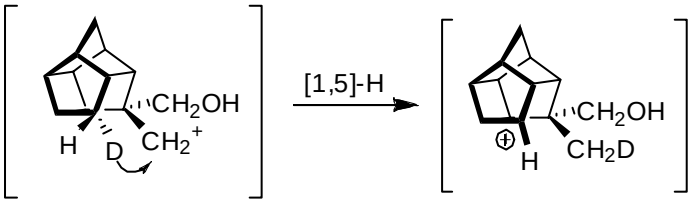
Versions which involve carbocations stabilized by aromatic rings[20] and β-silicon groups[21] have also been reported.

Scheme 4.13: [1,5]-Hydride Shift with Acetylenic Monoprotected Diols



Furthermore, the stability of 2° versus 1° carbocations was sufficient to promote the hydride shift in a highly constrained system.[22]

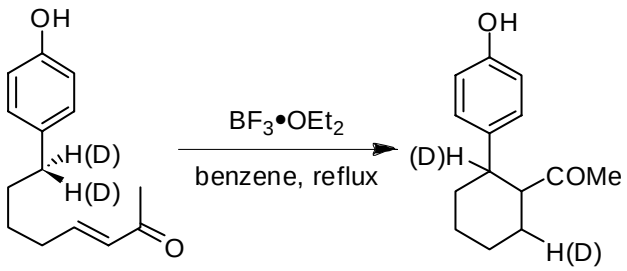
Scheme 4.14: Intermediates of [1,5]-Hydride Shift in Highly Constrained 2° Carbocations



In 1969, Atkinson published a very brief communication outlining a [1,5]-hydride shift / cyclization which took place under strong Lewis acidic conditions.[23] However, this account differs from those previously discussed as the heteroatom is now located *para* on a connected benzene ring (Scheme 4.15). This activates a benzylic hydrogen which performs conjugate addition, and after cyclization gives a substituted cyclohexane ring. Deuterium labelling of the benzylic protons showed no loss of deuterium after treatment

with BF_3•OEt_2, and a 1:1 mixture of D_0 and D_2 substrates showed at most 6% which was the product of an intermolecular shift after reacting according to the standard conditions.

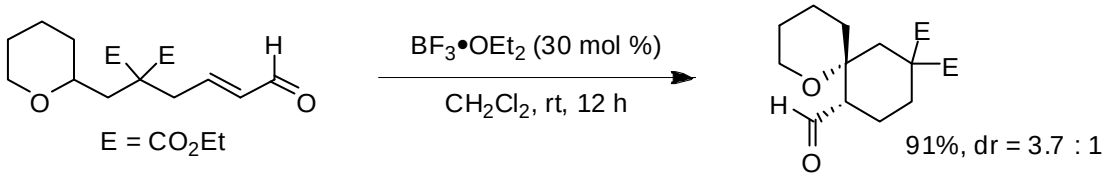
Scheme 4.15: [1,5]-Hydride Shift of *p*-Hydroxybenzyl Hydrogens



A full examination of this hydride shift was subsequently published in 1974.[24] Therein, they disclosed that the transformation proceeded both for the phenol and anisole substrates, but that only α,β-unsaturated ketones would react, and only in 63% yield with a large excess of boron trifluoride. Perchloric acid and *p*-toluenesulfonic acid could both promote the cyclization, but gave lower yields.

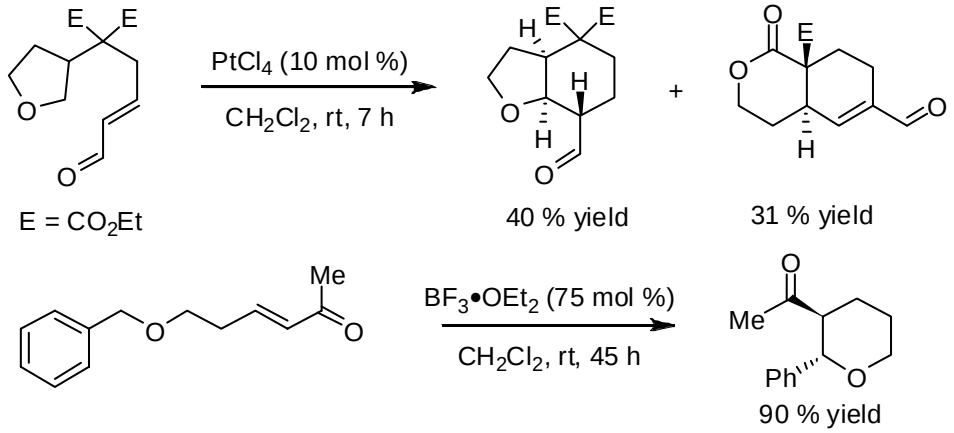
In 2005 the Sames group reported their success in employing cyclic ethers to effect an intramolecular [1,5]-hydride shift / cyclization with α,β-unsaturated carbonyls in the presence of Lewis acids in high yields and dr's from 1:0.8 to >15:1 (Scheme 4.16).[25] Their approach employed a tertiary carbocation intermediate to allow for the synthesis of *spiro* bicycles with quaternary stereocentres.

Scheme 4.16: [1,5]-Hydride Shift / Cyclization with Cyclic Ether Derivatives



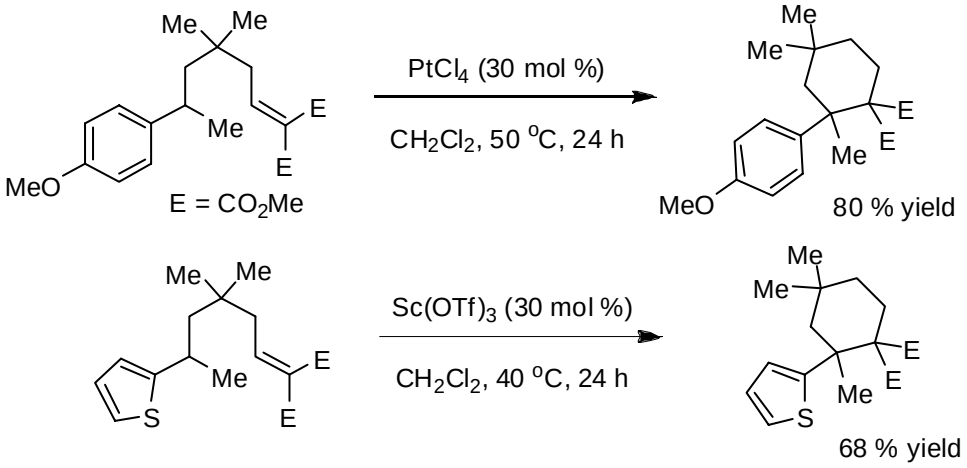
Their approach works for aldehydes and ketones, and malonate-derived diesters also furnish the product in high yields. Both 5- and 6-membered ring ethers undergo the transformation, and the pendant ester groups on the chain are not necessary for high reactivity, but are used more for ease of synthesis of the substrates. Other substrates prepared have dimethyl groups in the same location, and while higher yields are obtained on the unsubstituted chain, it requires 6 times as long to go to completion. A variety of Lewis acids are capable of performing the transformation, although BF_3•OEt_2 is often preferred as more active acids gave undesired byproducts. Secondary carbons also undergo this tandem reaction, although stronger Lewis acids, higher catalyst loading or long reaction times are required (Scheme 4.17).

Scheme 4.17: [1,5]-Hydride Shift / Cyclization with Secondary Carbons



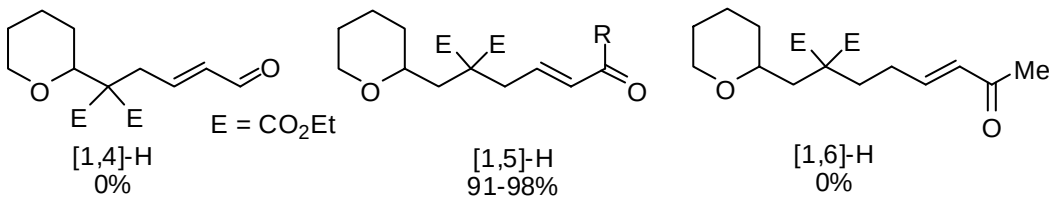
Sames also showed that using anisole derivatives and heteroaromatics the reaction could also proceed, again with an intermediate tertiary carbocation (Scheme 4.18). Elevated reaction temperatures were also required, as well as stronger Lewis acids.

Scheme 4.18: [1,5]-Hydride Shift / Cyclization with Aromatic Derivatives



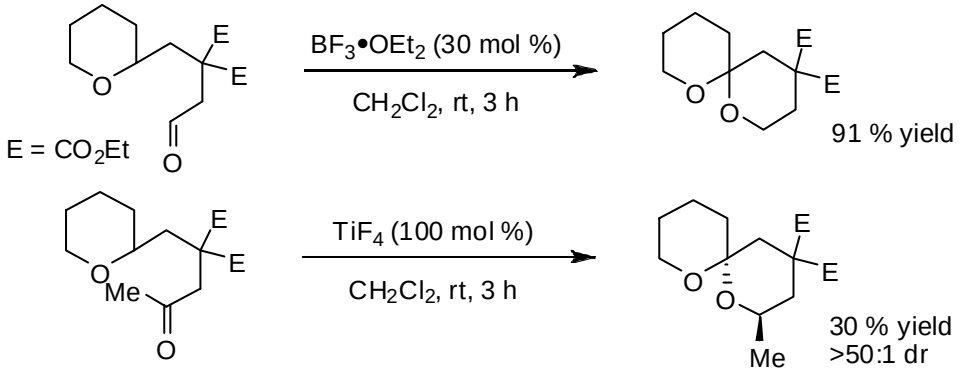
The 1,5- relationship was also found to be very important to the reaction. Substrates identical save for the number of methylene spacers were prepared to try the [1,4]- and [1,6]-hydride shift, and under the optimized conditions gave no trace of product. The majority of literature examples of these hydride shifts proceed through six-membered transition states, and this is in keeping with this (Figure 4.2). [19,26]

Figure 4.2: Necessity of [1,5]-Relationship for Hydride Shift / Cyclization Reaction



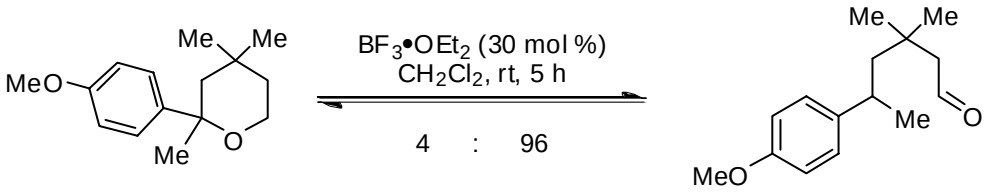
Subsequently, Sames has published an extension to this methodology wherein the hydride transfers to a carbonyl group from similar starting materials (Scheme 4.19).[27] Generally aldehydes were employed and one example with a ketone was presented which required much more forcing conditions (TiF_4 or $GaCl_3$ rather than BF_3•OEt_2) and gave a much lower yield. Substrates with the shifting proton substituted for deuterium were prepared, and when mixtures of the deuterated starting material and a different starting material with no deuterium were reacted, no crossover of ^2H was observed between the products, again attesting to the intramolecular nature of this process.

Scheme 4.19: [1,5]-Hydride Shift / Cyclization with Carbonyl Compounds



Again the transformation was attempted with anisole derivatives in place of the pyran system; however in this case the conditions did not give more than a trace of the product. The Lewis acid in these reactions is proposed to catalyze the equilibrium between the aldehyde and spiroketal pyran substrate, and indeed when the ketal substrate of the *p*-$OMeC_6H_4$ compound was subjected to the reaction conditions, 96% reverted to the aldehyde form (Scheme 4.20).

Scheme 4.20: Equilibrium Between Aromatic-Containing Pyran and Aldehyde Substrates in [1,5]-Hydride Shift / Cyclization



DFT calculations gave a ΔH_{calc} of +1.21 kcal/mol for the pyran as compared to the aldehyde, and this uphill difference results in the observed ratio. In the spiroketal substrates, the anomeric effect is proposed to be responsible for making spiroketal formation favourable.

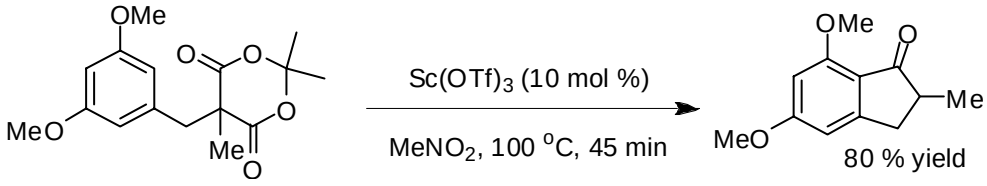
In the pursuit of further functionalizations for alkylidene Meldrum's acids, the [1,5]-hydride shift emerged as a possible avenue to pursue. Based on the past successes of alkylidene malonates being acceptors for the transfer, it was reasoned that the Meldrum's acid versions, being more electrophilic at the β-position of the olefin than the malonate,[28] would participate highly in this reaction. Furthermore, if the activating group was aromatic-based such as in Scheme 4.20, the product of this hydride shift/ cyclization would be perfectly oriented to undergo Lewis acid-catalyzed Friedel-Crafts acylation.

The order of this tandem reaction is set by the reactivity of the Meldrum's acid moiety present. Although alkylidene derivatives react in good yields for intermolecular Friedel-Crafts alkylation,[29] their use in the Lewis acid-catalyzed Friedel-Crafts acylation reaction has been only employed sparsely, and at elevated temperatures.[30] Furthermore, based on

Sames' work, the hydride shift and cyclization might proceed at low temperatures, while the conjugate addition reaction was performed in refluxing nitromethane, which should allow for control over products formed.

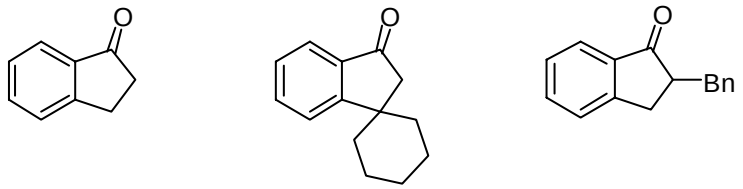
Mono- and disubstituted Meldrum's acids react in moderate to excellent yields as electrophiles for intramolecular Friedel-Crafts acylation.[31,32,33] Optimized conditions employed rare earth triflates $Yb(OTf)_3$ or $Sc(OTf)_3$ or other strong Lewis acids such as BF_3•OEt_2 or triflic acid in refluxing nitromethane, and were generally done within 60 minutes for electron rich aromatic nucleophiles (Scheme 4.21).

Scheme 4.21: Friedel-Crafts Acylation with Disubstituted Meldrum's Acid



In the monosubstituted (enolizable) acylation, the aromatic ring generally required *ortho* and *para* substituted electron donating groups for high yields to be obtained. When the overall π-nucleophilicity of the arene was reduced by groups *meta* such as methoxy the efficiency of the cyclization was highly reduced. Other substitutions on the substrate could have a beneficial effect, as substitution at the benzylic position increased the reactivity of the system. Indeed, under standard conditions, monoalkylated benzyl Meldrum's acid with no benzylic substituents only gave 13% yield, whereas the cyclohexyl-substituted benzylic position gave 56% yield in a fraction of the time (Figure 4.3).

Figure 4.3: Effect of Substituents on Friedel-Crafts Acylation

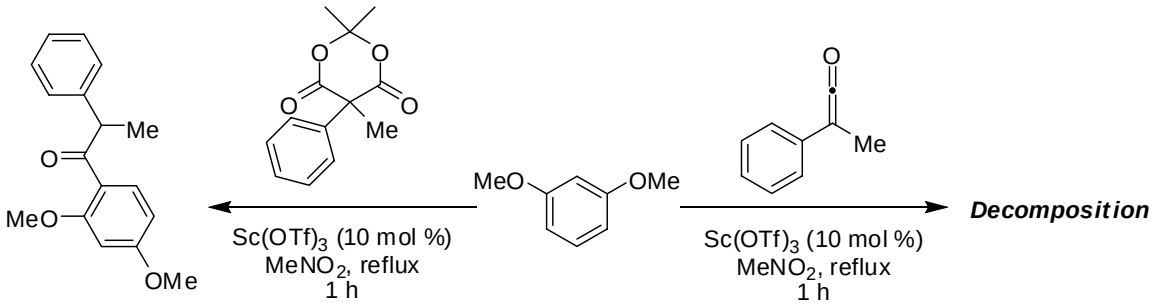


540 min, 13% yield 30 min, 56% yield 50 min, 66% yield

For disubstituted (non-enolizable) Meldrum's acids, π-nucleophilicity was not as crucial as was observed for the enolizable substrates, and even unsubstituted benzyl substrates were able to cyclise in good yield. Electron withdrawing groups like fluoro and nitro *meta* to the nucleophilic carbon gave no product even after prolonged reaction times, although the di(3-fluorobenzyl) Meldrum's acid would react in high yield (93% under standard conditions).

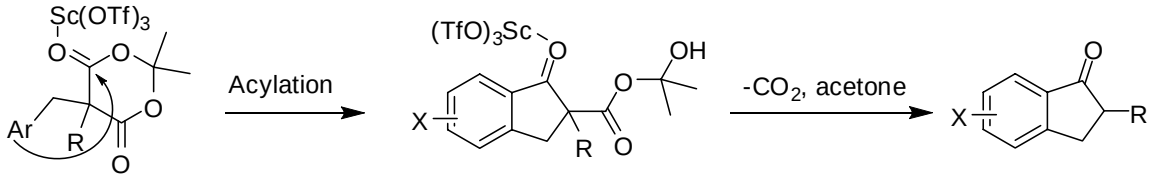
The mechanism of the Friedel-Crafts acylation of non-enolizable Meldrum's acids with a Lewis acid catalyst has been examined in some detail, and it is suggested that a ketene is not the reactive species in the acylation reaction, in contrast to the enolizable case where this is still considered to be plausible.[34] When phenylmethyl ketene was heated with catalytic $Sc(OTf)_3$ and 1,3-dimethoxybenzene, complete decomposition of the starting material was observed. Although it was argued that the ketene could more readily undergo side reactions than the intermolecular attack by the aromatic, the phenyl methyl Meldrum's acid gave 83% yield of the anticipated acylation product under identical conditions in one hour (Scheme 4.22).

Scheme 4.22: Determination of Intermediate in Non-Enolizable Acylation Reaction



Direct acylation of a Lewis acid activated carbonyl or (for metal triflates) the formation of a triflic anhydride is two pathways through which the reaction could thus be proceeding. However, as this reaction can proceed in high yields with boron trifluoride and there is no report of acid fluoride formation using BF_3•OEt_2 in the literature. Furthermore, starting material is recovered if the nucleophile is not sufficiently electron rich, whereas an acid fluoride intermediate would lead to decomposition. Thus, the most plausible pathway involves coordination of the Lewis acid to the carbonyl, followed by acylation, then loss of acetone and carbon dioxide to yield the indanone (Scheme 4.23).

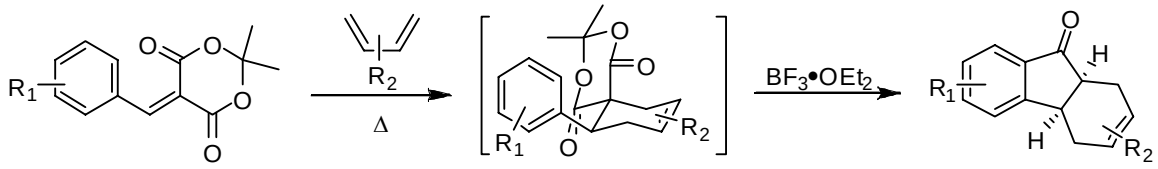
Scheme 4.23: Possible Mechanism for Friedel-Crafts Acylation with Non-Enolizable Meldrum's Acids



The enolizability of the Meldrum's acids plays a key role in the reactivity of the system. For highly π-nucleophilic systems, such as the monoalkylated 3,5-dimethoxybenzyl

Meldrum's acid, the cyclization could be thermally promoted, while without a catalyst the corresponding disubstituted system shows no reactivity. This was exploited in a one-pot synthesis of tetrahydrofluorenones by thermal Diels-Alder cycloaddition onto alkylidene Meldrum's acids, followed by Lewis acid-catalyzed Friedel-Crafts acylation (Scheme 4.24).

Scheme 4.24: One Pot Thermal Diels-Alder / Lewis Acid-Catalyzed Friedel-Crafts with Alkylidene Meldrum's Acids



Spiro Meldrum's acids derivatives were found to react cleanly in refluxing dichloroethane with BF_3•OEt_2, as other solvents (MeCN, toluene, benzene) were found unsuitable for the Friedel-Crafts acylation, and other Lewis acids such as $Sc(OTf)_3$ or TMSOTf were discounted as they gave mixtures of products when tetrasubstituted alkenes were present. Much like the previous Friedel-Crafts investigations, highly π-nucleophilic aromatic rings gave the best results, with 3,5-dimethoxy- and 3,4,5-trimethoxybenzene derivatives producing yields greater than 85% for the one-pot transformation.

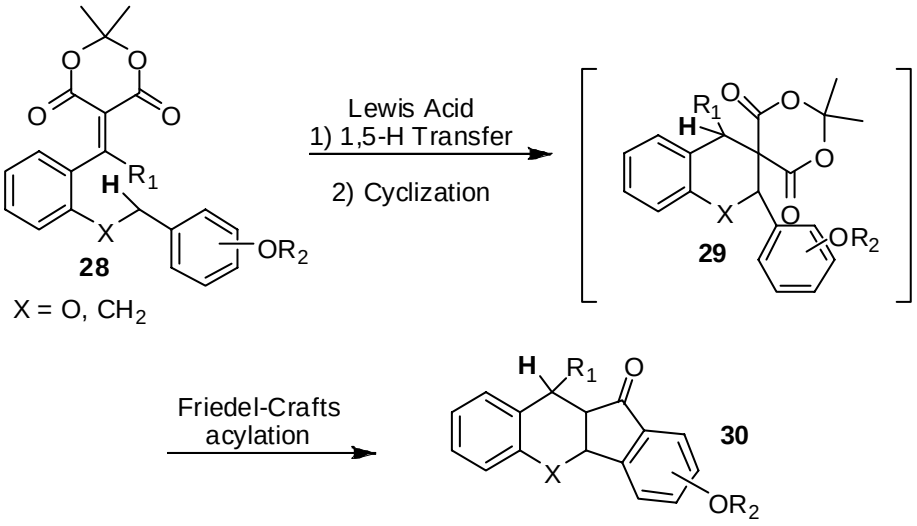
Results and Discussion

The Lewis acid-promoted [1,5]-hydride shift from sp^3-hybridized carbons with proximal oxygen or electron rich aromatic groups has been shown to allow the functionalization of these less reactive bonds. Excellent yields have been obtained with highly stabilized tertiary carbons α- to the activating group, for secondary carbons stabilized both by aromatic rings and oxygen, or with less stabilized carbons at elevated temperatures with higher catalyst loading. The subsequent cyclization has formed tertiary and quaternary stereocentres on highly substituted substrates in high diastereoselectivity and yield. Alkylidene malonates have proved to be viable electrophiles for this transformation, although their use with aromatic-based activating groups required more forcing conditions. It was thought that the superior electrophilicity of alkylidene Meldrum's acids would allow for the hydride shift to proceed on less-substituted carbons, and at lower temperatures and lower catalyst loading. By employing electron rich aromatic rings, the hydride shift / cyclization product was envisaged to then be perfectly situated for intramolecular Friedel-Crafts acylation.

In order to activate the benzylic carbon to undergo a [1,5]-hydride shift, the literature examples have employed both benzyl ethers and *p*-hydroxy- and *p*-methoxyphenyl groups. Furthermore, gem-dialkyl or dicarbonyl groups have been employed on the alkyl spacer, and this has had an accelerating effect on the reaction. In order to facilitate the reaction, maintaining proximity of the reactive termini was planned using the fixed geometry of an aromatic group as spacer. This also serves to facilitate the synthesis of the

alkylidene, as condensation of Meldrum's acid onto aromatic aldehydes is easily accomplished in generally high yields.[35] The alkylidene **28** in Scheme 4.25 was therefore the targeted substrate for the sequential reaction.

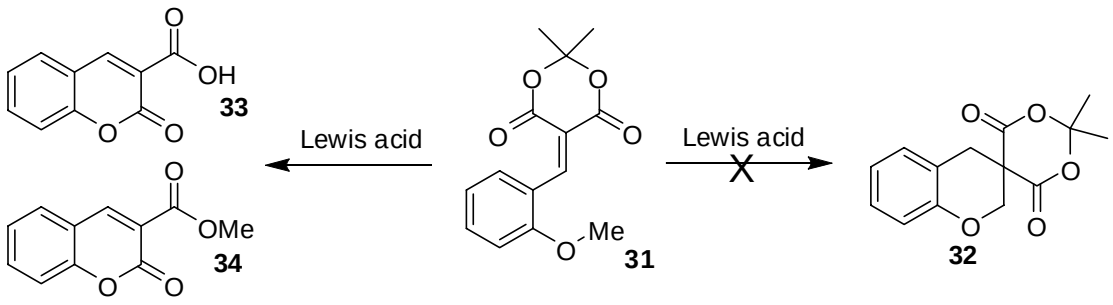
Scheme 4.25: Sequential [1,5]-Hydride Shift / Cyclization and Friedel-Crafts Acylation with Alkylidene Meldrum's Acids



Before trying the key step on the target substrate, a test alkylidene (**31**) was prepared from *o*-anisaldehyde and Meldrum's acid to examine exclusively the hydride shift / cyclization. As this is a primary carbon, the stabilization of the oxonium intermediate is lower than for the secondary or tertiary ether carbons typically employed; however it structurally similar to ones which were successfully employed with tertiary amines (see Scheme 4.10) and Meldrum's alkylidenes for [1,5] hydride shift / cyclization reactions. However, when it was mixed with Lewis acids ranging in strength from $Zn(OTf)_2$ to $TiCl_4$, no hydride shift (**32**) was observed, rather it decomposed to a mixture of products

of which 3-carboxycoumarin **33** and the methyl ester version **34** were the main components (Scheme 4.26).

Scheme 4.26: Attempts at [1,5]-Hydride Shift with 2-OMe-Benzylidene Meldrum's Acid



It has previously been reported that by heating these alkylidenes with H_2SO_4 the formation of carboxycoumarins was possible in good yields,[36] and it appeared that Lewis, as well as Brønstead acids were capable of promoting this reaction (Table 4.1).

Table 4.1: Attempted Conditions for [1,5]-Hydride Shift with 2-OMe-Benzylidene Meldrum's Acid 31

Entry	Lewis Acid	Solvent	Temperature	Yield of H-Shift Product **32**
1	$TiCl_4$	$(CH_2Cl)_2$	rt	0[a]
2	$Sc(OTf)_3$	$(CH_2Cl)_2$	rt	0[a]
3	$Zn(OTf)_2$	$MeNO_2$	rt to 70 °C	0[a]
4	$Mg(OTf)_2$	$MeNO_2$	rt to 70 °C	0[a]
5	$Yb(OTf)_3$	$MeNO_2$	rt to 70 °C	0[a]
6	$Sc(OTf)_3$	$MeNO_2$	rt to 70 °C	0[a]
7	$TiCl_4$	$MeNO_2$	rt to 70 °C	0[a]
8	$AlCl_3$	$MeNO_2$	rt to 70 °C	0[a]
9	BF_3•OEt_2	$MeNO_2$	rt to 70 °C	0[a]
10	None	$MeNO_2$	rt to 70 °C	S.M.

[a] Decomposition to the coumarin derivatives **33** + **34** was the majority of product

In this case, the aromatic-bound oxygen is more readily attacking a carbonyl of the Meldrum's alkylidene than promoting the hydride transfer. In order to increase the stability of the carbocation which is formed from the hydride shift, a second substrate was prepared from PMB-protected salicylaldehyde **35** (Scheme 4.27). Here the methylene group which is to transfer the hydride is activated by two oxygens and the aromatic ring, giving it three sources of stabilization. It was thought that this would have an optimal electronic environment for the hydride shift (**36)**. However, with all Lewis acids screened the result was identical to those seen for the 2-OMe substrate (Table 4.2).

Scheme 4.27: Attempts at [1,5]-Hydride Shift with 2-OPMB-Benzylidene Meldrum's Acid

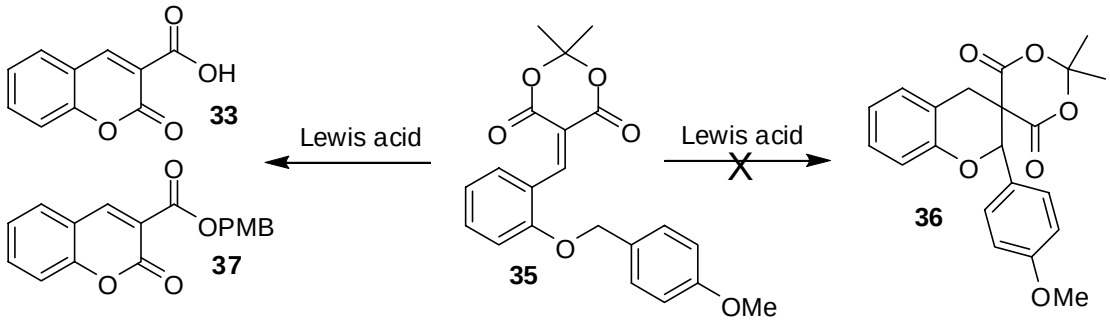


Table 4.2: Attempted Conditions for [1,5]-Hydride Shift with 2-OPMB-Benzylidene Meldrum's Acid

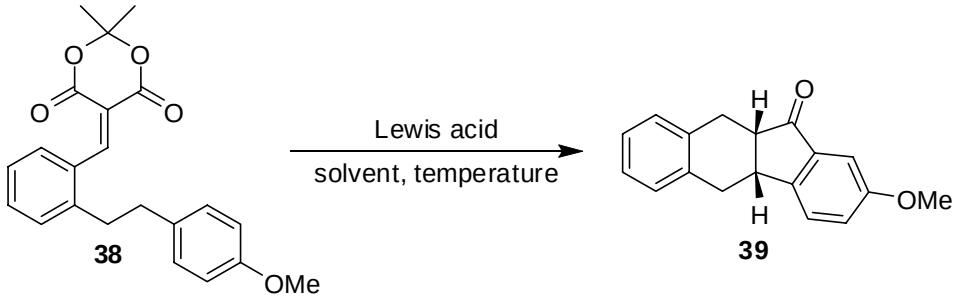
Entry	Lewis Acid	Solvent	Temperature	Yield of H-Shift Product **36**
1	$Zn(OTf)_2$	$MeNO_2$	rt to 70 °C	0[a]
2	$Mg(OTf)_2$	$MeNO_2$	rt to 70 °C	0[a]
3	$Yb(OTf)_3$	$MeNO_2$	rt to 70 °C	0[a]
4	$Sc(OTf)_3$	$MeNO_2$	rt to 70 °C	0[a]
5	$TiCl_4$	$MeNO_2$	rt to 70 °C	0[a]
6	$AlCl_3$	$MeNO_2$	rt to 70 °C	0[a]
7	$BF_3•OEt_2$	$MeNO_2$	rt to 70 °C	0[a]
8	None	$MeNO_2$	rt to 70 °C	S.M.

[a] Decomposition to the coumarin derivatives was the majority of product

While the *p*-methoxybenzyl group would be more stabilizing for the hydride transfer, it is also very stabilizing for cleavage of the PMB group itself, and the coumarin product was again the major component of a mixture of decomposition products.

At this point it was rationalized that the problem was not in the activation of the methylene for the hydride shift, but the aromatic-bound oxygen in these substrates which more readily attacked the Meldrum's acid's carbonyl. As a result, a third substrate was prepared with a methylene spacer in place of the oxygen group (**38**). With this substrate in hand, the hydride shift was attempted with a variety of Lewis acids (Table 4.3).

Table 4.3: Conditions for [1,5]-Hydride Shift / Cyclization and Friedel-Crafts Acylation with 2-(4-Methoxyphenethyl)Benzylidene Meldrum's Acid



Entry	Lewis Acid	Solvent	Temperature	Time	Yield of **39**
1	$Zn(OTf)_2$ (20 mol %)	$(CH_2Cl)_2$	40 °C to 70 °C	40 h	0 (S.M.)
2	TMSCl (20 mol %)	$(CH_2Cl)_2$	40 °C to 70 °C	40 h	0 (S.M.)
3	BF_3•OEt_2 (20 mol %)	$(CH_2Cl)_2$	40 °C to 70 °C	40 h	15 %
4	$Sc(OTf)_3$ (20 mol %)	$(CH_2Cl)_2$	40 °C to 70 °C	40 h	26 %
5	None	$(CH_2Cl)_2$	70 °C	48 h	0 (S.M.)

After 18 h at 40 °C there were no new spots visible by TLC, so the reactions were heated to 70 °C for 24 h, at which point a new product was observed in the reactions catalyzed by $Sc(OTf)_3$ and BF_3•OEt_2 to a lesser degree (entries 3 and 4). Gratifyingly, after

purification the tetracyclic product **39** was obtained, although only in low yield. With this in hand, attempts to optimize the reaction were undertaken. The solvent was switched to nitromethane as it was previously seen to be optimal for the Friedel-Crafts reaction, and the temperature effects were investigated with scandium triflate as Lewis acid. At 40 °C there were again no new spots observed by TLC, and the yield of **39** decreased when run at 70 °C for 24 h, but increased to 31% at 100 °C, and no starting material remained after 1 h (Table 4.4).

Table 4.4: Temperature Effects on the Tandem Reaction – 1st Examination

Entry	Lewis Acid	Solvent	Temperature	Time	Yield of **39**
1	$Sc(OTf)_3$ (10 mol %)	$MeNO_2$	40 °C	24 h	0
2	$Sc(OTf)_3$ (10 mol %)	$MeNO_2$	70 °C	24 h	22 %
3	$Sc(OTf)_3$ (10 mol %)	$MeNO_2$	100 °C	1 h	31 %

In an attempt to ascertain why the yields were modest, the crude reaction mixtures from entries 2 and 3 were checked by ^{1}H NMR, and two distinct products were observed: the tetracyclic product **39** and a new compound bearing an alkene that was α,β-unsaturated and of *trans* geometry. However, full structural elucidation of this unknown was complicated by difficulty in isolating it from other decomposition products and its sluggish elution off silica. At 100 °C there was roughly a 1:1.3 ratio of product to unknown (by ^{1}H NMR), and to try to improve the selective formation of the product, several higher boiling solvents were screened. (Table 4.5).

Table 4.5: Solvent Selection and Ratio of Product to Unknown

Entry	Lewis Acid	Solvent	Temperature	Time	Ratio
1	$Sc(OTf)_3$ (10 mol %)	$MeNO_2$	100 °C	1 h	1:1.3
2	$Sc(OTf)_3$ (10 mol %)	Toluene	100 °C	1 h	1:0.9
3	$Sc(OTf)_3$ (10 mol %)	$(CH_2Cl)_2$	100 °C	1 h	1:1.5

Toluene, showing the highest ratio of product to unknown was selected as the best solvent for this transformation. To try to learn more about the formation of the unknown, the reaction was tried in toluene at 70 °C and 100 °C, and mesitylene at 150 °C.

Table 4.6: Temperature Effect on Yield of Product and Unknown in Toluene

Entry	Lewis Acid	Solvent	Temperature	Time	Yield of **39**
1	$Sc(OTf)_3$ (10 mol %)	Toluene	70 °C	24 h	48 %
2	$Sc(OTf)_3$ (10 mol %)	Toluene	100 °C	2 h	34 %
3	$Sc(OTf)_3$ (10 mol %)	Mesitylene	150 °C	1 h	0[a]

[a] Only Unknown was seen by ^1H NMR, but predominantly decomposition

Toluene at 70 °C resulted in the highest isolated yield, and a selection of Lewis acids were then examined. It has been observed that numerous metal trifluoromethanesulfonates (aluminum, magnesium, trimethylsilyl), magnesium bis(trifluoromethanesulfonyl)amide and Brønstead acids like trifluoroacetic acid and trifluoromethanesulfonic acid were capable catalysts for the Friedel-Crafts acylation of non-enolizable Meldrum's acids, so the formation of product hinged on their ability to promote the hydride shift.

Table 4.7: Screening of Lewis and Brønstead Acids and Catalyst Loading In Toluene at 70 °C for 24 h

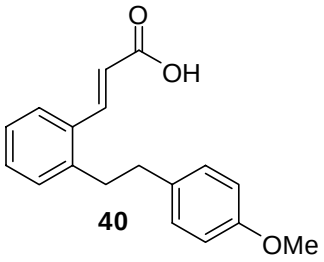
Entry	Lewis Acid	Yield of **39**
1	TMSOTf (20 mol %)	0[a]
2	$Al(OTf)_3$ (20 mol %)	0 (S.M.)
3	$AlCl_3$ (20 mol %)	0 (S.M.)
4	$PdCl_2$ (20 mol %)	0 (S.M.)
5	$Mg(NTf_2)_2$ (20 mol %)	0 (S.M.)
6	$Sc(NTf_2)_3$ (10 mol %)	17 %
7	TFA (20 mol %)	0 (S.M.)
8	TfOH (20 mol %)	19 %
9	$Sc(OTf)_3$ (20 mol %)	37 %
10	BF_3•OEt_2 (30 mol %)	45 %
11	BF_3•OEt_2 (100 mol %)	39 %

[a] Very clean partial conversion to unknown product, S.M. remains

Increasing the catalyst loading (Table 4.7, entry 9) gave a decrease in yield both for scandium triflate and BF_3•OEt_2 (entries 10, 11) which gave comparable yields of product. $Sc(NTf_2)_3$ has been seen in the literature to be an excellent Lewis acid for the Friedel-Crafts acylation with carboxylic acids, with higher yields reported compared to $Sc(OTf)_3$;[37] however its use here gave both lower yield and incomplete conversion. For protic acids, TfOH was capable of catalyzing this reaction, although in poor yield, while the weaker trifluoroacetic acid showed no catalysis. TMSOTf, a capable catalyst for the Friedel-Crafts acylation of quaternary Meldrum's acids, resulted in no product formation; rather it exclusively, yet incompletely formed the unknown product. Flash chromatography (5:1 Hex/EtOAc then CH_2Cl_2 flush) furnished the pure unknown **40**, and allowed for determination that it was indeed an α,β-unsaturated compound, but only the product of decomposition of the Meldrum's acid to the conjugated mono-acid. Although

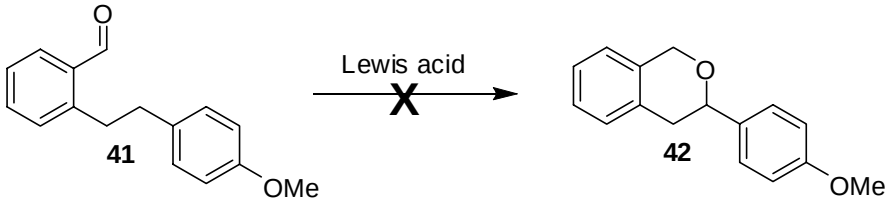
all reactions were setup in anhydrous conditions with dry solvents, it seemed that there was still sufficient moisture to decompose the starting material (Figure 4.4).

Figure 4.4: Decomposition Product



In order to come to a greater understanding of the initial reaction, and also because the alkylidene **38** was degrading to a highly detrimental degree, an investigation into the [1,5]-hydride shift onto the aldehydes was initiated (Table 4.8).

Table 4.8: Attempted [1,5]-Hydride Shift / Cyclization with Aldehydes

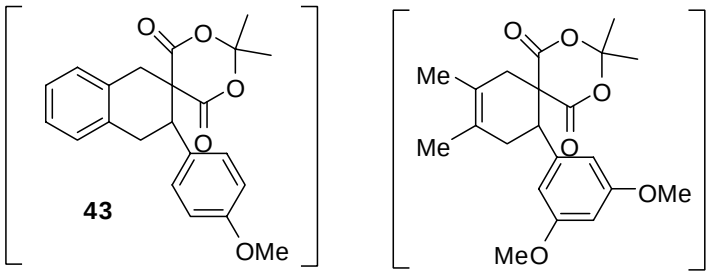


Entry	Lewis Acid	Solvent	Temperature	Time	Yield
1	$Yb(OTf)_3$ (10 mol %)	Toluene	70 °C	48 h	0 (S.M.)
2	$Mg(NTf_2)_2$ (10 mol %)	Toluene	70 °C	48 h	0 (S.M.)
3	BF_3•OEt_2 (10 mol %)	Toluene	70 °C	48 h	0 (S.M.)
4	$Sc(OTf)_3$ (10 mol %)	Toluene	70 °C	48 h	0 (S.M.)

However, in keeping with the DFT calculations and experimental evidence gathered for the aromatic-based system reported by Sames, there was no product **42** observed by ^{1}H NMR for the direct addition / cyclization reaction (Table 4.8).

At this juncture, with yields still only moderate at best, the reactivity of the system was reconsidered. In their account of the [1,5]-hydride shift / cyclization reaction, the Sames group reported high yields for aryl-based activating groups at lower temperatures. Despite the change from trisubstituted carbocation to secondary in this case, the high electrophilicity of the alkylidene Meldrum's acids should have allowed for the reaction to proceed to the intermediate. Furthermore, variations of these compounds have been prepared in the Fillion group by Diels-Alder cycloaddition, and were purified in high yields, so the intermediate (**43**) should not be decomposing in the workup (Figure 4.5).

Figure 4.5: Current and Previously Isolated *spiro*-Meldrum's Acid Synthetic Intermediates



Current Intermediate

Previously Isolated Intermediate

Previously, all determinations of reaction progress were done by TLC, as it was assumed that the hydride shift / cyclization product's Rf would be sufficiently different so as to be able to monitor in this way. However, in order to ascertain whether the intermediate could form at low temperatures, a series of reactions were set up between room temperature and 40 °C, and were monitored by ^{1}H NMR. Gratifyingly, it was found that

the intermediate **43** was being produced very cleanly at room temperature by $Sc(OTf)_3$ in toluene (Table 4.9), and that its Rf was almost identical to the starting material.

Table 4.9: [1,5]-Hydride Shift / Cyclization at Room Temperature

Entry	Lewis Acid	Solvent	Temperature	Time	% Conversion[a]
1	$Sc(OTf)_3$ (10 mol %)	Toluene	rt	18 h	64
2	$Sc(OTf)_3$ (40 mol %)	Toluene	rt	18 h	100
3	$Sc(OTf)_3$ (20 mol %)	Toluene	rt	12 h	100[b]
4	$Sc(OTf)_3$ (20 mol %)	$MeNO_2$	rt	48 h	9
5	$Sc(OTf)_3$ (20 mol %)	$(CH_2Cl)_2$	rt	48 h	48

[a] Determined by ^1H NMR. [b] 90 % isolated yield of **43**.

These intermediates can be purified by aqueous workup to give material which is pure enough for characterisation. Entry 3 was purified in this manner to afford a 90 % yield of the hydride shift/ cyclization product shown in Figure 4.5. Interestingly, reaction progress can be qualitatively gauged as the hydride shift / cyclization product is sufficiently insoluble in toluene that it crashes out of solution as the reaction proceeds. No attempts to purify by filtration were undertaken though. This product is also stable on silica gel and can be purified in this manner if the $Sc(OTf)_3$ is first removed by aqueous workup. This workup seems to be necessary for maintaining product integrity when purifying by flash chromatography, based on an observation from when 40 mol % catalyst was employed (Table 4.9, entry 2), as the crude mixture showed almost exclusively the cyclization product **43**, but a trace of Friedel-Crafts product **39** was also present. This material was loaded directly onto a column without workup and flashed to yield 33 % of the cyclization product **43**, as well as 32% of **39**. The cause of this acylation is currently unknown, but could be from the combination of silica and scandium triflate.

With this success, the Friedel-Crafts acylation was attempted, both from the purified intermediate **43** and as a one-pot process.

Table 4.10: Friedel-Crafts Acylation of Purified Intermediate and One-Pot Process

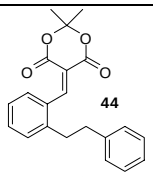
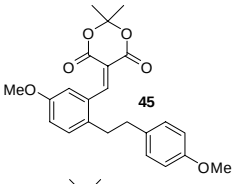
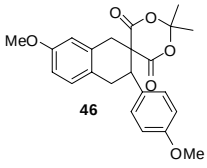
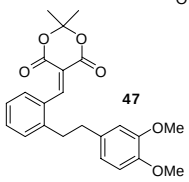
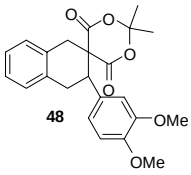
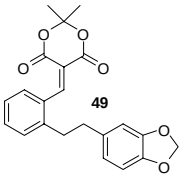
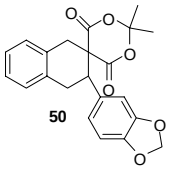
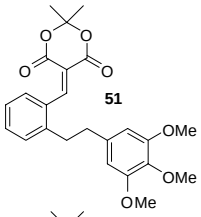
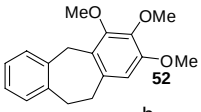
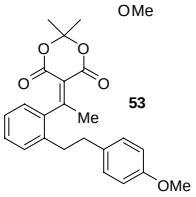
Entry	Lewis Acid	Solvent	Temperature	Time	Yield of **39**
1	$Sc(OTf)_3$ (20 mol %)	Toluene	rt to 70 °C	12 + 24 h	63 %
2	$Sc(OTf)_3$ (20 mol %)	Toluene	rt to 100 °C	12 + 1.5 h	75 %
3	$Sc(OTf)_3$ (20 mol %)	Toluene	rt to 100 °C	12 + 1.5 h	78[a] %
4	$Sc(OTf)_3$ (20 mol %)	Toluene	100 °C	1.5 h	60[b] %

[a] Aqueous workup then column. [b] **43** was used as starting material in place of the alkylidene **39**.

The one-pot [1,5]-hydride shift / cyclization and Friedel-Crafts acylation gave the tetracyclic product **39** in up to 78 % yield (entry 3), whereas the reaction starting from the intermediate **43** fared worse in this reaction (entry 4). One possibility for this is not having dried the intermediate as rigorously as the alkylidene starting material, leading to greater amounts of decomposition. As was previously observed for the intramolecular Friedel-Crafts acylation on non-enolizable substrates, the reaction runs quickly and in high yields at 100 °C, although in this case toluene proves to be a superior solvent whereas it was explicitly rejected as inferior in previous accounts of this transformation.

With these newly optimized conditions in hand, this protocol was then applied to a variety of substrates. First is the room temperature [1,5]-hydride shift / cyclization (Table 4.11), and second is the one-pot shift / cyclization / acylation reaction (Table 4.12).

Table 4.11: [1,5]-Hydride Shift / Cyclization on Alkylidene Meldrum's Acid Derivatives at Room Temperature in Toluene

Entry	Alkylidene Meldrum's Acid	Catalyst Loading	Time	Product (yield)
1	 **44**	20 mol %	24 h	(0 %)
2	 **45**	20 mol %	15 h	 **46** (99 %)
3	 **47**	40 mol %	36 h	[ **48**] (55 % conversion)[a]
4	 **49**	40 mol %	96 h	[ **50**] (47% conversion)[a]
5	 **51**	40 mol %	48 h	 **52** (13 %)[b]
6	 **53**	20 mol %	24 h	(0 %)

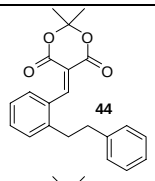
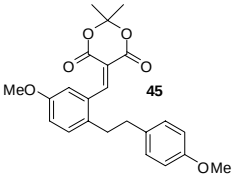
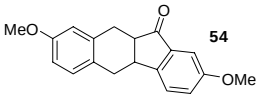
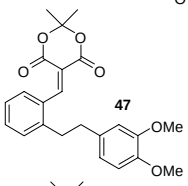
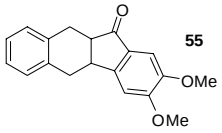
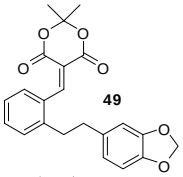
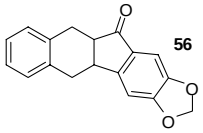
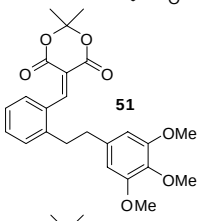
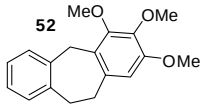
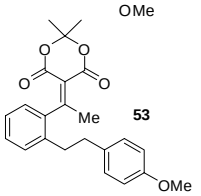
[a] not isolated. [b] Major product isolated from complex mixture.

The unsubstituted aromatic ring **44** (entry 1) did not show any reactivity under the standard conditions, with the starting material remaining after 24 h, which is in keeping with the method requiring an oxygen activating group on the aromatic ring. The 4,5'-

dimethoxy substrate **45** performed admirably in this reaction, producing a near quantitative yield of the cyclization product **46**. However, when substitution on the activating ring increased (entries 3 – 5) reaction completion decreased greatly, and multiple products could be obtained. Even with higher catalyst loading, the reaction stalled for the 3,4-dimethoxy (**47**) (entry 3) and 3,4-methylenedioxy (**49**) (entry 4) substrates, although the hydride shift / cyclization products **48** and **50** are observed in the crude reaction mixture by ^{1}H NMR. The highly electron rich trimethoxy substrate **51** (entry 5) produced a complex reaction mixture at room temperature, from which the tricyclic product **52** was isolated by flash chromatography, and only trace amounts of the cyclization intermediate were observed by ^{1}H NMR. Finally, the acetophenone-derived alkylidene **53** (entry 6) showed no reactivity at room temperature, which is in keeping with their less electrophilic nature.

The one-pot reaction was then tried using the optimized conditions on the variously substituted substrates. In the cases where the hydride shift / cyclization reaction stalled at room temperature, the reaction mixtures were heated to 100 °C until all the starting material and intermediate product had been consumed (Table 4.12).

Table 4.12: Tandem [1,5]-Hydride Shift / Cyclization and Friedel-Crafts Acylations with Alkylidene Meldrum's Acid Derivatives in Toluene

Entry	Alkylidene Meldrum's Acid	Catalyst Loading	Time (at rt + 100 °C)	Product (yield)
1	 **44**	20 mol %	24 + 24 h	(0 % - S.M.)
2	 **45**	20 mol %	15 + 2 h	 **54** (55 %)
3	 **47**	40 mol %	36 + 3 h	 **55** (52 %)
4	 **49**	40 mol %	36 + 3.5 h	 **56** (41 %)
5	 **51**	40 mol %	15 + 3 h	 **52** (21 %)[a]
6	 **53**	20 mol %	24 + 6 h	(0 % - decomposition)

[a] Major product isolated from complex mixture

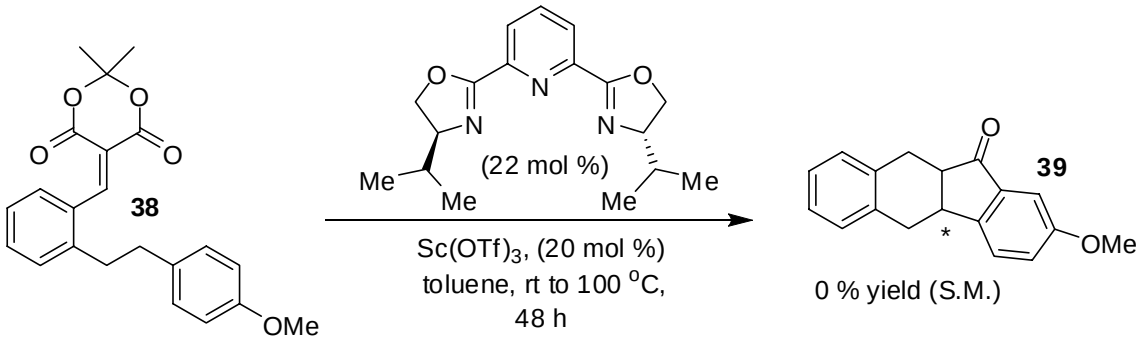
Again the unsubstituted aromatic ring **44** showed no reactivity with the system even after protracted heating with $Sc(OTf)_3$ (entry 1). Despite cleanly converting to the hydride shift

/ cyclization product, the 4,5'-dimethoxy substrate (**45**) gave only a modest yield of the tetracyclic product **54** after heating (entry 2). Repeating this experiment gave the same yield of product, so electron rich substituents on the non-activating ring could have a detrimental effect on the reaction. Entries 3 (**47**) and 4 (**48**) were expected to perform the Friedel-Crafts acylation to a greater degree than the monosubstituted substrate **38** because they bore electron donating groups *para*- to the nucleophilic carbon, however their yields were both much lower than with **38**. Their modest yields might then be attributed to the stalling of the hydride shift / cyclization step. The trimethoxy substrate **51** (entry 5) again proved to be difficult to employ cleanly, and the unusual tricycle **52** was found to be the major product of a complex mixture again. The acetophenone derivative **53** (entry 6) produced only a complex mixture of products, of which none were clearly major.

With only limited success in transferring the methodology to other substrates and limited time, preliminary investigations into the enantioselective variant of this reaction were undertaken. This tandem reaction generates three new chiral centres: a non-enolizable stereocentre at the benzylic carbon which transfers the hydride, another from the attack of the hydride onto the β-carbon of the alkylidene if it is disubstituted, and a third stereocentre α- to the carbonyl which will be *syn* to this first stereocentre. Reinhoudt has proposed that there is "self-reproduction" of chirality in the intramolecular [1,5]-hydride shift, however the compound employed in the preliminary investigation (like all that have been prepared thus far) bears no chiral centre. As well, using an aldehyde-derived substrate gives no stereocentre there. The intent of this investigation was therefore to see if the chiral Lewis acid could promote an enantioselective attack by an enolate onto the

carbon which transferred the hydride. In this tandem reaction, $Sc(OTf)_3$ has shown to be the optimal catalyst for the transformation, and the chiral Pybox complexes of scandium have been successfully employed as chiral Lewis acids in the literature.[38] A preliminary reaction was setup as illustrated in Scheme 4.28 using this catalyst system.

Scheme 4.28: Approach to the Enantioselective Tandem Hydride Shift / Cyclization and Friedel-Crafts Acylation Reaction

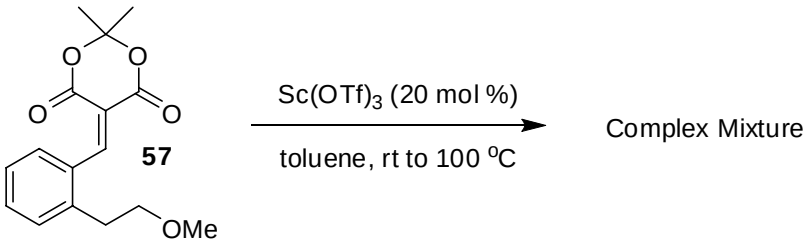


Unfortunately, even with extended reaction times at 100 °C, the starting material **38** was recovered untouched. Because the pybox ligands reduce the Lewis acidity of the metal centre, this could have prevented the scandium from adequately activating the carbonyl of the alkylidene Meldrum's acid. However, more investigation will be required before conclusions can be reached regarding this catalyst system.

In order to probe aspects of the hydride shift/ cyclization reaction on dialkyl ether substrates, 2-(Methoxyethyl)benzylidene Meldrum's acid (**57**) was prepared. This substrate was tested under the standard hydride shift conditions, as well as with heating,

and in all cases mixtures of products would form quickly with full consumption of the starting material (Scheme 4.29).

Scheme 4.29: [1.5]-Hydride Shift / Cyclization with Dialkyl Ether Substrate



These mixtures were difficult to identify from the ^{1}H NMR of the crude reaction mix, and attempts to separate by flash chromatography lead to decomposition of all compounds previously observed. By adding substituents onto the carbon transferring the hydride, this could help to stabilize the highly reactive carbocation formed, and could thus provide stable products for isolation.

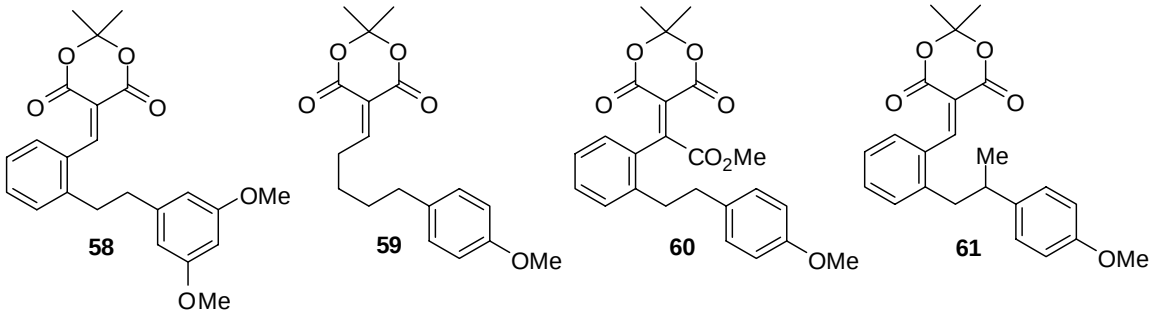
Conclusions

The functionalization of sp^3-hybridized carbons through a novel tandem [1,5]-hydride shift / cyclization and Friedel-Crafts acylation has been successfully performed in moderate to good yields on alkylidene Meldrum's acids bearing moderately electron-rich aromatic rings. The [1,5]-hydride shift / cyclization can proceed in excellent yields at lower temperatures and lower catalyst loading than known activated aromatic-based systems, although the reaction has been seen to stall even at higher catalyst loading for more electron-rich aromatic rings. Furthermore, the intramolecular Friedel-Crafts acylation of a *meta*-substituted aromatic ring with a non-enolizable Meldrum's acid has

been accomplished in moderate yield. Initial investigations using very electron-rich aromatic rings have resulted in the formation of complex mixtures, of which an unusual tricyclic system was isolated as the major product.

Structural variations have proven to be important to the success of the reaction, as the acetophenone-based system and the substrate activated by the dialkyl ether did not lead to formation of the intended products. Synthesis of substrates bearing other structural variations has been initiated (Figure 4.6), but were not ready in time for inclusion here.

Figure 4.6: Unfinished Substrates with Structural Variations



These include substrates with a tetrasubstituted alkylidene Meldrum's acid bearing an ester group (**60**), whose electron withdrawing properties helps to increase the electrophilicity of the β-position of the alkylidene. A potential reason for the acetophenone derivative's (**53**) unreactivity could be due to its lower electrophilicity, and this could help to promote the reaction. Furthermore, the synthesis of a substrate which is not derived from benzaldehyde, and thus does not have the bridging aryl group (**59**) would shed light on the effect that this aromatic ring has on the reaction. The 3,5-dimethoxy substrate (**58**) is ideally suited for the Friedel-Crafts reaction, but does not

bear a methoxy group which is capable of promoting the hydride shift, and this makes it too nucleophilic, and thus favours the Friedel-Crafts acylation. Finally, the substrate methylated on the carbon which loses the hydride, so as to have a tertiary *p*-OMe benzyl group (**61**), would likely have greater stabilization of the cation intermediate, and is anticipated to react well under the optimized conditions, generating an all-carbon quaternary benzylic stereocentre. Other possible variations include using electron-rich heteroaromatics such as thiophene and furan to promote the reaction, as it has previously been demonstrated that these types of aromatics can act as effective promoters.

Preliminary work on the enantioselective variation of this reaction have suggested that chiral complexes employed must be highly electrophilic, and further investigations into this reaction will serve to discover sufficiently activating groups and to establish if enantioselectivity can be obtained with this transformation.

Supporting Information

General Methods. All reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. CH_2Cl_2, THF, hexanes, $(CH_2Cl)_2$ and Et_2O were purified using an MBraun Solvent Purification System. Benzene was distilled from sodium-benzophenone ketyl under nitrogen. Et_3N was distilled from CaH_2 under nitrogen. Nitromethane and toluene were distilled from CaH_2 under nitrogen and degassed prior to use. Reagents were obtained from commercial sources and used without further purification unless otherwise specified. Trifluoromethanesulfonic acid was distilled and stored in a Schlenk flask prior to use. $BF_3{\cdot}OEt_2$ was distilled from CaH_2 and stored under nitrogen. 3,5-Dimethoxybenzaldehyde[39] and $Sc(NTf_2)_3$[40] were prepared according to literature procedures. ^1H NMR spectra were referenced to residual ^1H shift in $CDCl_3$ (7.26 ppm). $CDCl_3$ (77.0 ppm) was used as the internal reference for ^{13}C NMR. Reactions were monitored by thin-layer chromatography on commercially prepared plates with a particle size of 60 Å. Developed plates were viewed by UV lamp (254 nm), and with ceric ammonium molybdate or iodine stain. Flash chromatography was performed using 230-400 mesh silica gel. Melting points are uncorrected. High resolution mass spectra were run by Dr. R. Smith at the University of Waterloo with a source temperature of 200 °C, mass resolution of 9000 and electron energy of 70 eV.

General Procedure A – Preparation of Aryl Alkynes by Corey-Fuchs homologation: 4-Ethynyl-1-methoxybenzene[41], 4-ethynyl-1,2-dimethoxybenzene[42], 5-ethynyl-1,2,3-trimethoxybenzene[43], 5-ethynyl-1,3-dimethoxybenzene[44] and 5-ethynylbenzo-1,3-dioxolane[45] were prepared from the corresponding aldehydes according to the procedure

of Pelphrey et al. Spectral data matched the corresponding literature values. In a typical reaction, PPh_3 (3.0 eq) was added to a solution of CBr_4 (1.5 eq) in CH_2Cl_2 at 0 °C, and subsequently stirred for 15 minutes. A solution of the aldehyde in CH_2Cl_2 was added dropwise over 3 minutes and the mixture stirred an additional 30 minutes. The solvent was then removed under reduced pressure to typically produce a thick orange paste which was subsequently filtered through a plug of silica and washed with 600 mL Hex/EtOAc (5:1). The resulting solvent was removed under reduced pressure to yield the crude dibromo-olefin. This was then dissolved in dry THF and cooled to -78 °C under nitrogen. n-BuLi (4.0 eq) was added dropwise over 10 minutes and the solution was stirred at -78 °C for 30 minutes, followed by the addition of 15 mL saturated NH_4Cl in H_2O, and the solution warmed to room temperature. The layers were separated and the aqueous phase was extracted with ether. The combined organics were washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography.

General Procedure B – Sonogashira Coupling of Aryl Alkynes with Aryl Bromides:

The diarylalkynes were prepared from the arylalkynes of procedure A and substituted aryl bromides according to a modified procedure of Huang et al.[46] To a solution of the appropriate aryl alkyne (1.1 eq) and 2-bromobenzaldehyde or 2-bromoacetophenone (1.0 eq) in Et_3N were added $PdCl_2(PPh_3)_2$ (0.02 eq) and CuI (0.01 eq) under nitrogen and the solution was heated in an oil bath at 50 °C until no starting material was visible by TLC (typically 3 – 5 hours). The solvent was removed under vacuum and the ammonium salt was removed by filtration through silica with EtOAc. Removal of the solvent gave an oil which was the purified by flash chromatography.

General Procedure C – Hydrogenation of Diarylalkyne with Pd/C: Hydrogenation of the diarylalkynes to the corresponding 1,2-diarylethane substrates was performed by the procedure of Ezoe et al.[47] The diarylalkyne was dissolved in EtOAc and Pd (10 wt % on activated Carbon) equal to 10 % weight of the alkyne (1% Pd) was added with vigorous stirring. The air in the flask was twice removed under water aspirator vacuum and refilled with nitrogen, then removed once more and refilled with H_2. The mixture was stirred for 18 h under 1 ATM H_2, and then filtered through silica, washing with EtOAc. The solvent was removed under vacuum to provide the corresponding diarylethanes which were generally pure enough for characterization without further purification. In certain cases, reduction of the carbonyl also occurred, necessitating separation by flash chromatography and subsequent oxidation.

General Procedure D – Oxidation of Benzyl alcohols to Benzaldehydes or Acetophenones with Pyridinium Chlorochromate: Oxidation of the benzyl alcohols to the corresponding benzaldehydes or acetophenone with Pyridinium chlorochromate (PCC) proceeded via the procedure of Corey and Suggs.[48] To a solution of PCC in dry CH_2Cl_2 was added the alcohol in CH_2Cl_2 with stirring. The orange solution quickly darkened, and was allowed to stir at rt for 18 h at which point the solvent was removed under vacuum and the black gum was extracted three times with anhydrous ether. The combined organics were filtered through a short pad of celite or silica with ether. After removing the solvent under vacuum, the resulting carbonyl compound was generally pure enough for characterization without further purification.

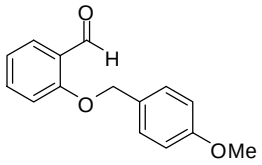
General Procedure E – Preparation of Alkylidene Meldrum's Acids from Benzaldehydes: Alkylidene Meldrum's Acids were prepared by Knoevenagel condensation of Meldrum's acid with benzaldehydes according to Fillion and coworkers' method. In a typical reaction, pyrrolidine (0.1 eq) and acetic acid (0.1 eq) are combined in dry benzene and added to a solution of the benzaldehyde (1.0 eq) and Meldrum's acid (1.1 eq) in benzene. This solution was capped and allowed to stir at room temperature for 24 h, at which point the solvent was removed under vacuum and the product was either recrystallized from methanol or purified by flash chromatography.

General Procedure F - [1,5]-Hydride Shift / Cyclization of Alkylidene Meldrum's Acids at Room Temperature: In the glove box, to a dry flask was added the alkylidene Meldrum's acid (generally 0.25 mmol), $Sc(OTf)_3$ and toluene (0.1 M), and the flask was sealed and allowed to stir at room temperature until no more starting material was observed. Reaction progress was measured by ^1H NMR of aliquots taken by syringe and dried by rotary evaporation and high vacuum. When the reaction has gone to completion the reaction mixture is dissolved in CH_2Cl_2 and washed with water (2x) and brine (1x), then dried with $MgSO_4$, filtered and concentrated by rotary evaporation and high vacuum to yield the product generally in high purity, or flash chromatography can be subsequently employed if mixtures are obtained.

General Procedure G - Tandem Lewis Acid-Catalyzed [1,5]-Hydride Shift / Cyclization and Friedel-Crafts Acylation with Alkylidene Meldrum's Acids: In the glove box, to a dry flask was added the alkylidene Meldrum's acid (generally 0.25

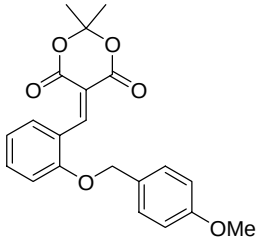
mmol), $Sc(OTf)_3$ and toluene (0.1 M) and the flask was sealed and allowed to stir at room temperature until no more starting material was observed by ^1H NMR. The flask was then placed in a 100 °C oil bath and stirred until full conversion had occurred. The reaction mixture was poured into CH_2Cl_2 and washed with water (2x) and brine (1x), then dried with $MgSO_4$, filtered and concentrated by rotary evaporation. The resulting crude mixture was purified by flash chromatography (column loaded with a small volume of acetone).

2-(4-Methoxybenzyloxy)benzaldehyde (62):[49]



Prepared according to the literature method to obtain a white powdery crystal in 98 % yield.

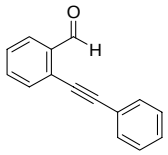
5-(2-(4-Methoxybenzyloxy)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (35):



Prepared from 2-(4-methoxybenzyloxy)benzaldeyde (**62**) using General Procedure E in 73 % yield as pale yellow crystals after recrystallization from MeOH. M.p. 116-118 °C (MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 8.4, 2H), 7.02 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.07 (s, 2H),

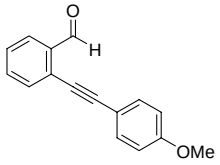
3.82 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 159.7, 158.5, 152.9, 134.5, 132.6, 129.8, 127.9, 121.9, 120.5, 115.7, 114.0, 112.4, 104.4, 70.6, 55.3, 27.2; HRMS(EI) *m/z* calcd for $C_{18}H_{14}O_5$ (M-C_3H_6O) 310.0840. Found 310.0849.

2-(2-Phenylethynyl)benzaldehyde (63):[50]



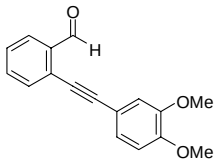
Prepared from phenylacetylene and 2-bromobenzaldehyde in 97% yield using Procedure B in 2 h. Purified by flash chromatography (20:1 Hex/EtOAc, Rf = 0.29) to provide a clear oil.

2-(4-Methoxyphenylethynyl)benzaldehyde (64):



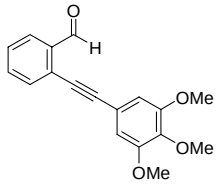
Prepared from 4-ethynyl-1-methoxybenzene and 2-bromobenzaldehyde in 80% yield using Procedure B in 5 h. Purified by flash chromatography (9:1 Hex/EtOAc, Rf = 0.35) to provide a yellow oil.

2-(3,4-Dimethoxyphenylethynyl)benzaldehyde (65):



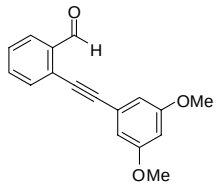
Prepared from 4-ethynyl-1,2-dimethoxybenzene and 2-bromobenzaldehyde in 83% yield using Procedure B in 5h. Purified by flash chromatography (5:1 Hex/EtOAc, Rf = 0.23) to give an orange solid M.p. 93-94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.65 (s, 1H), 7.94 (d, *J* = 9 Hz, 1H), 7.59 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 3.91 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.8, 150.1, 148.7, 135.6, 133.8, 133.0, 128.3, 127.2, 125.2, 114.4, 114.1, 111.0, 96.6, 83.6, 55.9, 55.9; HRMS(EI) *m/z* calcd for $C_{17}H_{14}O_3$ (M^+): 266.0943. Found .

2-(3,4,5-Trimethoxyphenylethynyl)benzaldehyde (66):



Prepared from 5-ethynyl-1,2,3-trimethoxybenzene and 2-bromobenzaldehyde in 77% yield using Procedure B in 6h. Purified by flash chromatography (9:1 Hex/EtOAc, Rf = 0.26) to give a yellow oil.

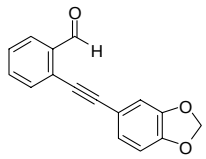
2-(3,5-Dimethoxyphenylethynyl)benzaldehyde (67):



Prepared from 5-ethynyl-1,3-dimethoxybenzene and 2-bromobenzaldehyde in 73% yield using Procedure B in 15h. Purified by flash chromatography (5:1 Hex/EtOAc, Rf = 0.39) to give a dark brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.65 (s, 1H), 7.96 (d, *J* = 9 Hz,

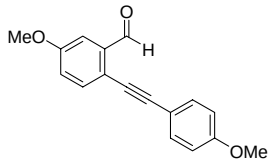
1H), 7.60 (m, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 6.72 (s, 2H), 6.51 (s, 1H), 3.82 (s, 6H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ ( ); HRMS(EI) *m/z* calcd for $C_{17}H_{14}O_3$ (M^+): 266.0943. Found .

2-(Benzo[1,3]dioxol-5-ylethynyl)benzaldehyde (68):



Prepared from 5-ethynylbenzo-1,3-dioxolane and 2-bromobenzaldehyde in 59% yield using Procedure B in 15h. Purified by flash chromatography (9:1 Hex/EtOAc, Rf = 0.44) to give a beige powder. M.p. 90-91 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.62 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.59 (m, 2H), 7.44 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.00 (s, 2H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.7, 148.6, 147.6, 135.7, 133.8, 133.1, 128.4, 127.3, 127.0, 126.6, 115.5, 111.5, 108.7, 101.5, 96.4, 83.5; HRMS(EI) *m/z* calcd for $C_{16}H_{10}O_3$ (M^+): 250.0630. Found .

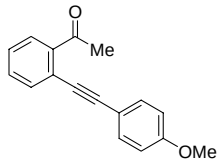
5-Methoxy-2-(2-(4-methoxyphenyl)ethynyl)benzaldehyde (69):



Prepared from 4-ethynyl-1-methoxybenzene and 2-bromo-5-methoxybenzaldehyde[51] in 65% yield using Procedure B in 4 h. Purified by flash chromatography (5:1 Hex/EtOAc, Rf = 0.25) to provide a brown crystal. M.p. 97-99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.61 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 4.5, 2.7 Hz, 2H), 7.42 (d, *J* = 2.7 Hz,

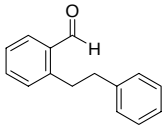
1H), 7.13 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.90 (dd, *J* = 6.9, 1.8 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.8, 160.0, 159.5, 137.0, 134.4, 133.0, 121.8, 120.1, 114.7, 114.1, 109.7, 95.0, 83.6, 55.6, 55.3; HRMS(EI) *m/z* calcd for $C_{17}H_{14}O_3$ (M^+): 266.0943. Found .

1-(2-(2-(4-Methoxyphenyl)ethynyl)phenyl)ethanone (70):[52]



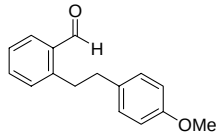
Prepared from 4-ethynyl-1-methoxybenzene and 2'-bromoacetophenone in 81% yield using Procedure B in 5 h. Purified by flash chromatography (9:1 Hex/EtOAc, Rf = 0.29) to provide a yellow oil.

2-Phenethylbenzaldehyde (71):[53]



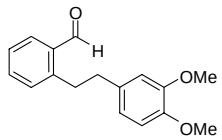
Prepared from 2-(2-phenylethynyl)benzaldehyde (**63**) in 98% yield using Procedure C to give a red crystalline product.

2-(4-Methoxyphenethyl)benzaldehyde (41):[54]



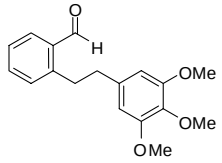
Prepared from 2-(4-methoxyphenylethynyl)benzaldehyde (**64**) in 99% yield using Procedure C as a pale yellow oil.

2-(3,4-Dimethoxyphenethyl)benzaldehyde (72):



Prepared from 2-(3,4-dimethoxyphenylethynyl)benzaldehyde (**65**) in 51% yield using Procedure C after flash chromatography (3:1 Hex/EtOAc, Rf = 0.39) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.21 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.39 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 6.74 (m, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.31 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.4, 1448.7, 147.4, 144.3, 133.8, 133.7, 132.5, 131.3, 126.6, 120.4, 111.9, 111.2, 55.9, 55.8, 37.9, 35.1; HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256. Found .

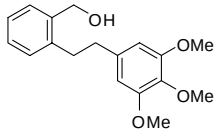
2-(3,4,5-Trimethoxyphenethyl)benzaldehyde (73):



Prepared from (2-(3,4,5-trimethoxyphenethyl)phenyl)methanol (**74**) in 40% yield over two steps from 2-(3,4,5-trimethoxyphenylethynyl)benzaldehyde (**66**) using Procedures C and D to obtain a white crystalline product. M.p. 86-87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.19 (s, 1H), 7.84 (dd, *J* = 7.5, 1.25 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.41 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.39 (s, 2H), 3.83 (s, 3H), 3.82 (s, 6H), 3.32

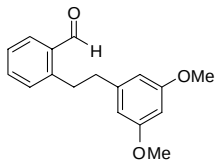
(t, J = 8.1 Hz, 2H), 2.84 (t, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.5, 153.1, 144.2, 136.9, 133.9. 133.7, 132.8, 131.4, 126.7, 105.5, 60.9, 56.1, 38.6, 35.1; HRMS(EI) *m/z* calcd for $C_{18}H_{20}O_4$ (M^+): 300.1362. Found .

(2-(3,4,5-Trimethoxyphenethyl)phenyl)methanol (74):



Overreduction of 2-(3,4,5-trimethoxyphenylethynyl)benzaldehyde (**66**) gave this product in 40% yield over 2 steps to the aldehyde using Procedure C, yielding a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, J = 7.5 Hz, 1H), 7.29 – 7.19 (m, 4H), 6.34 (s, 2H), 4.64 (s, 2H), 3.84 (s, 3H), 3.82 (s, 6H), 2.99 (dd, J = 10.5, 7.2 Hz, 2H), 2.86 (t, J = 10.5, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 139.8, 138.5, 137.3, 136.3, 129.6, 128.4, 128.1, 126.4, 105.5, 63.2, 60.9, 56.1, 38.1, 34.3; HRMS(EI) *m/z* calcd for $C_{18}H_{22}O_4$ (M^+): 302.1518. Found .

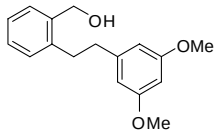
2-(3,5-Dimethoxyphenethyl)benzaldehyde (75):



Prepared from 2-(3,5-dimethoxyphenylethynyl)benzaldehyde (**67**) in 36% yield using Procedure C after flash chromatography (5:1 Hex/EtOAc, Rf = 0.42) as a yellow oil, along with 49% of the corresponding alcohol (Rf = 0.11). Also prepared from (2-(3,5-dimethoxyphenethyl)phenyl)methanol (**76**) in 56% yield using Procedure D. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.21 (s, 1H), 7.83 (dd, J = 7.5, 1.2 Hz, 1H), 7.49 (dt, J = 7.5,

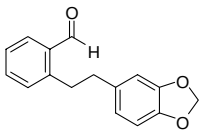
1.2 Hz, 1H), 7.39 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.24 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.35 (d, *J* = 2.1 Hz, 2H), 6.32 (t, *J* = 2.1 Hz, 1H), 3.76 (s, 6H), 3.32 (dd, *J* = 9.9, 7.8 Hz, 2H), 2.85 (dd, *J* = 9.9, 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.3, 160.8, 144.2, 143.5, 133.8, 133.8, 132.4, 131.2, 126.7, 106.6, 98.2, 55.3, 38.5, 34.7; HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256. Found .

(2-(3,5-Dimethoxyphenethyl)phenyl)methanol (76):



Prepared by overreduction of 2-(3,5-dimethoxyphenylethynyl)benzaldehyde (**67**) in 49% yield using Procedure C after flash chromatography (5:1 Hex/EtOAc, Rf = 0.11) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 1H), 7.24 (m, 3H), 6.32 (s, 3H), 4.67 (s, 2H), 3.76 (s, 6H), 3.00 (dd, *J* = 8.7, 5.4 Hz, 2H), 2.85 (dd, *J* = 8.7, 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7 143.9, 139.7, 138.3, 129.4, 128.2, 127.9, 126.3, 106.4, 97.9, 63.0, 55.2, 37.9, 34.0; HRMS(EI) *m/z* calcd for $C_{17}H_{20}O_3$ (M^+): 272.1412. Found .

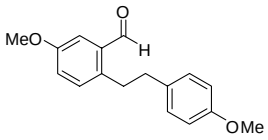
2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)benzaldehyde (77):



Prepared from 2-(benzo[1,3]dioxol-5-ylethynyl)benzaldehyde (**68**) in 98% yield using Procedure C as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.19 (s, 1H), 7.83 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 2H), 6.61(d, *J* = 7.8 Hz, 1H), 5.92 (s, 2H), 3.28 (dd, *J* = 9.6.

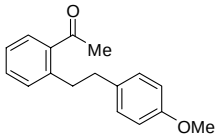
7.5 Hz, 2H), 2.82 (dd, *J* = 9.6. 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.2, 147.3, 145.6, 143.9, 134.8, 133.5, 132.3, 131.0, 126.4, 121.1, 108.8, 107.9, 100.5, 37.6, 34.9; HRMS(EI) *m/z* calcd for $C_{16}H_{14}O_3$ (M^+): 254.0943. Found .

2-(4-Methoxyphenethyl)-5-methoxybenzaldehyde (78):



Prepared from 5-methoxy-2-(2-(4-methoxyphenyl)ethynyl)benzaldehyde (**69**) in 99% yield using Procedure C as a yellow oil. . ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.15 (s, 1H), 7.34 (d, *J* = 2.7 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 2.7 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 3.22 (t, *J* = 7.5 Hz, 2H), 2.83 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.5, 158.2, 158.0, 136.9, 134.5, 133.1, 132.4, 129.5, 129.2, 120.9, 114.0, 113.8, 113.7, 55.5, 55.2, 37.9, 33.8; HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256. Found .

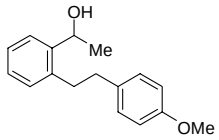
1-(2-(4-Methoxyphenethyl)phenyl)ethanone (79):



Prepared from 1-(2-(2-(4-methoxyphenyl)ethynyl)phenyl)ethanone (**70**) in 59% yield using Procedure C after flash chromatography (9:1 Hex/EtOAc, Rf = 0.32) as a colourless crystal, along with 43% of the corresponding alcohol. Also prepared from (1-(2-(4-methoxyphenethyl)phenyl)ethanol (**80**) in 80% yield using Procedure D. M.p. 55-56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H),

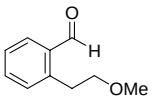
7.29 – 7.20 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.0, 157.8, 142.0, 137.8, 134.0, 131.5, 131.4, 129.5, 129.2, 125.9, 113.7, 55.2, 37.3, 36.6, 29.7; HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_2$ (M^+): 254.1307. Found .

1-(2-(4-Methoxyphenethyl)phenyl)ethanol (80):



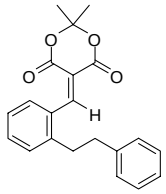
Prepared by overreduction of 1-(2-(2-(4-methoxyphenyl)ethynyl)phenyl)ethanone (**70**) in 43% yield using Procedure C after flash chromatography (9:1 Hex/EtOAc, Rf = 0.12) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, *J* = 6.9 Hz, 1H), 7.23 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.07 (q, *J* = 6.3 Hz, 1 H), 3.79 (s, 3H), 2.95 (m, 2H), 2.85 (m, 2H), 1.44 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 143.5, 138.0, 133.6, 129.4, 127.4, 126.6, 125.1, 113.8, 66.2, 55.2, 37.2, 34.4, 24.6; HRMS(EI) *m/z* calcd for $C_{17}H_{20}O_2$ (M^+): 256.1463. Found 256.1471.

2-(2-Methoxyethyl)benzaldehyde (81):



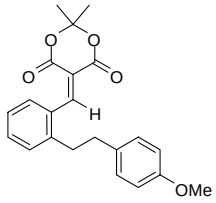
Prepared from isochromanone[55] by the literature method[56] to provide a pale yellow oil.

5-(2-Phenethylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (44):



Prepared from 2-phenethylbenzaldehyde (**71**) in 37% yield using Procedure E as a yellow crystalline solid after flash chromatography (2:1 Hex/EtOAc, Rf = 0.34). M.p. 48-50 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.61 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.27 – 7.22 (m, 4H), 7.18 (m, 1H), 7.10 (d, *J* = 7.0 Hz, 2H), 3.03 (t, *J* = 7.0 Hz, 2H), 2.87 (t, *J* = 7.0 Hz, 2H), 1.81 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.5, 159.2, 157.2, 142.7, 140.2, 132.3, 131.2, 130.3, 129.9, 128.6, 128.5, 128.4, 128.3, 126.1, 126.0, 125.8, 115.8, 104.5, 38.0, 36.4, 27.7; HRMS(EI) *m/z* calcd for $C_{18}H_{14}O_3$ (M^+): 278.0940. Found 278.0941.

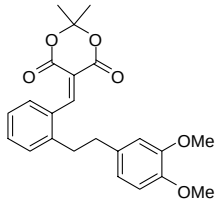
5-(2-(4-Methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (38):



Prepared from 2-(4-methoxyphenethyl)benzaldehyde (**41**) in 83% yield using Procedure E as a yellow powdery solid after recrystallization from methanol. M.p. 86-88 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.27 – 7.23 (m, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 1.81 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.6, 159.2, 158.0, 157.4, 143.0, 132.4, 131.3, 130.3, 130.0, 129.7, 129.2,

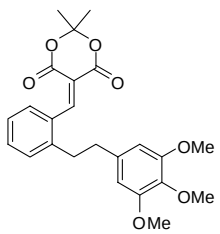
125.9, 115.2, 114.5, 104.5, 55.2, 37.2, 36.8, 27.8; HRMS(EI) *m/z* calcd for $C_{22}H_{22}O_5$ (M^+): 366.1467. Found .

5-(2-(3,4-Dimethoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (47):



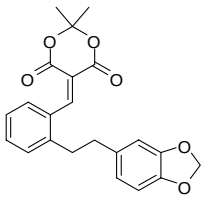
Prepared from 2-(3,4-dimethoxyphenethyl)benzaldehyde (**72**) according to General Procedure E in 55 % yield as a yellow oil after flash chromatography (2:1 Hex/EtOAC, Rf = 0.24). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.25 (m, 2H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.60 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.50 (d, *J* = 1.8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 1.81 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 159.2, 157.3, 148.7, 147.3, 142.9, 132.9, 132.3, 131.3, 130.3, 130.1, 125.9, 120.5, 115.2, 111.9, 111.3, 104.5, 55.8, 55.6, 37.8, 36.9, 22.8; HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_6$ (M^+) 396.1573. Found 396.1570.

2,2-Dimethyl-5-(2-(3,4,5-trimethoxyphenethyl)benzylidene)-1,3-dioxane-4,6-dione (51):



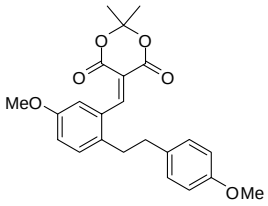
Prepared from 2-(3,4,5-trimethoxyphenethyl)benzaldehyde (**73**) using General Procedure E in 73 % yield as yellow crystals after recrystallization from MeOH. M.p. 130-132 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.24 (m, 2H), 6.24 (s, 2H), 3.79 (s, 3H), 3.77 (s, 6H), 3.04 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 1.81 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 159.3, 157.1, 153.0, 142.4, 136.1, 135.9, 132.3, 131.2, 130.1, 126.0, 115.5, 105.4, 104.6, 60.7, 55.9, 38.7, 36.7, 27.7; HRMS(EI) *m/z* calcd for $C_{24}H_{26}O_7$ (M^+) 426.1679. Found 426.1671.

5-(2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (49):



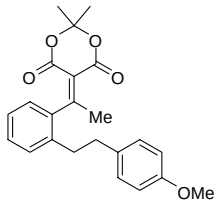
Prepared from 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)benzaldehyde (**77**) according to General Procedure E to produce a yellow crystalline solid in 82 % yield after recrystallization from MeOH. M.p. 87-89 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 8.4 Hz, 1H), 7.25 (m, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 1.8, Hz, 1H), 6.49 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.91 (s, 2H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 1.81 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 159.2, 159.3, 147.7, 146.0, 142.7, 134.2, 132.4, 131.3, 130.3, 129.9, 125.9, 121.7, 115.3, 109.1, 108.3, 104.5, 100.9, 37.7, 36.7, 27.8; HRMS(EI) *m/z* calcd for $C_{22}H_{20}O_6$ (M^+) 380.1260. Found 380.1258.

5-(5-Methoxy-2-(4-methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (45):



Prepared from 2-(4-methoxyphenethyl)-5-methoxybenzaldehyde (**78**) using General Procedure E to produce a bright yellow crystalline solid in 76 % yield after recrystallization from MeOH. M.p. 103-105 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.27 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.98 (m, 3H), 6.75 (d, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 1.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 159.1, 157.9, 157.2, 157.1, 135.7, 132.5, 131.8, 131.0, 129.7, 119.0, 115.1, 115.0, 114.0, 104.4, 55.4, 55.1, 37.5, 36.0, 27.7; HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_6$ (M^+) 396.1573. Found 396.1565.

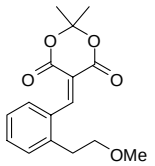
5-(1-(2-(4-Methoxyphenethyl)phenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (53):



Prepared by the Knoevenagel condensation of Meldrum's acid with 1-(2-(4-methoxyphenethyl)phenyl)ethanone (**79**) using Brown and coworkers' method.[57] A solution of $TiCl_4$ (2.1 equiv) in CH_2Cl_2 (5 M) was added dropwise under nitrogen to dry THF (0.3 M)at 0 °C to produce a yellow suspension. A solution containing the ketone

and Meldrum's acid in THF (1 M) was added dropwise via a syringe to the reaction flask. The flask containing the Meldrum's acid and ketone was rinsed with THF (2x) and added to the reaction mixture. After stirring 5 minutes, pyridine (5.0 equiv) was added dropwise over 30 seconds. The reaction mixture was allowed to warm to room temperature and stirred for 18 h, at which point no further conversion was observed. The reaction was quenched by the addition of water and diluted with EtOAc. After the solids had dissolved the layers were partitions, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with $NaHCO_3$ saturated solution (2x), brine (1x), dried over $MgSO_4$, filtered and concentrated. Purification by recrystallization gave 26 % yield as a pale yellow crystal, as well as recovery of 70 % unreacted starting material. M.p. 107-108 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 3H), 7.06 (dd, *J* = 6.6, 1.8 Hz, 2H), 6.84 – 6.80 (m, 3H), 3.78 (s, 3H), 2.93 – 2.70 (m, 4H), 2.59 (s, 3H), 1.72 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 161.1, 159.3, 158.0, 141.8, 136.4, 133.4, 129.3, 129.1, 128.3, 126.1, 123.8, 117.7, 113.8, 55.3, 35.6, 35.3, 27.6, 27.3, 27.0; HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_5$ (M^+) 380.1624. Found 380.1631.

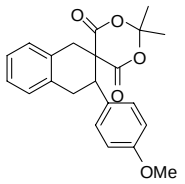
5-(2-(2-Methoxyethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (57):



Prepared from 2-(2-methoxyethyl)benzaldehyde (**81**) using General Procedure E in 74 % yield as an off-white crystal after recrystallization from MeOH. M.p. 133-134 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.63 (d, *J* = 7.5 Hz, 1H) 7.44 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.25 (m, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.29 (s, 3H), 2.98 (t, *J* = 6.6

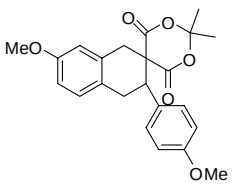
Hz, 2H), 1.83 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 159.3, 158.0, 140.2, 132.2, 131.9, 130.2, 130.1, 126.2, 116.6, 104.7, 73.1, 58.8, 34.4, 27.8; HRMS(EI) *m/z* calcd for $C_{16}H_{18}O_5$ (M^+) 290.1154. Found 290.1145.

3'-(4-Methoxyphenyl)-2,2-dimethyl-3',4'-dihydro-1'H-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (43):



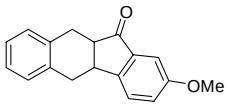
Prepared from 5-(2-(4-methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**38**) using General Procedure F in 90 % yield as an off-white powdery solid after aqueous workup. M.p. 180-182 °C**;** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (m, 4H), 7.10 (d, *J* = 7.3 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.77 – 3.66 (m, 3H), 3.23 (d, *J* = 17.1 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 1.64 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 167.0, 159.4, 135.5, 131.2, 130.8, 128.4, 127.9, 126.3, 126.2 ,114.1, 105.1, 55.3, 54.0, 46.8, 37.9, 32.7, 30.1, 27.8; HRMS(EI) *m/z* calcd for $C_{22}H_{22}O_5$ (M^+) 366.1467. Found 366.1473

7'-Methoxy-3'-(4-methoxyphenyl)-2,2-dimethyl-3',4'-dihydro-1'H-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (46):



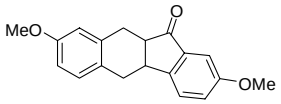
Prepared from 5-(5-methoxy-2-(4-methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**45**) using General Procedure F in 99 % yield as an off-white powdery solid after aqueous workup. M.p. 183-185 °C**;** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.76 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.64 (s, 1 H), 3.79 (s, 6H), 3.75 – 3.61 (m, 3H), 3.19 (d, *J* = 17.4 Hz, 1H), 2.97 (dd, *J* = 15.3, 4.5 Hz, 1H), 1.63 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 167.0, 159.4, 157.9, 132.2, 130.8, 129.8, 129.3, 128.2, 127.6, 114.1, 112.7, 105.1, 55.3, 55.2, 54.0, 47.2, 38.1, 31.9, 30.2, 27.7; HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_6$ (M^+) 396.1573. Found 396.1565.

2-Methoxy-10,10a-dihydro-4bH-benzo[b]fluoren-11(5H)-one (39):



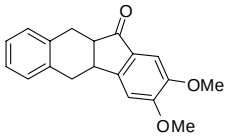
Prepared from 5-(2-(4-methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**38**) using General Procedure G in 78 % yield as an off-white powdery solid after flash chromatography (5:1 Hex/EtOAc, Rf = 0.36). M.p. 109-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 1H), 7.21 – 7.01 (m, 6H), 3.78 (s, 3H), 3.74 (q, J = 4.2 Hz, 1H), 3.20 (dd, *J* = 14.4, 6.3 Hz, 1H), 3.11 – 2.95 (m, 3H), 2.77 (dd, *J* = 14.4, 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 159.5, 150.7, 138.5, 136.9, 136.8, 127.5, 127.7, 126.6, 126.5, 126.1, 124.6, 104.5, 55.5, 47.8, 38.3, 34.6, 30.6; HRMS(EI) *m/z* calcd for $C_{18}H_{16}O_2$ (M^+) 264.1150. Found .

2,8-Dimethoxy-10,10a-dihydro-4bH-benzo[b]fluoren-11(5H)-one (54):



Prepared from 5-(5-methoxy-2-(4-methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**45**) using General Procedure G in 55 % yield as an off-white powdery solid after flash chromatography (5:1 Hex/EtOAc, Rf = 0.20). M.p. 113-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.73 (q, *J* = 4.2 Hz, 1H), 3.14 (dd, *J* = 14.6, 6.2 Hz, 1H), 3.11 – 2.94 (m, 3H), 2.72 (dd, *J* = 14.6, 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 159.4, 158.3, 150.8, 138.4, 137.9, 128.8, 128.2, 126.1, 124.6, 113.1, 111.7, 104.4, 55.4, 55.1, 47.6, 38.4, 33.6, 30.9; HRMS(EI) *m/z* calcd for $C_{19}H_{18}O_3$ (M^+) 294.1256. Found .

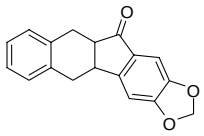
2,3-Dimethoxy-10,10a-dihydro-4bH-benzo[b]fluoren-11(5H)-one (55):



Prepared from 5-(2-(3,4-dimethoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**47**) using General Procedure G in 52 % yield as a colourless oil after flash chromatography (5:1 Hex/EtOAc, Rf = 0.22). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.7 Hz, 1H), 7.30 – 7.08 (m, 3H), 6.76 (s, 1H) 6.59 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75 (q, *J* = 4.2 Hz, 1H), 3.13 (dd, *J* = 14.6, 6.5 Hz, 1H), 3.09 – 2.95 (m, 3H), 2.74 (dd, *J* = 14.6, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 158.8, 157.2, 150.0, 138.5,

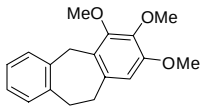
136.9, 128.8, 128.4, 126.3, 124.4, 104.4, 55.6, 55.3, 47.9, 38.6, 34.3, 30.7; HRMS(EI) *m/z* calcd for $C_{19}H_{18}O_3$ (M^+) 294.1256. Found .

2,3-Methylenedioxy-10,10a-dihydro-4bH-benzo[b]fluoren-11(5H)-one (56):



Prepared from 5-(2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**49**) using General Procedure G in 41 % yield as an brown oil after flash chromatography (3:1 Hex/EtOAc, Rf = 0.42). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 – 6.98 (m, 4H), 6.96 (s, 1H), 6.92 (s, 1H), 6.04 (s, 1H), 6.03 (s, 1H), 3.66 (q, J = 6.3 Hz, 1H), 3.16 (dd, *J* = 14.4, 6.2 Hz, 1H), 3.08 – 2.94 (m, 3H), 2.76 (dd, *J* = 14.4, 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 155.3, 154.5, 148.4, 136.8, 136.6, 131.9, 127.5, 127.4, 126.7, 126.5, 104.4, 102.2, 102.0, 47.5, 38.7, 34.4, 30.6; HRMS(EI) *m/z* calcd for $C_{18}H_{14}O_3$ (M^+) 278.0943. Found .

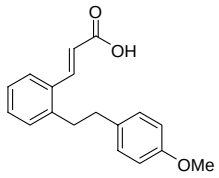
1,2,3-Trimethoxy-7,8-benzo-6,9-dihydro-5H-benzo[7]annulene (52):



Obtained as the major product of a complex mixture from the reaction of 2,2-dimethyl-5-(2-(3,4,5-trimethoxyphenethyl)benzylidene)-1,3-dioxane-4,6-dione (**51**) by General Procedure G in 21 % yield as a colourless oil after flash chromatography (2:1 Hex/EtOAc, Rf = 0.71). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19(m, 1 H), 7.10 (m, 3H), 6.49 (s, 1H), 4.12 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.15 (m, 4H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 151.4, 150.7, 140.4, 139.1, 138.8, 135.4, 129.8, 129.5, 126.4, 126.0, 125.8, 108.6, 61.4, 60.9, 56.0, 32.6, 30.8; HRMS(EI) *m/z* calcd for $C_{18}H_{20}O_3$ (M^+) 284.1412. Found .

(E)-3-(2-(4-Methoxyphenethyl)phenyl)acrylic acid (40):



Obtained from decomposition of the alkylidene Meldrum's acid (**38**) with various Lewis acids at elevated temperatures. In the glove box, mixing the alkylidene Meldrum's acid with TMSOTf (0.1 equiv) in toluene (0.1 M) in a dry flask, then sealing the flask and heating at 70 °C for 24 h gave 21 % of the acid decomposition product, along with 72 % recovered starting material after flash chromatography (5:1 Hex / EtOAc to remove the starting material then CH_2Cl_2 flush) to obtain the acid as a filmy solid. M.p. 150-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 15.5 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.34 (d, *J* = 15.5 Hz, 1H), 3.76 (s, 3H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 158.0, 144.2, 141.6, 133.1, 132.7, 130.5, 130.2, 129.5, 126.7, 118.2, 113.9, 55.2, 37.1, 35.8; HRMS(EI) *m/z* calcd for $C_{18}H_{18}O_3$ (M^+) 282.1256. Found .

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