Hydrogenolysis of Carbon-Carbon σ Bonds

by

Eric Beaton

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This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the 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.

Statement of Contributions

I performed the hydrogenolysis of substrate 2.**1c** under the heated conditions to determine the cis/trans ratio of the cyclohexane product 2.**2c'**. I also synthesized the cis and trans cyclohexanes separately to obtain the necessary characterization data. I performed the experiments with Meldrum's acid as an additive to suppress the over-reduction to the cyclohexane product. I demonstrated the additive experiments with toluene and the hydrogenolysis product to show competitive binding of the catalyst to the substrate. I performed the competition experiments for **2.7d** and **2.7h**. I performed the hydrogenolysis of spiro derivatives 2.**9** and 2.**10a** under ethyl acetate at 65 °C to show selective hydrogenation of the alkene in 2.**9** and inability of substrate 2.**10a** to undergo hydrogenolysis. I performed the synthesis of product 2.**16b** by an alternate route in order to confirm the absolute stereochemistry. Finally, I performed the majority of the deuterium-labelling studies, excluding the experiments performed on the enantioenriched derivatives.

Abstract

The modification of benzylic quaternary, tertiary, and secondary carbon centers through Pd-catalyzed hydrogenolysis of Csp^3-Csp^3 σ bonds is presented. When benzyl Meldrum's acid derivatives bearing quaternary benzylic centers are treated under mild hydrogenolysis conditions—palladium on carbon and atmospheric pressure of hydrogen—aromatics substituted with tertiary benzylic centers and Meldrum's acid are obtained with good to excellent yield. Analogously, substrates containing tertiary or secondary benzylic centers yield secondary or methyl derivatives, respectively. The scope of the reductive dealkylation reaction is explored and the limitations with respect to steric and electronic factors are determined. A mechanistic analysis of the reaction is described that consisted of deuterium labelling experiments and hydrogenolysis of enantioenriched derivatives. The investigation shows that the Csp^3-Csp^3 σ bond-cleaving events occur through an unprecedented mechanism, in which the palladium center displaces a carbon-based leaving group, namely Meldrum's acid, with inversion of configuration by a formal S_N2 process, followed by reductive elimination of palladium to furnish a C-H bond.

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List of Abbreviations

Ac   acetyl

nBu   1-butyl

tBu   *tert*-butyl

cod   cycloocta-1,5-diene

DCE   1,2-dichloroethane

DMAP   4-dimethylaminopyridine

DMF   N,N-dimethylformamide

DMSO   dimethylsulphoxide

Et   ethyl

iPr   isopropyl

Me   methyl

Ph   phenyl

Ra-Ni   Raney nickel

THF   tetrahydrofuran

TMS   trimethylsilyl

Ts   *para*-toluenesulphonyl

ttp   5, 10, 15, 20-tetratolylporphyrinato dianion

Chapter 1: Hydrogenolysis Reactions

1.1 Basic Principles

Hydrogenolysis reactions, which involve addition of hydrogen across a σ bond and results in cleavage of the σ bond, have been known in organic chemistry for a long time. The earliest observation of hydrogenolysis was in 1906 by Padoa and Ponti during studies on the reduction of furfural (**1.1**) using a nickel catalyst with hydrogen gas, where 2-methyltetrahydrofuran (**1.2**) and 2-pentanol (**1.3**) were noted as byproducts of the reaction (Scheme 1.1).[1] Since then, hydrogenolysis reactions have been studied extensively, especially for carbon-heteroatom bonds such carbon-oxygen, carbon-nitrogen, carbon-sulphur and carbon-halogen, and various mechanistic aspects have been elucidated.[2] In addition, numerous synthetic applications have been developed, such as protecting group strategies in both natural product and peptide synthesis. More recently, hydrogenolysis is being utilized to develop sustainable fuels from biomass such as carbohydrates and lignin.[3]
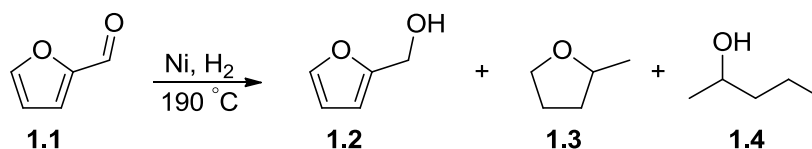
Scheme 1.1. Hydrogenolysis of Furfural

Hydrogenolysis reactions can be performed with either homogeneous or heterogeneous catalysts.[2] The mechanism of the reaction is different depending on the choice of catalyst. For homogeneous catalysis, the reaction takes place within the coordination sphere of the metal and can be described in terms of the standard organometallic processes of oxidative addition, hydrometallation, transmetallation (or ligand exchange), β-hydride elimination (or in some cases,

β-carbon elimination) and reductive elimination. In this case, each metal atom is available for the reaction. In addition, the catalyst can move freely through the solution and avoids problems of transporting the reactants to the catalyst and transporting the products away after the reaction is complete. Despite these advantages, homogeneous catalysis has not found widespread application in hydrogenolysis reactions, although they have proven to be quite useful in hydrogenations of alkenes (e.g. Wilkinson's catalyst).

For heterogeneous catalysts, the reaction mechanism is more complicated since more than one metal atom is involved in the process. Furthermore, the substrate must occupy a portion of the metal surface in order for the reaction to proceed. This will block adjacent metal atoms and prevent them from simultaneously catalyzing a reaction with other molecules of the substrate. As a result, only a fraction of the metal atoms are available to catalyze the reaction. In the first steps of the mechanism, hydrogen and the substrate form a type of covalent bond with the metal surface, called a chemisorptive bond (Scheme 1.2). Following this, hydrogen is transferred from the surface of the catalyst to the substrate and results in one or both of the products of cleavage being chemisorbed to the catalyst surface. Finally, the products can desorb from the catalyst surface to free the active site for further reactions. The hydrogen transfer usually occurs in the form of a nucleophilic hydride by S_N2, S_N1 or S_Ni mechanisms. In some cases, the hydrogenolysis is more correctly described by transfer of a hydrogen atom.

$$A-B \;\rightleftharpoons\; \overset{*}{\underset{*}{A-B}} \qquad\qquad H-H \;\overset{2\,*}{\rightleftharpoons}\; \underset{*}{H}\;\underset{*}{H}$$

$$\overset{\delta^+}{A}\!-\!\overset{\delta^-}{B} \;\longrightarrow\; HA \;+\; \underset{*}{BH} \;\longleftarrow\; A\!-\!B$$

hydride transfer   hydrogen transfer

HA + BH
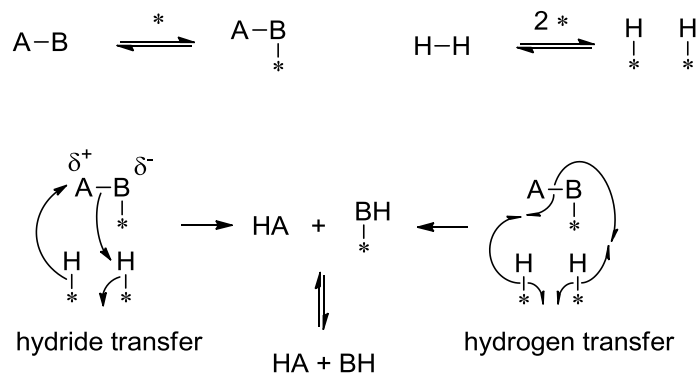
Scheme 1.2. General Mechanism of Hydrogenolysis under Heterogeneous Catalysis

Experimentally, these options can be distinguished by examining the electronic nature of the reaction. For hydride delivery, the transition state involves the development of a partial positive charge on the atom that is receiving the hydride (the electrophilic site) and a partial negative charge develops on the other atom attached to the bond being broken (the leaving group). As a result, the reaction can be accelerated by substituting the electrophilic site with electron-donating groups or retarded by substituting the electrophilic site with electron-withdrawing groups. For example, a series of styrene oxides have been hydrogenolyzed on platinum black (Scheme 1.3).[4] For the unsubstituted and electron-donating 4-methyl derivatives, the benzylic carbon-oxygen bond was selectively cleaved; however, for the weakly electron-withdrawing 3-methoxy and 4-bromo derivatives, some cleavage of the non-benzylic carbon-oxygen bond was observed (12% and 18%, respectively). For the 3,4-dichloro derivative, the selectivity is almost 2:1 in favour of cleavage of the non-benzylic carbon-oxygen bond.
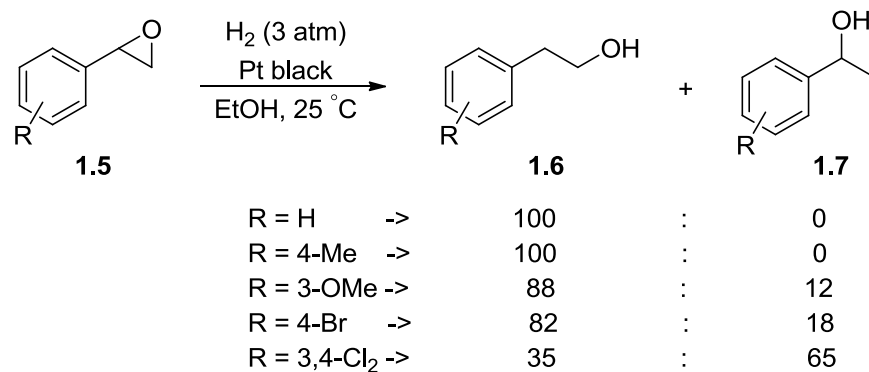
Scheme 1.3. Influence of Electronic Factors on Hydride Transfer Mechanism

R = H   ->   100   :   0
R = 4-Me   ->   100   :   0
R = 3-OMe   ->   88   :   12
R = 4-Br   ->   82   :   18
R = 3,4-Cl$_2$ ->   35   :   65

relative rates

R = Me -> 1.0
R = Et -> 0.47
R = iPr -> 0.033
R = tBu -> 0.0011

R = Me -> 1.0
R = Et -> 0.4
R = iPr -> 0.03
R = tBu -> 0.0001
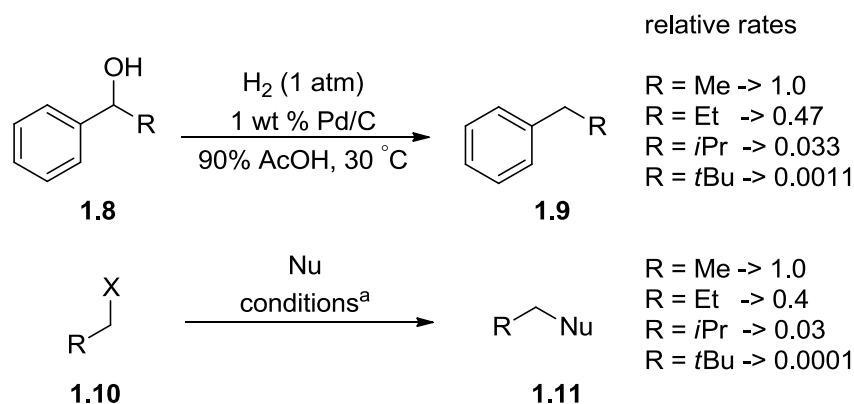
Scheme 1.4. Comparison of Steric Effects on Hydrogenolysis and Nucleophilic Substitution

Reactions

[a]Various conditions were used and the reported numbers are an average of the results obtained, see reference 6.

In addition to the electronic factors, the hydride transfer mechanism is retarded by the presence of sterically demanding groups near the electrophilic site. Comparing the carbon-oxygen hydrogenolysis of benzyl alcohol derivatives bearing one alkyl group on the benzylic center to the S$_N$2 displacement of the analogous series of primary alkyl halides reveals essentially the same pattern of reactivity (Scheme 1.4).[5,6] When the alkyl group is ethyl, the

reaction rate is slightly less than half the rate for a methyl substituent. For isopropyl, the rate is only 3% of the rate for methyl. Finally, for *tert*-butyl the rate of hydrogenolysis is 0.1% of the methyl rate, while the rate of S_N2 displacement is 0.01% of the methyl rate. For hydrogen delivery, the transition state is relatively charge neutral and the presence of electron-donating substituents and steric factors have little effect on the reactivity.

The leaving group ability is important in both the hydride transfer and hydrogen transfer mechanisms. In the above example of benzylic alcohol hydrogenolysis, 90% acetic acid was used as the solvent. The acid is necessary to protonate the alcohol and creates a good leaving group. Conversely, base can be added to retard the hydrogenolysis reaction if selective hydrogenation is required.[5] Hydrogenolysis of phenolic carbon-oxygen bonds provides an example of the importance of the leaving group in the hydrogen transfer mechanism. The sp^2-hybridized carbon of the aryl group is a very poor electrophile for nucleophilic substitution reaction, so hydride attack on the ipso carbon is not possible. Also, the aryl anion is a bad leaving group, thus hydride attack on the oxygen is equally impossible. However, hydrogenolysis of phenolic carbon-oxygen bonds can be accomplished by making the oxygen part of a good leaving group. There are several examples of different leaving groups, such as sulfonates, 1-phenyl-1*H*-tetrazol-5(4*H*)-one, benzo[d]oxazol-2(3*H*)-one and others (Scheme 1.5).[7,8] Notice also that the electronic nature of the aryl group has a negligible impact on the outcome of the transformation from **1.14** to **1.15**, as the 2-, 3- and 4-methoxy derivatives all give similar yields under the same conditions. The aryl carbon-oxygen hydrogenolysis has been applied to aromatic synthesis, since the ortho/para-directing abilities of the oxygen can be used for electrophilic aromatic substitution and then the hydroxyl group can be removed by hydrogenolysis after being converted to a good leaving group.
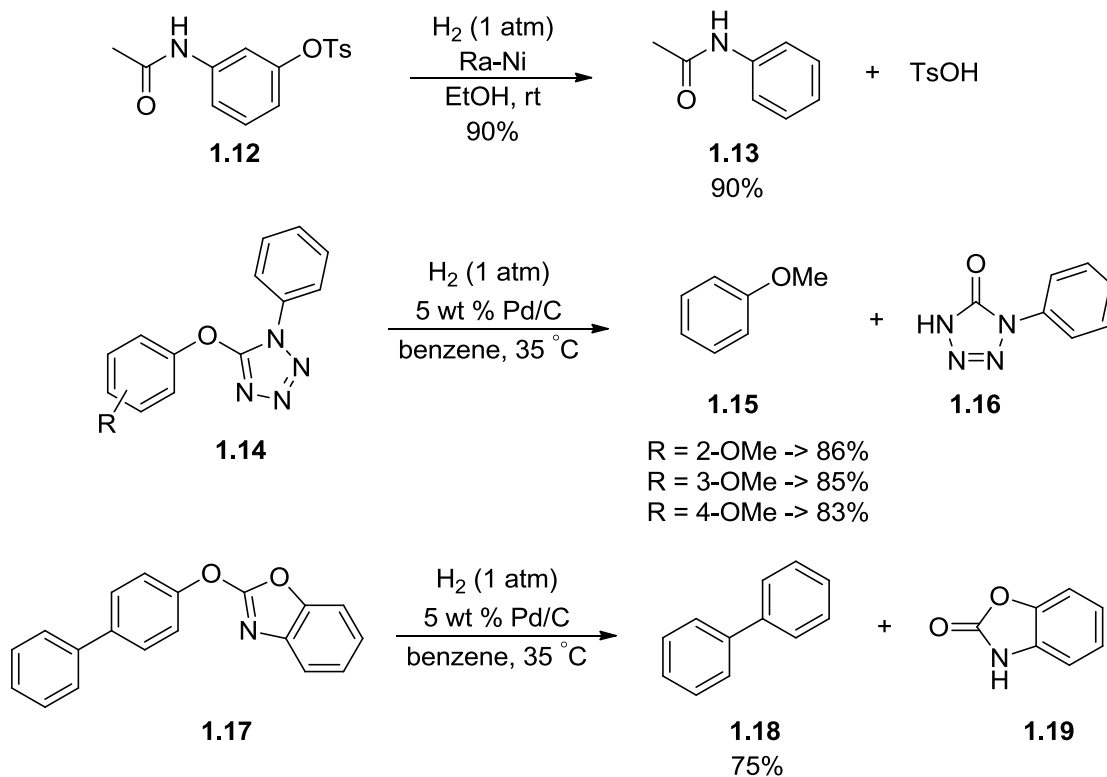
Scheme 1.5. Hydrogenolysis of Phenolic Carbon-Oxygen Bonds

Hydrogenolysis reactions can be stereoselective; however, the selectivity is often difficult to predict due to the many possible mechanisms and this area of hydrogenolysis chemistry is not fully understood. Hydrogenolyses of stereogenic tertiary benzylic alcohols catalyzed by palladium usually occur with inversion of configuration, while hydrogenolyses with Raney nickel typically result in retention of configuration (Scheme 1.6).[9] These results indicate that palladium delivers the hydride via an S_N2-like mechanism, while Raney nickel transfers the hydride via an S_Ni-like mechanism. Notably, the carboxylic acid derivative gave low selectivity for both catalysts. The explanation is ambiguous. It could possibly be due to increasing the acidity of the reaction, which activates the leaving group and lowers the transition state energy for both S_N2 and S_Ni pathways. It could also be a result of competitive adsorbtion modes

between the carboxylic acid and carboxylate. The ability of the substrate to adsorb to the metal surface can have a tremendous impact on the rate of reaction. The σ bond to be hydrogenolyzed usually does not have a high affinity for the catalyst surface and unsaturated groups, such as aryl, alkenyl or carbonyl, are required in order for the reaction to proceed. Heteroatoms, including nitrogen, sulphur and halogens, are also able to form chemisorptive bonds with the catalyst surface. Since the group that adsorbs to the catalyst is often unaffected by the hydrogenolysis process, the product and substrate will both compete to occupy the catalyst surface. Thus, catalytic activity usually decreases throughout the reaction as the product occupies more and more of the catalyst surface. In cases of extreme strength of the chemisorptive bond, the product will not desorb from the catalyst. This is known as poisoning.

| Pd/C -> | 0-40 | : | 60-100 |
| Ra-Ni -> | 45-100 | : | 0-55 |
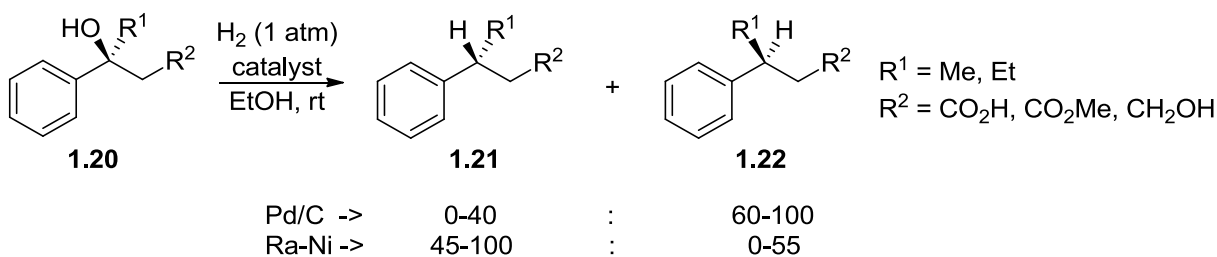
Scheme 1.6. Stereoselectivity in Hydrogenolysis Reactions

The structure and size of the active sites will be different depending on the formulation of the catalyst. The two main ways of employing a heterogeneous catalyst are in the pure state (often called metal black), either as a colloid or a suspension, or as a solid supported catalyst. Metal blacks were often used in the past; however, it is a fairly inefficient method since it enables the smallest fraction of metal atoms to participate in the reaction. Due to the high price of most metals, the use of metal blacks has been mostly abandoned in favour of solid supported

catalysts. An exception to this is Raney Nickel which, in addition to being a relatively cheap metal, has a very large surface area due to its preparation. Beginning from a nickel-aluminum alloy, treatment with aqueous base reacts with the aluminum to leave behind a very porous nickel sponge with a surface area of about 80 m^2/g.[2] Another example of a commonly used metal black is Adam's catalyst, which is platinum black generated in situ from platinum(IV) oxide on exposure to hydrogen gas.[10] When prepared in this way, platinum black forms a colloid which maximizes the activity of the metal. Platinum is known to have the highest hydrogenation activity of all the metals usually used for hydrogenation reactions. Although platinum usually does not catalyze hydrogenolysis reactions (in fact, it is the metal of choice when selective hydrogenation is required in the presence of hydrogenolyzable groups), it is able to promote the hydrogenolysis of aryl phosphates (Scheme 1.7).[11]
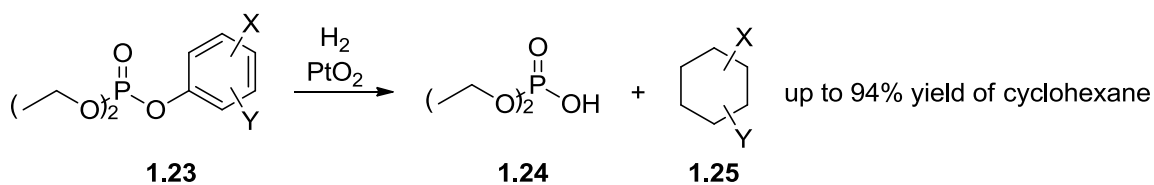
Scheme 1.7. Hydrogenolysis of Aryl Phosphates

For solid supported catalysts, the metal is distributed within another solid, typically carbon, silica or alumina. This is accomplished by first adsorbing a salt of the metal onto the support in solution phase, followed by reduction of the metal salt. The main advantage of the solid support is to increase the available surface area of the metal. It has been shown that decreasing the metal loading (i.e. decreasing the ratio of the metal to the solid support) increases the surface area of the metal. For example, 0.32 wt % palladium/alumina has a metal surface area

of 90 m^2/g, while 4.21 wt % palladium/alumina has a metal surface area of only 36 m^2/g and palladium black has a metal surface area of 5-10 m^2/g.[12]

The most used metals for hydrogenolysis reactions are nickel, palladium and platinum; copper, ruthenium, rhenium and rhodium have also been used in some cases.[2] In addition, metal alloys have been employed to modify the reactivity of the metal, although usually this lowers hydrogenolytic activity in favour of improving hydrogenation activity. Due to platinum's very high hydrogenation activity, it is very unselective and also reduces aryl groups, olefins and ketones under mild conditions. Palladium has a very high hydrogenolytic activity and is not able to reduce aryl groups or ketones easily, although alkene reduction or isomerization may occur. Nickel is a less active metal, but due to its low price can be used in larger amounts. This makes it particularly useful for reduction of carbon-sulphur bonds, since sulphur forms very strong chemisorptive bonds and can easily poison the catalyst. Thus, after the carbon-sulphur bond has been cleaved, the product prevents substrate molecules from adsorbing to the catalyst. In order to compensate, a large quantity of catalyst is required to push the reaction to completion; hence, the utility of nickel.

1.2 Hydrogenolysis of Carbon-Carbon Bonds

The functionalization or interconversion of C-C σ bonds is a challenging synthetic problem. The main difficulty is that C-H bonds are typically more abundant and more accessible to reactive species like transition metal complexes than C-C bonds.[13] As a result, carbon-hydrogen bond activation usually occurs preferentially and has been well-explored, while only limited examples of carbon-carbon bond activation are known.[14,15]

Early examples of C-C bond hydrogenolysis were shown by Taylor et al. involving the reactions of simple alkanes such as ethane.[16] Using a nickel catalyst with ethane and hydrogen gas, they showed that the C-C bond begins to cleave slowly at 157 °C and ethane can be completely converted to methane at temperatures above 180 °C (Scheme 1.8). They also showed that increasing the ratio of hydrogen to ethane impairs the C-C bond hydrogenolysis, likely due to competitive binding to the catalyst surface. Kinetic studies were undertaken and they showed that the activation energy for the hydrogenolysis process is about 43 kcal/mol using hydrogen gas and about 0.5 kcal/mol higher when deuterium gas is used. The authors conclude that the reaction proceeds through dissociative adsorption to the catalyst and that this process occurs more readily for C-H bonds than C-C bonds. Extending the studies to the hydrogenolysis of propane revealed similar results, although it was found that C-C bond scission occurred at a lower temperature. The activation energy of the process was determined to be 34 kcal/mol. The hydrogenolysis of fluorocarbons was also explored, although the very extreme conditions of 700-900 °C were used in order to promote carbon-fluorine hydrogenolysis.[17] Complex mixtures of hydrofluorocarbons resulted.

$$C_2H_6 \xrightarrow[\text{T}]{\text{Ni, H}_2} 2\ CH_4 \qquad \begin{array}{l} T = 157\ ^\circ C,\ 3\ h \rightarrow 11\%\ \text{conv.} \\ T = 184\ ^\circ C,\ 1\ h \rightarrow 92\%\ \text{conv.} \end{array}$$

1.26   **1.27**

$$C_3H_8 \xrightarrow[\text{T}]{\text{Ni, H}_2} C_2H_6\ +\ CH_4 \qquad T = 138\ ^\circ C,\ 5\ h \rightarrow 10\%\ \text{conv.}$$

1.28   **1.26**   **1.27**
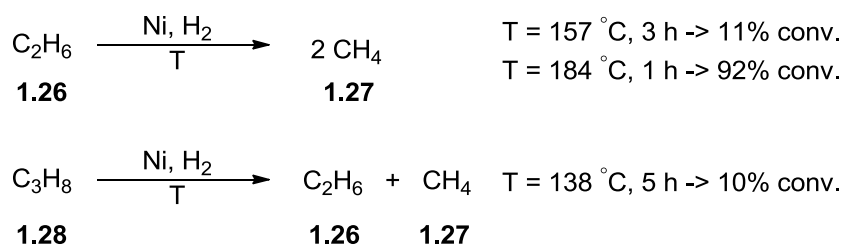
Scheme 1.8. Hydrogenolysis of Simple Alkanes

Some examples reported by Schleyer et al. involve catalytic hydrogenolysis of 1- and 2-adamantyl derivatives.[18] In particular, 1- and 2-methyladamantane could be hydrogenolyzed to

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produce adamantane via cleavage of a methyl group with at least 80% yield (Scheme 1.9). The reaction requires harsh conditions; the substrate must be vaporized at 235-280 °C and mixed with a stream of hydrogen gas before being passed over a catalyst bed composed of 30% nickel on alumina. Notably, 2-methyladamantane could be hydrogenolyzed at a lower temperature and provided a higher yield. This observation suggests that alkyl groups attached to secondary carbons are more labile than alkyl groups attached to tertiary carbons, likely due to sterics.

R$_1$ = Me, R$_2$ = H (**1.28a**), T = 280 °C -> 80%
R$_1$ = H, R$_2$ = Me (**1.28b**), T = 235 °C -> 99%
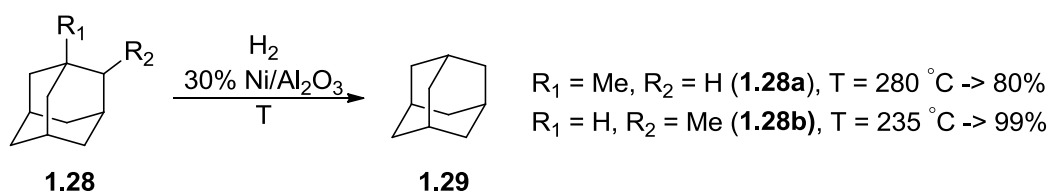
Scheme 1.9. Hydrogenolysis of Methyladamantane Derivatives

Schleyer and coworkers also showed a stepwise cleavage of 2-ethyladamantane, where a methyl groups is initially cleaved to form 2-methyladamantane, which can undergo a second cleavage to form adamantane.[19] By carefully controlling the temperature, either 2-methyladamantane or adamantane can be formed selectively with as much as 79% yield (Scheme 1.10).

T = 190 °C -> 79%   8% (13% SM)
T = 245 °C -> 0%   99%
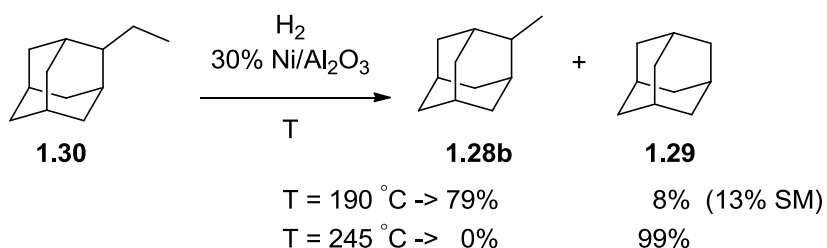
Scheme 1.10. Hydrogenolysis of 2-Ethyladamantane
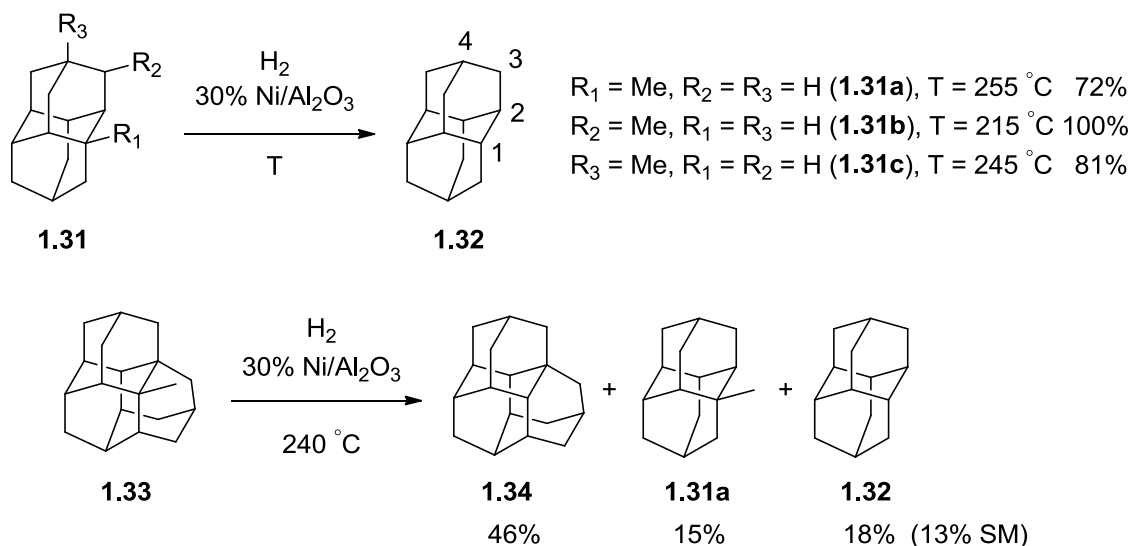
Scheme 1.11. Hydrogenolysis of Diadamantanes and Triadamantanes

The reaction was extended to methyldiamantanes and methyltriamantanes (Scheme 1.11). Once again, the importance of steric effects was outlined. In comparison of the hydrogenolysis of 1-, 3- and 4-methyldiamantane, 3-methyldiamantane could react at the lowest temperature and provided the highest yield, while 1-methyldiamantane required the highest temperature and did not react completely. When 2-methyltriamantane was subjected to hydrogenolysis, the adamantane skeleton preferentially hydrogenolyzes and only 46% yield of triamantane could be obtained.

The preceding examples have required high temperature conditions in order to proceed. These transformations are not synthetically useful because, as shown by the hydrogenolysis of ethane and propane, any C-C bond can be hydrogenolyzed when forcing enough conditions are applied and other decomposition pathways may become available depending on the substrate. More selective methods are required in order to develop C-C bond hydrogenolysis into an applicable methodology.

One strategy that has been employed with great success is the hydrogenolysis of C-C bonds in strained cyclic systems, where the release of ring strain provides the driving force for the reaction.[20] In particular, cyclopropanes have been shown to undergo hydrogenolysis easily, requiring only room temperature conditions. This is in part due to the lower activation energy of the C-C bond cleavage events, which is only 11-16 kcal/mol for cyclopropanes versus 43 kcal/mol for ethane.[21] Also, the cyclopropane has a higher affinity for the metal surface than a typical alkane due to the increased p-character of the cyclopropane C-C bonds. This means that the bonding in the cyclopropane ring can be considered more delocalized. In addition, the orbitals used to form the C-C bond are not in line with the bond axis and are more accessible to the metal.[22] The higher affinity facilitates the reaction by enabling the cyclopropane to adsorb to the metal without the assistance of unsaturations, although the presence of such features accelerates the reaction.

The cyclopropane opening usually occurs with high regioselectivity. For cyclopropanes bearing only alkyl substituents, the least sterically hindered bond is preferentially cleaved. For example, n-hexylcyclopropane reacts under palladium catalysis to form a 19:1 mixture of n-nonane and 2-methyloctane. In this case, scission of C-C bond between the terminal carbons (the distal bond) is favoured over rupturing the cyclopropane from one of the (statistically favoured) internal (or proximal) bonds (Scheme 1.12).
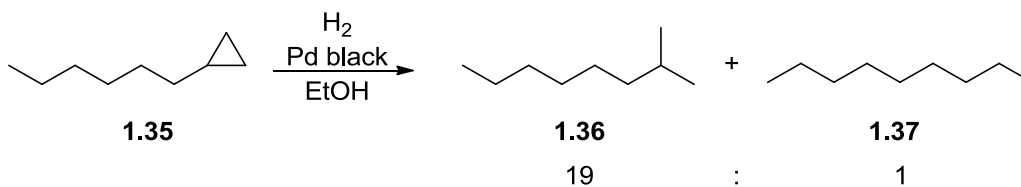
Scheme 1.12. Hydrogenolysis of n-Hexylcyclopropane

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This selectivity allows a general synthetic route to *tert*-butyl groups or *gem*-dimethyl quaternary carbons via cyclopropanation of isopropenyl groups or methylene groups, respectively, followed by hydrogenolysis. Some examples from Schleyer's group include the synthesis of 2-*tert*-butyladamantane and 2,2-dimethyladamantane from 2-isopropenyladamantane and 2-methyleneadamantane, respectively (Scheme 1.13).
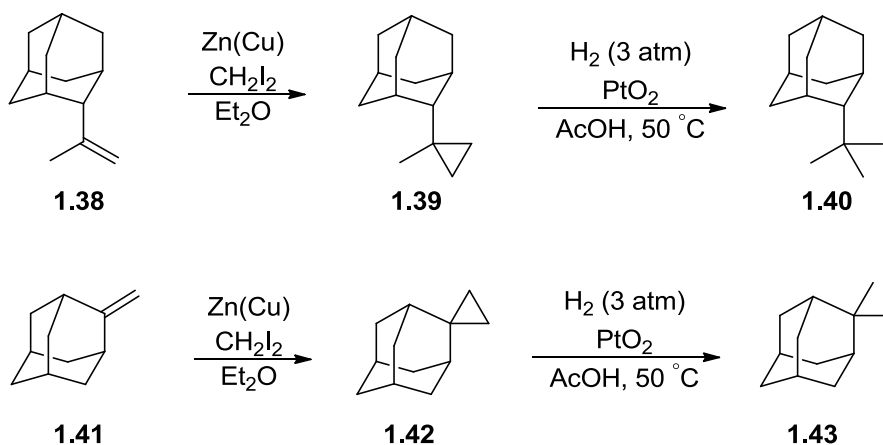
Scheme 1.13. Synthesis of *gem*-Dimethyl Quaternary Carbons

The selectivity can be altered by adding unsaturated substituents to the ring, such as vinyl, aryl or carbonyl groups. Regarding the palladium-catalyzed hydrogenolyses of 1-cyclopropylethanone and cyclopropylbenzene, one of the proximal bonds is broken selectively to furnish 2-pentanone and *n*-propylbenzene as the major products (Scheme 1.14). The effect of unsaturated substituents usually dominates over steric effects, where even the highly crowded 1-(1-methyl-2,2-diphenylcycloprop-1-yl)ethanone affords 3-methyl-5,5-diphenylpentan-2-one in quantitative yield upon cleavage of the C-C bond connecting the two quaternary centers (Scheme 1.15).

1.44 → **1.45**

H$_2$ (1 atm)
Pd
EtOH, 25 °C

1.46 → **1.47**

H$_2$ (1 atm)
Pd/C
EtOH, 25 °C
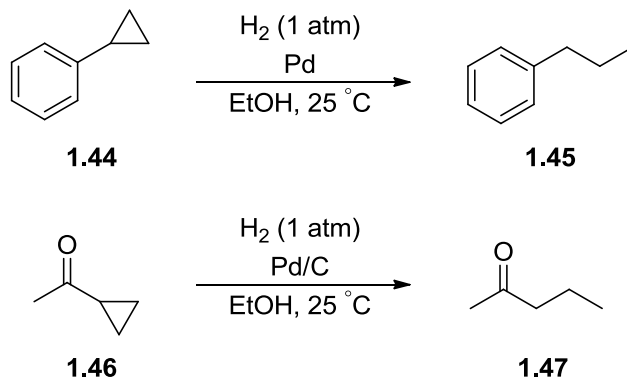
Scheme 1.14. Regioselective Hydrogenolysis of Conjugated Cyclopropanes

1.48 → **1.49**

H$_2$ (1 atm)
Pd/C
EtOH, 25 °C
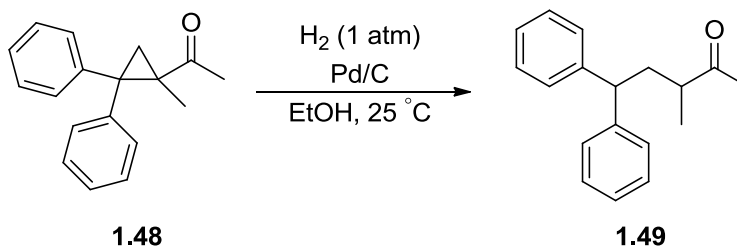
Scheme 1.15. Hydrogenolysis of a Sterically Crowded Cyclopropane

The explanation is that the unsaturation forms a strong chemisorptive bond to the catalyst surface and creates an unfavourable geometry for simultaneous adsorption of the distal C-C bond to the catalyst surface (Scheme 1.16). Thus, only the proximal bonds can lay flat against the surface in order to allow hydrogenolysis to occur. In the case of alkyl-susbtituted cyclopropanes, the alkyl group is oriented away from the surface in order to avoid steric interactions.

favoured   disfavoured   favoured   disfavoured
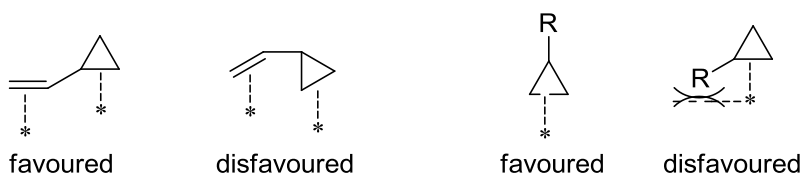
Scheme 1.16. Explanation of Regioselectivity for Cyclopropane Hydrogenolysis

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Larger rings are not hydrogenolyzed readily. For alkylcyclobutanes, typically temperatures above 200 °C are required to effect cleavage of the ring, although methylenecyclobutane can be hydrogenolyzed at 100 °C due to the ability of the olefin to promote adsorption to the catalyst (Scheme 1.17). In addition to the drastic conditions required, the regioselectivities observed in these reactions is fairly poor. Compared to cyclopropanes, cyclobutanes show a very weak influence of steric factors from the alkyl group, where primary alkyl groups (methyl and ethyl) resulted in 50:50 mixtures of linear and branched alkanes as the products and the presence of a more demanding isopropyl group was only able to push the ratio up to 70:30 in favour of 2,3-dimethylpentane.

		H$_2$ (1 atm) Pt/C 250 °C				
1.50				**1.51**		**1.52**
		R = Me, Et ->		50	:	50
		R = iPr ->		30	:	70
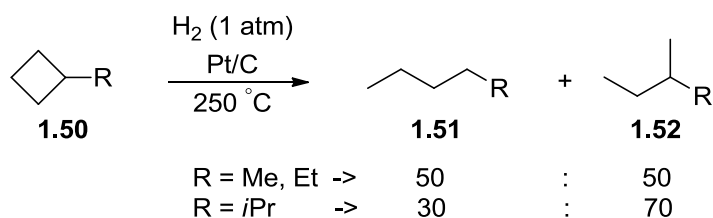
Scheme 1.17. Hydrogenolysis of Cyclobutanes

Alkylcyclopentanes are even more difficult to hydrogenolyze, requiring temperatures above 300 °C in order to proceed.[20] The influence of the steric factors of the alkyl substituent is similar to cyclopropanes; however, the regioselectivity is still an issue due to the increasing number of scissile bonds. Concerning methylcyclopropane, the C$_3$-C$_4$ is somewhat less hindered than the equivalent C$_2$-C$_3$ and C$_4$-C$_5$ bonds, but the equivalent bonds are statistically more available and results in the product ratio shown in Scheme 1.18. Having additional substituents can enhance the selectivity, as in the case of 1,2,3-trimethylcyclopentane, where the C-C bond connecting the two CH$_2$ groups can be selectively cleaved to produce 2,3,4-trimethylpentane as

the only product. Less detailed information is available for cyclopentanes bearing larger alkyl

groups, likely due to fragmentation of the alkyl chain resulting in complex product mixtures.
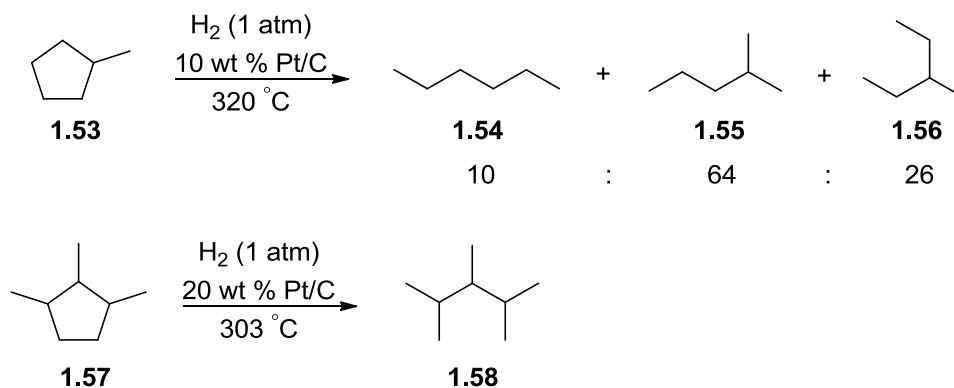
Scheme 1.18. Hydrogenolysis of Cyclopentanes
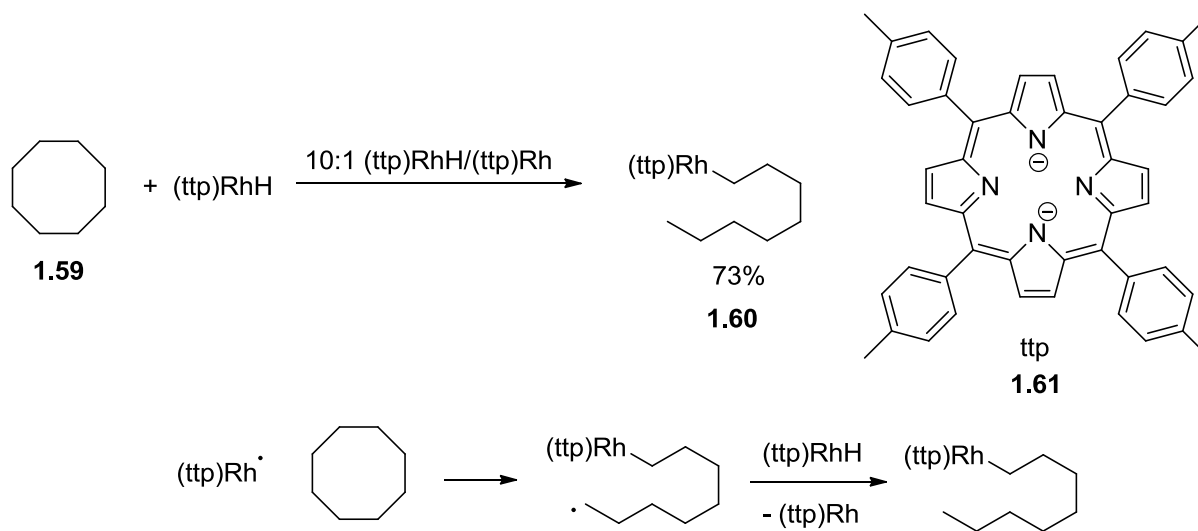
Scheme 1.19. Hydrometallation of Cyclooctane

Chan and Chan have reported a rhodium-catalyzed hydrometallation of cyclooctane with

(ttp)RhH (Scheme 1.19).[23] A mechanistic study of the reaction found that the reaction is

catalyzed by (ttp)Rh, which initially does a 1,2 addition to a carbon-carbon bond of cyclooctane

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to form an alkylrhodium(III) radical. The alkyl radical then abstracts hydrogen from (ttp)RhH to form (ttp)Rh(n-octyl) and regenerates (ttp)Rh. A carbon-hydrogen activation pathway is also available for (ttp)RhH and competes with the carbon-carbon activation pathway; however, optimal conditions were found that enable (ttp)Rh(n-octyl) to form selectively with 73% yield.
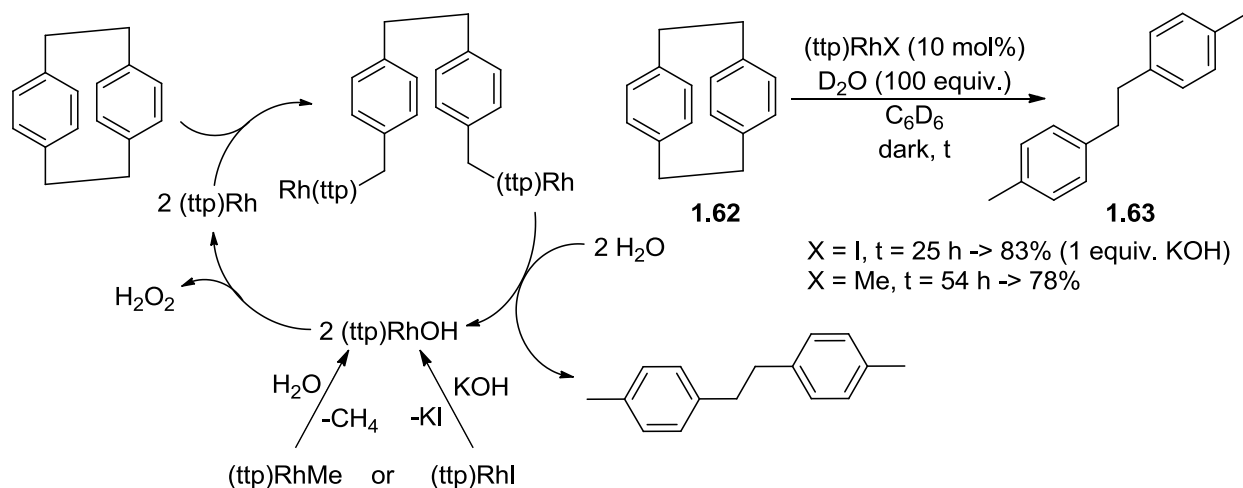
Scheme 1.20. Rhodium-Catalyzed Hydrogenolysis of [2.2]-Paracyclophane

Chan et al. have reported a related hydrogenolysis of [2.2]-paracyclophane using water as the hydrogen source (Scheme 1.20).[24] In this case, (ttp)Rh is generated by hydrolysis of either (ttp)RhI in basic solution or (ttp)RhMe in neutral water. The intermediate (ttp)RhOH decomposes to (ttp)Rh with concomitant formation of hydrogen peroxide. Once formed, two molecules of (ttp)Rh cleave one of the carbon-carbon σ bonds between two benzylic centers to form a bis(rhodiomethylbenzyl) complex. Finally, the bisrhodiumcomplex undergoes hydrolysis to form the hydrogenolyzed product and regenerates the intermediate (ttp)RhOH. Yields up to 83% were obtained.

Moving beyond cyclic system, another general carbon-carbon bond hydrogenolysis reaction involves the hydrogenolysis of cyanides. The cyanide ion is considered a pseudohalogen; thus, the ease of hydrogenolysis is not surprising since carbon-halogen bonds are readily reduced by hydrogenolysis. The reaction can be catalyzed by rhodium, iron or nickel, although nickel seems to be the most versatile.[25] Reactions can be performed using silanes, Grignard reagents or hydrogen gas as the hydrogen source. A report by Maiti's group employs bis(cycloocta-1,5-dienyl)nickel(II) with a phosphine ligand and hydrogen gas in the presence of 3 equivalents of trimethylaluminum as a Lewis acid (Scheme 1.21). The scope of the reaction is very broad; aryl and heteroaryl cyanides as well as alkyl cyanides could all be reduced under these conditions, with isolated yields up to 93%.

$$Ar-CN \xrightarrow[\text{toluene}]{\begin{array}{c} H_2 \text{ (1 bar)} \\ Ni(cod)_2 \\ P(tBu)_3 \\ Me_3Al \text{ (3 equiv.)} \end{array}} Ar-H$$

1.64   1.65

36 examples up to 93% yield
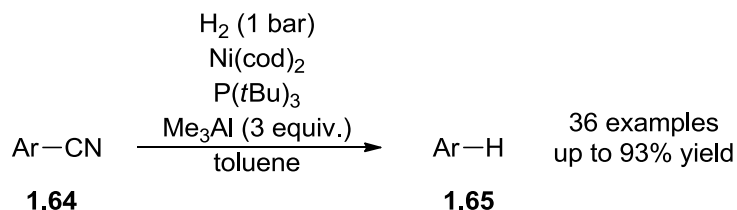
Scheme 1.21. Hydrogenolysis of Nitriles

Cyclohexadienones are well designed for hydrogenolysis of carbon-carbon σ bonds, since the intermediate product can aromatize into a phenol and provides the driving force for the reaction. Investigations by Miller and Lewis utilizing either cyclohexa-2,4-dien-1-ones or cyclohexa-2,5-dien-1-ones, the potentially labile groups allyl, 2-methylallyl and benzyl were carried out (Scheme 1.22).[26] For the allyl or 2-methylallyl groups, the terminal alkene was susceptible to hydrogenation but the allyl group could be cleaved with high selectivity when 1:3 acetic acid/methanol was used as the solvent. The benzyl group was cleaved readily in hexanes

and quantitative yields of the phenol products were obtained. The mechanism proposed by the authors involves hydride delivery to the carbon of the allyl or benzyl group that is directly attached to the cyclohexadienone to displace a phenoxide leaving group. This mechanism explains the increased reactivity of the allyl substituted cyclohexadienones in acetic acid/methanol; the solvent can hydrogen bond with the carbonyl oxygen to stabilize the developing negative charge in the transition state. When a 2,6-di-*tert*-butylcyclohexa-2,5-dienone was employed, no hydrogenolysis was observed and this was attributed to steric crowding of the carbonyl preventing the stabilizing hydrogen bond interactions.

Scheme 1.22. Hydrogenolysis of Cyclohexadienones

A similar example was reported by Carson in 1951 for the hydrogenolysis of lupulone; however, the structure of lupulone had not been properly assigned at the time (Scheme 1.23).[27] Amusingly, a publication by Harris and coworkers a year later argued that the structure of Carson must be incorrect because carbon-carbon bond hydrogenolysis is not possible and that there are no other known examples (which was untrue since Taylor et al. had already done their

studies on hydrogenolysis of simple alkanes).[28] Thus, Harris reassigned the structure such that carbon-oxygen hydrogenolysis could occur to produce the product observed in Carson's experiments. Ultimately, neither Carson nor Harris had assigned the structure correctly; the correct structure had been determined by Verzele and Govaert in 1949.[29]

| 1.70 | 1.71 | 1.72 |
| Carson | Harris | Verzele and Govaert |

1.73
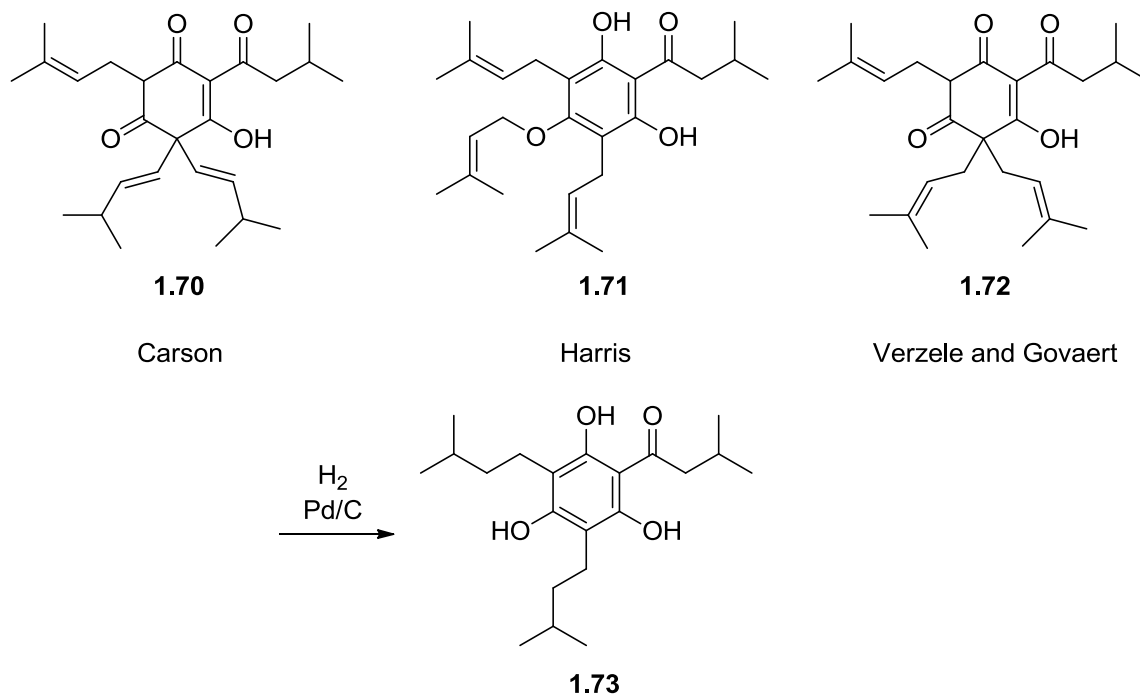
Scheme 1.23. Hydrogenolysis of Lupulone

1.3 1,3-Dicarbonyls as Leaving Groups

Recently, there has been a growing interest in using 1,3-dicarbonyl compounds as carbon-based leaving groups. During studies of nucleophilic substitution reactions involving π-allyl palladium complexes where 1,3-dicarbonyl compounds were employed as the nucleophile, various authors observed equilibration of regioisomeric products that could only be explained if the 1,3-dicarbonyl compound could also behave as a leaving group. Trost et al. performed a

crossover experiment with 5-(1-benzyloxyprop-2-en-1-yl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione and 5-(furan-2-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione in the presence of allylpalladium(II) chloride dimer, potassium *tert*-butoxide and a chiral ligand (Scheme 1.24).[30] They observed transfer of the 1-benzyloxyprop-2-en-1-yl group to the furan derivative and the formation of 5-(1-benzyloxyprop-2-en-1-yl)-5-(furan-2-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione.
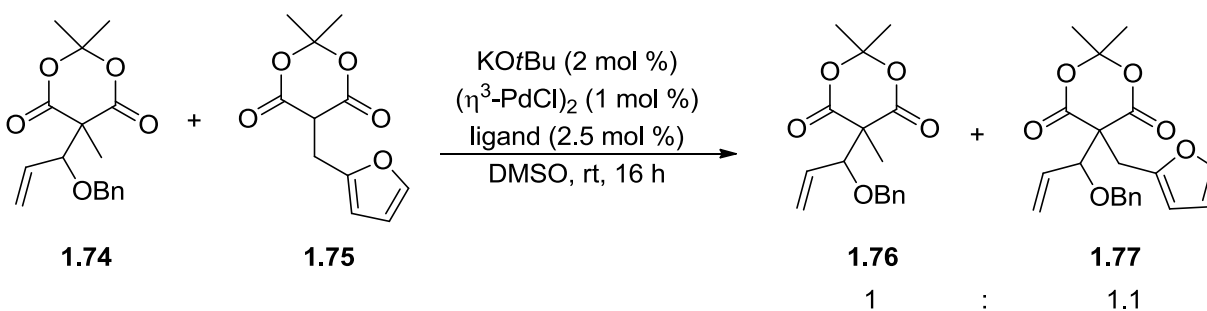
Scheme 1.24. Allyl Group Transfer between Meldrum's Acid Derivatives

Additional studies by Cazes and colleagues involved the displacement of 2-methylcyclopentane-1,3-dione by the enolate of diethyl malonate in the presence of tetrakis(triphenylphosphine)palladium(0) (Scheme 1.25).[31] By adding 2 equivalents of the nucleophile, the equilibrium is shifted towards the products and diethyl 2-allylmalonate was obtained in 83% yield. Similar examples were shown by Bäckvall and coworkers using the enolate of dimethyl 2-methylmalonate as the nucleophile to isomerize an unconjugated diene to a conjugated diene.[32] In this case, the conjugated diene is lower in energy than the starting material. Thus, the equilibrium is shifted towards the conjugated diene, which can be formed with high selectivity.
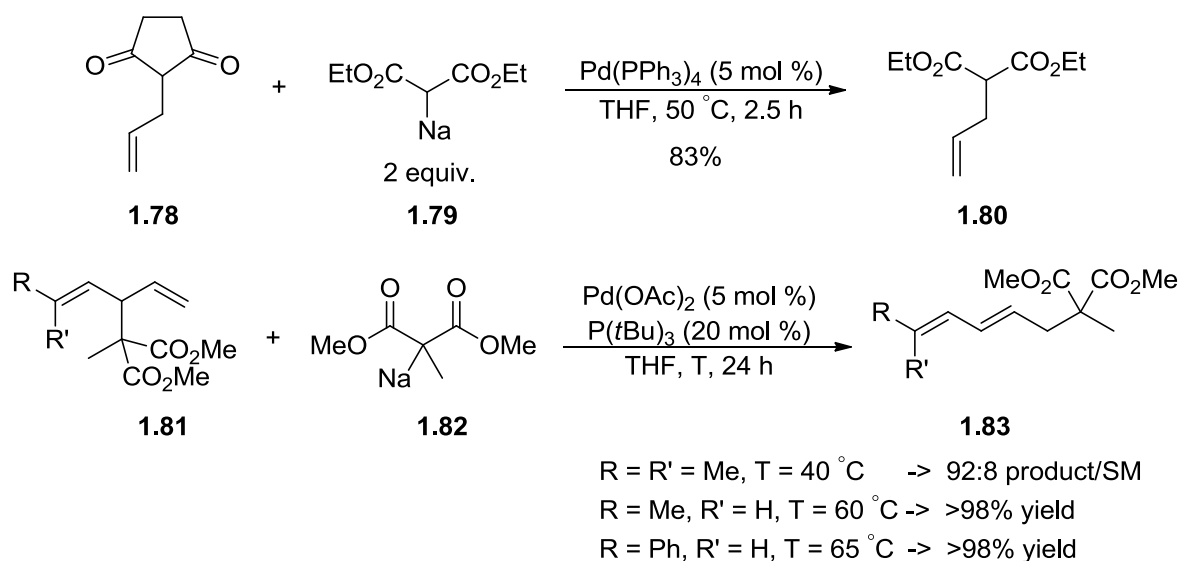
Scheme 1.25. Allylic Substitutions Involving 1,3-Dicarbonyl Compounds as Leaving Groups
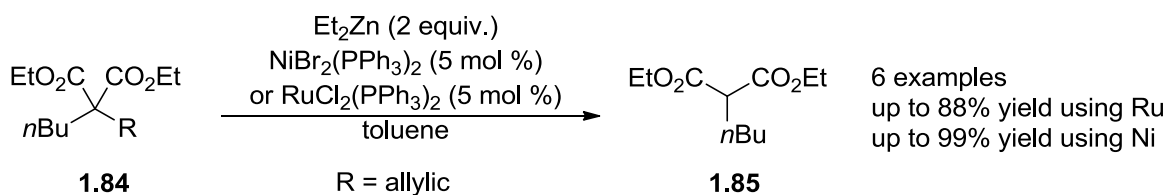
Scheme 1.26 Deallylation of Diethyl Malonates

Kotora's group investigated deallylation reactions of various 2-allylmalonates.[33] They showed that the deallylation reaction could be catalyzed by nickel, iron, cobalt, ruthenium, rhodium and palladium. Different selectivities were observed depending on the metal used. Nickel was found to be the most active, as it was able to deallylate most 2-allylmalonate derivatives, regardless of substitution. Ruthenium was found to be very sensitive to substitution on the allyl group and was only able to react on unsubstituted allyl groups. A similar reaction was shown by Oshima et al. using magnesium bromide as the Lewis acid instead of diethylzinc.[34]
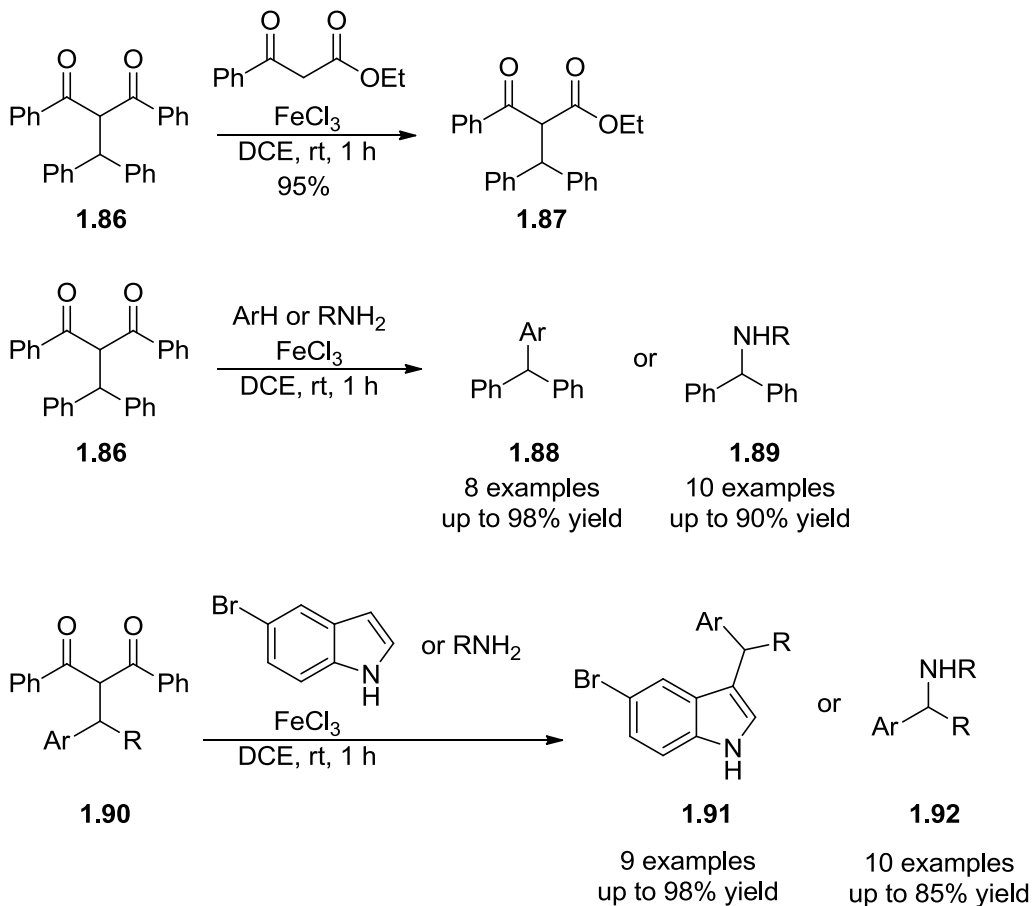
Scheme 1.27. Iron-Catalyzed Substitutions Involving a 1,3-Diketone Leaving Group

Li and coworkers showed some examples of nucleophilic substitution reactions catalyzed by iron(III) chloride (Scheme 1.27).[35] In these experiments 1,3-diphenylpropan-1,3-dione acted as the leaving group and could be displaced by either β-keto ester, amine or aryl (Friedel-Crafts) nucleophiles. They propose an S_N1 mechanism for this process, where the Lewis acid first removes the leaving group to generate a benzylic cation, which can then be trapped by any nucleophiles present. In both cases, the reaction is an equilibrium process that is driven towards the side with the weakest nucleophile.

Previous reports from the Fillion group have shown the utility of Meldrum's acid as a carbon-based leaving group in Lewis acid-promoted substitution reactions (Scheme 1.28).[36]

Beginning with 5-benzyl Meldrum's acid derivatives bearing quaternary benzylic centers, trimethylaluminum could be used to rapidly promote substitution of Meldrum's acid for a methyl group. In addition, aluminum chloride could be used in conjunction with an appropriate π-nucleophile to promote substitution with other groups. The reaction was found to be quite general, as virtually any aryl or heteroaryl group could be employed. Steric and electronic factors had minimal effect on the reactivity of the substrate. Furthermore, 12 nucleophiles were used in the study and excellent yields were obtained in most cases.
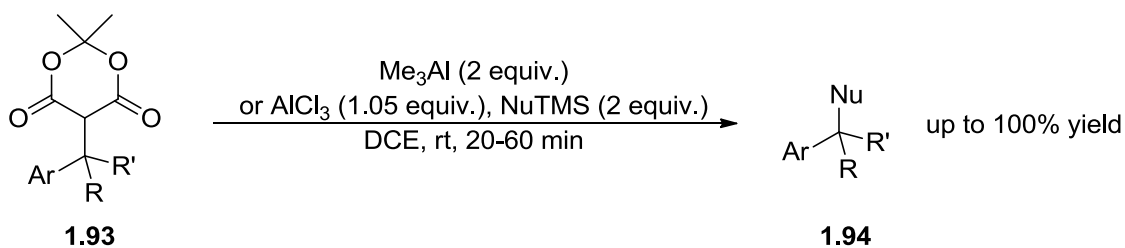
Scheme 1.28. Lewis Acid-Promoted Substitution Reactions of 5-Benzyl Meldrum's Acids

In addition to the Lewis acid-promoted substitution reactions of 5-benzyl Meldrum's acid derivatives bearing quaternary benzylic centers, the Fillion group has also reported a carbon-carbon bond hydrogenolysis reaction on these same substrates.[37] The following chapter is an extension of this reaction.

Chapter 2: Hydrogenolysis of Benzyl Meldrum's Acid Derivatives

2.1 Effect of the Aryl Group Substitution Pattern

The Csp^3-Csp^3 σ bond hydrogenolysis reaction was first explored by studying the effect of substitution on the aryl group in substrates **2.1**, containing an all-carbon benzylic quaternary center (Table 2.1). Hydrogenolysis of **2.1a** and **2.1b** using H_2 (1 atm), Pd/C (15 mol% Pd) in MeOH at room temperature resulted in excellent conversions and good isolated yields (Entries 1-2). Substitution by an alkoxy group produced different results depending on the position of the ether functionality (Entries 3-5). The hydrogenolysis of para **2.1c** and ortho **2.1e** derivatives led to isopropylbenzene **2.2c** and **2.2e** with good conversions and yields. On the contrary, the hydrogenolysis of meta-substituted derivative **2.1d** was sluggish and gave <10% conversion after 24 hours. These results have exposed the electronic demands of the reaction. For the ortho and para substrates, the alkoxy group is able to donate electrons to the aromatic carbon attached to the benzylic center by resonance. For the meta substrate, the alkoxy substituent cannot donate to the aromatic carbon attached to the benzylic center but it is electron-withdrawing by induction. Therefore, the reaction is accelerated by electron-donating groups and is retarded by electron-withdrawing groups. These results imply a nucleophilic mechanism for the transformation. Following the investigation of the reaction electronics, several alkyl-substituted derivatives (**2.1f-m**) were studied. Substrates bearing linear alkyl groups (ethyl or *n*-butyl) resulted in >95% conversion while the introduction of α-branched alkyl groups (*i*-propyl or *t*-butyl) led to poor reactivity regardless of the position of the group (Entries 6-11). This is in analogy to the observations previously reported for tertiary benzylic alcohols.2 Further studies revealed that α-branched alkyl groups (*i*-butyl or neopentyl) also exhibited high reactivity and conversions >95% were obtained (Entries 12-13). The analogous branched alkoxy groups (*i*-propoxide or *t*-

butoxide) gave similar results (Entries 14-15). Finally, fluoro substituted benzyl Meldrum's acids

2.1p and **2.1q** were inert towards the hydrogenolysis reaction at room temperature (Entries 16-17). Furthermore, having a tertiary or quaternary center directly attached to the aromatic ring, in addition to the all-carbon quaternary center bearing the Meldrum's acid moiety, is detrimental to the hydrogenolysis reaction. On the other hand, substrates with linear or α-branched alkyl chains attached to the aromatic ring were shown to give the hydrogenolysed products in good isolated yields.

Table 2.1. Scope of the Hydrogenolysis Reaction — Varying Substitution on the Aryl Group
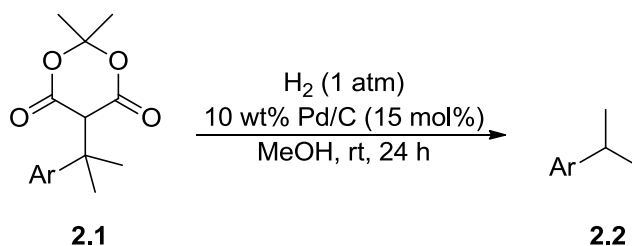
Entry	Ar	Conversion (%)[a]	Yield (%)
1	C_6H_5 (**2.1a**)	>95	80 (**2.2a**)[b]
2	$4\text{-}PhC_6H_4$ (**2.1b**)	>95	80 (**2.2b**)
3	$4\text{-}(H_{17}C_8O)C_6H_4$ (**2.1c**)	>95	78 (**2.2c**)
4	$3\text{-}(H_{17}C_8O)C_6H_4$ (**2.1d**)	<10	ND (**2.2d**)
5	$2\text{-}(H_{17}C_8O)C_6H_4$ (**2.1e**)	>95	90 (**2.2e**)[c]
6	$4\text{-}t\text{-}BuC_6H_4$ (**2.1f**)	<5	ND (**2.2f**)
7	$3\text{-}t\text{-}BuC_6H_4$ (**2.1g**)	NR	NR (**2.2g**)
8	$4\text{-}i\text{-}PrC_6H_4$ (**2.1h**)	10	ND (**2.2h**)
9	$4\text{-}n\text{-}BuC_6H_4$ (**2.1i**)	>95	90 (**2.2i**)
10	$3\text{-}EtC_6H_4$ (**2.1j**)	>95	83 (**2.2j**)
11	$2\text{-}EtC_6H_4$ (**2.1k**)	>95	64(**2.2k**)[d]

| 12	4-(t-BuCH$_2$)C$_6$H$_4$ (**2.1l**)	>95	81 (**2.2l**)
13	4-i-BuC$_6$H$_4$ (**2.1m**)	>95	70 (**2.2m**)
14	4-(t-BuO)C$_6$H$_4$ (**2.1n**)	>95	70 (**2.2n**)[d]
15	4-(i-PrO)C$_6$H$_4$ (**2.1o**)	>95	82 (**2.2o**)
16	4-FC$_6$H$_4$ (**2.1p**)	<5	ND (**2.2p**)
17	3-F-4-(MeO)C$_6$H$_3$(**2.1q**)	<5	ND (**2.2q**)

[a]Conversion determined from ratio of product to starting material in crude ^{1}H NMR spectrum.

[b]Yield of Meldrum's acid. [c]Reaction time is 48 h using 20 mol % Pd. [d]Reaction time is 48 h.

Next, in order to develop a general hydrogenolysis protocol, conditions had to be found that would allow the reaction of substrates bearing α-branched chains. From **2.1f**, increasing the temperature to 65 °C led to decomposition of the substrate—probably due to the known reaction of MeOH with Meldrum's acid derivatives.[38] This prompted the use of non-nucleophilic EtOAc, a common solvent for hydrogenolysis or hydrogenation reactions. In EtOAc at 65 °C, 20 mol % Pd led to >95% conversion after 48 hours, and product **2.2f** was isolated in 76% yield. The new conditions were applied to the various Meldrum's acid derivatives that did not react at room temperature in MeOH (Table 2.2). With some additional tweaking, substrates **2.1g**, **2.1h**, and **2.1q** resulted in good conversions and isolated yields (Entries 3, 4, and 6). Increasing catalyst loading to 50% enabled **2.1g** to react completely and **2.2g** was isolated with 62% yield and enabled **1q** to achieve 84% conversion and 60% yield of **2.2q** was obtained. A 96 h reaction time was necessary to completely react **2.1h** and obtain 91% yield. Unfortunately, compounds **2.1d** and **2.1p** still resulted in less than 50% conversion (Entries 2 and 5). Thus, some of the substrates that were problematic under the standard conditions due to sterics of the substituted aromatic ring reacted cleanly under optimized conditions but substrates bearing an electron-deficient

aromatic gave poor results, thus demonstrating an increased importance of the electronic effects of the reaction over the steric demands.

Table 2.2. Hydrogenolysis of α-Branched Substrates
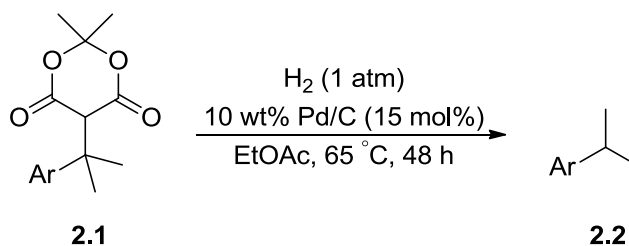
Entry	Ar	Conversion (%)[a]	Yield (%)
1	4-*t*-BuC$_6$H$_4$ (**2.1f**)	>95	76 (**2.2f**)
2	3-(C$_8$H$_{17}$O)C$_6$H$_4$ (**2.1d**)	38	ND (**2.2d**)
3	3-*t*-BuC$_6$H$_4$ (**2.1g**)	>95	62 (**2.2g**)[b]
4	4-*i*-PrC$_6$H$_4$ (**2.1h**)	>95	91 (**2.2h**)[c]
5	4-FC$_6$H$_4$ (**2.1p**)	42	ND (**2.2p**)
6	3-F-4-(MeO)C$_6$H$_3$ (**2.1q**)	84	60 (**2.2q**)[b]

[a]Conversion determined from ratio of product to starting material in crude ^{1}H NMR spectrum. [b]50 mol % Pd. [c]Reaction time is 96 h.

Of note, in EtOAc at 65 °C, electron-rich **2.1c** gave a 1:1 mixture of aromatic compound **2.2c** and its analogous hydrogenated derivative **2.2c'** (resulting from the reduction of the benzene ring), which were isolated in 33% and 39% yield, respectively (Scheme 2.1).The over-reduction was found to favour *cis*-**2.2c'** in the ratio 2:1 as determined by analysis of the crude reaction mixture by ^{1}H NMR. This transformation is usually difficult owing to the high stability of aromatic compounds and the numerous previous reports have all required harsh conditions (high temperature and pressure) or expensive catalysts with a high loading.[39] The origin of the

selectivity may be due to slow desorption of the initial hydrogenation product, where only one of the double bonds has been reduced. The product remains coordinated to the metal surface and allows the following hydrogenation steps to occur on the same side of the ring as the first hydrogenation, resulting in the two substituents being on the same side in the final product.
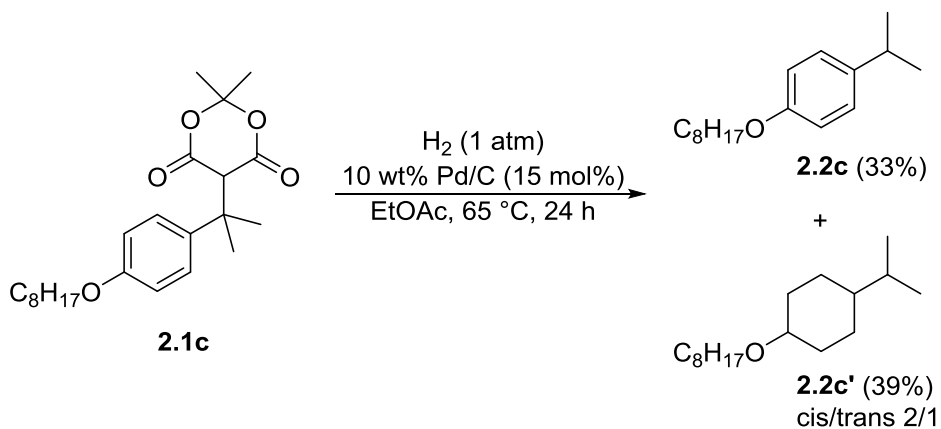
Scheme 2.1. Formation of Over-Reduced Products

Addition of 2 equivalents of Meldrum's acid prevented over-reduction and resulted in a clean hydrogenolysis reaction of **2.1c**, providing a 71% yield of **2.2c** (Scheme 2.2). This is similar to the results obtained in MeOH at room temperature (Table 2.1, Entry 3). The role of Meldrum's acid remains speculative, although it is likely an example of product inhibition of the reaction. This is similar to what was observed for experiments where hydrogenolysis product **2.2c** or toluene was shown to inhibit the hydrogenolysis process (see below, Scheme **2.3**).
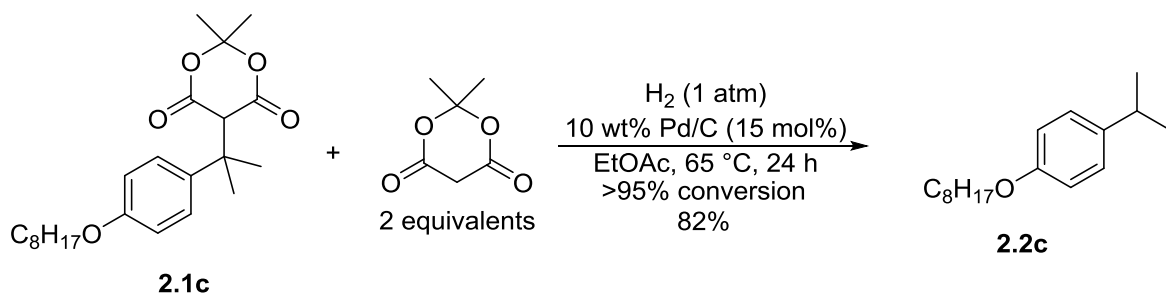
Scheme 2.2. Over-Reduction Suppression with Meldrum's Acid as Additive

2.2 Effect of the Benzylic Carbon Substitution Pattern

Table 2.3. Effect of the Benzylic Alkyl Substituents
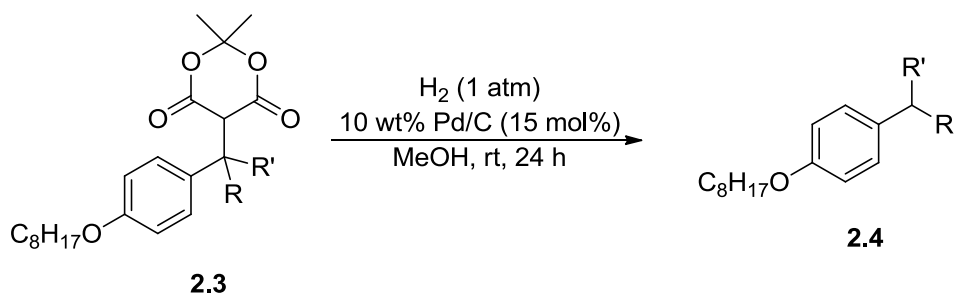
Entry	R; R'	Conversion (%)[a]	Yield (%)
1	Me; Me (**2.1c**)	>95	78 (**2.2c**)
2	Me; Et (**2.3a**)	>95	86 (**2.4a**)
3	Me;n-Bu (**2.3b**)	>95	90 (**2.4b**)
4	(CH$_2$)$_5$ (**2.3c**)	>95	82 (**2.4c**)
5	Me; i-Pr (**2.3d**)	20, >95	ND, 70[b] (**2.4d**)

[a]Conversion determined from ratio of product to starting material in crude ^{1}H NMR spectrum.

[a]100 mol % Pd

After looking at the role of the aromatic moiety, we then turned our attention to studying the influence of the substitution at the benzylic position of the substrates. Above, it has been shown that *gem*-dimethyl benzyl Meldrum's acids react smoothly with H_2 in the presence of a catalytic amount of Pd/C (Table 2.1). An array of substrates containing all-carbon quaternary benzylic centers substituted with different alkyl groups were subjected to the hydrogenolysis conditions at room temperature (Table 2.4).

Good conversions and yields were obtained by replacing one of the methyl groups with a linear alkyl chain (ethyl and *n*-butyl) (Table 2.3, entries 2-3). Cyclohexane derivative **2.3c** furnished product **2.4c** in 82% yield (Entry 4); however, substitution of one methyl by an α-branching alkyl group, namely isopropyl, resulted in a considerable decrease in reactivity (Entry 5). Conversion >95% could be achieved using a stoichiometric amount of the palladium catalyst.

2.3 Hydrogenolysis of Benzyl Meldrum's Acids with Mono or Unsubstituted Benzylic Centers

Unexpectedly, the hydrogenolysis of benzyl Meldrum's acids with mono or unsubstituted benzylic centers (**2.5a** and **2.5b**) was sluggish under both sets of conditions (Table 2.4, Entries 1-4). Under methanol at room temperature, very low conversion was observed, while EtOAc and 65 °C resulted in significant decomposition of the substrate. Alkylation of the C-5 position of the Meldrum's acid moiety to form compound **2.5c** and **2.5d** resulted in an enhancement of reactivity in the hydrogenolysis process (Table 2.4, entries 5-8); >95% conversion and good isolated yields were obtained when the reaction was performed at 65 °C in EtOAc.

Table 2.4. Effect of Substitution at the Benzylic Position and Meldrum's Acid 5-Position
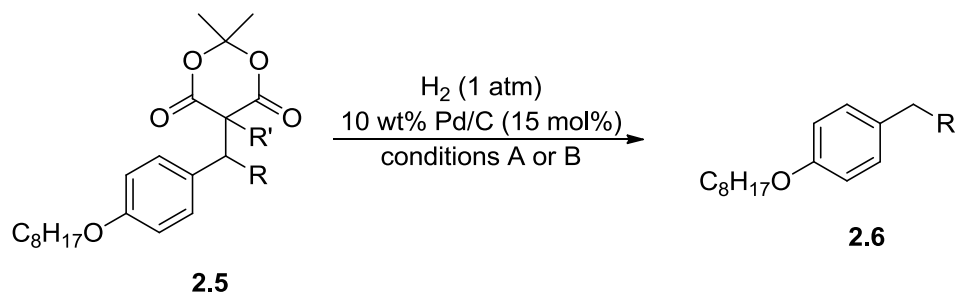
Entry	Conditions[a]	R;R'	Conversion (%)[b]	Yield (%)
1	A	Me; H (**2.5a**)	8	ND (**2.6a**)
2	B	Me; H (**2.5a**)	18	12 (**2.6a**)[c]
3	A	H; H (**2.5b**)	14	ND (**2.6b**)
4	B	H; H (**2.5b**)	20	10 (**2.6b**)[c]
5	A	Me; Me (**2.5c**)	47	ND (**2.6a**)
6	B	Me; Me (**2.5c**)	>95	94 (**2.6a**)
7	A	H; Me (**2.5d**)	62	55 (**2.6b**)
8	B	H; Me (**2.5d**)	>95	80 (**2.6b**)

[a]Conditions A: H_2 (1 atm), 10 wt % Pd/C (15 mol % Pd), MeOH, rt, 24 h. Conditions B: H_2 (1 atm), 10 wt % Pd/C (15 mol % Pd), EtOAc, 65 °C, 24 h. [b]Conversion determined from ratio of product to starting material in crude ^{1}H NMR spectrum. [c]Decomposition of the starting material (~30%) was observed as determined by analysis of the crude ^{1}H NMR.

2.4 Catalyst Inhibition by Hydrogenolysis Product

The enhanced adsorption of the product on the catalyst's surface versus the starting material could explain some of the limited conversion previously observed. Therefore, the influence of excess toluene and hydrogenolysis product **2.2c** on the reaction starting from **2.1c** was studied (Scheme 2.3). According to the experiments, the product of the reaction decreases

the rate of hydrogenolysis, and resulted in lower conversion over a 24-hour period. This is a common observation in Pd/C (catalyst surface) catalyzed reactions. Only a slight difference is observed between toluene and **2.2c**.
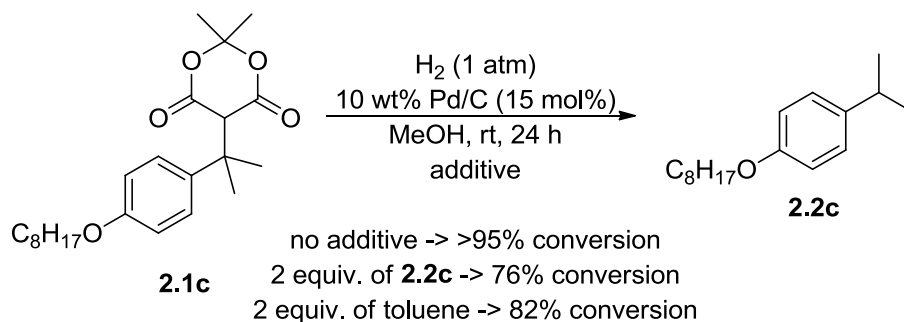

Scheme 2.3. Hydrogenolysis Reaction with Different Additives

2.5 Competition Experiments and Relative Rate of Cleavage of Benzylic Groups

Competition experiments were performed to obtain insights into the steric and electronic requirements of C-C bond cleavage (Table 2.5). Dibenzyl Meldrum's acid derivatives **2.7**, which contain two benzylic C-C σ bonds that could potentially be hydrogenolyzed, were prepared and submitted to hydrogenolysis conditions. As shown in Table 2.4, the lack of benzylic alkyl substituents requires this type of substrate to be hydrogenolyzed at 65 °C in EtOAc. Since the final product of the reaction is not alkylated at the 5-position of Meldrum's acid, it was anticipated to be inert under the reaction conditions. Hydrogenolysis of an unsubstituted benzyl group occurred selectively versus a benzyl group substituted with electron-donating groups— either alkoxy or alkyl—at either the para or ortho position (Entries 1-3). Reaction of substrate **2.7d** showed that hydrogenolysis of the 4-methylbenzyl group occurs more rapidly than the 4-methoxybenzyl group (Entry 4). Hydrogenolysis of substrate **2.7e** showed that hydrogenolysis favors linear alkyl substituents over α-branched alkyl groups (Entry 5). Branched substituents on

34

the aromatic ring likely prevent its adsorption onto the surface of the catalyst, hence the aromatic with an unbranched group is selectively cleaved.[11] Competition between electron-donating methoxy and alkoxy groups gave a mixture of products where cleavage of the benzyl group bearing the methoxy substituent was slightly favoured (Entry 6). In addition, it was found that electron donating groups substituted at either the ortho or para position are equivalent with respect to hydrogenolysis of the benzylic bond as a 50:50 mixture was obtained for substrate **2.7g** (Entry 7). As depicted in Entry 8, the electron-rich benzyl group is cleaved faster than the one substituted with fluoride.

Table 2.5. Competition Experiments
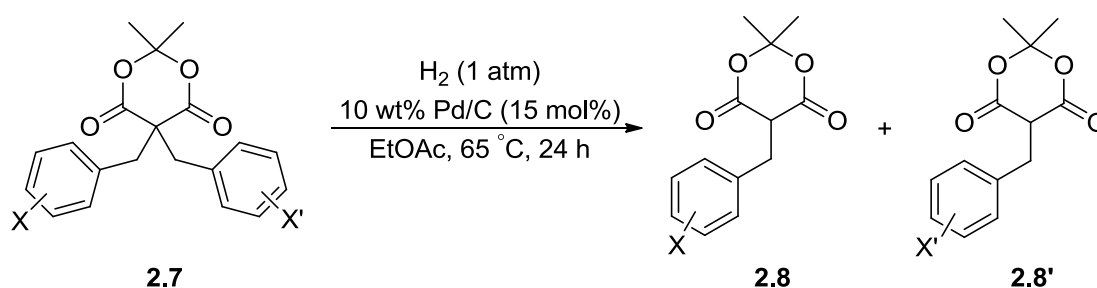
Entry	X/X'	Ratio 2.8/2.8'[a]	Yield (%)[b]
1	4-($H_{17}C_8O$)/H (**2.7a**)	>99/1	65 (**2.5b**)
2	4-*n*-Bu/H (**2.7b**)	>99/1	57 (**2.8a**)
3	2-(MeO)/H (**2.7c**)	>99/1	85 (**2.8b**)
4	4-(MeO)/4-Me (**2.7d**)	87/13	46/6 (**2.8c/2.8d**)
5	4-*n*-Bu/4-*t*-Bu (**2.7e**)	1/>99	34 (**2.8e**)
6	4-(MeO)/4-($H_{17}C_8O$) (**2.7f**)	39/61	71 (**2.8c/2.5b**)[c]
7	4-(MeO)/2-(MeO) (**2.7g**)	50/50	62 (**2.8c/2.8b**)[d]
8	4-($H_{17}C_8O$)/4-F (**2.7h**)	1/>99	51 (**2.8f**)

[a]Determined from analysis of the crude ^{1}H NMR spectrum. [b]Conversion in all cases was >95 %. [c]Mixture of **2.8c** and **2.5b**. [d]Mixture of **2.8c** and **2.8b**.

Table 2.6. Hydrogenolysis of Spiro Substrate **2.9**
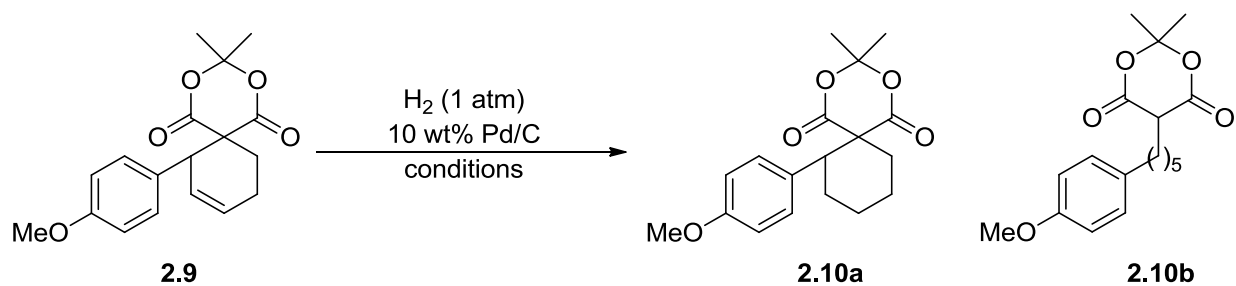
Entry	Conditions	Yield **2.10a** (%)	Yield **2.10b** (%)
1	15 mol % Pd, MeOH, rt	13	77
2	30 mol % Pd, MeOH, rt	18	69
3	15 mol % Pd, EtOAc, 65 °C	54	ND

The scope of the reaction was also investigated with spiro Meldrum's acid derivative **2.9**, which contain a cyclic alkene (Table 2.6). Under standard conditions (Entry 1), the starting material **2.9** was fully converted to a mixture of **2.10a** and **2.10b**. Cyclohexane derivative **2.10a** results from hydrogenation of the olefin and was isolated with only 14% yield while compound **2.10b**, resulting from both hydrogenation and hydrogenolysis processes, was obtained in 70% yield. By increasing the catalyst loading from 15 mol % to 30 mol % of Pd similar results were obtained (Entry 2). Surprisingly, using high temperature conditions in EtOAc resulted in inversion of the product ratio in favor of the hydrogenated product and cyclohexane **2.10a** was isolated with 54% yield and only traces of **2.10b** were observed.

These results could be explained by the sluggish reactivity of **2.10a** towards hydrogenolysis in addition to solvent effects. In Meldrum's acid **2.9**, the Csp^3-Csp^3 σ bond is both benzylic and allylic, while in Meldrum's acid **2.10a** the Csp^3-Csp^3 σ bond is only benzylic, with a decreased reactivity in the hydrogenolysis process. In MeOH, hydrogen bonding with the Meldrum's acid carbonyl groups can stabilize the negative charge developing on the leaving

group in the transition state, while in EtOAc no hydrogen bonding can occur. Therefore, the hydrogenolysis reaction is faster in MeOH than in EtOAc. On the other hand, the transition state for the alkene hydrogenation cannot be stabilized by hydrogen bonding effects and the rate of reaction is not significantly different between the two solvents. As a result, hydrogenolysis occurs faster than hydrogenation in MeOH and significant ring opening occurs prior to hydrogenation; however, in EtOAc the hydrogenation occurs more rapidly and limited hydrogenolysis can occur prior to reduction. The proposed acyclic alkene intermediate was not detected in the crude ^{1}H NMR spectra. As illustrated in Scheme 2.4, treatment of **2.10a** with either set of conditions did not result in significant hydrogenolysis after 24 h.
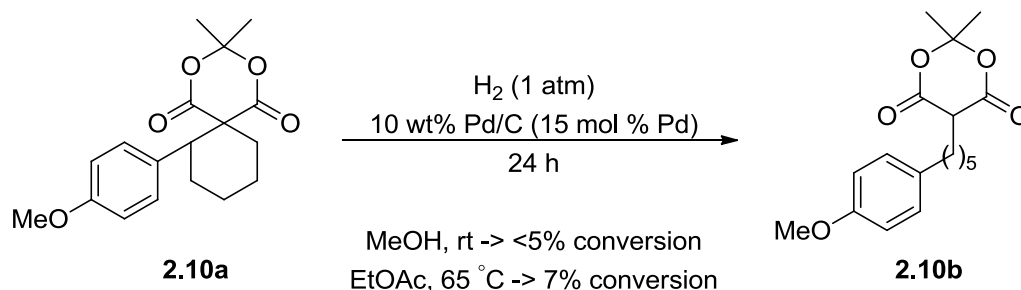
Scheme 2.4. Hydrogenolysis Reaction of Spiro Meldrum's Acid **2.10a**

2.6 Diarylmethane Synthesis

Diarylmethane compounds are an important subunit in a number of biologically active molecules.[40] Different synthetic pathways to these compounds are known which usually involve cross-coupling methodology using organoboron,[41] organostannane,[42] organozinc,[43] or other reagents.[44] Reduction of diarylmethanols is also frequently employed.[45] As previously discussed, the hydrogenolysis reaction is sluggish for enolizable benzyl Meldrum's acid derivatives with tertiary benzylic centers but it was postulated that the presence of two aryl groups could promote

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the reaction resulting in the formation of diarylmethane products. In Table 2.7, it is shown that

the reaction proceeds in excellent yield for a variety of electron rich and electron poor substrates

and for substrates with sterically demanding aryl substituents. Most examples, including the

seemingly problematic 4,4'-di-tert-butyl and 3,3'-dimethoxy substrates, proceeded in nearly

quantitative yield (Entries 1-6). Only the fluoro substituted substrates resulted in a slight

decrease in yields (Entries 7, 8).

Table 2.7. Synthesis of Diarylmethanes

$$ \text{2.11} \xrightarrow[\substack{\text{10 wt\% Pd/C (15 mol \% Pd)} \\ \text{MeOH, rt, 24 h}}]{\text{H}_2 \text{ (1 atm)}} \text{Ar} \wedge \text{Ar' } \quad \text{2.12} $$
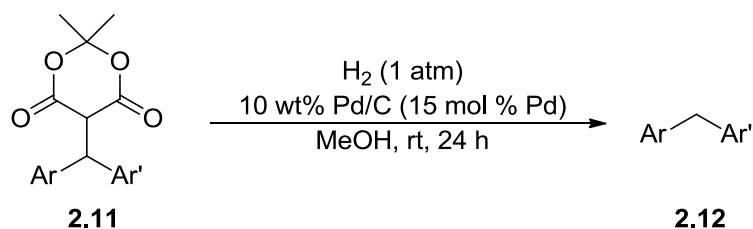
Entry	Ar/Ar'	yield (%)[a]
1	4-(MeO)C$_6$H$_4$/4-(MeO)C$_6$H$_5$ (**2.11a**)	96 (**2.12a**)
2	2-(MeO)C$_6$H$_4$/C$_6$H$_5$ (**2.11b**)	98 (**2.12b**)
3	3-(MeO)C$_6$H$_4$/C$_6$H$_5$ (**2.11c**)	95 (**2.12c**)
4	4-t-BuC$_6$H$_4$/C$_6$H$_5$ (**2.11d**)	96 (**2.12d**)
5	4-t-BuC$_6$H$_4$/4-t-BuC$_6$H$_4$ (**2.11e**)	99 (**2.12e**)
6	3-(MeO)C$_6$H$_4$/3-(MeO)C$_6$H$_4$ (**2.11f**)	93 (**2.12f**)
7	4-(MeO)C$_6$H$_4$/4-FC$_6$H$_4$ (**2.11g**)	81 (**2.12g**)
8	4-FC$_6$H$_4$/C$_6$H$_5$ (**2.11h**)	81 (**2.12h**)

[a]Conversion >95% in all cases (determined from ratio of product to starting material in crude

^{1}H NMR spectrum).

2.7 Mechanistic Studies. Hydrogenolysis of Enantioenriched Quaternary Centers

Table 2.8. Hydrogenolysis of Enantioenriched Quaternary Centers with Inversion of Configuration
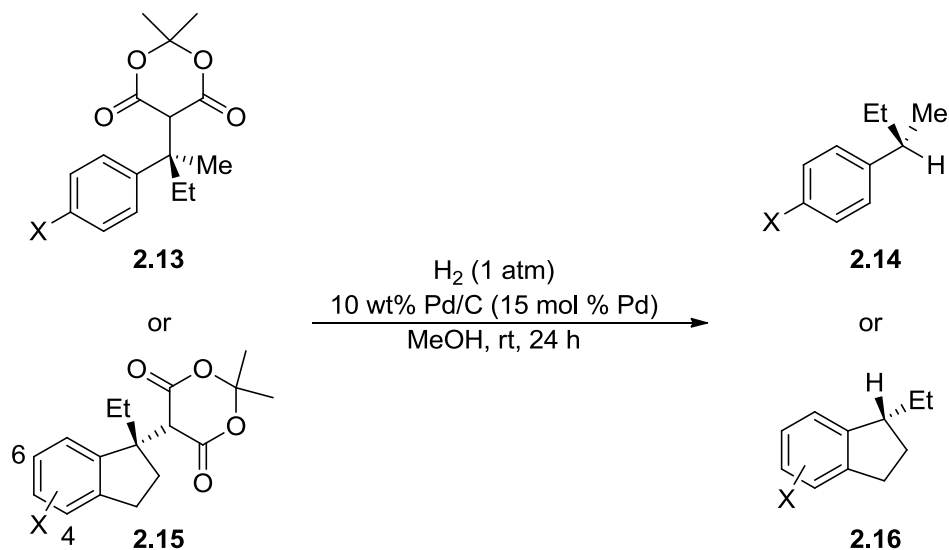

Entry	X	er (**2.13, 2.15**) (R/S)	er (**2.14, 2.16**) (S/R)	% Inversion[a] (% Yield)[b]
1	Ph [(R)-**2.13a**]	98:2	95.5:4.5	92 (82) [(S)-**2.14a**]
2[c]	C$_8$H$_{17}$O [(R)-**2.3a**]	98.5:1.5	96:4	97 (93) [(S)- **2.4a**]
3[d]	MeO [(R)-2.**13b**]	98.5:1.5	94.5:5.5	96 (72) [(S)- **2.14b**]
4[e]	4-MeO [(S)-**2.15a**]	86:14	79:21	93 (49)[f] [(R)- **2.16a**]
5	6-MeO [(S)-**2.15b**]	99:1	91:9	92 (62)[g] [(R)- **2.16b**]

[a]Inversion of er. [b]Isolated yield. Conversion >95% unless stated otherwise (determined from ratio of product to starting material in crude ^{1}H NMR spectrum). [c]Using 30 mol% Pd. [d]Using EtOAc, 65 °C. [e]Using 50 mol% Pd. [f] 90% Conversion. [g]65% Conversion.

In order to rationalize the results presented above, we embarked on an investigation of the reaction mechanism, initially by evaluating the stereochemical integrity of the reaction. Enantioenriched Meldrum's acid derivatives **2.13** and **2.15** previously reported by our group

were subjected to hydrogenolysis (Table 2.8).[46] It was shown that the reaction proceeds with near complete inversion of configuration, with a level of inversion of 92-97%. This is suggestive of an S_N2-like displacement of Meldrum's acid by a nucleophilic hydride species. The absolute stereochemistry of benzyl derivatives **2.14** were determined by comparison with the known compound *(S)*-**2.14b**. The absolute stereochemistry of *(S)*-**2.16b** was proven by synthesis of chiral indanes from a modified literature procedure (Scheme #).[47]

Beginning from 3-anisaldehyde (**2.17a**), a decarboxylative Knoevenagel condensation with malonic acid in pyridine with catalytic piperidine provided *trans*-3-methoxycinnamic acid (**2.17b**) in excellent yield. Next, a chiral auxiliary approach was employed to install the benzylic stereocenter. The auxiliary was attached by converting cinnamic acid **2.17b** to an acyl chloride with oxalyl chloride and catalytic DMF. A mixture of (*S*)-4-benzyloxazolidin-2-one and NaH in THF was added to the acyl chloride solution to produce acyl oxazolidinone **2.17c**. A diastereoselective conjugate addition was performed by adding a solution of oxazolidinone **2.17c** to a mixture of allylmagnesium chloride and CuBr•SMe$_2$ in THF at -78 °C. The reaction occurs with complete diastereoselectivity to form alkenyl oxazolidinone (*S,S*)-**2.17d** and the undesired diastereomer (*S,R*)-**2.17d** was not observed in the crude reaction mixture. The chiral auxiliary was then removed with LiAlH$_4$ in THF. The resulting alcohol **2.17e** was protected as an acetate group with acetyl chloride in CH$_2$Cl$_2$ in the presence of triethylamine and catalytic DMAP. The resulting alkenyl acetate **2.17f** was subjected to oxidative cleavage using NaIO$_4$ and KMnO$_4$ in 1:1 water/acetone. The carboxylic acid **2.17g** obtained was used in a Friedel-Crafts acylation reaction with SnCl$_4$ via an acyl chloride intermediate that was generated in situ with oxalyl chloride and catalytic DMF. No cyclization to form the possible 1,2,3-trisubstituted benzene ring was observed and the desired indanone **2.17h** was obtained exclusively. Indanone **2.17h** was
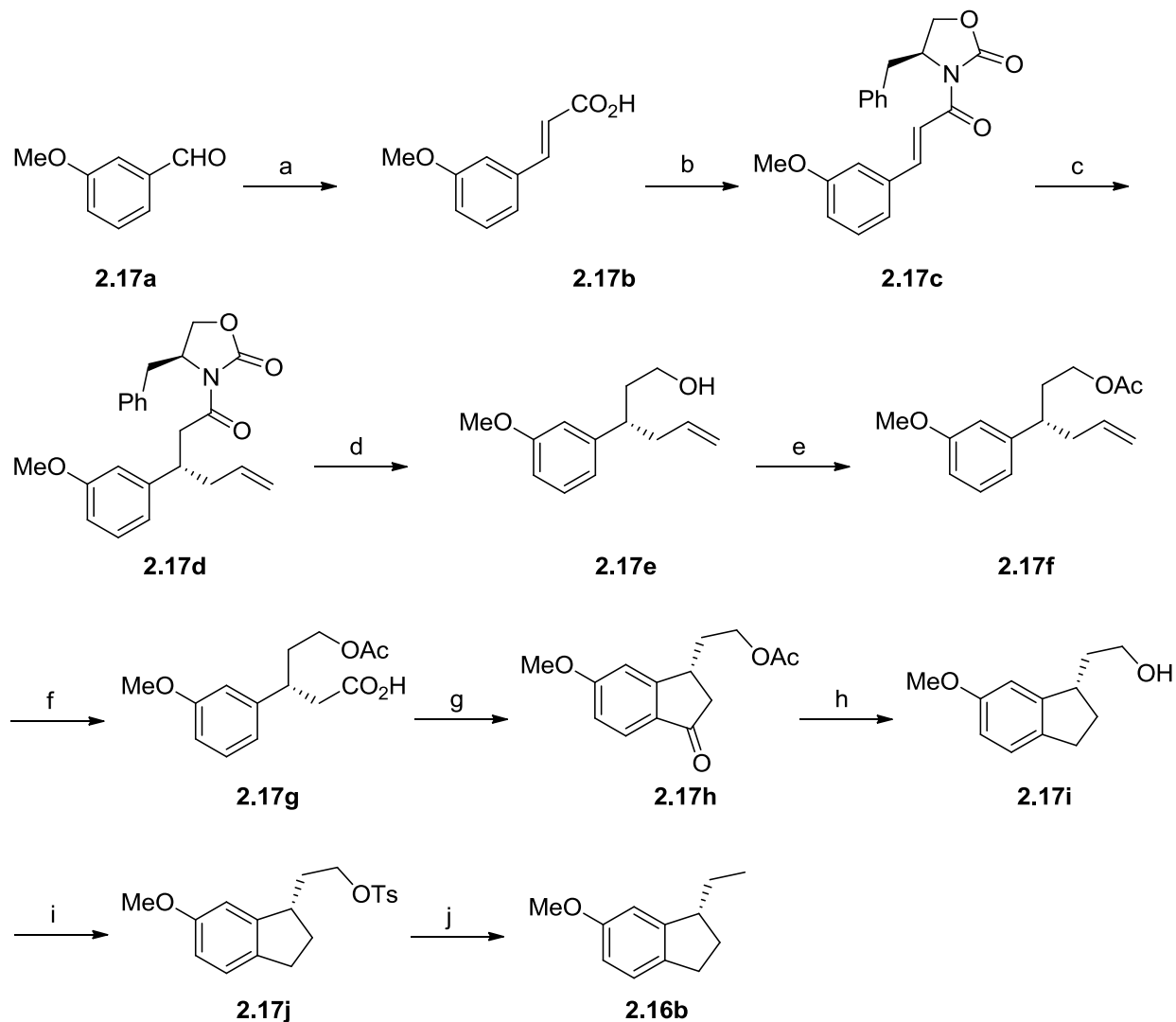
a) malonic acid, piperidine, pyridine, 85 °C, 24 h. b) (COCl)2, cat. DMF, CH₂Cl₂, 3 h then NaH, (*S*)-4-benzyloxazolidin-2-one, THF, 0 °C to rt, 5 h. c) allylmagnesium chloride, CuBr•SMe₂, THF, -78 °C, 4 h. d) LiAlH₄, THF, -78 °C, 1 h. e) AcCl, NEt₃, DMAP, CH₂Cl₂, rt, 2 h. f) NaIO₄, KMnO₄, 1:1 H₂O/acetone, rt, 4 h. g) (COCl)₂, cat. DMF then SnCl₄, THF, 0 °C to rt, 4 h. h) H₂, Pd/C, H2SO₄, EtOH, 60 °C, 1 h. i) TsCl, pyridine, rt, 8 h. j) Super-Hydride®, THF, 0 °C to reflux, 5 h.

Scheme 2.5. Determination of Absolute Configuration of Chiral Indane **2.16b**

hydrogenated with Pd/C, H_2SO_4 and atmospheric pressure of H_2, which resulted in reduction of the carbonyl with simultaneous removal of the acetyl group to form primary alcohol **2.17i**. Dehydroxylation of alcohol **2.17i** was carried out in a two-step sequence involving tosylation with TsCl in pyridine followed to form tosylate **2.17j**, followed by reduction of the C-O bond with Super-Hydride® in THF/Et_2O to obtain the desired chiral indane.

2.8 Deuterium-Labeling Experiments

It was postulated that either a hydride would directly displace Meldrum's acid, or a Pd species would perform the displacement followed by reductive elimination. Therefore, to obtain more knowledge about the nature of the nucleophilic species involved, several deuterium-labeling experiments were performed (Table 2.9). The hydrogenolysis of **2.1c** and **2.1e** were performed using different combinations of D_2 or H_2 and CD_3OD or CH_3OH. When excess gas is used (balloon), incomplete deuterium incorporation was observed in the mixed cases using either H_2/CD_3OD or D_2/CH_3OH (Entries 1-2); however, near complete deuterium incorporation was achieved for D_2/CD_3OD (Entry 3). In addition, a small amount (<5 %) of deuterium incorporation could be observed at the homobenzylic position under all three sets of conditions. The percentage of deuterium incorporation at the benzylic position was difficult to reproduce and this was attributed to difficulties controlling the amount of hydrogen available to the reaction (balloon size, refilling). The incomplete deuterium incorporation and inconsistent results in the mixed cases can be explained by a benzylic hydrogen exchange process that has been described by Sajiki et al.[48] They report an efficient methodology for converting a benzylic C-H bond to a C-D bond using conditions similar to our standard hydrogenolysis protocol. Using a limited quantity of H_2 (sealed tube) and catalytic Pd/C, hydrogen from the benzylic C-H can selectively

Table 2.9. Labelling Studies on the Hydrogenolysis Reaction
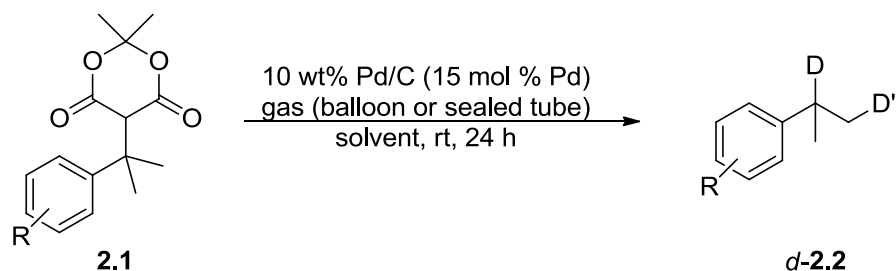
Entry	Gas/Solvent	D-Incorporation (%)[a,b,c]	
		$R = 4\text{-}(H_{17}C_8O)$ **(2.1c)**	$R = 2\text{-}(H_{17}C_8O)$ **(2.1e)**
excess gas (balloon)			
1	H_2/CD_3OD	52	17^d
2	D_2/CH_3OH	32	45^d
3	D_2/CD_3OD	>95	94^d
2 equivalents of gas (sealed tube)			
4	H_2/CD_3OD	90 (85)	$75\ (41)^e$
5	D_2/CH_3OH	2 (77)	$3\ (38)^f$
6	D_2/CD_3OD	>95 (54)	$>95\ (37)^f$

[a]At the benzylic position (determined by ^{1}H NMR). [b]Isolated yields (%) provided in parentheses. [c] <5% D'-incorporation in each case. [d]20 mol % Pd. [e]45% Conversion. [f]53% Conversion. Conversion determined from ratio of product to starting material in crude ^{1}H NMR spectrum.

be exchanged with deuterium from the solvent. This exchange obfuscates the analysis because, regardless of the source of the original hydride, it can be exchanged with the solvent. The deuterium labelling experiments were repeated using limited quantity of gas (2 equivalents in a sealed tube, assuming the volume of hydrogen is equivalent to the flask volume less the solvent volume) and the solvent was found to be the major contributor to the benzylic hydrogen of the product. When CD$_3$OD was used with either H$_2$ or D$_2$, high deuterium incorporations were

observed; however, negligible deuterium incorporation was observed when CH_3OH was used with D_2 (Entries 4-6). These results indicate that the exchange is an equilibrium process where the most abundant hydrogen source is incorporated to the benzylic position. When the gas is limited, the solvent is more abundant and dominates, but when excess gas is used, it competes with the solvent for incorporation. Unfortunately, the 2-alkoxy derivative did not react completely (45-53% conversion) and low isolated yields (37-41%) of the deuterated product were obtained. This is surprising as previous experiments have shown negligible difference between 2- and 4-substituted derivatives when the substituent is the same (Table 2.1, Entry 3 versus Entry 5 and Table 2.6, Entry 7).

The existence of an exchange reaction in our system was further confirmed using the regioisomeric hydrogenolysis products **2.2c**, **2.2d** and **2.2e** (Table 2.10). Using 2 equivalents of H_2 with CD_3OD in a sealed tube, Product *d*-**2.2c** was obtained with 84% deuterium incorporation at the benzylic position and a similar result was obtained for substrate **2.2d** (Entries 1-2); however, the deuterium incorporation for the 2-alkoxycompound **2.2e** is very low (less than 5%) after 24 h.[49] This difference of reactivity observed might be due to steric effects. The methyl groups of the isopropyl group will have a steric interaction with the ortho substituent, resulting in the molecule adopting a conformation where the benzylic hydrogen is in close proximity to the ortho substituent. This can be seen from the difference in δ of the benzylic hydrogen in ^{1}H NMR, where the ortho isomer is much less shielded than the meta or para isomers. This is a result of repulsion between the lone pairs on oxygen and the electrons in the benzylic C-H bond, which pushes the electrons away from the proton and towards the carbon (Scheme #).

Table 2.10. Hydrogen-Deuterium Exchange Investigation

2.2 → d-2.2
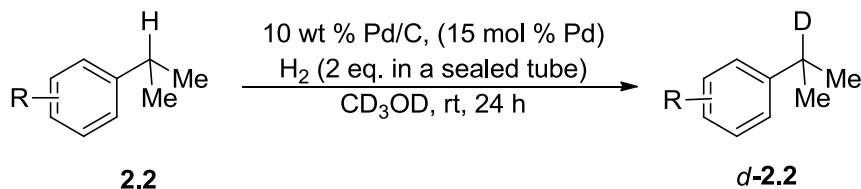
Entry	R	Deuterium Incorporation (%)[a,b]	$\delta_{benzylic}$ (ppm)
1	4-OC$_8$H$_{17}$ (**2.2c**)	84 (78)(d-**2.2c**)	2.86
2	3-OC$_8$H$_{17}$ (**2.2d**)	77 (74) (d-**2.2d**)	2.86
3	2-OC$_8$H$_{17}$ (**2.2e**)	2 (98) (d-**2.2e**)	3.33

[a]At the benzylic position (determined by ^{1}H NMR). [b]Isolated yields (%) provided in parentheses.
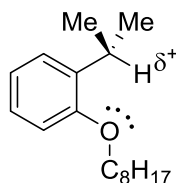
Scheme 2.6. Steric Effects in Benzylic Hydrogen Exchange

The influence of the acidic proton of Meldrum's acid was then studied. In order to minimize the effects of the benzylic hydrogen exchange reaction, ortho-substituted **2.1e** was labelled with deuterium at the Meldrum's acid 5-position to form d-**2.1e**. The deuterium labelled substrate was then subjected to the same conditions (sealed tube) and the results were similar to those obtained with undeuterated compound **2.1e** (Table 2.11). Once again, the solvent was the dominant deuterium source where 84% D-incorporation was obtained when CD$_3$OD was used with H$_2$ and when CD$_3$OD was used with D$_2$ the D-incorporation was 93%; however, when CH$_3$OH was used with D$_2$, only 1% D-incorporation was achieved. Thus, the influence of the acidic Meldrum's acid proton is negligible with respect to deuterium incorporation.
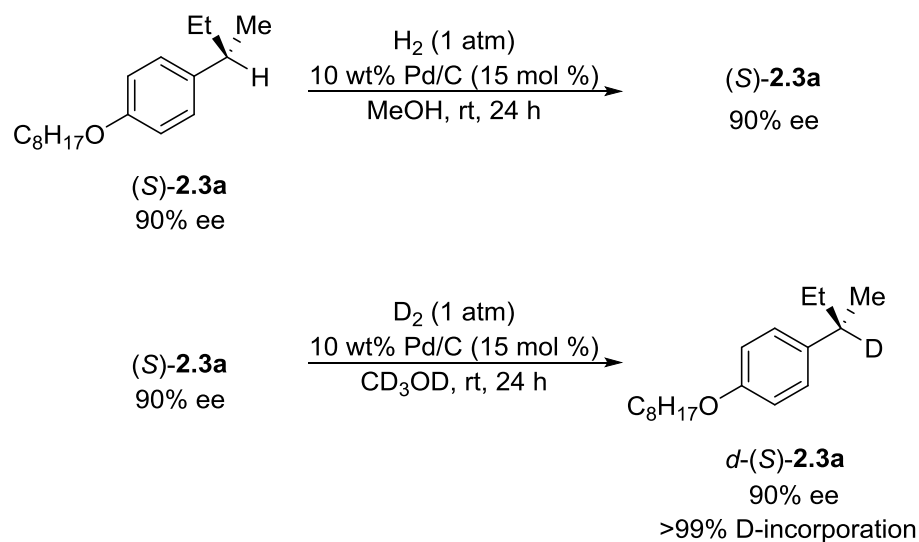
Table 2.11. Deuterium Labeling Experiments

d-**2.1e** → *d*-**2.2e**

10 wt % Pd/C, (20 mol % Pd), gas (1 atm)

Solvent, rt, 24 h
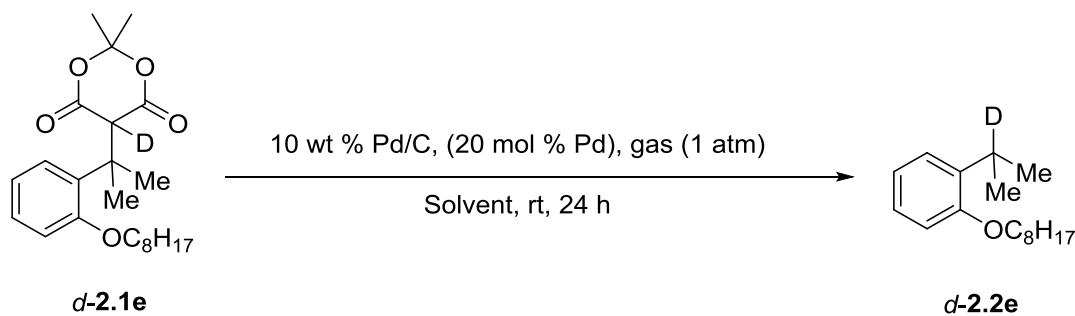
Entry	Gas	Solvent	Deuterium Incorporation (%)[a,b]
1	H_2	CD_3OD	84 (46)[c]
2	D_2	CH_3OH	1 (36)[d]
3	D_2	CD_3OD	93 (33)[e]

[a]At the benzylic position (determined by ^{1}H NMR); [b]Isolated yields (%) provided in parentheses. [c]Conversion 55%. [d]Conversion 56%. [e]Conversion 41%. Conversion determined from ratio of product to starting material in crude ^{1}H NMR spectrum.

The existence of an exchange reaction at the benzylic center required the stereochemical integrity of the final product of the hydrogenolysis reaction to be verified. The enantioenriched benzyl compound (*S*)-**2.3a** was employed in two exchange (H-H or H-D) reactions under the standard conditions with excess H_2 or D_2 (Scheme 2.5). Compounds (*S*)-**2.3a** and *d*-(*S*)-**2.3a** were obtained with total retention of configuration, demonstrating that the H-D exchange reaction at the benzylic position is stereospecific and occurs with complete retention of configuration. This supports that the inversion of configuration observed in the hydrogenolysis reaction is solely due to the C-C bond cleaving process.

Scheme 2.7. H-H and H-D Exchange with Retention of Configuration

H_2 (1 atm)
10 wt% Pd/C (15 mol %)
MeOH, rt, 24 h

(S)-**2.3a**
90% ee

(S)-**2.3a**
90% ee

D_2 (1 atm)
10 wt% Pd/C (15 mol %)
CD$_3$OD, rt, 24 h

(S)-**2.3a**
90% ee

d-(S)-**2.3a**
90% ee
>99% D-incorporation

Table 2.12. Deuterium Labeling Experiments of Enantioenriched Meldrum's Acids

2.13

D_2 (1 atm)
10 wt % Pd/C (15 mol % Pd)
CD$_3$OD, rt, 24 h

d-**2.14** + d$_2$-**2.14**
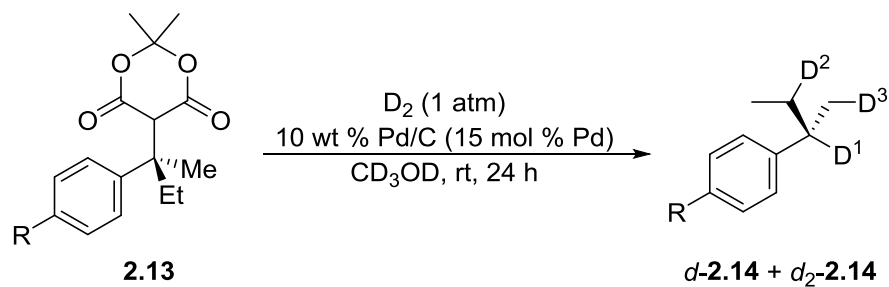
Entry	R	Loss of ee (%)	β-Incorporation (%D^2 + %D^3)[a]
1	C$_8$H$_{17}$O [(R)- **2.3a**]	6	4
2	Ph [(R)- **2.13a**]	14	17
3	MeO [(R)- **2.13b**]	7	11

[a]Determined by ^{1}H and ^{2}H NMR.

After confirming that the inversion of configuration observed in the hydrogenolysis reaction occurs only due to the C-C bond cleavage event, it was proposed that the incomplete inversion observed in the initial investigations of enantioenriched derivatives may be related to

the observed deuterium incorporation at the homobenzylic position. This was verified by performing deuterium-labeling experiments on enantioenriched Meldrum's acid derivatives **13** (Table 2.12). The deuterium incorporation at positions D^2 and D^3 observed (^1H and ^2H NMR) for all the examples is well correlated with the loss of ee obtained (HPLC analysis).

2.9 Discussion and Conclusions

From the numerous parameters of the reaction that were studied, different information and guidelines can be extracted. First of all, the nature (substitution) of the aromatic ring has a strong influence on the reaction. Introduction of a bulky group on the aromatic ring limited the reaction, a result that has already been shown for other hydrogenolysis processes.[50] It is observed that the reaction rate is diminished due to low adsorption of a hindered starting material onto the surface of the catalyst. The importance of electronic effects also appears in this study: the reactivity is subdued by electron-withdrawing aryl groups but is enhanced by the presence of electron-donating groups. This is consistent with the proposed S_N2-like reaction mechanism, where the electron donating groups can facilitate the reaction by stabilizing the partial positive charge on the benzylic center in the transition state. An optimization of the reaction conditions revealed that using EtOAc as the solvent and increasing the temperature to 65 °C allows the reaction to be performed on substrates with less labile benzyl groups. In some cases, an augmentation of the catalyst loading is also necessary.

Second, the study of the benzylic alkyl group substitution revealed a strong and somewhat peculiar influence on the reaction. For substrates with quaternary benzylic centers bearing two alkyl groups, secondary alkyl groups (isopropyl) were shown to hinder the reaction while primary alkyl groups (ethyl, *n*-butyl, indanyl) and methyl groups allowed complete

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hydrogenolysis reactions. This is consistent with the proposed S_N2-like mechanism, where branching near the electrophilic site prevents approach of the nucleophilic species. In addition, the branching could also prevent adsorption of the substrate onto the catalyst surface. An interesting result is observed when the substrate contains a secondary or tertiary benzylic center. In these examples, the hydrogenolysis reaction proceeds very poorly and low conversions are achieved. This is atypical for S_N2 processes, which prefer decreased substitution of the electrophilic site. This could be indicative of a late transition state with some carbocation character that is stabilized by increasing alkyl substitution. Apparently, the stabilization from donating substituents is enough to offset the steric crowding of the electrophilic site; although, increasing the size of the alkyl substituent can disfavour the process, as shown for the substrate bearing an ispropyl group on the benzylic center (Table 2.3, Entry 5). Surprisingly, removal of the enolizable proton via alkylation of the Meldrum's acid C5 position greatly improved the reactivity. This difference in reactivity between enolizable and non-enolizable structures is difficult to rationalize, as the difference in acidity between Meldrum's acid (pka = 7.32 in DMSO) and 5-methyl Meldrum's acid (pka = 7.42 in DMSO) is minimal and does not explain the large rate and reactivity difference.[51] X-ray analysis shows only a small difference in the length of the scissile C-C bonds (Table 2.13).

The competition experiments performed showed that hydrogenolysis occurs preferentially for benzyl groups bearing non-substituted aromatics, then alkoxy-substituted aromatics, followed by aromatics bearing non-bulky alkyl substituents. Benzyl groups that are electron deficient or sterically hindered are not cleaved readily. This selectivity matches with the results obtained in Table 1. The competition reactions demonstrated that the least substituted aromatic ring, although not electronically favored, is preferentially cleaved. This underlines the

importance of an optimal coordination to the metal surface; the aromatic ring must lay flat against the metal surface in order for the reaction to proceed.2

**Table 2.13.** X-Ray Analysis of Meldrum's Acid Derivatives **2.18**
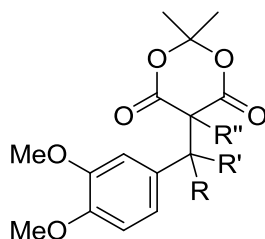
Entry	R	R'	R"	C(5)-C(11) bond length (Å)
1 (**2.1r**)	Me	Me	H	1.565
2 (**2.18a**)	H	H	H	1.541
3 (**2.18b**)	Me	H	H	1.562
4 (**2.18c**)	H	H	Me	1.566
5 (**2.18d**)	Me	H	Me	1.568

Next, the scope of the hydrogenolysis reaction was broadened by the efficient and very clean synthesis of diarylmethanes. The high reactivity of diarylmethyl Meldrum's acid can be explained by the decreasing of the steric hindrance around the aromatic part of the breakable C-C bond as well as the electronic contributions from both aromatic rings stabilizing the carbocation character of the late transitions state. Similar observations were made for spiro substrate **2.9**.

Finally, the research was directed towards investigation of the mechanism. First, near complete inversion of configuration is observed for the hydrogenolysis of enantioenriched substrates, which suggests an unprecedented S_N2-like mechanism. The positive influence of electron donating substituents on the aromatic ring and the very good reaction described starting from diarylmethyl Meldrum's acid derivatives support this conclusion. The presence of electron

donating groups stabilizes the partial positive charge at the reactive site in the S_N2-like mechanism and benzylic activation resulting from overlap of the π system of the aromatic with the S_N2 transition state augments the reactivity.

Conclusions about the nature of the nucleophilic species can now be proposed. According to labeling experiments, the hydrogen in the reaction comes from the gas while a secondary process exchanges the benzylic hydrogen of the product with the solvent. Carreira and coworkers have studied a similar reaction involving hydrogenolysis of benzylic nitro groups.[52] In their studies, they found that the resulting benzylic hydrogen comes solely from the solvent. They propose that palladium displaces the nitro group to form a benzylic palladium species that is then protonated by the solvent before undergoing reductive elimination to furnish the product. Another key observation is the limited deuterium incorporation at the methyl position, which could occur due to hydrogenation of an alkene derivative resulting from β-hydride elimination of a benzylic palladium intermediate. Compiling these results allows the following mechanism to be proposed (Scheme 2.6).
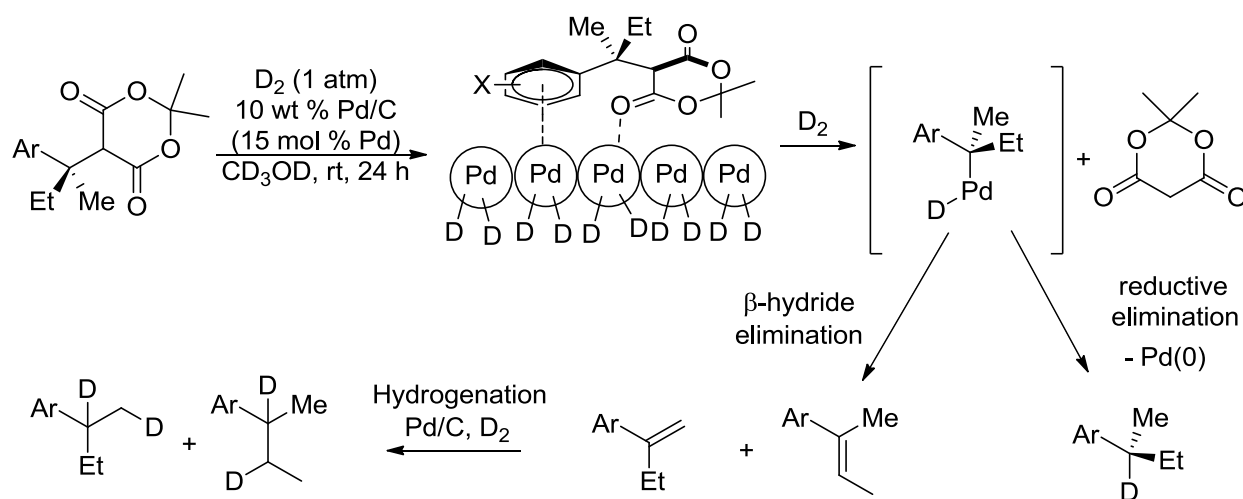
Scheme 2.8. Proposed Hydrogenolysis Mechanism

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The first step is the S_N2 displacement of Meldrum's acid by a nucleophilic palladium hydride species. It is suggested that this displacement is assisted by coordination of Meldrum's acid to the palladium(II) surface upon adsorption of H_2 by the catalyst. The complexation to the Lewis acidic catalyst would help in the C-C bond breaking events step and would proceed through a polar transition state, explaining the facile displacement at an all-carbon quaternary center in comparison to less substituted carbon. Reductive elimination to form the inverted product occurs rapidly but a small amount of β-hydride elimination occurs, destroying the stereogenic center. The resulting alkene is hydrogenated to a racemic mixture of products. This mechanism explains the loss of enantiomeric excess observed in the hydrogenolysis of enantioenriched compounds and deuterium incorporation at the homobenzylic position. Importantly, the deuterium labeling experiments with enantioenriched derivatives showed that the loss of ee was correlated with the deuterium incorporation at the homobenzylic position.

In conclusion, we have presented a facile hydrogenolysis of Csp^3-Csp^3 σ bonds catalyzed by Pd/C that occurs through an unprecedented mechanism, where the metal center behaves as a nucleophile in a formal S_N2 process with inversion of configuration of stereogenic centers. The reaction was shown to be fairly general and allows the synthesis of tertiary, secondary and methyl benzylic centers as well as diarylmethanes, although the crucial electronic and steric requirements were thoroughly outlined. We also demonstrated the stereoselectivity of the Pd/C catalyzed benzylic hydrogen exchange, which occurs with complete retention of configuration.

2.10 Experimental

2.10a General Methods

Reactions

THF was freshly distilled from sodium-benzophenone ketyl under nitrogen prior to use. DME was distilled from sodium-benzophenone ketyl under nitrogen and degassed via freeze-pump-thaw method (3 cycles) and stored in a sealed Schlenk flask under argon. Et_2O was purified by a solvent system based on the published procedure.[53] MeMgBr (3.0 M in Et_2O), EtMgBr (3.0 M in Et_2O), and PhMgCl (2.0 M in THF) were obtained from commercial sources and titrated against salicylaldehyde phenylhydrazone prior to use.[54] The other Grignard reagents used were prepared from the corresponding aryl bromides with magnesium powder (-20+100 mesh, 99.8%) in THF. Et_2Zn (1.0 M in hexanes), Super-Hydride® (1.0 M in THF) and palladium (10 wt. % Pd on activated carbon) were purchased from Sigma-Aldrich and used as received. Potassium carbonate was dried by heating to 150 °C in a sand bath under a gentle stream of nitrogen. All other reagents and solvents were purchased from commercial sources 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.

Characterization

^1H 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 $CHCl_3$ (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 ^1H 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. Chiral HPLC was performed using a Chiralcel AD-H or OD-H 250 mm × 4.6 mm column. Optical rotations were recorded in cells with 1 dm path length.

Synthesis of Starting Materials

**2.10b General Procedure A – Preparation of Quaternary Benzyl Meldrum's Acids**
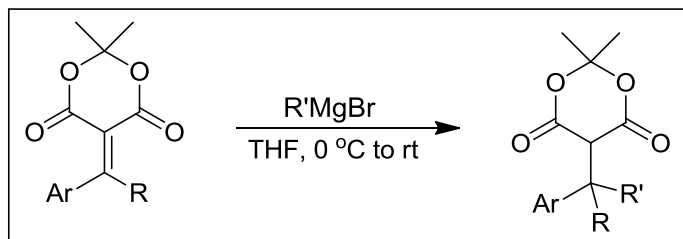
Quaternary benzyl Meldrum's acids were prepared by the addition of Grignard reagents (1.5-4 equiv, dropwise addition or alternatively syringe pump addition at a rate of 0.34 mL/min) to a solution of alkylidene Meldrum's acids in dry THF (0.5 M) under nitrogen atmosphere at 0 °C. The reactions were stirred 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.

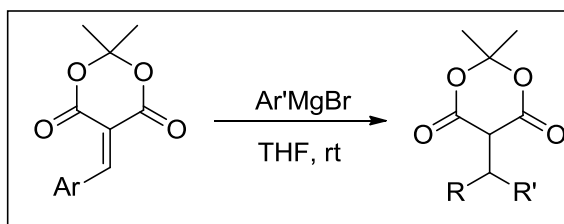**2.10c General Procedure B – Preparation of Quaternary Benzyl Meldrum's Acids**
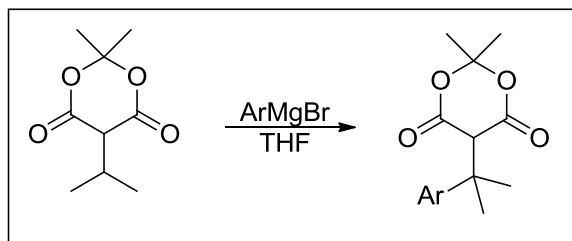
Benzyl Meldrum's acids were prepared by the addition of aryl Grignard reagents (1-4 equiv) to a solution of 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione[55] in dry THF (0.5 M) under nitrogen atmosphere at 0 °C. The reactions were stirred at room temperature until completion or for 24 h. The reactions were quenched with 5% HCl at 0 °C 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 recrystallization or flash chromatography, as indicated.

2.10d General Procedure C – Alkylation of Benzyl Meldrum's Acids
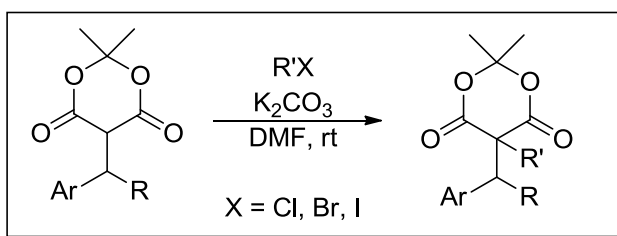
Meldrum's acid derivative (1.0 equiv) was dissolved in DMF (1.0 M); anhydrous K$_2$CO$_3$ (1.5 equiv) was added at room temperature. The electrophile R'X was added to the well-stirred suspension and the mixture was stirred for 16 h. Deionized water was added to the reaction mixture, followed by CH$_2$Cl$_2$. The layers were partitioned and the aqueous layer was extracted with CH$_2$Cl$_2$ (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, as indicated.

## 2.10e General Procedure D – Alkylation of Benzyl Meldrum's Acids
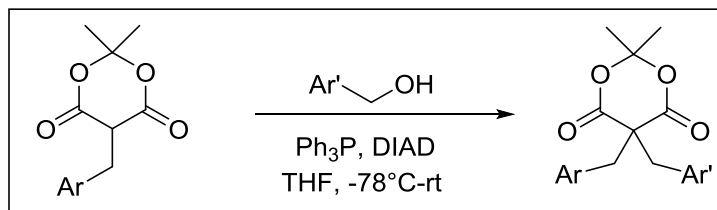
The alkylation was carried out according to the literature procedure.[56] DIAD (1.0 equiv.) was added dropwise to a stirring solution of Ph_3P (1.0 equiv) in THF (0.25 M) at -78 °C. A solution of alcohol (1.1 equiv) in THF (1 M) was added dropwise to the reaction mixture at -78 °C and stirred for 5 min. 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.

2.10f General Procedure E – Preparation of Diaryl Meldrum's Acids

Diaryl Meldrum's acids were prepared by the addition of aryl Grignard reagents (1-4 equiv) to a solution of benzylidene Meldrum's acids in dry THF (0.5-1.0 M) under N_2 at 0 °C. The reaction was stirred at room temperature until completion of reaction or for 24 h. The reaction was quenched with 5% HCl 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 flash chromatography or recrystallization.

## 2.10g General Procedure F – Preparation of Enantioenriched Meldrum's Acids
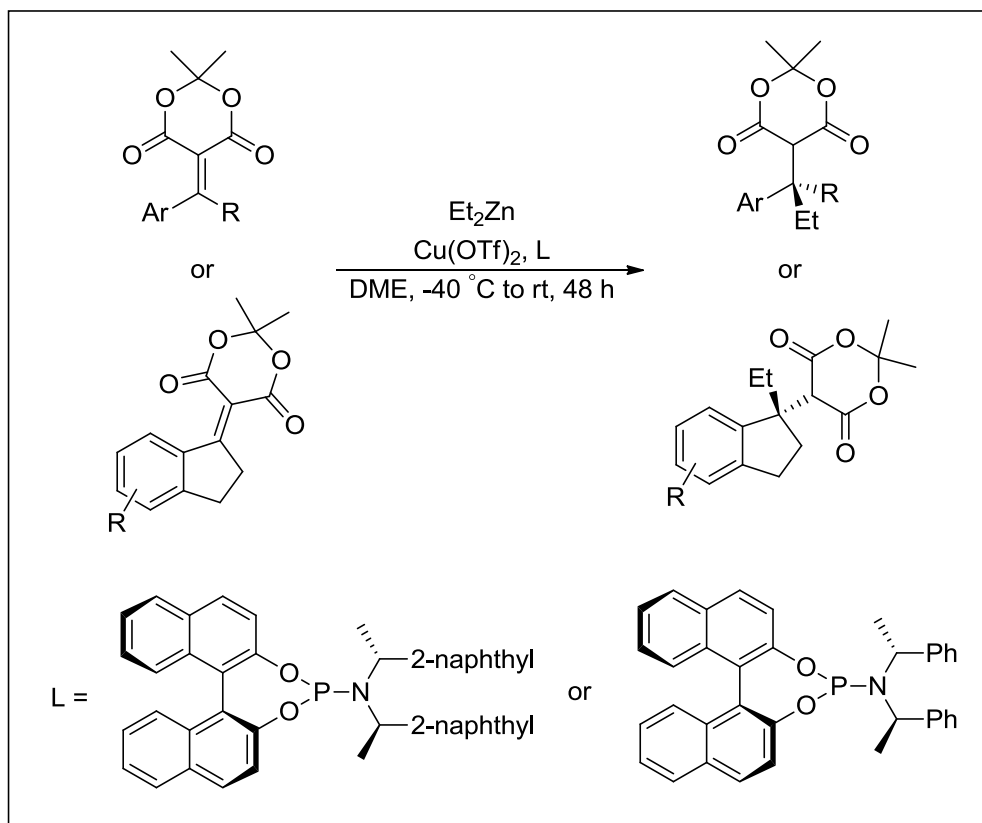
Enantioenriched benzyl Meldrum's acids were prepared by the conjugate addition of Et$_2$Zn to alkylidene Meldrum's acids.[57] In a glove box, Cu(OTf)$_2$ (5 mol %) and the phosphoramidite ligand (10 mol %) were charged in a flame-dried round bottom flask. Outside the box, DME was added to the round bottom flask ([Cu(OTf)$_2$] = 0.02 M) and the reaction mixture was allowed to stir at ambient temperature for 15 minutes before being cooled to -40 °C. Et$_2$Zn solution (2.0 equiv) was added dropwise to the pale yellow copper solution and the resulting solution stirred for 5 min. A 1.0 M solution of alkylidene Meldrum's acid (1.0 equiv) in DME was added dropwise and then the reaction mixture was allowed to warm up slowly to room temperature. After 24 h of stirring, 5% HCl and EtOAc were added to the reaction mixture. The layers were partitioned and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed once with brine, dried over MgSO$_4$, filtered and concentrated. The

crude residue was purified by flash column chromatography on silica gel using EtOAc/hexanes to yield the desired product.

2.10h Substrate Specific Information

The following starting materials were prepared according to literature procedures and the spectral data obtained were in agreement with those reported; consequently, data will not be repeated here: 2,2-dimethyl-5-(2-phenylpropan-2-yl)-1,3-dioxane-4,6-dione (**2.1a**), 5-(2-([1,1'-biphenyl]-4-yl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1b**), 2,2-dimethyl-5-(2-(4-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**2.1c**), 2,2-dimethyl-5-(2-(3-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**2.1d**), 2,2-dimethyl-5-(2-(2-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**2.1e**), 5-(2-(2-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1k**), 5-(2-(3,4-dimethoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1r**), (*R*)-5-(2-([1,1'-biphenyl]-4-yl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((*R*)-**2.3a**), 2,2-dimethyl-5-(2-(4-octyloxyphenyl)hexan-2-yl)-1,3-dioxane-4,6-dione (**2.3b**), 2,2-dimethyl-5-(1-(4-octyloxyphenyl)cyclohexyl)-1,3-dioxane-4,6-dione (**2.3c**), 2,2-dimethyl-5-(3-methyl-2-(4-octyloxyphenyl)butan-2-yl)-1,3-dioxane-4,6-dione (**2.3d**), 2,2-dimethyl-5-(1-(4-octyloxyphenyl)ethyl)-1,3-dioxane-4,6-dione (**2.5a**), 5-(bis(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11a**), (*R*)-5-(2-([1,1'-biphenyl]-4-yl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((*R*)-**2.13a**), (*R*)-5-(2-(4-methoxyphenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((*R*)-**2.13b**), (*S*)-5-(1-ethyl-6-methoxyindan-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((*S*)-**2.15a**), (*S*)-5-(1-ethyl-4-methoxyindan-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((*S*)**- 2.15b**), 5-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.17a**), 5-(1-(3,4-dimethoxyphenyl)ethyl)-2,2-dimethyl-1,3-

dioxane-4,6-dione (**2.17b**), 5-(3,4-dimethoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**2.17c**).[37,46,58,59]
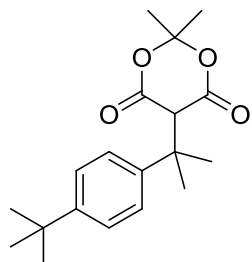
5-(2-(4-*tert*-Butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione[36] **(2.1f)**: Prepared according to General Procedure B by the dropwise addition of (4-*tert*-butylphenyl)magnesium bromide (55 mL, 55 mmol, 1.0 M in THF) to 2,2-dimethyl-5-(propan-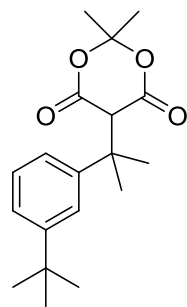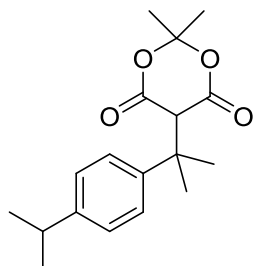2-ylidene)-1,3-dioxane-4,6-dione (5.0 g, 27.1 mmol). Recrystallization from MeOH afforded a white solid (3.02 g, 35% yield). M.p. 148-150 °C (MeOH); ^{1}H NMR (CDCl$_3$, 300 MHz) 7.33 (d, J = 8.5 Hz, 2H), 7.25 (d overlapping with CHCl$_3$, 2H), 3.48 (s, 1H), 1.67 (s, 6H), 1.57 (s, 3H), 1.27 (s, 9H), 1.05 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 164.3 (C), 149.9 (C), 140.7 (C), 125.9 (CH), 125.3 (CH), 105.3 (C), 57.7 (CH), 42.5 (C), 34.3 (C), 31.2 (CH$_3$), 29.5 (CH$_3$), 27.9 (CH$_3$), 26.9 (CH$_3$). HRMS (EI) m/z calcd for C$_{19}$H$_{26}$O$_4$ (M$^+$): 318.1831. Found: 318.1826.

5-(2-(3-*tert*-Butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione[36] **(2.1g)**: Prepared according to General Procedure B by the dropwise addition of (3-*tert*-butylphenyl)magnesium bromide (7.9 mL, 11 mmol, 1.4 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.40 g, 7.60 mmol). Recrystallization from MeOH afforded a white solid (1.05 g, 44% yield). M.p. 80-83 °C (MeOH); ^{1}H NMR (acetone-d$_6$, 300 MHz) 7.49 (s, 1H), 7.25-7.21 (m, 3H), 4.20 (s, 1H), 1.75 (s, 3H), 1.65 (s, 6H), 1.31 (s slightly overlapping with s at 1.30 ppm, 3H), 1.30 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) 164.4 (C), 151.0 (C), 143.1 (C), 128.1 (CH), 124.1 (CH), 123.6

(CH), 123.5 (CH), 105.3 (C), 57.9 (CH), 43.2 (C), 34.8 (C), 31.3 (CH$_3$), 29.7 (CH$_3$), 28.2 (CH$_3$), 27.1 (CH$_3$); HRMS (EI) *m/z* calcd for C$_{19}$H$_{26}$O$_4$ (M$^+$): 318.1831. Found: 318.1821.
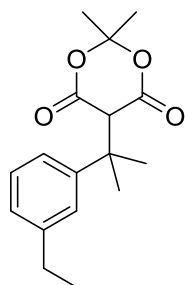

5-(2-(4-Isopropylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1h): Prepared according to General Procedure B by dropwise addition of (4-isopropylphenyl)magnesium bromide (9.0 mL, 12.6 mmol, 1.4 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.16 g, 6.30 mmol, 1 equiv). 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.
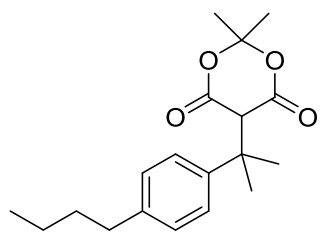
5-(2-(4-Butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1i): Prepared according to General Procedure B by dropwise addition of (4-butylphenyl)magnesium bromide (10.1 mL, 14.2 mmol, 1.4 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.3 g, 7.1 mmol, 1 equiv). Recrystallization 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 (app. 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),
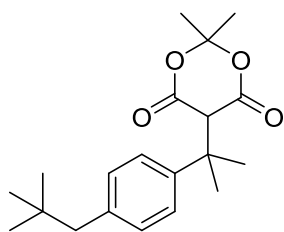
35.0 (CH$_2$), 33.5 (CH$_2$), 29.5 (CH$_3$), 27.9 (CH$_3$), 27.2 (CH$_3$), 22.3 (CH$_2$), 13.9 (CH$_3$). HRMS (EI)

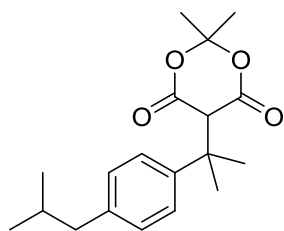*m/z* calcd for C$_{19}$H$_{26}$O$_4$ (M$^+$): 318.1831. Found: 318.1835.

5-(2-(3-Ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1j):
Prepared according to General Procedure B by dropwise addition of (3-ethylphenyl)magnesium bromide (5.5 mL, 11 mmol, 2 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.0 g, 5.5 mmol).
Purification by recrystallization from MeOH afforded the product as a white solid (584 mg, 37% yield). M.p. 60-62 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.21 (d, *J* = 7.8 Hz, 1H), 7.15-7.13 (m, 2H), 7.06 (d, *J* = 7.3 Hz, 1H) 3.54 (s, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.66 (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 164.1 (C), 144.11 (C), 144.05 (C), 128.2 (CH), 126.3 (CH), 125.8 (CH), 123.4 (CH), 105.0 (C), 57.4 (CH), 42.5 (C), 29.1 (CH$_3$), 28.9 (CH$_2$), 27.8 (CH$_3$), 27.1 (CH$_3$), 15.5 (CH$_3$). HRMS (EI) *m/z* calcd for C$_{17}$H$_{26}$O$_4$N (M + NH$_4$$^+$): 308.18563. Found: 308.18562.

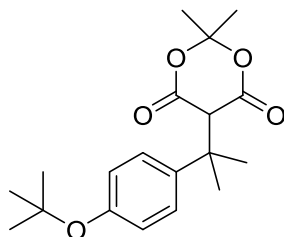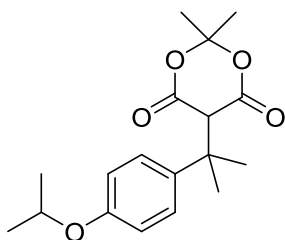**5-(2-(4-Neopentylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1l)**: Prepared according to General Procedure A by the addition of methylmagnesium bromide (7.1 mL, 14.2 mmol, 2.0 M solution in THF) via syringe pump (0.34 mL/min) to 2,2-dimethyl-5-(1-(4-neopentylphenyl)ethylidene)-1,3-dioxane-4,6-dione (1.5 g, 4.7 mmol, 1 equiv). However, the crude was subjected to the Grignard reaction two more times to reach an over 90% conversion of alkylidene Meldrum's acid. 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-Isobutylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1m): Prepared according to General Procedure B by dropwise addition of (4-isobutylphenyl)magnesium bromide (2 equiv) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.3 g, 7.1 mmol, 1 equiv) and (4-isobutylphenyl)magnesium bromide (10.1 mL, 14.2 mmol, 1.4 M in THF). 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 7.22 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *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.
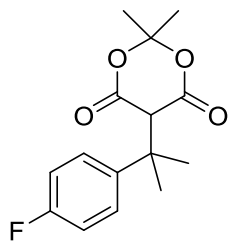
5-(2-(4-(*tert*-Butoxy)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1n): Prepared according to General Procedure A by the addition of methylmagnesium bromide (0.94 mL, 1.88 mmol, 2.0 M solution in THF) via syringe ump (0.34 mL/min) to 5-(1-(4-(*tert*-butoxy)phenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (150 mg, 0.47 mmol, 1 equiv). 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 (2.1o): 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) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.3 g, 7.1 mmol, 1 equiv). 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: 320.1620.
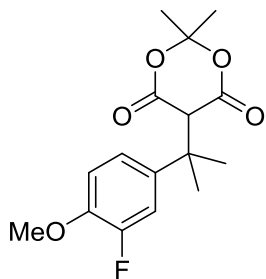
5-(2-(4-Fluorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione[36] **(2.1p)**: Prepared according to General Procedure B from 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (1.0 g, 5.4 mmol, 1 equiv) and (4-fluorophenyl)magnesium bromide (4 equiv). Recrystallization from MeOH afforded a white solid (1.0 g, 66% yield). M.p. 118-119 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.31

(m, 2H), 6.99 (t, J = 8.6 Hz, 2H), 3.56 (s, 1H), 1.64 (s, 6H), 1.62 (s, 3H), 1.33 (s, 3H); ^{13}C NMR

(CDCl$_3$, 75 MHz) δ 163.9 (C), 161.5 (d, ^1J = 244.7 Hz, C), 140.4 (d, ^4J = 3.3 Hz, C), 127.8 (d, ^3J

= 7.9 Hz, CH), 114.9 (d, ^2J = 20.9 Hz, CH), 104.9 (C), 57.4 (CH), 41.9 (C), 28.9 (CH$_3$), 27.7

(CH$_3$), 27.4 (CH$_3$). HRMS(EI) m/z calcd for C$_{15}$H$_{17}$FO$_4$ (M$^+$): 280.1111. Found: 280.1102.

5-(2-(3-Fluoro-4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1q): 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, 1 equiv).

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, ^1J = 243.6 Hz, C), 146.2 (d, ^2J = 10.6 Hz, C), 138.2 (d,

^3J = 5.3 Hz, C), 121.8 (d, ^3J = 3.2 Hz, CH), 114.3 (d, ^2J = 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.
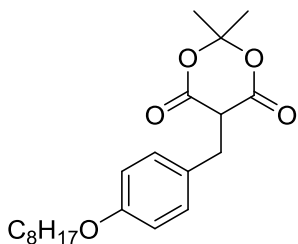
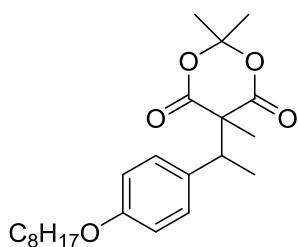**5-(4-Octyloxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.5b)**: Prepared according to literature procedure.[59] 4-n-Octyloxybenzaldehyde (15 g, 64 mmol, 1.0 equiv) and Meldrum's acid (9.69 g, 67.2 mmol, 1.05 equiv) were dissolved in EtOH (135 mL, 0.5

M) at rt. Piperidine (0.67 mL, 0.1 equiv) was added dropwise, followed by glacial acetic acid

(0.4 mL, 0.1 equiv). The reaction 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 5-6 portions. 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 (12.0 g, 52% yield). M.p. 52-53 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.22 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 3.87 (t, J = 6.5 Hz, 2H), 3.69 (t, J = 4.8 Hz, 1H), 3.40 (d, J = 4.8 Hz, 2H), 1.77-1.73 (m, 5H), 1.41 (s, 3H), 1.40-1.26 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.4 (C), 158.2 (C), 130.8 (CH), 128.8 (C), 114.5 (CH), 105.1 (CH), 67.9 (CH$_2$), 48.2 (CH), 31.7 (CH$_2$), 31.4 (CH$_2$), 29.3 (CH$_2$), 29.1 (2xCH$_2$), 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-(1-(4-octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (2.5c): Prepared according to General Procedure C from 2,2-dimethyl-5-(1-(4-octyloxyphenyl)e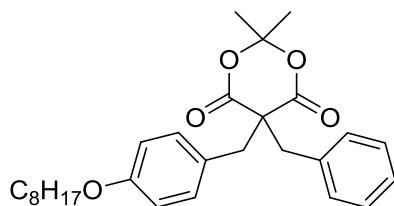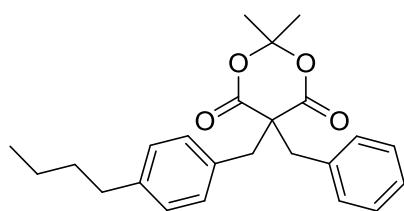thyl)-1,3-dioxane-4,6-dione (**2.5a**) (2.3 g, 6.1 mmol, 1 equiv), K$_2$CO$_3$ (1.3 g, 9.4 mmol, 1.5 equiv) and iodomethane (1.90 mL, 30.5 mmol, 5 equiv). Purification by flash column chromatography eluting with 5:1 hexanes:EtOAc afforded a clear oil (2.24 g, 94% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.05 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 3.88 (t, J = 6.6 Hz, 2H), 3.44 (q, J = 7.2 Hz, 1H), 1.72 (app. quintet, J = 6.8 Hz, 2H), 1.62 (s, 3H), 1.54-1.49 (m, 6H), 1.37 (app. quintet, J = 6.8 Hz, 2H), 1.37-1.25 (m, 8H), 1.02 (s, 3H), 0.85 (t, J = 6.2 Hz, 3H); ^{13}C NMR

(CDCl$_3$, 75 MHz) δ 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 (CH), 47.9 (CH), 31.8 (CH$_2$), 30.2 (CH$_3$), 29.3 (CH$_2$), 29.2 (2xCH$_2$), 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.
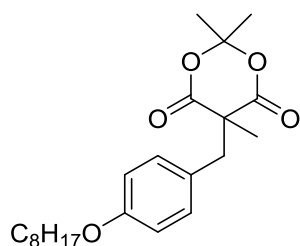
5-(4-Octyloxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (2.5d): Prepared according to General Procedure C from 2,2-dimethyl-5-(4-octyloxybenzyl)-1,3-dioxane-4,6-dione (**2.5b**) (3.0 g, 8.3 mmol, 1 equiv), K$_2$CO$_3$ (1.72 g, 12.4 mmol, 1.5 equiv) and iodomethane (1.03 mL, 16.5 mmol, 2 equiv). Recrystallization from MeOH afforded a white solid (2.55 g, 82% yield). M.p. 53-54 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.05 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.24 (s, 2H), 1.73-1.66 (m, 5H), 1.58 (s, 3H), 1.39 (app. quintet, *J* = 7.8 Hz, 2H), 1.34-1.25 (m, 8H), 0.95 (s, 3H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 169.9 (C), 158.7 (C), 131.1 (CH), 127.2 (C), 114.7 (CH), 105.2 (C), 67.9 (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$_2$), 14.1 (CH$_3$). HRMS(EI) *m/z* calcd for C$_{22}$H$_{32}$O$_5$ (M$^+$): 376.2250. Found: 376.2240.

5-(4-Octyloxybenzyl)-5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (2.7a): Prepared according to General Procedure C from 5-(4-octyloxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (700 mg, 1.93 mmol, 1 equiv), K$_2$CO$_3$ (400 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 (app. quintet, J = 6.8 Hz, 2H), 1.39 (app. 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.

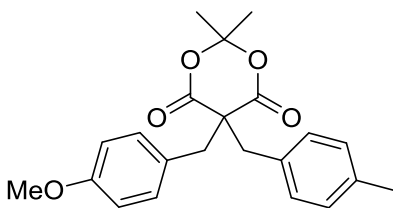**5-(4-Butylbenzyl)-5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (2.7b)**: Prepared according to General Procedure D from 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (0.52 g, 2.2 mmol, 1 equiv), Ph$_3$P (0.58 g, 2.2 mmol, 1 equiv), DIAD (0.45 mL, 2.3 mmol, 1.1 equiv) and (4-butylphenyl)methanol (0.38 g, 2.3 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, 46% 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 (app. quintet, J = 7.7 Hz, 2H), 1.24 (app. 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.
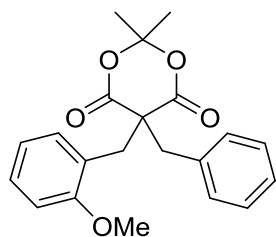
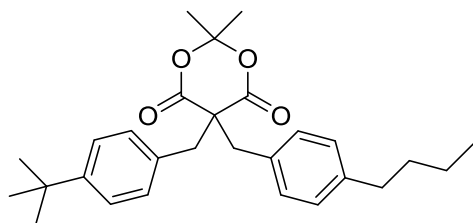**5-Benzyl-5-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione**

(2.7c): Prepared according to General Procedure C from 5-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.06 g, 4.00 mmol, 1 equiv), K_2CO_3 (0.8 g, 6.0 mmol, 1.5 equiv) and (bromomethyl)benzene (1.0 mL, 8.4 mmol, 2.1 equiv). Recrystallization from MeOH afforded a white solid (1.0 g, 71% 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-(4-Methoxybenzyl)-2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione (2.7d): Prepared according to General Procedure C from 2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione (1.13 g, 3.97 mmol, 1.0 equiv.), K_2CO_3 (830 mg, 6.0 mmol, 1.5 equiv.) and 4-methoxybenzyl chloride (0.81 mL, 6.0 mmol, 1.5 equiv.). Recrystallization from MeOH afforded a beige solid (1.28 g, 87%). M.p. °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.08 (d, J = 8.5 Hz, 2H), 7.04 (s, 4H), 6.76 (d, J = 8.5 Hz, 2H), 3.71 (s, 3H), 3.35 (s, 4H), 2.24 (s, 3H), 0.68 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 168.5, 159.2, 137.5, 131.9, 131.3, 130.0, 129.4, 127.0, 114.2, 105.8, 60.3, 55.3, 44.5, 44.2, 28.9, 28.6, 21.0; HRMS (EI) m/z calc'd for $C_{22}H_{28}O_5N$ (M + NH$_4^+$): 386.19620, found: 386.19617.
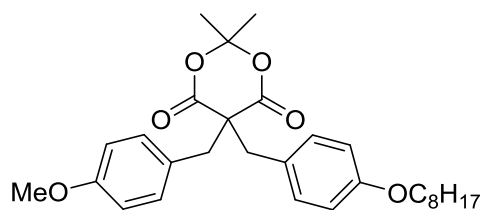
5-(4-*tert*-Butylbenzyl)-5-(4-butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.7e): Prepared according to General Procedure D from 5-(4-*tert*-butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.0 g, 3.4 mmol, 1 equiv), Ph$_3$P (0.9 g, 3.4 mmol, 1 equiv), DIAD (0.7 mL, 3.5 mmol, 1 equiv) and (4-butylphenyl)methanol (0.6 g, 3.6 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, 58% 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 (app. 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.
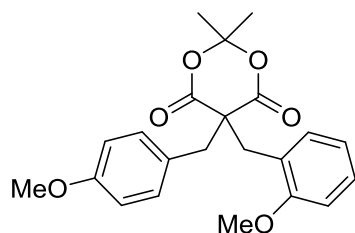

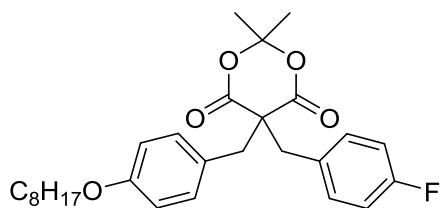**5-(4-Methoxybenzyl)-2,2-dimethyl-5-(4-octyloxybenzyl)-1,3-dioxane-4,6-dione (2.7f)**: Prepared according to General Procedure C from 5-(4-octyloxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.70 g, 1.9 mmol, 1 equiv), K$_2$CO$_3$ (0.40 g, 2.9 mmol, 1.5 equiv) and 4-methoxy benzyl chloride (0.3 mL, 2.2 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 (app. quintet, *J* = 6.6

Hz, 2H), 1.39 (app. 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 (2.7g): 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$_3$P (0.80 g, 3.0 mmol, 1 equiv), DIAD (0.6 mL, 3.0 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-(4-Octyloxybenzyl)-5-(4-fluorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.7h): Prepared according to General Procedure C from 5-(4-octyloxybenzyl)-2,2-
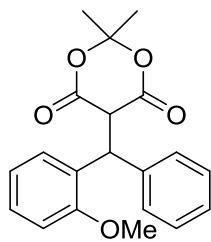
dimethyl-1,3-dioxane-4,6-dione (700 mg, 1.93 mmol, 1 equiv), K_2CO_3 (1.10 g, 7.96 mmol, 4 equiv) and 4-fluoro benzyl bromide (0.3 mL, 2.4 mmol, 1.2 equiv). Purification by flash column chromatography eluting with 20:1 hexanes:EtOAc, followed by 9:1 hexanes:EtOAc afforded a white solid (0.58 g, 63% yield). M.p. 61-63 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.18-7.13 (m 2H), 7.08 (d, J = 8.6 Hz, 2H), 6.96 (t, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 3.87 (t, J = 6.6 Hz, 2H), 3.38 (s, 2H), 3.36 (s, 2H), 1.70 (app. quintet, J = 7.6 Hz, 2H), 1.38 (app. quintet, J = 7.4 Hz, 2H), 1.34-1.26 (m, 8H), 0.85 (t, J = 7.0 Hz, 3H), 0.73 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 168.3 (C), 162.4 (d, ^1J = 246.9 Hz, C), 158.8 (C), 131.7 (d, ^3J = 8.0 Hz, CH), 131.2 (CH), 130.8 (d, ^4J = 3.3 Hz, C), 126.6 (C), 115.6 (d, ^2J = 21.3 Hz, CH), 114.9 (CH), 105.9 (C), 68.0 (CH$_2$), 60.2 (C), 44.2 (CH$_2$), 43.9 (CH$_2$), 31.8 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 29.1 (CH$_2$), 28.9 (CH$_3$), 28.7 (CH$_3$), 25.9 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$). HRMS(EI) m/z calcd for C$_{28}$H$_{35}$FO$_5$ (M$^+$): 470.2469. Found: 470.2463.

Preparation of 7-(4-methoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione:
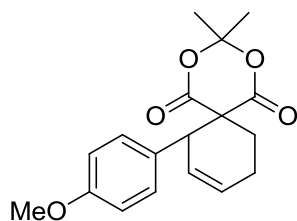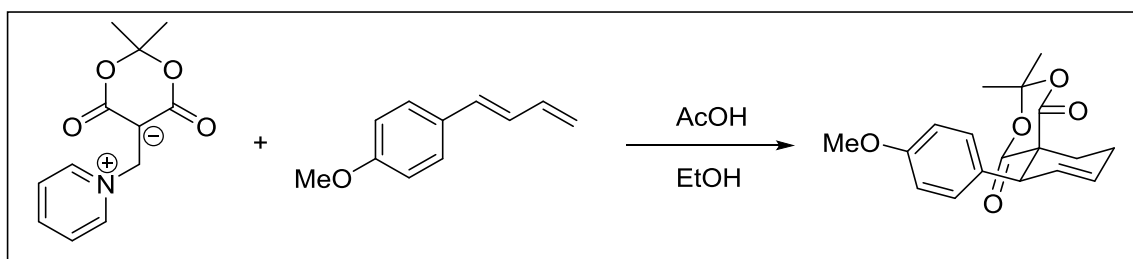
7-(4-Methoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (2.9): To a flame-dried flask under N$_2$ was charged with 1-((E)-buta-1,3-dienyl)-4-methoxybenzene[60] (0.15 g, 0.94 mmol, 1.0 equiv), dry EtOH (7 mL) and AcOH (0.05 mL). A solution of 2,2-

dimethyl-4,6-dioxo-5-(pyridin-1-ium-1-ylmethyl)-1,3-dioxan-5-ide[61] (0.22 g, 0.94 mmol, 1.0 equiv) in dry EtOH (7 mL) was added dropwise to the reaction flask and stirred at rt for 24 h. The solvent was removed by rotary evaporation. The residue was diluted with Et$_2$O, washed with water (1X) and brine (1X). The crude was purified by flash column chromatography eluting with 9:1 hexanes/EtOAc afforded a white solid (230 mg, 78% yield). M.p. 122-124 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.10 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 5.99-5.96 (m, 1H), 5.74 (dd, J_1 = 10.2, J_2 = 1.8 Hz, 1H), 4.33 (s, 1H), 3.73 (s, 3H), 2.47-2.39 (m, 2H), 2.30-2.11 (m, 2H), 1.56 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.3 (C), 165.3 (C), 159.1 (C), 131.4 (C), 130.6 (CH), 127.2 (CH), 126.9 (CH), 113.9 (CH), 104.8 (C), 55.2 (CH$_3$), 54.4 (C), 46.3 (CH), 32.1 (CH$_2$), 29.0 (CH$_3$), 28.6 (CH$_3$), 22.1 (CH$_2$). HRMS(EI) m/z calcd for C$_{18}$H$_{20}$O$_5$ (M$^+$): 316.1311. Found: 316.1316.

5-((2-Methoxyphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.11b): Prepared according to General Procedure E from 5-(2-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.2 g, 4.6 mmol, 1 equiv) and phenyl ma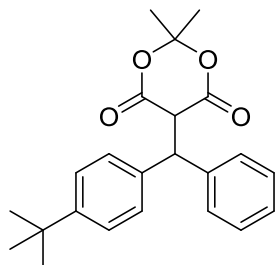gnesium bromide (2 equiv). Recrystallization from MeOH afforded a white solid (0.76 g, 49% yield). M.p. 133-134 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.40-7.17 (m, 6H), 6.87-6.83 (m, 3H), 5.44 (d, J = 2.7 Hz, 1H), 4.28 (d, J = 2.8 Hz, 1H), 3.83 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.5 (C), 164.7 (C), 156.1 (C), 140.7 (C), 130.8 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 127.9 (C), 127.1 (CH), 120.6 (CH), 109.9 (CH), 104.5 (C), 54.9 (CH$_3$), 50.4 (CH), 44.8 (CH), 28.2 (CH$_3$), 27.6 (CH$_3$). HRMS(EI) m/z calcd for C$_{20}$H$_{20}$O$_5$ (M$^+$): 340.1311. Found: 340.1319.
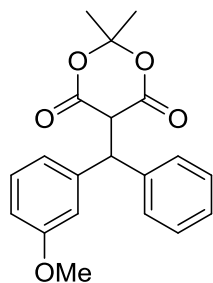
5-((3-Methoxyphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione

(2.11c): Prepared according to General Procedure E from 5-(3-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.79 g, 3.0 mmol, 1 equiv) and phenylmagnesium bromide (2 equiv). Recrystallization from MeOH afforded a white solid (224 mg, 22% yield). M.p. 97-99 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.19-7.29 (m, 6H), 6.88 (m, 2H), 6.78 (dd, J = 8.1, 2.2 Hz, 1H), 5.34 (d, J = 2.5 Hz, 1H), 4.27 (d, J = 2.5 Hz, 1H), 3.73 (s, 3H), 1.73 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 164.8 (C), 164.7 (C), 159.5 (C), 141.7 (C), 139.9 (C), 129.3 (CH), 129.2 (CH), 128.4 (CH), 127.1 (CH), 121.5 (CH), 115.4 (CH), 112.2 (CH), 105.1 (C), 55.1 (CH$_3$), 51.1 (CH), 49.0 (CH), 28.2 (CH$_3$), 27.4 (CH$_3$). HRMS(EI) m/z calcd for C$_{20}$H$_{20}$O$_5$ (M$^+$): 340.1311. Found: 340.1315.

5-((4-*tert*-Butylphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.11d): Prepared according to General Procedure E from 5-(4-*tert*-butylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.86 g, 3.0 mmol, 1 equiv) and phenylmagnesium bromide (2.3 equiv). Recrystallization from MeOH afforded a white solid (0.2 g, 18% yield). M.p. 123-125 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (m, 5H), 7.22 (m, 4H), 5.34 (d, J = 2.5 Hz, 1H), 4.27 (d, J = 2.5 Hz, 1H), 1.72 (s, 3H), 1.47 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 164.8 (C), 164.7 (C) 150.0 (C), 140.3 (C), 136.9 (C), 129.2 (CH), 128.8 (CH), 128.4 (CH), 127.1 (CH), 125.4 (CH), 105.1 (C), 51.2 (CH), 48.9 (CH), 34.4 (C), 31.3 (CH$_3$), 28.3 (CH$_3$), 27.7 (CH$_3$). HRMS(EI) m/z calcd for C$_{23}$H$_{26}$O$_4$ (M$^+$): 366.1831. Found: 366.1824.
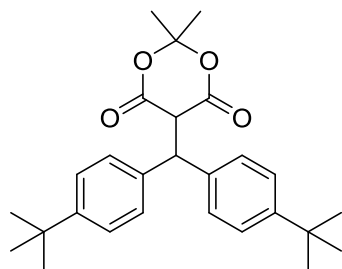
5-(Bis-(4-*tert*-butylphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.11e): Prepared according to General Procedure E from 5-(4-*tert*-butylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.86 g, 3.0 mmol, 1 equiv) and (4-*tert*-butylphenyl)magnesium bromide (2.3 equiv). Recrystallization from MeOH af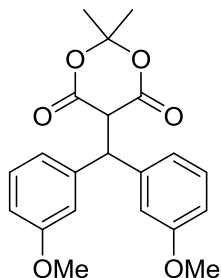forded 0.65 mg (52% yield) of a white solid. M.p. 149-152 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.34 (d, J = 8.4 Hz, 4H), 7.26 (d, J = 8.4 Hz, 4H), 5.34 (d, J = 2.6 Hz, 1H), 4.30 (d, J = 2.6 Hz, 1H), 1.75 (s, 3H), 1.48 (s, 3H), 1.33 (s, 18H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 164.9 (C), 149.8 (C), 137.1 (C), 128.8 (CH), 125.3 (CH), 105.1 (C), 51.3 (CH), 48.6 (CH), 34.4 (C), 31.3 (CH$_3$), 28.2 (CH$_3$), 27.7 (CH$_3$). HRMS(EI) *m/z* calcd for C$_{27}$H$_{34}$O$_4$ (M$^+$): 422.2457. Found: 422.2451.

5-(Bis-(3-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.11f): Prepared according to General Procedure E from 5-(3-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.52 g, 2 mmol, 1 equiv) and (3-methoxyphenyl)magnesium bromide (3 equiv). Recrystallization from MeOH 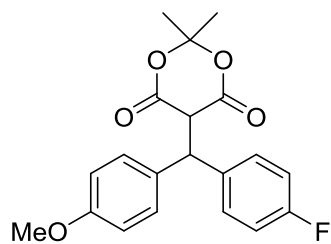afforded a white solid (175 mg, 24% yield). M.p. 94-96 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.20 (t, J = 8.0 Hz, 2H), 6.86 (m, 4H), 6.78 (dd, J = 8.0, 2.0 Hz, 2H), 5.30 (d, J = 2.4 Hz, 1H), 4.28 (d, J = 2.4 Hz, 1H), 3.73 (s, 6H), 1.72 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 164.7 (C), 159.5 (C), 141.5 (C), 129.3 (CH), 121.4 (CH), 115.3 (CH), 112.3 (CH), 105.1 (C), 55.1 (CH$_3$), 51.2 (CH), 49.0 (CH), 28.2 (CH$_3$), 27.5 (CH$_3$). HRMS(EI) *m/z* calcd for C$_{21}$H$_{22}$O$_6$ (M$^+$): 370.1416. Found: 370.1418.

5-((4-Fluorophenyl)(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[62] **(2.11g)**: Prepared according to General Procedure E from 5-(4-fluorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.60 g, 2.4 mmol, 1 equiv) and (4-methoxyphenyl)magnesium bromide (3 equiv). Purification by flash column chromatography eluting with 4:1 hexanes/EtOAc, followed by 1:1 hexanes:EtOAc, then recrystallized from MeOH to afford a light yellow solid (154 mg, 18% yield). M.p. 148-150 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28-7.23 (m, 2H), 7.19 (d, J = 8.7 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.30 (bs, 1H), 4.27 (d, J = 2.7 Hz, 1H), 3.76 (s, 3H), 1.72 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 164.6 (2xC), 161.6 (d, ^1J = 245.9 Hz, C), 158.6 (C), 136.1 (d, ^4J = 3.3 Hz, C), 131.7 (C), 130.7 (d, ^3J = 8.0 Hz, CH), 130.2 (CH), 115.0 (d, ^2J = 21.2 Hz, CH), 113.7 (CH), 105.0 (C), 55.1 (CH$_3$), 51.2 (CH), 47.6 (CH), 28.1 (CH$_3$), 27.4 (CH$_3$). HRMS(EI) m/z calcd for C$_{20}$H$_{19}$FO$_5$ (M$^+$): 358.1217. Found: 358.1206.
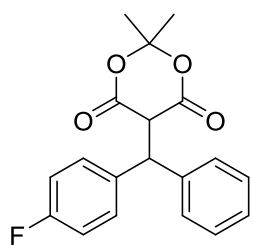
5-((4-Fluorophenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[62] **(2.11h)**: Prepared according to General Procedure E from 5-(4-fluorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.75 g, 3.0 mmol, 1 equiv) and phenylmagnesium chloride (2.3 equiv). Recrystallization from MeOH afforded a white solid in (0.31 g, 32% yield). M.p. 124-127 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.35-7.29 (m, 7H), 7.01 (t, J = 8.6 Hz, 2H), 5.41 (d, J = 2.4 Hz, 1H), 4.30 (d, J = 2.4 Hz, 1H), 1.79 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 164.7 (C), 164.5 (C), 161.7 (d, ^1J = 245 Hz, C), 139.9 (C), 135.8 (d, ^4J = 3.6 Hz, C), 131.0 (d, ^3J = 8.1 Hz, CH), 129.0 (CH), 128.5 (CH), 127.3 (CH), 115.2 (d, ^2J = 21.1 Hz, CH), 105.2 (C), 51.2 (CH), 48.3 (CH), 28.3

(CH$_3$), 27.6 (CH$_3$); ^{19}F NMR (CDCl$_3$, 282 MHz) δ -115; HRMS(EI) *m/z* calcd for C$_{19}$H$_{17}$FO$_4$ (M$^+$): 328.1111. Found: 328.1112.
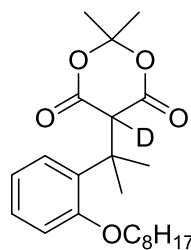
2,2-Dimethyl-5-(2-(2-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione-5-*d* (***d*-2.1e**): Prepared by dissolving 2,2-dimethyl-5-(2-(2-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**2.1e**) (1.0 g, 2.6 mmol, 1.0 equiv.) in CH$_3$OD (13 mL) then adding K$_2$CO$_3$ (18 mg, 0.13 mmol, 5 mol%) and DMF (0.64 mL). The suspension was stirred at rt for 18 h before being poured into D$_2$SO$_4$/D$_2$O (1 mL/13 mL). The aquoues layer was extracted 3x with CH$_2$Cl$_2$ and the combined organic layers were dried with MgSO$_4$, filtered and concentrated by rotary evaporation. A white solid was obtained after recrystallization from CH$_3$OD (570 mg, 57%, 94% D-incorporation). M.p. 50-51 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.33 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 2H), 1.96-1.74 (m, 5H), 1.69 (s, 3H), 1.64 (s, 6H), 1.45-1.41 (m, 2H), 1.41-1.20 (m, 8H), 0.89-0.82 (m, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 164.1 (C), 156.0 (C), 134.9 (C), 127.6 (CH), 127.2 (CH), 120.8 (CH), 112.0 (CH), 103.7, 68.1 (CH$_2$), 52.5 (CD, "t", *J* = 19.1 Hz), 40.3 (C), 31.7 (CH$_2$), 29.5 (CH$_2$), 29.2 (CH$_2$), 29.1 (CH$_2$), 28.5 (CH$_3$), 26.8 (CH$_3$), 26.2 (CH$_2$), 25.0 (CH$_3$), 22.6 (CH$_2$), 14.0 (CH$_3$).
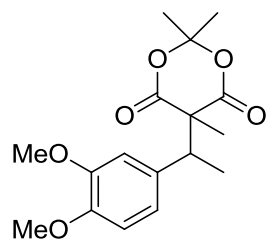
5-(1-(3,4-dimethoxyphenyl)ethyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (2.17d): Prepared according to General Procedure C from 5-(1-(3,4-dimethoxyphenyl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**15b**) (700 mg, 2.3 mmol, 1.0 equiv.), K$_2$CO$_3$ (500 mg, 3.6 mmol, 1.6 equiv.) and iodomethane (0.70 mL, 11 mmol, 4.9 equiv.). Purification by flash chromatography eluting with

3:1 hexanes–EtOAc afforded 638 mg (86 % yield) of a white solid. M. p. 69-71 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.77-6.67 (m, 3H), 3.83-3.82 (two overlapping singlets, 6H), 3.45 (q, J = 7.3 Hz, 1H), 1.64 (s, 3H), 1.55-1.53 (m, 6H), 1.03 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 170.5 (C), 168.8 (C), 148.7 (C), 148.4 (C), 132.9 (C), 120.7 (CH), 111.5 (CH), 110.9 (CH), 104.8 (C), 55.8 (CH$_3$), 54.3 (C), 48.2 (CH), 30.0 (CH$_3$), 27.5 (CH$_3$), 22.3 (CH$_3$), 15.4 (CH$_3$); HRMS(EI) m/z calcd for C$_{17}$H$_{22}$O$_6$ (M$^+$): 322.14164. Found: 322.14107.

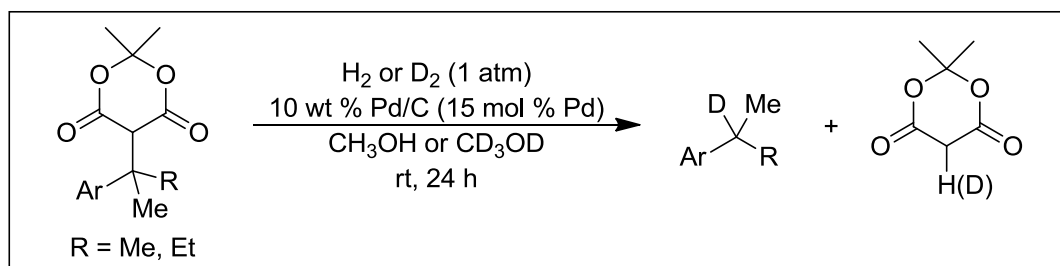## 2.10i General Procedure G – Hydrogenolysis of Benzyl Meldrum's Acids
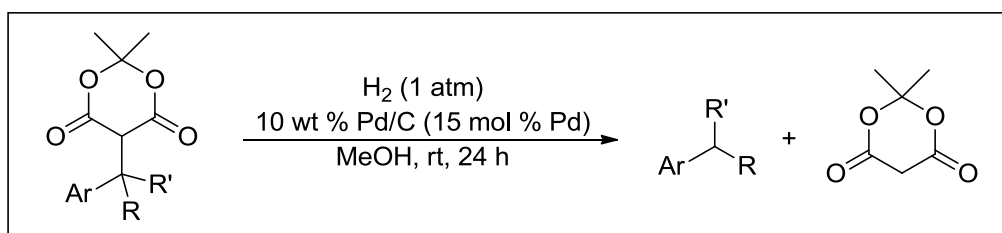
The reactions were carried out using 0.1-0.5 mmol of substrate. MeOH (ACS grade) was degassed with vacuum and then refilled with nitrogen (3X). To a 20 mL vial was added benzyl Meldrum's acid and 10% Pd/C (15 mol % Pd). MeOH was added slowly to the vial through a septum via a syringe under nitrogen. The vial was degassed with vacuum and then refilled with H$_2$ balloon (3X). The reaction was stirred under an atmosphere of hydrogen (balloon) for 24 h then filtered through a pad of celite and washed with CH$_2$Cl$_2$. Due to the low boiling points of some of the products, the solvent was removed under reduced pressure at 0 °C. The crude material was purified by flash chromatography or washed with a saturated sodium bicarbonate solution and was extracted with CH$_2$Cl$_2$ (3X). The combined organic layers were washed with brine (1X), dried over MgSO$_4$ and concentrated under reduced pressure at 0 °C.

2.10j General Procedure H – Hydrogenolysis of Benzyl Meldrum's Acids
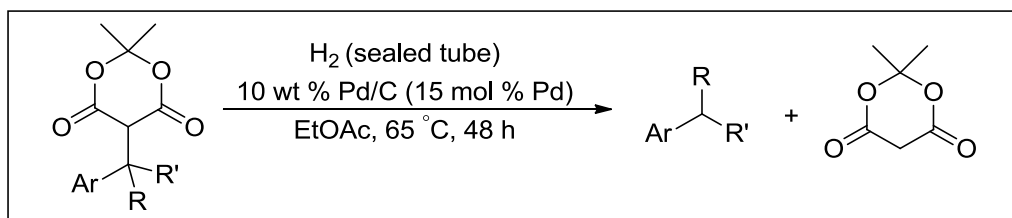
The reactions were carried out using 0.1-0.5 mmol of substrate. EtOAc (ACS grade) was degassed with vacuum and then refilled with nitrogen (3X). To a Schlenk tube was added benzyl Meldrum's acid and 10% Pd/C (15 mol % Pd). EtOAc (0.1 M relative to benzyl Meldrum's acid) was added to the Schlenk tube through a septum via a syringe. The suspension was degassed with vacuum and then refilled with H_2 gas (3X) with the help of balloon. The tube was sealed and the suspension was stirred at 65 °C in an oil bath for 24 h. The mixture was filtered through a pad of celite, rinsing 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. The product was dried under reduced pressure at 0 °C.


2.10k General Procedure I – Deuterium Labeling Studies

The reactions were carried out using 0.1-0.2 mmol of substrate. To a 5 mL flask was added benzyl Meldrum's acid and 10% Pd/C (15 mol % Pd). CH_3OH or CD_3OD (0.1 M relative to benzyl Meldrum's acid) was added slowly to the flask through a septum via a syringe under nitrogen. The vial was degassed with vacuum and then refilled with H_2 or D_2 balloon (3x) before

being stirred for 24 h. The reaction was 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 product was purified by flash chromatography. The product was dried under reduced pressure at 0 °C. The amount of deuterium incorporation was determined using ^{1}H NMR and ^{2}H NMR.

2.10l General Procedure J – Benzylic Hydrogen Exchange
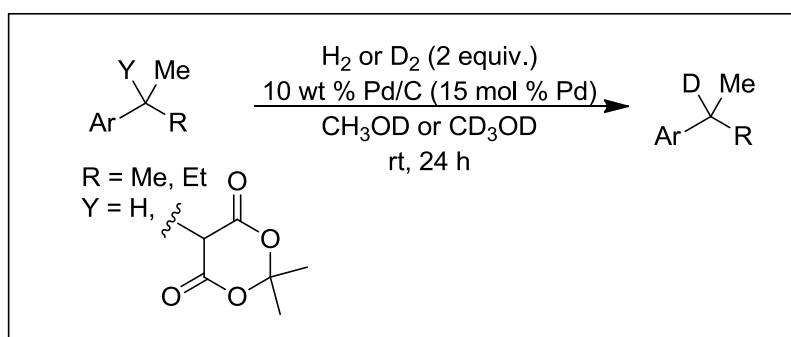
The reactions were carried out using 0.5 mmol of substrate. To a 30 mL Shlenk tube was added benzyl Meldrum's acid and 10% Pd/C (15 mol % Pd) followed by CH_3OH or CD_3OD (5.0 mL, added rapidly from freshly opened ampoules). The tube was degassed with vacuum and refilled with H_2 or D_2 (3x) before the tube was sealed and allowed to stir for 24 h. The volume of gas was assumed equal to the Shlenk volume less the solvent volume (25 mL @ 1 atm, 298 K = 1.0 mmol, 2.0 equiv.). The mixture was filtered through a pad of celite with Et_2O and concentrated under reduced pressure at 0 °C. The product was purified by flash chromatography and dried under reduced pressure at 0 °C. The amount of deuterium incorporation was determined by ^{1}H NMR.

2.10m Product Specific Information

The following products were previously known and the spectral data obtained were in agreement with those reported; consequently, data will not be repeated here: 4-isopropyl-1,1'-biphenyl (**2.2b**), 1-isopropyl-4-octyloxybenzene (**2.2c**), 1-isopropyl-2-octyloxybenzene (**2.2e**), (*S*)-1-*sec*-butyl-4-octyloxybenzene ((*S*)-**2.4a**), 1-(hexan-2-yl)-4-octyloxybenzene (**2.4b**), 1-cyclohexyl-4-octyloxybenzene (**2.4c**), 1-(3-methylbutan-2-yl)-4-octyloxybenzene (**2.4d**), bis(4-methoxyphenyl)methane (**2.12a**), (*S*)-4-*sec*-butyl-1,1'-biphenyl ((*S*)-**2.14a**), and (*S*)-1-*sec*-butyl-4-methoxybenzene ((*S*)-**2.14b**).[37]
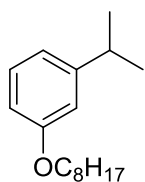
1-Isopropyl-3-octyloxybenzene (2.2d): Prepared according to General Procedure H from 2,2-dimethyl-5-(2-(3-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**2.1d**) (0.10 g, 0.26 mmol) and 10% Pd/C (41 mg, 0.038 mmol, 15 mol% Pd). Purification by flash column chromatography eluting with 100% pentane, followed by 9:1 hexanes:EtOAc afforded a clear oil (46.5 mg, 73% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.20 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H), 6.72 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.88 (septet, *J* = 6.9 Hz, 1H), 1.79 (app. quintet, *J* = 7.8 Hz, 2H), 1.47 (app. quintet, *J* = 7.6 Hz, 2H), 1.33-1.30 (m, 8H), 1.25 (d, *J* = 6.9 Hz, 6H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 159.2 (C), 150.5 (C), 129.2 (CH), 118.7 (CH), 113.0 (CH), 111.2 (CH), 67.8 (CH$_2$), 34.2 (CH), 31.8 (CH$_2$), 29.4 (2xCH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 23.9 (CH$_3$), 22.7 (CH$_2$), 14.1 (CH$_3$). GC/MS *m/z* calcd for C$_{17}$H$_{28}$O (M$^+$): 248. Found: 248.
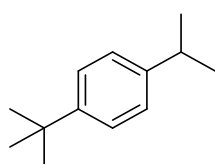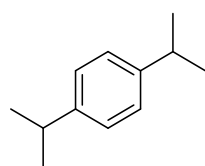
1-*tert*-Butyl-4-isopropylbenzene[63] (**2.2f**): Prepared according to General Procedure E from 5-(2-(4-*tert*-butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-

dioxane-4,6-dione (**2.1f**)[118] (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 % pentane 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 m/z calcd for C$_{13}$H$_{20}$ (M$^+$): 176.2. Found (LRMS): 176.1.
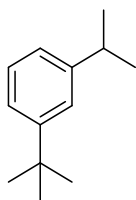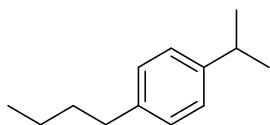
1-*tert*-Butyl-3-isopropylbenzene (2.2g): Prepared according to General Procedure F from 5-(2-(3-*tert*-butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1g**) (96.3 mg, 0.302 mmol) and 10% Pd/C (53 mg, 0.06 mmol, 20 mol % Pd). Purification by flash column chromatography eluting with 100% 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 m/z calcd for C$_{13}$H$_{20}$ (M$^+$): 176.2. Found (LRMS): 176.2.
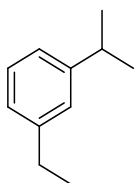
1,4-Diisopropylbenzene (2.2h): Prepared according to General Procedure F from 5-(2-(4-isopropylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1h**) (96.4 mg, 0.317 mmol) 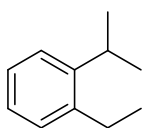and 10% Pd/C (67.5 mg, 0.0634 mmol, 20 mol % Pd). Purification by flash column chromatography eluting with 100 % pentane afforded a clear oil (47 mg, 91% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.15 (s, 4H), 2.87 (septet, J = 6.9 Hz, 2H), 1.23 (d, J = 6.9 Hz, 12H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 146.2 (C), 126.3 (CH), 33.6 (CH), 24.0 (CH$_3$). GC/MS m/z calcd for C$_{12}$H$_{18}$ (M$^+$): 162.1. Found (LRMS): 162.1.

1-Butyl-4-isopropylbenzene[64] (**2.2i**): 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) (**2.1i**) and 10% Pd/C (51 mg, 0.048 mmol, 15 mol % Pd). Purification by flash column chromatography eluting 100 % pentane 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 m/z calcd for C$_{13}$H$_{20}$ (M$^+$): 176.2. Found (LRMS): 176.1.
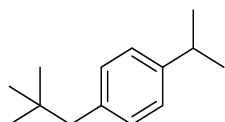
1-Ethyl-3-isopropylbenzene (**2.2j**): Prepared according to General Procedure E from 5-(2-(3-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1j**) (101mg, 0.348 mmol) and 10% Pd/C (55.6 mg, 0.0522 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with pentane afforded 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 m/z calcd for C$_{13}$H$_{20}$O (M+): 148.1. Found (LRMS): 148.1
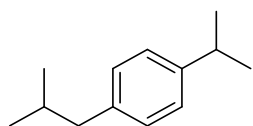
1-Ethyl-2-isopropylbenzene[65] (**2.2k**): Prepared according to General Procedure E from 5-(2-(2-ethylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1k**) (101 mg, 0.348 mmol) and 10% Pd/C (55.6 mg, 0.0522 mmol, 15 mol % Pd). Purification by

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 m/z calcd for C$_{11}$H$_{16}$ (M$^+$): 148.1. Found (LRMS): 148.1

**1-Isopropyl-4-neopentylbenzene (2.2l)**: Prepared according to General Procedure E from 5-(2-(4-neopentylphenyl)propan-2-yl)-2,2-dimethy-1,3-dioxane-4,6-dione (**2.1l**) (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 m/z calcd for C$_{14}$H$_{22}$ (M$^+$): 190.2. Found (LRMS): 190.1.

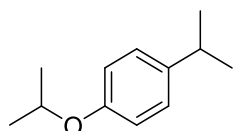**1-Isobutyl-4-isopropylbenzene**[66] **(2.2m)**: Prepared according to General Procedure E from 5-(2-(4-isobutylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1m**) (106 mg, 0.333 mmol) and 10% Pd/C (53 mg, 0.05 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 100 % pentane 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 m/z calcd for C$_{13}$H$_{20}$ (M$^+$): 176.2. Found (LRMS): 176.1
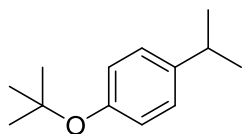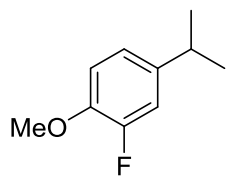
1-*tert*-Butoxy-4-isopropylbenzene[67] (**2.2n**): Prepared according to General Procedure F from 5-(2-(4-(*tert*-butoxy)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1n**) (103 mg, 0.308 mmol). 10% Pd/C (49.2 mg, 0.0462 mmol, 15 mol % Pd). Purification by flash column chromatography eluting 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 m/z calcd for C$_{13}$H$_{20}$O (M+): 192.2. Found: 192.2

1-Isopropoxy-4-isopropylbenzene[68] (**2.2o**): Prepared according to General Procedure F from 5-(2-(4-isopropoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1o**) (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 % pentane afforded a colorless oil (45 mg, 82% yield). ^{1}H 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 m/z calc'd for C$_{12}$H$_{18}$O (M$^+$): 178.1. Found (LRMS): 178.1.

2-Fluoro-4-isopropyl-1-methoxybenzene (2.2q): Prepared according to general procedure H from 5-(2-(3-fluoro-4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1q**) (120 mg, 0.387 mmol). 10% Pd/C (206 mg, 0.193 mmol, 50 mol% Pd) was used instead of 15 mol % Pd. Purification by flash column chromatography eluting with 5:1 hexanes:CH_2Cl_2 afforded a clear oil (39 mg, 60% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.96-6.83 (m, 3H), 3.85 (s, 3H), 2.81 (septet, J = 6.9 Hz, 1H), 1.20 (d, J = 6.9 Hz, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 152.3 (d, [1]J = 243.2 Hz, C), 145.4 (d, [2]J = 10.9 Hz, C), 142.2 (d, [3]J = 5.5 Hz, C), 121.7 (d, [3]J = 3.3 Hz, CH), 114.0 (d, [2]J = 17.9 Hz, CH), 113.4 (d, [4]J = 1.7 Hz, CH), 56.4 (CH$_3$), 33.2 (CH), 23.9 (CH$_3$). GC/MS m/z calc'd for $C_{10}H_{13}FO$ (M$^+$): 168. Found: 168.
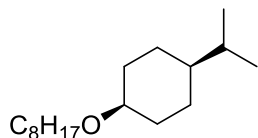
***cis*-1-Isopropyl-4-octyloxycyclohexane (*cis*-2.2c')**: Prepared by adding *cis*-4-isopropylcyclohexanol[69] (100 mg, 0.70 mmol, 1.0 equiv.) to a stirring suspension of NaH (42 mg, 1.1 mmol, 1.5 equiv.) in anhydrous DMF (3.5 mL) followed by 1-bromooctane (0.18 mL, 1.1 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 24 h before cooling to 0 °C and carefully adding 5% HCl. The solution was extracted 3 times with Et$_2$O and the combined organic layers were washed twice with brine, dried over MgSO$_4$, filtered and concentrated by rotary evaporation at 0 °C. Purification by flash chromatography eluting with pentane afforded the product as a pale yellow oil (104 mg, 58% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.46 (bs, 1H), 3.34 (t, J = 6.6 Hz, 2H), 1.84 (app. quintet, J = 4.3 Hz, 2H), 1.53 (app. quintet, J = 6.9 Hz, 2H), 1.46-1.19 (m, 17H), 1.04-0.96 (m, 1H), 0.88-0.82 (m, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 73.5 (CH), 67.6 (CH$_2$), 43.4 (CH), 32.1 (CH), 31.9 (CH$_2$), 30.2

(CH$_2$), 29.9 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 26.3 (CH$_2$), 24.1 (CH$_2$), 22.7 (CH$_2$), 19.9 (CH$_3$), 14.1 (CH$_3$). GC/MS m/z calcd for C$_{17}$H$_{34}$O (M$^+$): 254. Found: 254.
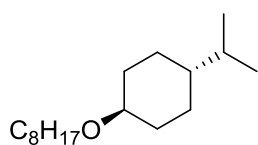
**$trans$-1-Isopropyl-4-octyloxycyclohexane ($trans$-2.2c')**: Prepared from $trans$-4-isopropylcyclohexanol[69] (100 mg, 0.70 mmol, 1.0 equiv.) following the above procedure for the cis isomer. Purification by flash chromatography eluting with pentane afforded the product as a pale yellow oil (112 mg, 63% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.41(t, J = 6.8 Hz, 2H), 3.09 (tt, J =10.8, 4.2 Hz, 1H), 2.02 (d, J = 11.4 Hz, 2H), 1.72 (d, J = 9.4 Hz, 2H), 1.55-1.48 (m, 1H), 1.44-1.09 (m, 14H), 1.02-0.92 (m, 3H), 0.85 (m, 3H), 0.83 (d, J = 6.8 Hz, 6H) ; ^{13}C NMR (CDCl$_3$, 75 MHz) δ 78.4 (CH), 68.1 (CH$_2$), 43.4 (CH), 32.5 (CH), 32.5 (CH$_2$), 31.8 (CH$_2$), 30.2 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 28.0 (CH$_2$), 26.2 (CH$_2$), 22.7 (CH$_2$), 19.9 (CH$_3$), 14.1 (CH$_3$). GC/MS calcd for C$_{17}$H$_{34}$O (M$^+$): 254. Found: 254.
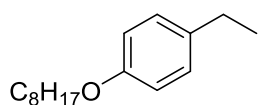
**1-Ethyl-4-octyloxybenzene (2.6a)**: Prepared according to General Procedure F from 2,2,5-trimethyl-5-(1-(4-octyloxyphenyl)ethyl)-1,3-dioxane-4,6-dione (**2.5c**) (95.5 mg, 0.245 mmol) and 10% Pd/C (39 mg, 0.037 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with hexanes, followed by 5:1 hexanes:CH$_2$Cl$_2$ afforded a clear oil (54 mg, 94% yield). ^{1}H 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 (app. quintet, J = 7.6 Hz, 2H), 1.45 (app. 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$^+$): 234.2 Found (LRMS): 234.2.
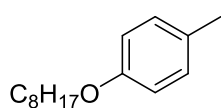
1-Methyl-4-octyloxybenzene[70] **(2.6b)**: Prepared according to General Procedure F from 5-(4-octyloxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**2.5d**) (100 mg, 0.266 mmol) and 10% Pd/C (43 mg, 0.040 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 5:1 hexanes:CH$_2$Cl$_2$ 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 (app. quintet, J = 6.8 Hz, 2H), 1.44 (app. 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$^+$): 220.2. Found (LRMS): 220.
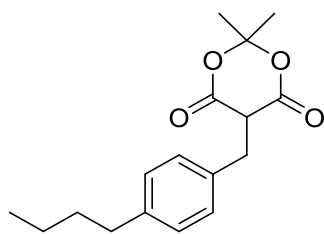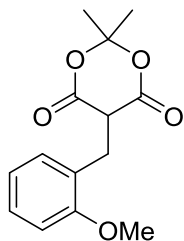
5-(4-Butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **(2.8a)**: Prepared according to General Procedure F from 5-(4-butylbenzyl)-5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.7b**) (98.1 mg, 0.258 mmol) and 10% Pd/C (42 mg, 0.039 mmol, 15 mol % Pd). Purification by flash column chromatography eluting 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 (app. 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.

5-(2-Methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[71] (**2.8b**): Prepared according to General Procedure H from 5-benzyl-5-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.7c**) (36 mg, 0.10 mmol). 10% Pd/C (53 mg, 0.050 mmol, 50 mol % Pd) was used instead of 15 mol % Pd. Purification by flash column chromatography eluting with 9:1 hexanes:EtOAc afforded white solid (23 mg, 87% 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.
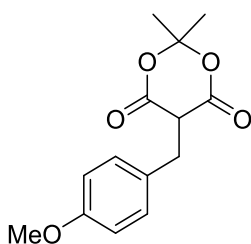
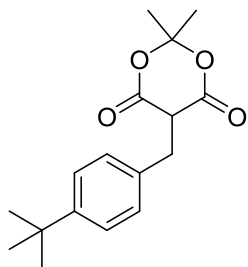**5-(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione**[71] (**2.8c**): Prepared according to General Procedure H from 5-(4-methoxybenzyl)-2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione (**2.7d**) (100 mg, 0.28 mmol, 1.0 equiv.) and Pd/C (43 mg, 0.041 mmol, 15 mol%). Purified by flash chromatography eluting with 9:1 hexanes/EtOAc to afford a white solid (31 mg, 46% yield). M.p. 72-73 °C; ^{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.
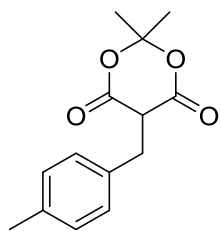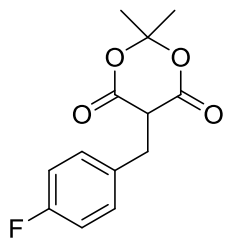
2,2-Dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione[71] **(2.8d)**: Compound **2.8d** was isolated as a white solid from the above reaction (4.1 mg, 6% yield). M.p. 116-117 ºC; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.22 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 3.77 (t, J = 4.9 Hz, 1H), 3.46 (d, J = 4.9 Hz, 2H), 2.32 (s, 3H), 1.74 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.3, 136.7, 134.1, 129.5, 129.2, 105.1, 48.1, 31.7, 28.3, 27.1, 20.9; HRMS (EI) m/z calcd for C$_{14}$H$_{17}$O$_4$ (M + H$^+$): 249.11214. found 249.11241.

5-(4-*tert*-Butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[72] **(2.8e)**: Prepared according to General Procedure F from 5-(4-*tert*-butylbenzyl)-5-(4-butylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.7e**) (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.
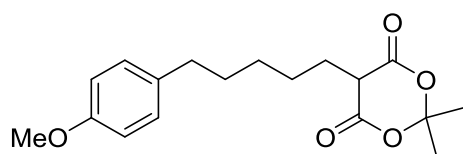
5-(4-Fluorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[71] (**2.8f**): Prepared according to General Procedure G from 5-(4-octyloxybenzyl)-5-(4-fluorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.7h**) (0.15 g, 0.32 mmol). 10% Pd/C (0.17 g, 0.16 mmol, 50 mol % Pd) was used instead of 15 mol % Pd/C. Purification by flash column chromatography eluting with 9:1 hexanes/EtOAc, followed by 3:1 hexanes:EtOAc afforded a white solid (63 mg, 78% yield). M.p. 96-98 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29-7.24 (m, 2H), 6.96-6.90 (m, 2H), 3.73 (t, J = 4.9 Hz, 1H), 3.43 (d, J = 4.9 Hz, 2H), 1.71 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.1 (C), 161.9 (d, ^1J = 244.3 Hz, C), 132.7 (d, ^4J = 3.2 Hz, C), 131.5 (d, ^3J = 7.9 Hz, CH), 115.3 (d, ^2J = 21.2 Hz, CH), 105.2 (C), 48.1 (CH), 31.2 (CH$_2$), 28.3 (CH$_3$), 27.1 (CH$_3$). HRMS(EI) *m/z* calcd for C$_{13}$H$_{13}$FO$_4$ (M$^+$): 252.0798. Found: 252.0806.
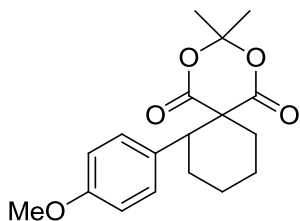
7-(4-Methoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undecane-1,5-dione (2.10a): Prepared according to General Procedure G from 7-(4-methoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (**2.8**) (50 mg, 0.16 mmol) and 10% Pd/C (25 mg, 0.024 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with 5:1 hexanes/EtOAc afforded a white solid (6.5 mg, 13% yield). M.p. 86-88 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.12 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 3.73 (s, 3H), 3.39 (dd, J = 13.2, 3.8 Hz, 1H), 2.57 (dq, J = 13.2, 3.6 Hz, 1H), 2.18-2.09 (m, 2H), 1.99-1.93 (m, 2H), 1.75-1.66 (m, 2H), 1.65-1.50 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.4 (C), 167.4 (C), 158.9 (C), 133.1 (C), 129.9 (CH), 113.9 (CH), 104.8 (C), 55.6 (CH$_3$), 55.2 (C), 47.9 (CH), 35.8 (CH$_2$), 29.1 (CH$_3$),

28.4 (CH$_3$), 27.1 (CH$_2$), 25.3 (CH$_2$), 20.4 (CH$_2$). HRMS(EI) *m/z* calcd for C$_{18}$H$_{22}$O$_5$ (M$^+$): 318.1467. Found: 318.1463.
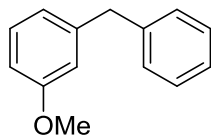
5-(5-(4-Methoxyphenyl)pentyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.10b): Isolated as a second product to elute from the above column and isolated as a white solid (39 mg, 77% yield). M.p. 69-71 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.06 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 3H), 3.46 (t, *J* = 5.0 Hz, 1H), 2.52 (t, *J* = 7.4 Hz, 2H), 2.07 (app. quintet, *J* = 5.3 Hz, 2H), 1.75 (s, 3H), 1.73 (s, 3H), 1.56 (app. quintet, *J* = 7.4 Hz, 2H), 1.49-1.30 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.6 (C), 157.6 (C), 134.5 (C), 129.2 (CH), 113.6 (CH), 104.7 (C), 55.2 (CH$_3$), 46.0 (CH), 34.7 (CH$_2$), 31.2 (CH$_2$), 28.9 (CH$_2$), 28.4 (CH$_3$), 26.9 (CH$_3$), 26.5 (CH$_2$), 26.2 (CH$_2$). HRMS(EI) *m/z* calcd for C$_{18}$H$_{24}$O$_5$ (M$^+$): 320.1624. Found: 320.1624.
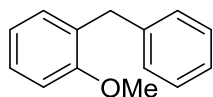
1-Methoxy-2-benzylbenzene[73] **(2.12b)**: Prepared according to General Procedure G from 5-((2-methoxyphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11b**) (102 mg, 0.30 mmol) and 10% Pd/C (48 mg, 0.045 mmol, 15 mol % Pd). The crude material was washed with a saturated sodium bicarbonate solution and was extracted with CH$_2$Cl$_2$ (3X). The combined organic layers were washed with brine (1X), dried over MgSO$_4$, filtered and concentrated to afford a clear oil (59 mg, 98% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29-7.19 (m, 6H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.90 (m, 2H), 4.01 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 157.4 (C), 141.0 (C), 130.3 (CH), 129.7 (C), 129.0 (CH), 128.3 (CH), 127.4 (CH), 125.6 (CH), 120.5 (CH), 110.4 (CH), 55.4 (CH$_3$), 35.9 (CH$_2$). HRMS(EI) *m/z* calcd for C$_{14}$H$_{14}$O (M$^+$): 198.1045. Found: 198.1040.
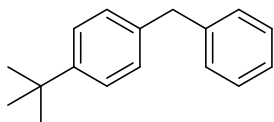
1-Methoxy-3-benzylbenzene[74] (**2.12c**): Prepared according to General Procedure G from 5-((3-methoxyphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11c**) (34 mg, 0.10 mmol) and 10% Pd/C (16 mg, 0.015 mmol, 15 mol % Pd). The crude material was washed with a saturated sodium bicarbonate solution and was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to afford a clear oil (19 mg, 95% yield). ^1H NMR (CDCl$_3$, 300 MHz) δ 7.28 (m, 3H), 7.21 (m, 3H), 6.82-6.76 (m, 3H), 3.96 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 159.6 (C), 142.6 (C), 140.8 (C), 129.3 (CH), 128.8 (CH), 128.4 (CH), 126.0 (CH), 121.3 (CH), 114.7 (CH), 111.2 (CH), 55.1 (CH$_3$), 41.9 (CH$_2$). HRMS(EI) m/z calcd for $C_{14}H_{14}O$ (M$^+$): 198.1045. Found: 198.1048.

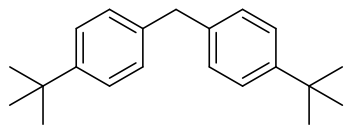**1-*tert*-Butyl-4-benzylbenzene**[75] (**2.12d**): Prepared according to General Procedure G from 5-((4-*tert*-butylphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11d**) (105 mg, 0.287 mmol) and 10% Pd/C (46 mg, 0.043 mmol, 15 mol % Pd). The crude material was washed with a saturated sodium bicarbonate solution and was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to afford a clear oil (62 mg, 96% yield). ^1H NMR (CDCl$_3$, 300 MHz) δ 7.28 (t, J = 8.5 Hz, 4H), 7.19 (d, J = 7.2 Hz, 3H), 7.11 (d, J = 8.1 Hz, 2H), 3.95 (s, 2H), 1.30 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 148.8 (C), 141.2 (C), 138.0 (C), 128.9 (CH), 128.44 (CH), 128.37 (CH), 125.9 (CH), 125.3 (CH), 41.4 (CH$_2$), 34.3 (C), 31.3 (CH$_3$). HRMS(EI) m/z calcd for $C_{17}H_{20}$ (M$^+$): 224.1565. Found: 224.1564.

Bis-(4-*tert*-butylphenyl)methane[76] (**2.12e**): Prepared according to General Procedure G from 5-(bis-(4-*tert*-phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11e**) (211 mg, 0.50 mmol) and 10% Pd/C (80 mg, 0.075 mmol, 15 mol % Pd). The crude material was washed with a saturated sodium bicarbonate solution and was extracted with CH_2Cl_2 (3X). The combi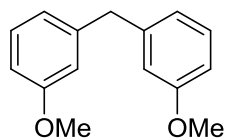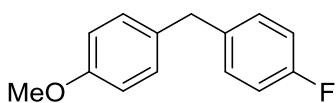ned organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to afford a white solid (139 mg, 99% yield). M.p. 68-69 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) 7.43 (d, J = 8.1 Hz, 4H), 7.26 (d, J = 8.1 Hz, 4H), 4.05 (s, 2H), 1.43 (s, 18H); ^{13}C NMR (CDCl$_3$, 125 MHz) 148.8 (C), 138.4 (C), 128.7 (CH), 125.4 (CH), 41.0 (CH$_2$), 34.5 (C), 31.5 (CH$_3$). HRMS(EI) *m/z* calcd for $C_{21}H_{28}$ (M$^+$): 280.2191. Found: 280.2183.
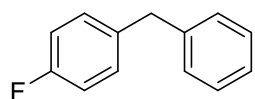
Bis-(3-methoxyphenyl)methane[77] (**2.12f**): Prepared according to General Procedure G from 5-(bis-(3-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11f**) (37 mg, 0.10 mmol) and 10% Pd/C (16 mg, 0.015 mmol, 15 mol % Pd). The crude material was washed with a saturated sodium bicarbonate solution and was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to afford a clear oil (21 mg, 93% yield). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.22 (t, J = 8.2 Hz, 2H), 6.78 (m, 6H), 3.95 (s, 2H), 3.80 (s, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 159.7 (C), 142.5 (C), 129.4 (CH), 121.4 (CH), 114.8 (CH), 111.4 (CH), 55.2 (CH$_3$), 44.0 (CH$_2$). HRMS(EI) *m/z* calcd for $C_{15}H_{16}O_2$ (M$^+$): 228.1150. Found: 228.1148.

1-Fluoro-4-(4-methoxybenzyl)benzene[78] (**2.12g**): Prepared according to General Procedure G from 5-((4-fluorophenyl)(4-

methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11g**) (36 mg, 0.10 mmol) and 10 % Pd/C (16 mg, 0.015 mmol, 15 mol % Pd). The crude material was washed with a saturated sodium bicarbonate solution and was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to afford a clear oil (17.5 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (m, 2H), 7.10 (d, J = 8.6, 2H), 6.99 (tt, J = 8.7, 2.0 Hz, 2H), 6.86 (td, J = 8.6, 2.0 Hz, 2H), 3.92 (s, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.4 (d, ^1J = 242 Hz, C), 158.1 (C), 137.2 (d, ^4J = 2.9 Hz, C), 133.1 (C), 130.1 (d, ^3J = 8.1 Hz, CH), 129.8 (CH), 115.2 (d, ^2J = 21.1 Hz, CH), 113.9 (CH), 55.3 (CH_3), 40.2 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -117; HRMS(EI) m/z calcd for $C_{14}H_{13}FO$ (M$^+$): 216.0950. Found: 216.0951.

1-Fluoro-4-benzylbenzene[79] (**2.12h**): Prepared according to General Procedure G from 5-((4-fluorophenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.11h**) (44.5 mg, 0.136 mmol) and 10% Pd/C (22 mg, 0.020 mmol, 15 mol % Pd). The crude material was washed with a saturated sodium bicarbonate solution and was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to afford a clear oil (20.5 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (t, J = 7.2 Hz, 2H), 7.23-7.02 (m, 5H), 6.98 (t, J = 8.6 Hz, 2H), 3.96 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.0 (d, ^1J = 242.5 Hz, C), 140.9 (C), 136.7 (d, ^4J = 3.1 Hz, C), 130.2 (d, ^3J = 7.8 Hz, CH), 128.8 (CH), 128.5 (CH), 126.2 (CH), 115.1 (d, ^2J = 21.1 Hz, CH), 41.0 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -117; HRMS(EI) m/z calcd for $C_{13}H_{11}F$ (M$^+$): 186.0845. Found: 186.0846.
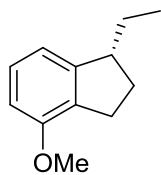
(R)-1-Ethyl-4-methoxyindane ((R)-2.16a): Prepared according to General Procedure G from (S)-5-(1-ethyl-4-methoxyindan-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((S)-**2.15a**) (40.0 mg, 0.126 mmol) with an enantiomeric ratio of 86:14 (*S*:*R*). 10% Pd/C (67 mg, 0.063 mmol, 50 mol % Pd) was used instead of 15 mol % Pd. Purification by flash column chromatography eluting with hexane, followed by 9:1 hexanes:EtOAc afforded a clear oil (11 mg, 49% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.14 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.09-2.99 (m, 1H), 2.94-2.84 (m, 1H), 2.79-2.68 (m, 1H), 2.27 (dddd, *J* = 16.4, 12.7, 8.1, 4.8 Hz, 1H), 1.86 (dddd, *J* = 14.9, 12.3, 7.5, 4.8 Hz, 1H), 1.68 (dddd, *J* = 16.2, 14.8, 7.4, 7.4 Hz, 1H), 1.50-1.35 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (CDCl$_3$,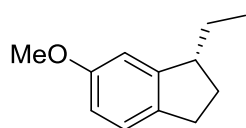 75 MHz) δ 155.8 (C), 149.6 (C), 131.4 (C), 127.3 (CH), 116.1 (CH), 107.8 (CH), 55.1 (CH$_3$), 46.8 (CH), 31.1 (CH$_2$), 27.8 (CH$_2$), 27.7 (CH$_2$), 11.8 (CH$_3$). GC/MS calcd for C$_{12}$H$_{16}$O (M$^+$): 176. Found: 176. An enantiomeric ratio of 79:21 (*R*:*S*) was measured by chiral HPLC OD-H, 100% *n*-heptane, 0.5 mL/min, t$_{R1}$ = 21.1 min (*R*), t$_{R2}$ = 24.3 min (*S*). [α]^{25}$_D$ = - 9.6 (*c* 0.18, CH$_2$Cl$_2$). Absolute stereochemistry was assigned by analogy to (*R*)-1-ethyl-6-methoxyindane (**13b**).

(R)-1-Ethyl-6-methoxyindane ((R)-2.16b): Prepared according to General Procedure G from (S)-5-(1-ethyl-6-methoxyindan-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((S)-**2.15b**) [58] (60 mg, 0.19 mmol) with an enantiomeric ratio of 99.5:0.5 (*S/R*) and 10% Pd/C (30 mg, 0.028 mmol, 15 mol % Pd). Purification by flash column chromatography eluting with hexanes, followed by 9:1 hexanes:EtOAc afforded a clear oil (20.5 mg, 62% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.09 (d, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.1, 2.0 Hz, 1H), 3.78 (s, 3H), 2.99-2.85 (m, 1H), 2.83-2.74 (m, 2H), 2.27 (dddd, *J* = 12.6, 7.8,

4.9, 4.9 Hz, 1H), 1.86 (dddd, J = 15.0, 12.3, 7.5, 4.9 Hz, 1H), 1.68 (ddd, J = 15.1, 12.5, 7.7 Hz, 1H), 1.45-1.25 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 158.6 (C), 149.2 (C), 136.1 (C), 124.7 (CH), 111.8 (CH), 109.4 (CH), 55.4 (CH$_3$), 46.7 (CH), 32.1 (CH$_2$), 30.5 (CH$_2$), 27.6 (CH$_2$), 11.9 (CH$_3$). GC/MS calcd for C$_{12}$H$_{16}$O (M$^+$): 176. Found: 176. An enantiomeric ratio of 91:9 (*R:S*) was measured by HPLC, using chiral column AD-H, 100% *n*-heptane, 1.0 mL/min, t_{R1} = 6.04 min (*R*), t_{R2} = 6.66 min (*S*). $[\alpha]^{25}_D$ = -10.04 (*c* 0.38, CH$_2$Cl$_2$). Absolute stereochemistry was determined via synthesis using a modified procedure of Lu et al. (see below).[80]
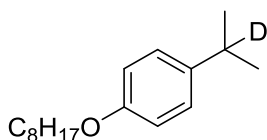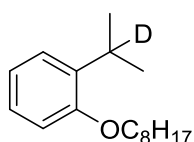

1-Octyloxy-4-(propan-2-yl-2-*d*)benzene (*d*-2.2c): Prepared according to General Procedure J from 2,2-dimethyl-5-(2-(4-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**2.1c**) (200 mg, 0.51 mmol) using CD$_3$OD and H$_2$. Purification via flash chromatography, eluting with pentane, furnished the product as a pale yellow oil (108 mg, 85% yield, 90% D-incorporation). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.41 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 1.78 (app. quintet, J = 7.0 Hz, 2H), 1.46-1.23 (m, 16H), 0.92-0.88 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 157.2 (C), 140.7 (C), 127.1 (CH), 114.2 (CH), 67.9 (CH$_2$), 32.8 (CD, "t", J = 19.3 Hz), 31.8 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 24.1 (CH$_2$), 24.0 (CH$_3$), 22.7 (CH$_2$), 14.1 (CH$_3$). GC/MS *m/z* calcd for C$_{17}$H$_{27}$DO (M$^+$): 249.2. Found (LRMS): 249.2.
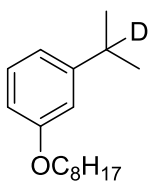

1-Octyloxy-3-(propan-2-yl-2-*d*)benzene (*d*-2.2d): Prepared according to General Procedure J from 1-isopropyl-3-octyloxybenzene (**2.2d**) (125 mg, 0.50 mmol) using H$_2$ and CD$_3$OD. Purification by flash chromatography, eluting with pentane,

provided the product as a pale yellow oil (92 mg, 72% yield, 74% D-incorporation). ^{1}H NMR

(CDCl$_3$, 300 MHz) δ 7.23 (t, J = 7.7 Hz, 1H), 6.85-6.82 (m, 2H), 6.74 (dd, J_1 = 8.3 Hz, J_2 = 2.0

Hz, 2H), 1.81 (app. quintet, J = 7.0 Hz, 2H), 1.50-1.27 (m, 16H), 0.95-0.91 (m, 3H); ^{13}C NMR

(CDCl$_3$, 75 MHz) δ 159.2 (C), 150.5 (C), 129.2 (CH), 118.7 (CH), 113.0 (CH), 111.2 (CH), 67.8

(CH$_2$), 34.2 (CD, "t", 18.8 Hz), 31.2 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 26.2 (CH$_2$), 23.9 (CH$_3$), 22.7

(CH$_2$), 14.1 (CH$_3$). GC/MS m/z calcd for C$_{17}$H$_{27}$DO (M$^+$): 249.2. Found (LRMS): .

**1-Octyloxy-2-(propan-2-yl-2-*d*)benzene (*d*-2.2e)**: Prepared according to General Procedure J from 2,2-dimethyl-5-(2-(4-octyloxyphenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**2.1e**) (200 mg, 0.51 mmol) using D$_2$ and CD$_3$OD. Purification by flash

chromatography, eluting with pentane, provided the product as a pale yellow oil (47 mg, 37%

yield, >95% D-incorporation). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.25 (d, J = 7.5 Hz, 1H), 7.18 (td,

J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 4.00 (t, J = 6.4

Hz, 2H), 1.85 (app. quintet, J = 6.9 Hz, 2H), 1.56-1.26 (m, 16H), 0.96-0.92 (m, 3H); ^{13}C NMR

(CDCl$_3$, 75 MHz) δ 156.2 (C), 136.9 (C), 126.4 (CH), 125.9 (CH), 120.2 (CH), 111.0 (CH), 67.8

(CH$_2$), 31.7 (CH$_2$), 29.3 (CH$_2$), 29.24 (CH$_2$), 29.17 (CH$_2$), 26.4 (CD), 26.1 (CH$_2$), 22.6 (CH$_2$),

22.4 (CH$_3$), 14.0 (CH$_3$). GC/MS m/z calcd for C$_{17}$H$_{27}$DO (M$^+$): 249.2. Found (LRMS): 249.2.
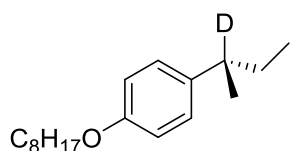
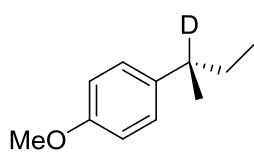**(*S*)-1-(Butan-2-yl-2-*d*)-4-octyloxybenzene (*d*-(*S*)-2.4a)**: Prepared according to General Procedure I from (*R*)-2,2-dimethyl-5-(2-(4-octyloxyphenyl)butan-2-yl)-1,3-dioxane-4,6-dione ((*R*)-**2.3a**) (80 mg,

0.20 mmol) using D$_2$ and CD$_3$OD. Purification by flash chromatography provided the product as

a clear oil. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.05 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.91

(t, J = 6.6 Hz, 2H), 1.75 (app. quintet, J = 7.3 Hz, 2H), 1.54-1.18 (m, 15H), 0.88-0.84 (m, 3H),

0.79 (t, J = 7.4 Hz, 3H); ^{2}H NMR (CDCl$_3$, 46.1 MHz) δ 2.50, 1.15; ^{13}C NMR (CDCl$_3$, 75 MHz)

δ 157.2 (C), 139.5 (C), 127.8 (CH), 114.2 (CH), 67.9 (CH$_2$), 40.3 (CD, "t", J = 19.1 Hz), 31.8

(CH$_2$), 31.2 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 26.1 (CH$_2$), 22.7 (CH$_2$), 21.9 (CH$_3$), 14.1 (CH$_3$), 12.2

(CH$_3$). GC/MS m/z calcd for C$_{18}$H$_{29}$DO (M$^+$): 263.2. Found (LRMS): 263.1.
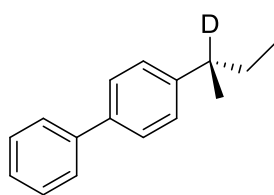
(S)-4-(Butan-2-yl-2-d)-1,1'-biphenyl (d-(S)-2.14a): Prepared according to General Procedure I from (R)-5-(2-([1,1'-biphenyl]-4-yl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((R)-**2.13a**) (60 mg, 0.17 mmol) using D$_2$ and CD$_3$OD. Purification by flash chromatography, eluting with pentane, provided the

product as a clear oil. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.63 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.1

Hz, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 1.67 (q, J =

7.2 Hz, 2H), 1.31 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H); ^{2}H NMR (CDCl$_3$, 46.1 MHz) δ 2.63, 1.62,

1.24; ^{13}C NMR (CDCl$_3$, 125 MHz) δ 146.8 (C), 141.2 (CH), 138.7 (C), 128.7 (CH), 127.5 (CH),

127.02 (CH), 127.01 (CH), 126.95 (CH), 40.9 (CD, "t", J = 19.3 Hz), 31.1 (CH$_2$), 21.7 (CH$_3$),

12.3 (CH$_3$). GC/MS m/z calcd for C$_{16}$H$_{17}$D (M$^+$): 211.1. Found (LRMS): 211.2.

(S)-1-(Butan-2-yl-2-d)-4-methoxybenzene (d-(S)-2.14b): Prepared according to General Procedure I from (R)-5-(2-(4-methoxyphenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione ((R)-**2.13b**) (60 mg, 0.20 mmol) using D$_2$ and CD$_3$OD. Purification by flash chromatography, eluting with pentane, provided the

product as a clear oil. ^{1}H NMR (CD$_3$OD, 300 MHz) δ 7.09-7.04 (m, 2H), 6.83-6.80 (m, 2H),

3.74 (s, 3H), 1.54 (q, J = 7.2 Hz, 2H), 1.17 (s, 3H), 0.78 (t, J = 7.4 Hz, 3H); ^{2}H NMR (CD$_3$OD,

46 MHz) δ 2.51, 1.52, 1.16; ^{13}C NMR (CD$_3$OD, 75 MHz) δ 157.9 (C), 139.3 (C), 127.4 (CH), 113.3 (CH), 54.2 (CH$_3$), 40.3 (CD, "t", J = 19.3), 30.9 (CH$_2$), 21.1 (CH$_3$), 11.2 (CH$_3$). GC/MS *m/z* calcd for C$_{11}$H$_{15}$DO (M$^+$): 165.1. Found (LRMS): 165.1.

Absolute Stereochemistry Determination for Compound 2.16b:

The following compounds were prepared by Lu et al. and the spectral data obtained was in agreement with the reported values and, consequently, the data will not be repeated here: (*E*)-3-(3-methoxyphenyl)acrylic acid (**2.17b**), (*S,E*)-4-benzyl-3-(3-(3-methoxyphenyl)acryloyl)oxazolidin-2-one (**2.17c**), (*S*)-4-benzyl-3-((*S*)-3-(3-methoxyphenyl)hex-5-enoyl)oxazolidin-2-one (**2.17d**), (*S*)-3-(3-methoxyphenyl)hex-5-en-1-ol (**2.17e**), (*S*)-3-(3-methoxyphenyl)hex-5-en-1-yl acetate (**2.17f**), (*R*)-5-acetoxy-3-(3-methoxyphenyl)pentanoic acid (**2.17g**), (*R*)-2-(6-methoxyindan-3-one-1-yl)ethyl acetate (**2.17h**), and (*S*)-2-(6-methoxyindan-1-yl)ethanol (**2.17i**).[47]
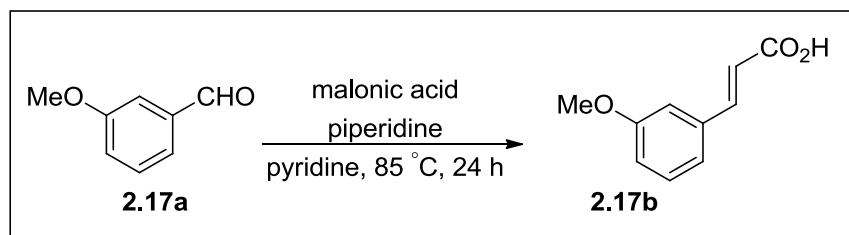
(*E*)-3-(3-Methoxyphenyl)acrylic acid (2.17b): Prepared following a procedure by Zhu et al.[81] 3-Anisaldehyde (25.0 mL, 205 mmol, 1.0 equiv.) and malonic acid (25.6 g, 246 mmol, 1.2 equiv.) were dissolved in pyridine (220 mL) in a 500 mL round-bottomed flask equipped with a reflux condenser. Piperidine (2.5 mL, 25 mmol, 0.12 equiv.) was added and the solution was heated to 85 °C for 24 h. The reaction was allowed to cool and excess pyridine was removed by rotary evaporation (50 °C). 10% HCl (100 mL) was added and the resulting pale yellow

precipitate was filtered over a Buchner funnel to obtain **2.17b** as a pale yellow solid (35.2 g, 97%

yield). The product was used in the next step without further purification.

**2.17b**   **2.17c**
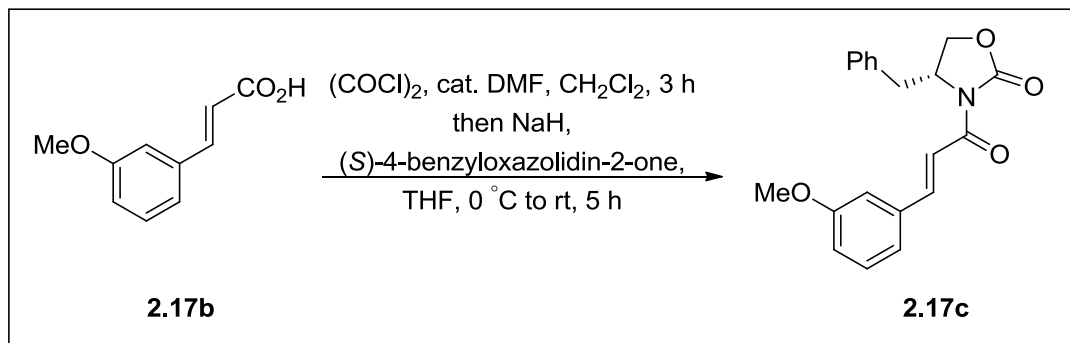
(**S**,**E**)-4-benzyl-3-(3-(3-methoxyphenyl)acryloyl)oxazolidin-2-one (2.17c): Prepared following

the procedure of Nishida et al.[82] (*E*)-3-(3-Methoxyphenyl)acrylic acid (**2.17b**) (17.8 g, 100

mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (40 mL) in a 100 mL round-bottomed flask and then

DMF (0.5 mL) was added followed by $(COCl)_2$. The solution was stirred for 3 h at room

temperature. In a 1 L round-bottomed flask, (*S*)-4-Benzyloxazolidin-2-one (21.3 g, 120 mmol,

1.2 equiv.) was dissolved in THF (480 mL) and the solution was cooled to 0 °C before adding

NaH (60 wt% in mineral oil, 5.2 g, 130 mmol, 1.3 equiv.). The mixture was allowed to stir for 30

min at 0 °C before being warmed to room temperature and stirring for an additional 1 h. The 1 L

flask was again cooled to 0 °C before the cinnamyl chloride solution was added via cannula. The

mixture was allowed to warm to rt and stir for 5 h before being quenched by careful addition of

water (160 mL). The layers were partitioned and the aqueous layer was extracted with EtOAc

(3x 150 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated.

The crude oil was purified by flash chromatography, eluting with 4:1 hexanes/EtOAc to afford

**2.17c** as a white solid (28.4 g, 84% yield).
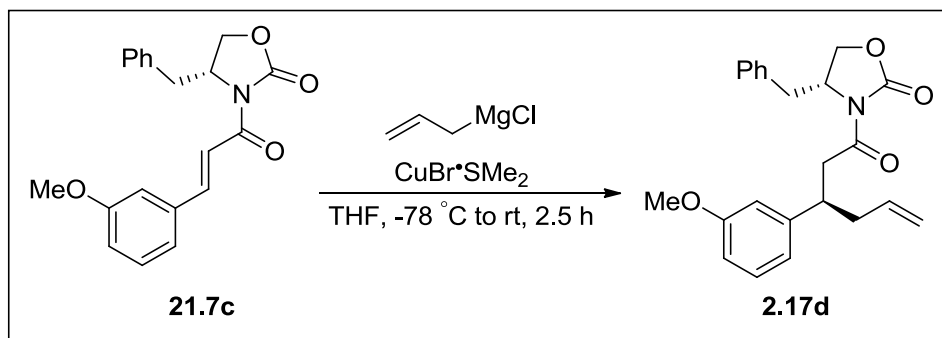
(*S*)-4-benzyl-3-((*S*)-3-(3-methoxyphenyl)hex-5-enoyl)oxazolidin-2-one **(2.17d)**: Prepared following a procedure of Burke et al.[83] A slurry of CuBr•SMe$_2$ (22.9 g, 107 mmol, 1.5 equiv.) in THF (400 mL) in a 1 L round-bottomed flask was cooled to -78 °C before adding allylmagnesium chloride solution (92 mL, 2.0 M in THF, 194 mmol, 2.6 equiv.). The mixture was stirred for 1.5 h at -78 °C before a solution of **2.17c** (24.0 g, 71.1 mmol, 1.0 equiv.) in THF (71 mL) was added via cannula. The reaction was stirred for an additional 2.5 h at -78 °C before being quenched with sat. NH$_4$Cl (300 mL). The layers were partitioned and the aqueous layer was extracted with ethyl acetate (3x 200 mL). The combined organic layers were dried with MgSO$_4$, filtered and concentrated by rotary evaporation. The resulting oil was purified by flash chromatography eluting with 9:1 hexanes/EtOAc to obtain **2.17d** as a very viscous yellow oil (21.3 g, 78% yield).
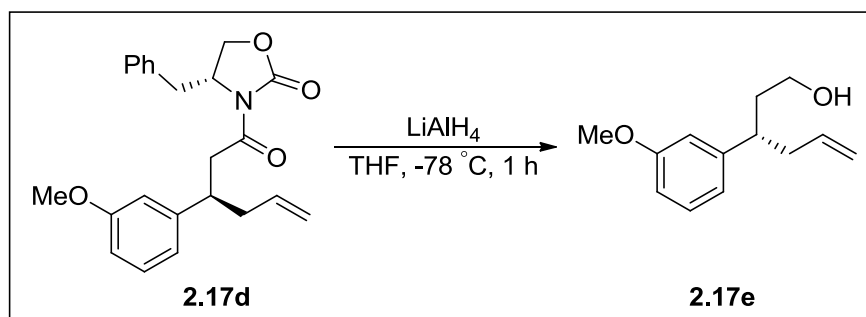
**(*S*)-3-(3-methoxyphenyl)hex-5-en-1-ol (2.17e)**: Prepared following a procedure of Cane et al.[84] A solution of LiAlH$_4$ (6.0 g, 158 mmol, 3.0 equiv.) in THF (160 mL) was prepared at -78 °C. A solution of oxazolidinone **2.17d** (20.0 g, 52.7 mmol, 1.0 equiv.) in Et$_2$O (160 mL) was added to the LiAlH$_4$ solution via cannula and stirring was continued for 1 h at -78 °C. The reaction was then allowed to warm to room temperature before careful addition of NaOH (10 mL, 2 M in H$_2$O). The solid precipitate was removed by filtration and washed with ether. The filtrate was dried with MgSO$_4$, filtered and concentrated by rotary evaporation. The crude oil was purified by flash chromatography eluting with 4:1 hexanes/EtOAc to obtain **2.17e** as a clear oil (4.02 g, 37% yield).
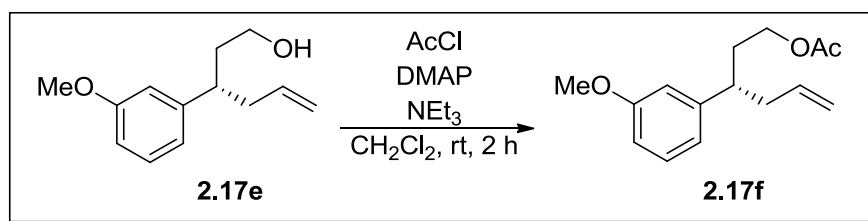
(*S*)-3-(3-methoxyphenyl)hex-5-en-1-yl acetate (2.17f): Prepared following a procedure of Tan et al.[85] Alcohol **2.17e** (3.74 g, 18.1 mmol, 1.0 equiv.), DMAP (222 mg, 1.8 mmol, 0.1 equiv.) and NEt$_3$ (5.1 mL, 36 mmol, 2.0 equiv.) were dissolved in CH$_2$Cl$_2$ (180 mL) and the solution was stirred at room temperature for 2 h. Sat. NaHCO$_3$ (100 mL) was added and the layers were partitioned. The aqueous layer was extracted with Et$_2$O (3x 100 mL) and the combined organic layers were dried with MgSO$_4$, filtered and concentrated by rotary evaporation. The crude oil was purified by flash chromatography eluting with 9:1 hexanes/EtOAc to afford **2.17f** as a clear oil (4.28 g, 96% yield).
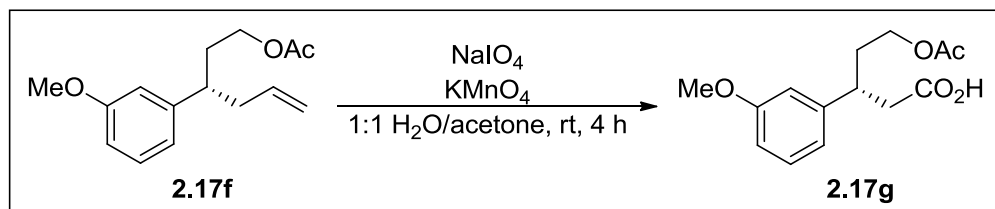
(R)-5-acetoxy-3-(3-methoxyphenyl)pentanoic acid (2.17g): Prepared following a procedure of

Lu et al.[47] Alkene **2.17f** (4.0 g, 16.1 mmol, 1.0 equiv.) was dissolved in 1:1 acetone/water (320

mL) before $NaIO_4$ (16.0 g, 77 mmol, 4.8 equiv.) and $KMnO_4$ (1.6 g, 10 mmol, 0.65 equiv.) were

added. The mixture was allowed to stir at room temperature for 4 h before adding 17 g of

$NaS_2O_3 \cdot H_2O$ and stirring for an additional 30 min. Then, 10% aqueous $NaHSO_3$ was added until

the mixture completely dissolved. The mixture was extracted with CH_2Cl_2 (3x 200 mL) and the

combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated

by rotary evaporation. The crude oil was purified by flash chromatography eluting with 4:1

hexanes/EtOAc to afford the **2.17g** as a yellow oil (2.21 g, 52% yield).
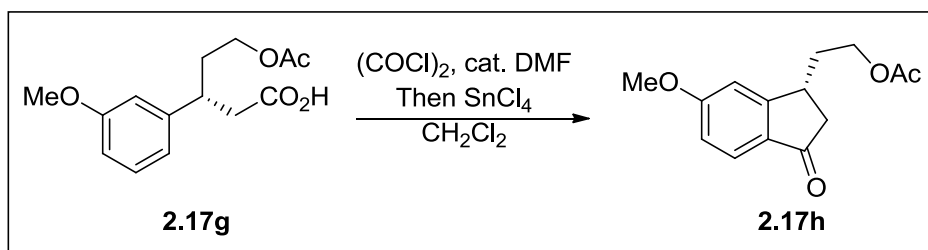
(R)-2-(6-methoxyindan-3-one-1-yl)ethyl acetate (2.17h): Prepared following a procedure by

Corey et al.[86] Acid **2.17g** (1.5 g, 5.6 mmol, 1.0 equiv.) and DMF (1 drop) were dissolved in

CH_2Cl_2 (30 mL) and cooled to 0 °C before adding oxalyl chloride (1.4 g, 16.8 mmol, 3.0 equiv.).

The mixture was allowed to warm to room temperature and stirred for 2 h before removal of the

solvent by rotary evaporation. DMF was removed under high vacuum (0.5 mmHg) and the crude

acyl chloride was redissolved in CH_2Cl_2 (16 mL). The solution was cooled to -20 °C before

adding a solution of $SnCl_4$ (1.3 mL, 11 mmol, 2.0 equiv.) in CH_2Cl_2 (11 mL). After stirring for 4

h at -20 °C, the reaction was quenched by addition of sat. NH₄Cl (20 mL). The layers were partition and the aqueous layer was extracted with Et₂O (3x 20 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated by rotary evaporation. The crude oil was purified by flash chromatography eluting with 9:1 hexanes/ethyl acetate to afford **2.17h** as a pale yellow oil (1.19g, 86% yield).


2.17h   H₂ / Pd/C / H₂SO₄ / EtOH, 60 °C, 1 h   **2.17i**
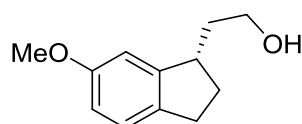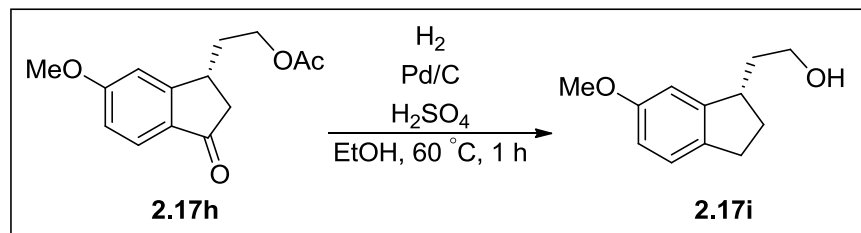
(S)-2-(6-methoxyindan-1-yl)ethanol (2.17i): Prepared following a procedure from Ladd et al.[87] Indanone **2.17h** (0.94 g, 3.8 mmol, 1.0 equiv.) was dissolved in EtOH (32 mL) and then Pd/C (101 mg, 0.095 mmol, 2.5 mol % Pd) and H₂SO₄ (4 drops) were added. The reaction was degased and refilled with hydrogen (3x) before the reaction vessel was placed in an oil bath heated to 60 °C and placed under a hydrogen pressure of 3.5 bar. The reaction was stirred for 1 h before being removed from the oil bath. The reaction was transferred to a round-bottomed flask and the EtOH was removed by rotary evaporation. The residue was dissolved in Et₂O (30 mL) and washed with sat. NaHCO₃ (2x 30 mL), dried with MgSO₄, filtered and concentrated by rotary evaporation. The crude oil was purified by flash chromatography eluting with 9:1 hexanes EtOAc to obtain **2.17i** as a clear oil (0.63 g, 86% yield).
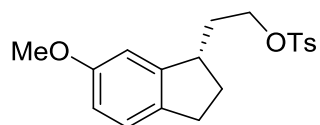

2.17i   TsCl / pyridine, rt, 8 h   **2.17j**
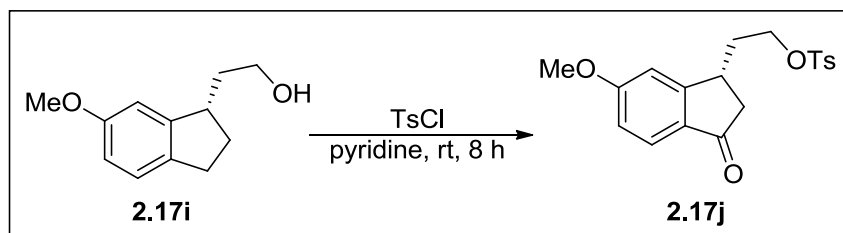
(S)-2-(6-Methoxyindan-1-yl)ethyl 4-methylbenzenesulfonate ((S)-2.18b): Procedure adapted from Kumada et al.[88] (S)-2-(6-methoxyindan-1-yl)ethan-1-ol (**2.17i**) (132 mg, 0.69 mmol, 1.0 equiv.) was dissolved in pyridine (7 mL) followed by TsCl (196 mg, 1.0 mmol, 1.5 equiv.). The resulting solution was stirred at room temperature for 8 h before the addition of 5% HCl. The mixture was extracted 3x with Et_2O and the combined organic extracts were washed sequentially with 5% HCl, water, sat. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated via rotary evaporation. The product was purified via flash chromatography, eluting with 9:1 hexanes/EtOAc (R_f = 0.22). Obtained as a yellow oil, yield = 212 mg (89%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.80 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.1 Hz, 1H), 6.68 (dd, J_1 = 8.1 Hz, J_2 = 2.2 Hz, 1H), 6.62 (s, 1H), 4.19-4.11 (m, 2H), 3.75 (s, 3H), 3.14 (m, 1H), 2.79-2.70 (m, 2H), 2.44 (s, 3H), 2.21-2.12, (m, 2H), 1.74-1.155 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 158.6 (C), 147.3 (C), 144.7 (C), 135.5 (C), 133.0 (C), 129.8 (CH), 127.8 (CH), 124.9 (CH), 112.3 (CH), 109.1 (CH), 69.0 (CH$_2$), 55.3 (CH$_3$), 41.1 (CH), 33.7 (CH$_2$), 32.2 (CH$_2$), 30.3 (CH$_2$), 21.6 (CH$_3$); HRMS calcd for C$_{19}$H$_{23}$O$_4$S (MH$^+$): 347.13116. Found: 347.13125; [α]$^{28}_D$ = -8.8 (c 0.76, CH$_2$Cl$_2$).
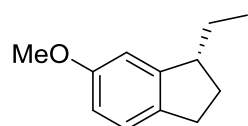
(R)-1-Ethyl-6-methoxyindane ((R)-2.16b): (S)-2-(6-methoxyindan-1-yl)ethyl 4-methylbenzenesulfonate ((S)-**2.18b**) (200 mg, 0.58 mmol, 1.0 equiv.) was dissolved in anhydrous Et_2O before drop-wise addition of Super-Hydride® (0.87 mL, 0.87 mmol, 1.5 equiv.). The solution was stirred at room temp. for 10 min before being held at reflux for 5 h. The reaction was cooled to 0 °C before quenching with water. The mixture was

acidified with 5% HCl then extracted 3x with Et$_2$O. The combined organic layers were washed once with brine, dried with MgSO$_4$, filtered and concentrated via rotary evaporation. The product was purified via flash chromatography, eluting with 100% hexanes to afford 33 mg (32%) of a clear oil. HPLC analysis using a Chiralcel AD-H column eluting with 100% *n*-heptane at 1.0 mL/min gave t_{R1} = 6.06 min (major, *R*) and t_{R2} = 6.94 min (minor, *S*). The retention times correspond to the above values for **13b** (t_{R1} = 6.04 min (major), t_{R2} = 6.66 min (minor)).

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