Functionalization of sp^3-Hybridized Carbon Centers through Carbon-Carbon σ Bond Cleavage Methods

by

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Author's Declaration

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

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

Abstract

Methods for the modification and functionalization of sp^3-hybridized carbon centers via cleavage of unstrained carbon-carbon σ bonds are proposed. The bond breaking/forming reactions are promoted by Lewis acids and transition metals, in which Meldrum's acid and 5-methyl Meldrum's acid act as leaving groups. Under mild reaction conditions and relatively short reaction times, modification of quaternary and tertiary benzylic sp^3-hybridized carbon centers are achieved. Both methodologies show broad scope in terms of substrates and proceed in good to excellent yields. In addition, insights into the hydrogenolysis and substitution mechanisms have been obtained and are discussed.

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The time I have spent pursuing graduate degree was an enjoyable and rewarding experience. I have gained a tremendous amount of theoretical knowledge and practical skills in the field of chemistry.

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Most of all, I would like to thank my parents for their love, patience, and support. My mom, Maryna (D.D.S.) is an excellent role model, who tells me that I can reach the top. My dad, Andriy (Master Mariner) is an astonishingly intelligent person who always supports my new beginnings (emotionally and financially). My Grandmother, Svetlana (M.D.) is the

smartest woman I have ever met, who always encourages me to challenge myself. My Grandmother, Lida (M.D.) is responsive person, who always cheers me up through hard times.

Dedication

Dedicated to my Mom, Dad and Grandmothers
who told me that there is nothing impossible
and all the challenges can be overcome.

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List of Abbreviations

Ac	Acetyl
$AllenylSnBu_3$	Allenyltributyltin
$AllylSnBu_3$	Allyltributyltin
AllylTMS	allyltrimethylsilane
aq	Aqueous
Ar	Aryl
Bu	Butyl
Calcd	Calculated
Cat	Catalytic
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminum hydride
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
Et	Ethyl
EtOAc	Ethyl acetate
Ether	diethyl ether
Equiv	Equivalents
er	Enantiomeric ratio
et al	et alii
EWG	electron withdrawing group
GC-MS	tandem gas chromatography-mass spectrometry
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i-Bu	Isobutyl
i-Pr	Isopropyl

IR	Infrared
J	spin coupling constant
L	Ligand
L*	chiral ligand
L. A.	Lewis acid
LRMS	low resolution mass spectrometry
m	Multiplet
M	metal or molarity (moles/litre)
Me	Methyl
Meldrum's acid	2,2-dimethyl-1,3-dioxane-4,6-dione
MethallylTMS	Methallyltrimethylsilane
mg	Milligram
MHz	mega hertz
min	Minute
Mm	Millimeter
mmol	Millimole
M.p.	melting point
M.S.	molecular sieves
m/z	mass/charge
N/A	not applicable or non-available
ND	not determined
NMR	nuclear magnetic resonance
NR	no reaction
Nu	nucleophile
Pd/C	palladium on charcoal
Ph	Phenyl
ppm	parts per million
PropargylTMS	propargyltrimethylsilane
q	Quartet
Quant	Quantitative
Quint	Quintet
rt	room temperature
s	Singlet
sept	Septet
SM	starting material
t	Triplet
t-Bu	*tert*-butyl
Temp	temperature

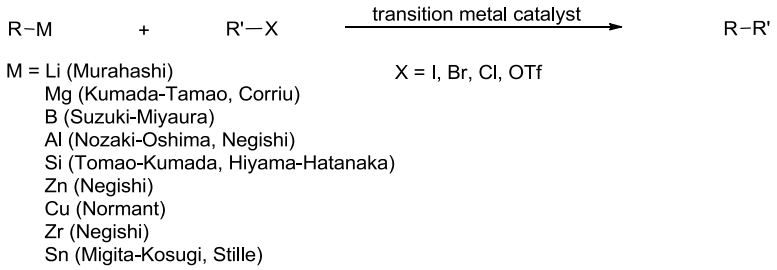
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMS	Trimethylsilyl
UV	Ultraviolet

Chapter 1

1.0 Introduction

1.1 Transition Metal Insertion into C-C Bond

Transition metal-catalyzed reactions are useful and powerful tools that aid in many transformations in preparative organic chemistry. These reactions contribute to a common class of synthetic transformations, commonly referred to as cross-coupling reactions.[1] Transition metal-mediated cross-coupling reactions between organometallic reagents and organic electrophiles are effective for a wide range of C-C, C-H, C-N, C-O, C-S, C-P bond forming processes (Scheme 1.1).[1]



Scheme 1.1 Examples of Cross-Coupling Reactions using Transition Metal Catalysts

There are several reasons why transition metals have been used so extensively in organometallic chemistry.[2] Firstly, the reactivity of the functional groups can be modified upon coordination to transition metals; increase in regio- and chemoselectivity is observed.[2] Secondly, generation of several bonds by a single process can be achieved with the help of transition metal catalysts.[2] Lastly, upon activation of C-C bonds a variety of different functionalizations are possible. Therefore, activation of C-C bonds implementing transition metal catalysis has become a desirable and challenging transformation to achieve in organic chemistry.

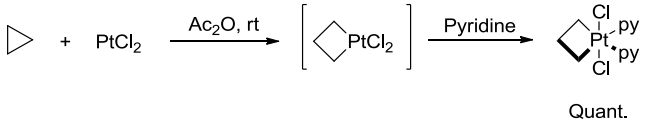
Transition metal insertion into a C-C σ bond provides a direct method for C-C bond cleavage. According to Murakami *et al.*, unstrained C-C single bonds remain the least reactive and more difficult bonds to break.[2] Oxidative addition of transition metals into unstrained C-C bonds is difficult, due to the high thermodynamic stability of unstrained C-C bonds (356 kJ/mol) compared to C-M bonds (~293 kJ/mol). Also, the weak coordinating character of unstrained C-C single bonds in comparison to C=C bonds makes such single

bonds inert towards activation by transition metals.[2] Finally, unstrained C-C single bonds are usually more hindered compared to C-H bonds, which restricts metal approach for C-C bond activation.[2] Activation of unstrained C-C bonds with transition metals remains a challenging exercise in organometallic chemistry; thus, development of new methods to overcome this challenge is of great importance.

1.1.1 C-C Bond Activation by Transition Metals in Strained Rings

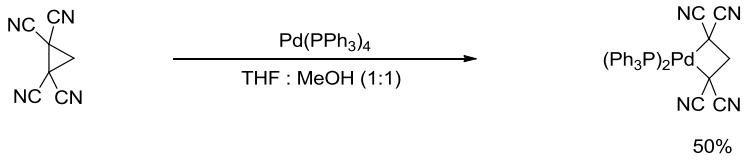
To facilitate C-C bond activation with transition metal complexes, the energy state of the starting materials must be increased.[2] By using three- or four-membered ring compounds, ring-strain in such small ring molecules is relieved. To compensate for the thermodynamic disadvantage of C-C bond activation, more stable ring-expanded metallacyclic complexes are formed through metal insertion into the strained C-C bonds in small ring compounds.[2]

The use of small-membered rings for inserting transition metals into C-C bonds has been utilized since Tipper who reported the formation of a platinacyclobutane complex (Scheme 1.2).[3]



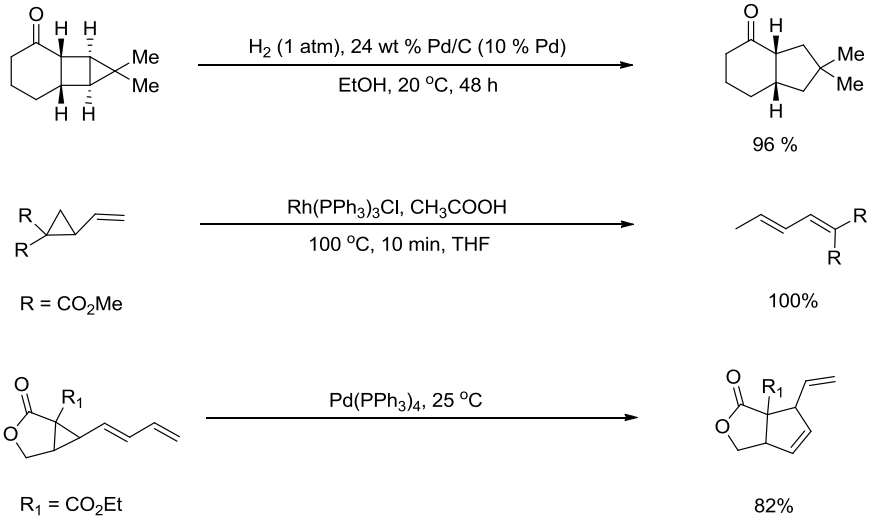
Scheme 1.2 Formation of Platinacyclobutane Complex

Platinum and palladium were shown to insert into a sterically-congested C-C bond of a cyclopropane ring, rather than a more sterically-accessible one (Scheme 1.3).[4] The insertion of palladium catalyst into more sterically-congested position of cyclopropane ring can be explained by the electronic effect exhibited by electronegative substituents (cyano groups) on the carbon atoms directly attached to them. The palladium complex inserts into the most electrophilic bond, the C-C bond between the two carbon atoms bearing gem cyano groups each. The presence of a partial positive charge on the carbon atoms directly attached to cyano groups has been confirmed by theoretical calculations.[5]



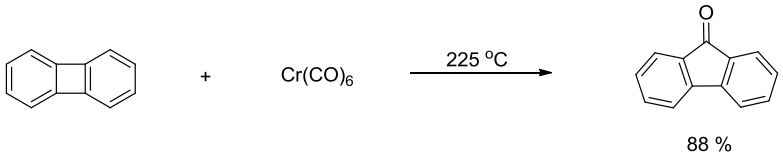
Scheme 1.3 Palladium Complex Insertion into Sterically Congested C-C Bond

A number of literature reports use derivatives of cyclopropane rings that have additional strain, unsaturation, or substituents making them more reactive towards C-C bond activation by transition metal complexes (Scheme 1.4).[6]



Scheme 1.4 Transition Metal Catalyzed C-C Bond Activation of Cyclopropane Rings[7]

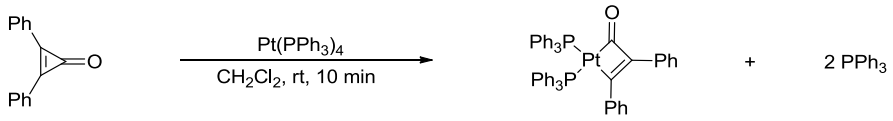
Transition metal insertion into a C-C bond in four-membered rings is known, and has been studied extensively.[8] One of the first reactions explored was the oxidative addition of chromium into biphenylene to generate 9H-fluoren-9-one.[8] The product was produced from insertion of $Cr(CO)_6$ into the central C-C bond between two aromatic rings, subsequent carbonylation, and reductive elimination (Scheme 1.5).[8]



Scheme 1.5 Chromium Insertion into Biphenylene

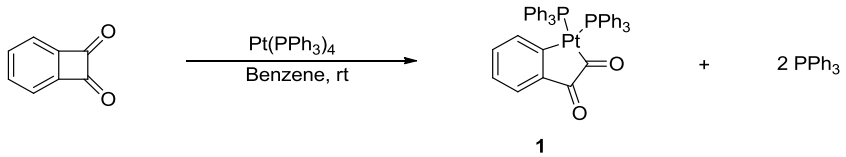
1.1.2 Utilization of Carbonyl Functionality in C-C Bond Activation under Transition Metal Catalysis

Transition metal insertions in C-C bond become more promising when aided by nearby carbonyl groups. Carbon-carbon σ bonds between a carbonyl carbon and the α-carbon in organic molecules are weaker than other C-C single bonds.[2] Carbonyl groups also kinetically facilitate insertion of a transition metal into C-C σ bond adjacent to carbonyl group.[2] One of the examples of transition metal insertion into C-C bond facilitated by nearby carbonyl group is cyclometallation of cyclic ketones with platinum or rhodium complexes.[9] Platinum (0) undergoes regioselective insertion into a cyclopropenone, giving a platinacyclobutenone (Scheme 1.6).[9]



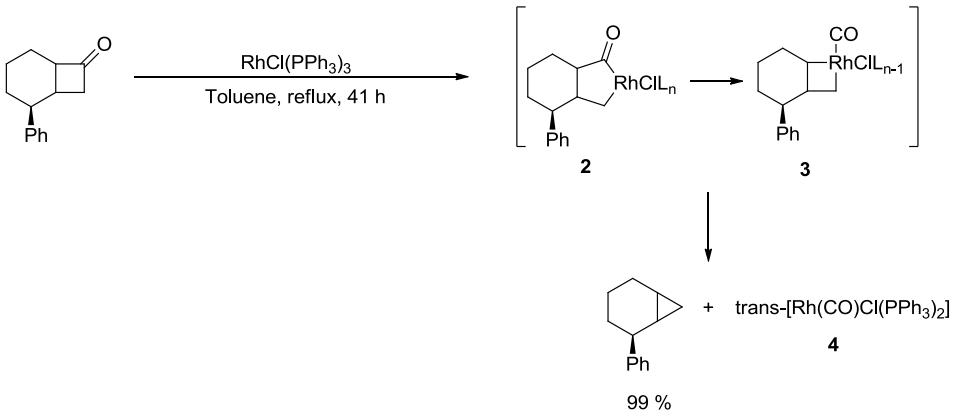
Scheme 1.6 Insertion of a Platinum Catalyst into Diphenylcyclopropenone

Diketones were reported to undergo C-C bond cleavage with $Pt(PPh_3)_4$, affording unsymmetrically-cleaved metal complex **1** (Scheme 1.7).[10]



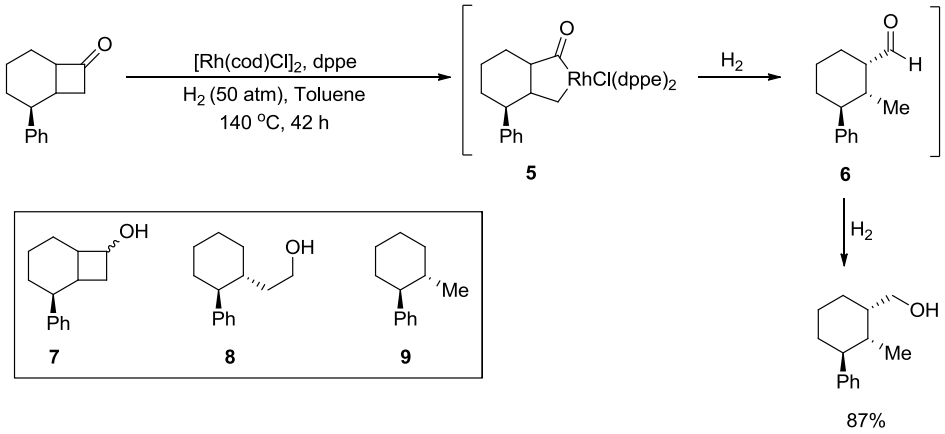
Scheme 1.7 $Pt(PPh_3)_4$ Insertion into Bicyclo[4.2.0]octa-1,3,5-triene-7,8-dione

Cyclic mono-ketones also participated in C-C σ-bond cleavage with $RhCl(PPh_3)_3$ (Scheme 1.8).[11] Treatment of cyclobutanone with $RhCl(PPh_3)_3$ resulted in decarbonylation, and produced the corresponding cyclopropane together with rhodium complex **4**.[11] Decarbonylation was accomplished via rhodium catalyst insertion into the bond between carbonyl group and α-carbon, loss of carbon monoxide, and subsequent reductive elimination (Scheme 1.8).[11] C-C bond scission reactions were enhanced by the carbonyl functionality.[11] The below transformations (Scheme 1.8) were also performed on cyclopentanones only at higher pressure.[11]



Scheme 1.8 Reaction of Cyclic Mono-Ketones with $RhCl(PPh_3)_3$

Murakami *et al.* reported selective rhodium-mediated activation and successive hydrogenolysis of an α-carbonyl C-C bond under high temperature and pressure conditions (Scheme 1.9).[11]

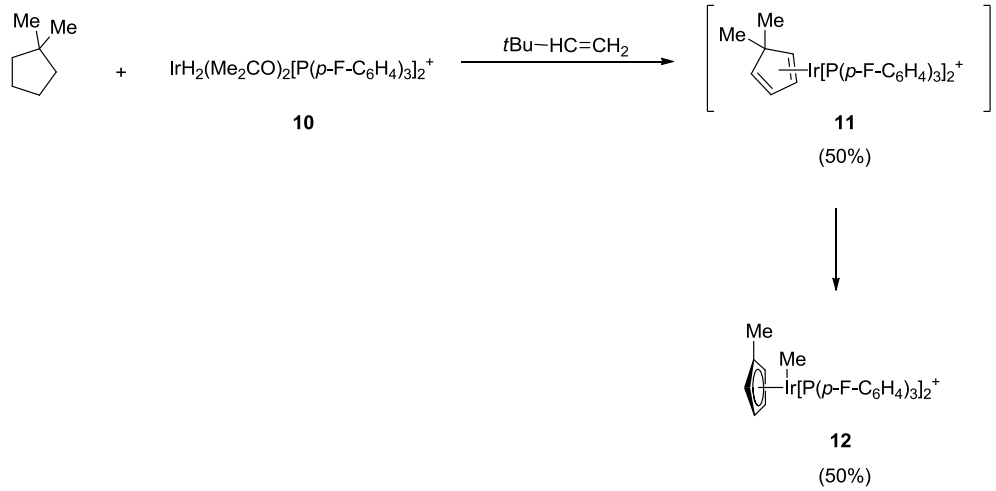


Scheme 1.9 Rhodium-Mediated Activation of C-C Bond with Successive Hydrogenolysis

Aldehyde **6** is likely formed first by the addition of hydrogen gas to activated rhodium-cyclobutanone complex **5**.[11] Direct formation of alcohol **7** from the starting material was not observed, indicating that oxidative addition of the C-C bond proceeds more rapidly than direct hydrogenation of the carbonyl group under the conditions specified.[11] Moreover, alcohol **8** was not produced, demonstrating that the insertion of Rh(I) took place selectively into the less-substituted C-C bond. The choice of phosphine ligand is also important for enhancing selectivity. Decarbonylation product **9** (15% yield) was observed when $RhCl(PPh_3)_3$ catalyst was used instead of $[Rh(cod)Cl]_2$. Murakami *et al.* suggested that formation of product **9** under $RhCl(PPh_3)_3$ catalysis can be explained by hydrogenation of the rhodacycle **3** (Scheme 1.8).[11]

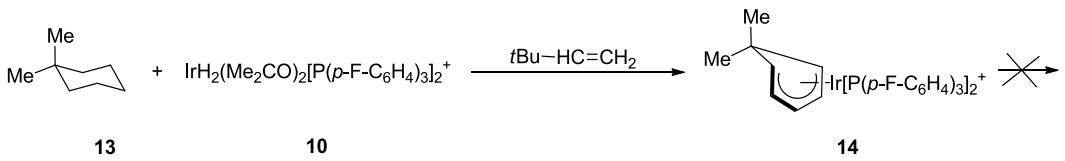
1.1.3 Utilization of Aromatization in C-C Bond Activation by Transition Metal Complexes

The driving force for C-C bond cleavage can also be aromatization of pre-aromatic systems. Formation of pentamethylcyclopentadienyl complexes in reactions catalyzed by rhodium and iridium complexes,[12] as well as with iron,[13] manganese[14] and rhenium,[15] are some of the first such systems reported. Crabtree *et al.* reported migration of a methyl group on a cyclopentadienyl ring with an iridium complex that involved C-C bond cleavage (Scheme 1.10).[16] Reaction of 1,1-dimethylcyclopentane with cationic iridium complex **10** in the presence of an olefin as a hydrogen scavenger afforded dehydrogenated complex **11** that subsequently undergoes C-C bond cleavage of the ligand to give complex **12** (Scheme 1.10).[16]



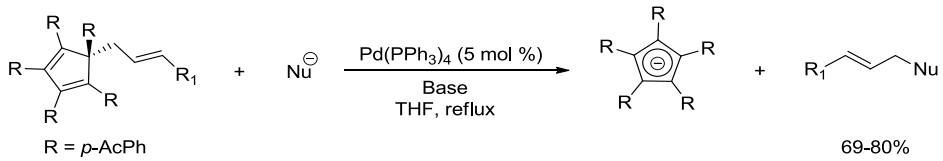
Scheme. 1.10 C-C Single Bond Activation Driven by Aromatization

No C-C σ bond cleavage was observed with the analogous saturated 18-electron complex **14** containing a dialkylcyclohexadienyl ligand using various reaction conditions, suggesting that coordinative unsaturation plays a key role in C-C bond activation (Scheme 1.11).[16] The energy gained from aromatization in the system described above makes the overall reaction thermodynamically feasible.[16] Moreover, the orientation of methyl groups towards the metal center in the rigidly-coordinated cyclopentadiene complex also makes the overall process kinetically possible (Scheme 1.10).[16]



Scheme 1.11 Attempted C-C Single Bond Activation in 1,1-Dimethylcyclohexane

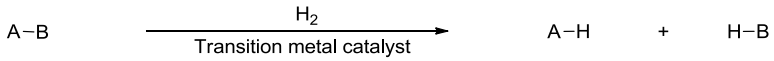
A recent example of aromatization as a driving force for C-C bond cleavage was reported by Fisher and Lambert (Scheme 1.12).[17] Formation of aromatic cyclopentadienyl anions was identified as the reason that the reaction proceeded under the conditions specified.



Scheme 1.12 Palladium-Catalyzed Allylation Reaction

1.2 Hydrogenolysis of C-C Bonds Catalyzed by Transition Metals

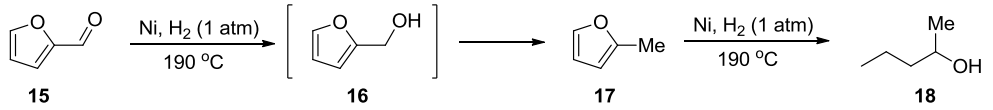
Hydrogenolysis has been defined as the hydrogen (H_2) addition across a C-C or C-X σ-bond resulting in the reductive cleavage of a C-C or C-X σ-bond (Scheme 1.13).[18] Hydrogenolysis of C-X bonds (X = O, N, S, Halogen) are more common than the hydrogenolysis of C-C bonds.[19]



Scheme 1.13 Hydrogenolysis Reaction

Because of their ability to catalyze cleavage of H-H and C-X bonds, transition metals have become key players in hydrogenolysis processes. Palladium catalysts have been used extensively for hydrogenolysis of a variety of bonds, as well as other transition metal complexes (nickel, platinum, copper).[18]

The first evidence of hydrogenolysis reaction was given by Padoa and Ponti in 1906.[20] Fural **15,** in the presence of finely divided nickel, was reduced by H_2 at 190 °C to methylfuran **17**, tetrahydromethylfuran, and finally secondary amyl alcohol (18) (Scheme 1.14).[20]

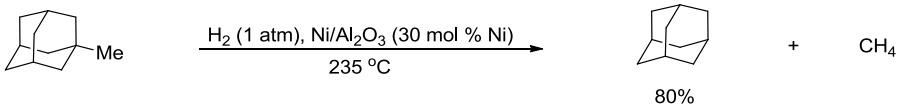


Scheme 1.14 Hydrogenolysis of Fural with Nickel Catalyst

Investigations into the mechanism of this reaction began in 1947, when Brenner and Keeys proposed that the furfuryl alcohol (16) was produced as an intermediate in the course of catalytic hydrogenolysis of furfuryl aldehyde **15** to methylfuran **17**.[21]

Sabatier *et al.* observed the hydrogenolysis of benzyl alcohol to toluene in 1915.[22] Since then, many C-C bonds hydrogenolysis reactions of cyclopropyl rings have been reported (Section 1.2.1), as well as other reactions of hydrogen (H_2) addition to C-C bond (Sections 1.2.2 and 1.2.3).

Many known hydrogenolysis procedures involving transition metals catalysts are performed at high temperature or pressure because of the absence of any driving force for the hydrogenolysis reaction (strain relief or aromatization in pre-aromatic systems) (Scheme 1.15).[23]



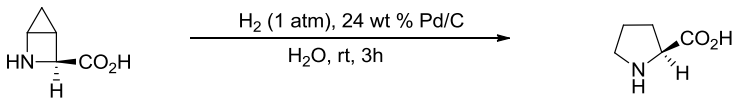
Scheme 1.15 Hydrogenolysis Procedure at High Temperature

Other hydrogenolysis procedures involve relieving ring strain in small rings, or cleavage of C-C bonds driven by aromatization in pre-aromatic systems.[24] Hydrogenolysis reactions of C-C σ bonds under mild reaction conditions are scarce.

However, relief of strain and aromatization in pre-aromatic systems as driving forces for the hydrogenolysis reaction can also be compensated with unsaturation (aryl, vinyl or carbonyl group) present near a potentially cleavable C-C bond. Presence of unsaturation aids the molecule in complexing to the catalyst and accelerating the hydrogenolysis reaction by stabilizing the transition state. Moreover, the unsaturated moiety serves as a "handle" that brings this cleavable C-C bond closer to the catalytic surface, thus increasing the rate of the reaction.[25] In general, hydrogenolysis of the C-C bond is activated by the electronic effect in the "handle" attached to it.[25]

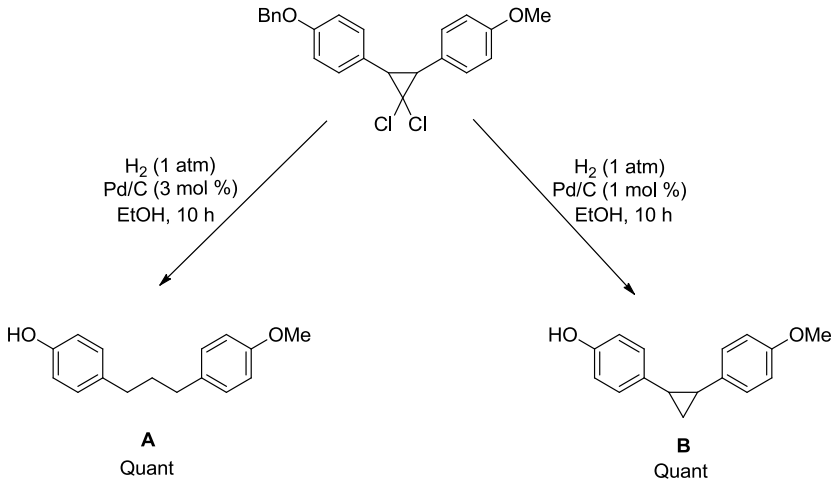
1.2.1 Hydrogenolysis of Strained C-C σ Bonds

Most palladium-catalyzed hydrogenolysis reactions of C-C bonds are achieved on cyclopropyl derivatives.[25] The main driving force for these reactions is strain release upon opening of the cyclopropyl ring.[25] For instance, Sekizawa *et al.* described hydrogenolysis of a fused three-membered ring to prepare proline (Scheme 1.16).[25]



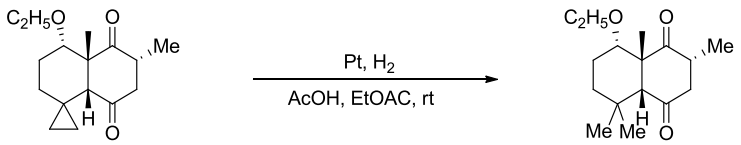
Scheme 1.16 Pyrrolidine Product Synthesis Catalyzed by Palladium

Pento *et al.* showed that 1,1-dichloro-substituted cyclopropanes undergo hydrogenolysis of the three-membered ring under Pd/C catalyst to give product **A**, while a lower percentage (1%) of the catalyst produced only dechlorination product **B** (Scheme 1.17).[26]



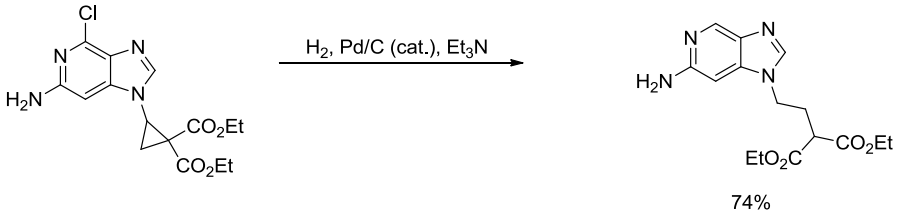
Scheme 1.17 Hydrogenolysis of Cyclopropyl Ring Under Different Catalytic Loading of Pd/C

Hydrogenolytic cleavage of cyclopropanes is also convenient for introducing geminal methyl groups into organic molecules (Scheme 1.18).[27] Introduction of geminal alkyl groups *via* hydrogenolysis is important in natural products synthesis, and has been applied to the synthesis of (±)erigerol and $\Delta^{9(12)}$-capnellene.[28]



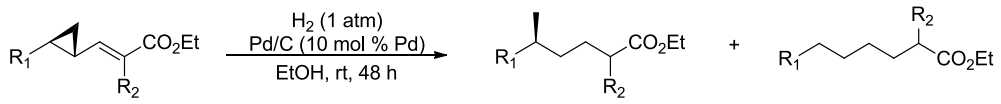
Scheme 1.18 Synthesis of Geminal Methyl Groups by Hydrogenolysis of Cyclopropane

In some cases oxygen and nitrogen can act as directing groups in hydrogenolytic cleavage of highly substituted C-C bond of cyclopropane rings to enhance rate of the reaction, as well as to control regioselectivity of the hydrogenolysis reaction (Scheme 1.19).[28] The presence of directing groups increases the adsorption of the starting material on the surface of the catalysts.[25]



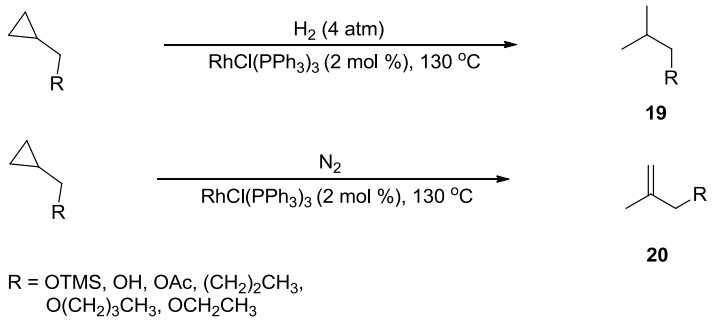
Scheme 1.19 Dehalogenation and 1,2-Cyclopropane Scission Under Palladium Catalyzed Conditions

Some examples of palladium-catalysed C-C bond cleavage in small-ring systems include hydrogenolysis of vinylcyclopropanes (Scheme 1.20).[29] Methyl-containing products were obtained when R_1 was an alkyl group, while straight-chain products were obtained when R_1 was an aryl or acrylate group.[30]



Scheme 1.20 Hydrogenolysis of Vinylcyclopropanes

Recently, Bart and Chirik reported selective C-C bond activation of a cyclopropane derivative using Wilkinson's catalyst (Scheme 1.21).[30] Performing the C-C bond activation reactions under N_2 atmosphere rather than H_2 resulted in catalytic alkene formation, giving product **20** (Scheme 1.21).[31]

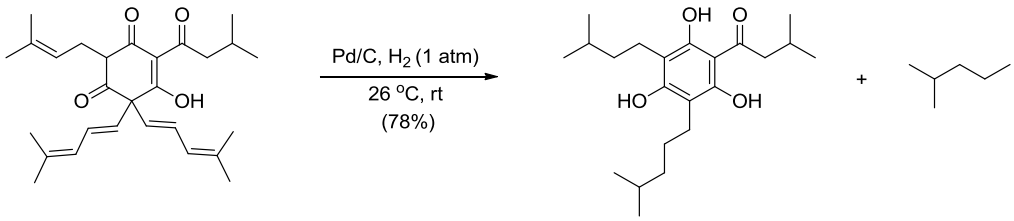


Scheme 1.21 Cyclopropane Ring Opening Using $RhCl(PPh_3)_3$

The ring strain, together with the enhanced *p*-character of C-C σ-bonds in three-membered rings, permits reductive cleavage to occur under mild conditions.[31] The main driving force for the hydrogenolysis reaction presented on Scheme 1.21 is strain relief. Thus, the free energies of activation for hydrogenolysis of C-C bonds in cyclopropanes are 20-40 kcal/mol lower than those for unstrained C-C bonds.[25]

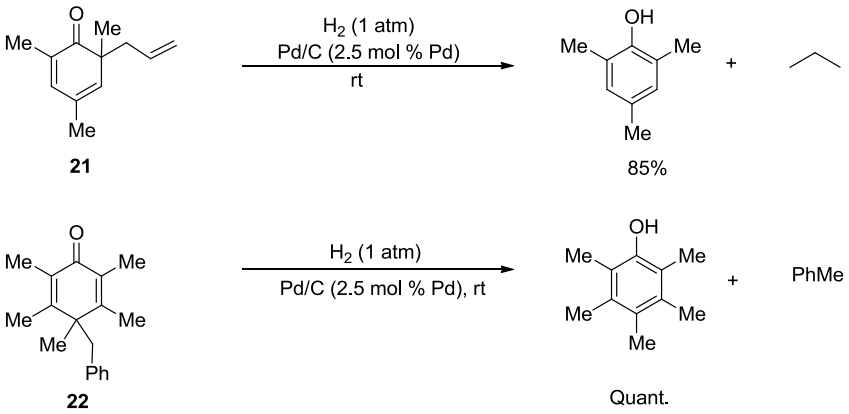
1.2.2 Hydrogenolysis of C-C Bond in Pre-Aromatic Systems

In general, hydrogenolysis of C-C bonds requires either extreme reaction conditions (Scheme 1.15) or strain release in small cyclic molecules as described in Section 1.2.1. Hydrogenolysis of pre-aromatic systems can eliminate these requirements, as shown by hydrogenolysis of lupulone at room temperature (Scheme 1.22).[24b]



Scheme 1.22 Hydrogenation of Lupulone in the Presence of Pd/C

Subsequently, Miller and Lewis observed hydrogenolysis of allyl- and benzyl-substituted cyclohexadienones **21** and **22** (Scheme 1.23).[24a]

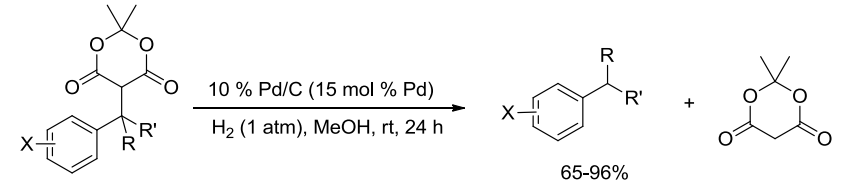


Scheme 1.23 Hydrogenolysis Reactions Driven by Aromatization

The presence of π-bonds adjacent to the C-C bonds to be cleaved and the subsequent aromatization of the cyclohexadienone systems are both responsible for the facile C-C bond hydrogenolysis in the systems described above.[24]

1.2.3 Recent Precedents in Hydrogenolysis of C-C Bonds.

Precedents for hydrogenolysis of C-C bonds catalyzed by transition metals usually include the reactions driven by ring strain relief and aromatization as discussed earlier (Sections 1.2.1 and 1.2.2). However, there are examples of hydrogenolysis reactions that are not driven by these factors, including the hydrogenolysis of unstrained C-C σ bonds of quaternary Meldrum's acid derivatives observed by Fillion *et al.* (Scheme 1.24).[31] Exposure of benzyl Meldrum's acid derivatives to Pd/C in the presence of hydrogen gas induced reductive scission of benzylic carbon-carbon σ-bonds to release an aromatic ring and Meldrum's acid (Scheme 1.24).[32] Therefore, modification of sp^3-hybridized quaternary benzylic carbon centers was achieved with the generation of substituted aromatic rings bearing a benzylic stereocenter.[32]

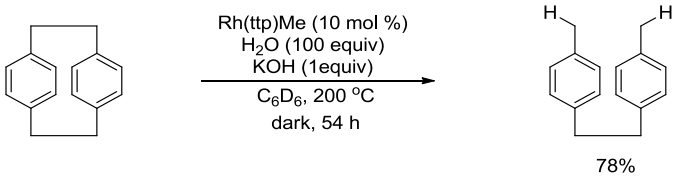


X = 4-H, 4-Ph, 4-(OC_8H_{17}), 2-(OC_8H_{17}), 4-OMe

R = Me, H; R' = Me, Et, *n*-Bu, *i*-Pr, 4-$MeOC_6H_4$; R = R' = $(CH_2)_5$

Scheme 1.24 Palladium-Catalyzed Hydrogenolysis of Benzyl Meldrum's Acids

Another recent example of C-C bond hydrogenolysis is the cleavage of a C-C bond in [2.2]paracyclophane with rhodium catalyst and water (Scheme 1.25).[32] The hydrogen from water is transferred to the hydrocarbon during this catalytic reaction.



Scheme 1.25 Hydrogenolysis of [2.2]paracyclophane with a Rhodium Catalyst

1.2.4 Mechanistic Considerations of Hydrogenolysis Reactions

Hydrogenolysis reactions can be carried out under homogeneous and heterogeneous conditions.[25] Homogeneously-catalyzed hydrogenolysis is usually a process catalyzed by a soluble catalyst in which each metal atom is available for reaction. Generally, homogeneous catalysts exhibit no or very little activity for the hydrogenolysis reaction. Heterogeneous catalyst represents a suspension in a solvent, and the active site of non-soluble catalyst cannot be defined precisely.[25] The mechanism of the hydrogenolysis reaction may be often described in terms of homolytic or heterolytic displacement reactions, where **A** or **B** of the A-B σ-bond is considered as the leaving group.[25] In this way, different phenomena concerning stereoselectivity and the rate of the reaction are explained by the use of general concepts derived from other organic reactions.[25] Heterogeneous and homogeneous catalysis can give an understanding of electronic and steric interactions between reactants and the metal surface.[25] It is proposed that hydrogen is dissociatively chemisorbed on the surface of the catalyst, and the hydrogenolysis reaction has to be considered as a stepwise addition of two hydrogen atoms from the catalyst to the reactant (Figure 1.1).[25]

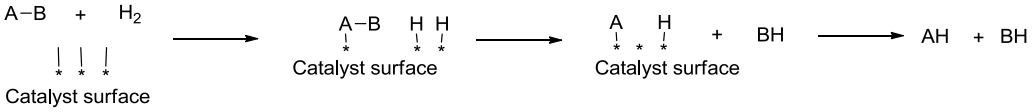
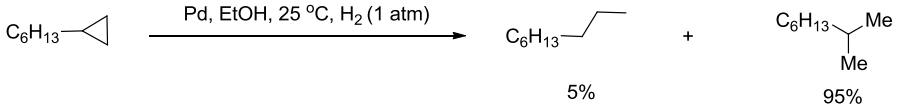


Figure 1.1 Schematic Depiction of Hydrogenolysis

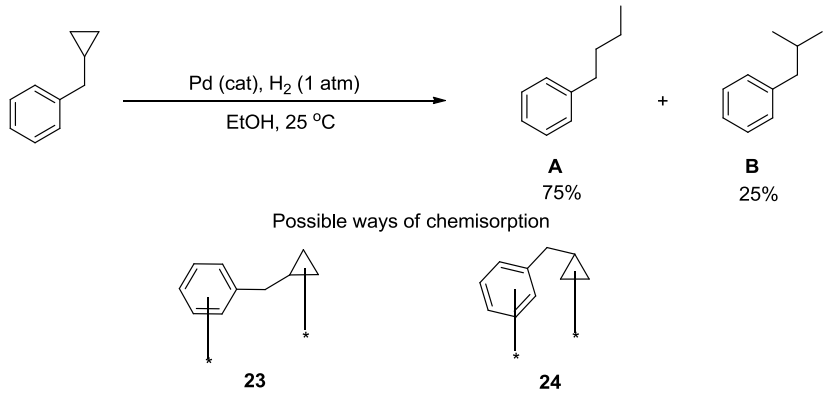
1.2.4.1 Regioselectivity of Hydrogenolysis Reactions

The regioselectivity of the hydrogenolysis process on heterogeneous catalyst usually involves the preferential cleavage of the least-substituted or least-hindered C-C bond (Scheme 1.26).[25]



Scheme 1.26 Regioselective Hydrogenolysis of Alkylcyclopropanes

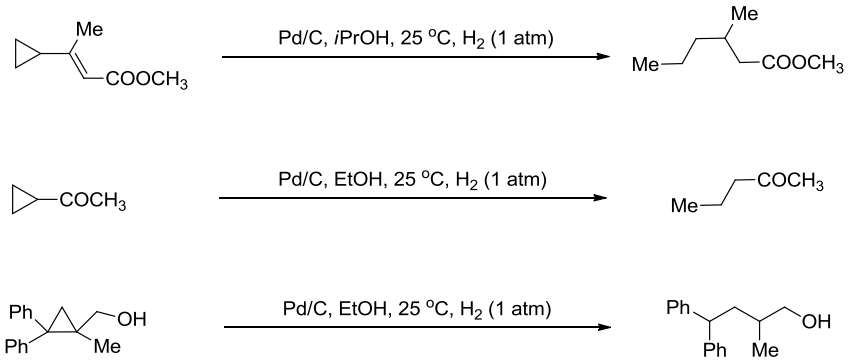
Irwin and McQuillin reported the regioselective hydrogenolysis reaction of benzylcyclopropane (Scheme 1.27).[33] The reaction reported favours the hydrogenolysis of the most-substituted C-C bond which is opposite of what was stated earlier (Scheme 1.26). Cleavage of benzylcyclopropane with hydrogenolysis procedure can be rationalized when two possible models (**23** and **24**) for chemisorption of benzene and cyclopropane rings are proposed. Model **23** is favored because of the optimal flat adsorption of the system without any internal van der Waals repulsion, and, consequently, the major product formed is product **A**.[25]



Scheme 1.27 Hydrogenolysis of Benzylcyclopropane

Vinyl-, acyl-, oxycarbonyl- and aryl-substituted cyclopropanes show preferred cleavage of the C-C bond adjacent to the functional group (Scheme 1.28). The unsaturated "handle" at the cyclopropane ring is promoting the hydrogenolysis of the adjacent C-C bond.[25] In addition, the hydrogenolysis of the C-C bond is generally activated by the electronic effects in the "handle".[25] As a consequence, the strength of adsorption of the "handle-containing" hydrogenolysis reaction product will often be comparable to that of the

reactant; the product formed will compete with the reactant for active sites on the catalyst. Thus, many hydrogenolysis reactions proceed at a progressively decreasing rate of the reaction because the adsorption equilibrium causes a decreasing surface concentration of reactant during the reaction.[25] Therefore, the mentioned functional group effect overrules the opposite effect caused by alkyl substituents.[25]



Scheme 1.28 Hydrogenolysis Reactions of Cyclopropane Rings

1.2.4.2 Stereochemistry of Hydrogenolysis Reaction

The stereochemistry of cyclopropane ring hydrogenolysis depends on the occurrence of two possible modes of hydrogen attack on the two carbon atoms. The first one includes suprafacial hydrogen attack, in which configuration is retained or inverted at both carbon atoms. The second one incorporates antarafacial hydrogen attack, in which the configuration is retained at one carbon atom and inverted at the other (Figure 1.2).[25]

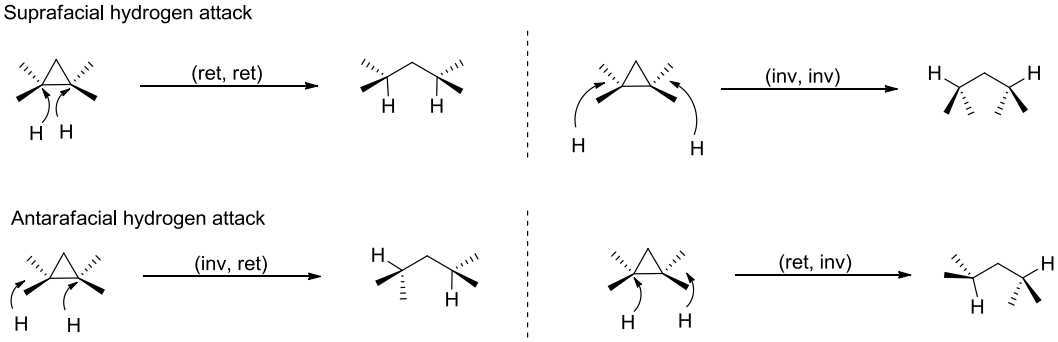
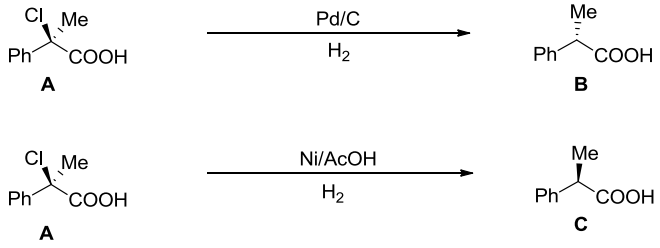


Figure 1.2 Modes of Hydrogen Attack on Cyclopropane Ring

In most other cases, the mode of hydrogen addition to the carbon atoms is not reflected in the products formed, because of the lack of substituents on both carbon atoms of

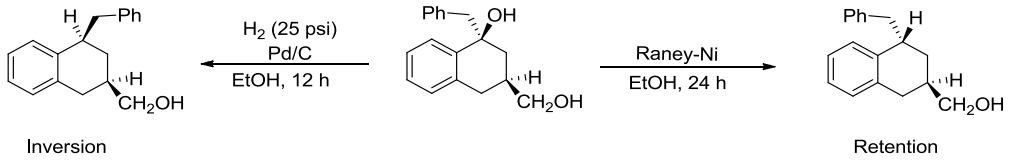
the σ-bond to be cleaved. Stereospecificity is then described in terms of inversion/retention at one of the carbon atoms.[25]

Ott *et al.* reported that (+)-α-phenylpropionic acid **B** was obtained when (-)-α-phenyl-α-chloropropionic acid **A** was subjected to catalytic hydrogenolysis using Pd/C as a catalyst.[34] Moreover, Bonner *et al.* obtained the product **C** with the inversion of configuration under nickel-catalyzed conditions (Scheme 1.29).[35]



Scheme 1.29 Hydrogenolysis of (-)-α-Phenyl-α-Chloropropionic Acid

In 1973, Roberts *et al.* showed that 1-benzyl-1-hydroxy-3-hydroxymethyltetraline can be hydrogenolysed with Pd/C to give the product with inversion of configuration (*cis* diastereomer is formed), while Raney-Ni gives the product with retention of configuration forming the *trans* product (Scheme 1.30).[36]



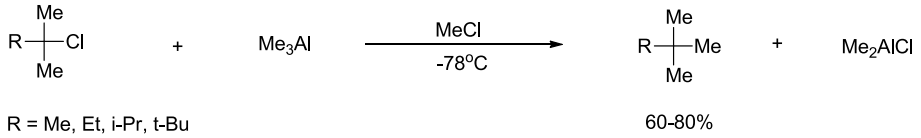
Scheme 1.30 Stereospecific Catalytic Hydrogenolysis under Pd/C and Raney-Ni Catalysts

The stereochemical outcome of the hydrogenolysis reaction does not rely solely on regiochemical factors, and also depends on the nature of the transition metal catalysts used in the reaction.[25] Hydrogenolysis reactions performed with nickel and palladium catalysts revealed that nickel catalysts give products with retention of stereochemical configuration, whereas palladium catalysts give products with inversion of stereochemical configuration.[25] Therefore, it can be concluded that hydrogenolysis reactions of stereodefined carbon centers can selectively give products either with retention (nickel, copper, cobalt) or inversion (palladium) of configuration. Investigations into the mechanistic details of hydrogenolysis reactions may enable the creation of new methods for selective synthesis of specific enantiomers and diastereomers, and lead to the development of asymmetric transition metal-catalysed hydrogenolysis reactions.

1.3 Organoaluminum in Substitution Reactions

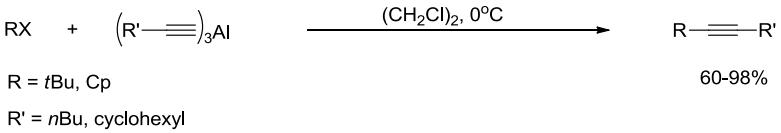
As mentioned in Section 1.1, transition metals play key roles in the activation of cleavable C-C bonds in organic chemistry. Another method for the activation of cleavable bonds in substitution reactions is Lewis acid catalysis.

Kennedy showed that tertiary alkyl halides and secondary alkyl sulfonates react readily with trimethylaluminum, although low temperatures were required for suppression of side reactions (Scheme 1.31).[37]



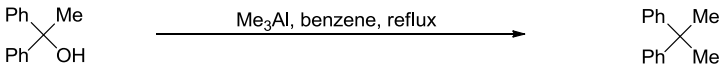
Scheme 1.31 Reaction of Tertiary Alkyl Halides with Trimethyaluminum

Noteworthy is the reaction of alkynylalanes with tertiary and secondary alkyl sulfonates, which permits clean coupling and gives disubstituted alkynes in good to excellent yields (Scheme 1.32).[38]



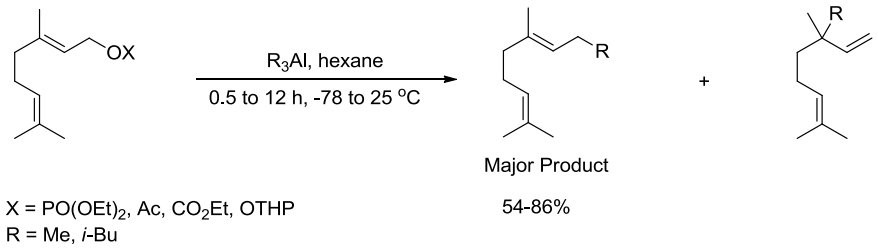
Scheme 1.32 Alkyl-Alkynyl Coupling Reaction

Organoalanes also react with alcohols, but the reactions require high temperatures (80-200°C) and are of limited scope (Scheme 1.33).[39]



Scheme 1.33 Reaction of Trimethylaluminum with Tertiary Alcohols

Allylic alcohols react with organoalanes (Scheme 1.34).[40] The coupling reaction proceeds smoothly with acetate, formate, and carbonate esters by trialkylaluminum reagents, producing products in high yield.

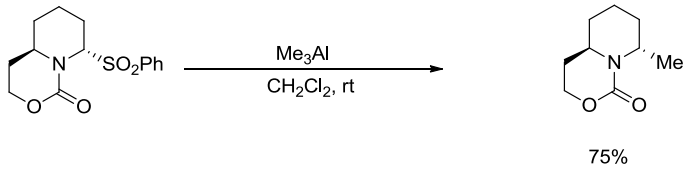


Scheme 1.34 Allylic Alcohols Reaction with Organoaluminums

Displacements of functional groups by trimethylaluminum have been described. Uemura *et al.* described stereoselective methylation of benzylic acetates and the corresponding alcohols of η^6-arene tricarbonylchromium complexes, giving *endo*-alkyl chromium complexes in high yields (Scheme 1.35).[41]

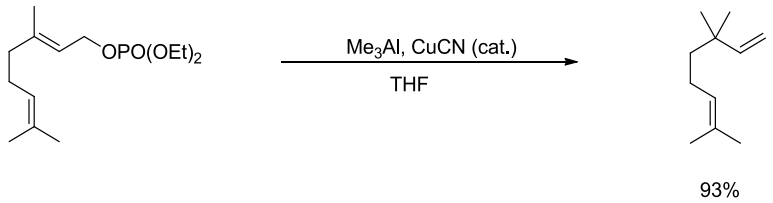
Scheme 1.35 Stereoselective Methylation at Benzylic Position of η^6-Arene Tricarbonylchromium

Brown *et al.* showed nucleophilic displacement of phenylsulfonyl group at the second position of a piperidine derivative (Scheme 1.36).[42] The first series of displacement reactions of sulfones were investigated with aryl and vinylorganometallic reagents generated from Grignard reagents and zinc bromide. However, the results were not satisfactory; thus, Me_3Al was used, which furnished the product in 75% yield with retention of configuration (shown in scheme 1.36).



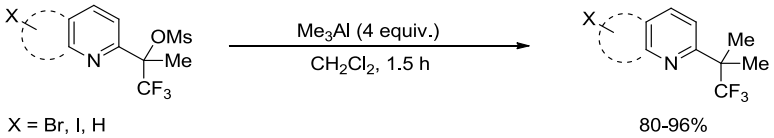
Scheme 1.36 Substitution of a Phenylsulphonyl Group with a Methyl Group

Selective S_N2' reactions of allylic phosphates with Me_3Al were observed by Flemming *et al.* (Scheme 1.37).[43] Addition of catalytic amounts of CuCN significantly influenced the regioselectivity of the reaction between aluminum alkyls and allylic phosphates in THF to effect a highly-selective S_N2' reaction for Me_3Al. This methodology is especially attractive for generating quaternary carbon centers.



Scheme 1.37 Copper Catalyzed S_N2' Reactions of Me_3Al

Shishido *et al.* used a similar procedure by methylating aromatic compounds containing trifluoromethyl groups at the benzylic position (Scheme 1.38).[44] This synthetic method proved versatile for the synthesis of methylated benzylic compounds containing substituted aromatic and heterocyclic rings.

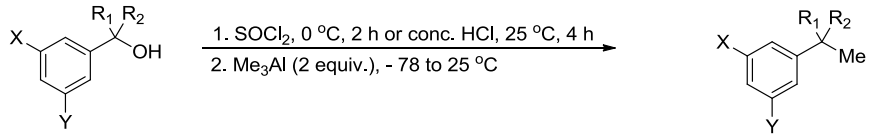


X = Br, I, H

80-96%

Scheme 1.38 Displacement of Tertiary Mesylates Using Trimethylaluminum

Recently, Hartsel *et al.* reported that *tert*-alkyl aromatic compounds can be generated by activating tertiary benzylic alcohols, and subsequent treatment with trimethylaluminum (Scheme 1.39).[45]



X = OMe, Me, Ph, Cl; Y = OMe, H, Me
R_1 = Me, Et; R_2 = Me, Et

70-95%

Scheme 1.39 Methylation of Activated Tertiary Benzylic Alcohols

Functionalization of the benzylic position was met (Scheme 1.39), allowing for the indirect displacement of a tertiary alcohol with an alkyl group and formation of a new C-C σ bond. In summary, many C-C bond-forming reactions have been achieved using organoaluminum reagents; however, the main challenge of stereoselectivity in the synthesis of organic targets with organoaluminum compounds still needs to be addressed.

1.4 Leaving Group Effect on Nucleophilic Substitution Reactions

The leaving group has been defined as an atom or group of atoms which break away from the rest of the molecule and takes along a pair of electrons.[46] Leaving groups usually

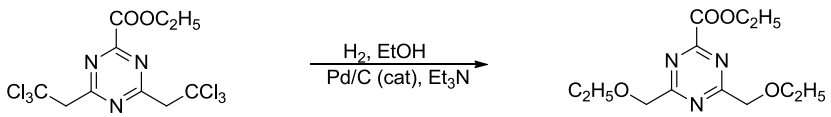
contain electronegative atom, or atoms on which a negative charge can be stabilized by resonance.[47] The leaving group departure is a complex process involving several aspects that include for instance, the polarizability of the leaving group, the involved reaction mechanism, the basicity of the nucleophile, solvent effects, nucleophile-leaving group interactions.[47] The best leaving groups are very weak bases: halides, sulfonates, mesylates.

Many leaving groups require prior activation either by protonation or by conversion to a reactive moiety in order to enhance leaving group ability, for instance, complexation of alcohols with Lewis acid. Currently, many methods to increase leaving group ability are known; for example, conversion to better leaving groups (tosylate) or use of acid-catalysis.[47]

Leaving groups play important roles in many organic reactions, including nucleophilic and electrophilic substitutions, as well as elimination reactions. Despite the variability represented by common leaving groups, their performance in the synthetic organic reactions requires improvement. Competing reaction pathways are usually associated with commonly used leaving groups. For example methylation of tertiary halides (Scheme 1.39) leads to an elimination by-product, which is inseparable from the desired product by chromatography.[46] Thus, directed efforts have been made to develop new leaving groups with improved selectivity, reaction rates, scalability, and atom economy.

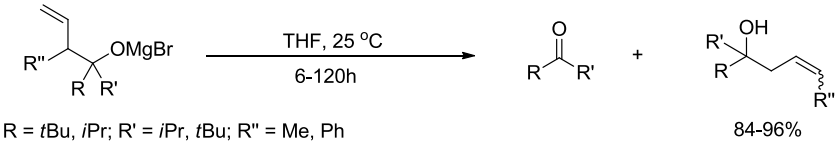
1.4.1 Carbon-Based Leaving Groups

There are fewer carbon-based leaving groups compared to other commonly-used leaving groups in organic chemistry, such as halides, tosylates, mesylates, and acetates. However, several carbon-based leaving groups are known, including those in the haloform and retro-aldol reactions that have been used extensively from the past till nowadays. Kreutzberger has shown that trichloromethyl can serve as carbon-based leaving group (Scheme 1.40).[47]



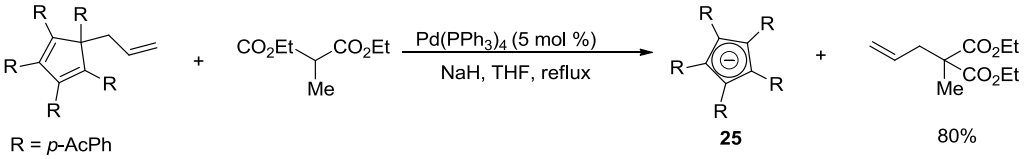
Scheme 1.40 Trichloromethyl as Leaving Group under Palladium Catalysis

Among the other carbon-based leaving groups discovered are reversible Grignard reactions. In particular, Benkeser *et al.* reported a reversible crotyl Grignard reaction (Scheme 1.41).[48]



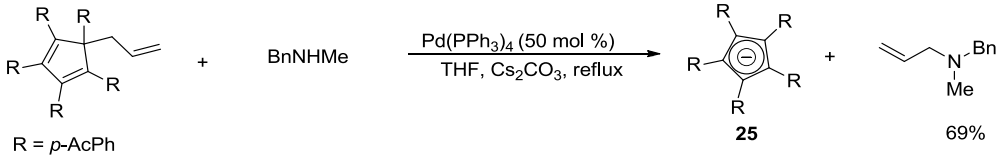
Scheme 1.41 Reverse Grignard Reaction

A substituted cyclopentadienyl moiety was also shown to act as a good leaving group for metal-catalyzed allylic substitution reactions (Scheme 1.42).[17] Fisher *et al.* predicted that the cyclopentadienyl anion could serve as a good leaving group, based on high stability of the anion **25** formed (Section 1.1.3).[17] In addition, the electronic properties of cyclopentadienyl anions are highly tunable, which creates the possibility to develop novel methodologies based on these diverse anions serving as good carbon-based leaving groups.[49]



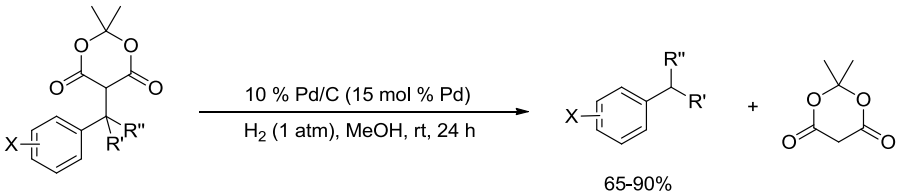
Scheme 1.42 Palladium-Catalyzed Nucleophilic Displacement of Cyclopentadienyl Anions

Moreover, Fisher *et al.* showed that it is possible to construct carbon-heteroatom bonds using the above reaction (Scheme 1.43).[17] The C-C bond can be replaced easily with a C-N bond, using N-benzylmethylamine as the nucleophile and 50 mol % palladium catalyst loading.[17]



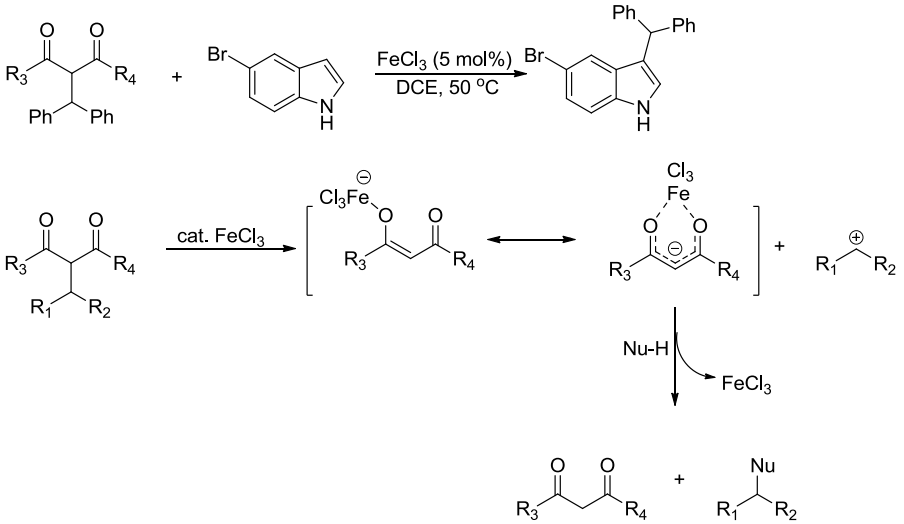
Scheme 1.43 Construction of C-N Bond using Cyclopentadienyl Anion Leaving Groups

Fillion *et al.* described a novel carbon-based leaving group in hydrogenolysis reaction of Meldrum's acid derivatives (Scheme 1.44).[32] The reaction allowed the modification of sp^3-hybridized carbon centred through palladium-catalyzed reductive cleavage of unstrained C-C σ bonds.[32]



Scheme 1.44 Hydrogenolysis of Meldrum's Acid Derivaties

Li *et al.* showed that $FeCl_3$ catalyzes substitution reactions where a 1,3-dicarbonyl functional groups act as a leaving groups via the formation of benzylic carbocations (Scheme 1.45).[51] $FeCl_3$ acts as a Lewis acid catalyst that coordinates with the 1,3-dicarbonyl unit and helps to cleave the benzylic C-C bond.[50]



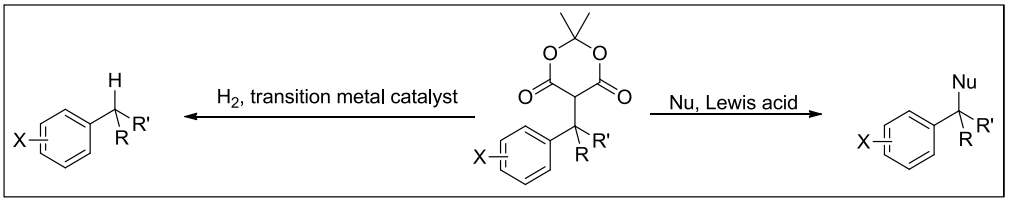
Scheme 1.45 The Reaction of Diones with 5-Bromoindole and its Tentative Reaction Pathway

Carbon-based leaving groups are not as often used as halides, tosylates, mesylates, activated alcohols. Therefore, the discovery of new carbon-based leaving groups opens new horizons for potential expansion of substitution reactions in organic chemistry.

1.5 Research Plan

In this thesis, novel methodologies for functionalizing sp^3-hybridized benzylic carbon centers through cleavage of unstrained Csp^3-Csp^3 bonds catalyzed by Lewis acids and transition metals are presented and discussed. Two designed methodologies will be

investigated: Lewis acid promoted catalysis or transition metal-mediated cleavage of the benzylic C-C bonds (Scheme 1.46).



Scheme 1.46 Lewis Acid and Transition Metal Promoted Substitution Reactions Employing Meldrum's Acid as a Carbon-Based Leaving Group

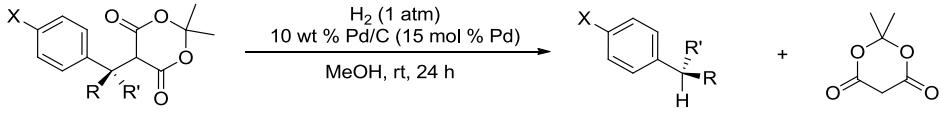
Chapter 2

2.0 Modification of sp^3-Hybridized Carbon Centers Through Lewis Acid-Promoted Substitution Reactions

2.1 Introduction

In 2009, Fillion *et al.* reported that Meldrum's acid functioned as an effective leaving group in palladium-catalyzed hydrogenolysis of benzylic Meldrum's acids.[32] In these reactions, unstrained benzylic σ C-C bonds were cleaved, with the subsequent formation of sp^3-hybridized C-H bonds. Stereospecificity in the hydrogenolysis project was also investigated, and results are shown in Table 2.1.[32] The mechanism of the hydrogenolysis protocol was investigated through labeling studies and data obtained from the hydrogenolysis of enantioenriched substrates. It was proposed that the hydrogenolysis reaction goes through a "loose" S_N2 mechanism (see Chapter 3 for discussion).

Table 2.1 Hydrogenolysis of Enantioenriched Meldrum's Acid Derivatives



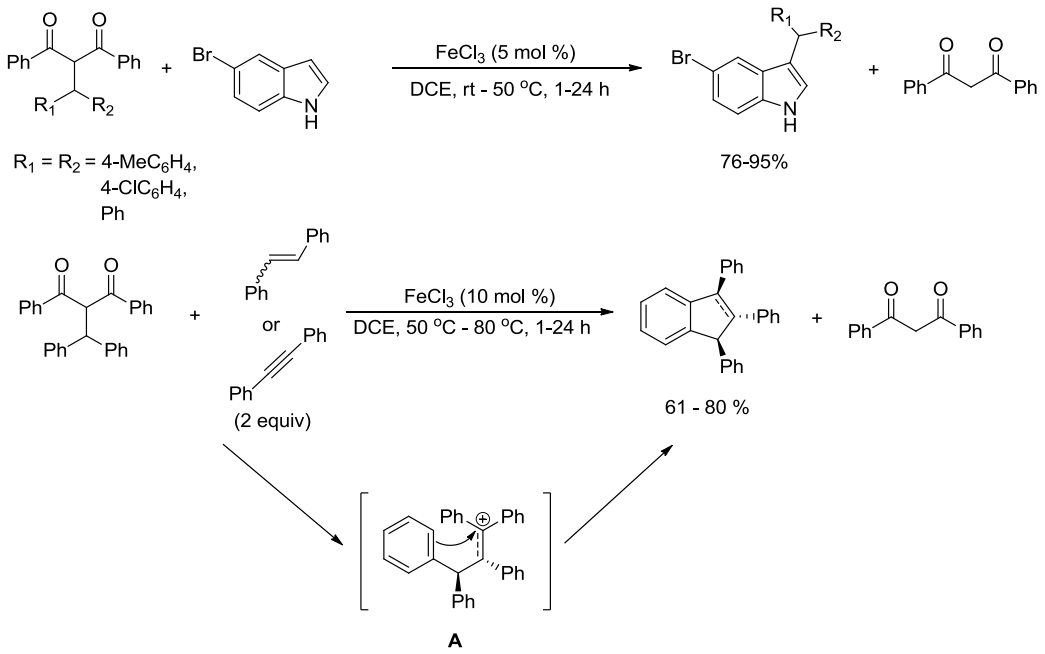
(R)-26 *(S)*-27

Entry	R; R'	X	Er of 1 (R/S)	Er of 2 (S/R)	Inversion of Er (%)	Yield[a] (%)
1	R = R' = Me	4-(OC_8H_{17})	-	-	-	76
2	R = R' = Me	4-Ph	-	-	-	71
3	R = R' = Me	H	-	-	-	80[b]
4	R = R' = Me	3-(OC_8H_{17})	-	-	-	N/A[c]
5	R = R' = Me	2-(OC_8H_{17})	-	-	-	71[d]
6	R = H; R' = Me	4-(OC_8H_{17})	-	-	-	N/A[e]
7	R = Et; R' = Me	4-(OC_8H_{17})	98.5:1.5	96:4	97	93
8	R = Et; R' = Me	Ph [(R)-1a]	98:2	90.5:9.5	92	51

[a] Conversion in all cases was >95 %, unless stated otherwise; [b] Yield for the isolation of Meldrum's acid; [c] 9 % conversion was reported; [d] 92 % conversion was reported; [e] <5 % conversion was reported.

Li *et al.* demonstrated substitution reactions at tertiary sp^3-hybridized diaryl, benzylic or allylic carbon centers under iron trichloride catalysis, aided by bromoindoles and electron rich alkenes, and employing 1,3-diphenylpropane-1,3-dione as a leaving group (Scheme 2.1).[51] The resulting products were obtained through addition and cyclization proceeding

through cationic intermediate **A**, with formation of the most thermodynamically stable products (Scheme 2.1).



Scheme 2.1 Iron-Catalyzed C-C Bond Activation with 1,3-Dicarbonyl Units as Leaving Groups

Based on these results Li *et al.* suggested a possible reaction pathway (Scheme 1.45) in which $FeCl_3$ acts as a Lewis acid catalyst to cleave the C-C σ bond through the coordination of iron with the 1,3-dicarbonyl unit.[51] The carbocation intermediates formed are trapped with nucleophiles, giving the most thermodynamically stable alkylation products (Scheme 1.45).

2.2 Proposal

Discovery and development of the hydrogenolysis reaction protocol by Fillion *et al.* led to the displacement of Meldrum's acid moiety with hydride under transition metal-mediated conditions.[32] Research reported by Li *et al.* showed the Lewis acid-promoted displacement of 1,3-dicarbonyl functionality by bromoindoles.[51] Therefore, based on previous studies[32,51] the proposed research seeks to develop methodology for the functionalization of benzylic carbon centers using transition metal activation or Lewis acid catalysis. Cleavage of unstrained Csp^3-Csp^3 bonds is proposed, and introduction of different

nucleophiles at the benzylic position of the molecules of interest will be attempted. Moreover, the substitution reaction mechanism with expanded substrate scope will be explored.

Thus, this research aims to expand the scope of nucleophilic displacement of Meldrum's acid at benzylic positions to get benzylic functionalization for the creation of quaternary carbon centers (Figure 2.1). In this chapter, Lewis acid activation is used for the cleavage of unstrained σ C-C bonds with a variety of nucleophilic species, while in Chapter 3, a transition metal-mediated approach is used, with hydrogen acting as the nucleophile.

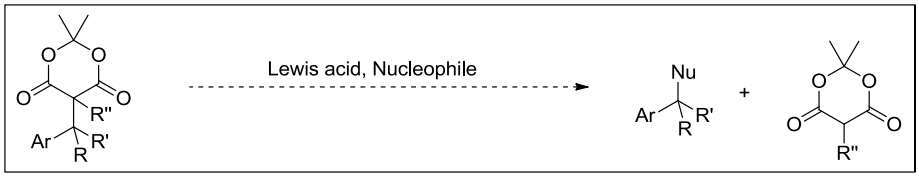
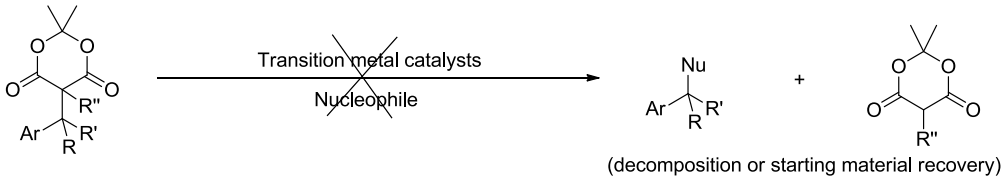


Figure 2.1 Proposed Meldrum's Acid Substitution under Lewis Acid Promoted Catalysis

2.3 Results and Discussion

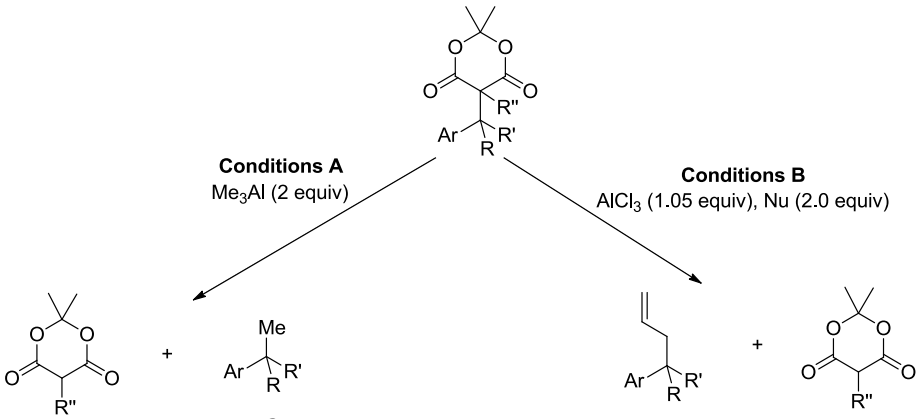
Attempted substitution of Meldrum's acid with nucleophilic agents was performed under transition metal catalysis based on the group's previous work on hydrogenolysis (Scheme 2.2).[32] However, experiments employing a variety of transition metals as catalysts (homogeneous and heterogeneous) were not successful, as they resulted in either decomposition, or starting materials recovery.



Scheme 2.2 Transition Metal Catalyzed Substitution of Meldrum's Acid

After unsuccessful attempts with transition metal catalysis, substitution of Meldrum's acid moiety starting from benzyl Meldrum's acid using Lewis acid catalysis was investigated.

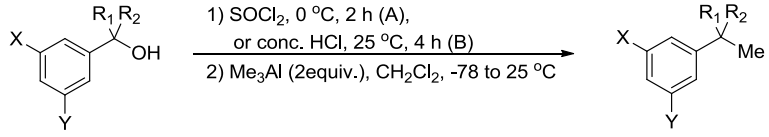
Optimization studies regarding choice of Lewis acid, solvent, temperature, and reaction time were performed. Based on these results, two sets of reaction conditions were devised, giving either methylated (Conditions **A**), or allylated products (Conditions **B**) (Scheme 2.3).



Scheme 2.3 Modification of sp^3-Hybridized Carbon Centers Through Lewis Acid-Promoted Substitution Reactions

One set of reaction conditions included dichloromethane as solvent and Me_3Al as Lewis acid (Conditions **A**, Scheme 2.3). The choice of Me_3Al as a Lewis acid for the substitution reaction is based on its combined Lewis acidity and nucleophilic properties upon complexation with the Meldrum's acid moiety.[46] The choice of Me_3Al is also supported by previous reports of successful methylation of benzylic carbon centers from activated tertiary alcohols (Table 2.2).[51] Tertiary benzylic alcohols are activated by treatments with $SOCl_2$ (method A) or concentrated HCl (method B), and, in many cases, reacted rapidly with Me_3Al at or below room temperature.[45] A variety of examples with different substitution patterns are shown in Table 2.2, including substrates bearing electron-donating and electron-withdrawing groups. In addition to the desired products, undesired elimination by-products were produced in the devised protocol for the methylation of activated tertiary benzylic alcohols (Table 2.2; Entries 5, 7, and 8).[45] Formation of the by-products helped to get some insights into the mechanism pathway which the substitution reaction is undertaking.

Table 2.2 Transformation of Tertiary Benzylic Alcohols to *tert*-Alkylbenzenes[45]



Entry	X	Y	R_1	R_2	Activation Method	Yield (%)
1	OMe	OMe	Me	Me	A	88
2	OMe	H	Me	Me	A	93
3	Me	Me	Me	Me	A	85
4	Ph	H	Me	Me	A	70

5	Cl	H	Et	Me	A	78[a] (87:13)
6	Cl	H	Et	Me	B	95
7	Cl	H	Et	Et	A	90[a] (56:44)
8	Cl	H	Et	Et	B	95[a] (96:4)

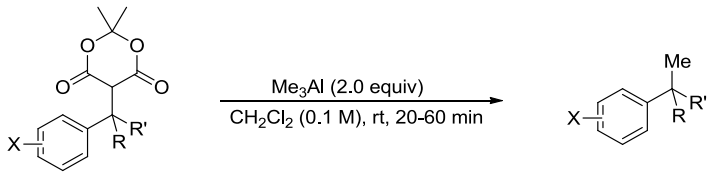
[a] Weight recovery of a mixture of the intended methylated and unwanted elimination product (alkene) following chromatography; the mole ratio (^{1}H NMR is given in parentheses).

The other set of reaction conditions devised for the substitution protocol of Meldrum's acid derivatives used aluminum trichloride as the Lewis acid (Conditions **B**) in order to increase the reactivity of the substrates towards weakly nucleophilic stannyl or silyl reagents.

2.4 Substitution Reactions at Quaternary Benzylic Centers and Tertiary Dibenzylic Centers

Substitution reactions showed a good generality in terms of substrate scope. Methyl substitution reactions gave excellent yields (>95 %) of final products, regardless of the nature of the substituents at various positions on the aromatic ring. Electron-donating, electron-neutral, and electron-withdrawing groups were tolerated, affording desired products and having no significant impact on the efficiency of the reactions in terms of steric and electronic factors. Excellent conversions and high yields were obtained (Table 2.3).

Table 2.3 Trimethylaluminum as a Nucleophile in Substitution Reactions of Quaternized Benzyl Centers



(1a-1n) (1.1a-1.1n)

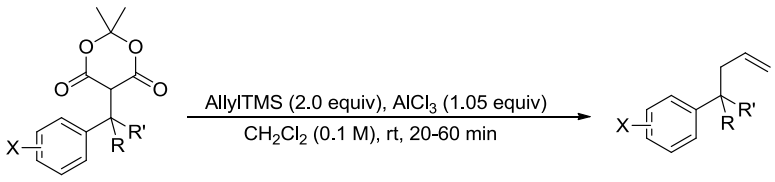
Entry	X	R, R'	Yield[a] (%)
1	H	R - R' = $(CH_2)_5$ **(1a)**	Quant. **(1.1a)**
2	4-*t*Bu	R = R' = Me **(1b)**	96 **(1.1b)**
3	4-(MeO)	R = R' = Me **(1c)**	93 **(1.1c)**
4	4-($C_8H_{17}O$)	R = R' = Me **(1d)**	95 **(1.1d)**
5	4-Cl	R - R' = $(CH_2)_5$ **(1e)**	Quant. **(1.1e)**
6	4-F	R - R' = $(CH_2)_5$ **(1f)**	95 **(1.1f)**
7	2-Et	R = R' = Me **(1g)**	91 **(1.1g)**

8	2-($C_8H_{17}O$)	R = R' = Me **(1h)**	94 **(1.1h)**
9	2-F	R - R' = $(CH_2)_5$ **(1i)**	96 **(1.1i)**
10	3-*t*Bu	R = R' = Me **(1j)**	98 **(1.1j)**
11	3-(C_6H_{13})	R = R' = Me **(1k)**	97 **(1.1k)**
12	3-($C_8H_{17}O$)	R = R' = Me **(1l)**	89 **(1.1l)**
13	3-TMS	R = R' = Me **(1m)**	Quant. **(1.1m)**
14	3-F	R - R' = $(CH_2)_5$ **(1n)**	98 **(1.1n)**

[a] In all cases, conversion was >95 % unless stated otherwise; This part of the project was done in collaboration with Dr. S. J. Mahoney.

In contrast, allylation reactions were not as effective as methylation (Scheme 2.4). The allylation substitution conditions employed gave lower yields, employing $AlCl_3$ as the Lewis acid and allylTMS as the nucleophile. Although some of the allylation reactions gave excellent yields (Entries 1-7) others were more affected by substrates bearing electron-donating, electron-neutral (alkyl substituents), as well as electron-withdrawing groups (Entries 7-14). When allylation reaction conditions were used on Meldrum's acid derivative bearing a *para*-F substituent, the reaction gave low yield of the desired product. Allyl$SnBu_3$ gave better results when used with *para*-F substituted benzyl Meldrum's acid derivative due to the greater nucleophilicity of allyl$SnBu_3$ compared with allylTMS (Entry 6). Heating of some substrates was required (50 or 65 °C), particularly ones that were inert under room temperature conditions (Entry 13). Thus, dichloroethane was chosen as the solvent for reactions performed at elevated temperatures due to its higher boiling point.[52] Reactions that gave lower yields (Entries 8-14) underwent competing reaction pathways: alkene and indane formations were observed.

Table 2.4 AllylTMS as a Nucleophile in Substitution Reactions of Quaternized Benzyl Centers



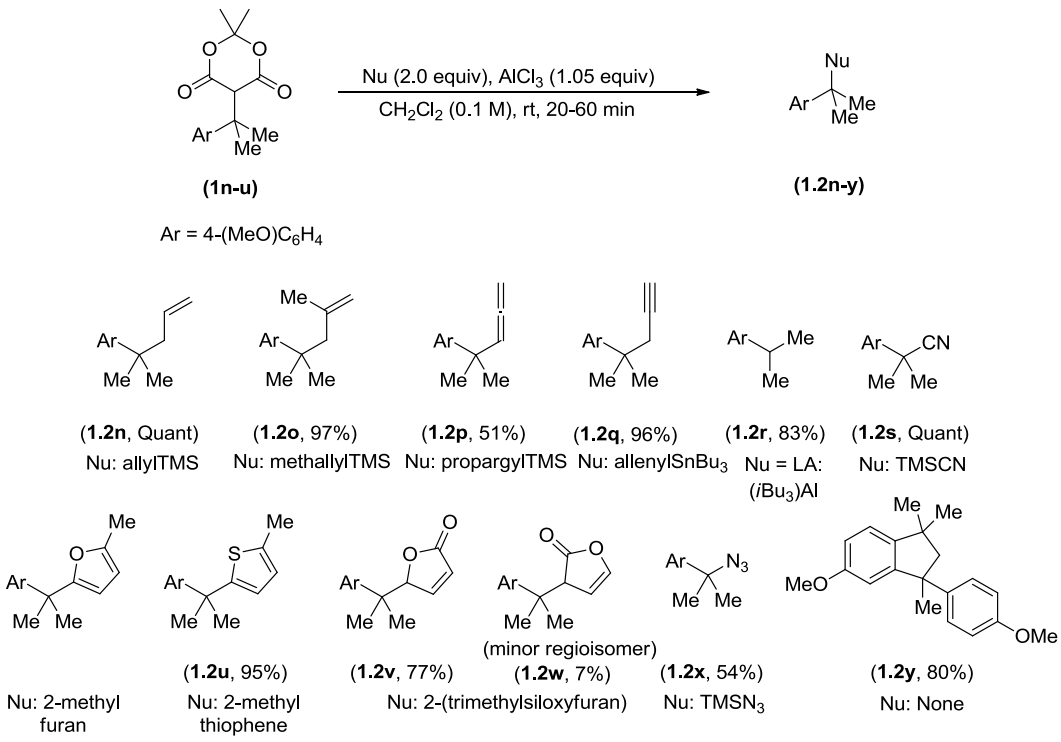
(1b-1y) (1.2a-1.2n)

Entry	X	R; R'	Yield[a] (%)
1	H	R = R' = Me **(1u)**	89 **(1.2c)**
2	4-*t*Bu	R = R' = Me **(1b)**	91 **(1.2b)**
3	4-(MeO)	R = R' = Me **(1c)**	Quant. **(1.2n)**
4	4-(OC_8H_{17})	R = R' = Me **(1d)**	Quant. **(1.2a)**

5	4-Cl	R = R' = Me **(1p)**	88[b] **(1.2d)**
6	4-F	R - R' = $(CH_2)_5$ **(1f)**	88[b] **(1.2e)**
7	2-(MeO)	R = R' = Me **(1v)**	82 **(1.2f)**
8	2-($C_8H_{17}O$)	R = R' = Me **(1h)**	59/57[b] **(1.2g)**
9	2-F	R = R' = Me **(1i)**	39 **(1.2h)**
10	3-*t*Bu	R = R' = Me **(1j)**	62 **(1.2i)**
11	3-(C_6H_{13})	R = R' = Me **(1k)**	59 **(1.2j)**
12	3-TMS	R = R' = Me **(1l)**	68 **(1.2k)**
13	3-(MeO)	R = R' = Me **(1y)**	29[c] **(1.2l)**
14	3-F	R = R' = Me **(1o)**	26 **(1.2m)**

[a] In all cases, conversion was >95 % unless stated otherwise; [b] $AllylSnBu_3$ was used as the nucleophile; [c] $(CH_2Cl)_2$, 50 °C, 24 h; This part of the project was done in collaboration with Dr. S. J. Mahoney.

After determining the substrate scope for methylation and allylation reactions, the range of nucleophiles was explored in the substitution reaction (Figure 2.2). AllylTMS, TMSCN and methallylTMS nucleophilic reagents furnished the final products in quantitative yields (both reactions using AllylTMS and TMSCN as nucleophiles) and 97 % yields, respectively. Products obtained with propargylTMS and $allenylSnBu_3$ reagents were obtained in good yields [**1.2p** (51 %) and **1.2q** (96 %)]. Triisobutylaluminum gave product **1.2r** (83 %) showing complementary product formation to the hydrogenolysis reaction. Other nucleophilic reagents [2-methylfuran (**1.2t**) and 2-methylthiophene (**1.2u**)] gave final products in good to excellent yields. Nucleophile 2-(trimethylsiloxy)furan gave a mixture of regioisomers (**1.2v, 1.2w**). $TMSN_3$ led to the construction a new C-N bond (**1.2x**). Formation of the indane product was observed while performing the substitution reaction in the absence of an external nucleophile (**1.2y**).



[a]In all cases, conversion was >95%, unless stated otherwise; This part of the project was done in collaboration with Dr. S. J. Mahoney.

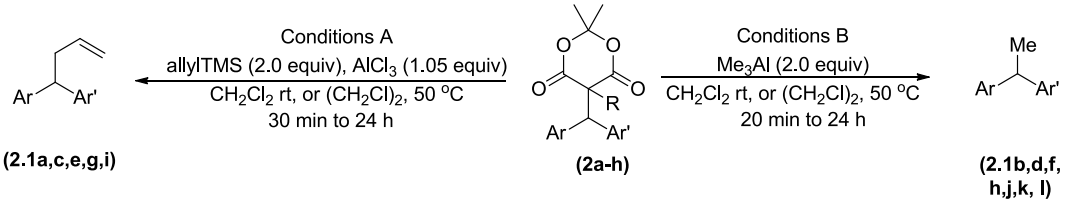
Figure 2.2 Allyltrimethylsilane and Other Nucleophiles in Substitution Reactions of Quaternized Benzyl Centers

Having determined the scope of the substitution at the quaternary benzylic Meldrum's acids in terms of electrophiles and nucleophiles, the project was expanded by screening reactivities of dibenzyl Meldrum's acids (Table 2.5). Methylation or allylation of the dibenzyl Meldrum's acid derivatives led to recovery of the starting materials with evolution of gas. This suggests deprotonation of the Meldrum's acid moiety with possible generation of methane (Entries 1-2). The use of allyl$SnBu_3$ did not improve the allylation reactions (Entry 1-2). Methylation at the C5-position of the Meldrum's acid moiety allowed for the substitution to proceed and gave an excellent yield (92 %) of the product (Entry 4). Allylation of unsubstituted dibenzylic Meldrum's acids, where the C5-position of Meldrum's acid was quaternized, furnished the final product in 93 % yield (Entry 3). The results in Table 2.5 indicate that the substitution is affected by the electronic nature of the substituents present on both aromatic rings.

Substrates bearing electron-donating groups on one or both aromatic rings furnished substitution products for both allylation and methylation conditions in excellent yields, and

did not require quaternization of the Meldrum's acid moiety (Table 2.5; Entries 5-10). Substrates with electron-withdrawing groups on both aromatic rings at the *para*-position resulted in either poor yield under allylation conditions (Entry 11), or no conversion under methylation reaction conditions (Entry 12). In spite of that, when methylation of the Meldrum's acid moiety was performed, both allylation and methylation proceeded smoothly (Entries 13-14).

Table 2.5 Allylation and Methylation at Dibenzylic Centers



Entry	Conditions	Ar, Ar'	R	Conversion (%)	Yield[a] (%)
1	A	Ar = Ar' = C_6H_5 **(2a)**	H	>95	50 **(2.1a)**
2	B	Ar = Ar' = C_6H_5 **(2a)**	H	<5	N/A **(2.1b)**
3	A	Ar = Ar' = C_6H_5 **(2b)**	Me	>95	93 **(2.1a)**
4	B	Ar = Ar' = C_6H_5 **(2b)**	Me	>95	92 **(2.1b)**
5	A	Ar = Ar' = 4-(OMe)C_6H_5 **(2c)**	H	>95	94 **(2.1c)**
6	B	Ar = Ar' = 4-(OMe)C_6H_5 **(2c)**	H	>95	Quant. **(2.1d)**
7	A	Ar = 4-(OMe)C_6H_5; Ar' = C_6H_5 **(2d)**	H	>95	96 **(2.1e)**
8	B	Ar = 4-(OMe)C_6H_5; Ar' = C_6H_5 **(2d)**	H	>95	95 **(2.1f)**
9	A	Ar = 4-(OMe)C_6H_5; Ar' = 4-ClC_6H_5 **(2e)**	H	>95	91 **(2.1g)**
10	B	Ar = 4-(OMe)C_6H_5; Ar' = 4-ClC_6H_5 **(2e)**	H	>95	87 **(2.1h)**
11	A	Ar = Ar' = 4-ClC_6H_5 **(2f)**	H	>95	42 **(2.1i)**
12	B	Ar = Ar' = 4-ClC_6H_5 **(2f)**	H	<5	N/A **(2.1j)**
13	A	Ar = Ar' = 4-ClC_6H_5 **(2g)**	Me	>95	94 **(2.1i)**
14	B	Ar = Ar' = 4-ClC_6H_5 **(2g)**	Me	>95	96 **(2.1j)**
15	B	Ar = 2-naphthyl; Ar' = 3,4,5-$(OMe)_3$Ph **(2h)**	Me	>95	99 **(2.1k)**

[a] This part of the project was done in collaboration with Dr. S. J. Mahoney.

The utility of the newly-devised methodology (Table 2.5, Entry 15) was demonstrated further by applying the methylation conditions to the synthesis of a biologically

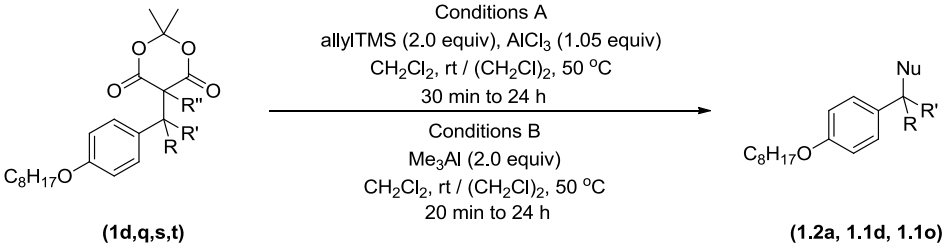
active molecule. Synthesized compound **28** is a potent inhibitor of tubulin polymerization (Scheme 2.4).[53]

Scheme 2.4 Synthesis of Potent Tubulin Polymerization Inhibitor

2.5 Effect of the Benzylic Alkyl Substituents

Generality and efficiency of the substitution reactions were further investigated with the alteration of the substitution patterns at the benzylic position of Meldrum's acid derivatives (Table 2.6). Substitution at quaternary, tertiary, and secondary benzylic centers of Meldrum's acids were studied under allylation and methylation conditions. Quaternary benzylic Meldrum's acids delivered complete conversion and high yields of the final products under methylation and allylation conditions (Entries 1-2). Substitution at tertiary and secondary benzylic Meldrum's acid derivatives produced lower yields compared to quaternary benzylic centers (Entries 3-8). These results suggest that quaternary benzylic carbon centers are able to stabilize the build-up of positive charge in the transition state, and allow the substitution reaction to occur efficiently. Interestingly, upon removal of the acidic proton at the 5-position of Meldrum's acid moiety, the allylation reactions for tertiary benzylic centers significantly improved (Entry 5). This observation is not fully understood and further investigation of this issue is ongoing.

Table 2.6 Allylation and Methylation Reactions at Secondary, Tertiary and Quaternary Benzylic Carbon Centers

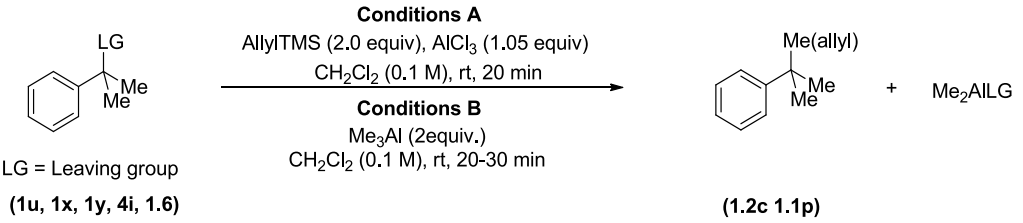


Entry	Conditions	R; R'; R''	Conversion (%)	Yield (%)
1	A	R = R' = Me; R'' = H **(1d)**	>95	Quant. **(1.2a)**
2	B	R = R' = Me; R'' = H **(1d)**	>95	95 **(1.1d)**
3	A	R = Me; R' = R'' = H **(1t)**	>95	68 **(1.1o)**
4	B	R = Me; R' = R'' = H **(1t)**	<5	N/A
5	A	R = R'' = Me; R' = H **(1s)**	>95	77 **(1.1o)**
6	B	R = R'' = Me; R' = H **(1s)**	<5	N/A
7	A	R = R' = R'' = H **(1q)**	<5	N/A
8	B	R = R' = R'' = H **(1q)**	<5	N/A

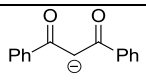
2.6 Direct Comparison of Meldrum's Acid Leaving Group Ability

The ability of Meldrum's acid to act as a leaving group was compared to commonly-employed leaving groups under two sets of substitution reaction conditions (Table 2.7). As previously reported (Section 2.3; Table 2.4; Entry 1) substrate **1u** provided excellent result under allylation and methylation reaction conditions (Table 2.7; Entries 1-2). Meldrum's acid as a leaving group was superior to chloride, hydroxide, acetate, and dibenzoyl methane under both sets of substitution reaction conditions (Entries 3-10).[54] Lower yields for commonly-employed leaving groups were attributed to competing elimination and indane formation pathways.

Table 2.7 Leaving Group Ability in Substitution Reactions of Quaternized Benzyl Centers



Entry	Conditions	Leaving Group	Yield[a] (%)
1	A	**(1u)**	89 **(1.2c)**
2	B	**(1u)**	63 **(1.1p)**
3	A	**(4i)**	62 **(1.2c)**

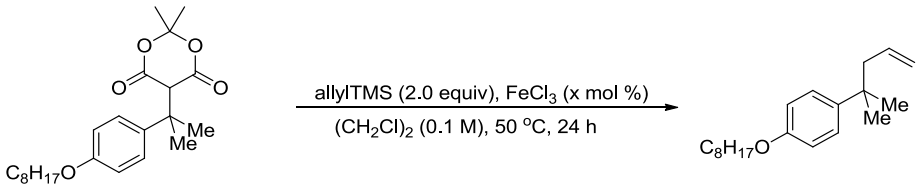
4	B	 **(4i)**	82 **(1.1p)**
5	A	 **(1.6)**	46 **(1.2c)**
6	B	 **(1.6)**	83 **(1.1p)**
7	A	**(1x)**	42 **(1.2c)**
8	B	**(1x)**	54 **(1.1p)**
9	A	 **(1y)**	50 **(1.2c)**
10	B	 **(1y)**	NA[b]

[a] In all cases, conversion was >95 %, unless noted otherwise; [b] Deprotonation of the starting material was observed.

2.7 Allylation Reactions at Quaternized Benzyl Centers of Meldrum's Acid Derivatives Under $FeCl_3$ Catalysis

Aluminum and iron trichlorides were shown to achieve desired allylation reactions under stoichiometric reaction conditions. Iron trichloride was also shown to catalyze the allylation reaction (Table 2.8). Twenty mole percent of iron trichloride was optimal for the reaction to obtain excellent conversions and good yields (Entry 1), whereas lower catalyst loading resulted in low conversions or yields (Entries 2-4).

Table 2.8 Optimization of Substitution Reactions: Catalyst Loading



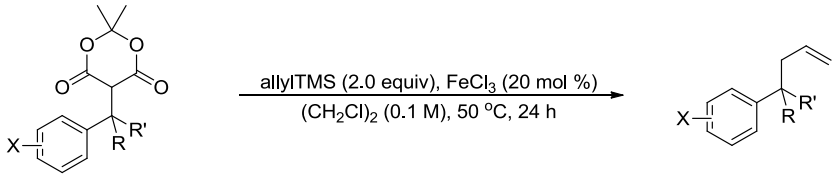
(1d) **(1.2a)**

Entry	Catalyst loading (mol %)	Conversion (%)	Yield (%)
1	20	>95	80
2	15	>95	73
3	10	>95	71
4	5	50	32

The next step was to determine the scope of the catalyzed substitution reactions. Substrates bearing electron-donating, electron-withdrawing, and electron-neutral substituents were screened under allylation conditions (Table 2.9). Substrates bearing electron-donating

groups at the *para*-position of the aromatic ring of benzyl Meldrum's acids gave complete conversion and good yields (Entries 1-2). The other electrophiles were shown to lead to lower yields (Entries 3-5). Therefore, the generality of the catalyzed reaction was limited, working only for the substrates bearing *para*-alkoxy substituents on the aromatic rings.

Table 2.9 Scope of Iron-Catalyzed Allylation Reactions



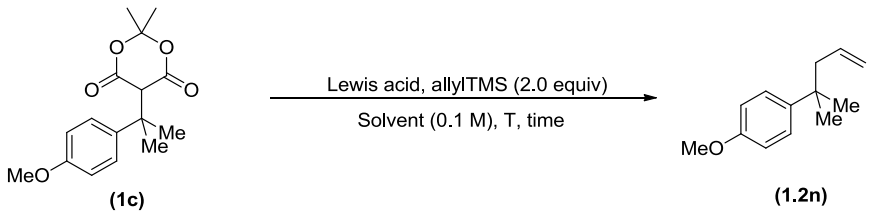
(1b,c,d,p,u) (1.2a,b,c,d,n)

Entry	X	Yield[a] (%)
1	4-OMe **(1c)**	85 **(1.2n)**
2	4-OC_8H_{17} **(1d)**	80 **(1.2a)**
3	4-*t*-Bu **(1b)**	32 **(1.2b)**
4	H **(1u)**	25 **(1.2c)**
5	4-Cl **(1p)**	18 **(1.2d)**

[a] In all cases, conversion was >95 %, unless noted otherwise.

In addition, the purity of either of the Lewis acids used [$AlCl_3$ (99.99+%) or $FeCl_3$ (99.99+% or 97 %)] in the allylation substitution reactions had a negligible effect on the reaction (Table 2.10).

Table 2.10 Comparison of $AlCl_3$ and $FeCl_3$ Purity for Promoting Allylic Substitution



(1c) (1.2n)

Entry	Lewis Acid	Loading (equiv)	Solvent	T (°C)	Time	Yield[a] (%)
1	$AlCl_3$ (99.99+%)	1.05	CH_2Cl_2	rt	20 min	Quant.
2	$FeCl_3$ (97%)	1.05	CH_2Cl_2	rt	20 min	82
3	$AlCl_3$ (99.99+%)	0.20	$(CH_2Cl)_2$	50 °C	24 h	ND[c]
4	$FeCl_3$ (97%)	0.20	$(CH_2Cl)_2$	50 °C	24 h	85
5	$FeCl_3$ (99.99+%)	0.20	$(CH_2Cl)_2$	50 °C	24 h	86

[a] In all cases, conversion was >95 %, unless noted otherwise; [b] This part of the project was done in collaboration with Dr. S. J. Mahoney; [c] An inseparable mixture of **1.2n** : 1-methoxy-4-(prop-1-en-2-yl)benzene (the elimination product) was obtained in a 5:1 ratio respectively.

2.8 Proposed substitution Reaction and Competing Pathway Mechanisms

Although the mechanism of the substitution reaction has not been elucidated, by-products formed in the course of the reaction give some insight into the mechanism. As reported previously by Li *et al.*[51], the C-C bond is cleaved with the help of the iron trichloride Lewis acid, which coordinates to the 1,3-dicarbonyl unit. We expect different reaction pathways depending on the substitution at the benzylic position. In general, we envisioned that trimethylaluminum/aluminum trichloride achieves σ-complexation with one of the carbonyl groups of the Meldrum's acid moiety, furnishing nucleophilic organoaluminum reagent **29** (Figure 2.3). Thus, complexation aids in the cleavage of C-C bond via the intermediacy of cation **30**, which is trapped by the nucleophile. Therefore, the desired C-C bond cleavage is achieved via an S_N1 reaction mechanism by the attack of the internal or external nucleophile on a carbocation intermediate. A similar mechanism is proposed for the $AlCl_3$/nucleophile pair.

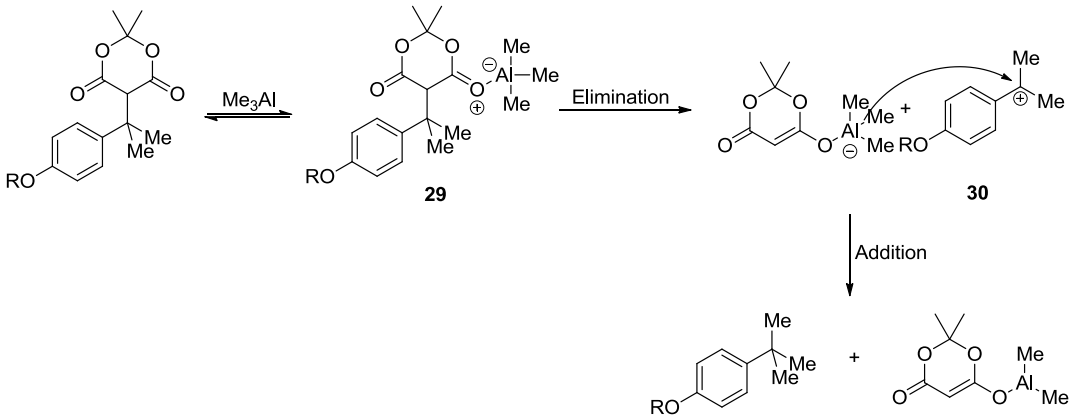


Figure 2.3 Tentative Benzylic Substitution Mechanism

Alternatively, we can account for formation of the competing indane and elimination products by the intramolecular attack on the carbocation intermediate by the π-nucleophile, or by deprotonation, respectively (Figure 2.4). The indane product formation product likely undergoes a similar mechanism as reported by Reeves *et al* (Figure 2.4).[55] After Lewis acid coordination to one of the carbonyl group of the Meldrum's acid derivatives, formation of the benzylic cation **A** is proposed. Intermediate **A** undergoes proton loss to give E1 product **B**. Attack of **B** onto **A** gives intermediate **C** which cyclizes to form indane.

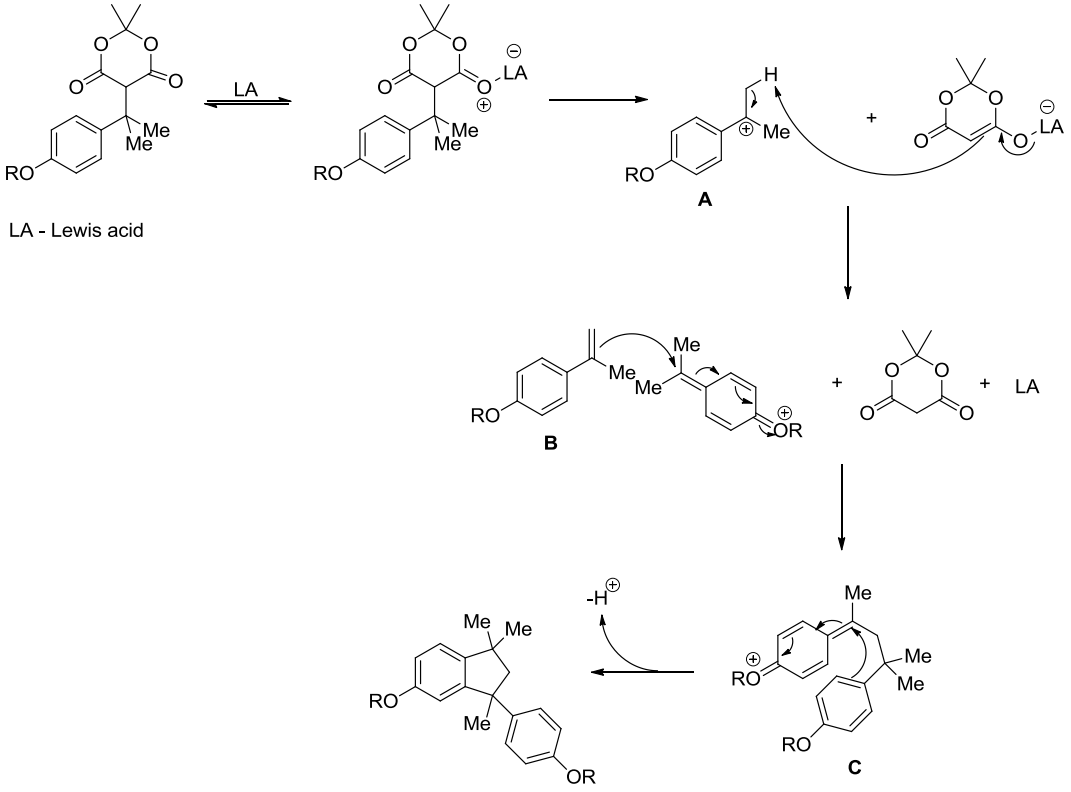
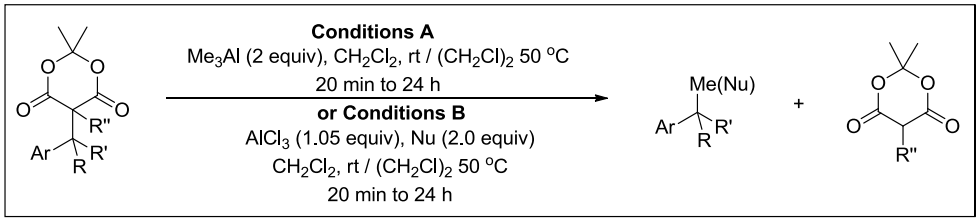


Figure 2.4 Proposed Reaction Mechanisms for Elimination and Indane Formation Pathways

2.9 Summary

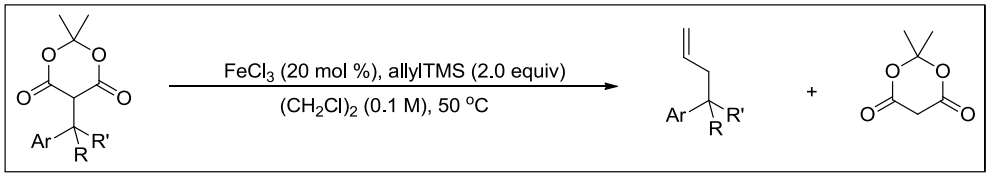
Novel substitution reactions were developed for the modification of sp^3-hybridized carbon centers through displacement of Meldrum's acid with modest to excellent yields (Scheme 2.5). In addition, substitution reactions were shown to proceed with quaternary and tertiary benzylic carbon centers.



Scheme 2.5 Developed Methylation and Allylation Protocols

Substitution reactions were shown to have a wide scope of both substrates and nucleophiles under stoichiometric Lewis acidic conditions. Catalytic substitution reactions

proceeded for electron-rich substrates (Scheme 2.6); however, further investigations are required in order to broaden the substrate scope.



Scheme 2.6 $FeCl_3$-Catalyzed Allylation Reaction under Catalytic Amount of $FeCl_3$

Benzylic carbon-carbon σ bonds were transformed into Csp^3-X bonds, where X is C, H, or N. Moreover, the methylation method was applied to the construction of a biologically active target of choice.[54] The superiority of Meldrum's acid as a leaving group was shown by direct comparison with commonly-employed leaving groups (dibenzoyl methane, acetate, chloride, and hydroxide).

In conclusion, mild reaction conditions, wide substrate and nucleophile scope, as well as functionalization of sp^3-hybridized benzylic carbon centers, makes this methodology a good choice for achieving the synthesis of complex organic targets.

2.10 Future Work

Current efforts are focused on broadening the scope of substitution reactions. Catalytic substitution reactions are the next step for this project. As $FeCl_3$-catalyzed allylation reactions had limited scope (only electron-rich substrates were shown to participate in the reaction), it would be beneficial to identify the optimal Lewis acid conditions (solvent, temperature, reaction time) to carry out the substitution reaction (Figure 2.5).

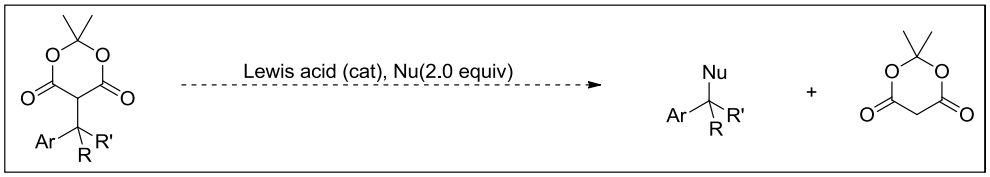
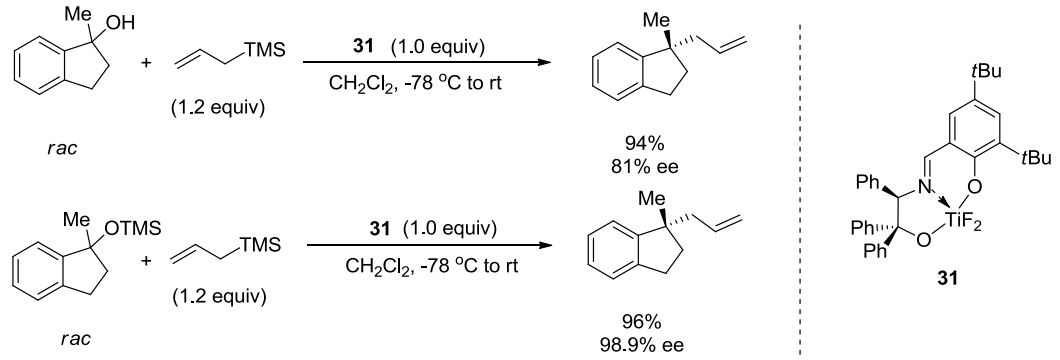


Figure 2.5 Proposed Substitution Reactions under Lewis Acid-Catalyzed Conditions

Preliminary investigations into using enantioenriched substrates for developing the substitution reaction returned no appreciable results, giving racemic mixtures of the product under methylation reaction conditions.[56] The obtained results (racemic mixture under

methylation reaction conditions) correlate with our proposed S_N1 reaction mechanism. One suggestion to overcome this limitation is to use the methodology described by Braun *et al*.[57] By means of the chiral titanium (IV) Lewis acid, the asymmetric substitution of hydroxyl, or silyloxy group by allylic residue is achieved (Scheme 2.7).[58] This method allows the generation of quaternary carbon centers in a highly enantioselective manner.[58]



Scheme 2.7 Titanium (IV)-Catalyzed Dyamic Kinetic Asymmetric Transformation of Alcohols and Silyl Ethers under Carbon Allylation

2.11 Experimental

General Considerations

Reactions

THF was distilled over sodium/benzophenone ketyl before use. 1,2-Dichloroethane and DMF were distilled over CaH_2 and the former was then degassed via 3 freeze-pump-thaw cycles following distillation. HPLC grade dichloromethane and pentane were used as received from commercial sources. The following Grignard and organoaluminum reagents were obtained from commercial sources and used without further purification: MeMgBr (3.0 M in Et_2O), PhMgBr (3.0 M in Et_2O), PhMgCl (2.0 M in THF), 4-F(C_6H_4)MgBr (1.0 M in THF), 4-Cl(C_6H_4)MgBr (1.0 M in Et_2O), 4-MeO(C_6H_4)MgBr (0.5 M in THF), 3-MeO(C_6H_4)MgBr (1.0 M in THF), BnMgCl (2.0 M in THF), Me_3Al (2.0 M in heptane), $^{i}Bu_3Al$ (1.0 M in hexanes), and DIBAL-H (1.5 M in PhMe). The other Grignard reagents used were prepared from the corresponding aryl bromides with magnesium in THF. Potassium carbonate was dried in an oven (140 °C) overnight prior to use. Triethylamine was distilled over CaH_2 prior to use. Chlorotrimethylsilane was distilled prior to use. Anhydrous lithium chloride was heated in a 140 °C oil bath under vacuum (0.5 mm Hg) overnight prior

to use. Anhydrous aluminum chloride (99.99+% - Al PURATREM), iron chloride (97 %, reagent grade) and iron chloride (99.99+%, sublimed grade) were used as received from commercial sources. Reactions were monitored by thin-layer chromatography on commercially prepared plates. Developed plates were viewed under a UV lamp (254 nm) and with ceric ammonium molybdate stain. Flash chromatography was performed using 230-400 mesh silica gel.

The following starting materials were prepared according to literature procedures and the spectral data obtained were in agreement with those reported and consequently, data will not be repeated here: 2,2-dimethyl-5-(1-phenylcyclohexyl)-1,3-dioxane-4,6-dione (**1a**),[58] 5-(2-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1c**),[59] 2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**1d**),[32] 5-(2-(2-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione **(1g)**,[59] 2,2-dimethyl-5-(2-(2-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**1h**),[32] 2,2-dimethyl-5-(2-(3-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**1l**),[32] 2,2-dimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**1t**),[32] 2,2-dimethyl-5-(2-phenylpropan-2-yl)-1,3-dioxane-4,6-dione (**1u**),[59] 5-(2-(2-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1v**),[59] 5-(2-(3-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione **(1y)**[59] and 5-(bis(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2c**).[32]

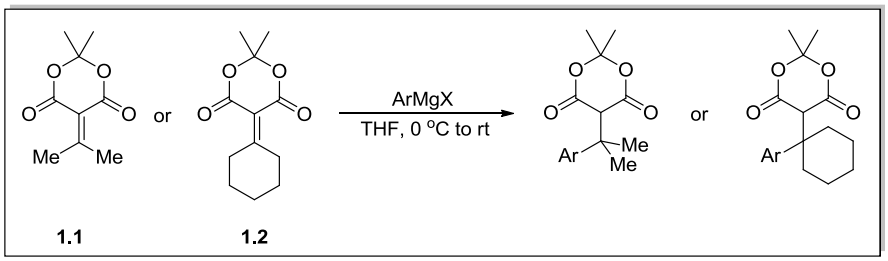
Characterization

^{1}H and ^{13}C NMR spectra for all compounds were obtained in $CDCl_3$ or acetone-d_6 at 300 MHz and 75 MHz, respectively, unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual $CHCl_3$ (7.24 ppm) or acetone (2.05 ppm), and carbon spectra were calibrated to $CDCl_3$ (77.0 ppm). Carbon multiplicities (C, CH, CH_2, CH_3) were determined by combined DEPT 90/135 experiments. ^{19}F NMR spectra were recorded with ^{1}H decoupling in $CDCl_3$ referenced to TFA (-76.5 ppm). IR spectroscopy was obtained using a Perkin Elmer Spectrum RX I FT-IR system.

Melting points are uncorrected. High resolution mass spectra were run at the University of Waterloo Mass Spectrometry facility and the AIMS facility at the University of Toronto.

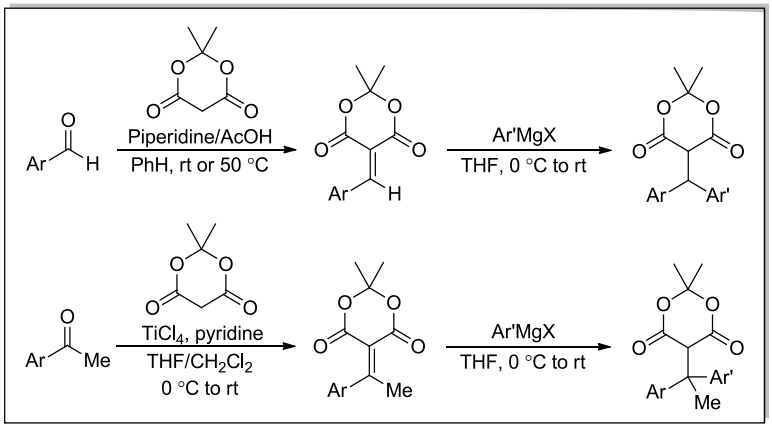
Synthesis of Starting Materials

General Procedure A - Preparation of Quaternary Benzyl Meldrum's Acids



Quaternary benzyl Meldrum's acids were prepared by the addition of aryl Grignard reagents (2-3 equiv, dropwise addition or alternatively syringe pump addition at a rate of 0.34 mL/min) to a solution of 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione[32] (**1.1**) or 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione[59] (**1.2**) in dry THF under nitrogen at 0 °C. The reaction was stirred at room temperature until completion of reaction by TLC or for 24 h. The reaction was quenched with 5 % HCl at 0 °C and was extracted with EtOAc (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by recrystallization or flash chromatography as indicated.

General Procedure B - Preparation of Tertiary and Quaternary Benzyl Meldrum's Acids

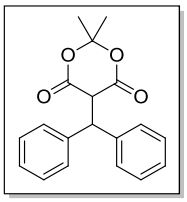


Alkylidene Meldrum's acids were prepared according to previously established literature procedures. When condensing aromatic aldehydes, the piperidinium acetate protocol[60] was used and alternatively, when condensing aromatic ketones the $TiCl_4$/pyridine method[61] was employed unless specified otherwise.

Tertiary and quaternary benzyl Meldrum's acids were prepared by the addition of aryl Grignard reagents (2-3 equiv, dropwise addition or syringe pump addition at a rate of 0.34 mL/min) to a solution of alkylidene Meldrum's acids in dry THF under nitrogen at 0 °C. The reaction was stirred at room temperature until completion of reaction by TLC or for 24 h. The reaction was quenched with 5 % HCl at 0 °C and was extracted with EtOAc (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by either recrystallization or flash chromatography as indicated.

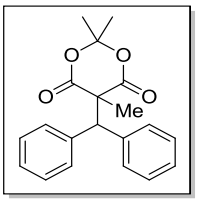
The following starting materials were prepared according to the general procedures A and B specified: 5-(2-(4-*tert*-Butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1b**),[62] 5-(1-(4-Chlorophenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1e**),[63] 5-(1-(4-Fluorophenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1f**),[60] 5-(2-(3-(*tert*-butyl)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1j**),[63] 5-(2-(3-Hexylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1k**),[63] 2,2-Dimethyl-5-(2-(3-(trimethylsilyl)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**1m**),[63] 5-(1-(3-Fluorophenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1n**),[63] 5-(2-(3-Fluorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1o**),[63] 5-(2-(4-Chlorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1p**),[63] 5-((4-Methoxyphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2d**), [64] 5-((4-Chlorophenyl)(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2e**),[63] 5-(Bis(4-chlorophenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2f**),[63] 5-(Bis(4-chlorophenyl)methyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**2g**),[63] Naphthalen-2-yl(3,4,5-trimethoxyphenyl)methanol (**1.3**), [65] 2-(Chloro(3,4,5-trimethoxyphenyl)methyl)naphthalene (**1.4**),[63] 2,2,5-Trimethyl-5-(naphthalen-2-yl(3,4,5-trimethoxyphenyl)methyl)-1,3-dioxane-4,6-dione (**2h**).[63]

5-Benzhydryl-2,2-dimethyl-1,3-dioxane-4,6-dione (2a)[64]



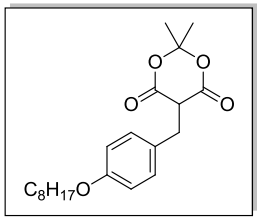
Prepared according to General Procedure B by the addition of phenylmagnesium bromide (7.47 mL, 22.4 mmol, 3.0 M solution in Et_2O) via syringe pump (0.34 mL/min) to 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione[61] (2.08 g, 8.96 mmol) in THF (8.96 mL); 12 h reaction time. Recrystallization from MeOH afforded a white solid (1.73 g, 62 % yield). M.p. 134-135 °C (MeOH) [148-149 °C (ether/hexane)[65]]; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25 7.19 (m overlapping with $CHCl_3$, 10H), 5.34 (d, *J* = 2.6 Hz, 1H), 4.25 (d, *J* = 2.6 Hz, 1H), 1.69 (s, 3H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.6 (C), 140.0 (C), 129.1 (CH), 128.4 (CH), 127.1 (CH), 105.1 (C), 51.1 (CH), 49.0 (CH), 28.2 (CH_3), 27.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{19}H_{22}NO_4$ ($[M + NH_4]^+$): 328.15488. Found: 328.15597.

5-Benzhydryl-2,2,5-trimethyl-1,3-dioxane-4,6-dione (2b)[66]



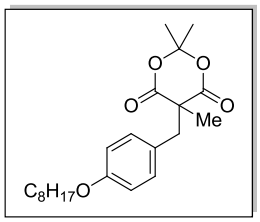
The following chemicals were added sequentially to an oven dried round bottom flask equipped with a magnetic stir bar at room temperature: 5-benzhydryl-2,2-dimethyl-1,3-dioxane-4,6-dione (**2a**) (1.50 g, 4.83 mmol), K_2CO_3 (1.00 g, 7.30 mmol), DMF (4.8 mL), followed by addition of iodomethane (3.0 mL, 48 mmol) at 0 °C; the reaction was allowed to stir for 19 h at rt. The workup consisted of adding water and extracting with CH_2Cl_2 (3X), and then the combined organic layers were washed with sat. brine solution (1X), dried over $MgSO_4$, filtered and concentrated. Trituration from MeOH (2X) afforded a white solid (0.458 g, 29 % yield). M.p. 170-172 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.51 (dd, *J* = 7.6, 1.4 Hz, 4H), 7.32-7.21 (m overlapping with $CHCl_3$, 6H), 4.72 (s, 1H), 1.61 (s, 3H), 1.54 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.9 (C), 138.3 (C), 130.3 (CH), 128.5 (CH), 127.7 (CH), 105.2 (C), 60.6 (CH), 54.4 (C), 30.0 (CH_3), 27.7 (CH_3), 24.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{24}NO_4$ ($[M + NH_4]^+$): 342.17053. Found: 342.17069.

2,2-Dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (1q)



4-*n*-Octyloxybenzaldehyde[62] (15 g, 64 mmol, 1.0 equiv) and Meldrum's acid (9.69 g, 67.2 mmol, 1.05 equiv) were dissolved in EtOH (135 mL, 0.5 M) at rt. Piperidine (0.67 mL, 0.1 equiv) was added dropwise, followed by glacial acetic acid (0.4 mL, 0.1 equiv), and the resulting mixture was stirred at rt for 30 min. The reaction was placed in an ice bath and sodium cyanoborohydride (6.33 g, 100 mmol, 1.5 equiv) was added in 6 portions over 30 min. The reaction was stirred at rt overnight and concentrated under reduced pressure. The mixture was quenched with 3 M HCl and was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. Recrystallization from MeOH afforded a white solid (12 g, 52 % yield). M.p. 52-53 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.19 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.70 (t, *J* = 4.8 Hz, 1H), 3.41 (d, *J* = 4.7 Hz, 2H), 1.75-1.69 (m, 5H), 1.45 (s, 3H), 1.41-1.26 (m, 10H), 0.86 (br t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.4 (C), 158.2 (C), 130.8 (CH), 128.8 (C), 114.4 (CH), 105.1 (C), 67.9 (CH_2), 48.2 (CH), 31.7 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 29.1 (2 x CH_2), 28.4 (CH_3), 27.2 (CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_5$ (M^+): 362.2093. Found: 362.2095.

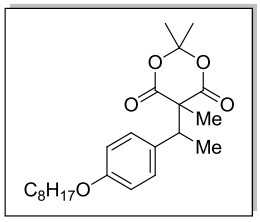
2,2,5-Trimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (1r)



The following chemicals were added sequentially to a flame dried round bottom flask equipped with a magnetic stir bar at room temperature: 2,2-dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (**1q**) (3.0 g, 8.3 mmol), K_2CO_3 (1.72 g, 12.4 mmol), DMF (9 mL), followed by addition of iodomethane (1.03 mL, 16.5 mmol) at 0 °C; the resulting reaction mixture was allowed to stir for 24 h at rt. The workup consisted of adding water and extracting with CH_2Cl_2 (3X), and then the combined organic layers were washed

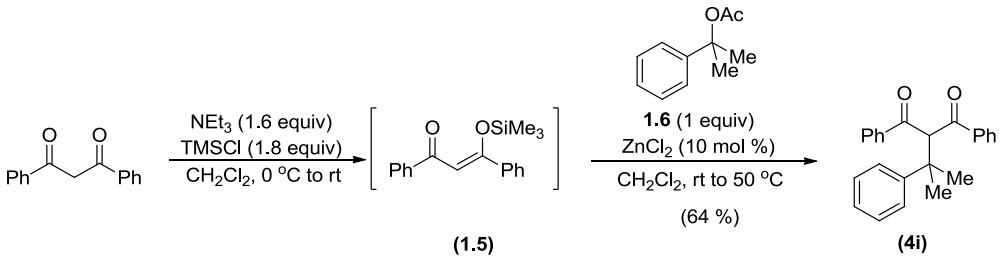
with sat. brine solution (1X), dried over $MgSO_4$, filtered and concentrated to afford a white solid (2.6 g, 82 % yield). M.p. 53-54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.05 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.25 (s, 2H), 1.74-1.66 (m, 5H), 1.58 (s, 3H), 1.39 (quintet, *J* = 7.8 Hz, 2H), 1.34-1.25 (m, 8H), 0.95 (s, 3H), 0.86 (br t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.9 (C), 158.7 (C), 131.1 (CH), 127.2 (C), 114.7 (CH), 105.2 (C), 68.0 (CH_2), 52.3 (C), 44.2 (CH_2), 31.8 (CH_2), 29.4 (CH_3), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.4 (CH_3), 25.9 (CH_2), 25.7 (CH_3), 22.6 (CH_2), 14.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{22}H_{32}O_5$ (M^+): 376.2250. Found: 376.2240.

2,2,5-Trimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (1s)

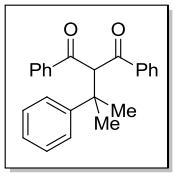


The following chemicals were added sequentially to an oven dried round bottom flask equipped with a magnetic stir bar at room temperature: 2,2-dimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**1t**) (2.3 g, 6.1 mmol), K_2CO_3 (1.3 g, 9.4 mmol), DMF (6 mL), followed by addition of iodomethane (1.9 mL, 30 mmol) at 0 °C; the resulting reaction mixture was allowed to stir for 17 h at rt. The workup consisted of adding water and extracting with EtOAc (3X), and then the combined organic layers were washed with sat. $NaHCO_3$ solution (2X), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography eluting with hexanes:EtOAc (5:1) afforded a clear oil (2.2 g, 94 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.03 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.86 (t, *J* = 6.6 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 1H), 1.70 (quintet, *J* = 6.8 Hz, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.37 (quintet, *J* = 6.8 Hz, 2H), 1.37-1.24 (m, 8H), 1.00 (s, 3H), 0.84 (br t, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.5 (C), 168.8 (C), 158.6 (C), 132.2 (C), 129.5 (CH), 114.4 (CH), 104.8 (C), 67.9 (CH_2), 54.4 (C), 47.9 (CH), 31.7 (CH_2), 30.2 (CH_3), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.5 (CH_3), 25.9 (CH_2), 22.6 (CH_2), 22.1 (CH_3), 15.4 (CH_3), 14.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{23}H_{34}O_5$ (M^+): 390.2406. Found: 390.2401.

Scheme 1 - Preparation of 1,3-Diphenyl-2-(2-phenylpropan-2-yl)propane-1,3-dione



1,3-Diphenyl-2-(2-phenylpropan-2-yl)propane-1,3-dione (4i)

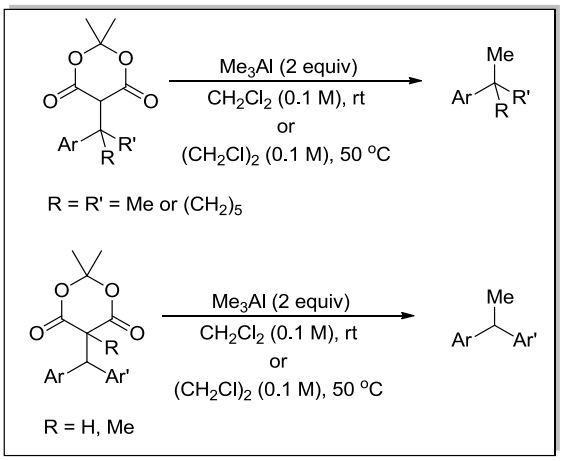


The method of preparation of (**4i**) was based on a report by Reetz and Hüttenhain, [67] and began with the *in situ* formation of 1,3-diphenyl-3-((trimethylsilyl)oxy)prop-2-en-1-one (**1.5**) as follows: a solution of dibenzoylmethane (500 mg, 2.23 mmol, 1 equiv) in CH_2Cl_2 (2.2 mL, 1.0 M) was stirred under a nitrogen atmosphere in an icebath for 7 minutes before the dropwise addition of triethylamine (0.50 mL, 3.6 mmol, 1.6 equiv). After stirring for an additional 1 h in the ice bath, chlorotrimethylsilane (0.51 mL, 4.0 mmol, 1.8 equiv) was added and the reaction mixture was stirred for a further 14 h at rt. The *in situ* prepared 1,3-diphenyl-3-((trimethylsilyl)oxy)prop-2-en-1-one (**1.5**)[68] (660 mg, 2.23 mmol, 1 equiv) was then cannulated into a stirred suspension of zinc chloride (30 mg, 0.22 mmol, 10 mol %) in dichloromethane (2.2 mL, 1.0 M) under a nitrogen atmosphere at rt. This was followed by the dropwise addition of 2-phenylpropan-2-yl acetate (**1.6**)[70] (400 mg, 2.23 mmol, 1 equiv) and the reaction mixture was then stirred in a 50 °C oil bath for 24 h. The workup consisted of cooling the reaction mixture to rt, followed by the addition of a saturated $NaHCO_3$ solution and extraction of the organic layer with CH_2Cl_2 (3X). The combined organic layers were then washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography eluting with toluene afforded a white solid (490 mg, 64 % yield). M.p. 135-136 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.73 (d, *J* = 8.0 Hz, 4H), 7.46-7.38 (m, 4H), 7.30 (t, *J* = 7.6 Hz, 4H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.2 Hz, 1H), 5.90 (s, 1H), 1.64 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 194.6 (C), 147.9 (C), 138.0 (C), 132.8 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 126.2 (CH), 126.1 (CH), 63.8

(CH), 42.2 (C) 26.6 (CH_3); HRMS (DART) *m/z* calcd for $C_{24}H_{26}NO_2$ ($[M + NH_4]^+$): 360.19635. Found: 360.19719.

Substitution Reactions

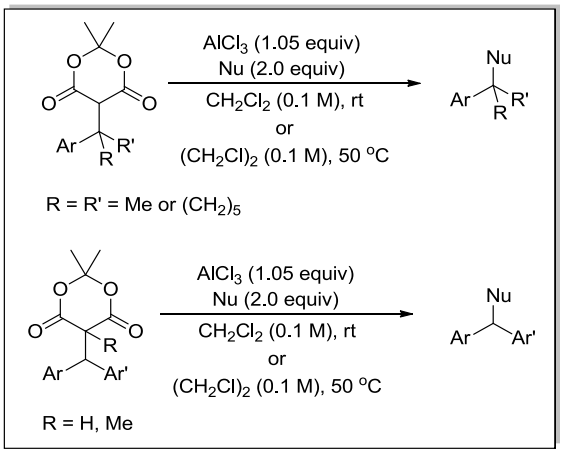
General Procedure C - Me_3Al Promoted Substitution Reactions of Benzyl Meldrum's Acids



In a glove box, benzyl Meldrum's acid (1 equiv) and CH_2Cl_2 or $(CH_2Cl)_2$ (0.1 M) were charged in an oven-dried sample vial with a magnetic stir bar. Trimethylaluminum (2.0 equiv, 2.0 M solution in heptane) was then added to this solution. The vial was capped with a rubber septum and the reaction mixture was stirred at rt or in a pre-heated 50 °C oil bath outside of the glove box. The reaction progress was monitored via TLC and the workup consisted of cooling the vial in an ice bath before 5 % HCl was slowly added to the reaction mixture. The layers were partitioned and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using silica gel with the indicated solvent gradient.

Note: For products with relatively low boiling points, the solvent was removed under reduced pressure (10-15 mm Hg) in an ice bath.

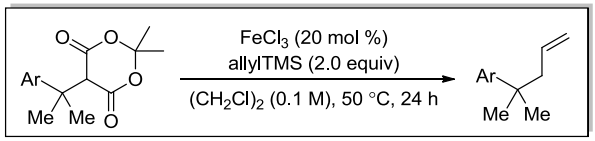
General Procedure D - $AlCl_3$ Promoted Substitution Reactions of Benzyl Meldrum's Acids



In a glove box, benzyl Meldrum's acid (1 equiv) and CH_2Cl_2 or $(CH_2Cl)_2$ (0.1 M) were charged in an oven-dried sample vial with a magnetic stir bar. The appropriate nucleophile (2.0 equiv) was first added into this solution, followed by the addition of aluminum (III) chloride (99.99+% - Al PURATREM, 1.05 equiv). The vial was then capped with a rubber septa and the reaction mixture was stirred at rt or in a pre-heated 50 °C oil bath outside of the glove box. The reaction progress was monitored via TLC and the workup consisted of cooling the vial in an ice bath before 5 % HCl was slowly added to the reaction mixture. The layers were partitioned and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using silica gel with the indicated solvent gradient.

Note: For products with relatively low boiling points, the solvent was removed under reduced pressure (10-15 mm Hg) in an ice bath.

General Procedure E* – $FeCl_3$-Catalyzed *Allylation of Benzyl Meldrum's Acids

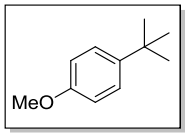


In a glove box, benzyl Meldrum's acid (1 equiv) and $(CH_2Cl)_2$ (0.1 M) were charged in an oven-dried sample vial with a magnetic stir bar, followed by the addition of allyltrimethylsilane (2 equiv) and then iron(III) chloride (20 mol %, 97 % reagent grade). The

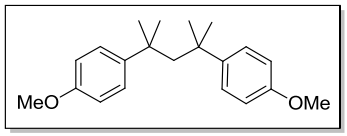
vial was then capped with a rubber septum and the reaction mixture was stirred in a pre-heated 50 °C oil bath outside of the glove box for 24 h. The workup consisted of cooling the vial in an ice bath before 5 % HCl was slowly added to the reaction mixture. The layers were partitioned and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using silica gel and eluting with pentane. The spectral properties of the products obtained from General Procedure E (reported in Table 4.5) were identical to those from General Procedure D.

The following substitution products were prepared according to the general procedures C and D specified: (1-Methylcyclohexyl)benzene (**1.1a**), [69] 1,4-Di-*tert*-butylbenzene (**1.1b**), [70] 1-Chloro-4-(1-methylcyclohexyl)benzene (**1.1e**),[63] 1-Fluoro-4-(1-methylcyclohexyl)benzene (**1.1f**),[65] 1-Fluoro-2-(1-methylcyclohexyl)benzene (**1.1i**),[65] 1,3-Di-*tert*-butylbenzene (**1.1j**), [71] 1-(*tert*-Butyl)-3-hexylbenzene (**1.1k**), [72] (3-(*tert*-Butyl)phenyl)trimethylsilane (**1.1m**),[73] 1-Fluoro-3-(1-methylcyclohexyl)benzene (**1.1n**),[63] 1-(1-Allylcyclohexyl)-4-fluorobenzene (**1.2e**), [74] 1-Fluoro-2-(2-methylpent-4-en-2-yl)benzene (**1.2h**),[63] 1-(*tert*-Butyl)-3-(2-methylpent-4-en-2-yl)benzene (**1.2i**),[63] 1-Hexyl-3-(2-methylpent-4-en-2-yl)benzene (**1.2j**),[63] Trimethyl(3-(2-methylpent-4-en-2-yl)phenyl)silane (**1.2k**),[72] 1-Fluoro-3-(2-methylpent-4-en-2-yl)benzene (**1.2m**),[63] 1-(2,4-Dimethylpent-4-en-2-yl)-4-methoxybenzene (**1.2o**),[63] 1-Methoxy-4-(2-methylpenta-3,4-dien-2-yl)benzene (**1.2p**),[63] 1-Methoxy-4-(2-methylpent-4-yn-2-yl)benzene (**1.2q**),[63] 2-(4-Methoxyphenyl)-2-methylpropanenitrile (**1.2s**),[75] 3-(2-(4-Methoxyphenyl)propan-2-yl)furan-2(3*H*)-one (**1.2v**)[65] and 5-(2-(4-Methoxyphenyl)propan-2-yl)furan-2(5*H*)-one (**1.2w**),[63] 1-(2-Azidopropan-2-yl)-4-methoxybenzene (**1.2x**),[76] 4,4'-(Ethane-1,1-diyl)bis(methoxybenzene) (**2.1d**),[77] 4,4'-(But-3-ene-1,1-diyl)bis(methoxybenzene) (**2.1c**),[78] 1-Methoxy-4-(1-phenylethyl)benzene (**2.1f**),[79] 1-Methoxy-4-(1-phenylbut-3-en-1-yl)benzene (**2.1e**), [80] 1-Chloro-4-(1-(4-methoxyphenyl)ethyl)benzene (**2.1h**), [81] 1-Chloro-4-(1-(4-methoxyphenyl)but-3-en-1-yl)benzene (**2.1g**), [82] 4,4'-(Ethane-1,1-diyl)bis(chlorobenzene) (**2.1j**),[63] 4,4'-(But-3-ene-1,1-diyl)bis(chlorobenzene) (**2.1i**),[63,79] 2-(1-(3,4,5-Trimethoxyphenyl)ethyl)naphthalene (**2.1k**).[63]

1-(*tert*-Butyl)-4-methoxybenzene (1.1c) [83] **and 4,4'-(2,4-Dimethylpentane-2,4-diyl)bis(methoxybenzene) (1.1.1c)**

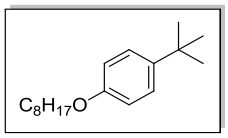


Prepared according to General Procedure C from Meldrum's derivative (**1c**) (198 mg, 0.677 mmol), Me_3Al (0.68 mL, 1.4 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (6.8 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane:diethyl ether (100:1) afforded a colourless oil (103 mg, 93 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.31 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.3 (C), 143.3 (C), 126.2 (CH), 113.3 (CH), 55.2 (CH^3), 34.0 (C), 31.5 (CH^3); HRMS (DART) *m/z* calcd for $C_{11}H_{17}O$ ($[M + H]^+$): 165.12794. Found: 165.12833.



Compound **1.1.1c** was second to elute from the above column, having increased the solvent polarity to pentane:diethyl ether (50:1), and was isolated as a colorless oil (7 mg, 7 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.12 (d, *J* = 8.8 Hz, 4H), 6.75 (d, *J* = 8.7 Hz, 4H), 3.77 (s, 6H), 2.09 (s, 2H), 1.00 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.2 (C), 142.3 (C), 126.9 (CH), 113.0 (CH), 57.8 (CH_2), 55.2 (CH_3), 37.9 (C), 31.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{21}H_{32}NO_2$ ($[M + NH_4]^+$): 330.24330. Found: 330.24359.

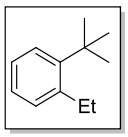
1-(*tert*-Butyl)-4-(octyloxy)benzene (1.1d)[84]



Prepared according to General Procedure C from Meldrum's derivative (**1.d**) (204 mg, 0.522 mmol), Me_3Al (0.53 mL, 1.06 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (5.2 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a pale yellow oil (129 mg, 94 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30 (dd, *J* = 7.8, 2.1 Hz, 2H), 6.80 (dd, *J* = 7.8, 2.0 Hz, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 1.77 (quintet, *J* = 7.1 Hz, 2H), 1.45-1.40 (m, 2H), 1.30 (m, 17H), 0.87 (br t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.9 (C), 143.1 (C), 126.1 (CH), 113.9 (CH), 67.9 (CH_2), 34.0 (C), 31.8 (CH_2), 31.5 (CH_3), 29.4 (2 x CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3);

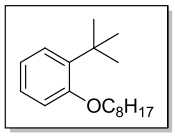
HRMS (DART) *m/z* calcd for $C_{18}H_{31}O$ ($[M + H]^+$): 263.23749. Found: 263.23749. Run #2 = 95 % yield; Avg = 95 % yield.

1-(*tert*-Butyl)-2-ethylbenzene (1.1g)[85]



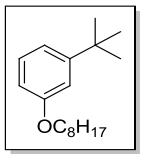
Prepared according to General Procedure C from Meldrum's derivative (**1g**) (67 mg, 0.23 mmol), Me_3Al (0.23 mL, 0.46 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (2.3 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a yellow oil (34 mg, 91 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.34 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.21-7.09 (m, 3H), 2.88 (q, *J* = 7.4 Hz, 2H), 1.40 (s, 9H), 1.25 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 147.1 (C), 143.0 (C), 131.1 (CH), 126.0 (CH), 125.9 (CH), 125.4 (CH), 35.7 (C), 31.6 (CH_3), 27.1 (CH_2), 17.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{12}H_{18}$ (M^+): 162.1409. Found: 162.1406.

1-(*tert*-Butyl)-2-(octyloxy)benzene (1.1h)



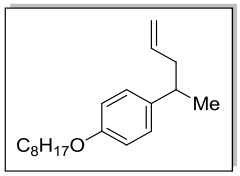
Prepared according to General Procedure C from Meldrum's derivative (**1h**) (26 mg, 0.066 mmol), Me_3Al (0.07 mL, 0.13 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (0.66 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes:EtOAc (9:1) afforded a light yellow liquid (16 mg, 94 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.26 (d overlapping with $CHCl_3$, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.86 (t overlapping with d at 6.84 ppm, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 1.82 (quintet, *J* = 6.9 Hz, 2H), 1.52 (m, 2H), 1.37 (s, 9H), 1.24 (m, 8H), 0.87 (br t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.9 (C), 137.9 (C), 126.9 (CH), 126.5 (CH), 119.9 (CH), 111.7 (CH), 67.7 (CH_2), 34.8 (C), 31.8 (CH_2), 29.8 (CH_3), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{18}H_{31}O$ ($[M + H]^+$): 263.23749. Found: 263.23808.

1-(*tert*-Butyl)-3-(octyloxy)benzene (1.1l)



Prepared according to General Procedure C from Meldrum's derivative (**1l**)[59] (200 mg, 0.512 mmol), Me_3Al (0.51 mL, 1.0 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (5.1 mL); 5 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (119 mg, 89 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.20 (t, *J* = 7.9 Hz, 1H), 6.96-6.92 (m, 2H), 6.69 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.93 (t, *J* = 6.6 Hz, 2H), 1.76 (quintet, *J* = 7.0 Hz, 2H), 1.49-1.28 (m overlapping with singlet at 1.29, 19H), 0.87 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.9 (C), 152.8 (C), 128.9 (CH), 117.6 (CH), 112.6 (CH), 110.4 (CH), 67.8 (CH_2), 34.7 (C), 31.8 (CH_2), 31.3 (CH_3), 29.4 (2 x CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (DART) *m*/*z* calcd for $C_{18}H_{31}O$ ([M + H]$^+$): 263.23749. Found: 263.23847.

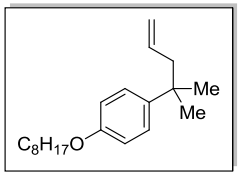
1-(Octyloxy)-4-(pent-4-en-2-yl)benzene (1.1o)



Prepared according to General Procedure D from 2,2,5-trimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**1s**) (187 mg, 0.479 mmol), allyltrimethylsilane (0.15 mL, 0.96 mmol), $AlCl_3$ (67 mg, 0.50 mmol) and CH_2Cl_2 (4.79 mL); 24 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (101 mg, 77 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.08 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.69 (ddt, *J* = 17.0, 10.1, 7.1 Hz, 1H), 4.97 (d slightly overlapping with d at 4.93, *J* = 15.2 Hz, 1H), 4.93 (d, *J* = 8.2 Hz, 1H), 3.91 (t, *J* = 6.6 Hz, 2H), 2.72 (sextet, *J* = 7.0 Hz, 1H), 2.38-2.18 (m, 2H), 1.75 (quintet, *J* = 7.0 Hz, 2H), 1.43-1.38 (m, 2H), 1.37-1.27 (m, 8H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.87 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.2 (C), 138.8 (C), 137.2 (CH), 127.6 (CH), 115.6 (CH_2), 114.2 (CH), 67.9 (CH_2), 42.8 (CH_2), 38.8 (CH), 31.7 (CH_2), 29.3 (2xCH_2), 29.1 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 21.6 (CH_3), 13.9 (CH_3); HRMS (DART) *m*/*z* calcd for $C_{19}H_{34}NO$ ([M + NH_4]$^+$): 292.26404. Found: 292.26424.

Alternatively prepared according to General Procedure D from 2,2-dimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**1t**) (197 mg, 0.523 mmol), allyltrimethylsilane (0.20 mL, 1.05 mmol), $AlCl_3$ (73 mg, 0.55 mmol) and CH_2Cl_2 (5.2 mL); 24 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (97 mg, 68 % yield). The spectral properties were identical to those reported above.

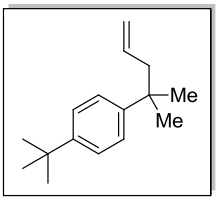
1-(2-Methylpent-4-en-2-yl)-4-(octyloxy)benzene (1.2a)



Prepared according to General Procedure D from 2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**1.d**) (60 mg, 0.15 mmol), allyltrimethylsilane (0.05 mL, 0.3 mmol), $AlCl_3$ (22 mg, 0.16 mmol) and CH_2Cl_2 (1.5 mL); 30 min reaction time at rt. Flash column chromatography eluting with pentane:CH_2Cl_2 (9:1), having dry packed the sample, afforded a pale yellow oil (44 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.57 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 4.96 (d overlapping with d at 4.95 ppm, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 9.9 Hz, 1H), 3.94 (t, *J* = 6.6 Hz, 2H), 2.34 (d, *J* = 7.3 Hz, 2H), 1.78 (quintet, *J* = 7.0 Hz, 2H), 1.46-1.41 (m, 2H), 1.40-1.28 (m which overlaps with s at 1.28, 14H), 0.90 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.9 (C), 141.1 (C), 135.7 (CH), 126.7 (CH), 116.7 (CH_2), 113.8 (CH), 67.8 (CH_2), 48.9 (CH_2), 36.9 (C), 31.8 (CH_2), 29.4 (2xCH_2), 29.2 (CH_2), 28.7 (CH_3), 26.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{33}O$ ([M + H]$^+$): 289.25314. Found: 289.25378.

Also prepared in analogy to General Procedure E from 2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**1.d**) (167 mg, 0.428 mmol), allyltrimethylsilane (0.14 mL, 0.86 mmol), $FeCl_3$ (14 mg, 0.086 mmol, 20 mol %) and $(CH_2Cl)_2$ (4.28 mL); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (98 mg, 80 % yield).

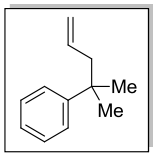
1-(*tert*-Butyl)-4-(2-methylpent-4-en-2-yl)benzene (1.2b)



Prepared according to General Procedure D from Meldrum's derivative (**1b**) (200 mg, 0.628 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (88 mg, 0.66 mmol) and CH_2Cl_2 (6.3 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a colourless oil (123 mg, 91 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 5.61 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.00 (d overlapping with d at 4.98 ppm, *J* = 17.7 Hz, 1H), 4.98 (d, *J* = 9.4 Hz, 1H), 2.38 (d, *J* = 7.2 Hz, 2H), 1.34 (s, 9H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.0 (C), 146.2 (C), 135.8 (CH), 125.4 (CH), 124.8 CH), 116.7 (CH_2), 48.8 (CH_2), 37.1 (C), 34.2 (C), 31.4 (CH_3), 28.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{16}H_{28}N$ ($[M + NH_4]^+$): 234.22217. Found: 234.22319.

Also prepared in analogy to General Procedure E from Meldrum's derivative (**1b**) (43.7 mg, 0.137 mmol), allyltrimethylsilane (0.043 mL, 0.27 mmol), $FeCl_3$ (4.4 mg, 0.027 mmol, 20 mol %) and $(CH_2Cl)_2$ (1.37 mL); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (9.6 mg, 32 % yield).

(2-Methylpent-4-en-2-yl)benzene (1.2c)[81]



Prepared according to General Procedure D from Meldrum's derivative (**1u**) (232 mg, 0.884 mmol), allyltrimethylsilane (0.28 mL, 1.8 mmol), $AlCl_3$ (124 mg, 0.930 mmol) and CH_2Cl_2 (8.8 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (126 mg, 89 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35-7.26 (m, 4H), 7.18-7.13 (m, 1H), 5.53 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1H), 4.94 (d overlapping with d at 4.92 ppm, *J* = 18.1 Hz, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 2.35 (d, *J* = 7.2 Hz, 2H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 149.2 (C), 135.5 (CH), 128.0 (CH), 125.8 (CH), 125.5 (CH), 116.9 (CH_2), 48.8 (CH_2), 37.6 (C), 28.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{12}H_{17}$ ($[M + H]^+$): 161.13303. Found: 161.13253. Run #2 = 88 % yield; Avg 89 % yield.

Also prepared in analogy to General Procedure D from 1,3-diphenyl-2-(2-phenylpropan-2-yl)propane-1,3-dione (**4i**)[86] (169 mg, 0.494 mmol), allyltrimethylsilane (0.16 mL, 0.99 mmol), $AlCl_3$ (70 mg, 0.52 mmol) and CH_2Cl_2 (4.9 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (49 mg, 62% yield). The spectral properties were identical to those reported above. Run #2 = 61 % yield; Avg 62 % yield.

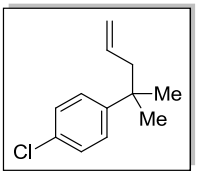
Also prepared in analogy to General Procedure D from 2-phenylpropan-2-yl acetate (**1.6**)[68] (230 mg, 1.29 mmol), allyltrimethylsilane (0.41 mL, 2.6 mmol), $AlCl_3$ (180 mg, 1.35 mmol) and CH_2Cl_2 (12.9 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (99 mg, 48 % yield). The spectral properties were identical to those reported above. Run #2 = 44 % yield; Avg 46 % yield.

Also prepared in analogy to General Procedure D from (2-chloropropan-2-yl)benzene (**1x**)[87] (202 mg, 1.31 mmol), allyltrimethylsilane (0.42 mL, 2.6 mmol), $AlCl_3$ (184 mg, 1.38 mmol) and CH_2Cl_2 (13.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (86 mg, 41 % yield). The spectral properties were identical to those reported above. Run #2 = 42 % yield; Avg 42 % yield.

Also prepared in analogy to General Procedure D from 2-phenylpropan-2-ol (**1y**) (183 mg, 1.34 mmol), allyltrimethylsilane (0.43 mL, 2.7 mmol), $AlCl_3$ (188 mg, 1.41 mmol) and CH_2Cl_2 (13.4 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (106 mg, 49 % yield). The spectral properties were identical to those reported above. Run #2 = 51 % yield; Avg 50 % yield.

Also prepared in analogy to General Procedure E from Meldrum's derivative (**1u**) (196 mg, 0.747 mmol), allyltrimethylsilane (0.24 mL, 1.5 mmol), $FeCl_3$ (24.2 mg, 0.15 mmol, 20 mol %) and $(CH_2Cl)_2$ (7.47 mL); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (30.2 mg, 25 % yield).

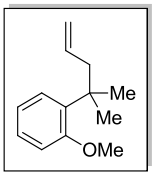
1-Chloro-4-(2-methylpent-4-en-2-yl)benzene (1.2d)



Prepared according to General Procedure D from Meldrum's derivative (**1p**) (100 mg, 0.337 mmol), allyltrimethylsilane (0.11 mL, 0.67 mmol), $AlCl_3$ (48 mg, 0.36 mmol), and CH_2Cl_2 (3.3 mL); 25 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a pale yellow oil (58 mg, 88 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23 (app s overlapping with $CHCl_3$, 4H), 5.50 (ddt, *J* = 17.0, 10.6, 7.3 Hz, 1H), 4.93 (d overlapping with d at 4.92 ppm, *J* = 15.2 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 2.31 (d, *J* = 7.3 Hz, 2H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 147.7 (C), 135.0 (CH), 131.2 (C), 128.0 (CH), 127.3 (CH), 117.2 (CH_2), 48.7 (CH_2), 37.4 (C), 28.5 (CH_3); HRMS (EI) *m/z* calcd for $C_{12}H_{15}Cl$ (M^+): 194.0862. Found: 194.0868. Run #2 = 85 % yield; Avg 87 % yield.

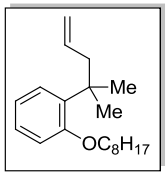
Also prepared in analogy to General Procedure E from Meldrum's derivative (**1.2d**) (194 mg, 0.654 mmol), allyltrimethylsilane (0.21 mL, 1.3 mmol), $FeCl_3$ (21.2 mg, 0.13 mmol, 20 mol %), and $(CH_2Cl)_2$ (6.54 mL); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (22.6 mg, 18 % yield).

1-Methoxy-2-(2-methylpent-4-en-2-yl)benzene (1.2f)



Prepared according to General Procedure D from Meldrum's derivative (**1v**) (200 mg, 0.684 mmol), allyltrimethylsilane (220 μL, 1.37 mmol), $AlCl_3$ (96 mg, 0.72 mmol) and CH_2Cl_2 (6.8 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a colourless oil (107 mg, 82 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23-7.18 (m, 2H), 6.93-6.87 (m, 2H), 5.52 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 4.94 (d slightly overlapping with d at 4.88 ppm, *J* = 17.1 Hz, 1H), 4.88 (d, *J* = 10.3 Hz, 1H), 3.84 (s, 3H), 2.62 (d, *J* = 7.3 Hz, 2H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.3 (C), 136.7 (CH), 136.2 (C), 127.5 (CH), 127.1 (CH), 120.2 (CH), 115.8 (CH_2), 111.3 (CH), 54.9 (CH_3), 45.1 (CH_2), 37.9 (C), 27.9 (CH_3); HRMS (DART) *m/z* calcd for $C_{13}H_{19}O$ ($[M + H]^+$): 191.14359. Found: 191.14353.

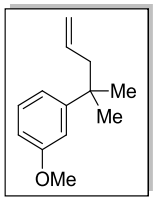
1-(2-Methylpent-4-en-2-yl)-2-(octyloxy)benzene (1.2g)



Prepared according to General Procedure D from Meldrum's derivative (**1h**) (198 mg, 0.507 mmol), allyltrimethylsilane (0.16 mL, 1.0 mmol), $AlCl_3$ (71 mg, 0.53 mmol) and CH_2Cl_2 (5.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (86 mg, 59 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28-7.19 (m overlapping with $CHCl_3$, 2H), 6.95-6.89 (m, 2H), 5.57 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 4.95 (d overlapping slightly with d at 4.92 ppm, *J* = 17.1 Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.03 (t, *J* = 6.5 Hz, 2H), 2.69 (d, *J* = 7.3 Hz, 2H), 1.91 (quintet, *J* = 7.0 Hz, 2H), 1.60-1.52 (m, 2H), 1.42-1.21 (m that overlaps with s at 1.42, 14H), 0.95 (br t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.7 (C), 136.7 (CH), 135.9 (C), 127.5 (CH), 127.1 (CH), 119.9 (CH), 115.8 (CH_2), 111.6 (CH), 67.7 (CH_2), 45.0 (CH_2), 37.9 (C), 31.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.9 (CH_3), 26.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m*/*z* calcd for $C_{20}H_{33}O$ ($[M + H]^+$): 289.25314. Found: 289.25352.

Alternatively prepared according to General Procedure D from Meldrum's derivative (**4.1o**) (195 mg, 0.499 mmol), allyltributyltin (0.30 mL, 0.97 mmol), $AlCl_3$ (72 mg, 0.54 mmol) and CH_2Cl_2 (5.1 mL); 1 h reaction time at rt. Flash column chromatography eluting with pentane (2 columns were necessary to remove all traces of organostannanes) afforded a colourless oil (82 mg, 57 % yield). The spectral properties were identical to those reported above.

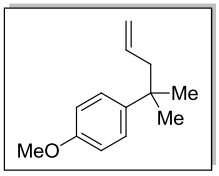
1-Methoxy-3-(2-methylpent-4-en-2-yl)benzene (1.2l)



Prepared according to General Procedure D from Meldrum's derivative (**1y**) (179 mg, 0.613 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (86 mg, 0.64 mmol) and $(CH_2Cl)_2$ (1.5 mL, 0.4 M); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (34 mg, 29 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22 (t overlapping with $CHCl_3$, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.88 (s,

1H), 6.71 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.54 (ddt, *J* = 17.3, 10.0, 7.2 Hz, 1H), 4.94 (d overlapping with d at 4.93, *J* = 18.7 Hz, 1H), 4.93 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 2.33 (d, *J* = 7.2 Hz, 2H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4 (C), 151.1 (C), 135.5 (CH), 128.9 (CH), 118.4 (CH), 116.9 (CH_2), 112.6 (CH), 110.0 (CH), 55.1 (CH_3), 48.7 (CH_2), 37.7 (C), 28.5 (CH_3); HRMS (DART) *m*/*z* calcd for $C_{13}H_{19}O$ ($[M + H]^+$): 191.14359. Found: 191.14391

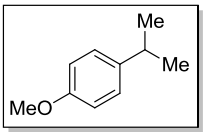
1-Methoxy-4-(2-methylpent-4-en-2-yl)benzene (1.2n)[81]



Prepared according to General Procedure D from Meldrum's derivative (**1c**) (90 mg, 0.31 mmol), allyltrimethylsilane (0.10 mL, 0.62 mmol), $AlCl_3$ (43 mg, 0.32 mmol) and CH_2Cl_2 (3.1 mL); 30 min reaction time at rt. Flash column chromatography eluting on a gradient with hexanes:EtOAc (100:0 to 9:1) afforded a pale yellow oil (58 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.57 (ddt, *J* = 17.4, 10.3, 7.2 Hz, 1H), 4.94 (d overlapping with d at 4.93 ppm, *J* = 16.9 Hz, 1H), 4.93 (d, *J* = 10.3 Hz, 1H), 3.78 (s, 3H), 2.32 (d, *J* = 7.2 Hz, 2H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.3 (C), 141.4 (C), 135.7 (CH), 126.8 (CH), 116.8 (CH_2), 113.3 (CH), 55.2 (CH_3), 48.9 (CH_2), 37.0 (C), 28.7 (CH_3); HRMS (DART) *m*/*z* calcd for $C_{13}H_{19}O$ ($[M + H]^+$): 191.14359. Found: 191.14393.

Also prepared in analogy to General Procedure E from Meldrum's derivative (**1c**) (202 mg, 0.691 mmol), allyltrimethylsilane (0.22 mL, 1.4 mmol), $FeCl_3$ (22 mg, 0.14 mmol, 20 mol %) and $(CH_2Cl)_2$ (6.9 mL); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (112 mg, 85 % yield).

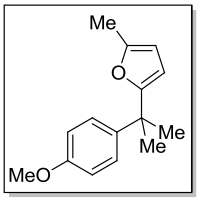
1-Isopropyl-4-methoxybenzene (1.2r)[88]



Prepared in analogy to General Procedure C from Meldrum's derivative (**1c**) (200 mg, 0.684 mmol), (*i*Bu)$_3$Al (1.4 mL, 1.4 mmol, 1.0 M solution in hexanes), and CH_2Cl_2 (6.8 mL); 30 min reaction time at rt. Flash column chromatography eluting with

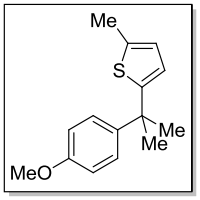
CH_2Cl_2:pentane (1:9), having dry packed the sample, afforded a pale yellow liquid (83 mg, 81 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.14 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 2.85 (septet, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.6 (C), 141.0 (C), 127.2 (CH), 113.6 (CH), 55.2 (CH_3), 33.2 (CH), 24.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{10}H_{15}O$ ($[M + H]^+$): 151.11229. Found: 151.11235. Run #2 = 86 % yield; Avg 84 % yield.

2-(2-(4-Methoxyphenyl)propan-2-yl)-5-methylfuran (1.2t)



Prepared according to General Procedure D from Meldrum's derivative (**1c**) (178 mg, 0.609 mmol), 2-methylfuran (0.12 mL, 1.2 mmol), $AlCl_3$ (85 mg, 0.64 mmol) and CH_2Cl_2 (6.1 mL); 20 min reaction time at rt. Flash column chromatography eluting on a gradient (pentane:Et_2O, 100:0 to 100:0.5) afforded a yellow oil (105 mg, 75 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.15 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.92 (d, *J* = 3.0 Hz, 1H), 5.85 (d, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 2.21 (s, 3H), 1.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.8 (C), 157.7 (C), 150.6 (C), 140.4 (C), 127.0 (CH), 113.4 (CH), 105.5 (CH), 104.8 (CH), 55.2 (CH_3), 39.4 (C), 28.7 (CH_3), 13.6 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{19}O_2$ ($[M + H]^+$): 231.13850. Found: 231.13855. Run #2 = 76 % yield; Avg 76 % yield.

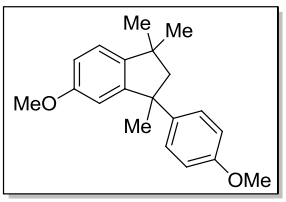
2-(2-(4-Methoxyphenyl)propan-2-yl)-5-methylthiophene (1.2u)



Prepared according to General Procedure D from Meldrum's derivative (**1c**) (160 mg, 0.547 mmol), 2-methylthiophene (0.10 mL, 1.1 mmol), $AlCl_3$ (77 mg, 0.57 mmol) and CH_2Cl_2 (5.5 mL); 20 min reaction time at rt. Flash column chromatography eluting on a gradient (pentane:Et_2O, 100:0 to 100:0.5) afforded a pale yellow oil (128 mg, 95 % yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.24 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 3.4 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 3.76 (s, 3H), 2.37 (s, 3H), 1.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.7 (C), 154.4 (C), 141.9 (C), 137.7 (C), 127.1 (CH), 124.1 (CH),

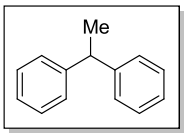
122.6 (CH), 113.2 (CH), 55.1 (CH_3), 40.9 (C), 31.9 (CH_3), 15.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{19}OS$ ($[M + H]^+$): 247.11566. Found: 247.11675.

5-Methoxy-3-(4-methoxyphenyl)-1,1,3-trimethyl-2,3-dihydro-1*H*-indene (1.2y)[89]



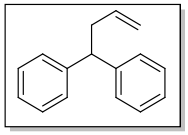
Prepared in analogy to General Procedure D from Meldrum's derivative (**1c)** (88 mg, 0.30 mmol), $AlCl_3$ (43 mg, 0.32 mmol) and CH_2Cl_2 (3.0 mL); 20 min reaction time at rt. Flash column chromatography eluting on a gradient (pentane:Et_2O, 100:0 to 100:1) afforded a yellow oil (36 mg, 81 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.10-7.06 (m, 3H), 6.82 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 2.4 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.34 (d, *J* = 13.0 Hz, 1H), 2.15 (d, *J* = 13.0 Hz, 1H), 1.64 (s, 3H), 1.30 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.9 (C), 157.3 (C), 150.5 (C), 144.5 (C), 143.0 (C), 127.7 (CH), 123.1 (CH), 113.24 (CH), 113.20 (CH), 109.9 (CH), 59.7 (CH_2), 55.4 (CH_3), 55.2 (CH_3), 50.1 (C), 42.2 (C), 30.9 (CH_3), 30.8 (CH_3), 30.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{25}O_2$ ($[M + H]^+$): 297.18545. Found: 297.18582.

Ethane-1,1-diyldibenzene (2.1b)[80]



Prepared according to General Procedure C from Meldrum's derivative (**2b**) (49 mg, 0.15 mmol), Me_3Al (0.15 mL, 0.30 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (1.5 mL); 1 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (25 mg, 92 % yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.28-7.26 (m, 8H), 7.19-7.13 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 1H), 1.62 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 146.3 (C), 128.3 (CH), 127.6 (CH), 126.0 (CH), 44.7 (CH), 21.8 (CH_3); HRMS (DART) *m/z* calcd for $C_{14}H_{18}N$ ($[M + NH_4]^+$): 200.14392. Found: 200.14453.

But-3-ene-1,1-diyldibenzene (2.1a)[81]



Prepared according to General Procedure D from Meldrum's derivative (**2a**) (165 mg, 0.532 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (74 mg, 0.56 mmol) and $(CH_2Cl)_2$ (5.3 mL); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a-colourless oil (55 mg, 50 % yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.34-7.25 (m, 8H), 7.18-7.13 (m, 2H), 5.72 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.90 (dd, *J* = 10.2, 0.8 Hz, 1H), 4.06 (t, *J* = 7.9 Hz, 1H), 2.85 (app t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 144.5 (C), 136.8 (CH), 128.4 (CH), 127.9 (CH), 126.1 (CH), 116.3 (CH_2), 51.2 (CH), 39.9 (CH_2); HRMS (DART) *m/z* calcd for $C_{16}H_{20}N$ ([M + NH_4]$^+$): 226.15957. Found: 226.15972.

Alternatively prepared according to General Procedure D in higher yield from Meldrum's derivative (**2b**) 200 mg, 0.616 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (86 mg, 0.65 mmol), and CH_2Cl_2 (6.1 mL); 30 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a colourless oil (119 mg, 93 % yield). The spectral properties were identical to those reported above.

Chapter 3

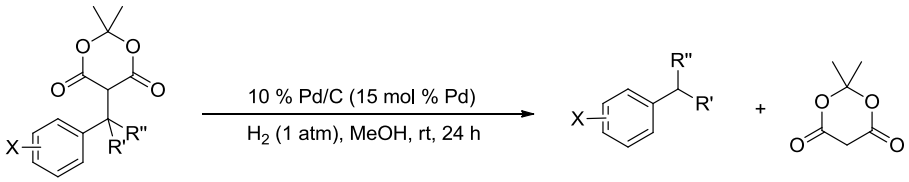
3.0 Modification of sp^3-Hybridized Carbon Centers Through Transition Metal Catalyzed Substitution Reactions

3.1 Introduction

As presented in Chapter 2, modifications of quaternary benzylic centers bearing a Meldrum's acid moiety with carbon-based nucleophiles (Me_3Al, allylTMS, etc.) via substitution reactions proceed well under Lewis acid-catalyzed conditions.[63] The other method for activation of unstrained C-C σ bond involves transition metal-mediated substitution reactions. One of the successful reactions of C-C bond activation catalyzed by transition metals that has been reported include hydrogenolysis of C-C σ bond.[32] The large majority of published reports on hydrogenolysis reactions has limitations regarding the scope and the structure of the starting materials. Several hydrogenolysis methods applied to C-C bond deal with strain relief in small rings (Section 1.2.1),[25] aromatization-driven reactions (Section 1.2.2),[24] or reaction conditions involving high temperature and pressure[23] (Section 1.2, Scheme 1.15). Reports on the hydrogenolysis of the C-C bond under mild conditions are scarce.

Fillion *et al.* described the hydrogenolysis of benzyl Meldrum's acids for the synthesis of tertiary benzylic carbon centers (Table 3.1).[32] Unprecedented cleavage of unstrained benzylic C-C σ bonds was achieved, with high conversions and yields. The study describes a new activation of unstrained C-C σ bonds in Meldrum's acid derivative resulting in C-H bond formation with construction of tertiary benzylic stereocenter. The transformation is catalyzed by readily available, air and moisture stable Pd/C at room temperature and atmospheric pressure of hydrogen gas (H_2).[32] Fillion *et al.* reported the scope and limitations of the new unstrained C-C σ bond modification, as well as determination of the reaction's limitations were achieved (Entries 4, 9-10).[32] Different benzyl Meldrum's acid structures were tested, including substrates having substituted aromatic rings (Entries 1-2, 4-11), as well as non-substituted ones (Entry 3).[32]

Table 3.1 Palladium-Catalyzed Hydrogenolysis of Benzyl Meldrum's Acids



Entry	R; R'	X	Conversion (%)	Yield (%)
1	R = R' = Me	4-(OC_8H_{17})	>95	76
2	R = R' = Me	4-Ph	>95	71
3	R = R' = Me	H	>95	80[a]
4	R = R' = Me	3-(OC_8H_{17})	9	N/A
5	R = R' = Me	2-(OC_8H_{17})	80 (92)[b]	65 (71)[b]
6	R = R' = $(CH_2)_5$	4-(OC_8H_{17})	91	81
7	R = Me; R' = Et	4-(OC_8H_{17})	>95	86
8	R = Me; R' = *n*Bu	4-(OC_8H_{17})	>95	90
9	R = Me; R' = *i*Pr	4-(OC_8H_{17})	20 (>95)[c]	N/A (70)[c]
10	R = H; R' = Me	4-(OC_8H_{17})	<5	N/A
11	R = H; R' = 4-$MeOC_6H_4$	4-(OC_8H_{17})	>95	96

[a] Yield for the isolation of Meldrum's acid; [b] The conversion and yield in parentheses were obtained using 20 mol % Pd; [c] The conversion and yield in parentheses were obtained using 100 mol % Pd.

Although published report describing hydrogenolysis of unstrained C-C σ bonds has been reported by Fillion et al.,[32] there is a possibility to expand the substrate scope and mechanistic insights into steric and electronic requirements needed for increased conversion and yield of the hydrogenolysis process**.**

3.2 Proposal

Fillion *et al.* reported the hydrogenolysis of unstrained C-C σ bonds utilizing Meldrum's acid as a carbon-based leaving group.[32] In this chapter, the initial reaction conditions proposed by Fillion *et al.* (Scheme 3.1) were applied to a wide array of substrates. Moreover, additional mechanistic insights were obtained by performing competition experiments with two potentially-cleavable C-C bonds, and achieving the hydrogenolysis of enatioenriched substrates.

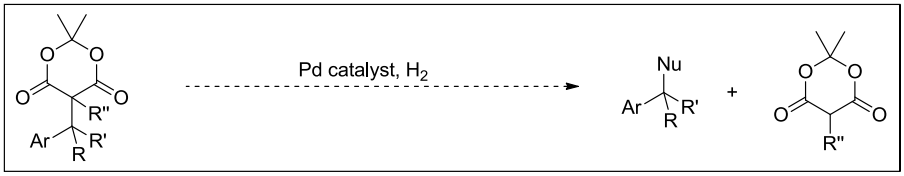


Figure 3.1 Proposed Reductive Cleavage of benzyl Meldrum's Acid with Hydrogen under Pd-Catalyzed Conditions

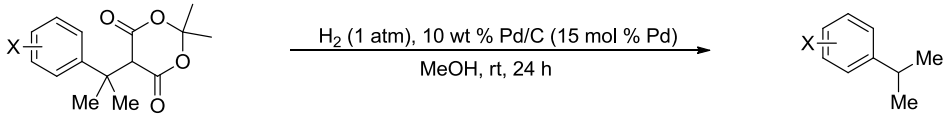
3.3 Results and Discussion. Scope of the Palladium-Catalyzed Hydrogenolysis Reaction

The first step in optimizing the hydrogenolysis reaction conditions was to choose an appropriate catalyst. A variety of conditions were tested (including $Pd(OH)_2/C$, EtOAC, 65 °C; AcOH, acetone, PhH, THF), and palladium on charcoal was chosen as an optimal catalyst, as it gave complete conversions and high yields of the final products (data not shown).

Initial studies on the hydrogenolysis reaction included studying the effect of substitution of the aryl ring containing an all-carbon benzylic quaternary center (Table 3.2). In hydrogenolysis reactions performed it was noticed that both electronic factors and adsorption of the reactants on the surface of the catalyst must be taken into account. Hydrogenolysis of Meldrum's acid derivatives bearing no substituents, electron-donating groups at the *para* position, and unbranched alkyl groups at different positions on the aryl ring gave excellent conversions and good to excellent isolated yields (Entries 1-3, 9-13). This was likely due to the electron donating effect of those substituents, making the starting material more electron rich and increasing the rate of the hydrogenolysis reaction. Despite promising results, problems were encountered regarding the inertness of the substrates bearing branched alkyl substituents on the aromatic ring (Table 3.2); these were successfully resolved by modifying the reaction conditions (Table 3.3). Positioning the alkoxy-group at the *meta*-position of the aryl ring resulted in low conversion at room temperature, which is probably due to the inductive deactivation effect of this group on the rate of the hydrogenolysis reaction (Entry 4).[90] Placement of the octyloxy-group at the *ortho* position of the aromatic ring required a longer reaction time and increased catalytic loading of Pd/C (Entry 5), which is likely due to steric factors of the long chain octyloxy substituent

hindering the approach of the palladium catalyst. Branched alkyl derivatives gave low conversion regardless of the position of substituents (Entries 6-8). However, the attachment of a neopentyl group at the *para*-position of the aromatic ring produced no decrease in the reaction rate and gave the final product in 81 % yield (Entry 10). Because the branched alkyl groups hampered the hydrogenolysis reaction to proceed at room temperature, corresponding ethers at the *para*-position of aromatic ring were investigated (Entries 14-15). This change significantly increased both conversion and yield. The fluoro-substituted aryl ring was inert toward the hydrogenolysis reaction (Entry 16). Therefore, it can be concluded that having branched substituents on the aromatic ring lowers the adsorption of the substrates on the surface of the catalyst. Thus, the adsorption of the aromatic starting material is not favorable. [25,91] The orientation of the aromatic ring in space towards the surface of the catalyst is not flat. Thus, the adsorption of the starting material on the surface of the catalyst is weak; therefore, the rate of the hydrogenolysis reaction is decreased.[25]

Table 3.2 Scope of the Hydrogenolysis Reaction, Varying the Substituent on the Aromatic Ring of Meldrum's Acid Derivatives



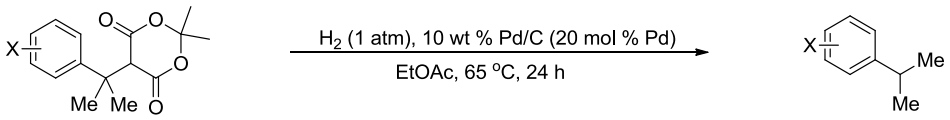
(3a-3p) (3.1a-3.1p)

Entry	X	Conversion (%)	Yield (%)
1	H **(3a)**	>95	80[a] **(3.1a)**
2	4-Ph **(3b)**	>95	80 **(3.1b)**
3	4-($C_8H_{17}O$) **(3c)**	>95	78 **(3.1c)**
4	3-($C_8H_{17}O$) **(3d)**	9	N/D
5	2-($C_8H_{17}O$) **(3e)**	>95	90[b] **(3.1e)**
6	4-*t*Bu **(3f)**	<5	N/D
7	3-*t*Bu **(3g)**	NR	N/A[d]
8	4-*i*Pr **(3h)**	10	N/D[d]
9	4-*i*Bu **(3i)**	>95	70 **(3.1i)**
10	4-(*t*Bu-CH_2) **(3j)**	>95	81 **(3.1j)**
11	4-*n*Bu **(3k)**	>95	90 **(3.1k)**
12	2-Et **(3l)**	>95	83 **(3.1l)**
13	3-Et **(3m)**	>95	64[b] **(3.1m)**
14	4-(*t*BuO) **(3n)**	>85	70[c] **(3.1n)**
15	4-(*i*PrO) **(3o)**	>95	82 **(3.1o)**
16	3-F-4-(MeO) **(3p)**	<5	N/D[d]

[a] Yield of Meldrum's acid; [b] Reaction time is 48 h, 20 mol % Pd; [c] Reaction time is 48 h; [d] Results obtained by Yen Nguyen.

Since branched alkyl groups proved detrimental for the hydrogenolysis at room temperature in MeOH, alternative reaction conditions were developed to improve the reactivity of these substrates and expand the scope of the hydrogenolysis reaction. Therefore, EtOAc was chosen as a non-nucleophilic solvent to run the reaction at 65°C under 20 mol % loading of Pd/C (Table 3.3).

Table 3.3 Optimization of Hydrogenolysis Reaction Conditions



(3d,f,g,h,p) **(3f,g,h,p)**

Entry	X	Conversion (%)	Yield[a] (%)
1	3-($C_8H_{17}O$) **(3d)**	38	ND
2	4-*t*Bu **(3f)**	>95	76[a] **(3.1f)**
3	4-*i*Pr **(3h)**	>95	91[b] **(3.1h)**
4	3-*t*Bu **(3g)**	>95	62[c,d] **(3.1g)**
5	3-F-4-(MeO) **(3p)**	32, 84	N/D, 60[c] **(3.1p)**

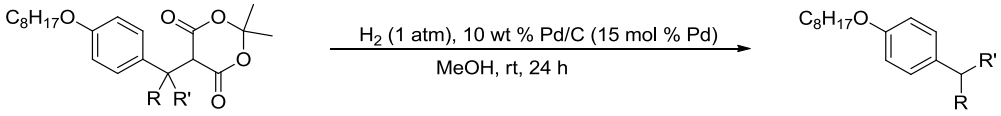
[a] Reaction time is 48 h; [b] Reaction time is 96 h; [c] Catalyst loading is 50 mol %; [d] Results obtained by Yen Nguyen.

Substrates bearing branched alkyl groups at the *para* and *meta* positions of the aryl ring gave complete conversion upon heating the reaction (Entries 2-4). However, both longer reaction times (from 48 to 96 hours) and increased catalyst loading were required. Octyloxy substitution at the *meta* position of the aromatic ring gave poor conversion, suggesting a predominant deactivating electronic effect (Entry 1). Fluoro-substituted aromatic rings required up to 50 mol % catalyst loading to proceed to an 84 % conversion, also suggesting that an electronic effect of the substituents on the aromatic ring playing a key role in decreasing the reaction rate. Thus, the increase in the temperature and catalytic loading helped to overcome poor adsorption of the starting materials bearing branched alkyl substituents on the aromatic ring. Poor reactivity of the substrate having a substituent with deactivating electronic effect (Entry 1) still needs to be overcome. In some particular cases (Entry 5), an increase of the catalyst loading is also necessary.

3.4 Effect of the Benzylic Alkyl Substitution of the Meldrum's Acid Derivatives on Hydrogenolysis Reactions

The next step in investigating the hydrogenolysis of Meldrum's acid derivatives was to study the effect of the substitution patterns at the benzylic position (Table 3.4). Substitution of one or two methyl groups at the α-position of Meldrum's acid derivative with Et, *n*Bu, cyclohexyl, *i*Pr groups was achieved. The replacement of one or both methyl groups with the specified unbranched groups (Et, *n*Bu, cyclohexyl) did not adversely affect conversions or yields of the hydrogenolysis reactions (Entries 1-4). However, the *i*Pr group decreased reactivity, and complete conversion was only possible using a stoichiometric amount of palladium (Entry 5). The results show that unbranched alkyl substituents at the benzylic position did not affect the efficiency of the hydrogenolysis reaction, whereas branched isopropyl groups gave poor results. The study of the C-C bond structure performed suggests the influence of steric factors on the hydrogenolysis.

Table 3.4 Hydrogenolysis Reactions with Benzylic Alkyl Substituents



(3q-3u) (3.1q-3.1u)

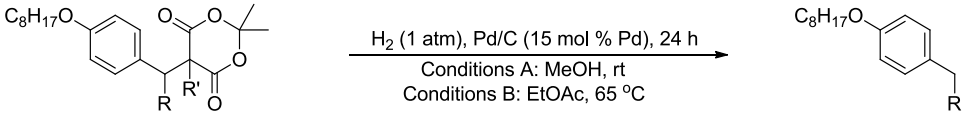
Entry	R; R'; R''	Conversion (%)	Yield[a] (%)
1	R = R' = Me **(3c)**	>95	80 **(3.1c)**
2	R = Me; R' = Et **(3q)**	>95	86 **(3.1q)**
3	R = Me; R' = *n*Bu **(3r)**	>95	90 **(3.1r)**
4	R = R' = $(CH_2)_5$ **(3s)**	>95	81 **(3.1s)**
5	R = Me; R' = *i*Pr **(3t)**	20, >95	N/D. 70[b] **(3.1t)**

[a] Results obtained by Yen Nguyen; [b] 100 mol % Pd.

The results (Section 3.3; Tables 3.2 and 3.3) showed that the hydrogenolysis reaction produces high yields for quaternary benzylic Meldrum's acid derivatives. Next, hydrogenolysis reaction conditions were applied to benzyl Meldrum's acids with mono or unsubstituted benzylic centers that were less hindered than quaternary benzylic centers (Table 3.5). The substrates were subjected to two sets of conditions [Pd/C (15 mol %), H_2 (1 atm), MeOH, rt, 24 h and Pd/C (20 mol %), H_2 (1 atm), EtOAc, 65°C, 24 h), and low

conversions were observed (Entries 1-4). Removing the acidic proton at the 5-position of Meldrum's acid moiety by methylation resolved the problem of low reactivity of the substrates; the reactions went to completion and gave the products in good yields with heating (Entries 6, 8). At room temperature, low conversion and yields were obtained (Entries 5, 7).

Table 3.5 Hydrogenolysis Reactions at Secondary, Tertiary and Quaternary Benzylic Carbon Centers



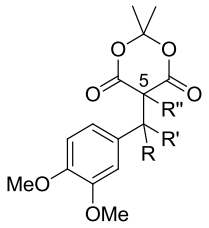
(3v-3y) (3.1v-3.1w)

Entry	Conditions	R; R'	Conversion (%)	Yield (%)
1	A	R = Me; R' = H **(3u)**	8[a]	N/D
2	B	R = Me; R' = H **(3u)**	18	12 **(3.1u)**[a]
3	A	R = R' = H **(3v)**	14[a]	N/D
4	B	R = R' = H **(3v)**	20[a,b]	10[a] **(3.1v)**
5	A	R = R' = Me **(3w)**	47[a]	N/D
6	B	R = R' = Me **(3w)**	>95	94 **(3.1u)**
7	A	R = H; R' = Me **(3x)**	62[a]	55 **(3.1v)**
8	B	R = H; R' = Me **(3x)**	>95	80 **(3.1v)**

[a] Results obtained by Yen Nguyen; [b] In this case around 30 % of decomposition starting material was observed on the crude ^{1}H NMR.

Thus, substitution reaction under palladium catalysis proved to proceed on secondary and tertiary benzylic centers, having the requirement to bear the quaternization of Meldrum's acid. This difference in reactivity between enolizable and non-enolizable Meldrum's acid derivatives is hard to explain. The difference in acidity between Meldrum's acid (pKa = 7.32) and methyl Meldrum's acid (pKa = 7.42) is very low and can't be a good justification.[92] Previous crystallographic analysis of quaternary, tertiary and secondary enolizable and non-enolizable benzylic Meldrum's acid derivatives showed only a small difference in the length of breakable C-C bonds (Table 3.6). Thus, the investigation of the reactivity of non-enolizable Meldrum's acid derivatives under hydrogenolysis reaction conditions is still ongoing.

Table 3.6 Analysis of the Length of Cleavable C-C Bond in Different Meldrum's Acid Derivatives



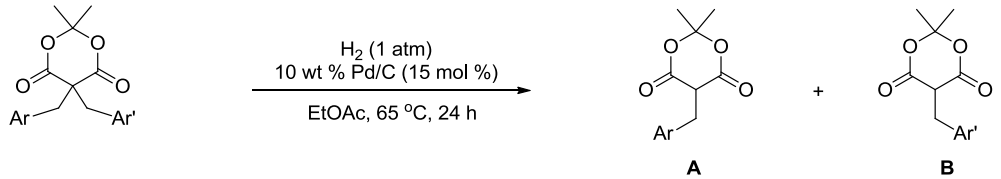
Entry	R	R'	R''	C(5)-C(11) bond length (Å)[a]
1	Me	Me	H	1.565
2	H	H	H	1.541
3	Me	H	H	1.562
4	H	H	Me	1.566
5	Me	H	Me	1.568

[a] Unpublished results obtained by Dr. A. Wilsily.

3.5 Competition Studies Performed on the Hydrogenolysis Reaction Under Palladium Catalysis

To gain insight into steric and electronic factors controlling the hydrogenolysis reaction, a study using dibenzyl Meldrum's acid substrates was conducted with two potentially breakable benzylic C-C bonds (Table 3.7). The chemoselectivity was determined by varying the sterics and electronics on the aromatic rings. The reactions were performed in MeOH with Pd/C catalyst loading of 15 or even 50 mol %.

Table 3.7 Competition Experiments



(4a-4h) (4.1a-4.1k)

Entry	Ar	Ar'	A/B	Yield[a] (%)
1	4-($C_8H_{17}O$)-C_6H_4	C_6H_5 **(4a)**	100/0 **(4.1a)**	65
2	4-*n*Bu-C_6H_4	C_6H_5 **(4b)**	100/0 **(4.1b)**	57
3	4-(MeO)-C_6H_4	4-Me-C_6H_4 **(4c)**	85/15 **(4.1c)/(4.1d)**	45/8
4	4-*n*BuC_6H_4	4-*t*-Bu-C_6H_4 **(4d)**	0/100 **(4.1e)**	34
5	4-(MeO)-C_6H_4	4-(OC_8H_{17})-C_6H_4 **(4e)**	35.3/64.7 **(4f)/(4g)**	71[b]
6	4-(MeO)-C_6H_4	2-(MeO)-C_6H_4 **(4f)**	50/50 **(4h)/(4i)**	62[b]
7	2-(MeO)-C_6H_4	C_6H_5 **(4g)**	100/0 **(4j)**	85
8	2-Me-C_6H_4	C_6H_5 **(4h)**	100/0 **(4k)**	26

[a] Conversion in all cases was >95 %, unless stated otherwise; [b] Mixture of A and B.

Hydrogenolysis of the phenyl ring occurred preferentially when the other aromatic ring bears either electron-donating or electron-neutral groups (Entries 1-2, 7-8), suggesting the non-substituted aromatic ring reacts more rapidly under hydrogenolysis conditions. Results of the competition study between *para*-methoxy- and *para*-methyl-substituted aromatic rings showed that hydrogenolysis of the electron-rich group occurs slower than with alkyl-substituted aromatics (Entry 3). Competition between benzyl groups bearing aromatic rings with *n*Bu and *t*Bu groups showed that the aromatic ring having non-bulky alkyl substituent is hydrogenolyzed selectively (Entry 4). Unbranched substituents on the aromatic ring likely facilitate adsorption of this side of the starting material on the surface of the catalyst compared to the aromatic ring bearing the branched alkyl groups.[25] Competition between electron-donating methoxy and alkoxy groups gave a mixture of products (Entry 5), suggesting similar electronic effect exhibited by two electron-donating groups on the aromatic rings of the Meldrum's acid derivative.

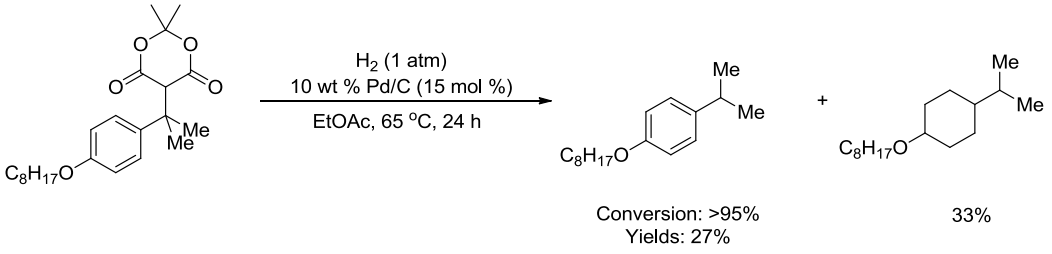
In addition, the influence of the position (*ortho* and *para)* of the methoxy-group on the two aromatic rings was studied, and methoxy groups in these positions gave a 50/50 ratio in hydrogenolysis reactions (Entry 6), indicating no selectivity for the hydrogenolysis reaction of Meldrum's acid derivative with two methoxy groups at *para* and *ortho* positions on the aromatic ring due to the similar electronic effects of those substituents (both activating *ortho*, *para*-directors).

Therefore, several general trends were observed for the hydrogenolysis reactions performed in the study of two potentially cleavable benzylic C-C bonds. First, in all the competition reactions performed, phenyl rings are cleaved preferentially although arenes are not electronically favoured. These experimental results underline optimal adsorption of arene

on the surface of the catalyst. As it has been shown the aromatic ring lies flat on the metal surface.[25] Second, benzyl group bearing electron-neutral substituent is hydrogenolysed preferentially to benzyl group bearing electron-donating group. This result suggests that the adsorption of the aromatic ring substituted with unbranched alkyl group overrides the electronic effect of the aromatic ring bearing electron-donating group. Third, the adsorption issue comes into play with aromatic rings bearing branched and unbranched alkyl groups. Branched alkyl groups decrease the adsorption of the aromatic ring on the metal surface of the catalyst, thereby facilitating hydrogenolysis of the ring carrying unbranched alkyl substituents. The results obtained from the competition experiments are somewhat suprising, as adsorption factors are showing to play greater role in facilitating the hydrogenolysis reaction than the electronic factors exhibited by the substituents of the aromatic ring. Thus, it would be beneficial to perform more competition experiments on the substrates having various alkyl and electron-donating groups on different positions of the aromatic rings to see if the obtained trend is further supported experimentally.

3.6 Additional Observations

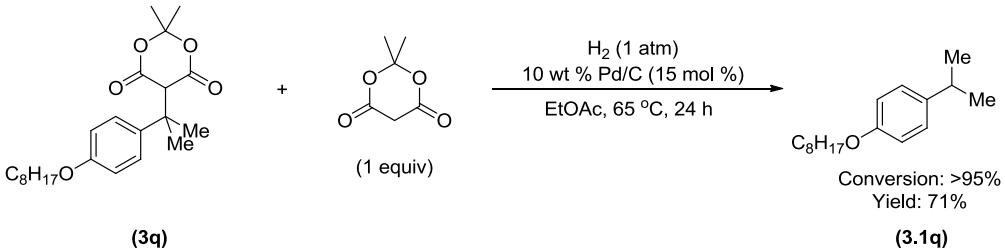
While performing hydrogenolysis reactions at 65 °C, over-reduction of the aromatic ring was observed as a competing reaction pathway, especially for the reactions bearing electron-donating groups (Scheme 3.1). For electron-rich starting materials, hydrogenolysis produced an over-reduction product.



Scheme 3.1 Over-Reduction of the Electron-Rich Aromatic Rings

This over-reduction product significantly lowered the yield of the hydrogenolysis. Aromatic hydrogenation was suppressed by the addition of one equivalent of Meldrum's acid

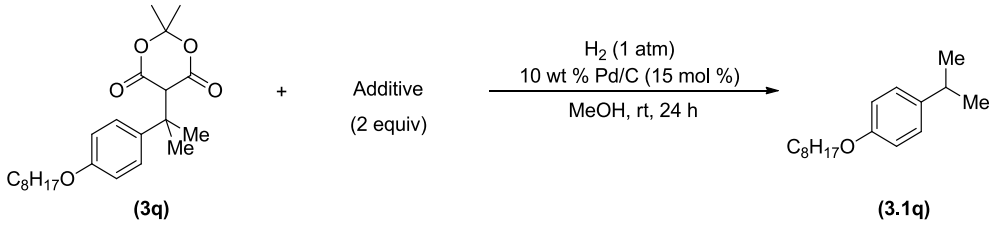
to the hydrogenolysis reactions in EtOAc (Scheme 3.2). One possibility is that Meldrum's acid may compete with the hydrogenolysis reaction product for the surface of the catalyst. This would reduce the amount of the adsorbed product on the surface of the palladium, and prevent the catalyst from further reducing the hydrogenolysis product.

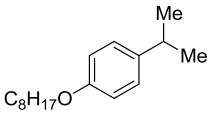
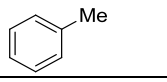


Scheme 3.2 Suppression of the Over-Reduction Product Formation

As Meldrum's acid eliminated the formation of the over-reduction by-product, the influence of some additives on the efficiency of the hydrogenolysis reaction was investigated (Table 3.8). Toluene and the hydrogenolysis reaction product were introduced as additives into the reaction mixture in order to study if the hydrogenolysis would be inhibited by the final product (Entries 2-3). The reaction product and toluene suppressed the rate of hydrogenolysis, which is commonly observed for Pd/C-catalyzed reactions and further supports the hypothesis that competition for the surface of palladium catalyst occurs between the starting materials and the hydrogenolysis reaction product.[25]

Table 3.8 Influence of Additives on the Rate of the Hydrogenolysis Reaction

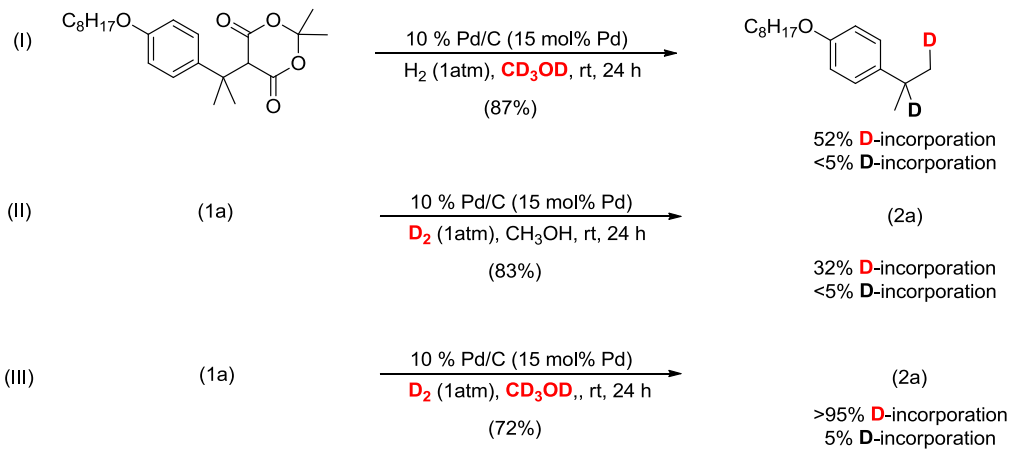


Entry	Additive	Conversion[a] (%)
1	-	95 **(3.1q)**
2		75 **(3.1q)**
3		77 **(3.1q)**

[a] Results obtained by Yen Nguyen.

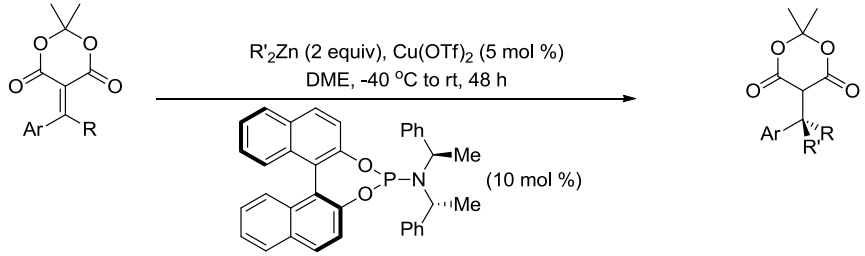
3.7 Mechanistic Studies of Hydrogenolysis Reaction. Proposed Hydrogenolysis Reaction Mechanism

Initial investigations into the reaction mechanism of hydrogenolysis were reported by Fillion *et al*.[32] The mechanism was investigated further using three sets of conditions in labeling studies in order to obtain insights into the nature of the nucleophilic species involved in the reaction.[32] The first set used deuterated solvent and hydrogen gas, and the amount of deuterium incorporated into the benzylic position was 52 %. The second set used deuterium gas and MeOH as a solvent, and 32 % of deuterium was incorporated into the benzylic position. The last set of conditions used deuterium and CD_3OD simultaneously, and >95 % of the deuterium was incorporated. In all three experiments, <5 % deuterium incorporation was observed at the methyl position of isopropyl group.[32] The labeling studies suggest that both hydrogen gas and solvent participate in hydrogen/deuterium incorporation. Information on the nature of the nucleophilic species can be extracted from the labeling equilibration between H_2 and CH_3OH experiments described. It is expected that a palladium nucleophilic species is present in the reaction, which was confirmed by the existence of an exchange reaction between the gas and the solvent observed in some deuterium experiments.[32] The nucleophilic attack [either by palladium hydride or by Pd (0)] is slower than the isotopic dilution which occurs through exchange on the palladium surface between the reactive palladium species and the acidic proton of the solvent (Scheme 3.3, I, II).[32] Finally, the observation of deuterium incorporation at the methyl position was observed in labeling studies. This incorporation could result from the hydrogenation of an alkene derivative, which results from β-hydride elimination of palladium species intermediate (Figure 3.2).[32]



Scheme 3.3 Deuterium Labeling Studies

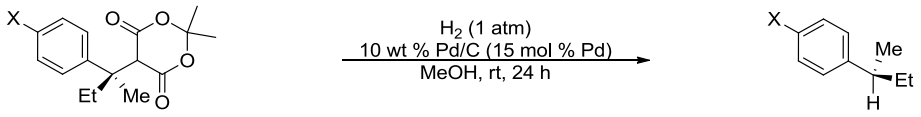
To gain further insight into the mechanism of the hydrogenolysis reaction, the hydrogenolysis reaction conditions were applied to enantioenriched substrates to determine the stereochemical outcome under palladium-catalysed conditions. The substrates were prepared based on a previously published protocol (Scheme 3.4).[93]



Scheme 3.4 Enantioselective 1,4-Addition to Alkylidene Meldrum's Acids

Derivatives were subjected to hydrogenolysis conditions (Section 3.3; Table 3.2), and the results are shown in Table 3.9.[32] The products obtained had nearly complete inversion of configuration at the benzylic center under palladium-catalyzed conditions.

Table 3.9 Hydrogenolysis of Enantioenriched Meldrum's Acid Derivatives with Inversion of Configuration[34]



(R)-1

(4i-4k)

(S)-2

(4.1l-4.1n)

Entry	X	Er of 1 (R/S)	Er of 2 (S/R)	Inversion of Er (%)	Yield[a,b] (%)
1	Ph [(R)-1-a] **(4i)**	98:2	90.5:9.5	92	51 **(4.1l)**
2	OC_8H_{17} [(R)-1-b] **(4j)**	98.5:1.5	96:4	97	93 **(4.1m)**
3	OMe [(R)-1-c] **(4k)**	98.5:1.5	94.5:5.5	96	72 **(4.1n)**

[a] Conversion of all cases was >95 %, unless stated otherwise; [b] Results obtained by Yen Nguyen.

Based on the previous results (high inversion of the configurations observed in the hydrogenolysis of enantioenriched substrates), a mechanism for the hydrogenolysis reaction was proposed to be an S_N2 mechanism. Positive influence of electron-donating groups on the aromatic ring and excellent results for the hydrogenolysis reaction described from diaryl methyl benzyl Meldrum's acid derivatives, support this suggestion. The presence of electron-donating substituents on the aromatic rings resulted in an increase of the stabilization of the transition state and increase in the rate of hydrogenolysis reaction (Tables 3.2 and 3.7). As presented and discussed earlier introduction of branching on the aromatic ring and benzylic position of Meldrum's acid derivatives slows down the rate of the hydrogenolysis reaction because of the decreased adsorption of the starting material on the surface of the catalyst. Based on published deuterium labeling studies, we proposed that the displacement of Meldrum's acid moiety occurs by a palladium hydride to yield the benzylic organopalladium intermediate **32** that undergoes reductive elimination (Figure 3.2).[32] Slight erosion of the enantiomeric ratio during the reaction can occur as a result of β-hydride elimination[32] or alkene formation pathway.[94]

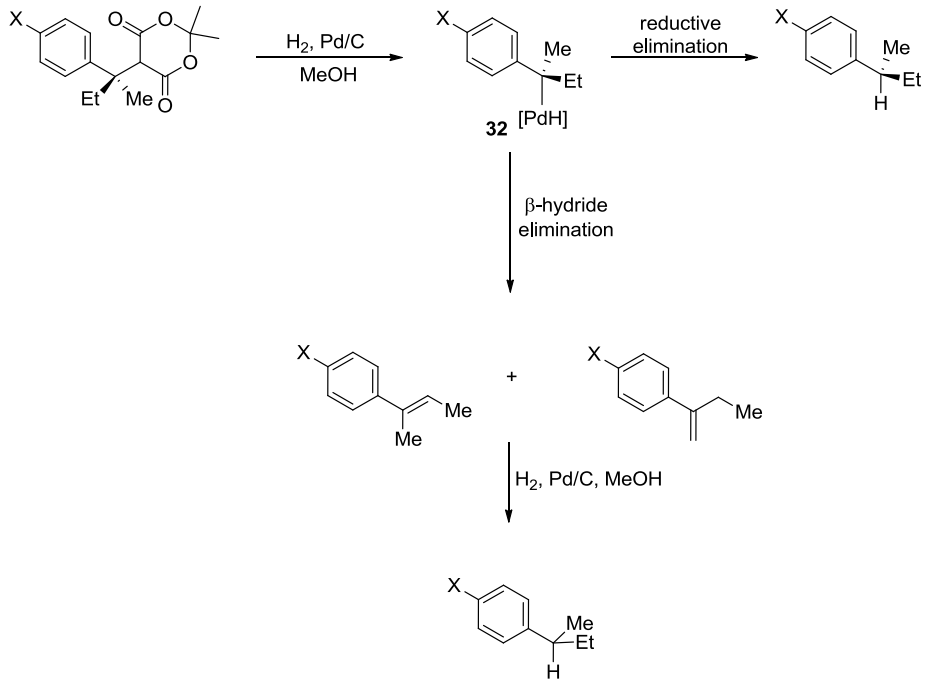
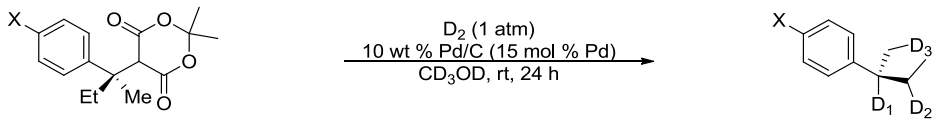


Figure 3.2 Proposed Reaction Mechanism

In order to obtain confirmation into the proposed mechanism, some deuterium labeling studies were performed on enantioenriched Meldrum's acid derivatives (Table 3.10). A correlation between deuterium incorporation at the CH_2-ethyl (D_2) and methyl (D_3) positions and the loose of ee was expected. According to the mechanism propose (Figure 3.2) the loss of ee should be equal to the global deuterium incorporation at positions D_2 and D_3.

Table 3.10 Deuterium Labeling Experiments of Enantioenriched Meldrum's Acid Drivatives



(R)-1

(4i-4k)

(S)-2

Entry	X	Loss of ee (%)	$D_2 + D_3$[a,b] (%)
1	Ph [(R)-1-a] **(4i)**	7	11
2	OC_8H_{17} [(R)-1-b] **(4j)**	6	4
3	OMe [(R)-1-c] **(4k)**	14	17

[a] Conversion of all cases was >95 %, unless stated otherwise; [b] Results obtained by Yen Nguyen.

The deuterium incorporation at positions D_2 and D_3 observed (^1H and ^2H NMR) for all the compounds corresponded to the loss of ee obtained (HPLS analysis) and confirmed the proposed mechanism.

Overall, mechanistic studies showed that reductive cleavage of enantioenriched benzylic quaternary centers proceeds with inversion of configuration, supporting a S_N2 pathway.[32]

3.8 Summary

In summary, we have developed and expanded the reductive cleavage of Meldrum's acid derivatives bearing all-carbon benzylic quaternary centers under transition metal catalysis. The hydrogenolysis reaction were shown to work preferentially with Meldrum's acid derivatives having a phenyl ring, or an aromatic ring with electron-donating groups (*para* and *ortho* positions) or unbranched alkyl substituents under MeOH and room temperature conditions. The reaction was shown to be sensitive to substitution of the aromatic ring by an electron-withdrawing group. A decrease in the reaction efficacy was observed when branched alkyl groups were introduced into aromatic ring of the Meldrum's acid derivatives, suggesting decreased adsorption of the starting material. The reduced reactivity of those derivatives was solved upon heating the reaction mixture and increasing the catalytic loading. The study of cleavable C-C bond structure showed the influence of the steric factors on the hydrogenolysis. Introduction of a bulky substituent (*i*Pr-group) on the quaternary benzylic center resulted in a decrease in yields under catalytic amount of palladium catalyst (10 wt. % Pd/C 15 mol %). The synthesis of primary and secondary benzylic compounds was allowed by reactivity of non-enolizable Meldrum's acid derivatives. The competition experiments showed that hydrogenolysis occurs with complete conversions and good yields with the following order of substituents present nearby cleavable C-C bond: phenyl rings > aromatic rings bearing non-bulky alkyl > aromatic rings having electron-donating substituents. These results suggest that the adsorption of the starting material is important for the reaction. If the adsorption of the reactants is decreased the rate of the reaction will also deacrease.

Investigation of the reaction mechanism was conducted by applying hydrogenolysis reaction to enantioenriched substrates. In addition, deuterium labeling studies helped to get some insights into the nature of nucleophilic species, as well as to explain the loss of enantiomeric ratio observed in the hydrogenolysis of enantioenriched compounds. The results suggested that the hydrogenolysis reaction proceeds with inversion of configuration via an S_N2 mechanism.

3.9 Future Work

Future work will focus on investigating conditions under which the hydrogenolysis reaction would produce products with retention of stereochemical configuration, (Figure 3.3) possibly by using a different transition metal catalyst.

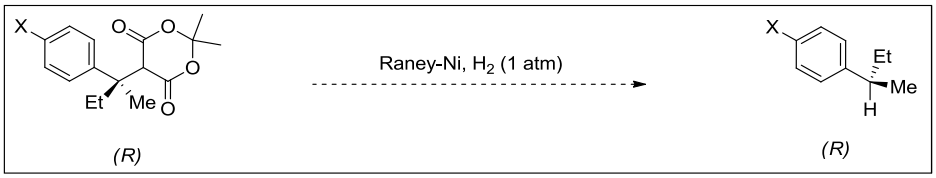
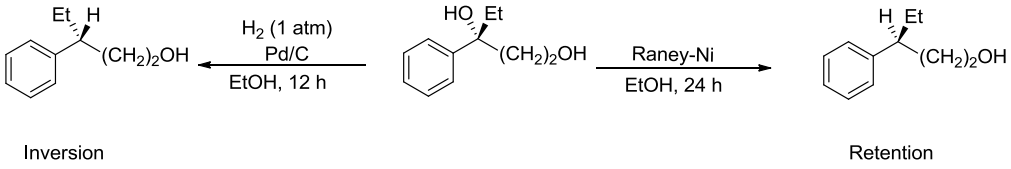


Figure 3.3 Proposed Hydrogenolysis Reaction Giving Retention of Configuration

Kobayashi *et al.* reported the hydrogenolysis of tertiary benzylic alcohols (Scheme 3.5) that gives the products with inversion of configuration under palladium-catalyzed conditions and retention of configuration in the final product under nickel catalysis.[95]



Scheme 3.5 Stereospecific Hydrogenolysis of Benzyl Alcohol under Pd/C and Ra-Ni Catalysts

3.10 Experimental

General Considerations

Reactions

1,2-Dimethoxyethane and THF were distilled from sodium-benzophenone ketyl under nitrogen and degassed via freeze-pump-thaw method. CH_2Cl_2 and $(CH_2Cl)_2$ were dried and purified from a solvent system based on the published procedure.[96] MeOH (ACS grade), EtOAc (ACS grade), MeMgBr (3.0 M in Et_2O), EtMgBr (3.0 M in Et_2O), Et_2Zn (1.0 M in hexanes), PhMgCl (2.0 M in THF) were obtained from commercial sources and used without further purification. The other Gringard reagents used were prepared from the corresponding aryl bromides with magnesium powder in THF. Potassium carbonate was dried in an oven (140 °C) overnight prior to use. Palladium (10 wt. % on activated carbon) was purchased from Sigma-Aldrich and used as received. Reactions were monitored by thin-layer chromatography on commercially prepared plates. Developed plates were viewed under a UV lamp (254 nm) and with ceric ammonium molybdate stain. Flash chromatography was performed using 230-400 mesh silica gel.

The following starting materials were prepared according to literature procedures and the spectral data obtained were in agreement with those reported and consequently, data will not be repeated here: 2,2-dimethyl-5-(2-phenylpropan-2-yl)-1,3-dioxane-4,6-dione (**3a**),[32] 5-(2-([1,1'-biphenyl]-4-yl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**),[32] 2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**3c**),[32] 2,2-dimethyl-5-(2-(3-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**3d**),[63] 2,2-dimethyl-5-(2-(2-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**3e**),[63] 5-(2-(4-(tert-butyl)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3f**),[63] 5-(2-(3-(tert-butyl)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3g**),[63] 5-(2-(2-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3l**),[63] 2,2-dimethyl-5-(2-(3-(octyloxy)phenyl)butan-2-yl)-1,3-dioxane-4,6-dione (**3q**),[32] 2,2-dimethyl-5-(2-(3-(octyloxy)phenyl)hexan-2-yl)-1,3-dioxane-4,6-dione (**3r**),[32] 2,2-dimethyl-5-(1-(3-(octyloxy)phenyl)cyclohexyl)-1,3-dioxane-4,6-dione (**3s**),[32] 2,2-dimethyl-5-(3-methyl-2-(3-(octyloxy)phenyl)butan-2-yl)-1,3-dioxane-4,6-dione (**3t**),[32] 2,2-dimethyl-5-(1-(4-

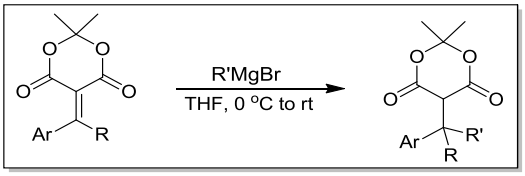
(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**3u**),[32] 2,2-dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (**3v**)[63] 2,2,5-trimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**3w**),[63] 2,2,5-trimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (**3x**),[63] (R)-5-(2-([1,1'-biphenyl]-4-yl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4i**),[32] (R)-2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)butan-2-yl)-1,3-dioxane-4,6-dione (**4j**),[32] (R)-5-(2-(4-methoxyphenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4k**).[32]

Characterization

^{1}H and ^{13}C NMR spectra for all compounds were obtained in $CDCl_3$ at 300 MHz and 75 MHz, respectively unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual $CDCl_3$ (7.24 ppm), and carbon spectra were calibrated to $CDCl_3$ (77.0 ppm). Carbon multiplicities (C, CH, CH_2, CH_3) were determined by combined DEPT 90-135 experiments. ^{19}F NMR spectra were recorded with ^{1}H decoupling in $CDCl_3$ referenced to TFA (-76.5 ppm). Melting points are uncorrected. High resolution mass spectra were run at the University of Waterloo Mass Spectrometry facility and the AIMS facility at the University of Toronto. Low resolution mass spectra (LRMS) were run at the University of Waterloo on low resolution GC-MS machine.

Synthesis of Starting Materials

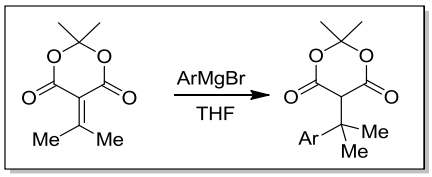
General Procedure A – Preparation of Quaternary Benzyl Meldrum's Acids



Quaternary benzyl Meldrum's acids were prepared by the addition of Grignard reagents (1.5-4 equiv, dropwise addition or alternatively syringe pump addition at a rate of 0.34 mL/min) to a solution of alkylidene Meldrum's acids in dry THF (0.5 M at 0 °C) under nitrogen atmosphere. The reactions were stirred at room temperature until completion of reaction by TLC or for 24 h. The reactions were quenched with 5 % HCl at 0 °C and were extracted with EtOAc (3X). The combined organic layers were washed with brine (1X), dried

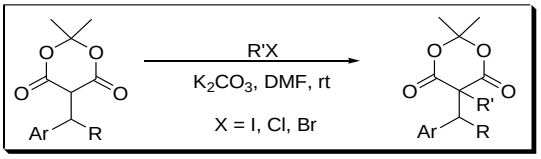
over $MgSO_4$, filtered and concentrated. The crude products were purified by recrystallization or flash chromatography as indicated.

General Procedure B – Preparation of Quaternary Benzyl Meldrum's Acids



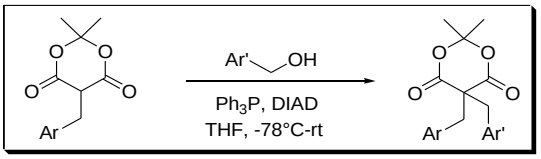
Benzyl Meldrum's acids were prepared by the addition of aryl Grignard reagents (1-4 equiv) to a solution of 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione[97] in dry THF (0.5 M) under nitrogen atmosphere at 0 °C. The reactions were stirred at room temperature until completion or for 24 h. The reactions were quenched with 5 % HCl and extracted with EtOAc (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. The crude products were purified by either flash chromatography or recrystallization.

General Procedure C – Alkylation of Benzyl Meldrum's Acids



Meldrum's acid derivative (1.0 equiv) was dissolved in DMF (1.0 M); K_2CO_3 (1.5 equiv) was added at room temperature. The electrophile R'X was added to the resulting solution and the mixture was stirred for 16 h. Distilled water was added to the reaction mixture. The layers were partitioned and the aqueous layer was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography or recrystallization.

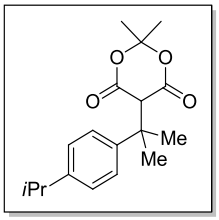
General Procedure D – Alkylation of Benzyl Meldrum's Acids



The alkylation was carried out according to the literature procedure.[98] To a stirred solution of Ph_3P (1.0 equiv) in THF (0.25 M) at -78 °C under N_2 was added dropwise DIAD (1.0 equiv) at -78 °C. A solution of alcohol (1.1 equiv) in THF (1 M) was added dropwise to the reaction mixture at -78 °C and stirred for 5 min. A solution of benzyl Meldrum's acid (1.0 equiv) in THF (1 M) was added dropwise and stirred for an additional 5 min. The reaction mixture was then stirred at room temperature for 4 h and concentrated under reduced pressure. The crude product was purified by either flash chromatography or recrystallization.

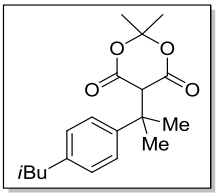
Substrate Specific Information

5-(2-(4-Isopropylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3h)



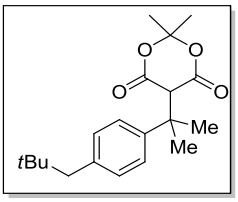
Prepared according to General Procedure B by dropwise addition of 4-(isopropylphenyl)magnesium bromide (9.0 mL, 12.6 mmol, 1.4 M in THF) via syringe pump (0.34 mL/min) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.16 g, 6.30 mmol) in THF (6.3 mL); Recrystallization from MeOH afforded a white solid (1.15 g, 60 % yield). M.p. 130-131 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 3.54 (s, 1H), 2.89 (septet, J = 6.9 Hz, 1H), 1.70 (s, 6H), 1.61 (s, 3H), 1.23 (d, J = 6.9 Hz, 6H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3 (C), 147.6 (C), 141.3 (C), 126.4 (CH), 126.2 (CH), 105.2 (C), 57.7 (CH), 42.5 (C), 33.5 (CH), 29.5 (CH_3), 27.9 (CH_3), 27.0 (CH_3), 23.8 (CH_3). HRMS(EI) *m/z* calcd for $C_{18}H_{24}O_4$ (M^+): 304.1675. Found: 304.1676.

5-(2-(4-Isobutylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3i)



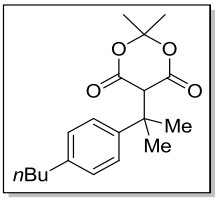
Prepared according to General Procedure B by dropwise addition of (4-isobutylphenyl)magnesium bromide (10.1 mL, 14.2 mmol, 1.4 M in THF) via syringe pump (0.34 mL/min) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.3 g, 7.1 mmol) in THF (7.1 mL). Recrystallization from MeOH afforded a white solid (0.95 g, 42 % yield). M.p. 98-99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, *J* = 8.2 Hz, 2H), 7.08 (s, *J* = 8.2 Hz, 2H), 3.50 (s, 1H), 2.42 (d, *J* = 7.1 Hz, 2H), 1.81 (m, 1H), 1.66 (s, 6H), 1.58 (s, 3H), 1.51 (s, 3H), 0.86 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4 (C), 141.3 (C), 140.5 (C), 129.1 (CH), 126.0 (CH), 105.2 (C), 57.7 (CH), 44.8 (CH_2), 42.6 (C), 30.1 (CH), 29.5 (CH_3), 28.0 (CH_3), 27.2 (CH_3), 22.3 (CH_3). HRMS(EI) *m/z* calcd for $C_{19}H_{26}O_4$ (M^+): 318.1831. Found: 318.1833

5-(2-(4-Neopentylphenyl)propan-2-yl)-2,2-dimethy-1,3-dioxane-4,6-dione (3j)



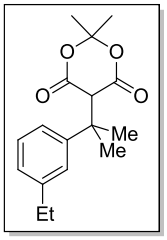
Prepared according to General Procedure A by the addition of methylmagnesium bromide (7.1 mL, 14.1 mmol, 2.0 M solution in THF) via syringe pump (0.34 mL/min) to 2,2-dimethyl-5-(1-(4-neopentylphenyl)ethylidene)-1,3-dioxane-4,6-dione (1.5 g, 4.7 mmol) in THF (4.7 mL). Purification by flash column chromatography eluting with 12:1 hexanes:EtOAc, followed by 9:1 hexanes:EtOAc afforded a white solid (0.68 g, 44 % yield). M.p. 73-75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 3.50 (s, 1H), 2.44 (s, 2H), 1.66 (s, 6H), 1.58 (s, 3H), 1.13 (s, 3H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3 (C), 141.3 (C), 138.6 (C), 130.4 (CH), 125.6 (CH), 105.2 (C), 57.7 (CH), 49.6 (CH_2), 42.6 (C), 31.7 (C), 29.5 (CH_3), 29.3 (CH_3), 28.1 (CH_3), 27.3 (CH_3). HRMS(EI) *m/z* calcd for $C_{20}H_{28}O_4$ (M^+): 332.1988. Found: 332.1997.

5-(2-(4-Butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3k)



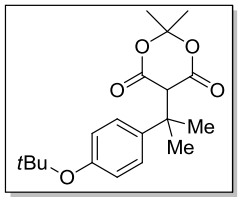
Prepared according to General Procedure B by dropwise addition of (4-butylphenyl)magnesium bromide (10.1 mL, 14.2 mmol, 1.4 M in THF) via syringe pump (0.34 mL/min) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.3 g, 7.1 mmol) in THF (7.1 mL). Recrystallization from MeOH afforded a white solid (0.93 g, 41 % yield). M.p. 92-93 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 3.51 (s, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.65 (s, 6H), 1.58 (s, 3H), 1.58-1.49 (m, 2H), 1.33 (quintet, *J* = 7.6 Hz, 2H), 1.15 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3 (C), 141.7 (C), 141.3 (C), 128.4 (CH), 126.1 (CH), 105.2 (C), 57.6 (CH), 42.6 (C), 35.0 (CH_2), 33.5 (CH_2), 29.5 (CH_3), 27.9 (CH_3), 27.2 (CH_3), 22.3 (CH_2), 13.9 (CH_3). HRMS(EI) *m/z* calcd for $C_{19}H_{26}O_4$ (M^+): 318.1831. Found: 318.1835.

5-(2-(3-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3m)



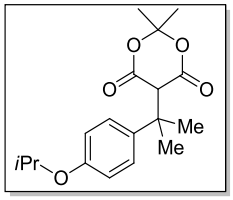
Prepared according to General Procedure B by the addition of (3-ethylphenyl)magnesium bromide (5.4 mL, 10.8 mmol, 2.0 M solution in THF) via syringe pump (0.34 mL/min) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (100 mg, 5.4 mmol) in THF (5.4 mL). Recrystallization from MeOH afforded a white solid (0.58 g, 37 % yield). M.p. 60-62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (m, 1H), 7.14 (d, *J* = 5.6 Hz, 2H), 7.07 (d, *J* = 7.43 Hz, 1H), 3.52 (s, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.67 (s, 6H), 1.59 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4 (C), 144.3 (C), 144.1 (C), 128.4 (CH), 126.6 (CH), 126.0 (CH), 123.6 (CH), 105.3 (C), 57.7 (CH) 42.8 (C), 29.5 (C), 29.0 (CH_2), 27.9 (CH_3), 27.2 (CH_3), 15.7 (CH_3). HRMS(EI) *m/z* calcd for $C_{19}H_{26}O_5$ (M^+): 290.1518. Found: 290.1518.

5-(2-(4-(*tert*-Butoxy)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3n)



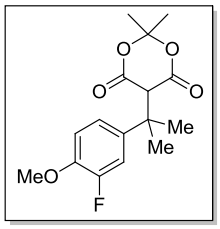
Prepared according to General Procedure A by the addition of methylmagnesium bromide (0.94 mL, 1.88 mmol, 2.0 M solution in THF) via syringe pump (0.34 mL/min) to 5-(1-(4-(*tert*-butoxy)phenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (150 mg, 0.47 mmol) in THF (0.5 mL). Recrystallization from MeOH afforded a white solid (85 mg, 54 % yield). M.p. 106-108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.45 (s, 1H), 1.65 (s, 6H), 1.56 (s, 3H), 1.30 (s, 9H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4 (C), 154.4 (C), 138.4 (C), 127.0 (CH), 123.6 (CH), 105.3 (C), 78.4 (C), 57.8 (CH), 42.6 (C), 29.6 (CH_3), 28.8 (CH_3), 28.2 (CH_3), 27.2 (CH_3). HRMS(EI) *m/z* calcd for $C_{19}H_{26}O_5$ (M^+): 334.1780. Found: 334.1786.

5-(2-(4-Isopropoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3o)



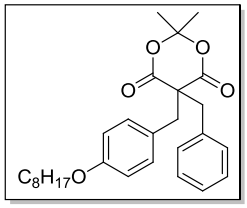
Prepared according to General Procedure B by dropwise addition of (4-isopropoxyphenyl)magnesium bromide (10.1 mL, 14.2 mmol, 1.4 M in THF) via syringe pump (0.34 mL/min) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.3 g, 7.1 mmol) in THF (7.1 mL). Purification by flash column chromatography eluting with 5:1 hexanes/EtOAc, then recrystallized from MeOH to afford a white solid (1.05 g, 46 % yield). M.p. 80-81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.49 (septet, *J* = 6.1 Hz, 1H), 3.46 (s, 1H), 1.64 (s, 6H), 1.58 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 6H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4 (C), 156.7 (C), 135.8 (C), 127.5 (CH), 115.5 (CH), 105.2 (C), 69.7 (CH), 57.8 (CH), 42.4 (C), 29.5 (CH_3), 28.2 (CH_3), 27.1 (CH_3), 21.9 (CH_3). HRMS(EI) *m/z* calcd for $C_{18}H_{24}O_5$ (M^+): 320.1624. Found: 320.

5-(2-(3-Fluoro-4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3p)



Prepared according to General Procedure A by the addition of methylmagnesium bromide (10 mL, 20 mmol, 2.0 M solution in THF) via syringe ump (0.34 mL/min) to 5-(1-(3-fluoro-4-methoxyphenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (3.0 g, 10 mmol) in THF (10 mL). Purification by flash column chromatography eluting with 3:1 hexanes:EtOAc afforded a white solid (1.86 g, 60 % yield). M.p. 113-114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08-7.01 (m, 2H), 6.91-6.86 (m, 1H), 3.85 (s, 3H), 3.54 (s, 1H), 1.64 (s, 3H), 1.60 (s, 6H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9 (C), 151.8 (d, ^{1}J = 243.6 Hz, C), 146.2 (d, ^{2}J = 10.6 Hz, C), 138.2 (d, ^{3}J = 5.3 Hz, C), 121.8 (d, ^{3}J = 3.2 Hz, CH), 114.3 (d, ^{2}J = 19.1 Hz, CH), 112.9 (CH), 104.9 (C), 57.2 (CH), 56.1 (CH_3), 41.7 (C), 28.8 (CH_3), 27.6 (2xCH_3). HRMS(EI) *m/z* calcd for $C_{16}H_{19}FO_5$ (M^+): 310.1217. Found: 310.1208.

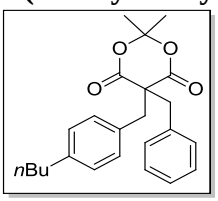
5-(4-(Octyloxy)benzyl)-5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (4a)



Prepared according to General Procedure C from 5-(4-(octyloxy)benzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (700 mg, 1.93 mmol, 1 equiv), K_2CO_3 (401 mg, 2.90 mmol, 1.5 equiv) and benzyl bromide (0.3 mL, 2.5 mmol, 1.3 equiv). Purification by flash column chromatography eluting with 8:1 hexanes:EtOAc afforded a white solid (838 mg, 95 % yield). M.p. 49-50 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.17 (m, 5H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.41 (s, 2H), 3.38 (s, 2H), 1.71 (quintet, *J* = 6.8 Hz, 2H), 1.39 (quintet, *J* = 7.2 Hz, 2H), 1.28-1.25 (m, 8H), 0.85 (t, *J* = 6.5 Hz, 3H), 0.69 (s, 3H), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3 (C), 158.7 (C), 134.9 (C), 131.2 (CH), 130.1 (CH), 128.8 (CH), 127.7 (CH), 126.7 (C), 114.8 (CH), 105.8 (C), 68.0 (CH_2), 60.2 (C), 44.8 (CH_2), 44.3 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1

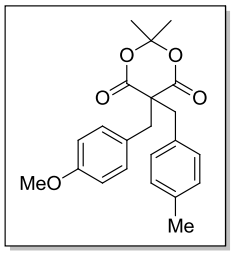
(CH_2), 28.8 (CH_3), 28.6 (CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS(EI) *m/z* calcd for $C_{28}H_{36}O_5$ (M^+): 452.2563. Found: 452.2555.

5-(4-Butylbenzyl)-5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (4b)



Prepared according to General Procedure D from 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (0.58 g, 2.5 mmol, 1 equiv), Ph_3P (0.66 g, 2.5 mmol, 1 equiv), DIAD (0.55 mL, 2.8 mmol, 1.1 equiv) and (4-butylphenyl)methanol (0.46 g, 2.8 mmol, 1.1 equiv). Purification by flash column chromatography eluting with 5:1 hexanes:EtOAc, followed by 3:1 hexanes:EtOAc and 1:1 hexanes:EtOAc, then recrystallized from MeOH to afford a white solid (0.39 g, 41 % yield). M.p. 102-103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.17 (m, 5H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 3.42 (s, 2H), 3.40 (s, 2H), 2.52 (t, *J* = 7.7 Hz, 2H), 1.48 (quintet, *J* = 7.7 Hz, 2H), 1.24 (sextet, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.63 (s, 3H), 0.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.2 (C), 142.6 (C), 134.9 (C), 132.0 (C), 130.1 (CH), 130.0 (CH), 128.9 (CH), 128.8 (CH), 127.7 (CH), 105.8 (C), 60.2 (C), 44.9 (CH_2), 44.6 (CH_2), 35.1 (CH_2), 33.6 (CH_2), 28.6 (CH_3), 28.5 (CH_3), 22.0 (CH_2), 13.8 (CH_3). HRMS(EI) *m/z* calcd for $C_{24}H_{28}O_4$ (M^+): 380.1988. Found: 380.1982.

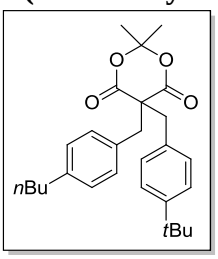
5-(4-methoxybenzyl)-2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione (4c)



Prepared according to General Procedure C from 2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione (1.14 g, 4.59 mmol, 1 equiv), K_2CO_3 (952 mg, 6.89 mmol, 1.5 equiv) and 1-(bromomethyl)-4-methoxybenzene (0.86 mL, 6.0 mmol, 1.3 equiv). Purification by flash column chromatography eluting with 8:1 hexanes:EtOAc afforded a white solid (1.28 g, 76 % yield). M.p. 49-50 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, *J* = 8.5 Hz, 6H), 6.97 (d, *J* = 8.5 Hz, 2H), 3.91 (s, 3H), 3.55 (s, 4H), 2.44 (s, 3H), 088 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5 (C), 159.2 (C), 137.5 (C), 131.9 (CH),

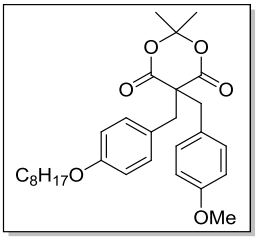
131.3 (CH), 130.0 (CH), 129.4 (CH), 127.0 (C), 114.2 (C), 105.8 (CH), 105.8 (C), 60.3 (C), 55.3 (CH_3), 44.5 (CH_2), 44.2 (CH_2), 28.9 (CH_3), 28.6 (CH_3), 21.0 (CH_3). HRMS(EI) *m/z* calcd for $C_{28}H_{36}O_5$ (M^+): 368.1624 Found: 368.1624.

5-(4-*tert*-Butylbenzyl)-5-(4-butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4d)



Prepared according to General Procedure D from 5-(4-*tert*-butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.0 g, 3.4 mmol, 1 equiv), Ph_3P (0.9 g, 3.4 mmol, 1 equiv), DIAD (0.73 mL, 3.7 mmol, 1.1 equiv) and (4-butylphenyl)methanol (0.61 g, 3.7 mmol, 1.1 equiv). Purification by flash column chromatography eluting with 9:1 hexanes:EtOAc, then recrystallized from MeOH to afford a white solid (0.87 g, 59 % yield). M.p. 97-99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.08-7.04 (m, 4H), 3.39 (s, 4H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.48 (quintet, *J* = 7.7 Hz, 2H), 1.28-1.23 (m, 11H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.62 (s, 3H), 0.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3 (C), 150.9 (C), 142.5 (C), 132.1 (C), 131.9 (C), 129.9 (CH), 129.8 (CH), 128.9 (CH), 125.7 (CH), 105.8 (C), 60.4 (C), 44.5 (CH_2), 44.4 (CH_2), 35.1 (CH_2), 34.4 (C), 33.6 (CH_2), 31.2 (CH_3), 28.6 (CH_3), 28.3 (CH_3), 22.0 (CH_2), 13.8 (CH_3). HRMS(EI) *m/z* calcd for $C_{28}H_{36}O_4$ (M^+): 436.2614. Found: 436.2608.

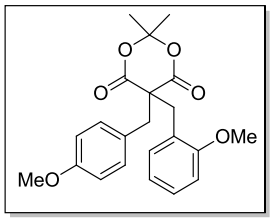
5-(4-Methoxybenzyl)-2,2-dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (4e)



Prepared according to General Procedure C from 5-(4-(octyloxy)benzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.70 g, 1.93 mmol, 1 equiv), K_2CO_3 (0.40 g, 2.9 mmol, 1.5 equiv) and 4-methoxybenzyl chloride (0.28 mL, 2.1 mmol, 1.1 equiv). Purification by flash column chromatography eluting with 9:1 hexanes/EtOAc afforded a white solid (0.88 g, 95 % yield). M.p. 75-77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12-7.07 (m,

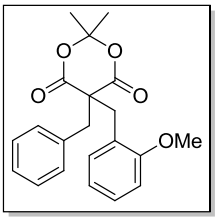
4H), 6.80-6.76 (m, 4H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.73 (s, 3H), 3.35 (s, 4H), 1.71 (quintet, *J* = 6.6 Hz, 2H), 1.39 (quintet, *J* = 7.1 Hz, 2H), 1.28-1.25 (m, 8H), 0.85 (t, *J* = 6.4 Hz, 3H), 0.71 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5 (C), 159.2 (C), 158.7 (C), 131.2 (CH), 131.1 (CH), 127.0 (C), 126.8 (C), 114.8 (CH), 114.1 (CH), 105.8 (C), 68.0 (CH_2), 60.4 (C), 55.2 (CH_3), 44.1 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (2xCH_2), 28.8 (CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS(EI) *m/z* calcd for $C_{29}H_{38}O_6$ (M^+): 482.2668. Found: 482. 2666.

5-(2-Methoxybenzyl)-5-(4-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4f)



Prepared according to General Procedure D from 5-(4-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.80 g, 3.0 mmol, 1 equiv), Ph_3P (0.80 g, 3.0 mmol, 1 equiv), DIAD (0.71 mL, 3.6 mmol, 1.2 equiv) and (2-methoxyphenyl)methanol (0.50 g, 3.6 mmol, 1.2 equiv). Purification by flash column chromatography eluting with 5:1 hexanes:EtOAc, then recrystallized from MeOH to afford a white solid (0.72 g, 62 % yield). M.p. 152-154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (t, *J* = 7.8 Hz, 1H), 7.15-7.12 (m, 3H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.44 (s, 2H), 3.39 (s, 2H), 0.92 (s, 3H), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2 (C), 158.9 (C), 157.8 (C), 132.1 (CH), 131.7 (CH), 129.1 (CH), 127.6 (C), 123.1 (CH), 120.6 (CH), 113.9 (CH), 110.3 (CH), 105.3 (C), 58.7 (C), 55.2 (CH_3), 54.9 (CH_3), 42.4 (CH_2), 40.5 (CH_2), 29.5 (CH_3), 28.1 (CH_3). HRMS(EI) *m/z* calcd for $C_{22}H_{24}O_6$ (M^+): 384.1573. Found: 384.1580.

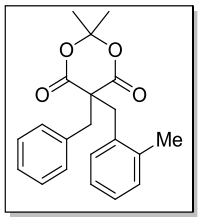
5-Benzyl-5-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4g)



Prepared according to General Procedure C from 5-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.06 g, 4.01 mmol, 1 equiv), K_2CO_3 (0.8 g, 6.0 mmol, 1.5

equiv) and benzyl bromide (1.0 mL, 8.4 mmol, 2.1 equiv). Recrystallization from MeOH afforded a white solid (1.0 g, 70 % yield). M.p. 121-122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.14 (m, 7H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 3.75 (s, 3H), 3.48 (s, 2H), 3.46 (s, 2H), 0.91 (s, 3H), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0 (C), 157.8 (C), 135.5 (C), 132.1 (CH), 130.6 (CH), 129.1 (CH), 128.6 (CH), 127.5 (CH), 123.0 (C), 120.6 (CH), 110.3 (CH), 105.3 (C), 58.5 (C), 54.9 (CH_3), 43.1 (CH_2), 40.6 (CH_2), 29.3 (CH_3), 28.0 (CH_3). HRMS(EI) *m/z* calcd for $C_{21}H_{22}O_5$ (M^+): 354.1467. Found: 354.1464.

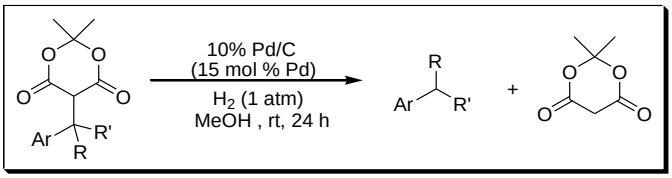
5-Benzyl-5-(2-methylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4h)



Prepared according to General Procedure C from 2,2-dimethyl-5-(2-methylbenzyl)-1,3-dioxane-4,6-dione (0.87 g, 3.5 mmol, 1 equiv), K_2CO_3 (0.73 mg, 5.3 mmol, 1.5 equiv) and benzyl bromide (0.83 mL, 7.0 mmol, 2.0 equiv). Recrystallization from MeOH afforded a white solid (0.59 mg, 50 % yield). M.p. 152-155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.17 (m, 6H), 7.16-7.10 (m, 3H), 3.53 (s, 2H), 3.47 (s, 2H), 2.35 (s, 3H), 0.77 (s, 3H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4 (C), 137.3 (C), 134.9 (C), 133.1 (C), 131.1 (CH), 130.6 (CH), 130.4 (2xCH), 128.7 (CH), 127.7 (CH), 126.1 (CH), 105.8 (C), 59.0 (C), 44.6 (CH_2), 41.6 (CH_2), 29.0 (CH_3), 28.3 (CH_3), 19.4 (CH_3). HRMS(EI) *m/z* calcd for $C_{21}H_{22}O_4$ (M^+): 318.1518. Found: 318.1520.

Hydrogenolysis Reactions

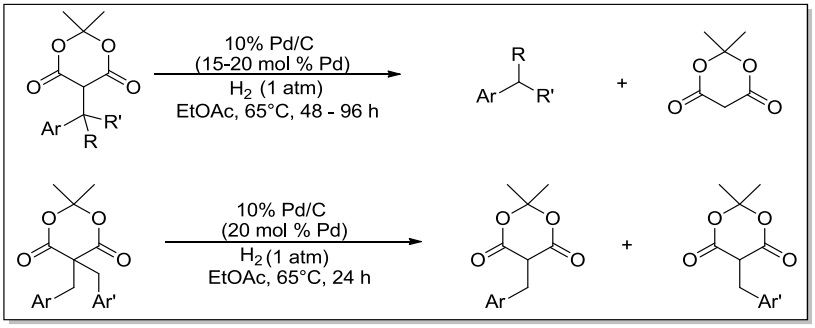
General Procedure E – Hydrogenolysis of Benzyl Meldrum's Acids



The reactions were carried out using 0.1-0.5 mmol of substrates. MeOH (ACS grade) was distilled and degassed under vacuum and then refilled with nitrogen (3 cycles). To a 20 mL vial was added benzyl Meldrum's acid and 10 % Pd/C (15 mol % Pd). MeOH was added

to the vial through a septum via a syringe under nitrogen. The vial was degassed with vacuum and then refilled with hydrogen (3 cycles). The reaction was stirred under an atmosphere of hydrogen (1 atm) for 24 h then filtered through a pad of celite and washed with CH_2Cl_2. Due to the low boiling points of the products, the solvent was removed under reduced pressure at 0 °C. The crude material was purified by flash column chromatography.

General Procedure F – Hydrogenolysis of Benzyl Meldrum's Acids

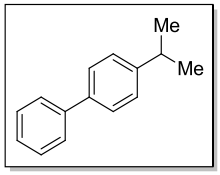


The reactions were carried out using 0.1-0.5 mmol of substrates. EtOAc (ACS grade) was degassed with vacuum and then refilled with nitrogen (3 cycles). To a Schlenk tube was added benzyl Meldrum's acid and 10 % Pd/C (20 mol % Pd). EtOAc (0.1 M relative to benzyl Meldrum's acid) was added to the Schlenk tube through a septum via a syringe. The suspension was degassed with vacuum and then refilled with H_2 gas (3 cycles) with the help of balloon (1 atm). The tube was sealed and the balloon was removed. The suspension was stirred at 65 °C in an oil bath for 24 h then filtered through a pad of celite and washed with CH_2Cl_2. The solvent was removed under reduced pressure at 0 °C due to the low boiling points of the products. The crude material was purified by flash chromatography.

Product Specific Information

The following products were prepared according to literature procedures[32] and the spectral data obtained were in agreement with those reported and consequently, data will not be repeated here: Isopropyl-benzene (**3.1a**),[32] 1-(sec-butyl)-4-(octyloxy)benzene (**3.1c**),[32] 1-(hexan-2-yl)-4-(octyloxy)benzene (**3.1r**),[32] 1-cyclohexyl-4-(octyloxy)benzene (**3.1s**),[32] 1-(3-methylbutan-2-yl)-4-(octyloxy)benzene (**3.1t**).[32]

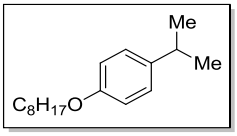
4-Isopropyl-biphenyl (3.1b)[32]



Run #1. Prepared according to General Procedure E from 5-(1-Biphenyl-4-yl-1-methyl-ethyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (**3b**)[32] (107 mg, 0.316 mmol) and 10 % Pd/C (50.4 mg, 0.0477 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 100% pentane afforded clear oil (49 mg, 79 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 3H), 2.95 (septet, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 147.9 (C), 141.2 (C), 138.7 (C), 128.7 (CH), 127.1 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 33.8 (CH), 24.0 (CH_3). GC/MS calcd for $C_{15}H_{16}$ (M^+): 196.1252. Found (LRMS): 196.1.

Run #2 = 80 % yield; Average Yield = (80 % +79 %)/2 = 79.5 % = 80 % yield.

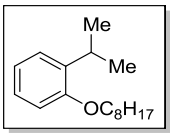
1-Isopropyl-4-octyloxy-benzene (3.1c)[32]



Run #1. Prepared according to General Procedure E from 2,2-Dimethyl-5-[1-methyl-1-(4-octyloxy-phenyl)-ethyl]-[1,3]dioxane-4,6-dione (**3c**)[32] (98 mg, 0.25 mmol) and 10 % Pd/C (39.9 mg, 0.0375 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 100 % pentane afforded clear oil (49 mg, 79 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 2.86 (septet, *J* = 6.9 Hz, 1H), 1.77 (quintet, *J* = 7.8, 2H), 1.47 (quintet, *J* = 7.3 Hz, 2H), 1.32-1.29 (m, 8H), 1.23 (d, *J* = 7.0 Hz, 6H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.2 (C), 140.8 (C), 127.16 (CH), 114.3 (CH), 68.0 (CH_2), 33.3 (CH), 31.8 (CH_2), 29.4 (2xCH_2), 29.3 (CH_2), 26.1 (CH_2), 24.2 (CH_3), 22.7 (CH_2), 14.1 (CH_3). GC/MS calcd for $C_{17}H_{28}O$ (M^+): 248.2140. Found (LRMS): 248.2.

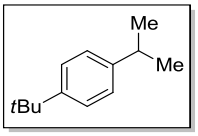
Run #2 = 76 % yield; Average yield = (79 % + 76 %)/2 = 77.5 % = 78 % yield.

1-Isopropyl-2-octyloxy-benzene (3.1e)[32]



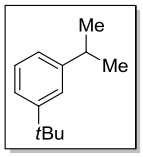
Prepared according to General Procedure E from 2,2-Dimethyl-5-[1-methyl-1-(2-octyloxy-phenyl)-ethyl]-[1,3]dioxane-4,6-dione (**3e**)[63] (100 mg, 0.256 mmol) and 10 % Pd/C (54.5 mg, 0.0512 mmol, 20 mol % Pd) was used instead of 15 mol % Pd. Purification by flash column chromatography eluting with 100 % pentane afforded clear oil (57 mg, 90 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.16 (dt, *J* = 7.7, 1.6 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.36 (septet, *J* = 6.9 Hz, 1H), 1.82 (quintet, *J* = 6.6 Hz, 2H), 1.51 (quintet, *J* = 5.7 Hz, 2H), 1.45-1.30 (m, 8H), 1.24 (d, *J* = 6.9 Hz, 6H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3 (C), 137.0 (C), 126.4 (CH), 126.0 (CH), 120.3 (CH), 111.1 (CH), 67.8 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.9 (CH), 26.2 (CH_2), 22.6 (CH_2), 22.6 (CH_3), 14.1 (CH_3). GC/MS calcd for $C_{17}H_{28}O$ (M_+): 248.2140. Found (LRMS): 248.2.

1-*tert*-Butyl-4-isopropylbenzene [CAS: 4132-49-4] (3.1f)[99]



Prepared according to General Procedure E from 5-(2-(4-*tert*-butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3f**)[103] (100 mg, 0.314 mmol) and 10 % Pd/C (66.8 mg, 0.0628 mmol, 20 mol % Pd). Purification by flash column chromatography eluting with 100 % pentanes afforded a clear oil (42 mg, 76 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 2.90 (septet, *J* = 6.9 Hz, 1H), 1.33 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4 (C), 145.7 (C), 126.0 (CH), 125.1 (CH), 34.3 (C), 33.5 (CH), 31.4 (CH_3), 24.0 (CH_3). GC/MS calcd for $C_{13}H_{20}$ (M^+): 176.1565. Found (LRMS): 176.1.

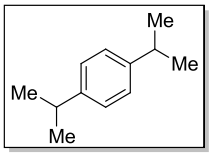
1-*tert*-Butyl-3-isopropylbenzene (3.1g) [CAS: 20033-12-]



Prepared according to General Procedure F from 5-(2-(3-(*tert*-butyl)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3g**)[103] (96.3 mg, 0.302

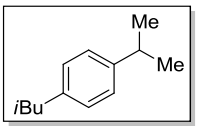
mmol) and 10 % Pd/C (53 mg, 0.06 mmol, 20 mol % Pd). Purification by flash column chromatography eluting with 100% pentane afforded a clear oil (20.9 mg, 39 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (m, 3H), 7.03 (m, 1H), 2.89 (septet, *J* = 6.9 Hz, 1H), 1.31 (s, 9H), 1.24 (d, *J* = 6.9 Hz, 6H) ^{13}C NMR ($CDCl_3$, 75 MHz) 150.9 (C), 149.4 (C), 127.9 (CH), 123.6 (CH), 123.2 (CH), 122.7 (CH), 34.6 (C), 34.3 (CH), 31.4 (CH_3), 24.1 (CH_3). GC/MS calcd for $C_{13}H_{20}$ (M^+): 176.1565. Found (LRMS): 176.2.

1,4-Diisopropylbenzene [CAS: 100-18-5] (3.1h)



Prepared according to General Procedure F from 5-(2-(4-isopropylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3h**) (96.4 mg, 0.317 mmol) and 10 % Pd/C (67.5 mg, 0.0634 mmol, 20 mol % Pd). Purification by flash column chromatography eluting 100 % pentanes afforded a clear oil (47 mg, 91 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (s, 4H), 2.87 (septet, *J* = 6.9 Hz, 2H), 1.23 (d, *J* = 6.9 Hz, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.2 (C), 126.3 (CH), 33.6 (CH), 24.0 (CH_3). GC/MS calcd for $C_{12}H_{18}$ (M^+): 162.1409. Found (LRMS): 162.1.

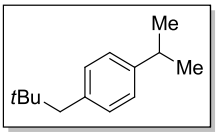
1-Isobutyl-4-isopropylbenzene [CAS: 34349-70-7] (3.1i)[100]



Run #1. Prepared according to General Procedure E from 5-(2-(4-isobutylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3i**) (106 mg, 0.333 mmol) and 10 % Pd/C (53 mg, 0.05 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 100 % pentanes afforded a colorless oil (42 mg, 72 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 2.88 (septet, *J* = 6.9 Hz, 1H), 2.44 (d, *J* = 7.1 Hz, 2H), 1.85 (septet, *J* = 6.8 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.0 (C), 138.9 (C), 128.9 (CH), 126.6 (CH), 45.1 (CH_2), 33.7 (CH), 30.2 (CH), 24.1 (CH_3), 22.4 (CH_3). GC/MS calcd for $C_{13}H_{20}$ (M^+): 176.1565 Found (LRMS): 176.1

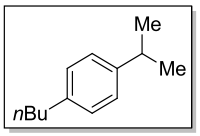
Run #2 = 67 % yield; Average yield = (72 % + 67 %)/2 = 70 % yield.

1-Isopropyl-4-neopentylbenzene [CAS: 37920-33-5] (3.1j)



Prepared according to General Procedure E from 5-(2-(4-neopentylphenyl)propan-2-yl)-2,2-dimethy-1,3-dioxane-4,6-dione (**3j**) (80 mg, 0.24 mmol) and 10 % Pd/C (38 mg, 0.036 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 100% pentane afforded a clear oil (37 mg, 81 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, *J* = 7.4 Hz, 2H), 7.05 (d, *J* = 7.7 Hz, 2H), 2.88 (septet, *J* = 6.9 Hz, 1H), 2.46 (s, 2H), 1.25 (d, *J* = 6.9 Hz, 6H), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1 (C), 137.0 (C), 130.4 (CH), 125.6 (CH), 49.8 (CH_2), 33.6 (CH), 31.7 (C), 29.4 (CH_3), 24.1 (CH_3). GC/MS calcd for $C_{14}H_{22}$ (M^+): 190.1722. Found (LRMS): 190.1.

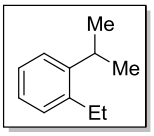
1-Butyl-4-isopropylbenzene [CAS: 55169-03-4] (3.1k)[101]



Run #1. Prepared according to General Procedure E from 5-(2-(4-butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (102 mg, 0.320 mmol) (**3k**) and 10 % Pd/C (51 mg, 0.048 mmol, 15 mol % Pd). Purification by flash column chromatography eluting 100 % pentanes afforded a colorless oil (51 mg, 90 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17-7.09 (m, 4H), 2.89 (septet, *J* = 6.9 Hz, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.6-1.55 (m, 2H), 1.39 (sextet, *J* = 7.6 Hz, 2H), 1.25 (d, *J* = 6.9 Hz, 6H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.0 (C), 140.2 (C), 128.3 (CH), 126.2 (CH), 35.2 (CH_2), 33.7 (CH_2), 33.6 (CH), 24.1 (CH_3), 22.4 (CH_2), 13.9 (CH_3). GC/MS calcd for $C_{13}H_{20}$ (M^+): 176.1565. Found (LRMS): 176.1.

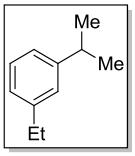
Run #2 = 89 % yield; Average yield = (90 % + 89 %)/2 = 90 % yield.

1-Ethyl-2-isopropyl-benzene [CAS: 18970-44-0] (3.1l)[102]



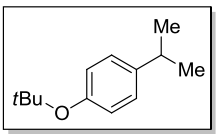
Prepared according to General Procedure E from 5-(2-(2-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3l**) (101 mg, 0.348 mmol) and 10 % Pd/C (55.6 mg, 0.0522 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with pentane afforded a colorless oil (43 mg, 83 % yield).^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 1H), 7.20-7.08 (m, 3H), 3.46 (septet, *J* = 6.9 Hz, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.18 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.3 (C), 140.9 (C), 128.5 (CH), 126.1 (CH), 125.6 (CH), 125.1 (CH), 28.4 (CH), 25.7 (CH_2), 23.9 (CH_3), 15.9 (CH_3). GC/MS calcd for $C_{11}H_{16}$ (M^+): 148.1252. Found (LRMS): 148.1

1-ethyl-3-isopropylbenzene [CAS: 4920-99-4] (3.1m)



Prepared according to General Procedure E from 5-(2-(3-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3m**) (101mg, 0.348 mmol) and 10 % Pd/C (55.6 mg, 0.0522 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with pentane afforded a colorless oil (33 mg, 64 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (t, *J* = 7.7 Hz, 1H), 7.02 (m, 3H), 2.87 (septet, *J* = 6.9 Hz, 1H), 2.63 (q, *J* = 7.6 Hz, 2H) 1.25 (s, 4H), 1.23 (s, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.9 (C), 144.2 (C), 128.2 (CH), 126.1 (CH), 125.2 (CH), 123.6 (CH), 34.1 (CH), 28.9 (CH_3), 24.0 (CH_3), 15.6 (CH_3); GC/MS calcd for $C_{13}H_{20}O$ (M+): 148.1252. Found (LRMS): 148.1

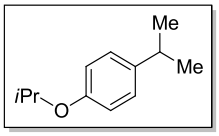
1-*tert*-Butoxy-4-isopropylbenzene [CAS: 16215-76-2] (3.1n)[103]



Prepared according to General Procedure F from 5-(2-(4-(*tert*-butoxy)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3n**) (103 mg, 0.308 mmol). 10 % Pd/C (49.2 mg, 0.0462 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 100 % pentane afforded a clear oil (42 mg, 70 % yield). ^{1}H

NMR ($CDCl_3$, 500 MHz) δ 7.14 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 2.90 (septet, *J* = 6.9 Hz, 1H), 1.35 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.1 (C), 143.7 (C), 126.6 (CH), 124.0 (CH), 78.0 (C), 33.4 (CH), 28.9 (CH_3), 24.2 (CH_3); GC/MS calcd for $C_{13}H_{20}O$ (M+): 192.1514. Found: 192.2

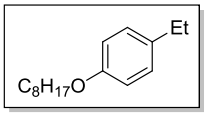
1-Isopropoxy-4-isopropylbenzene [CAS: 28530-6-1] (3.1o)[104]



Run # 1. Prepared according to General Procedure F from 5-(2-(4-isopropoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3o**) (99.1 mg, 0.309 mmol) and 10 % Pd/C (49.3 mg, 0.0464 mmol, 15 mol% Pd). Purification by flash column chromatography eluting 100 % pentanes afforded a colorless oil (45 mg, 82 % yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.50 (septet, *J* = 6.1 Hz, 1H), 2.85 (septet, d = 6.9 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9 (C), 140.9 (C), 127.2 (CH), 115.7 (CH), 69.8 (CH), 33.2 (CH), 24.2 (CH_3), 22.1 (CH_3). GC/MS calcd for $C_{12}H_{18}O$ (M^+): 178.1358. Found (LRMS): 178.1.

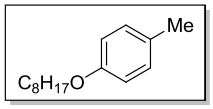
Run #2 = 82 % yield; Average yield = (82 % + 82 %)/2 = 82 % yield.

1-Ethyl-4-(octyloxy)benzene [CAS: 1379023-18-3] (3.1u)



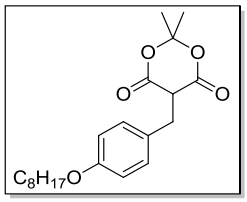
Prepared according to General Procedure F from 2,2,5-trimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**3w**)[32] (95.5 mg, 0.245 mmol) and 10 % Pd/C (39 mg, 0.037 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with hexanes, followed by 5:1 hexanes:CH_2Cl_2 afforded a clear oil (54 mg, 94 % yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.77 (quintet, *J* = 7.6 Hz, 2H), 1.45 (quintet, *J* = 6.4 Hz, 2H), 1.31-1.29 (m, 8H), 1.21 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.2 (C), 136.1 (C), 128.6 (CH), 114.4 (CH), 68.0 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 15.9 (CH_3), 14.1 (CH_3). GC/MS calcd for $C_{16}H_{26}O$ (M^+): 234.1984 Found (LRMS): 234.2.

1-Methyl-4-(octyloxy)benzene [CAS: 67698-82-2] (3.1v)[105]



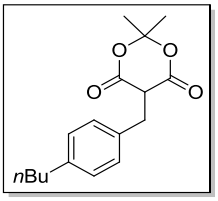
Prepared according to General Procedure F from 5-(4-(octyloxy)benzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**3x**)[32] (100 mg, 0.266 mmol) and 10 % Pd/C (43 mg, 0.040 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 5:1 hexanes:CH_2Cl_2 afforded a clear oil (50 mg, 80 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 3.91 (t, *J* = 6.6 Hz, 2H), 2.27 (s, 3H), 1.76 (quintet, *J* = 6.8 Hz, 2H), 1.44 (quintet, *J* = 7.1 Hz, 2H), 1.31-1.29 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.0 (C), 129.8 (CH), 129.6 (C), 114.4 (CH), 68.1 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 20.4 (CH_3), 14.1 (CH_3). GC/MS calcd for $C_{15}H_{24}O$ (M^+): 220.1827. Found (LRMS): 220.

2,2-dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (4.1a)



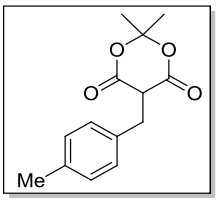
Prepared according to General Procedure F from 5-benzyl-2,2-dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (**4a**) (100 mg, 0.221 mmol) and 10 % Pd/C (35 mg, 0.033 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 5:1 hexanes/EtOAc afforded a white solid (52 mg, 65 % yield). M.p. 52-53 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.19 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.70 (t, *J* = 4.8 Hz, 1H), 3.41 (d, *J* = 4.7 Hz, 2H), 1.75-1.69 (m, 5H), 1.45 (s, 3H), 1.41-1.26 (m, 10H), 0.86 (br t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.4 (C), 158.2 (C), 130.8 (CH), 128.8 (C), 114.4 (CH), 105.1 (C), 67.9 (CH_2), 48.2 (CH), 31.7 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 29.1 (2 x CH_2), 28.4 (CH_3), 27.2 (CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_5$ (M^+): 362.2093. Found: 362.2095.

5-(4-Butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1b)



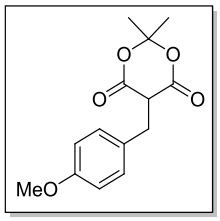
Prepared according to General Procedure F from 5-(4-butylbenzyl)-5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**4b**) (98.1 mg, 0.258 mmol) and 10 % Pd/C (42 mg, 0.039 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 5:1 hexanes/EtOAc afforded a white solid (43 mg, 57 % yield). M.p. 54-55 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 3.72 (t, *J* = 4.9 Hz, 1H), 3.44 (d, *J* = 4.9 Hz, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 1.70 (s, 3H), 1.53 (quintet, *J* = 7.7 Hz, 2H), 1.33 (s, 3H), 1.32-1.24 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4 (C), 141.9 (C), 134.3 (C), 129.6 (CH), 128.7 (CH), 105.2 (C), 48.2 (CH), 35.2 (CH_2), 33.6 (CH_2), 31.9 (CH_2), 28.5 (CH_3), 27.3 (CH_3), 22.3 (CH_2), 13.9 (CH_3). HRMS (EI) *m/z* calcd for $C_{17}H_{22}O_4$ (M^+): 290.3542. Found: 290.3542.

2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione (4.1d) and 5-(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1c)[106]



Run #1. Prepared according to General Procedure F from 5-(4-methoxybenzyl)-2,2-dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (**4c**) (95.7 mg, 0.260 mmol) and 10 % Pd/C (42 mg, 0.039 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 9:1 hexanes:EtOAc, and then 5:1 hexanes:EtOAc afforded a white solid (5.4 mg, 8 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 3.78 (t, *J* = 4.9 Hz, 1H), 3.46 (d, *J* = 1.8 Hz, 2H), 2.32 (s, 3H), 1.74 (s, 3H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.3 (C), 136.7 (C), 134.1 (C), 129.5 (CH), 129.2 (CH), 105.1 (C), 48.1 (CH), 31.7 (CH_2), 28.3 (CH_3), 27.1 (CH_3), 20.9 (CH_3); HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_5$ (M^+): 248.1049. Found: 248.1049.

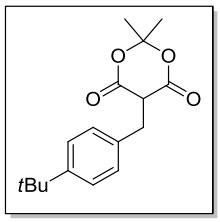
Run #2 = 7 % yield; Average yield = (7 % + 8 %)/2 = 8 % yield.



Run #1. Compound (**4.1c**) was the second product to elute from the above column and was isolated as the white solid (31.3 mg, 46 % yield). M.p. 72-73 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 3.74 (s, 3H), 3.71 (t, *J* = 4.8 Hz, 1H), 3.40 (d, *J* = 4.8 Hz, 2H), 1.69 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4 (C), 158.7 (C), 130.9 (CH), 129.0 (C), 113.9 (CH), 105.1 (C), 55.2 (CH_3), 48.2 (CH), 31.4 (CH_2), 28.4 (CH_3), 27.3 (CH_3). HRMS(EI) *m/z* calcd for $C_{14}H_{16}O_5$ (M^+): 264.0998. Found: 264.1000.

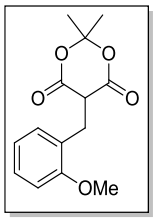
Run #2 = 43 % yield; Average yield = (46 % + 43 %)/2 = 45 % yield.

5-(4-*tert*-Butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1e)[107]



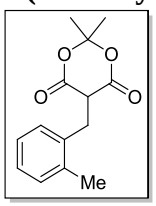
Prepared according to General Procedure F from 5-(4-*tert*-butylbenzyl)-5-(4-butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4d**) (99 mg, 0.23 mmol) and 10 % Pd/C (37 mg, 0.035 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 9:1 hexanes:EtOAc afforded white solid (23 mg, 34 % yield). M.p. 103-106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 3.73 (t, *J* = 4.9 Hz, 1H), 3.44 (d, *J* = 4.9 Hz, 2H), 1.70 (s, 3H), 1.43 (s, 3H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3 (C), 150.1 (C), 134.1 (C), 129.3 (CH), 125.5 (CH), 105.2 (C), 48.2 (CH), 34.4 (C), 31.6 (CH_2), 31.2 (CH_3), 28.4 (CH_3), 27.2 (CH_3). HRMS(EI) *m/z* calcd for $C_{17}H_{22}O_4$ (M^+): 290.1518. Found: 290.1510.

5-(2-Methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1j)[108]



Prepared according to General Procedure F from 5-benzyl-5-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4g**) (102 mg, 0.288 mmol) and 10 % Pd/C (46 mg, 0.043 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 9:1 hexanes:EtOAc afforded white solid (65 mg, 85 % yield). M.p. 86-88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, *J* = 7.3 Hz, 1H), 7.23 (m, 1H), 6.92 (d, *J* = 7.3 Hz, 1H), 6.83 (t, *J* = 8.2 Hz, 1H), 4.00 (t, *J* = 5.8 Hz, 1H), 3.81 (s, 3H), 3.39 (d, *J* = 5.8 Hz, 2H), 1.75 (s, 3H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3 (C), 157.1 (C), 131.9 (CH), 128.2 (CH), 125.6 (C), 120.6 (CH), 110.2 (CH), 104.8 (C), 55.2 (CH_3), 46.1 (CH), 28.6 (CH_3), 28.0 (CH_2), 26.6 (CH_3). HRMS(EI) *m/z* calcd for $C_{14}H_{16}O_5$ (M^+): 264.0998. Found: 264.1004.

5-(2-Methylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1k)



Prepared according to General Procedure F from 5-benzyl-5-(2-methylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4h**) (64 mg, 0.19 mmol) and 10 % Pd/C (31 mg, 0.029 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 9:1 hexanes:EtOAc afforded a white solid (12 mg, 26 % yield). M.p. 85-88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (m, 1H), 7.12 (m, 3H), 3.71 (t, *J* = 5.3 Hz, 1H), 3.44 (d, *J* = 5.3 Hz, 2H), 2.36 (s, 3H), 1.74 (s, 3H), 1.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2 (C), 136.4 (C), 136.3 (C), 130.5 (CH), 129.3 (CH), 127.0 (CH), 126.1 (CH), 105.1 (C), 47.5 (CH), 28.7 (CH_2), 28.6 (CH_3), 26.7 (CH_3), 19.5 (CH_3). HRMS(EI) *m/z* calcd for $C_{14}H_{16}O_4$ (M^+): 248.1049. Found: 248.104

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