Innovative Methods for the Catalyzed Construction of Carbon-Carbon and Carbon-Hydrogen Bonds

by

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Author’s Declaration

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

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Abstract

The selective transformation of carbon-carbon and carbon-hydrogen bonds represents an attractive approach and rapidly developing frontier in synthesis. Benefits include step and atom economy, as well as the ubiquitous presence in organic molecules. Advances to this exciting realm of synthesis are described in this thesis with an emphasis on the development of catalytic, selective reactions under mild conditions. Additionally some applications of the methodologies are demonstrated.

In Chapter 1, the first examples of inter-and intramolecular enantioselective conjugate alkenylations employing organostannanes are reported. A chiral, cationic Rh(I)-diene complex catalyzed the enantioselective conjugate addition of alkenylstannanes to benzylidene Meldrum's acids in moderate enantiomeric ratios and yields. Notably, the cationic and anhydrous conditions required for the asymmetric alkenylation are complementary to existing protocols employing other alkenylmetals.

In Chapter 2, a domino, one-pot formation of tetracyclic ketones from benzylidene Meldrum's acids using $Sc(OTf)_3$ via a [1,5]-hydride shift/cyclization/Friedel-Crafts acylation sequence is described. Respectable yields were obtained in accord with the ability to convert to the *spiro*-intermediate, and considering the formation of three new bonds: one C-H and two C-C bonds. An intriguing carbon-carbon bond cleavage was also serendipitously discovered as part of a competing reaction pathway.

In Chapter 3, the pursuit of novel C-H bond transformations led to the development of non-carbonyl-stabilized rhodium carbenoid Csp^3-H insertions. This methodology enabled the rapid synthesis of *N*-fused indolines and related complex heterocycles from *N*-aziridinylimines. By using a rhodium carboxamidate catalyst, competing processes were minimized and C-H insertions were found to proceed in moderate to high yields. Also disclosed is an expedient total synthesis of (±)-cryptaustoline, a dibenzopyrrocoline alkaloid, which highlights the methodology.

In Chapter 4, the Lewis acid promoted substitution of Meldrum's acid discovered during the course of the domino reaction was explored in detail. The protocol transforms unstrained quaternary and tertiary benzylic Csp^3-Csp^3 bonds into Csp^3-X bonds (X = C, N, H) and has even shown to be advantageous with regards to synthetic utility over the use of alternative leaving groups for substitutions at quaternary benzylic centers. This reaction has a broad scope both in terms of suitable substrates and nucleophiles with good to excellent yields obtained (typically >90%).

Acknowledgements

The decision to pursue graduate studies in chemistry was definitely an interesting and rewarding experience. I now appreciate more than ever how encompassing and competitive the field is. I found the diagnostic aspect of analyzing data from hitherto unknown reactions to be most engaging, coupled with searching for guidance in the literature. A number of people contributed to making my time spent on graduate research a positive pursuit.

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My gratitude also goes out to my Ph.D. committee members, Professors Mike Chong, Scott Taylor and William Tam, who are thanked for their guidance and interest in my research. Professors Daniel Seidel and Praveen Nekkar are thanked for acting as external examiners for my thesis. I am also indebted to NSERC, OGS and the University of Waterloo for graduate scholarships.

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Prof. Avinash Thadani is thanked for his unbridled enthusiasm in teaching senior undergraduate organic courses at the University of Windsor which helped confirm my interest in pursuing graduate studies in chemistry. He also recommended looking into Prof. Fillion's group in a discussion with me.

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I am most grateful for the love and support of my parents, Greg and Dorothy. They have been instrumental in my life and are excellent role models. My Mom is a renowned, published poet and teacher who always encouraged creativity and reading. My Dad is a Chartered Accountant by profession and an incredibly wise man with an unsurpassed ability to research

projects and connect with people. In addition to motivating me, they have kept me well fueled with kilogram bags of chocolate chips and coffee amongst many other spoils. My fearless and more intelligent brother, Matt, is a hero, great sport, and understands my references. I am lucky to grow up with him. My Oma's baked goods and cards also kept me in good spirits. My Grandma's kindness and eagerness for a card game was uplifting. Manfred, who passed away unexpectedly during the course of my studies, will be remembered fondly as a gentle giant.

To my incredibly understanding and talented girlfriend Jen (J.D.), thanks for your patience and helping me get through some trying times. Your sense of adventure has greatly broadened my taste in food as well as improved my navigational skills. I have felt at home in Kitchener-Waterloo thanks to you.

To Mom, Dad, Matt and Jen

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List of Abbreviations

Ac	acetyl
ACA	asymmetric conjugate addition
acac	acetylacetonate
acam	acetamide
ACCN	azobis(cyclohexanecarbonitrile)
AIBN	azobis(isobutyronitrile)
app	apparent
aq	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bpin	boron pinacol ester (pinacolato boron)
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
c	concentration (grams/100 mL)
calcd	calculated
CAN	ceric ammonium nitrate (diammonium cerium(IV) nitrate)
cap	caprolactamate
cat	catalytic
cod	cycloocta-1,5-diene
COSY	correlated spectroscopy
Cp	cyclopentadiene
Cy	cyclohexyl
d	doublet
DART	direct analysis in real time
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dppf	1,1`-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane

dr	diastereomeric ratio
dtbm	di-*tert*-butylmethoxy
DYKAT	dynamic kinetic asymmetric transformation
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
Et	ethyl
EtOAc	ethyl acetate
ether	diethyl ether
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
EWG	electron withdrawing group
F-C	Friedel-Crafts
GC-MS	tandem gas chromatography-mass spectrometry
h	hour
hal	halogen
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	*iso*-propyl
IR	infrared
J	spin coupling constant
KIE	kinetic isotope effect
L	ligand
L*	chiral ligand
L. A.	Lewis acid
LDA	lithium diisopropylamide
m	multiplet
m	meta
M	metal or molarity (moles/litre)
Me	methyl
MeCN	acetonitrile
Meldrum's acid	2,2-dimethyl-1,3-dioxane-4,6-dione

MHz	mega hertz
min	minute
mL	millilitre
mmol	millimole
mol	mole
M.p.	melting point
M.S.	molecular sieves
m/z	mass/charge
N/A	not applicable or non-available
NBS	*N*-bromosuccinimide
ND	not determined
NHC	*N*-heterocyclic carbene
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
NR	no reaction
Nu	nucleophile
o	ortho
OTf	triflate (trifluoromethanesulfonate)
O/N	overnight
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl (trimethylacetyl)
pK_a	-log of acid dissociation constant
ppm	parts per million
py	pyridine
q	quartet
quant	quantitative
quint	quintet
rac	racemic
$Rh(5S\text{-}MEPY)_4$	dirhodium(II) tetrakis[methyl-2-pyrrolidone-5(*S*)-carboxylate]
rt	room temperature
s	singlet
SM	starting material
t	triplet
t-Bu	*tert*-butyl
TCE	1,1,2-trichloroethane

temp	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	turnover frequency
t_R	retention time
Ts	tosyl (*p*-toluenesulfonyl)
UV	ultraviolet
wt	weight
X-C	cross-coupling

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“Never confuse a single defeat with a final defeat.”
— F. Scott Fitzgerald

Chapter 1. Asymmetric Conjugate Addition of Alkenylstannanes to Benzylidene Meldrum's Acids

Convergent synthesis has the obvious benefit of being able to combine functionalized components as opposed to doing a completely linear synthesis. This chapter describes efforts directed at the development of an asymmetric conjugate addition compatible with functionalized nucleophiles and electrophiles.

1.1. Introduction

1.1.1. Rhodium Catalyzed Asymmetric Conjugate Addition (ACA)

One of the most rapidly developing methods of enantioselectively forming carbon-carbon bonds is through 1,4-conjugate addition reactions (Figure 1.1).[1] In this regard the metal catalyzed conjugate addition of nucleophiles, operating with a transition metal with chiral ligands, has shown the broadest scope both in terms of applicable substrates and nucleophiles. Other successful strategies of the method have been organocatalyzed additions of nucleophiles by formation of an activated, chiral acceptor (typically by a chiral amine or chiral acid, then followed by Nu attack) or alternatively by in situ formation of a chiral boronate[2] (reaction proceeds through a 6-membered transition state with enones) both of which will not be discussed further.

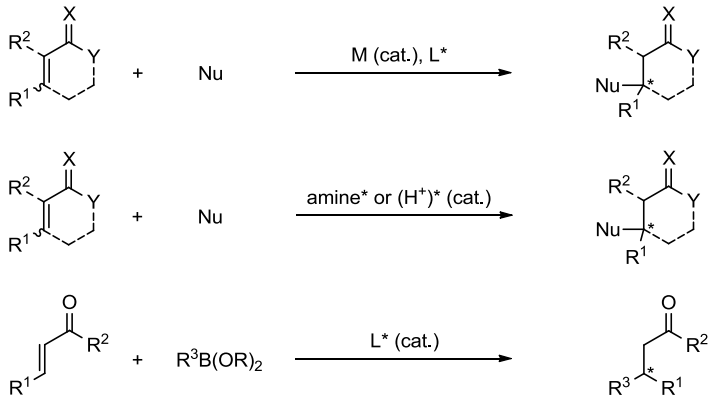


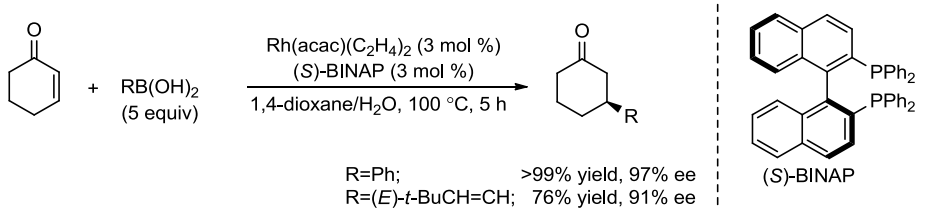
Figure 1.1 Asymmetric Conjugate Additions

Remaining challenges currently being addressed with metal catalyzed enantioselective conjugate additions are extensions to less reactive acceptors, including β,β-disubstituted acceptors to form quaternary centers, as well as adding functionalized nucleophiles. Fewer examples of the later have been reported in the literature,[3] plausibly due to incompatibilities with reaction conditions and substrates or difficulties in accessing the functionalized nucleophiles.

The asymmetric conjugate additions of aryl and alkenyl nucleophiles have proven most general under rhodium catalysis,[4] with rhodium undergoing transmetalation with organoborons, organosilicons, organostannanes, organoindiums, organozirconiums and organotitaniums in these protocols.[5] Limited synthetically useful methods also exist under copper[6] (limited to strong nucleophiles such as organomagnesiums) and more recently palladium catalysis[7] (acceptor scope limited to cyclic enones).

In 1998, Hayashi and coworkers reported the first execution of a rhodium catalyzed asymmetric conjugate addition of aryl and alkenylboronic acids with a rhodium(I) (*S*)-BINAP catalyst in high enantioselectivities and good yields to cyclic and acyclic enone acceptors (Scheme 1.1).[8] The choice of rhodium catalyst precursor was based on the ability of the ethylene ligands to undergo immediate displacement with BINAP as evidenced by ^{31}P and ^{1}H NMR. Furthermore, it was noted that the isolated Rh(acac)([(*S*)-BINAP] gave essentially the same catalytic activity as the in situ generated catalyst. An excess of organoboronic acid and higher temperature were requirements to obtain high yields.

Scheme 1.1. Pioneering Rhodium Catalyzed Enantioselective Conjugate Addition



In 2002, Hayashi's group published the seminal report of their mechanistic investigation of rhodium catalyzed 1,4-conjugate addition which provided evidence (by ^{31}P NMR) for hypothesized reaction intermediates.[9] The reaction mechanism has 3 steps: transmetalation,

insertion, followed by hydrolysis to turn the catalyst over (Figure 1.2). Their results supported the rate limiting step as being the transmetalation.

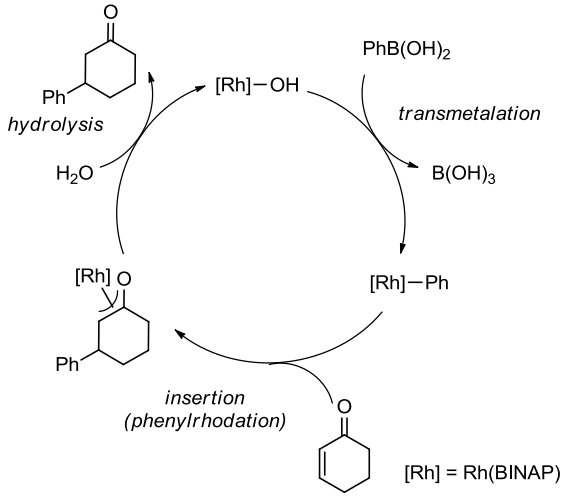


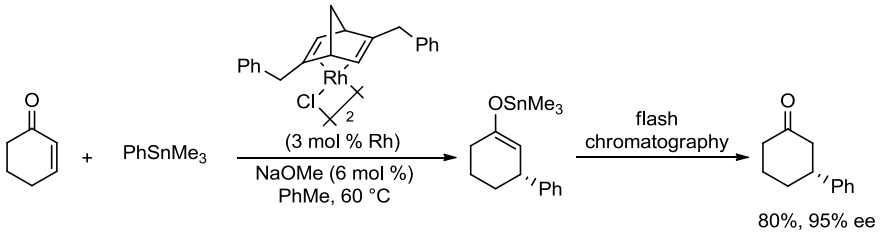
Figure 1.2. Mechanism of the Rhodium Catalyzed Conjugate Addition

Only in the last ten years have chiral dienes emerged as powerful steering ligands for permitting high asymmetric induction (especially in rhodium catalyzed conjugate addition reactions)[10] although most interestingly, Zeise's salt ($K[PtCl_3(C_2H_4)]\cdot H_2O$) which is known as the first organometallic complex was synthesized back in the early 1800's.[11] Since that initial breakthrough, the coordination chemistry of alkenes has been further explored as well as a better understanding of the bonding mode by the introduction of the Dewar-Chatt-Duncanson model. The synopsis is that if available pi orbitals of the ligand can donate electron density to the vacant d-orbitals of the metal and the metal in turn can donate electron density to the pi* orbital of the ligand; the metal to ligand bonding interaction is known as back-bonding. Thereafter achiral metal alkene complexes including rhodium complexes with cod ligands started seeing use in metal catalysis.

In 2003, Hayashi and coworkers reported the inaugural use of chiral diene ligands in asymmetric catalysis.[12] Their chiral diene rhodium catalyst was able to add aryl and alkenylborons (reduced to 2 equiv from 5; see Scheme 1.1) to α, β-unsaturated ketones and esters between 20-50 °C in excellent yields and selectivities. Most notably, the high catalytic activity of the chiral diene catalyst enabled the first asymmetric conjugate addition of an organostannane

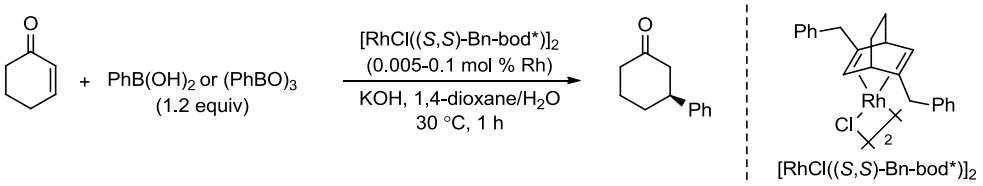
having added an arylstannane to cyclohexenone (Scheme 1.2). Under similar conditions with chiral BINAP rhodium catalysts gave <10% yield of the product in an undisclosed selectivity.

Scheme 1.2. Dawn of the Chiral Diene Catalysts



Notably, dienes permit rhodium catalyzed conjugate addition reactions to occur at lower temperatures and at an increased rate as opposed to rhodium complexes with phosphorus based ligands. Bonding modes are thought to be a chief contributor especially with regard to phosphorus being a better sigma donor ligand than dienes and conversely dienes having more pi back-bonding than phosphorus. Electron deficient olefins are often used to increase back donation from the rhodium center, enabling the diene to bind more strongly (observed experimentally by increased sp^3 character of the olefinic carbons).[13,14]

Table 1.1. High Catalytic Activity of Rhodium Diene Catalyst



entry	$PhB(OH)_2$ source	catalyst (mol % Rh)	yield (%)	% ee
1	$PhB(OH)_2$	0.05	95	96
2	$(PhBO)_3$	0.01	96	96
3[a]	$(PhBO)_3$	0.005	71	96

[a] The reaction of 1.73 g cyclohexenone.

High catalytic activity of chiral diene rhodium catalysts were demonstrated shortly after by Hayashi and coworkers by the addition of phenylboronic acid or phenylboroxine[15] under mild reaction conditions (Table 1.1).[16] By contrast under the same conditions as entry 2, the 1,4-addition did not proceed with rhodium catalysts coordinated to phosphorus ligands (ex. BINAP

or phosphoramidites). Remarkably, the turnover frequency (TOF) of the chiral diene catalyst (calculated from entry 3 as 1.4 x 10^4 h^{-1}) represented the highest TOF number for catalytic carbon-carbon bond forming reactions to the best of the authors' knowledge.

Consequently, there has been widespread interest of exploring chiral dienes (examples shown in Figure 1.3) for catalysis with a particular focus on the 1,4-conjugate addition.[10] The highest catalytic activities and enantioselectivities have been obtained using bridged bicyclic chiral dienes ([2.2.1],[12,17] [2.2.2],[18] [3.3.1],[19] and [3.3.2][20]) although other cyclic dienes have been described including a chiral bicyclo[3.3.0]octadiene.[21] Most recently, the group of Du and others have demonstrated the ability of acyclic chiral dienes[22] to impart enantioselectivity, albeit inferior results are obtained to the bicyclic chiral dienes. A key to the adoption of the utilization of chiral diene ligands by the synthetic community has been the development of accessible and scalable routes.[23] In that regard, Carreira's (*R*)-carvone[24] and the Hayashi/Rawal (*R*)-α-phellandrene based[25] chiral dienes boast expedient, modular syntheses from inexpensive chiral starting material and importantly have delivered both excellent yields and enantioselectivities.

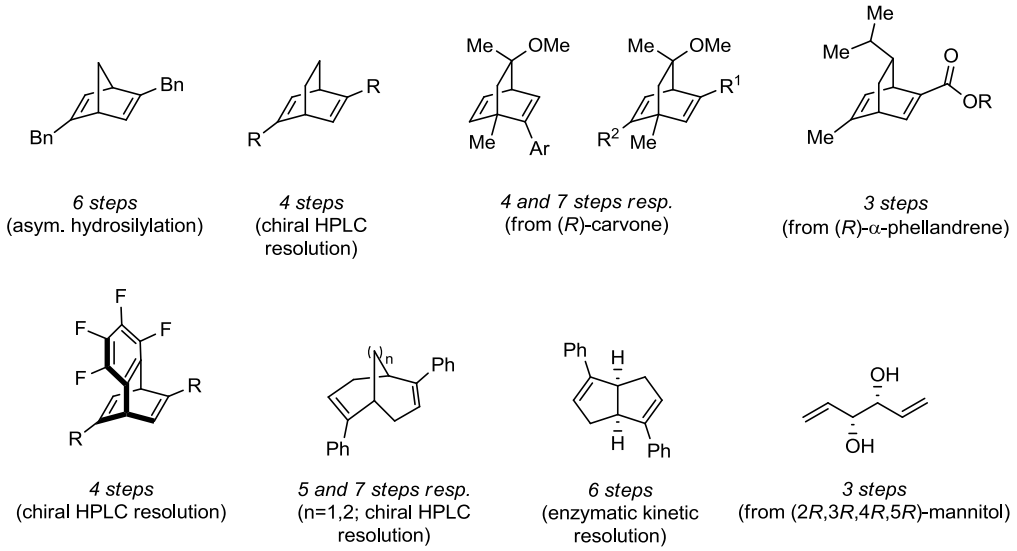
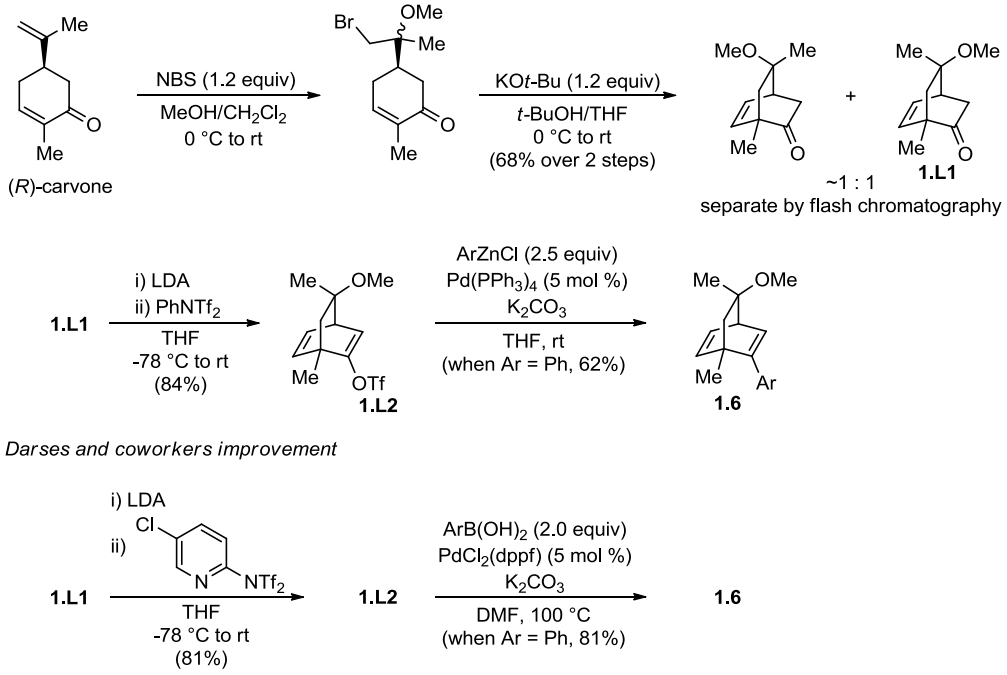


Figure 1.3. Representative Chiral Diene ligands for Rhodium Catalyzed Conjugate Addition

Carreira and coworkers have described a clever 4 step modular synthesis of chiral dienes from readily available and inexpensive (*R*)-carvone (either enantiomer available in bulk for <$100/kg) (Scheme 2.3).[24a] Gratifyingly the stereogenic center is already set in the starting

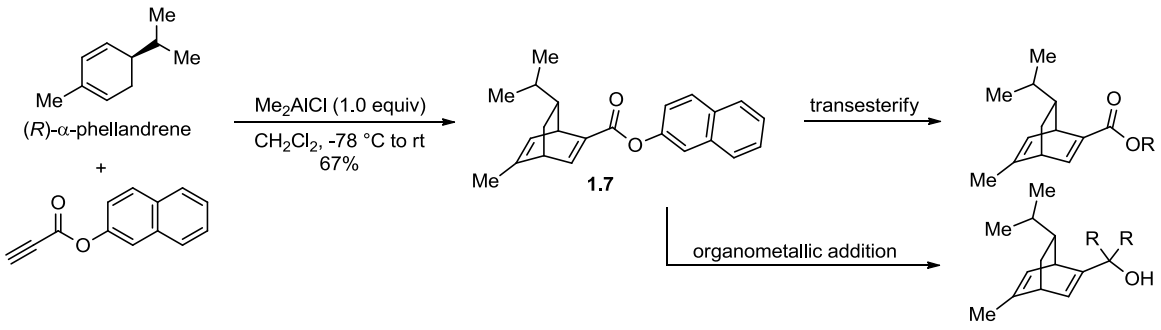
material and following separation of the diastereomers formed from the base promoted cyclization (standard flash chromatography on silica gel), formation of the alkenyl triflate opens up opportunities for cross-coupling with different partners. Later, Darses and coworkers reported improvements[26] to the chiral diene synthesis by using the more active Comins' reagent for the triflation and using arylboronic acids as opposed to arylzincs for the cross-coupling step (increased yields and operational simplicity). Later, Carreira and coworkers described a route to a class of second generation disubstituted (C-2/C-5) carvone based chiral diene ligands[24b] which in some cases provided higher selectivity for ACAs.

Scheme 1.3. Carreira's Carvone Based Chiral Dienes



Hayashi and Rawal have also described an expedient modular synthesis of chiral dienes from (*R*)-α-phellandrene (Scheme 2.4).[27] Again, the stereogenic center is already set in the starting material and a Diels-Alder reaction with a propargylic ester furnishes the chiral diene ligand (**1.7**). Flexibility in the synthesis is achieved by reacting alternate propargylic esters in the cycloaddition or alternatively performing functional group manipulations on the ester following cycloaddition.

Scheme 1.4. Hayashi/Rawal Phellandrene Based Chiral Dienes



Under rhodium catalysis, enantioselective conjugate additions of the following alkenyl nucleophiles to α,β-unsaturated acceptors have been demonstrated (Figure 1.4): boronic acids,[28] boronates,[29] trifluoroborates,[30] silanes[31] and zirconiums.[32] Surprisingly absent are alkenylstannanes despite potential advantages and some literature precedent of racemic protocols under rhodium catalysis.

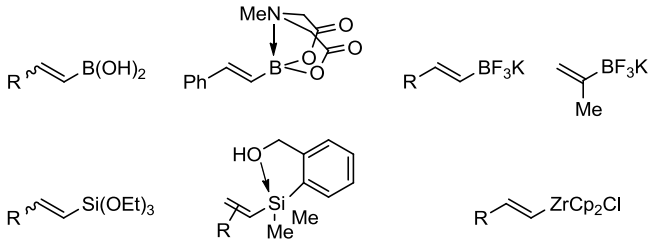


Figure 1.4. Alkenyl Nucleophiles Employed in Rhodium Catalyzed ACA

Access to alkenylstannanes does not pose a significant problem and hydrostannation of terminal alkynes represents a common route; furthermore, alkenylstannanes are air and moisture stable. Radical hydrostannation is known to selectively form the *E*-alkene (thermodynamic product) albeit with a significant amount of the other isomers.[33] Fortunately, recent advances of metal catalyzed protocols have been described to selectively synthesize the suite of isomers including Chong and coworkers palladium catalyzed *E*-selective hydrostannation,[34] a Lewis acid catalyzed protocol for *Z*-selective alkenes,[35] as well as a molybdenum catalyzed hydrostannation to access geminal alkenylstannanes (Figure 1.5).[36]

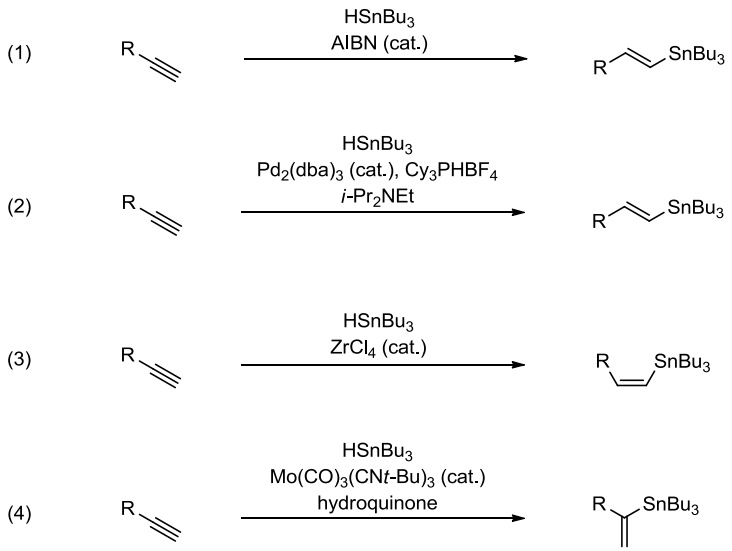


Figure 1.5. Hydrostannation Protocols of Terminal Alkynes

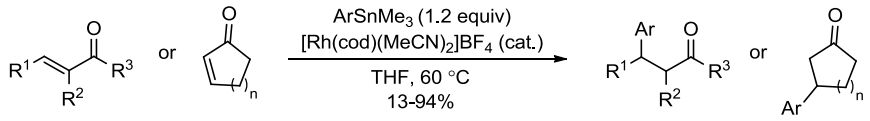
While exposure to dimethyl and trimethylstannanes have resulted in death,[37] the use of less volatile organotin compounds is the most commonly executed precautionary measure (ex. $HSnMe_3$ bp = 60 °C at 1 atm,[38] where $HSnBu_3$ bp = 68-71 °C at 0.3 Torr[39] which by pressure-temperature nomograph is equivalent to bp = 263-271 °C at 1 atm) at the trivial, in perspective, expense of atom economy.[40] However, trimethylorganostannanes still see use owing to an apparent increase of transmetalation rate (relative to the tributylorganostannane)[43] as well as the less greasy nature for forming crystalline compounds (facilitating absolute stereochemical determination by x-ray[41]). While in some cases the removal of tin byproducts or excess reagent may be tedious due to similar polarity of the compound of interest remedies do exist: 1) manipulations of the tin compound to alter polarity in the workup, 2) use of organotin reagents with one or more polar substituents or 3) polymer-supported reagents.[42]

1.1.2. Rhodium Catalyzed Conjugate Addition of Aryl and Alkenylstannanes

Oi and coworkers were first to describe conditions for the rhodium catalyzed conjugate addition of aryltrimethylstannanes to α,β-unsaturated ketones and esters in variable yields (Scheme 1.5).[43] Of the substrates examined, the addition of phenyltrimethylstannane to chalcone represented the highest in 94% yield. Notably, the arylstannane additions were able to proceed

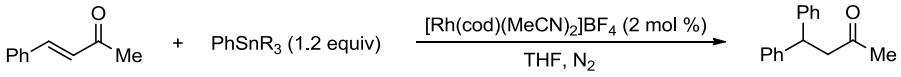
under mild, anhydrous conditions with the cationic rhodium diene catalyst. The authors also noted that the reactions initially form stannyl enol ethers which are hydrolyzed in the workup.

Scheme 1.5. Anhydrous Conditions for Arylstannane Addition



In studying the conjugate addition of arylstannanes Oi noted several important findings including that the reaction proceeded at an appreciable rate and efficacy under cationic rhodium catalysis when the reaction temperature was elevated to 60 °C (Table 1.2, entries 1 vs 2) and as opposed to under neutral rhodium catalysis (entry 3).[44] Interestingly, the addition of phosphine ligands resulted in reduced yields (entries 4-6) and the addition of water was found to increase yields (entry 7) by hydrolyzing the initially formed stannyl enol ether as it was observed to react further with the acceptor starting material (presumably by conjugate addition although not specified in the paper). Furthermore, it was apparent by the substantial reduction in yield that larger substituents (A values of $SnMe_3$ = 1.00, $SnPh_3$ = 1.44 kcal/mol)[45] on the tin atom were found to have a strong detrimental steric influence during transmetalation (entries 7-9).

Table 1.2. Additive Effects on the Conjugate Addition

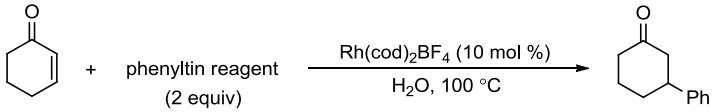


entry	$PhSnR_3$	additive	temp (°C)	time (h)	yield (%)
1	$PhSnMe_3$	none	rt	20	51
2	$PhSnMe_3$	none	60	2	86
3[a]	$PhSnMe_3$	none	60	2	53
4	$PhSnMe_3$	PPh_3 (0.02 equiv)	60	2	63
5	$PhSnMe_3$	PPh_3 (0.04 equiv)	60	2	15
6	$PhSnMe_3$	dppp (0.02 equiv)	60	2	48
7	$PhSnMe_3$	H_2O (1 equiv)	60	2	98
8	$PhSnBu_3$	H_2O (1 equiv)	60	2	70
9	$PhSnPh_3$	H_2O (1 equiv)	60	2	11

[a] $[RhCl(cod)]_2$ was used as the catalyst.

The electronic effect of substituents on aryltin reagents for the rhodium catalyzed conjugate addition has been studied by Li and coworkers (Table 1.3).[46] They found that the reaction was strongly inhibited by tin subtituents that had a dominant electron withdrawing effect (chlorides by induction) and that groups with a dominant electron donating effect permitted the reaction (alkyl, hydroxyl or alkoxy). Most notably, the addition of potassium hydroxide permitted the reaction of trichlorophenyltin[47] to proceed in comparable yield to the trialkylphenyltin at a reduced temperature due to presumed halogen-hydroxyl exchange. Transient organostannate complexes, formed under the basic conditions, were postulated to further enhance the reactivity of the carbon tin bonds to transmetalation with rhodium. It was noted that α,β-unsaturated esters undergo saponification under the basic conditions described for entries 6 and 7.

Table 1.3. Electronic Effects of Tin Substituents

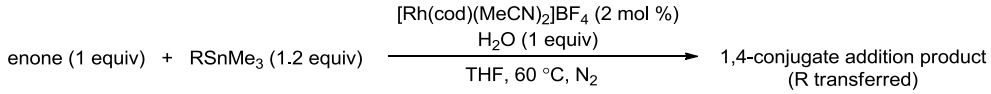


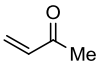
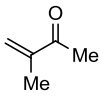
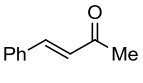
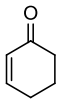
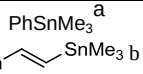
entry	phenyltin reagent	yield (%)
1	$PhSnMe_3$	85
2	Ph_3SnBu	62
3	Ph_3SnPh	11
4	Ph_3SnCl	trace
5	$PhSnCl_3$	trace
6	$PhSnCl_3$/KOH (10 equiv)	92
7[a]	$PhSnCl_3$/KOH (10 equiv)	82
8	Ph_3SnOH	52
9	Ph_3SnOMe	53

[a] Reaction was performed at rt with 2.5 mol % of the catalyst.

Oi and coworkers found marked differences in reactivity between phenyltrimethylstannane and (*E*)-trimethyl(styryl)stannane with the later reacting sluggishly with enones to deliver conjugate addition products in poor yields (Table 1.4).[44]

Table 1.4. Lower Reactivity of Alkenylstannanes

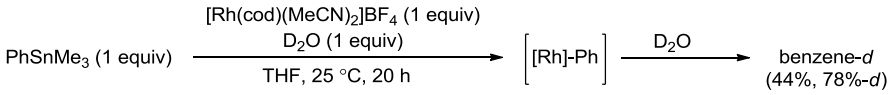


1,4-conjugate addition product	enone			
				
 [a]	80	88	98	93
[b]	70	45	0	23

[a] Reaction times of 2-5 h. [b] Reaction times of 20 h.

Further probing of the conjugate addition of organotins was carried out by reacting aryltrimethylstannane in the presence of equimolar amounts of D_2O and cationic rhodium catalyst (Scheme 1.6).[44] Full consumption of starting material was observed and deuterated benzene was isolated. This control reaction demonstrates that the arylrhodium species formed upon transmetalation is water-labile; however, it can react faster with α,β-unsaturated carbonyl compounds if present (see Table 1.3). Phenyltrimethylstannane was shown to be water stable in a separate control experiment.

Scheme 1.6. Water Instabilitiy of Arylrhodium Species



With the above experiments in mind as well as Hayashi's mechanism (Figure 1.6), Oi and coworkers suggested the following mechanism for the conjugate addition of alkenylstannanes under cationic rhodium catalysis.[44] The reaction consists of the same basic steps: transmetalation to form an organorhodium species, migratory insertion, followed by catalyst turnover by stannylation. The initially formed stannyl enol ether can then be hydrolyzed under aqueous conditions.

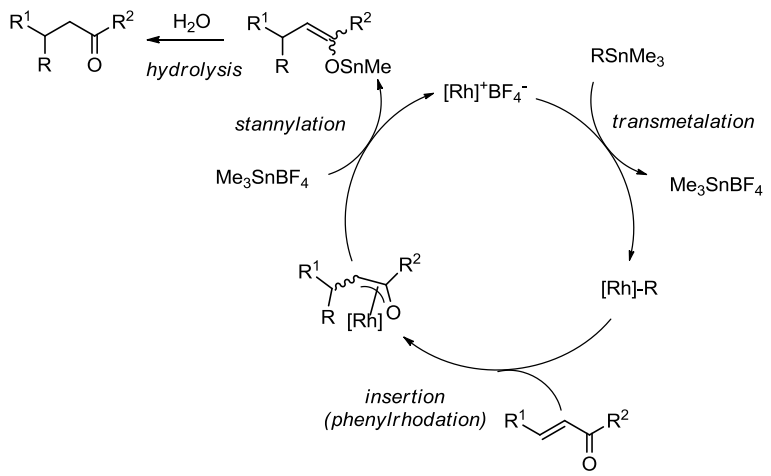
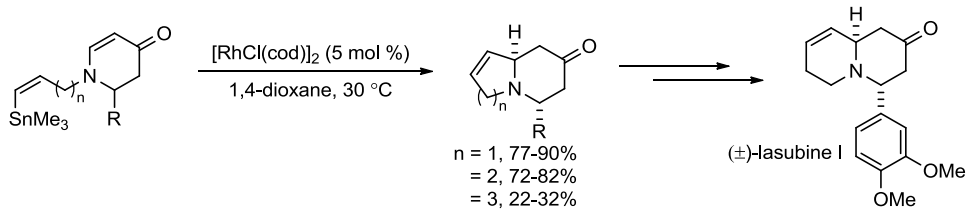


Figure 1.6. Mechanism of Rhodium Catalyzed Conjugate Addition

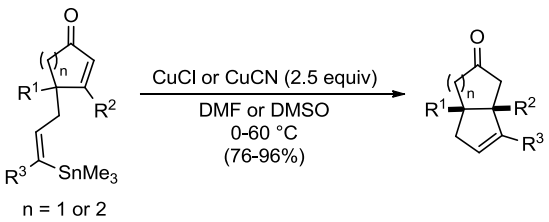
An intramolecular addition of alkenylstannanes has been described by Furman and coworkers to access 1-azabicycles with high diastereoselectivity (Scheme 1.7).[48] They have also applied the methodology to a synthesis of a natural product (racemic lasubine I).

Scheme 1.7. Rhodium Catalyzed Intramolecular Alkenylstannane Addition



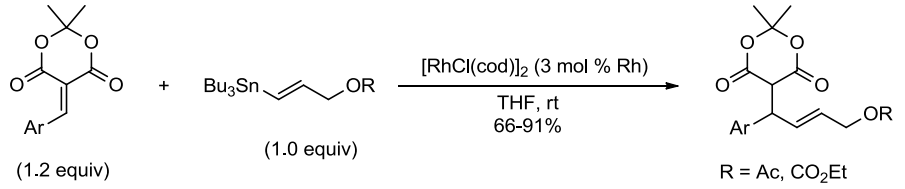
Of note, the catalytic nature of this conjugate addition is in contrast with Piers' research regarding intramolecular addition of alkenylstannanes[49] (Scheme 1.8) which requires an excess of copper (I) salt (recognized as an unfavourable, reversible transmetalation[50]).

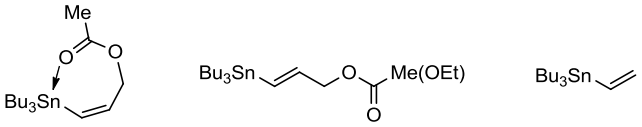
Scheme 1.8. Intramolecular Alkenylstannane Addition Stoichiometric in Copper



The Fillion group has described a mild, intermolecular addition of ambiphilic alkenylstannanes to benzylidene Meldrum's acids under rhodium catalysis (Scheme 1.9).[51] These alkenylstannanes are considered amibiphilic as the carbon-tin bond is a nucleophile and the allylic acetate or carbonate is an electrophile upon reacting with palladium. This method proceeded in moderate to high yields over a range of aromatic substitutions with both allylic acetate and carbonate vinylstannanes. The cationic rhodium catalyst Oi employed ($[Rh(cod)(MeCN)_2]BF_4$) afforded comparable yields. Furthermore, an increased reaction rate was observed with these alkenylstannanes when compared to vinyltributylstannane plausibly due to facilitation of the transmetalation by a more polarized carbon-tin bond and/or by a proximity effect by the binding of the carbonyl oxygen to the rhodium (Scheme 1.9). Of note, intramolecular activation could also aid the transmetalation in the case of the *Z*-alkenylstannane. This report also represented the extension of scope of addition of alkenylstannanes to α,β-unsaturated esters by using the highly electrophilic benzylidene Meldrum's acids and notably circumvents use of trimethylstannane derivatives.

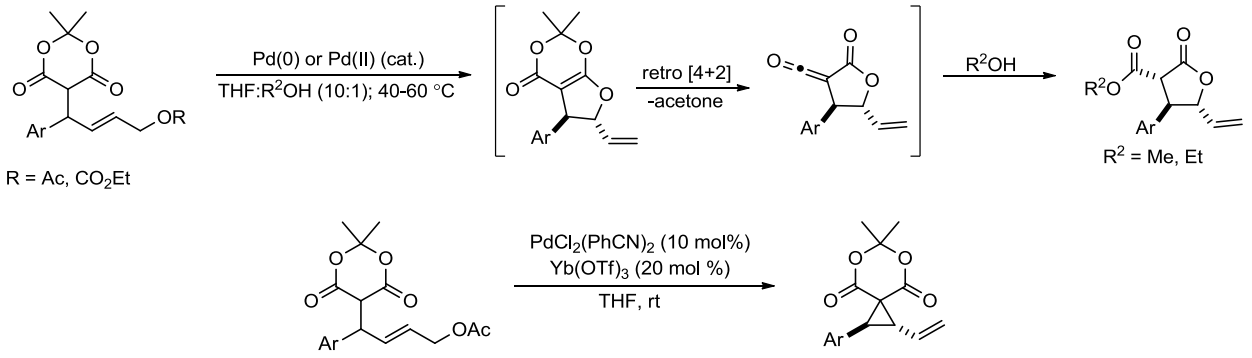
Scheme 1.9. Fillion Group Racemic Addition of Alkenylstannanes





Under palladium catalysis the products could be further transformed into γ-butyrolactones or cyclopropanes (O vs C-alkylation) with high diastereoselectivity (Scheme 1.10). The cyclopropane was formed as a single diastereomer whose stereochemistry was confirmed by x-ray analysis and butyrolactones were formed in 18:1 anti/syn to up to >20:1 dr.

Scheme 1.10. Palladium Catalyzed Transformations of Conjugate Addition Products



Prior to the research described in this chapter, the asymmetric conjugate addition of organostannanes remained undeveloped with the exception of Hayashi's pioneering single entry describing the addition of phenyltrimethylstannane to cyclohexenone with a chiral diene rhodium catalyst.[12]

1.2. Proposal

The objective was to develop a protocol for the intermolecular asymmetric conjugate addition of functionalized alkenylstannanes and then explore possible extensions of the methodology (Figure 1.7). The system previously studied by the Fillion group seemed like an ideal starting point as they had demonstrated the reaction proceeded in moderate to high yields with an achiral rhodium diene catalyst. [51]

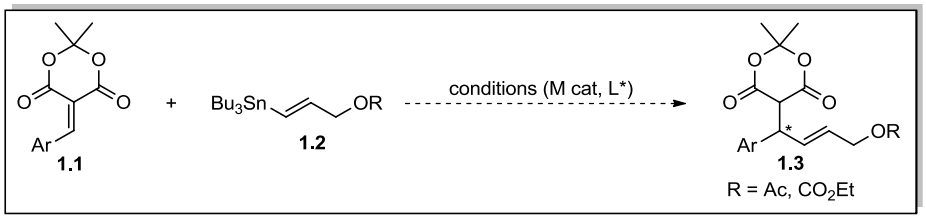


Figure 1.7. Proposal for Asymmetric Conjugate Addition of Alkenylstannanes

1.3. Results and Discussion

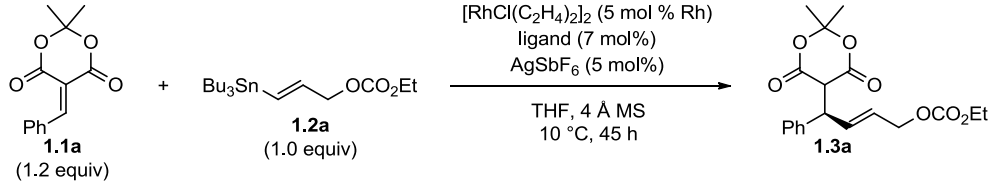
In evaluating suitable reactions conditions of benzylidene Meldrum's acid **1.1a** and (*E*)-allylic carbonate stannane **1.2a** (Table 1.5), the rhodium pre-catalyst [$RhCl(C_2H_4)_2$] was chosen as substitution of the weakly binding, ethylene ligands is known to be a facile process as opposed to the bidentate cod ligands used in the racemic methodology (of significance to circumventing a background reaction catalyzed by achiral catalyst).[51] Cognizant that the low reactivity of the C-Sn bond presents a barrier to transmetalation, ligand selection was a crucial consideration (Table 1.4). No conversion was observed when phosphorus based ligands including phosphoramidate **1.4** and (*R*)-BINAP (**1.5**) were implemented (entries 1 and 2). Fortunately, as described in the introduction, chiral diene ligands have recently emerged as a complementary alternative to privileged phosphine scaffolds as a way of overcoming low catalytic activity while maintaining high enantioselectivity.[4,52]

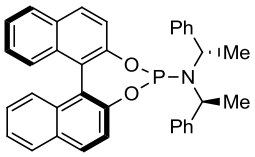
An encouraging result was obtained when (*R*)-carvone derived ligand (**1.6a**) was used, which afforded the desired product with excellent conversion and an enantiomeric ratio of 61:39 (entry 3). While introduction of an *ortho*-substituent of the aryl ring on the chiral diene provided an increase in selectivity (entry 4), the more interesting result was the large gain in er observed upon addition of $AgSbF_6$ to sequester the chloride ion from the Rh(I) complex (entry 5).[53] Continuing under these cationic conditions, it was found that while decreasing the temperature provides increased enantioselectivity, it does so at the eventual expense of conversion (entries 6-8). Known ligand **1.6c**, which has delivered higher enantioselectivity than **1.6a** and **1.6b** in other systems,[26] and newly synthesized 9-anthracenyl-containing **1.6d** (both of which have two ortho-substituents) were found to be poorly or not at all reactive (entries 9 and 10 respectively).

Based on these results, it was suggested that the optimal combination of selectivity and conversion would come from a ligand bearing an arene with a single, large group at the *ortho* position. Taking that approach, new ligands **1.6e-g** were prepared and all proved to be more selective than **1.6b** and to give higher conversion than **1.6c** (entries 11-15). Implementing $AgSbF_6$, diene **1.6f** was settled upon as the ligand of choice on the basis of its slight superiority in terms of enantioselectivity, conversion and its higher yielding preparation.[54] Lastly,

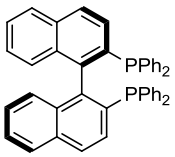
incorporation of powdered molecular sieves was found to be beneficial in preventing trace hydrolysis of the benzylidene (*vida infra*) leading to higher isolated yields (entry 16).

Table 1.5. Evaluation of Reaction Parameters

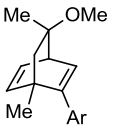




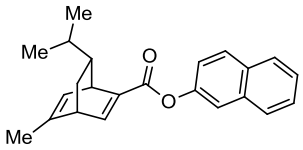
(**1.4**)



(**1.5**)



Ar = C_6H_5 (**1.6a**)
2-MeC_6H_4 (**1.6b**)
2,6-$(Me)_2C_6H_3$ (**1.6c**)
9-anthracene (**1.6d**)
2-*i*-PrC_6H_4 (**1.6e**)
2-$CF_3C_6H_4$ (**1.6f**)
2-CF_3-(4-OMe)C_6H_3 (**1.6g**)



(**1.7**)

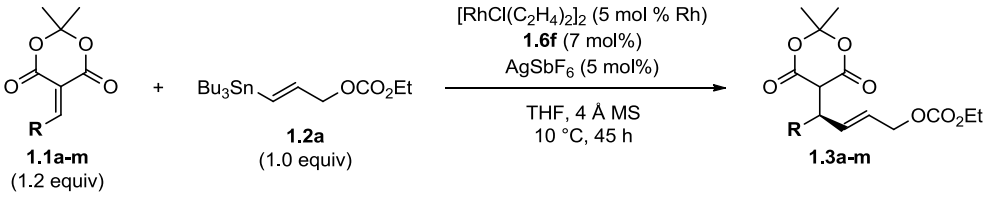
entry	ligand	temp (°C)	time (h)	conversion (%)	er
1[a]	**1.4**	rt	24	0	/
2[a]	**1.5**	rt	24	0	/
3[a]	**1.6a**	rt	24	>99	61:9
4[a]	**1.6b**	rt	24	>99	71:29
5	**1.6b**	rt	24	>99	88:12
6	**1.6b**	0	37	>99	91:9
7	**1.6b**	-10	24	37	93:7
8	**1.6b**	-20	24	20	93:7
9	**1.6c**	0	46	23	94:6
10	**1.6d**	0	45	0	/
11	**1.6e**	0	46	>99	93:7
12	**1.6f**	0	45	51	95:5
13[b]	**1.6f**	10	45	>99	93:7
14	**1.6f**	rt	45	>99	91:9
15	**1.6g**	10	45	>99	92:8
16[c]	**1.6f**	10	45	>99	94:6
17[d]	**1.7**	10	45	46	6:94

[a] Entries1-4 performed without $AgSbF_6$. [b] 66% isolated yield. [c] 4 Å molecular sieves added; isolated yield 84%. [d] 4 Å molecular sieves added; isolated yield 23%.

Subsequently, an initial trial of (*R*)-phellandrene derived diene (**1.7**) was found to deliver the opposite enantiomer in comparable selectivity, albeit with significantly inferior conversion and isolated yield (entry 17).

We were pleased to find that the addition of the (*E*)-allylic carbonate (**1.2a**) was general to a number of substituted benzylidene Meldrum's acids proceeding in comparable enantioselectivity regardless of the nature of the substituent on the phenyl ring (Table 1.6).[55] In addition the reaction tolerated aryl halides (entries 5, 6, and 12) and boronic esters (entries 3 and 10), highlighting the mild conditions and providing the potential for orthogonal reactivity. Less electrophilic benzylidene **1.1d** reacted sluggishly, albeit with good selectivity (entry 4) and conversely, non-aryl alkylidene **1.1m** reacted with relatively good yield albeit substantially lower selectivity (entry 13).

Table 1.6. Alkylidene Scope

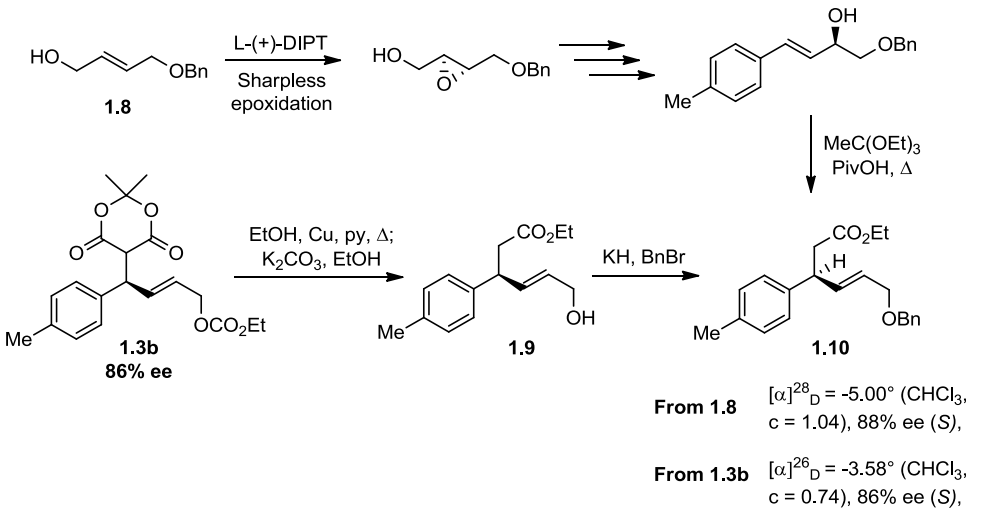


entry	R	yield (%)	er
1	C_6H_5 (**1.1a**)	84 (**1.3a**)	94:6
2	4-MeC_6H_4 (**1.1b**)	42 (**1.3b**)	93:7
3	4-(Bpin)C_6H_4 (**1.1c**)	39 (**1.3c**)	93:7
4	4-(OMe)C_6H_4 (**1.1d**)	17 (**1.3d**)	93:7
5	4-Br (**1.1e**)	39 (**1.3e**)	93:7
6	4-Cl (**1.1f**)	29 (**1.3f**)	90:10
7	2-naphthyl (**1.1g**)	49 (**1.3g**)	92:8
8	2-(OMe)C_6H_4 (**1.1h**)	58 (**1.3h**)	92:8
9	3-MeC_6H_4 (**1.1i**)	51 (**1.3i**)	93:7
10	3-(Bpin)C_6H_4 (**1.1j**)	57 (**1.3j**)	93:7
11	3-(OMe)C_6H_4 (**1.1k**)	54 (**1.3k**)	91:9
12	3-BrC_6H_4 (**1.1l**)	70 (**1.3l**)	95:5
13	Me (**1.1m**)	73 (**1.3m**)	77:23

[a] Absolute configuration assigned by analogy to a derivative of compound **1.3b**; see Scheme 1.11.

The absolute configuration of Meldrum's acid **1.3b** was determined by comparison to the optical rotation of known compound **1.10** (Scheme 1.11). In the synthesis by Takano and coworkers,[56] chirality was introduced by Sharpless asymmetric epoxidation (SAE) and transferred to the benzylic position via Claisen rearrangement. Aside from the predictability of the SAE, the configuration was further confirmed by Mosher ester analysis following ozonolysis and reduction of **1.10**. From Meldrum's acid **1.3b**, **1.9** was prepared by ring opening with EtOH in pyridine, followed by removal of the carbonate; these steps were confirmed to have not changed the enantiomeric excess by chiral HPLC. Reaction of the allylic alcohol with KH and BnBr then gave **1.10**. Comparison of the direction of optical rotation assigns **1.10** prepared from **1.3b** a (*S*)-configuration, and so **1.3b** was determined to be of (*R*)-configuration. The absolute configurations of all other chiral Meldrum's acids **1.3a-p** were assigned by analogy to **1.3b**.

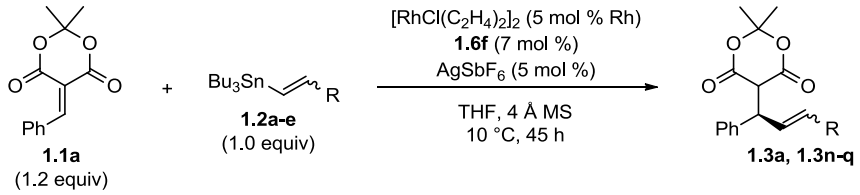
Scheme 1.11. Determination of Absolute Configuration



Other alkenylstannanes were added successfully albeit none matched the carbonate (**1.2a**) in terms of enantioselectiviy (Table 1.7). The addition of the (*E*)-allyl acetate tin reagent (**1.2b**) proceeded in a lower yield (possibly due to less basic carbonyl oxygen relative to **1.2a**) and its isomer (**1.2c**) proceeded with full retention of double bond geometry to afford (*Z*)-**1.3o** albeit in lower enantioselectivity. Likewise to the observation in the racemic methodology,[51] addition of vinyltributylstannane proceeded sluggishly and gave low conversion and selectivity. Furthermore, evidence of the accelerating effect of the allylic functionality in **1.2a-c** being not

solely linked to polarization created by electron withdrawal by the adjacent oxygen atom was provided with alkenylstannane **1.2e** producing no conversion (entry 5).

Table 1.7. Scope of Alkenylstannane

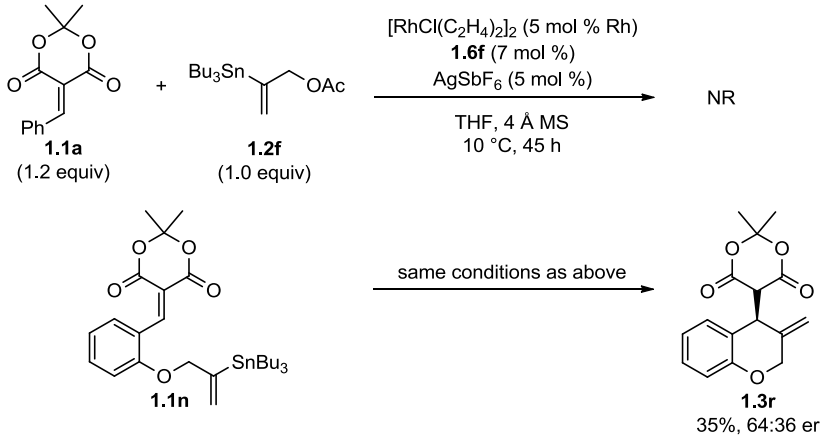


Entry	R	yield (%)	er
1	(*E*)-CH_2OCO_2Et (**1.2a**)	84 (**1.3a**)	94:6
2	(*E*)-CH_2OAc (**1.2b**)	61 (**1.3n**)	89:11
3	(*Z*)-CH_2OAc (**1.2c**)	87 (**1.3o**)	83:17
4	H (**1.2d**)	ND (**1.3p**)[a]	63:37
5	(*E*)-CO_2Et (**1.2e**)	NR (**1.3q**)	/

[a] Product **1.3p** was inseparable from excess benzylidene **1.1a**; see experimental for details.

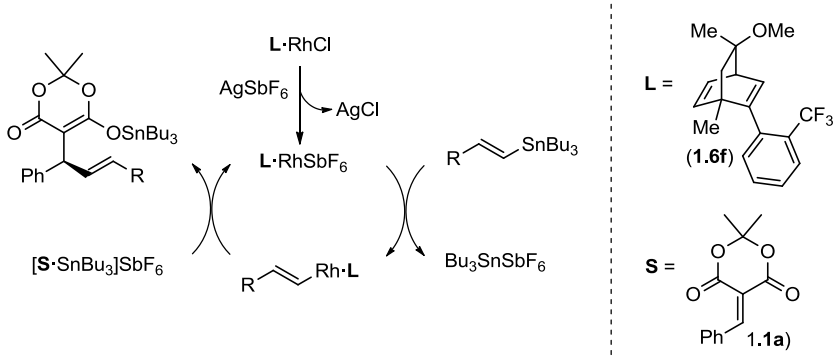
In contrast to the terminal alkenyltins studied, the analogous geminal stannane (**1.2f**) proved resistant to conjugate addition; however, the preparation of an intramolecular model substrate (**1.1n**) was met with some success (Scheme 1.12).[57] Notably, no isomerization of the sensitive exo-methylene group was observed.

Scheme 1.12. Inter- and Intramolecular Reactions of Geminal Alkenyl Stannanes



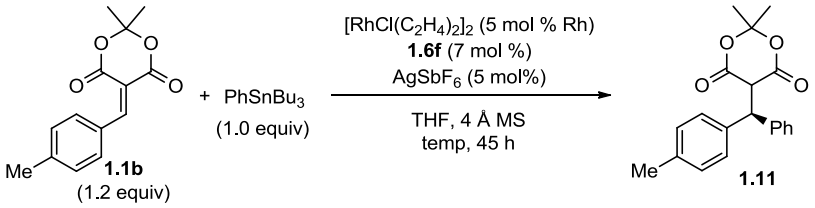
Considering the significant increase in enantioselectivity observed by introduction of $AgSbF_6$ to remove chloride from the Rh(I) precatalyst, we propose the mechanism outlined in Scheme 1.13. Following ligand exchange and removal of the chloride from the precatalyst, transmetalation between Rh and the alkenylstannane forms the active nucleophile while generating a cationic Sn species, which can act as a Lewis acid. Complexation of the benzylidene to Sn further activates the electrophile and leads directly to the stable Sn-enolate upon addition of the alkenyl rhodium. Significantly, a similar cooperative mechanism has recently been proposed in the additions of tetraarylborates to cycloalkenones[58] and this concept may open avenues for further improvement to our method.

Scheme 1.13. Proposed Mechanism



The conditions optimized for the alkenylstannane addition also proved directly applicable to the addition of phenyltributylstannane (Table 1.8). Again, the addition of $AgSbF_6$ was critical to obtaining higher enantioselectivity (entry 1 vs 2). Furthermore, the reaction proceeded in higher enantioselectivy at a reduced temperature (entries 2-4) which is consistent with a more facile tin to rhodium transmetalation relative to the alkenylstannane.

Table 1.8. Asymmetric Addition of Phenyltributylstannane



entry	temp	yield (%)	er
1[a]	rt	92	85:15
2	rt	76	93:7
3	10 °C	73	93:7
4	0 °C	80	96:4

[a] Reaction performed in absence of $AgSbF_6$.

1.4. Summary

In summary, the first examples of inter- and intramolecular enantioselective conjugate alkenylations employing organostannanes have been described.[59] Notably, the cationic and anhydrous conditions required for the asymmetric alkenylation is complementary to existing protocols employing other alkenylmetals (Figure 1.8). The modular synthesis of (*R*)-carvone based chiral diene ligands, introduced by Carriera and coworkers, was also of utmost importance in obtaining good conversions, selectivity and facilitating this investigation.

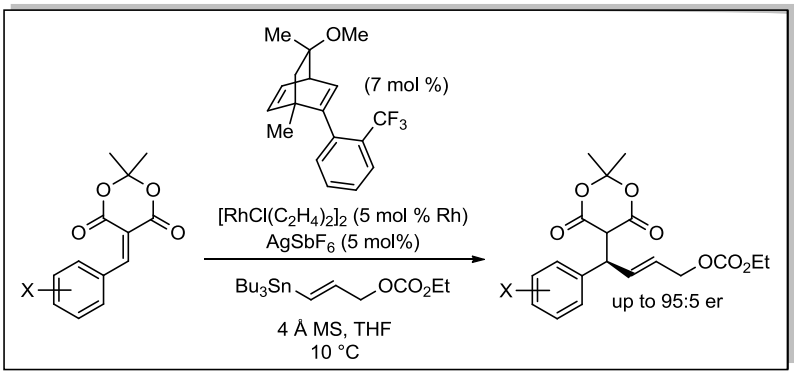


Figure 1.8. Developed Asymmetric Conjugate Addition

1.5. Future Work

Probing the increase in reaction rate with allylic carbonate and acetate alkenylstannanes as compared to vinylstannane could be further studied by synthesizing a series of alkenylstannanes with and without Lewis basic groups at various lengths on the tether (Figure 1.9). Furthermore, the application of the conditions to other tin-based nucleophiles to expand the reaction scope seems promising based on the aryltin addition result (Table 1.7). Also, continued screening of diene ligands may yield improvements in selectivity and conversion; however, to expand this methodology to both other acceptors (including less electrophilic β,β-disubstituted α,β-unsaturated esters) and nucleophiles as well as address the stigma of working with organostannanes, using triethanolamine based metallotrane nucleophiles (**1.13**) may be a promising direction (Scheme 1.14).

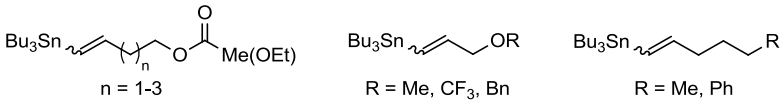
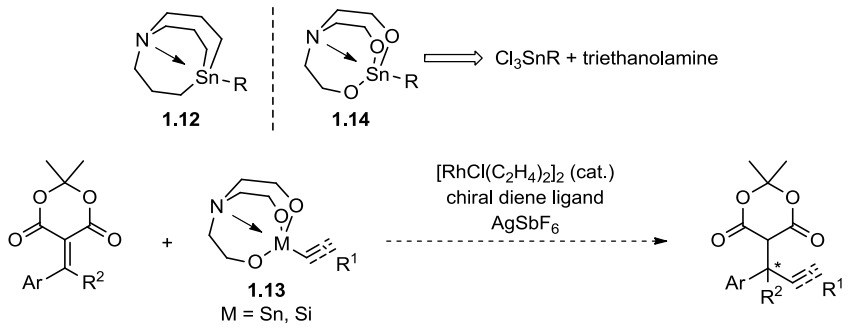


Figure 1.9. Alkenylstannane Probes

While organostannatranes (**1.12**) have been embraced for Stille couplings[60] they have not seen use in rhodium catalyzed conjugate additions. Stannatranes boast an unusually long exocyclic tin-carbon bond (on average 0.1 Å longer than a typical alkylstannane) and internal tin-nitrogen coordination which both facilitate transmetalation.

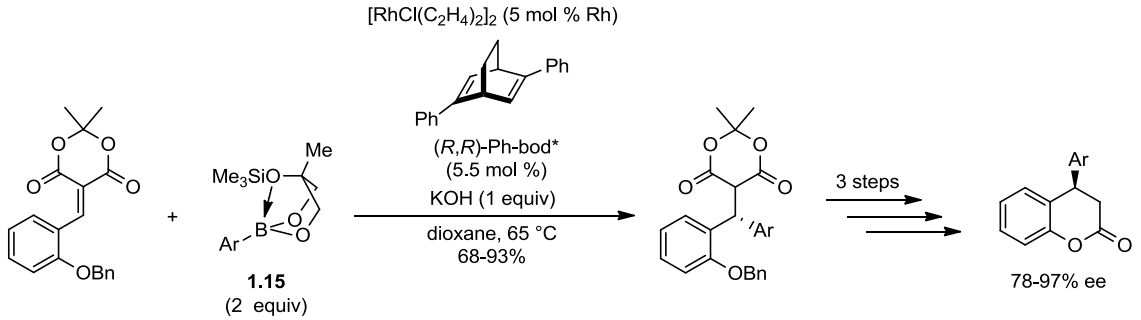
Based on the accelerating effect of electron releasing substituents (Table 1.3)[46] triethanolamine based metallatranes (**1.13**, stannotranes and silatranes), which have been readily accessed but the studies have been limited to coordination chemistry,[61] should facilitate transmetalation to a greater extent (as well as purification due to increased polarity). Furthermore, these monoorganotin compounds (**1.14**) would steer away from the stigma of working with toxic trialkylstannanes.

Scheme 1.14. Proposed Future Work – Triethanolamine Based Metallatranes



Alternatively, the addition of boron nucleophiles can be explored with benzylidene Meldrum's acid acceptors. In that regard Frost's group has described a similar strategy to that proposed above with asymmetric additions of silyl protected aryl dioxaborinanes (**1.15**) which proceed in moderate to high yields and enantioselectivity (Scheme 1.15).[62] Notably, hydrolysis of the Meldrum's acid derivatives was circumvented under these conditions. The dioxaborinanes are obtained from esterification of arylboronic acids with 2-(hydroxymethyl)-2-methylpropane-1,3-diol under Dean Stark conditions and then treatment with chlorotrimethylsilane and triethylamine. Amongst other conditions evaluated, poor conversions were obtained with arylboronic acids, aryltrifluoroborates and the unprotected dioxaborinane. The enantioselectivities of the conjugate addition step were measured upon conversion to the respective chromanone in 3 steps (decarboxylation, deprotection and esterification).

Scheme 1.15. Frost's Asymmetric Aryl Addition to Benzylidene Meldrum's Acids



1.6. Experimental

General Considerations

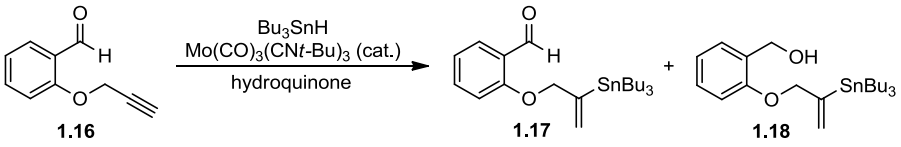
Reactions

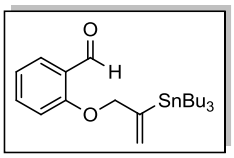
All reactions were carried out in oven or flame-dried glassware under dry nitrogen atmosphere. Glassware and stirbars used for conjugate addition reactions were washed with *aqua regia* (nitric and hydrochloric acid, 1:3 ratio) and rinsed with deionized water to remove trace metals. CH_2Cl_2, THF, and Et_2O were purified in solvent systems based on the published procedure; [63] THF was then degassed via 3 freeze-pump-thaw cycles. Benzene was distilled from sodium-benzophenone ketyl under nitrogen. DMF was distilled under vacuum over CaH_2 into a Schlenk flask under argon, and degassed by purging with argon. Pyridine was distilled over CaH_2 and stored in a Schlenk flask under nitrogen. EtOH was distilled over Mg/I_2 under argon and stored over 3Å molecular sieves. Powdered 4 Å molecular sieves used in conjugate additions were activated by drying in an oven at 140 °C for 18 h before being transferred into an inert atmosphere glovebox. 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 or iodine stain. Flash chromatography was performed using 230-400 mesh silica gel.

Characterization

^{1}H and ^{13}C NMR spectra for all compounds were obtained in $CDCl_3$ at 300 MHz and 75 MHz, respectively. 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 ^{1}H decoupling in $CDCl_3$ referenced to TFA (-76.5 ppm). Melting points are uncorrected. Optical rotations were recorded in cells with 1 dm path length. Chiral HPLC analyses were performed using a Chiralcel AD-H column (250 x 4.6 mm) with *i*PrOH:hexane solvent mixtures as eluent. High resolution mass spectra were run at the University of Waterloo Mass Spectrometry facility.

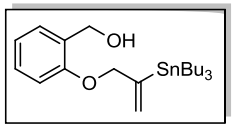
Synthesis of the aldehyde precursor to benzylidene Meldrum's acid 1.1n





2-(2-(Tributylstannyl)allyloxy)benzaldehyde (1.17) and (2-(2-(Tributylstannyl)allyloxy)phenyl)methanol (1.18)

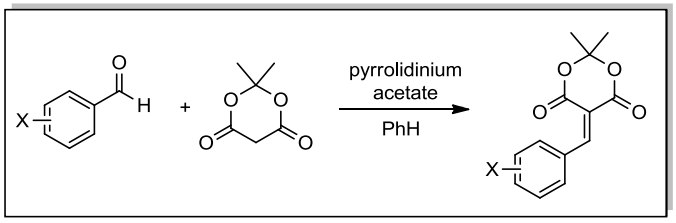
The procedure is based on the Mo-catalyzed hydrostannation reported by Kazmaier:[36] A flame dried Schlenk tube equipped with a stir bar was cooled under argon and charged with 2-(prop-2-ynyloxy)benzaldehyde[64] (**1.16**, 250 mg, 1.56 mmol, 1 equiv), hydroquinone (16 mg, 0.14 mmol, 9 mol %), $Mo(CO)_3(CN\textit{t}\text{-}Bu)_3$[65] (28 mg, 0.062 mmol, 4 mol %), and THF (1.56 mL). Freshly distilled $HSnBu_3$ (1.26 mL, 4.68 mmol, 3 equiv) was then added slowly to the mixture under argon, the Schlenk tube was sealed and immersed in a preheated 55 °C oil bath for 17 h. The reaction mixture was allowed to cool to room temperature before being passed through a pad of Celite with EtOAc as eluent, and then concentrated. The ^{1}H NMR of the crude reaction mixture revealed a 1:0.30 ratio of aldehyde **1.17**: alcohol **1.18**. The two compounds were isolated by silica gel chromatography (previously neutralized with NEt_3) eluting with a gradient from 100:0 to 1:1 hexanes:CH_2Cl_2. Aldehyde **1.17** eluted first and was isolated as a pale yellow oil (442 mg, 63% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 10.52 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.49 (dt, J = 7.9, 1.6 Hz, 1H), 7.05-6.93 (m, 2H), 6.02 (d, $J_{Sn\text{-}H}$ = 121.7, $J_{H\text{-}H}$ = 1.6 Hz, 1H), 5.39 (d, $J_{Sn\text{-}H}$ = 58.4, $J_{H\text{-}H}$ = 1.6 Hz, 1H), 4.78 (s, $J_{Sn\text{-}H}$ = 28.2 Hz, 2H), 1.52-0.81 (m, 27H): ^{13}C NMR ($CDCl_3$, 75 MHz) 189.3 (CH), 161.0 (C), 149.9 (C), 135.6 (CH), 128.2 (CH), 126.2 (CH_2), 124.9 (C), 120.5 (CH), 112.9 (CH), 75.4 (CH_2, $J_{Sn\text{-}C}$ = 39.2 Hz), 28.9 (CH_2, $J_{Sn\text{-}C}$ = 18.1 Hz), 27.2 (CH_2, $J_{Sn\text{-}C}$ = 57.9 Hz), 13.5 (CH_3), 9.5 (CH_2, $J_{Sn\text{-}C}$ = 339.8, 324.8 Hz); HRMS (ESI) *m/z* calcd for $C_{22}H_{36}O_2{}^{120}Sn^{23}Na$ ($[M + Na]^+$): 475.1635. Found: 475.1650.



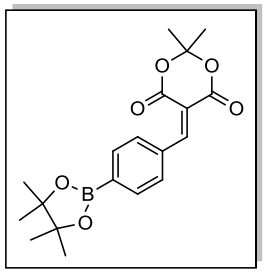
Alcohol **1.18** was isolated as the second product to elute from the above column and isolated as a colourless oil (120 mg, 17% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 5.99 (br s, $J_{Sn\text{-}H}$ = 123.9 Hz, 1H), 5.36 (br s, $J_{Sn\text{-}H}$ =

60.2 Hz, 1H), 4.76-4.66 (m, 4H), 2.23 (t, J = 6.6 Hz, 1H), 1.54-0.81 (m, 27H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.3 (C), 150.2 (C), 129.3 (C), 128.5 (CH), 128.3 (CH), 125.5 (CH_2), 120.6 (CH), 111.5 (CH), 74.7 (CH_2, J_{Sn-C} = 43.5 Hz), 61.7 (CH_2), 29.0 (CH_2, J_{Sn-C} = 20.0 Hz), 27.3 (CH_2, J_{Sn-C} = 56.8 Hz), 13.6 (CH_3), 9.5 (CH_2, J_{Sn-C} = 338.6, 323.6 Hz); HRMS (EI) *m/z* calcd for $C_{22}H_{38}O_2{}^{116}Sn$ (M^+-C_4H_9): 393.1185. Found: 393.1179.

Preparation of Benzylidene Meldrum's Acids (1.1a-n)

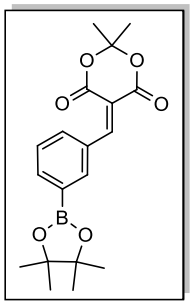


All benzylidene Meldrum's acids except **1.1m** were prepared by Knoevenagel condensation of the corresponding aldehydes with Meldrum's acid in benzene with pyrrolidinium acetate (10 mol %),[66] and purified by recrystallization from MeOH or flash column chromatography. 5-(Ethylidene) Meldrum's acid **1.1m** was prepared by addition of MeMgBr to 5-(dimethylaminomethylidene) Meldrum's acid[67] based on the known procedure.[68] Characterization data for previously unknown compounds are provided.



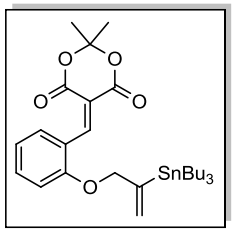
5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.1c)

Prepared by condensation of 4-formylphenylboronic acid pinacol ester (2.32 g, 10.0 mmol) with Meldrum's acid at 50 °C; purified by recrystallization from MeOH and isolated as a pale yellow solid (2.80 g, 72% yield). M.p. 167-169 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) 8.41 (s, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 1.79 (s, 6H), 1.33 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 162.9 (C), 159.4 (C), 157.8 (CH), 134.7 (CH), 133.8 (C), 131.9 (CH), 128.2 (C), 115.5 (C), 104.5 (C), 84.2 (C), 27.6 (CH_3), 24.8 (CH_3); HRMS (EI) *m/z* calcd for $C_{19}H_{23}O_6{}^{10}B$ (M^+): 357.1624. Found: 357.1625.



5-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.1j)

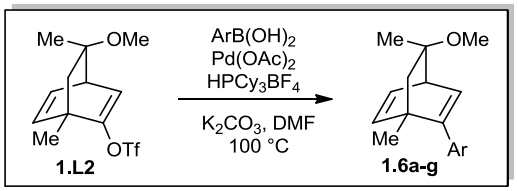
Prepared by condensation of 3-formylphenylboronic acid pinacol ester (2.32 g, 10.0 mmol) with Meldrum's acid at 50 °C; purified by recrystallization from MeOH and isolated as an off white solid (3.00 g, 85% yield). M.p. 94-95 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) 8.45 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.23 (s, 1H), 7.95 (d, J = 7.3 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 1.78 (s, 6H), 1.33 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 162.8 (C), 159.4 (C), 158.0 (CH), 140.5 (CH), 139.6 (CH), 135.0 (CH), 131.0 (C), 127.9 (CH), 114.6 (C), 104.3 (C), 83.9 (C), 27.4 (CH_3), 24.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{19}H_{23}O_6{}^{10}B$ (M^+): 357.1624. Found: 357.1628.



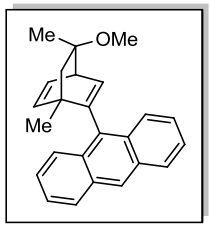
5-(2-(2-Tributylstannyl)allyloxy)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.1n)

Prepared by condensation of **1.17** (3.04 g, 6.7 mmol) with Meldrum's acid at rt. After stirring at rt for 17 h, additional pyrrolidinium acetate (10 mol %) was added and the reaction continued for 23 h more (>99% conversion by ^{1}H NMR). The mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution, and the aqueous phase extracted with EtOAc (3X) before the combined organic phases were dried over $MgSO_4$, filtered through a pad of silica gel, and concentrated to afford the product as a golden yellow oil (3.52 g, 90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.85 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.97 (br s, $J_{Sn\text{-}H}$ = 121.6 Hz, 1H), 5.36 (br s, $J_{Sn\text{-}H}$ = 56.1 Hz, 1H), 4.78 (s, $J_{Sn\text{-}H}$ = 24.9 Hz, 2H), 1.78 (s, 6H), 1.50-0.82 (m, 27H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.9 (C), 159.9 (C), 159.0 (C), 153.5 (CH), 149.4 (C), 134.9 (CH), 132.4 (CH), 125.7 (CH_2), 121.2 (C), 120.1 (CH), 114.3 (C), 112.4 (CH), 104.2 (C), 75.4 (CH_2, $J_{Sn\text{-}C}$ = 45.7 Hz), 28.9 (CH_2, $J_{Sn\text{-}C}$ = 19.9 Hz), 27.5 (CH_3), 27.2 (CH_2, $J_{Sn\text{-}C}$ = 54.2 Hz), 13.6 (CH_3), 9.4 (CH_2, $J_{Sn\text{-}C}$ = 339.4, 324.3 Hz); HRMS (EI) *m/z* calcd for $C_{28}H_{42}O_5{}^{116}Sn$ (M^+-C_4H_9): 517.1346. Found: 517.1320.

Synthesis of Ligands (1.6a-g)



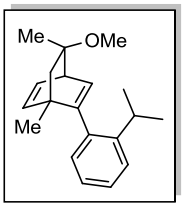
The procedure is based on the method reported by Darses and Genêt:[26] A septum-capped vial with stir bar was loaded with $Pd(OAc)_2$ (5 mol %), $HPCy_3BF_4$ (10 mol %) and K_2CO_3 (2-4 equiv), evacuated with water aspirator vacuum and backfilled with argon, at which point degassed DMF was added and the contents stirred at rt for 10 min. A second septum-capped vial with stir bar was loaded with triflate **1.L2**[24a] (1 equiv) and phenylboronic acid (2-4 equiv), evacuated with water aspirator vacuum and backfilled with argon, and the contents dissolved in degassed DMF. The solution of triflate and boronic acid was transferred via cannula to the suspension of catalyst, and the reaction vial placed in a preheated 100 °C oil bath. Reaction progress was monitored by concentrating aliquots and running ^{1}H NMR and ^{19}F NMR (**1.L2** and the coupled products have very similar R_f values; maximum conversion facilitates separation). When the reaction was complete or conversion remained unchanged over time, the reaction was cooled to rt, transferred into a round bottom flask with toluene and concentrated. The coupled products were isolated by flash column chromatography.



2-(Anthracen-10-yl)-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene (1.6d)

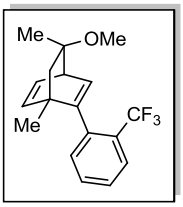
Prepared from **1.L2** (119 mg, 0.4 mmol) and 9-anthraceneboronic acid (169 mg, 0.8 mmol); reaction was stirred for 23h at 100 °C, purified eluting with EtOAc:hexanes (2.5:97.5) and isolated as a pale yellow solid (24 mg, 18% yield). M.p. 112-114 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.46-8.43 (m, 1H), 8.35 (s, 1H), 7.98-7.94 (m, 2H), 7.63 (d, J = 8.6 Hz, 1H), 7.43-7.33 (m, 4H), 6.56 (t, J = 6.6 Hz, 1H), 6.41 (t, J = 7.7 Hz, 2H), 3.86 (t, J = 5.6 Hz, 1H), 3.39 (s, 3H), 2.04 (d, J = 12.3 Hz, 1H), 1.41 (s, 3H), 1.40 (d overlapping with singlet at 1.41 ppm, J = 12.2 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 146.4 (C), 142.4 (CH),

135.1 (C), 133.7 (CH), 133.3 (CH), 131.5 (C), 131.1 (C), 130.9 (C), 130.8 (C), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.2 (CH), 125.8 (CH), 125.1 (CH), 125.0 (CH), 124.9 (CH), 124.8 (C), 84.2 (C), 49.9 (CH_3), 49.7 (CH_2), 47.8 (CH), 46.9 (C), 24.9 (CH_3), 20.1 (CH_3); $[\alpha]^{26}_{D}$ = -50.8 (*c* 0.39, $CHCl_3$). HRMS (EI) *m/z* calcd for $C_{25}H_{24}O$ (M^+): 340.1827. Found: 340.1835.



2-(2-Isopropylphenyl)-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene (1.6e)

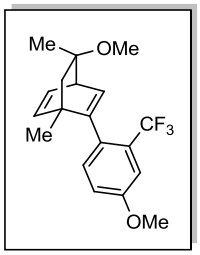
Prepared from **1.L2** (119 mg, 0.4 mmol) and 2-isopropylbenzeneboronic acid (125 mg, 0.8 mmol); reaction was stirred for 23 h at 100 °C, purified by eluting with EtOAc:hexanes (2:98) and isolated as a clear, pale yellow oil in an inseparable 59:41 mixture of atropisomers (18 mg, 18% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29-7.21 (m, 3.7H), 7.11-7.04 (m, 1.4H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 0.7H), 6.39-6.32 (m, 1.7H), 6.22 (d, *J* = 7.1 Hz, 0.7H), 6.15 (d, *J* = 6.8 Hz, 1H), 6.09 (d, *J* = 5.9 Hz, 0.7H), 6.03 (d, *J* = 5.8 Hz, 1H), 3.61 (br t, *J* = 7.5 Hz, 1.7H), 3.30-3.20 (m, overlapping septet and 2 singlets 5.8H), 2.67 (septet, *J* = 6.8 Hz, 1H), 1.72 (d, *J* = 12.1 Hz, 0.7H), 1.62 (d, *J* = 12.0 Hz, 1H), 1.30-1.14 (m, 14H), 1.07 (app d, *J* = 7.9 Hz, 5.1H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.9 (C), 148.1 (C), 147.4 (C), 147.3 (C), 142.6 (CH), 141.1 (CH), 138.3 (C), 138.1 (C), 134.0 (CH), 133.6 (CH), 131.4 (CH), 129.7 (CH), 129.3 (CH), 129.1 (CH), 127.1 (CH), 126.9 (CH), 125.2 (CH), 124.8 (CH), 124.6 (CH), 124.5 (CH), 84.1 (C), 83.9 (C), 50.5 (CH_2), 49.9 (CH), 49.6 (CH), 49.2 (CH_2), 47.9 (CH), 47.6 (CH), 45.8 (C), 45.7 (C), 30.3 (CH), 29.8 (CH), 25.0 (CH_3), 24.9 (CH_3), 24.7 (CH_3), 23.8 (CH_3), 22.4 (CH_3), 21.5 (CH_3), 21.0 (CH_3); $[\alpha]^{26}_{D}$ = -42.1 (*c* 0.22, $CHCl_3$). HRMS (EI) *m/z* calcd for $C_{20}H_{26}O$ (M^+-C_4H_8O): 210.1409. Found: 210.1402.



5-Methoxy-1,5-dimethyl-2-(2-(trifluoromethyl)phenyl)bicyclo[2.2.2]octa-2,7-diene (1.6f)

Prepared from **1.L2** (1.0 g, 3.2 mmol) and 2-trifluoromethylphenylboronic acid (2.43 g, 13.2 mmol); reaction was stirred for 3h at 100 °C, purified eluting with EtOAc:hexanes (2.5:97.5) and isolated as a colourless oil in an inseparable 80:20 mixture of atropisomers (527 mg, 53% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.65 (m, 1.2H), 7.46-7.38 (m, 1.2H), 7.35-7.30 (m,

1.2H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 0.2H), 6.37 (t, *J* = 6.6 Hz, 0.2H), 6.30-6.23 (m, 1.2H), 6.18 (d, *J* = 5.9 Hz, 0.2H), 6.13 (d, *J* = 7.2 Hz, 1H), 6.07 (d, *J* = 5.9 Hz, 1H), 3.67-3.63 (m, 1.2H), 3.20 (s, 3.6H), 1.87 (d, *J* = 12.1 Hz, 0.2H), 1.64 (d, *J* = 12.0 Hz, 1H), 1.35-1.26 (m, 4.8H), 1.09 (s, 0.6H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 145.7 (C), 145.5 (C), 142.5 (CH), 141.4 (CH), 138.9 (C), 138.9 (C), 134.5 (CH), 133.9 (CH), 131.9 (CH), 131.2 (CH), 131.2 (CH), 131.1 (CH), 130.7 (CH), 130.3 (CH), 128.9 (C, q, *J* = 29.2 Hz), 126.7 (CH), 126.5 (CH), 125.7 (CH, q, *J* = 5.1 Hz), 124.0 (C, q, *J* = 272.2 Hz), 83.9 (C), 83.8 (C), 51.0 (CH_2), 49.8 (CH_3), 49.7 (CH_3), 49.1 (CH), 47.4 (CH), 47.2 (CH_2), 45.7 (C), 25.3 (CH_3), 24.6 (CH_3), 21.0 (CH_3), 20.7 (CH_3); ^{19}F NMR ($CDCl_3$, 282 MHz) -57.79, -57.84; $[\alpha]^{26}_{D}$ = -0.77 (*c* 0.78, $CHCl_3$). HRMS (EI) *m/z* calcd for $C_{14}H_{11}F_3$ (M^+-C_4H_8O): 236.0813. Found: 236.0819.



5-Methoxy-2-(4-methoxy-2-(trifluoromethyl)phenyl)-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene (1.6g)

Prepared from **1.L2** (156 mg, 0.5 mmol) and 4-methoxy-2-trifluormethylphenylboronic acid (440 mg, 2.0 mmol); reaction was stirred for 3h at 100 °C, purified by eluting with EtOAc:hexanes (1:9) and isolated as a clear, pale yellow oil in an inseparable 80:20 mixture of atropisomers (69 mg, 41% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22-6.84 (m, 3.6H), 6.36 (t, *J* = 6.6 Hz, 0.2H), 6.28-6.21 (m, 1.2H), 6.16-6.10 (m, 1.2H), 6.05 (d, *J* = 5.9 Hz, 1H), 3.81 (s, 3.6H), 3.64-3.57 (m, 1.2H), 3.19 (s, 3.6H), 1.84 (d, *J* = 12.0 Hz, 0.2H), 1.65 (d, *J* = 10.0 Hz, 1H), 1.33-1.25 (m, 4.8H), 1.08-1.05 (m, 3.6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.1 (C), 145.5 (C), 145.2 (C), 142.5 (CH), 141.5 (CH), 134.4 (CH), 133.9 (C), 132.5 (CH), 131.9 (CH), 131.8 (CH), 130.8 (C), 130.7 (C), 130.2 (C, q, *J* = 29.2 Hz), 123.8 (C, q, *J* = 272.4 Hz), 116.3 (CH), 116.2 (CH), 111.1 (CH, q, *J* = 5.2 Hz), 110.9 (C, q, *J* = 5.3 Hz), 83.9 (C), 83.8 (C), 55.4 (CH_3), 50.9 (CH_2), 49.8 (CH_3), 49.7 (C), 49.1 (CH), 47.4 (CH), 47.2 (CH_2), 45.7 (C), 25.2 (CH_3), 24.6 (CH_3), 21.0 (CH_3), 20.7 (CH_3); ^{19}F NMR ($CDCl_3$, 282 MHz) -58.1, -58.3. $[\alpha]^{26}_{D}$ = -15.8 (*c* 2.43, $CHCl_3$). HRMS (EI) *m/z* calcd for $C_{19}H_{21}F_3O_2$ (M^+-C_4H_8O): 266.0919. Found: 266.0916.

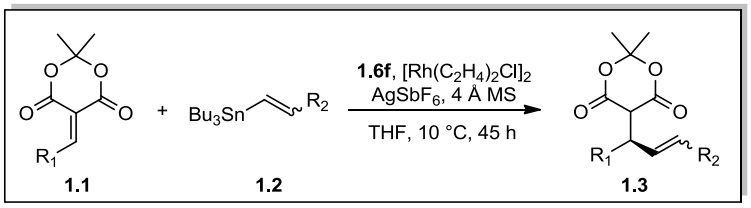
Preparation of Alkenylstannanes (1.2a-e)

(*E*)-Alkenylstannanes **1.2a** and **1.2b**, as well as gem-alkenylstannane **1.2f** were prepared by radical hydrostannation of propargyl alcohol followed by reaction with $ClCO_2Et$ or Ac_2O as previously described.[51] (*Z*)-alkenylstannane **1.2c** was prepared from $LiAlH_4$ reduction of propargyl alcohol and quenching with Bu_3SnCl as per Corey and Eckrich`s method[69], followed by acetylation. Vinyltributyltin **1.2d** was prepared from $CH_2CHMgBr$ and Bu_3SnCl as described[70] and was distilled before use. Alkenylstannane **1.2e** was prepared from radical hydrostannation of ethyl propiolate.[71]

Preparation of Racemic 1,4-Addition Products

Racemates were obtained as previously described[51] with the exception of **1.3p**, which was prepared by addition of $CH_2CHMgBr$ to benzylidene **1.1a** in THF at 0 °C followed by acidic workup.

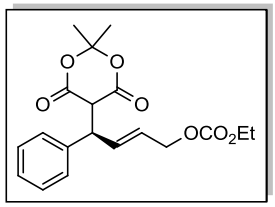
Asymmetric 1,4-Addition of Alkenylstannanes



In a glovebox, a screw-capped conical vial equipped with a stir bar was charged with $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 0.005 mmol, 5 mol % of Rh), and chiral diene ligand **1.6f** (4.3 mg, 0.014 mmol, 7 mol %) which was rinsed out of a pipette tip with THF (0.1 mL). The resulting solution was stirred for 10 min before adding $AgSbF_6$ (3.4 mg, 0.01 mmol, 5 mol %) which was rinsed out of a pipette tip with THF (0.1 mL). The resulting suspension was stirred for 10 minutes. Benzylidene Meldrum's acid **1.1** (0.24 mmol, 1.2 equiv) was then added to the vial, followed by alkenylstannane **1.2** (0.20 mmol, 1.0 equiv) which was rinsed out of a pipette tip

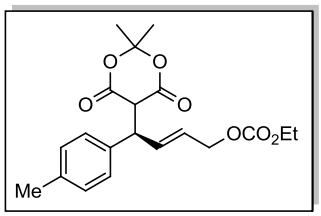
with THF (0.1 mL), resulting in a colour change from yellow to red. Powdered 4 Å molecular sieves (15 mg) were added to the vial, which was then capped tightly, removed from the box and immersed in an *i*PrOH bath maintained at 10 °C by cryocool. After 45 h, the reaction was transferred into a round bottom flask with CH_2Cl_2 and concentrated onto a small amount of silica gel. This was loaded to the top of a silica gel column prepacked with the required solvent system. Unless indicated otherwise, all products were eluted on a gradient from 1:4 to 1:2 EtOAc:hexanes.

Note: In some cases, hydrolysis of the excess benzylidene Meldrum's acid on the silica gel column can cause Meldrum's acid contamination of the isolated product. Should this occur, the desired product can be further purified by a second silica gel column or by dissolving the mixture in CH_2Cl_2 and extracting the Meldrum's acid contaminant into water by shaking with a small amount of saturated $NaHCO_3$ solution, drying the organic phase over $MgSO_4$, filtering, and concentrating.



(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-phenylbut-2-enyl ethyl carbonate (1.3a)

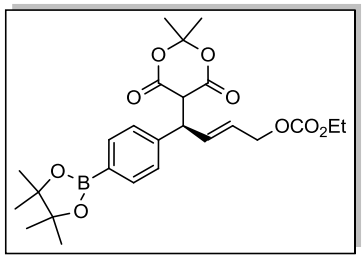
Prepared from benzylidene **1.1a** (55.7 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow film (61 mg, 84% yield). An enantiomeric ratio of 94:6 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 15.8 min (*major*), t_{R2} = 16.7 min). $[\alpha]^{26}_{D}$ = +15.8 (*c* 2.08, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**.



(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-*p*-tolylbut-2-enyl ethyl carbonate (1.3b)

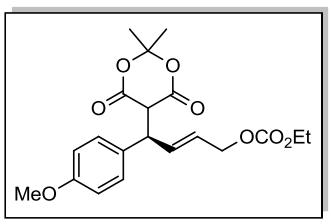
Prepared from benzylidene **1.1b** (59 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a colourless oil (32 mg, 42% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.20 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.51 (dd, *J* = 15.5, 8.9 Hz, 1H), 5.81 (dt, *J* = 15.4, 6.2 Hz, 1H), 4.62 (d, *J* = 6.1 Hz, 2H), 4.53 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.82 (d, *J*

= 2.8 Hz, 1H), 2.28 (s, 3H), 1.68 (s, 3H), 1.45 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.3 (C), 164.2 (C), 154.9 (C), 137.2 (C), 135.9 (C), 134.1 (CH), 129.3 (CH), 128.5 (CH), 126.9 (CH), 105.3 (C), 67.5 (CH_2), 64.0 (CH_2), 52.1 (CH), 46.4 (CH), 28.2 (CH_3), 27.6 (CH_3), 20.9 (CH_3), 14.2 (CH_3); An enantiomeric ratio of 93:7 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 0.5 mL/min, t_{R1} = 30.6 min (major), t_{R2} = 31.9 min). $[\alpha]^{26}{}_D$ = +21.5 (*c* 1.07, $CHCl_3$). Absolute configuration was determined by transformation of **1.3b** to known compound **2.10**. HRMS (EI) m/z calcd for $C_{20}H_{24}O_7$ (M^+-$C_3H_6O_3$): 286.1205. Found: 286.1197.



(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but-2-enyl ethyl carbonate (1.3c)

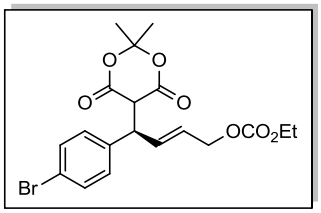
Prepared from benzylidene **1.1c** (86.0 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow wax (38 mg, 39% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.72 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 6.59 (dd, *J* = 15.5 Hz, 8.9 Hz, 1H), 5.83 (dt, *J* = 15.3 Hz, 6.1 Hz, 1H), 4.62 (d, *J* = 6.1 Hz, 2H), 4.61-4.56 (m, 1H, overlaps with signal at 4.62), 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (d, *J* = 2.5 Hz, 1H), 1.69 (s, 3H), 1.50 (s, 3H), 1.30 (s, 12H), 1.28-1.23 (m, 3H, overlaps with signal at 1.30); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.14 (C), 164.10 (C), 154.8 (C), 142.1 (C), 135.1 (CH), 133.5 (CH), 127.9 (CH), 127.5 (CH), 105.3 (C), 83.8 (C), 67.4 (CH_2), 64.1 (CH_2), 52.0 (CH), 46.7 (CH), 28.2 (CH_3), 27.6 (CH_3) 24.8 (CH_3), 14.2 (CH_3); An enantiomeric ratio of 93:7 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 16.5 min (*major*), t_{R2} = 21.0 min). $[\alpha]^{26}{}_D$ = +20.5 (*c* 1.70, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**. HRMS (ESI) *m/z* calcd for $C_{25}H_{37}NO_7{}^{11}B$ ([M + NH_4] $^+$): 506.2561. Found: 506.2543.



(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-(4-methoxyphenyl)but-2-enyl ethyl carbonate (1.3d)

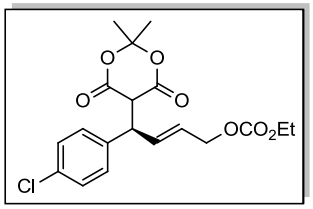
Prepared from benzylidene **1.1d** (62.9 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow film (13 mg, 17% yield). An

enantiomeric ratio of 93:7 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 27.3 min (*major*), t_{R2} = 29.1 min). $[\alpha]^{26}_{D}$ = +20.8 (*c* 0.39, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**.



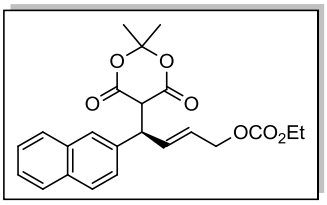
(4*R*,2*E*)-4-(4-Bromophenyl)-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)but-2-enyl ethyl carbonate (1.3e)

Prepared from benzylidene **1.1e** (105.9 mg) and alkenyltin **1.2a** (83.8 mg) and purified by silica gel chromatography (EtOAc:hexanes, 1:5 to 1:2 resp) and isolated as a pale yellow film (34 mg, 39% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.41 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.46 (dd, *J* = 15.4, 8.9 Hz, 1H), 5.82 (dt, *J* = 15.4, 6.0 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.53 (dd, *J* = 8.9, 1.9 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.82 (d, *J* = 2.7 Hz, 1H), 1.71 (s, 3H), 1.56 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.0 (C), 163.9 (C), 154.9 (C), 137.9 (C), 133.1 (CH), 131.7 (CH), 130.5 (CH), 127.7 (CH), 121.6 (C), 105.3 (C), 67.3 (CH_2), 64.1 (CH_2), 51.9 (CH), 45.9 (CH), 28.2 (CH_3), 27.5 (CH_3), 14.2 (CH_3); An enantiomeric ratio of 93:7 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 18.8 min (*major*), t_{R2} = 20.2 min). $[\alpha]^{26}_{D}$ = +12.9 (*c* 1.38, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**. HRMS (ESI) *m/z* calcd for $C_{19}H_{25}NO_7{}^{79}Br$ ($[M + NH_4]^+$): 458.0814. Found: 458.0830.



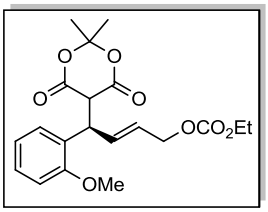
(4*R*,2*E*)-4-(4-Chlorophenyl)-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)but-2-enyl ethyl carbonate (1.3f)

Prepared from benzylidene **1.1f** (64.0 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow film (23 mg, 29% yield). An enantiomeric ratio of 90:10 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 16.4 min (*major*), t_{R2} = 17.9 min). $[\alpha]^{26}_{D}$ = +12.9 (*c* 0.67, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**.



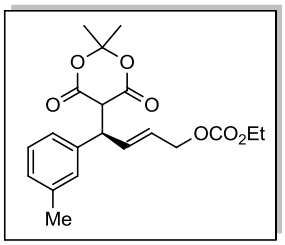
(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-(naphthalen-2-yl)but-2-enyl ethyl carbonate (1.3g)

Prepared from benzylidene **1.1g** (67.7 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow film (40 mg, 49% yield). An enantiomeric ratio of 92:8 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 22.1 min (*major*), t_{R2} = 24.3 min). Absolute configuration was assigned by analogy to **1.3b**.



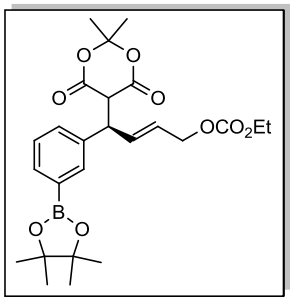
(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-(2-methoxyphenyl)but-2-enyl ethyl carbonate (1.3h)

Prepared from benzylidene **1.1h** (62.9 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow film (46 mg, 58% yield). An enantiomeric ratio of 92:8 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 16.6 min (*major*), t_{R2} = 28.5 min). $[\alpha]^{26}_{D}$ = -4.48 (*c* 1.54, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**.



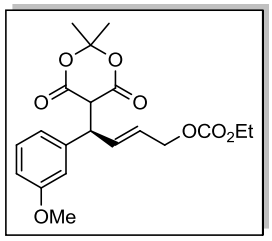
(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-*m*-tolylbut-2-enyl ethyl carbonate (1.3i)

Prepared from benzylidene **1.1i** (59 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a colourless oil (38 mg, 51% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.20-7.09 (m, 3H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.51 (dd, *J* = 15.4, 9.0 Hz, 1H), 5.82 (dt, *J* = 15.4, 6.2 Hz, 1H), 4.63 (d, *J* = 6.2 Hz, 2H), 4.52 (dd, *J* = 9.0, 2.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 2.9 Hz, 1H), 2.30 (s, 3H), 1.69 (s, 3H), 1.43 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.33 (C), 164.25 (C), 154.9 (C), 138.9 (C) 138.4 (C), 134.0 (CH), 129.3 (CH), 128.6 (CH), 128.3 (CH), 127.1 (CH), 125.5 (CH), 105.3 (C), 67.5 (CH_2), 64.0 (CH_2), 52.1 (CH), 46.8 (CH), 28.2 (CH_3), 27.7 (CH_3), 21.4 (CH_3), 14.2 (CH_3); $[\alpha]^{26}_{D}$ = +16.1 (*c* 1.77, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**. HRMS (EI) m/z calcd for $C_{20}H_{24}O_7$ (M^+-$C_3H_6O_3$): 286.1205. Found: 286.1214.



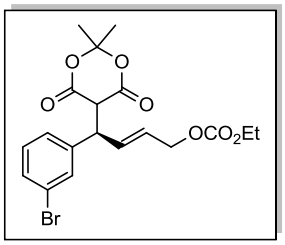
(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but-2-enyl ethyl carbonate (1.3j)

Prepared from benzylidene **1.1j** (86.0 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow film (52 mg, 57% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.68 (s, 1H), 7.67 (d overlapping with singlet at 7.68 ppm, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.46 (dd, *J* = 15.4, 9.0 Hz, 1H), 5.82 (dt, *J* = 15.3, 6.1 Hz, 1H), 4.61 (d, *J* = 6.2 Hz, 2H), 4.59 (dd overlapping with d at 4.61 ppm, *J* = 2.5 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.87 (d, *J* = 2.8 Hz, 1H), 1.70 (s, 3H), 1.52 (s, 3H), 1.31 (s, 12H), 1.28 (t overlapping with singlet at 1.31 ppm, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.3 (C), 163.9 (C), 154.8 (C), 138.6 (C), 134.6 (CH), 133.9 (CH), 133.3 (CH), 131.4 (CH), 128.1 (CH), 127.6 (CH), 105.2 (C), 83.8 (C), 67.5 (CH_2), 64.0 (CH_2), 52.2 (CH), 46.5 (CH), 28.2 (CH_3), 27.5 (CH_3), 24.9 (CH_3), 24.8 (CH_3), 14.2 (CH_3); An enantiomeric ratio of 93:7 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 8.5 min (*major*), t_{R2} = 10.0 min. $[\alpha]^{26}_{D}$ = +18.1 (*c* 0.78, $CHCl_3$). Absolute configuration was assigned by analogy to **2.3b**. HRMS (ESI) *m/z* calcd for $C_{25}H_{37}NO_7{}^{11}B$ ($[M + NH_4]^+$): 506.2561. Found: 506.2559.



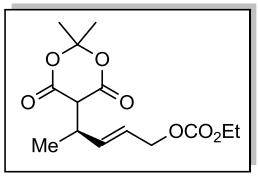
(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-(3-methoxyphenyl)but-2-enyl ethyl carbonate (1.3k)

Prepared from benzylidene **1.1k** (62.9 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a pale yellow film (42 mg, 54% yield). An enantiomeric ratio of 91:9 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 0.5 mL/min, t_{R1} = 44.1 min (*major*), t_{R2} = 46.3 min). $[\alpha]^{26}_{D}$ = +21.2 (*c* 1.56, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**.



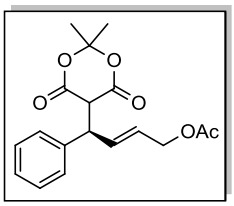
(4*R*,2*E*)-4-(3-Bromophenyl)-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)but-2-enyl ethyl carbonate (1.3l)

Prepared from benzylidene **1.1l** (105.9 mg) and alkenyltin **1.2a** (83.8 mg) and purified by silica gel chromatography (EtOAc:hexanes, 1:4 to 1:3) and isolated as a colourless oil (62 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.49 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.43 (dd, *J* = 15.4, 9.0 Hz, 1H), 5.83 (dt, *J* = 15.4, 6.1 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.53 (dd, *J* = 9.0, 2.2 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.84 (d, *J* = 2.7 Hz, 1H), 1.72 (s, 3H), 1.57 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.9 (C), 168.8 (C), 154.8 (C), 141.4 (C), 132.7 (CH), 131.7 (CH), 130.6 (CH), 130.1 (CH), 128.1 (CH), 127.3 (CH), 122.6 (C), 105.4 (C), 67.3 (CH_2), 64.1 (CH_2), 51.9 (CH), 45.9 (CH), 28.2 (CH_3), 27.4 (CH_3), 14.2 (CH_3); An enantiomeric ratio of 95:5 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 0.5 mL/min, t_{R1} = 31.0 min (*major*), t_{R2} = 32.6 min). $[\alpha]^{26}_{D}$ = +14.4 (*c* 2.47, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**. HRMS (EI) *m/z* calcd for $C_{19}H_{21}{}^{79}BrO_7$ (M^+-acetone): 382.0052. Found: 382.0042.



(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)pent-2-enyl ethyl carbonate (1.3m)

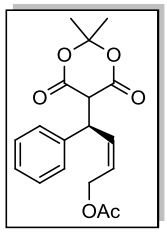
Prepared from alkylidene **1.1m** (40.8 mg) and alkenyltin **1.2a** (83.8 mg) and isolated as a colourless film (44 mg, 73% yield). An enantiomeric ratio of 23:77 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 10.1 min, t_{R2} = 10.7 min (*major*)). $[\alpha]^{26}_{D}$ = +3.60 (*c* 1.59, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**.



(4*R*,2*E*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-phenylbut-2-enyl acetate (1.3n)

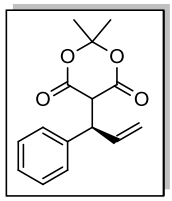
Prepared from benzylidene **1.1a** (55.7 mg) and alkenyltin **1.2b** (77.8 mg), purified by silica gel chromatography (EtOAc:hexanes 1:4 to 1:3 resp.) and isolated as a pale

yellow film (41 mg, 61% yield). An enantiomeric ratio of 89:11 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 16.3 min (*major*), t_{R2} = 17.1 min). $[\alpha]^{26}{}_{D}$ = +24.1 (*c* 1.16, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**.



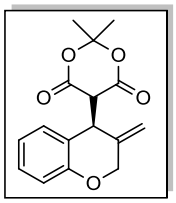
(4*R*,2*Z*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-phenylbut-2-enyl acetate (1.3o)

Prepared from benzylidene **1.1a** (55.7 mg) and alkenyltin 1**2.2c** (77.8 mg) and isolated as a pale yellow film (58 mg, 87% yield). An enantiomeric ratio of 83:17 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 14.0 min (*major*), t_{R2} = 21.5 min). Absolute configuration was assigned by analogy to **1.3b**.



(5*R*)-2,2-Dimethyl-5-(1-phenylallyl)-1,3-dioxane-4,6-dione (1.3p)

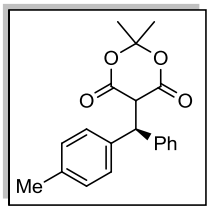
Prepared from benzylidene **1.1a** (55.7 mg) and vinyltributyltin **1.2d** (63.4 mg), purified by silica gel chromatography (EtOAc:hexanes, 1:5) and isolated as a pale yellow film (30 mg contaminated with benzylidene **1.1a**). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35-7.20 (m, 5H), 6.50 (ddd, *J* = 17.0, 10.1, 8.7 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 9.1 Hz, 1H), 4.54 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.86 (d, *J* = 2.8 Hz, 1H), 1.68 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.5 (C), 164.4 (C), 139.4 (C), 136.7 (CH), 128.6 (CH), 128.6 (CH), 127.4 (CH), 118.3 (CH_2), 105.2 (C), 52.2 (CH), 48.2 (CH), 28.2 (CH_3), 27.7 (CH_3); An enantiomeric ratio of 63:37 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 19.8 min (*major*), t_{R2} = 24.8 min); $[\alpha]^{26}{}_{D}$ = +0.93 (*c* 1.51, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**. HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_4$ (M^+-acetone): 202.0630. Found: 202.0632.



(5*S*)-2,2-Dimethyl-5-(3-methylene-3,4-dihydro-2H-chromen-4-yl)-1,3-dioxane-4,6-dione (1.3r)

Prepared from benzylidene **1.1n** (115.5 mg), purified by silica gel chromatography (EtOAc:hexanes, 1:4 to 1:3) and isolated as a pale yellow film (20 mg, 35%

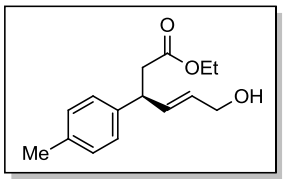
yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.14 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.93-6.88 (m, 2H), 5.24 (s, 1H), 5.19 (s, 1H), 4.76 (d, *J* = 13.0 Hz, 1H), 4.73 (d overlapping with d at 4.76 ppm, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 3.99 (d, *J* = 2.5 Hz, 1H), 1.75 (s, 3H), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.6 (C), 164.3 (C), 155.4 (C), 140.5 (C), 128.3 (CH), 126.9 (CH), 121.9 (C), 121.3 (CH), 117.6 (CH), 114.8 (CH_2), 105.2 (C), 69.6 (CH_2), 53.2 (CH), 39.1 (CH), 28.2 (CH_3), 27.9 (CH_3); An enantiomeric ratio of 64:36 was measured by chiral HPLC (AD-H, 7% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 12.7 min (*major*), t_{R2} = 18.5 min). $[\alpha]^{26}_{D}$ = -35.2 (*c* 0.72, $CHCl_3$). Absolute configuration was assigned by analogy to **1.3b**. HRMS (EI) *m/z* calcd for $C_{16}H_{16}O_5$ (M^+): 288.0998. Found: 288.0994.



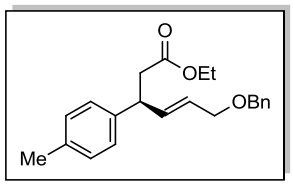
2,2-Dimethyl-5-(phenyl(*p*-tolyl)methyl)-1,3-dioxane-4,6-dione (1.11)

This procedure was performed in direct analogy to the alkenylstannane addition. In a glovebox, a screw-capped conical vial equipped with a stir bar was charged with $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 0.005 mmol, 5 mol % of Rh), and chiral diene ligand **1.6f** (4.3 mg, 0.014 mmol, 7 mol %) which was rinsed out of a pipette tip with THF (0.1 mL). The resulting solution was stirred for 10 min before adding $AgSbF_6$ (3.4 mg, 0.01 mmol, 5 mol %) which was rinsed out of a pipette tip with THF (0.1 mL). The resulting suspension was stirred for 10 minutes. Benzylidene **1.1b** (59.1 mg, 0.24 mmol, 1.2 equiv) was then added to the vial, followed by phenyltributylstannane (73.4 mg, 0.20 mmol, 1.0 equiv) which was rinsed out of a pipette tip with THF (0.1 mL), resulting in a colour change from yellow to red. Powdered 4 Å molecular sieves (15 mg) were added to the vial, which was then capped tightly, removed from the box and immersed in an *i*PrOH bath maintained at 0 °C by cryocool. After 45 h, the reaction was transferred into a round bottom flask with CH_2Cl_2 and concentrated onto a small amount of silica gel. This was loaded to the top of a silica gel column prepacked with the required solvent system used to elute the product (EtOAc:hexanes,1:9). Diaryl compound **1.11** was isolated as a pale yellow solid (52.1 mg, 80% yield). Mp 123-124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29-7.19 (m, 5H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 5.33 (d, *J* = 2.6 Hz, 1H), 4.27 (d, *J* = 2.8 Hz, 1H), 2.30 (s, 3H), 1.73 (s, 3H), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 164.79 (C), 164.76 (C), 140.3 (C), 137.0 (C), 136.8 (C), 129.15 (2xCH), 129.13 (CH), 128.4 (CH), 127.1 (CH), 105.1 (C), 51.2 (CH), 48.9 (CH), 28.3 (CH_3), 27.7 (CH_3), 21.0 (CH_3); An enantiomeric

ratio of 96:4 was measured by chiral HPLC (AD-H, 5% *i*-PrOH/hexanes, 0.5 mL/min, t_{R1} = 33.2 min (*major*), t_{R2} = 36.3 min); $[\alpha]^{26}_{D}$ = -3.67 (*c* 1.83, $CHCl_3$). HRMS(EI) *m/z* calcd for $C_{20}H_{20}O_4$ (M^+): 324.1362. Found: 324.1352. Absolute configuration was assigned by analogy to **1.3b**.



(3*R*, 4*E*)-Ethyl 6-hydroxy-3-*p*-tolylhex-4-enoate (1.9) Enantioenriched Meldrum's acid **1.3b** (50 mg, 0.13 mmol, 1.0 equiv, 86% ee) was dissolved in EtOH (1.0 mL) and treated with Cu powder (2.1 mg, 0.33 mmol, 0.25 equiv) and pyridine (4.0 mL). The reaction was heated to reflux under N_2 for 3.5 h, cooled to rt, and diluted with Et_2O (35 mL). The Et_2O was washed with 10% HCl (2X 20 mL), the combined aqueous phases were extracted with Et_2O (20 mL), and the combined organic phases were washed with H_2O (20 mL) and brine (20 mL) before being dried over $MgSO_4$ and filtered through a short pad of silica gel. The evaporated crude mixture was dissolved in EtOH (5 mL) and treated with K_2CO_3 (36 mg, 0.26 mmol, 2.0 equiv). The suspension was stirred vigorously at rt for 18 h, diluted with Et_2O (20 mL) and filtered through a pad of Celite. The filtrate was concentrated onto a small amount of silica gel, which was loaded to the top of a silica gel column packed using EtOAc:hexanes (1:2). Flash column chromotagraphy eluting with EtOAc:hexanes (1:2) gave the allylic alcohol as a colourless oil (20 mg, 62% yield over two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.11-7.05 (m, 4H), 5.83 (dd, *J* = 15.5, 7.2 Hz, 1H), 5.64 (dt, *J* = 15.5, 7.2 Hz, 1H), 4.08-4.02 (m, 4H), 3.82 (q, *J* = 7.5 Hz, 1H), 2.71 (dd, *J* = 15.1, 8.0 Hz, 1H), 2.65 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.29 (s, 3H), 1.36 (br s, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 171.8 (C), 139.4 (C), 136.3 (C), 134.3 (CH), 129.33 (CH), 129.28 (CH), 127.3 (CH), 63.4 (CH_2), 60.4 (CH_2), 44.0 (CH), 40.6 (CH_2), 21.0 (CH_3), 14.2 (CH_3); An enantiomeric ratio of 93:7 was measured by chiral HPLC (AD-H, 4% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 21.8 min (major), t_{R2} = 22.6 min). HRMS (EI) m/z calcd for $C_{15}H_{20}O_3$ (M^+-H_2O): 230.1306. Found: 230.1312.



(3*S*,4*E*)-Ethyl 6-(benzyloxy)-3-*p*-tolylhex-4-enoate (1.10)

Allylic alcohol **1.9** (20 mg, 0.08 mmol, 1.0 equiv) was dissolved in THF (0.3 mL). In a separate flask, KH (13 mg of 30% (wt/wt) suspension in mineral oil, washed with pentane, 0.1 mmol, 1.24 equiv) was suspended in THF

(0.3 mL) and the flask cooled to -10 °C. The solution of alcohol in THF was added to the suspension of KH dropwise over 3 min, resulting in a pale yellow suspension; the flask containing the alcohol was rinsed with additional THF (0.3 mL) and this was added to the KH suspension as well. After 5 min, benzyl bromide (24 μL, 2.0 mmol, 2.5 equiv) was added to the anion in a single portion. Stirring was continued at -10 °C for 45 min, at which point the flask was removed from the cooling bath and allowed to warm to rt. The reaction was diluted with Et_2O (30 mL) and quenched with 10% HCl (5 mL). The contents were poured into a separatory funnel, shaken and the layers separated. The organic phase was washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography eluting with EtOAc:hexanes (1:9) afforded the ether as a colourless oil (16 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.34-7.24 (m, 5H), 7.08 (app s, 4H), 5.85 (dd, *J* = 15.5, 7.1 Hz, 1H), 5.60 (dt, *J* = 15.5, 5.9 Hz, 1H), 4.45 (s, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.96 (d, *J* = 5.9 Hz, 2H), 3.84 (app q, *J* = 7.6 Hz, 1H), 2.72 (dd, *J* = 15.0, 7.9 Hz, 1H), 2.66 (dd, *J* = 15.0, 7.6 Hz, 1H), 2.29 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 171.8 (C), 139.4 (C), 138.3 (C), 136.2 (C), 135.8 (CH), 129.3 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 71.9 (CH_2), 70.5 (CH_2), 60.4 (CH_2), 44.1 (CH), 40.6 (CH_2), 21.0 (CH_3), 14.2 (CH_3); $[\alpha]^{26}_D$ = -3.58 (*c* 0.74, $CHCl_3$). Absolute configuration was assigned by optical rotation as described in Scheme 2.11.[56] HRMS (EI) m/z calcd for $C_{22}H_{26}O_3$ (M^+-C_2H_5O): 293.1542. Found: 293.1541.

Chapter 2. Domino [1,5]- Hydride Shift/Cyclization/Friedel-Crafts Acylation Reaction of Benzylidene Meldrum's Acids

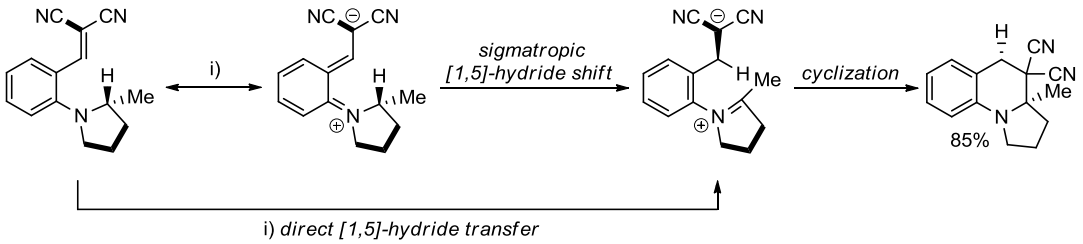
This chapter describes the development of a catalyzed, domino reaction to furnish complex tetracycles through an initial [1,5]-hydride shift, as well as the serendipitous discovery of a competing reaction pathway that cleaves Csp^3-Csp^3 bonds under mild conditions.

2.1. Introduction

An intriguing reaction that has gained increasing attention in the chemistry community is the [1,5]-hydride shift/cyclization which includes the *tert*-amino effect variety.[72] The term *tert*-amino effect was coined by Meth-Cohn and Suschitzky in 1972 due to the ability of *ortho*-substituted tertiary anilines to increase the hydricity of neighbouring alpha protons to initiate an intramolecular cyclization event. Reactions were typically thermally promoted to afford moderate to high yields of heterocycles with the primary substrate derivation being the conformationally restricting aromatic component.[72a,73]

A particularly illustrative example of the *tert*-amino effect is shown in Scheme 2.1 in which both regioselective hydride transfer and retention of chiral information were observed.[74] Reinhoudt and coworkers dubbed the later stereochemical result "self reproduction of chirality" and postulated that the chirality was transferred in the form of a chiral helical dipolar intermediate in which a conformationally controlled cyclization occurred on the same face that bore the migrated hydride. The mechanistic proposal for the thermal [1,5]-hydride shift/cyclization involves a rate determining hydride shift through either a [1,5]-sigmatropic hydride shift or a direct intramolecular [1,5]-hydride transfer.

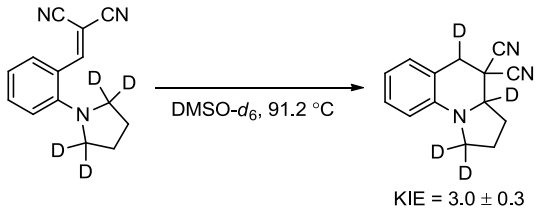
Scheme 2.1. Observed Stereochemical Outcome and Mechanistic Proposals of *tert*-Amino Effect



i) 1-butanol, reflux

Reinhoudt and coworkers observed a kinetic isotope effect that strongly suggested that the transfer of a hydrogen atom was the rate determining step in the transfer/cyclization reaction (Scheme 2.2.).[75] They also reported that the reaction rate was decreased by a factor of about 150 by using the apolar solvent toluene-d_8 which was indicative of charge separation taking place in the rate determining step.

Scheme 2.2. Intramolecular Process and Hydrogen Shift Rate Determining Step



It has been found that an extended π-system is not a structural requirement for the reaction to occur and a general outline of applicable structural motifs is given in Figure 2.1. The most prevalent mode of ring formation following the initial hydride migration has been a 6-endo-trig cyclization (also termed as a type 2 *tert*-amino effect when referring to an *ortho*-substituted tertiary aniline).[72a]

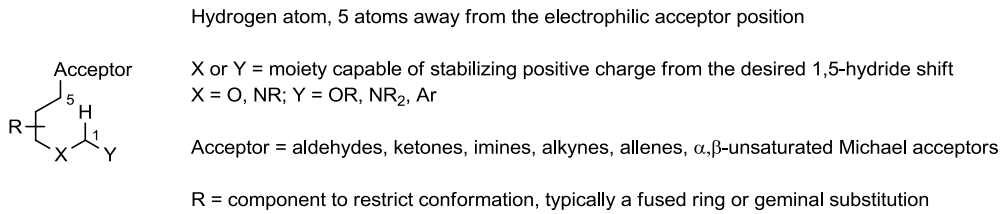
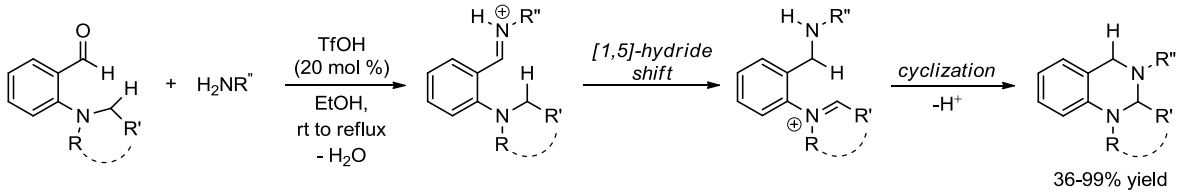


Figure 2.1. General Structural Motif of Substrates Shown to Undergo [1,5]-Hydride Shift/Cyclizations Under Catalysis

Characteristic features including regioselectivity and rate enhancements of the transformation are described below through recent catalytic protocols (including enantioselective). Increases in both the scope of acceptor and donor functionality are also summarized.

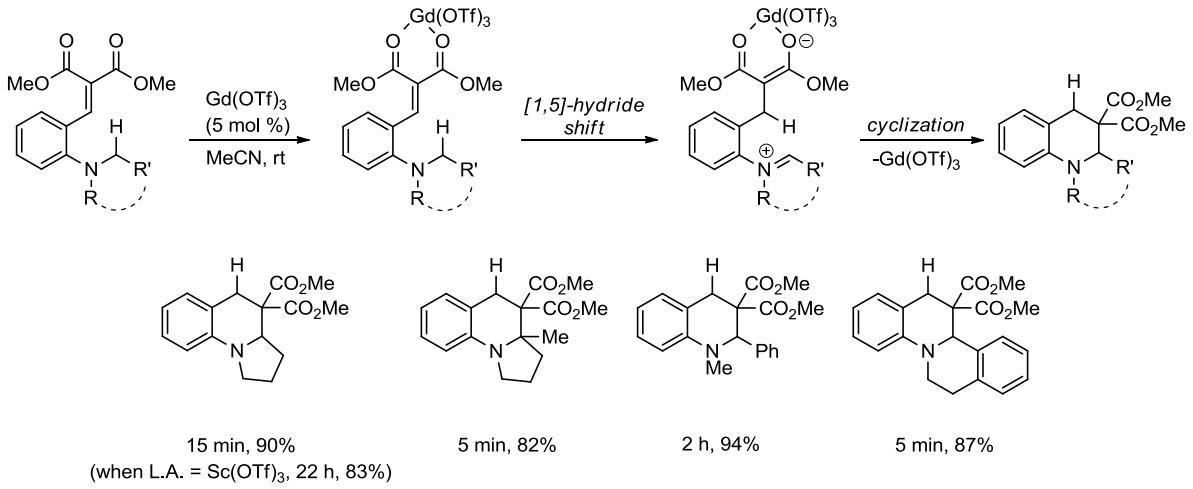
Seidel and coworkers developed a general method to access cyclic aminals in a "one-pot" Brønsted acid catalyzed protocol (Scheme 2.3).[76] A variety of ortho-*tert*-amino benzaldehydes were found to react with primary amines to afford the cyclic aminals which mechanistically proceeded through a [1,5]-hydride shift/cyclization sequence from an in situ formed iminium intermediate.

Scheme 2.3. Cyclic Aminals through Brønsted Acid Catalysis



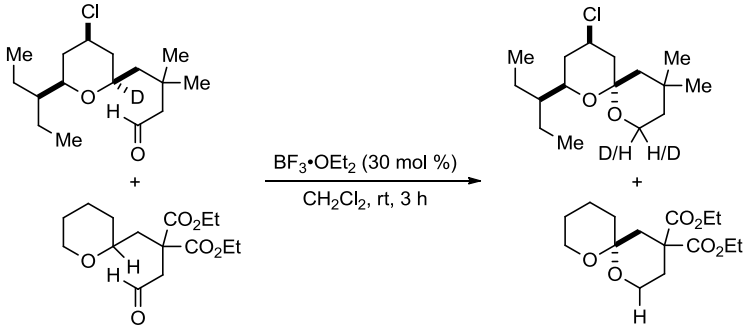
In developing an additional catalytic variant of the *tert*-amino effect Seidel's group found that the alkylidene malonate acceptor permitted the reaction to occur very efficiently with a Lewis acid especially gadolinium triflate (Scheme 2.4).[77] The process was also highly regioselective in regards to the hydride being transferred from the position most capable of stabilizing the developing positive charge.

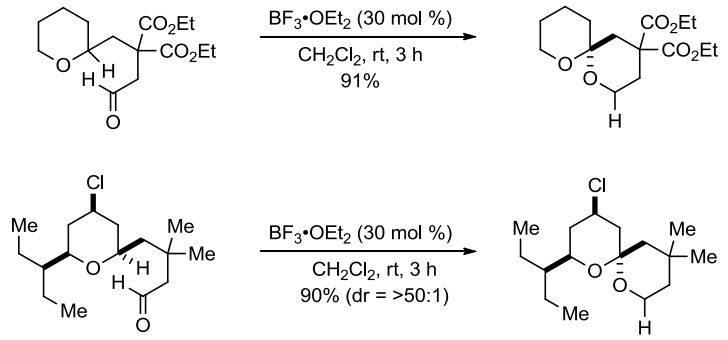
Scheme 2.4. Regioselectivity in the Formation of Tetrahydroquinolines



In studying hydride transfer reactions in pyran systems, the Sames group has shown the reaction proceeds intramolecularly (Scheme 2.5). A cross-over experiment using a deuterated substrate exhibited no loss of deuterium; however, deuteration was found to be rather unselective with regards to axial and equatorial position of the spirocycle product (~1.5:1 respectively).[78] In individual experiments the products were isolated in high yield and diastereoselectivity.

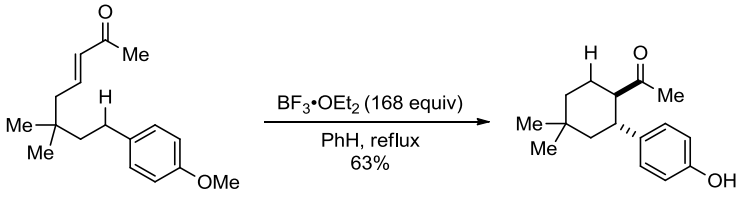
Scheme 2.5. Cross-over Experiment Demonstrating the Intramolecular Process





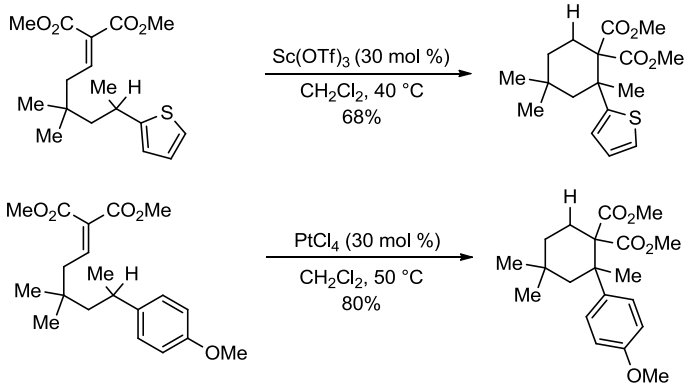
It has also been demonstrated that the hydride shift does not necessitate a heteroatom donor moiety. An early entry was described by Atkinson's group in which a super stoichiometric amount of Lewis acid promoted a benzylic hydride shift/cyclization sequence which also resulted in aryl ether deprotection as a consequence of the reaction conditions (Scheme 2.6).[79]

Scheme 2.6. Hydride Shift from Benzylic Position Under Stoichiometric Conditions



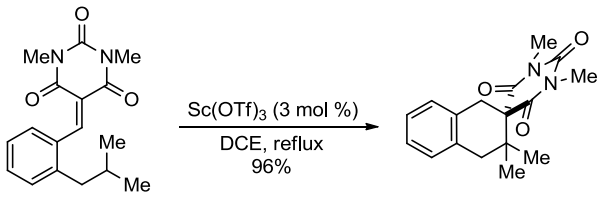
The Sames group has advanced this methodology to a mild protocol catalytic in Lewis acid with substrates bearing a diactivated malonate acceptor and a hydride transferred from a tertiary, aromatic stabilized position (Scheme 2.7).[80]

Scheme 2.7. Hydride Shifts from Benzylic Position under Catalytic Conditions



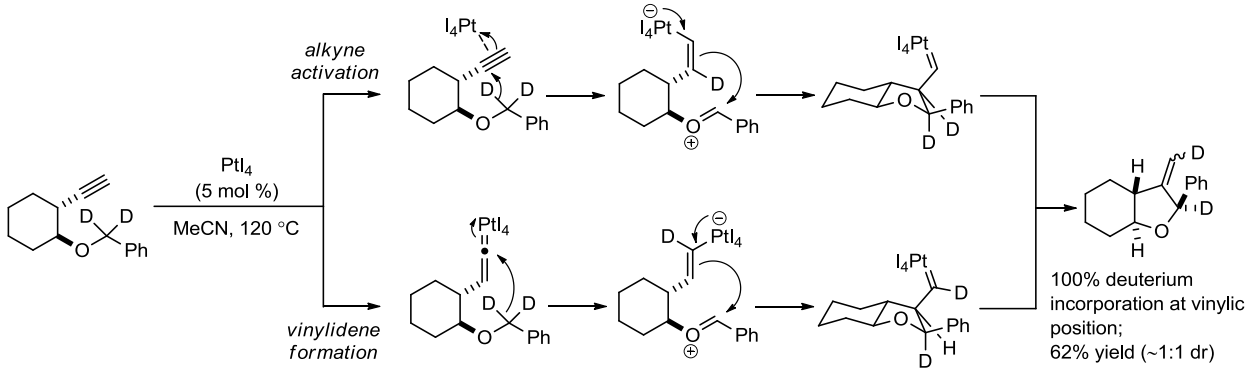
Analogously, Akiyama's group has expanded the scope of the hydride donor moiety to include *tert*-alkyl substituents within electrophilic barbituric acid derived substrates, albeit at higher temperature (Scheme 2.8).[81]

Scheme 2.8. *tert*-Alkyl Hydride Donor



Lewis acid activation of terminal alkynes has also resulted in products from a through space hydride shift/cyclization sequence (Scheme 2.9).[82] Following deuterium labelling studies two pathways were indistinguishably supported, namely alkyne activation and then an initial [1,5]-hydride shift or alternatively via vinylidene formation followed by an initial [1,6]-hydride shift.

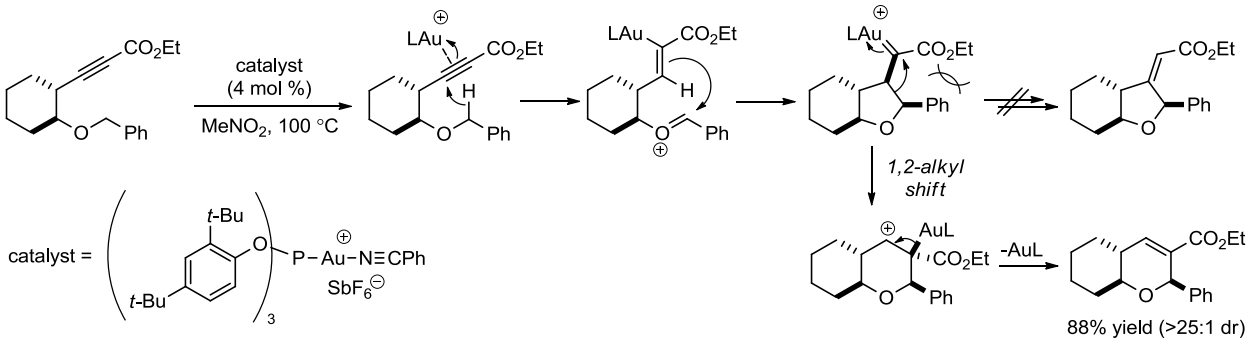
Scheme 2.9. Proposed Mechanism for Terminal Alkyne Acceptors



The substrate scope was later extended by the Gagosz group to include ester and bromide substituted, internal alkynes with a Au(I) Lewis acid catalyst to afford heterocycles including dihydrofurans (Scheme 2.10.).[83] The authors attributed the lack of a divergent product (observed in other systems analyzed) stemming from a 1,2-hydride shift due to sterics between the phenyl and ester groups which results in the observed 1,2-alkyl shift selectively. Also of note, while the

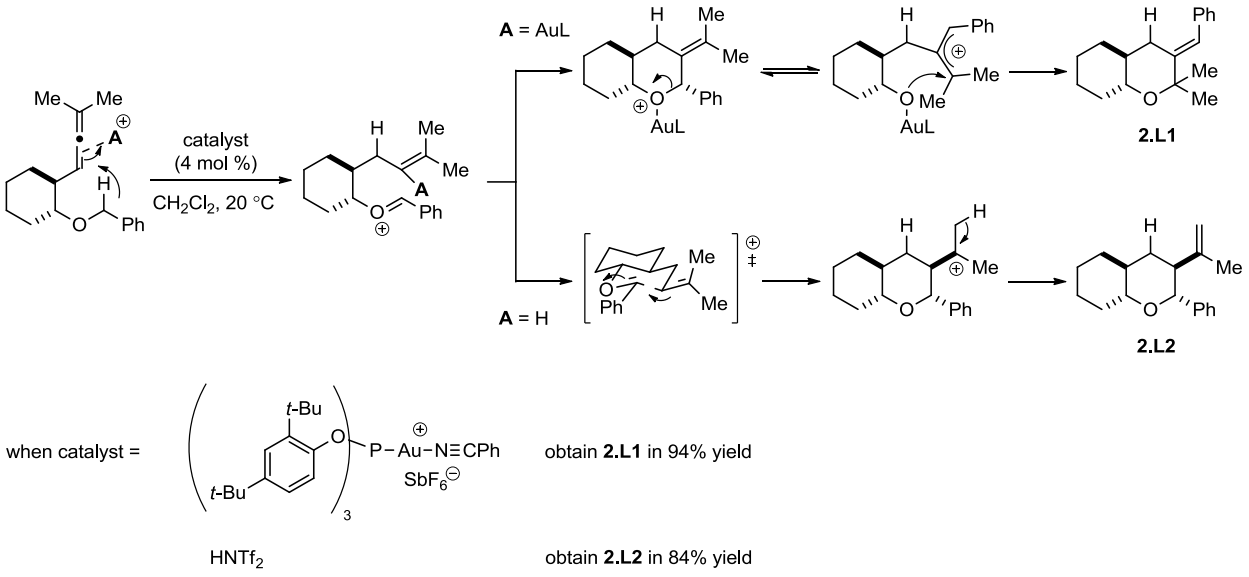
observed product can also be accounted for by carbonyl activation and then a [1,5]-hydride shift/cyclization sequence, gold (I) has been known to selectively complex alkynes.

Scheme 2.10. Internal Alkyne Acceptors and Proposed Mechanism



The Gagosz group has demonstrated that a similar strategy of activating allenes initiates a [1,5]-hydride shift followed by cyclization (Scheme 2.11.).[84] Interestingly, a divergence in product selectivity was observed when using a Lewis acid (Au(I)complex) or Brønsted acid. The formation of the single diastereomer **2.L2** was attributed to the highly ordered chair-like transition state during the cyclization in which the isopropenyl and phenyl groups adopt a pseudoequatorial position with a trans relationship to each other.

Scheme 2.11. Allene Acceptors and Catalyst Induced Divergence in Product Selectivity



The Seidel group has also demonstrated that an enantioselective variant of the reaction illustrated in Scheme 2.4 is possible with a chiral Lewis acid catalyst and subsequently analogous reactions with chiral Lewis or Brønsted acids have been reported (Figure 2.2.).[77,85,86]

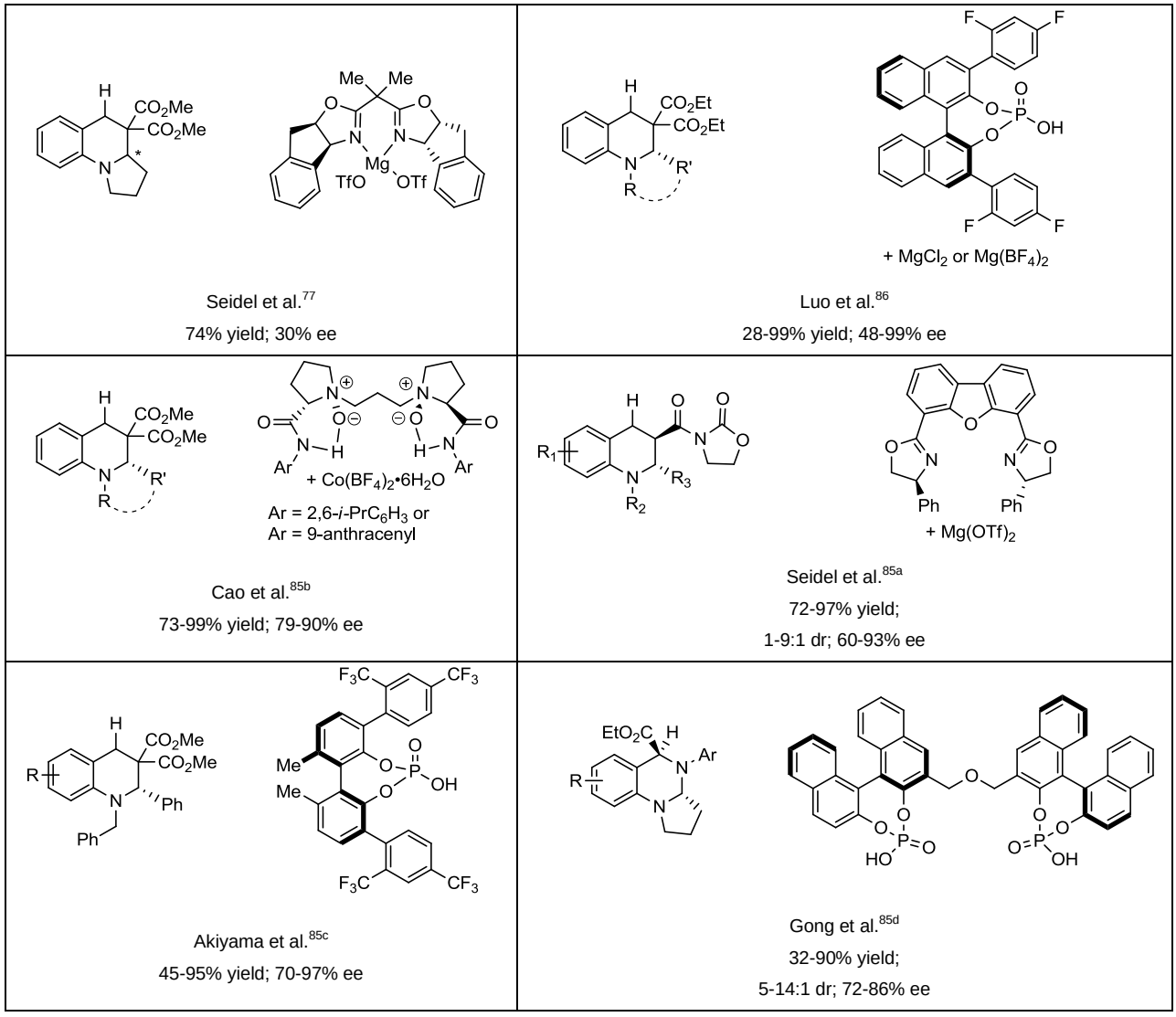
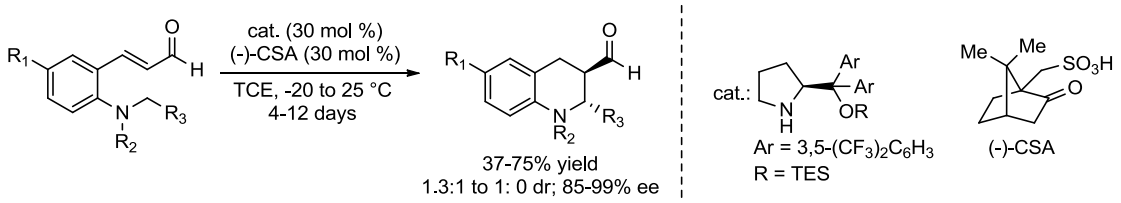


Figure 2.2. Structural Motifs Accessed Through Catalyzed Asymmetric [1,5]-Hydride Transfer Reactions with Chiral Lewis or Brønsted Acids

Alternatively an asymmetric, chiral amine catalyzed protocol was developed by Kim and coworkers (Scheme 2.12) using a proline derived amine catalyst in the presence of (-)-camphorsulfonic acid.[87] Of note, in optimizing the reaction the authors found that the use of the

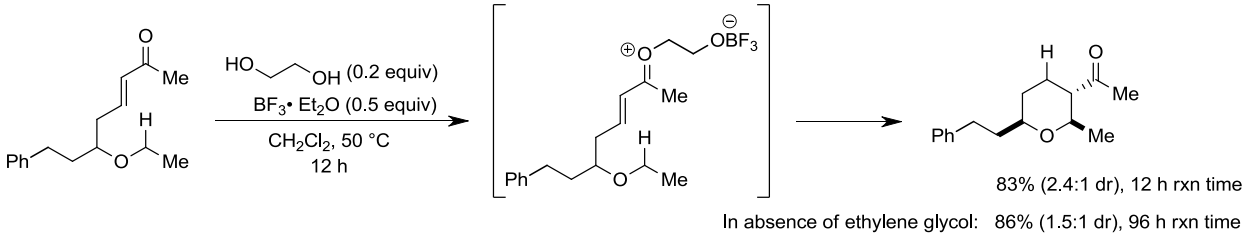
chiral amine catalyst furnished inferior enantioselectivities when using alternate readily available strong, achiral acids.

Scheme 2.12. Enantioselective, Organocatalytic Method



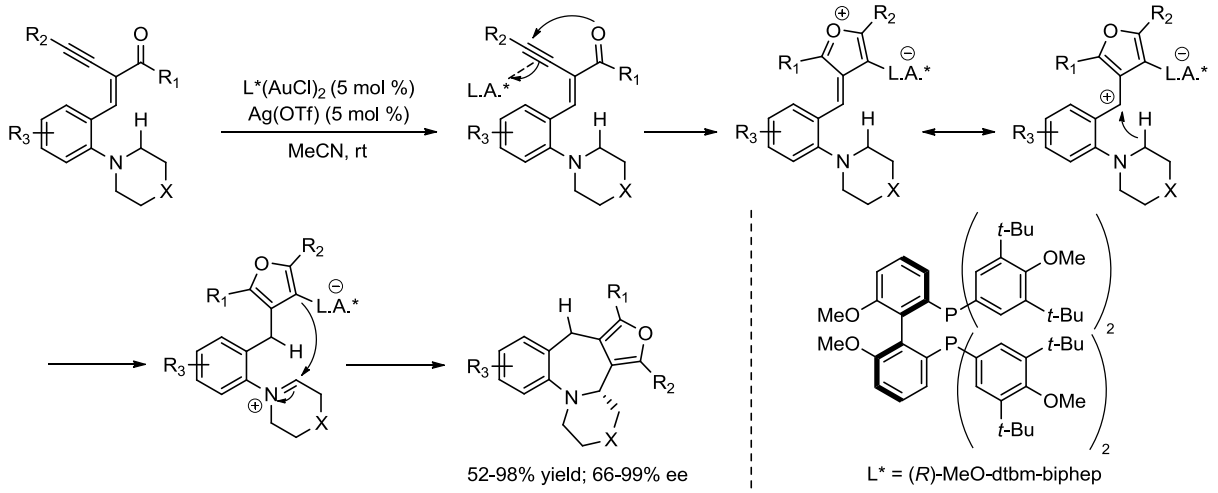
An elegant example of overcoming the lower hydricity of a primary alkyl ether onto an α,β-unsaturated ketone was reported by Sames and coworkers by adding ethylene glycol in addition to the Lewis acid.[88] The increased electrophilicity of the in situ formed oxonium ion greatly accelerated the hydride shift and also provided a higher diastereomeric ratio (Scheme 2.13). The same accelerating effect was shown by starting with the preformed acetal or ketal under Lewis acid catalysis without additional ethylene glycol added.

Scheme 2.13. Acceleration by In situ Formation of Oxonium Species



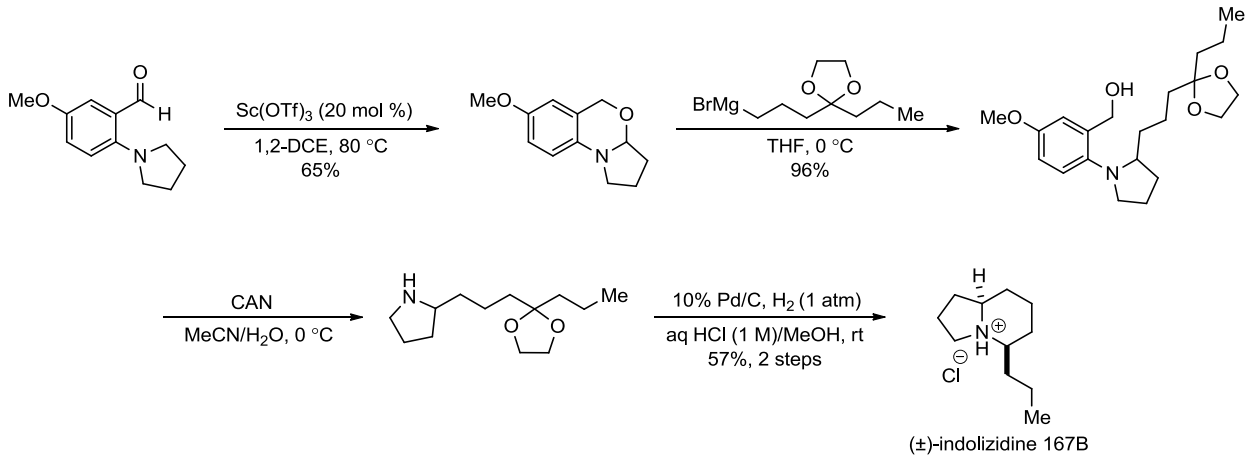
Furthermore, an impressive asymmetric domino reaction sequence was described by Zhang and coworkers by selectively activating the alkyne with a carbophilic[89] gold chiral catalyst to initiate furan formation resulting in hydride shift/cyclization and affording the azepine ring (Scheme 2.14).[90]

Scheme 2.14. Asymmetric Domino Reaction



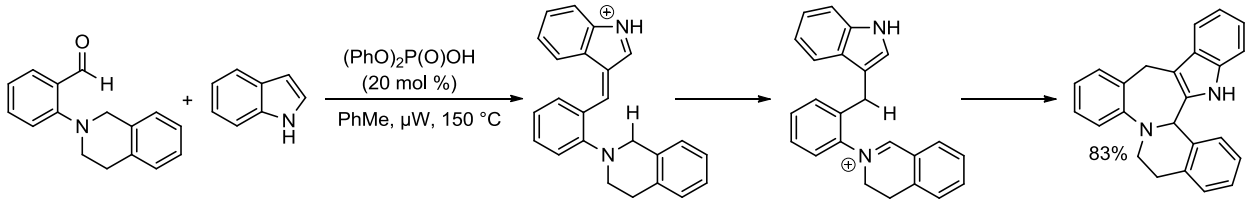
Recently Maulide and coworkers have described an interesting application of Lewis acid catalyzed [1,5]-hydride shift/cyclizations of *ortho*-*tert*-aminobenzaldehydes.[91] By opening the resultant hemiaminal ether with Grignards and alkynyl trifluoroborates followed by oxidative cleavage of the pendant aromatic (provided it bears a *para*- methoxy substituent) more broadly synthetically useful α-functionalized amines were accessed (as shown in 3rd step of Scheme 2.15). The authors highlighted the methodology by a short total synthesis of racemic indolizidine 167B.

Scheme 2.15. Utilization in Total Synthesis



Lastly, an expansion of this strategic disconnection has been reported by Seidel and coworkers in accessing the azepine skeleton through judicious use of nucleophile (Scheme 2.16).[92]

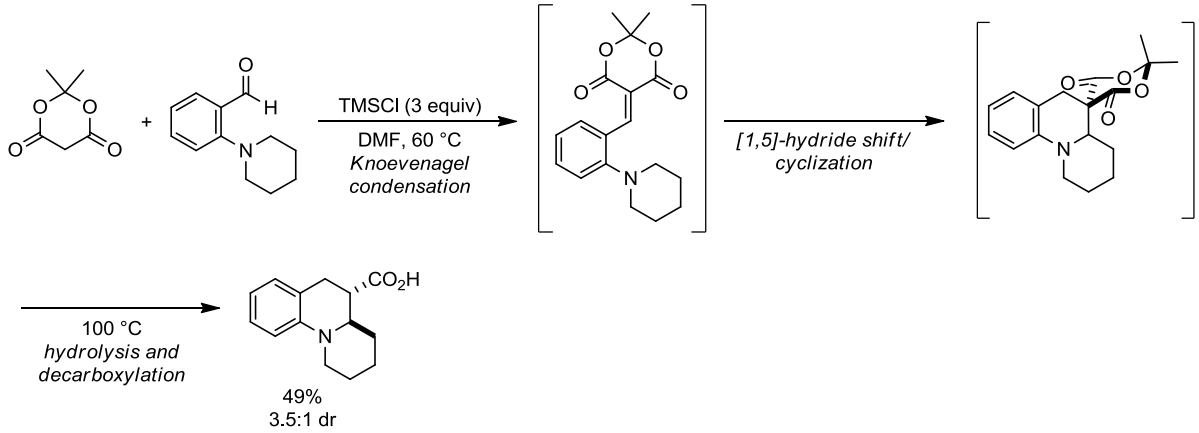
Scheme 2.16. Azepine Skeletal Access



2.2. Proposal

Benzylidene Meldrum's acids have also been utilized as acceptors in hydride transfer methodology (Scheme 2.17).[93] A three step, "one-pot" reaction sequence was devised under super stoichiometric Lewis acid conditions to furnish tricyclic carboxylic acids in moderate yields and diastereoselectivity.

Scheme 2.17. Benzylidene Meldrum's Acid Acceptor



On the basis of our group's success employing benzylidene Meldrum's acids as conjugate addition acceptors[51,59,94] and Meldrum's acid derivatives as powerful acylating agents,[96] both under catalytic Lewis acidic conditions,[95] we envisaged further amenable opportunities.

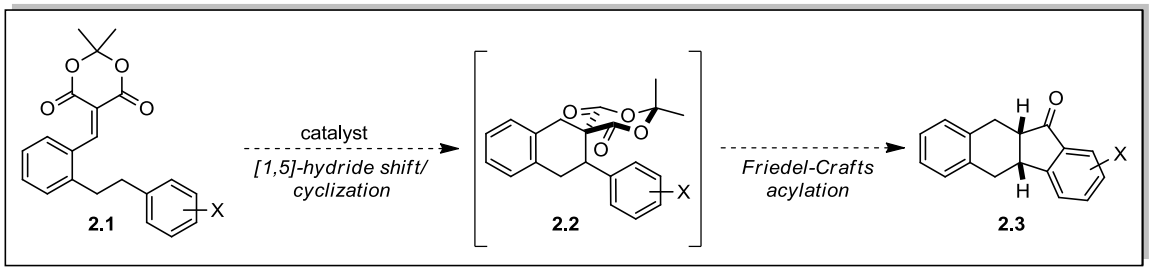


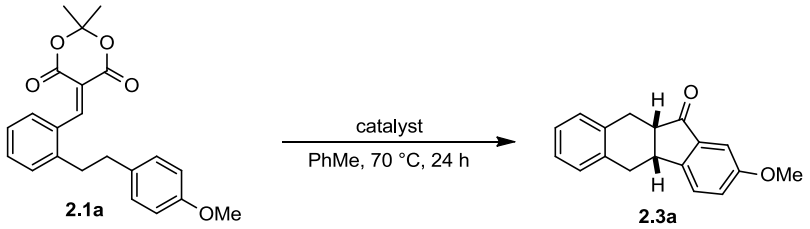
Figure 2.3. Proposed Domino Reaction

In this regard, we proposed that under Lewis or Brønsted acid catalysis, the high electrophilicity of benzylidene Meldrum's acids may enable benzylic hydride shifts to initiate a domino reaction proceeding through an intermediate spirocycle capable of undergoing an intramolecular Friedel-Crafts acylation to deliver complex tetracycles (Figure 2.3).

2.3. Results and Discussion

We began our investigation by subjecting benzylidene **2.1a** to a range of Brønsted and Lewis acids (Table 2.1). We reasoned that the activating *para*-methoxy group should be suitable for providing both stabilization for the developing carbocation at the benzylic position during the hydride shift while being sufficiently π-nucleophilic for the subsequent Friedel-Crafts acylation. While conducting the reaction in the absence of a catalyst resulted in starting material recovery (entry 1), the addition of several catalysts was found to successfully promote the desired reaction sequence; Lewis acids $Sc(OTf)_3$ (entries 6-8), $Sc(NTf_2)_3$ (entry 9) and $BF_3.OEt_2$ (entries 12-13) were effective as well as Brønsted acid TfOH (entry 15). The tetracyclic ketone **2.3a** was obtained in highest yield using $Sc(OTf)_3$ (10 mol %) in toluene (entry 7) and change of solvent to nitromethane, which was the optimal solvent for previous investigations employing Meldrum's acid as an acylating agent,[96] gave an inferior yield (entry 9).

Table 2.1. Evaluation of Promoters



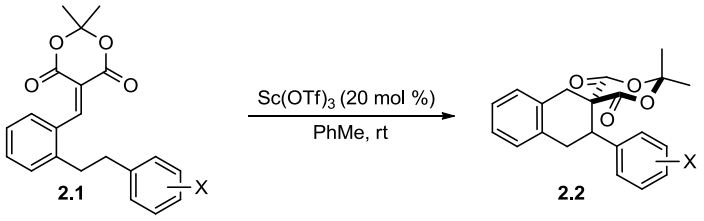
2.1a 2.3a

entry	catalyst	loading (mol %)	yield (%)
1	/	/	NR
2	$AlCl_3$	20	NR
3	$PdCl_2$	20	NR
4[a]	$TiCl_4$	20	NR
5	$Al(OTf)_3$	20	NR
6	$Sc(OTf)_3$	20	37
7	$Sc(OTf)_3$	10	48
8[b]	$Sc(OTf)_3$	10	22
9	$Sc(NTf_2)_3$	10	17
10	TMSOTf	20	NR
11	$Mg(NTf_2)_2$	20	NR
12	$BF_3.OEt_2$	30	45
13	$BF_3.OEt_2$	100	39
14	TFA	20	NR
15	TfOH	20	19

[a] Reaction performed at 50 °C; [b] Nitromethane used as solvent.

At this point it was thought that the reaction may be best improved by an understanding of the temperature requirements and yield for the initial hydride shift/cyclization step by attempting to isolate the spiro intermediate. In this regard, the effect of the electronics and substitution pattern of the stabilizing aromatic on the efficiency of the reaction was next probed (Table 2.2). Pleasingly, electron rich alkoxy substrate **2.1a** delivered spiro product **2.2a** in excellent yield at rt (entry 1)[97] while reactions of substrates bearing electron neutral and weakly electron donating substituents (entries 2 to 4) were found incapable of delivering the desired cyclization product **2.2** (or **2.3**) and resulted in starting material recovery or decomposition upon temperature elevation. Furthermore, electron rich dimethylamino substrate **2.1f** reacted successfully at a slightly increased temperature (likely as a result of competitive complexation of the Lewis acid to the nitrogen atom). Lastly, substrate **2.1f** bearing an ortho-anisole tether failed to furnish the desired product in contrast to entry 1.

Table 2.2. Scope of the $Sc(OTf)_3$ [1,5]-Hydride Transfer/Cyclization at Room Temperature



entry	X	time (h)	yield (%)
1	4-OMe (**2.1a**)	12	90 (**2.2a**)
2[a]	H (**2.1b**)	24	NR (**2.2b**)
3[a]	4-Me (**2.1c**)	15	NR (**2.2c**)
4[a]	4-F (**2.1d**)	19	NR (**2.2d**)
5[b]	4-NMe_2 (**2.1e**)	20	63 (**2.2e**)
6[a]	2-OMe (**2.1f**)	14	NR (**2.2f**)

[a] In separate experiments these starting materials were also found to be inert under otherwise identical reaction conditions at 70 °C; however, upon further temperature elevation to 100 °C, decomposition was observed. [b] Reaction performed at 70 °C.

Furthermore, investigation of substrates bearing tethers with a heteroaromatic moiety terminus to provide stabilization were found to be ineffective at promoting the desired reaction (Figure 2.4).

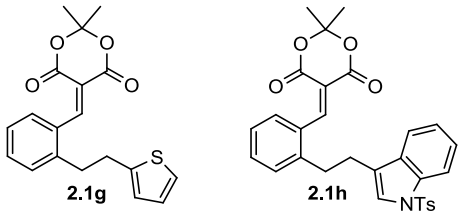
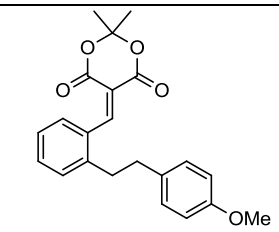
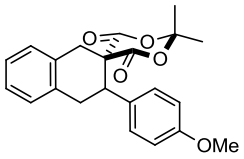
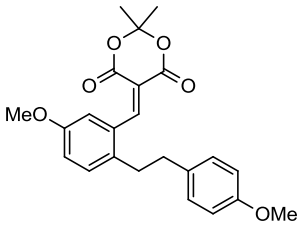
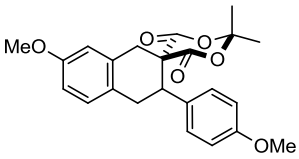
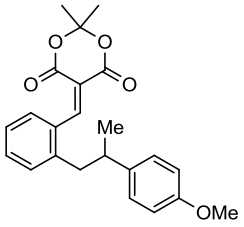
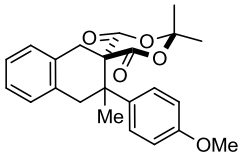
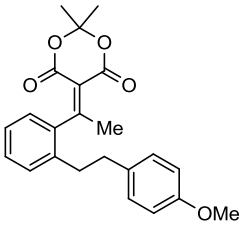
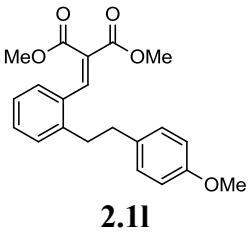
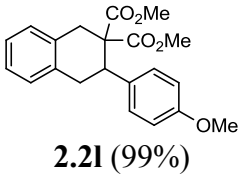


Figure 2.4. Substrates that did not Participate in the Reaction

Following the most promising lead (Table 2.2, entry 1; Table 2.3, entry 1), we focused our attention on exploring the scope of the reaction with regard to *para*-anisole tethered substrates (Table 2.3). Substrate **2.1i** bearing a *meta*-methoxy substituent on the bridging aromatic was found to deliver product **2.2i** in higher yield than **2.2a** presumably due to enhanced electrophilicity of the acceptor by induction (entry 2). Also, the anticipated rate acceleration was

Table 2.3. Hydride Shift/Cyclization Reactions of *para*-Anisole Tethered Substrates

entry	substrate	catalyst loading (mol%)/ time at rt (h)	product (yield)
1	 **2.1a**	20/12	 **2.2a** (90%)
2	 **2.1i**	20/15	 **2.2i** (99%)
3	 **2.1j**	20/1	 **2.2j** (21%)
4	 **2.1k**	40/43	NR
5[a]	 **2.1l**	20/4.5	 **2.2l** (99%)

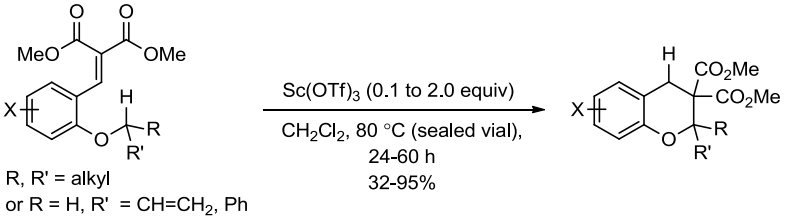
[a] Reaction performed at 100 °C.

observed with substrate **2.1j** forming a quaternary center in **2.2j**,[98] which would proceed through a more stabilized tertiary carbocation (entry 3). Extension of the acceptor moiety was next probed (entries 4 and 5) with ketone derived Meldrum's derivative **2.1k** and benzylidene

malonate substrate **2.1l**; the later successfully delivered the desired product at an elevated reaction temperature (reflective of the inferior electrophilicity relative to benzylidene Meldrum's acids).[99]

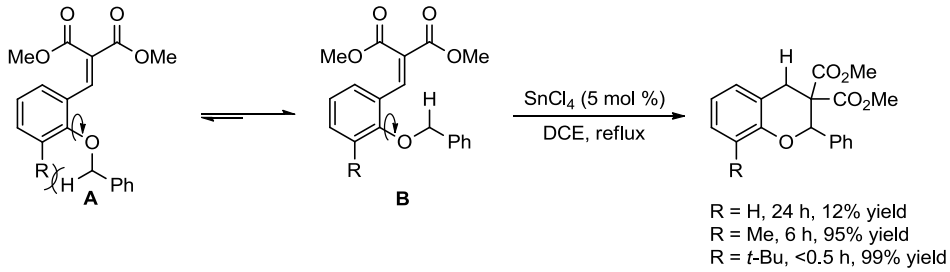
In the weeks following the publication of our work described in this chapter, a report from Sames and coworkers was released describing analogous cyclizations onto malonates under very similar conditions (Scheme 2.18).[100] Their work also revealed the lower reactivity of these acceptors which required elevated temperatures for prolonged reaction times.

Scheme 2.18. Sames' Dihydrobenzopyran Syntheses



Subsequently, Akiyama's group disclosed the rate acceleration observed by an ortho-substituent (application of the Thorpe-Ingold effect).[101] As the size of the *ortho*-substituent was increased, the equilibrium shifted to conformer B (aligned for hydride shift) due to steric repulsion in conformer A (Scheme 2.19).

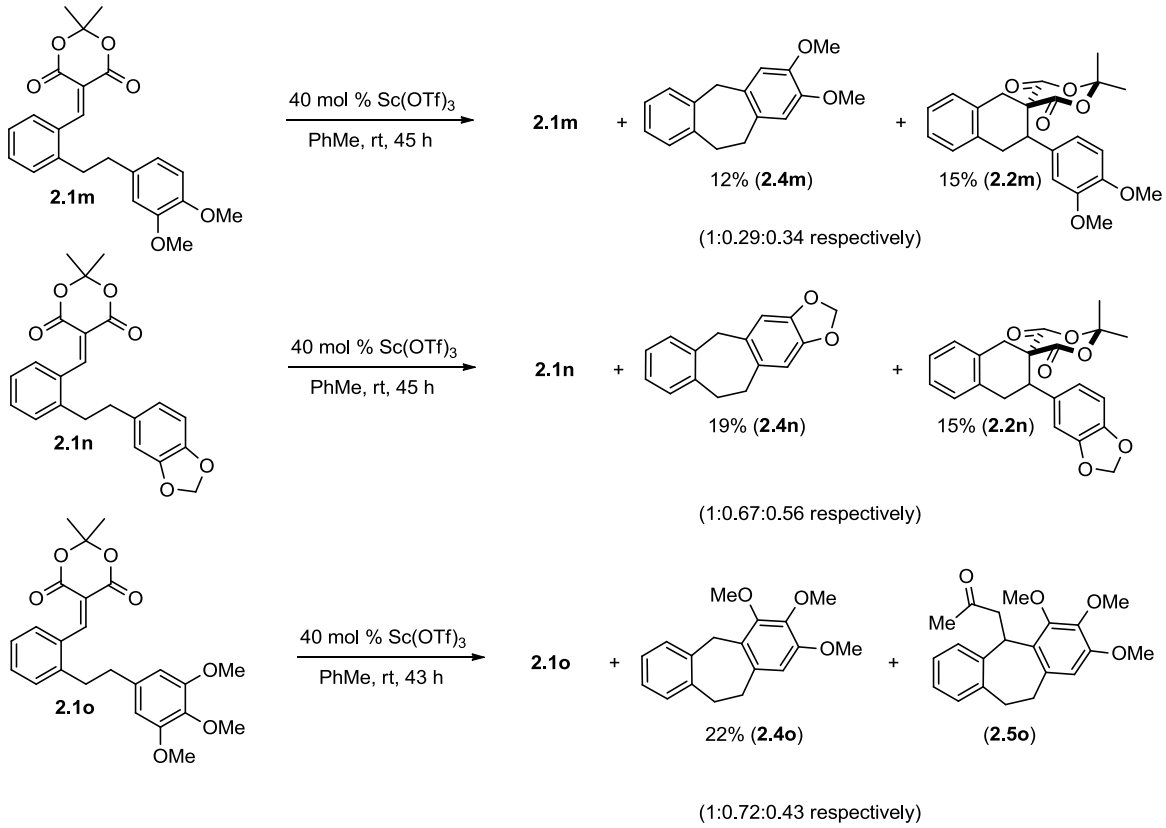
Scheme 2.19. Akiyama's Steric Buttressing Effect



In our study, substrates bearing additional alkoxy groups on the activating aromatic became sufficiently π-nucleophilic to undergo a competing intramolecular Friedel-Crafts alkylation sequence (Scheme 2.20). Dialkoxy models (**2.1m** and **2.1n**) were found to sluggishly

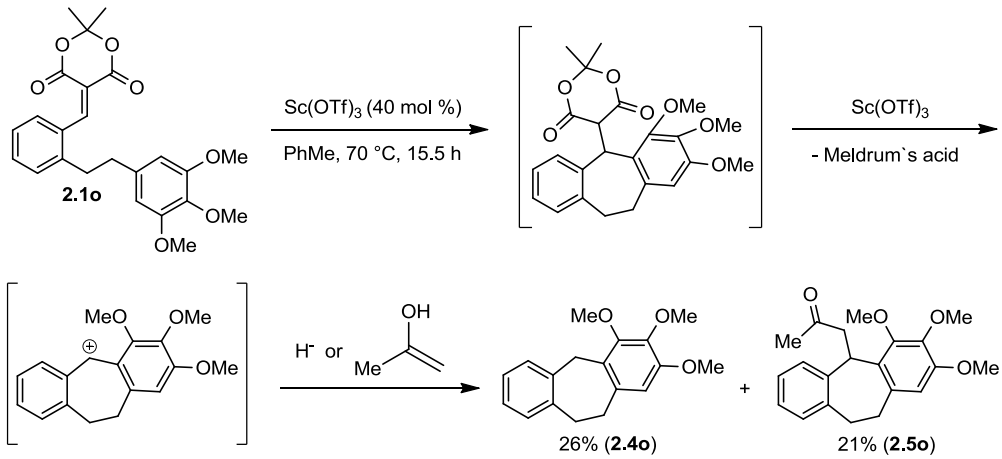
undergo both pathways without an apparent bias. The 3,4,5-trimethoxy substrate (**2.1o**) was found to exclusively undergo Friedel-Crafts alkylation enroute to forming two tricyclic compounds (**2.4o** and **2.5o**).

Scheme 2.20. Reaction of Substrates Bearing Di-and Tri-Alkoxysubstituted Tethers



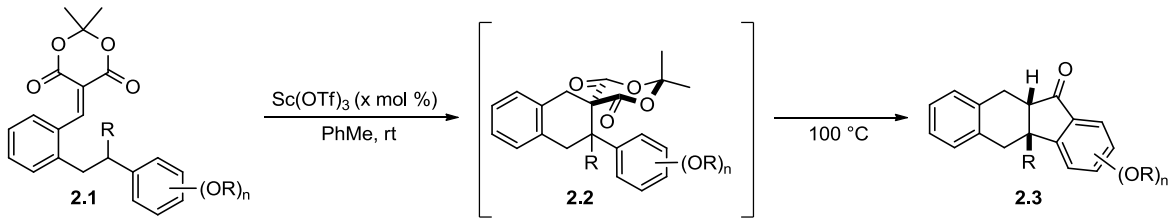
The reaction of the 3,4,5-trimethoxy substrate (**2.1o**) was pushed to completion at 70 °C and a mechanism is given to account for the isolated products (Scheme 2.21). In the presence of $Sc(OTf)_3$, Meldrum's acid is eliminated following the intramolecular Friedel-Crafts alkylation to form a stabilized diaryl carbocation, which is subsequently reduced by a hydride or trapped by acetone. The source of hydride remains to be identified. Acetone would be formed by the decomposition of Meldrum's acid. These displacements of unstrained benzylic Meldrum's acids are unprecendented and chapter 4 of this thesis explores the generality of the strategy with a Lewis acid and nucleophile.

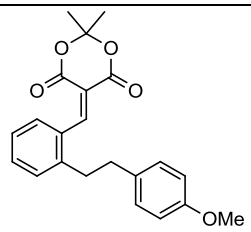
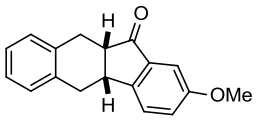
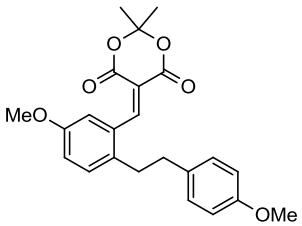
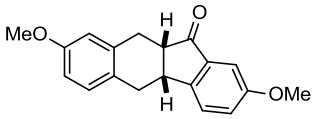
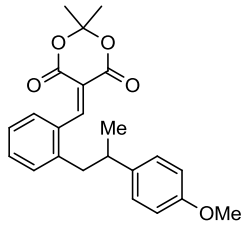
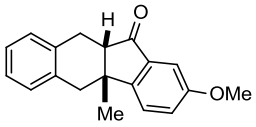
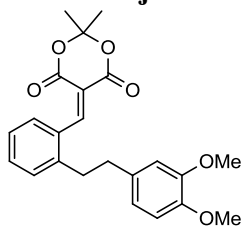
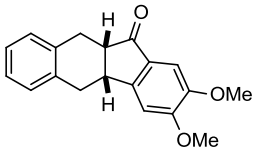
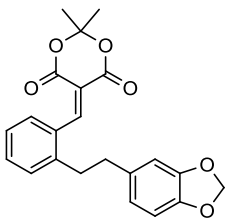
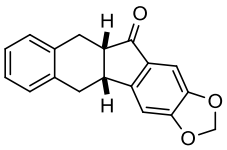
Scheme 2.21. Proposed Mechanism for Formation of Tricyclic Carbocycles



In revisiting the domino sequence, it was found to be advantageous to sequentially stir the benzylidene Meldrum's acid at rt in the presence of $Sc(OTf)_3$, allowing for complete formation of the *spiro*-intermediate before heating to 100 °C for the Friedel-Crafts acylation (Table 2.4). These tuned conditions resulted in the improvement of the yield of tetracycle **2.3a** from 48% (Table 2.1, entry 7) to 78% (Table 2.4, entry 1).[102] Applying these conditions furnished the desired tetracyclic products in respectable yield in accord with their ability to convert to the *spiro*-intermediate, and considering the formation of three new bonds.

Table 2.4. Scope of the Domino Reaction



entry	substrate	catalyst loading (mol%)/ time at rt (h)/time at 100 °C (h)	product (yield)
1	 **2.1a**	20/12/1.5	 **2.3a** (78%)
2	 **2.1i**	20/15/2	 **2.3i** (55%)
3	 **2.1j**	20/1/0.5	 **2.3j** (35%)
4		10/5/1	**2.3j** (61%)
5	 **2.1m**	40/36/3	 **2.3m** (52%)
6	 **2.1n**	40/36/3.5	 **2.3n** (41%)

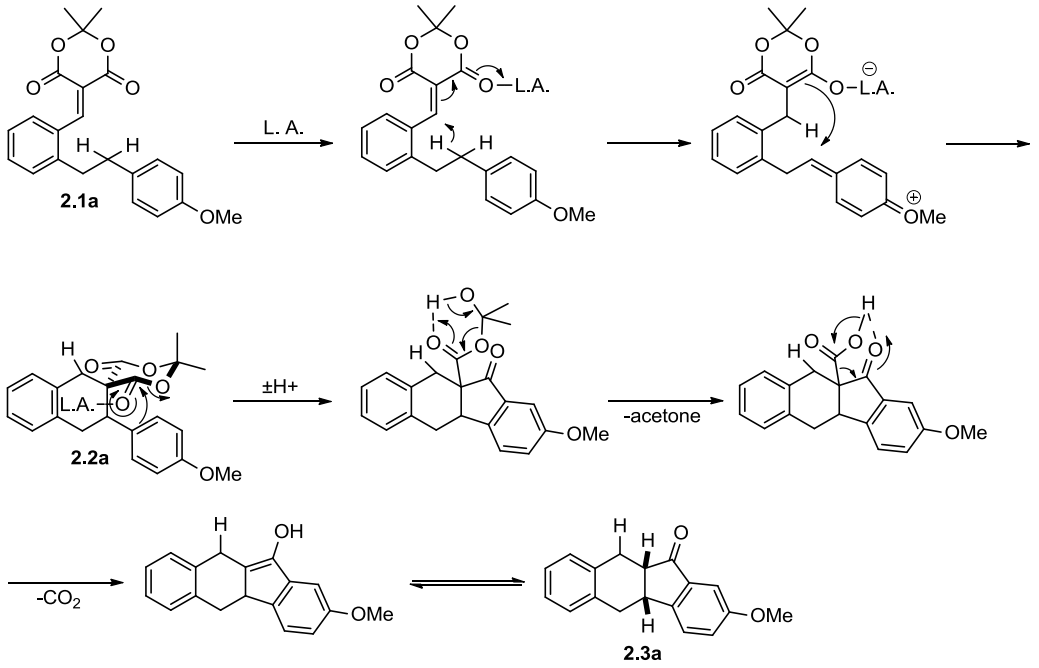


Figure 2.5. Proposed Mechanism of the Domino Reaction

The proposed mechanism of the disclosed domino reaction (Figure 2.5) is initiated by Lewis acid complexation of a carbonyl of Meldrum's acid **2.1a** which renders the alkene more electron deficient and [1,5] hydride shift results from the stabilized benzylic position. Subsequently, cyclization onto the stabilized benzylic carbocation ensues to furnish the spirocyclic intermediate **2.2a**. Next, upon elevation of the reaction temperature intramolecular Friedel-Crafts acylation ensues[103] to furnish the tetracyclic scaffold. Loss of acetone and carbon dioxide would afford the enol form (not observed) which readily tautomerizes to the keto product (**2.3a**).

2.4. Summary

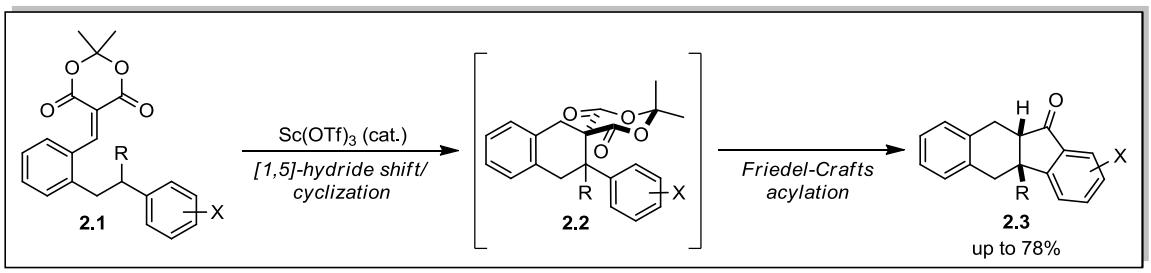


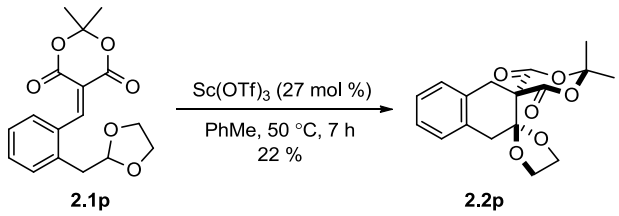
Figure 2.6. Developed Domino Sequence

In summary, a tandem one-pot formation of tetrahydrobenzo[*b*]fluoren-11-ones from benzylidene Meldrum's acids under Lewis acid catalysis, via [1,5]-hydride shift/cyclization/Friedel-Crafts acylation was described.[104] The net result was the formation of three new bonds: two carbon-carbon bonds and one carbon-hydrogen bond. The reaction sequence worked best with a *para*-alkoxy substituent on the tether to circumvent a competing Friedel-Crafts alkylation pathway.

2.5. Future Work

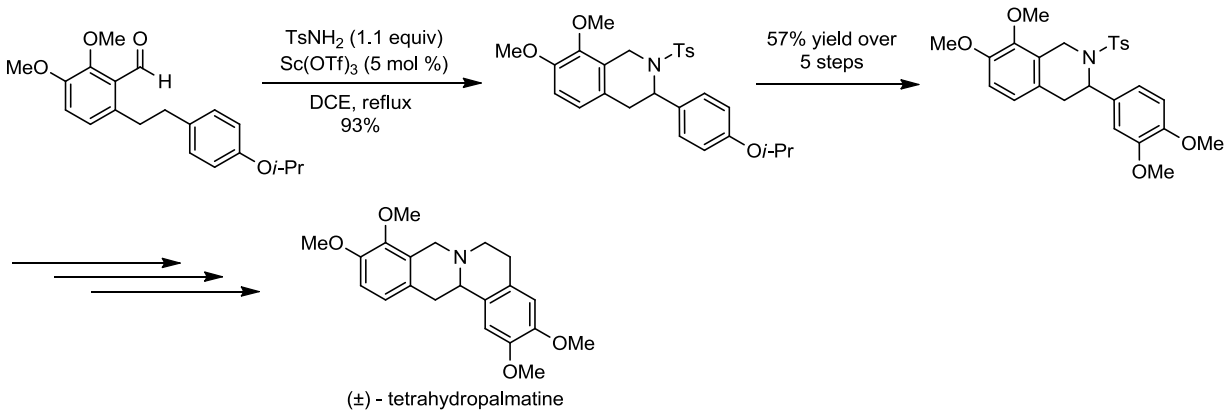
Preliminary experiments have identified the possibility of utilizing acetals as hydride donors (Scheme 2.22) which demonstrates the ability of umpolung reactivity in the hydride shift/cyclization sequence contrasting with Sames report utilizing acetals to enhance the electrophilicity of the acceptor moiety.[88]

Scheme 2.22. Unoptimized Umpolung Hydride Shift Cyclization



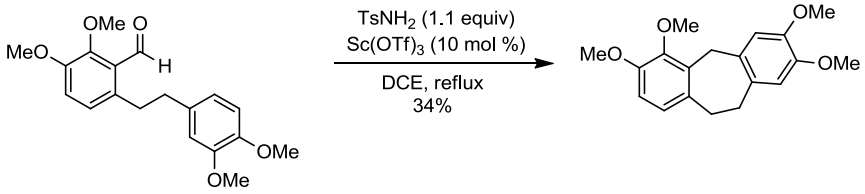
Other groups have recently reported a direct extension of the work described in this chapter to include tosylimine acceptors[105,106] and has been applied to a formal synthesis of an alkaloid (Scheme 2.23).[105]

Scheme 2.23. Tosylimine Acceptors



Of note, an analogous competing Friedel-Crafts reductive process occurred in the group of Akiyama as in our study which prevented access to a much more expedient formal total synthesis of racemic tetrahydropalmatine (Scheme 2.24).

Scheme 2.24. Competing Reaction Pathway in Akiyama's Extension



As mentioned in the results and discussion, the exploration of Meldrum's acid as a leaving group is further explored in Chapter 4 of this thesis.

2.6. Experimental

General Considerations

Reactions

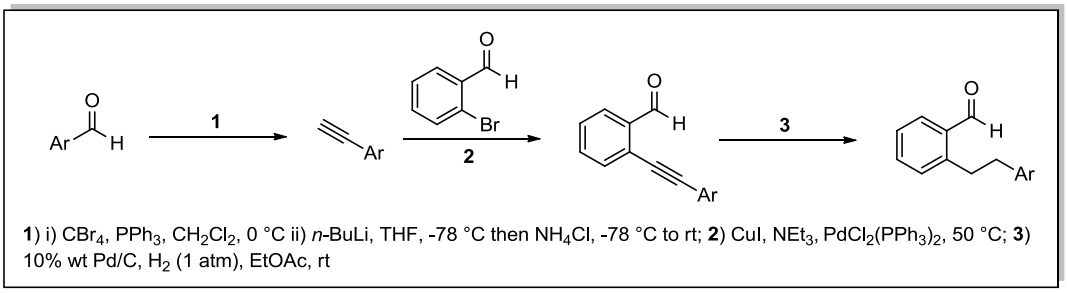
All reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. CH_2Cl_2, THF, and Et_2O were purified based on the published procedure.[107] Benzene was distilled from sodium-benzophenone ketyl under nitrogen. Et_3N and DMF were distilled from CaH_2 under nitrogen. Nitromethane and toluene were distilled from CaH_2 under nitrogen and degassed prior to use. Trifluoromethanesulfonic acid was distilled and stored in a resealable Schlenk flask prior to use. BF_3•OEt_2 was distilled from CaH_2 and stored under nitrogen. Commercial $Sc(OTf)_3$ was dried by heating at 180 °C under high vacuum (0.5 mm Hg) for 2 h, and stored in a glovebox. $Sc(NTf_2)_3$ was prepared according to literature.[108] NaH was washed 3X with pentane and dried under vacuum before use from 60% w/w NaH in mineral oil. 2-Thiophene carboxaldehyde was freshly distilled prior to use. Unless indicated otherwise, all other reagents were used as received from commercial sources. Reactions were monitored by thin-layer chromatography on commercially prepared plates. Developed plates were viewed under a UV lamp (254 nm) and with ceric ammonium molybdate or iodine 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. 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 (-76.53 ppm). Melting points are uncorrected. High resolution mass spectra were run at the University of Waterloo Mass Spectrometry facility.

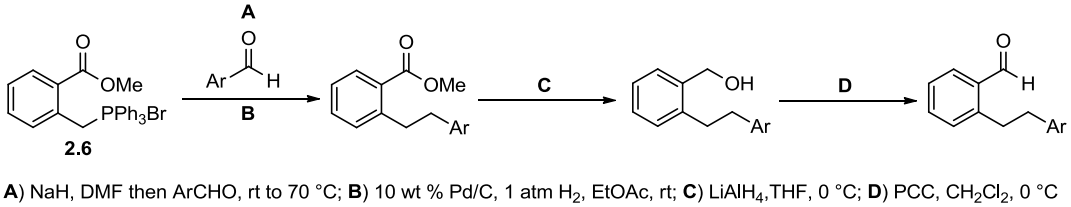
The synthesis of the following starting materials have already been disclosed in a coauthor's thesis in addition to our published manuscript according to Benzaldehyde Preparation Route A followed by Knoevenagel condensation and will not be repeated here:[104, 109]
5-(2-(4-methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1a**), 2,2-dimethyl-5-(2-phenethylbenzylidene)-1,3-dioxane-4,6-dione (**2.1b**), 5-(5-methoxy-2-(4-methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1i**), 5-(1-(2-(4-methoxyphenethyl)phenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1k**), 5-(2-(3,4-dimethoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1m**), 5-(2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.1n**), and 2,2-dimethyl-5-(2-(3,4,5-trimethoxyphenethyl)benzylidene)-1,3-dioxane-4,6-dione (**2.1o**).

Benzaldehyde Preparation Route A



1) i) CBr_4, PPh_3, CH_2Cl_2, 0 °C ii) *n*-BuLi, THF, -78 °C then NH_4Cl, -78 °C to rt; **2**) CuI, NEt_3, $PdCl_2(PPh_3)_2$, 50 °C; **3**) 10% wt Pd/C, H_2 (1 atm), EtOAc, rt

Benzaldehyde Preparation Route B



A) NaH, DMF then ArCHO, rt to 70 °C; **B**) 10 wt % Pd/C, 1 atm H_2, EtOAc, rt; **C**) $LiAlH_4$,THF, 0 °C; **D**) PCC, CH_2Cl_2, 0 °C

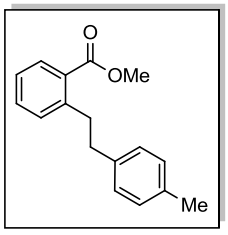
General Procedure A - Wittig Reaction and Subsequent Hydrogenation

Wittig reaction was performed according to Teitei's method.[110] To a stirred suspension of phosphonium salt **2.6**[111] (1.0 equiv) in dry DMF (0.2 M) was added NaH (1.0 equiv). NaH was washed 3X with pentane and dried under vacuum before use from 60% w/w NaH in mineral oil.

The mixture was stirred at rt until a clear orange solution resulted. The aldehyde was then added in DMF (~2.0 M) slowly to the reaction mixture which was followed by TLC analysis (typically stirred over night at rt) and the temperature was raised to 70 °C if the reaction was sluggish. The workup consisted of diluting the reaction mixture with Et_2O, washing with H_2O (3X) , drying over $MgSO_4$, filtering, concentrating under rotary and flash chromatography to typically afford ~1:1 *E*/*Z* mixtures of alkenes in high purity which were subjected to hydrogenation (General Procedure B) without further characterization.

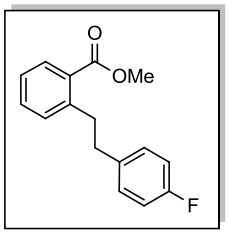
General Procedure B - Hydrogenation over Pd/C

Hydrogenation of the diarylalkenes to the corresponding 1,2-diarylethane substrates was performed by the procedure of Ezoe et al.[112] The diarylalkene mixture was dissolved in EtOAc and degassed while stirring (3X vacuum then refilled with nitrogen) and then Pd (10 wt % on activated carbon) equal to 10 % weight of the alkene (1 wt % Pd) was added. The reaction was then degassed (3X vacuum then refilled with hydrogen). The mixture was stirred for 18 h under 1 atm of H_2, and then filtered through silica, washing with EtOAc. The solvent was removed under vacuum to provide the corresponding diarylethanes in high purity.



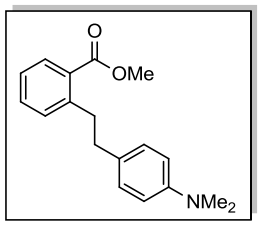
Methyl 2-(4-methylphenethyl)benzoate (2.7)

Prepared according to General Procedure A (flash chromatography eluent = EtOAc:hexanes, 1:19) followed by General Procedure B which afforded a pale yellow oil in 77% yield over 2 steps. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.88 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.26-7.19 (m, 2H), 7.12-7.06 (m, 4H), 3.89 (s, 3H), 3.21 (t, *J* = 8.1 Hz, 2H), 2.83 (t, *J* = 8.1 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.9 (C), 143.6 (C), 138.8 (C), 135.2 (C), 131.9 (CH), 131.1 (CH), 130.7 (CH), 129.4 (C), 128.9 (CH), 128.4 (CH), 125.9 (CH), 51.9 (CH_3), 37.7 (CH_2), 36.9 (CH_2), 20.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_2$ (M^+): 254.1307. Found: 254.1298.



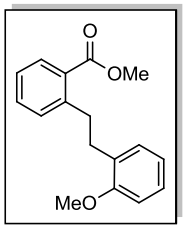
Methyl 2-(4-fluorophenethyl)benzoate (2.8)

Prepared according to General Procedure A (flash chromatography eluent = EtOAc:hexanes, 1:19) followed by General Procedure B which afforded a colourless oil in 84% yield over 2 steps. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.86 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.39 (dt, *J* = 7.4, 1.2 Hz, 1H), (dt, *J* = 7.5, 0.9 Hz, 1H), 7.16-7.12 (m, 3H), 6.94 (app t, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 3.23-3.18 (m, 2H), 2.88-2.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.8 (C), 161.3 (C, d, *J* = 241.7 Hz), 143.4 (C), 137.5 (C, d, *J* = 3.1 Hz), 131.9 (CH), 131.2 (CH), 130.8 (CH), 129.9 (CH, d, *J* = 7.8 Hz), 129.3 (C), 126.1 (CH), 114.9 (CH, d, *J* = 20.9 Hz), 51.9, 37.2, 36.9; ^{19}F NMR ($CDCl_3$, 282 MHz) -118.0. HRMS(EI) *m/z* calcd for $C_{16}H_{15}FO_2$ (M^+): 258.1056. Found: 258.1053.



Methyl 2-(4-(dimethylamino)phenethyl)benzoate (2.9)

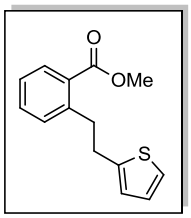
Prepared according to General Procedure A (flash chromatography eluent = EtOAc:hexanes, 1:12 to 1:9) followed by General Procedure B which afforded a white solid in 71% yield over 2 steps. M.p. 60-61 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.87 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.26-7.19 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 3.89 (s, 3H), 3.21-3.16 (m, 2H), 2.90 (s, 6H), 2.81-2.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.0 (C), 149.1 (C), 143.8 (C), 131.8 (CH), 131.1 (CH), 130.6 (CH), 130.2 (C), 129.4 (C), 129.0 (CH), 125.8 (CH), 112.9 (CH), 51.9 (CH_3), 40.9 (CH_3), 37.2 (2 x CH_2); HRMS(EI) *m/z* calcd for $C_{18}H_{21}NO_2$ (M^+): 283.1572. Found: 283.1581.



Methyl 2-(2-methoxyphenethyl)benzoate (2.10)

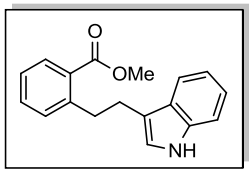
Prepared according to General Procedure A (flash chromatography eluent = EtOAc:hexanes, 1:20) followed by General Procedure B which afforded a colourless oil in 28% yield over 2 steps. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.84 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 6.9 Hz, 1H), 7.21-7.09 (m, 4H), 6.87-6.81 (m, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 3.23-3.18 (m, 2H), 2.92-2.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.2 (C), 157.4 (C), 143.9 (C), 131.7 (CH), 131.1 (CH), 130.4 (CH), 130.2 (C), 130.0 (CH), 129.7 (C), 127.1 (CH),

125.8 (CH), 120.3 (CH), 110.1 (CH), 55.2 (CH_3), 51.9 (CH_3), 34.6 (CH_2), 32.2 (CH_2); HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256. Found: 270.1253.



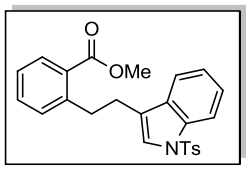
Methyl 2-(2-(thiophen-2-yl)ethyl)benzoate (2.11)

Prepared according to General Procedure A and followed by General Procedure B. The crude material was then resubjected to the General Procedure once to obtain higher conversion. Flash chromatography (EtOAc:hexanes, 1:40) afforded a pale yellow oil in 44% yield over 2 steps. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.90 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.28 -7.19 (m, 2H), 7.10 (d, *J* = 5.1 Hz, 1H), 6.90 (dd, *J* = 4.9, 3.5 Hz, 1H), 6.77 (d, *J* = 2.9 Hz, 1H), 3.90 (s, 3H), 3.29 (t, *J* = 7.7 Hz, 2H), 3.11 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.8 (C), 144.6 (C), 142.9 (C), 132.0 (CH), 131.2 (CH), 130.9 (CH), 129.4 (C), 126.7 (CH), 126.3 (CH), 124.4 (CH), 123.1 (CH), 51.9 (CH_3), 37.2 (CH_2), 31.9 (CH_2); HRMS(EI) *m/z* calcd for $C_{14}H_{14}O_2S$ (M^+): 246.0715. Found: 246.0719.



Methyl 2-(2-(1*H*-indol-3-yl)ethyl)benzoate (2.12)

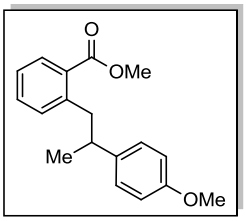
Prepared according to General Procedure A (flash chromatography eluent = EtOAc:hexanes, 1:4) followed by General Procedure B which afforded a maroon solid in 21% yield over 2 steps. M.p. 44-46 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.86 (d, *J* = 7.8 Hz, 2H), (d, *J* = 7.6 Hz, 1H), 7.39-7.09 (m, 5H), 6.89 (s, 1H), 3.81 (s, 3H), 3.35 (t, *J* = 7.3 Hz, 2H), 3.04 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.2 (C), 143.9 (C), 136.2 (C), 131.8 (CH), 131.1 (CH), 130.4 (CH), 129.6 (C), 127.4 (C), 125.8 (CH), 121.7 (CH), 121.5 (CH), 119.0 (CH), 118.9 (CH), 115.9 (C), 111.0 (CH), 51.9 (CH_3), 35.1 (CH_2), 27.4 (CH_2); HRMS(EI) *m/z* calcd for $C_{18}H_{17}NO_2$ (M^+): 279.1259. Found: 279.1266.



Methyl 2-(2-(1-tosyl-1*H*-indol-3-yl)ethyl)benzoate (2.13)

Prepared from **2.12** following a tosylation protocol.[96b] Potassium hydride (1.2 equiv from 30% wt suspension in mineral oil, washed 3X with pentane) was suspended in THF (0.3 M) and cooled to 0 °C. A solution of indole in THF (0.5 M)

was added dropwise to the reaction flask under nitrogen and stirred for 30 min. A solution of TsCl (1.5 equiv) in THF (0.8 M) was then added dropwise over 2 min and stirring was continued for 30 min at 0 °C. The reaction was quenched with a sat. NH_4Cl solution and poured into a separatory funnel containing water. The organic phase was extracted with EtOAc (3X), then dried with $MgSO_4$, and filtered through a pad of silica and concentrated. Flash chromatography (EtOAc:hexanes, 1:9) afforded a pale red oil in 31% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.95 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.33-7.16 (m, 7H), 7.11 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H), 3.29 (t, *J* = 7.4 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 167.7 (C), 144.5 (C), 143.1 (C), 135.2 (C), 135.1 (C), 131.9 (CH), 131.0 (CH), 130.9 (C), 130.6 (CH), 129.7 (CH), 129.3 (C), 126.6 (CH), 126.1 (CH), 124.4 (CH), 122.9 (CH), 122.8 (CH), 122.6 (C), 119.6 (CH), 113.5 (CH), 51.8 (CH_3), 34.1 (CH_2), 26.9 (CH_2), 21.4 (CH_3); HRMS(EI) *m/z* calcd for $C_{25}H_{23}NO_4S$ (M^+): 433.1348. Found: 433.1357.



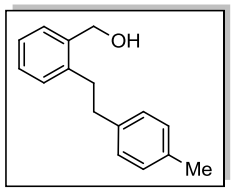
Methyl 2-(2-(4-methoxyphenyl)propyl)benzoate (2.14)

Prepared according to General Procedure A (flash chromatography eluent = EtOAc:hexanes, 1:20) followed by General Procedure B which afforded a pale yellow oil in 5% yield over 2 steps. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.83 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.17 (d, *J* = 7.2 Hz, 2H), 2.96 (app sextet, *J* = 7.0 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.1 (C), 157.7 (C), 142.6 (C), 138.9 (C), 131.9 (CH), 131.4 (CH), 130.6 (CH), 129.7 (C), 127.9 (CH), 125.9 (CH), 113.5 (CH), 55.1 (CH_3), 51.9 (CH_3), 43.4 (CH_2), 40.8 (CH), 21.2 (CH_3); HRMS(EI) *m/z* calcd for $C_{18}H_{20}O_3$ (M^+): 284.1412. Found: 284.1412.

General Procedure C – Reduction with Lithium Aluminum Hydride

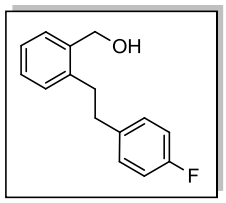
A 0.5 M solution of $LiAlH_4$ (0.75 equiv) in THF was made by first cooling the THF in an ice bath, then adding the $LiAlH_4$ in portions. The $LiAlH_4$ solution was allowed to stir at 0 °C for 15 min, before slowly adding a 0.5 M solution of the ester (1 equiv) in THF. The reaction was

allowed to stir at 0 °C for an additional 30 min after which time reaction progress was monitored by TLC. The reaction was worked up according to Fieser and Fieser.[113] If **X** grams $LiAlH_4$ were used **X** mL 15% NaOH were added slowly, then **X** mL H_2O slowly, followed by 3**X** mL 15% NaOH slowly; all additions were made while stirring at 0 °C. Then Et_2O was added as well as $MgSO_4$ before filtering the mixture over a pad of silica (Et_2O) and concentrating under rotary to afford alcohols in high purity.



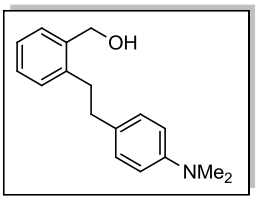
(2-(4-Methylphenethyl)phenyl)methanol (2.15)

Prepared according to General Procedure C from **2.7**. Filtering through silica (Et_2O) afforded a white solid in 97% yield. M.p. 74-75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.39 (d, *J* = 7.4 Hz, 1H), 7.29-7.24 (m, 3H), 7.14-7.07 (m, 4H), 4.67 (d, *J* = 5.5 Hz, 2H), 3.03-2.96 (m, 2H), 2.93-2.87 (m, 2H), 2.35 (s, 3H), 1.36 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 139.8 (C), 138.5 (C), 138.3 (C), 135.4 (C), 129.4 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 126.2 (CH), 62.9 (CH_2), 37.2 (CH_2), 34.4 (CH_2), 20.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{16}H_{18}O$ (M^+): 226.1358. Found: 226.1354.



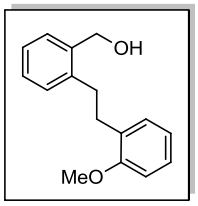
(2-(4-Fluorophenethyl)phenyl)methanol (2.16)

Prepared according to General Procedure C from **2.8**. Filtering through silica (Et_2O) afforded a white solid in 98% yield. M.p. 58-59 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.36 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.28-7.17 (m, 3H), 7.14-7.08 (m, 2H), 6.96 (app t, *J* = 8.6 Hz, 2H), 4.61 (s, 2H), 2.99-2.93 (m, 2H), 2.91-2.85 (m, 2H), 1.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 161.3 (C, d, *J* = 242. 1 Hz), 139.5 (C), 138.3 (C), 137.2 (C, d, *J* = 3.1 Hz), 129.8 (CH, d, *J* = 7.6 Hz), 129.4 (CH), 128.3 (CH), 127.9 (CH), 126.3 (CH), 115.0 (CH, d, *J* = 20.9 Hz), 62.9 (CH_2), 36.7 (CH_2), 34.3 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -117.6. HRMS(EI) *m/z* calcd for $C_{15}H_{15}FO$ (M^+ -water): 212.1001. Found: 212.1004.



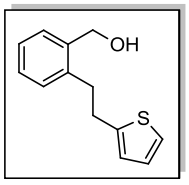
(2-(4-(Dimethylamino)phenethyl)phenyl)methanol (2.17)

Prepared according to General Procedure C from **2.9**. Filtering through silica (Et_2O) afforded a light red oil in quantitative yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35 (d, *J* = 6.7 Hz, 1H), 7.17-7.24 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.64 (d, *J* = 5.7 Hz, 2H), 2.95-2.89 (m, 2H, overlaps with signal at 2.89 ppm), 2.89 (s, 6H), 2.84-2.77 (m, 2H), 1.31 (t, *J* = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 149.1 (C), 139.9 (C), 138.4 (C), 129.8 (C), 129.4 (CH), 128.9 (CH), 128.1 (CH), 127.8 (CH), 126.1 (CH), 112.9 (CH), 62.9 (CH_2), 40.8 (CH_3), 36.7 (CH_2), 34.6 (CH_2); HRMS(EI) *m/z* calcd for $C_{17}H_{21}NO$ (M^+): 255.1623. Found: 255.1630.



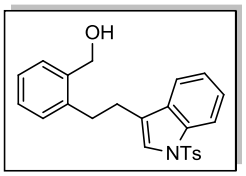
(2-(2-Methoxyphenethyl)phenyl)methanol (2.18)

Prepared according to General Procedure C from **2.10**. Filtering through silica (Et_2O) afforded a pale yellow oil in quantitative yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.38 (d, *J* = 6.4 Hz, 1H), 7.26-7.19 (m, 4H), 7.08 (dd, *J* = 7.2, 1.4 Hz, 1H), 6.92-6.86 (m, 2H), 4.70 (s, 2H), 3.83 (s, 3H), 2.95-2.87 (m, 4H), 1.99 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.3 (C), 140.3 (C), 138.6 (C), 130.0 (CH), 129.9 (C), 129.6 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 126.2 (CH), 120.5 (CH), 110.3 (CH), 63.0 (CH_3), 55.2 (CH_2), 32.9 (CH_2), 32.8 (CH_2); HRMS(EI) *m/z* calcd for $C_{16}H_{18}O_2$ (M^+): 242.1307. Found: 242.1300.



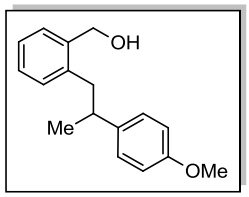
(2-(2-(Thiophen-2-yl)ethyl)phenyl)methanol (2.19)

Prepared according to General Procedure C from **2.11**. Filtering through silica (Et_2O) afforded a colourless oil in 86% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.36 (d, *J* = 7.0 Hz, 1H), 7.26-7.20 (m, 3H), 7.11 (d, *J* = 5.2 Hz, 1H), 6.90 (t, *J* = 4.2 Hz, 1H), 6.75 (d, *J* = 1.2 Hz), 4.66 (s, 2H), 3.16-3.10 (m, 2H), 3.07-3.01 (m, 2H), 1.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 144.2 (C), 139.1 (C), 138.3 (C), 129.3 (CH), 128.3 (CH), 127.9 (CH), 126.7 (CH), 126.4 (CH), 124.4 (CH), 123.1 (CH), 62.8 (CH_2), 34.4 (CH_2), 31.4 (CH_2); HRMS(EI) *m/z* calcd for $C_{13}H_{14}OS$ (M^+): 218.0765. Found: 218.0763.



(2-(2-(1-Tosyl-1*H*-indol-3-yl)ethyl)phenyl)methanol (2.20)

Prepared according to General Procedure C from **2.13**. Filtering through silica (Et_2O) afforded a pale orange oil in 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.99 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.36-7.14 (m, 9H), 4.63 (s, 2H), 3.06-2.96 (m, 5H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 144.7 (C), 139.6 (C), 138.3 (C), 135.2 (C), 130.8 (C), 129.7 (CH), 129.4 (CH), 128.4 (CH), 127.9 (CH), 126.7 (CH), 126.4 (CH), 124.6 (CH), 123.0 (CH), 122.8 (CH), 122.5 (C), 119.4 (CH), 113.6 (CH), 63.0 (CH_2), 31.7 (CH_2), 26.6 (CH_2), 21.5 (CH_3); HRMS(EI) *m/z* calcd for $C_{24}H_{23}NO_3S$ (M^+): 405.1399. Found: 405.1396.



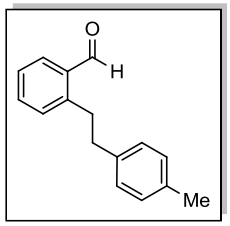
(2-(2-(4-Methoxyphenyl)propyl)phenyl)methanol (2.21)

Prepared according to General Procedure C from **2.14**. Filtering through silica (Et_2O) afforded a colourless oil in 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.32 (app t, *J* = 3.9 Hz, 1H), 7.18 (app t, *J* = 3.8 Hz, 2H), 7.08-7.02 (m, 3H), 6.79 (d, *J* = 8.5 Hz, 2 H), 4.55 (s, 2H), 3.76 (s, 3H), 2.97-2.84 (m, 3H), 1.40 (s, 1H), 1.26 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.8 (C), 138.7 (C), 138.6 (C), 130.1 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 126.2 (CH), 113.6 (CH), 62.7 (CH_2), 55.1 (CH_3), 41.4 (CH_2), 40.6 (CH), 21.3 (CH_3); HRMS(EI) *m/z* calcd for $C_{17}H_{20}O_2$ (M^+): 256.1463. Found: 256.1456.

General Procedure D - Oxidation with Pyridinium Chlorochromate

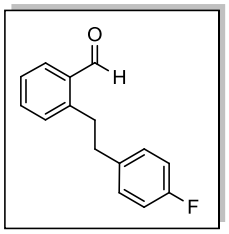
Oxidation of the benzyl alcohols to the corresponding benzaldehydes with pyridinium chlorochromate (PCC) proceeded via the modified procedure of Corey and Suggs.[114] A round bottom flask equipped with stir bar and 4 Å MS (equal #grams as PCC used) was flame dried under dry nitrogen, before adding PCC (1.5 equiv) and dry CH_2Cl_2 (0.3 M) at 0 °C. The alcohol (1 equiv) was then added in minimal CH_2Cl_2 (~1.0 M) and the reaction was allowed to continue to stir at 0 °C for 30 min. The reaction progress was monitored via TLC. The workup consisted of diluting the reaction mixture with CH_2Cl_2, filtering through a pad of silica with CH_2Cl_2 as

eluent, concentrating under rotary, followed by a second pad of silica (EtOAc:hexanes) to afford aldehydes in high purity.



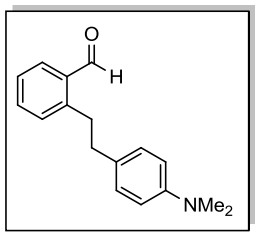
2-(4-Methylphenethyl)benzaldehyde (2.22)

Prepared according to General Procedure D from **2.15**. Filtering through silica (Et_2O then CH_2Cl_2), concentrating on rotary then filtering through a second silica pad (EtOAc:hexanes, 1:4) afforded a pale yellow oil in 91% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 10.19 (s, 1H), 7.81 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.48 (dt, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1 H), 7.07 (s, 4H), 3.31-3.26 (m, 2H), 2.87-2.82 (m, 2H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 192.2 (CH), 144.4 (C), 138.0 (C), 135.5 (C), 133.73 (C), 133.69 (CH), 132.1 (CH), 131.2 (CH), 129.0 (CH), 128.4 (CH), 126.6 (CH), 37.8 (CH_2), 34.9 (CH_2), 20.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{16}H_{16}O$ (M^+): 224.1201. Found: 224.1197.



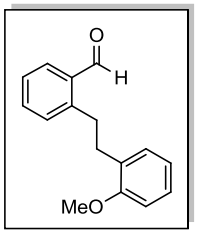
2-(4-Fluorophenethyl)benzaldehyde (2.23)

Prepared according to General Procedure D from **2.16**. Filtering through silica (Et_2O then CH_2Cl_2), concentrating on rotary then filtering through a second silica pad (EtOAc:hexanes, 1:5) afforded a white solid in 88% yield. M.p. 55-56 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 10.17 (s, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.19-7.11 (m, 3H), 6.94 (t, *J* = 8.6 Hz, 2H), 3.29 (t, *J* = 7.9 Hz, 2H), 2.86 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 192.4 (CH), 161.3 (C, d, *J* = 242.2 Hz), 143.8 (C), 136.8 (C, d, *J* = 3.2 Hz), 133.7 (C), 133.6 (CH), 132.9 (CH), 131.2 (CH), 129.9 (CH, d, *J* = 7.7 Hz), 126.9 (CH), 115.0 (CH, d, *J* = 20.9 Hz), 37.2 (CH_2), 35.1 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -117.6. HRMS(EI) *m/z* calcd for $C_{15}H_{13}FO$ (M^+): 228.0950. Found: 228.0951.



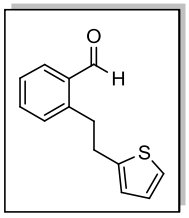
2-(4-(Dimethylamino)phenethyl)benzaldehyde (2.24)

Prepared under Swern conditions from **3.17**.[115] Filtering through silica (CH_2Cl_2) afforded a pale yellow solid in 90% yield. M.p. 60-62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 10.27 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 3.33 (t, *J* = 7.6 Hz, 2H), 2.96 (s, 6H), 2.87, (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 192.1 (CH), 149.2 (C), 144.7 (C), 133.7 (CH), 133.6 (C), 131.6 (CH), 131.1 (CH), 129.1 (C), 129.0 (CH), 126.4 (CH), 112.9 (CH), 40.8 (CH_3), 37.4 (CH_2), 35.0 (CH_2); HRMS(EI) *m/z* calcd for $C_{17}H_{19}NO$ (M^+): 253.1467. Found: 253.1472.



2-(2-Methoxyphenethyl)benzaldehyde (**2.25**)

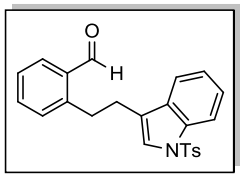
Prepared according to General Procedure D from **2.18**. Filtering through silica (Et_2O then CH_2Cl_2) afforded a white solid in 96% yield. M.p. 65-67 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 10.31 (s, 1H), 7.85 (d, *J* = 6.9 Hz, 1H), 7.49 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.27-7.17 (m, 2H), 7.06 (d, *J* = 6.4 Hz, 1H), 6.88-6.83 (m, 2H), 3.81 (s, 3H), 3.31-3.26 (m, 2H), 2.96-2.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 192.0 (CH), 157.4 (C), 145.2 (C), 133.9 (C), 133.7 (CH), 131.0 (CH), 130.0 (2 x CH), 129.2 (C), 127.5 (CH), 126.4 (CH), 120.4 (CH), 110.1 (CH), 55.1 (CH_3), 33.4 (CH_2), 32.5 (CH_2); HRMS(EI) *m/z* calcd for $C_{16}H_{16}O_2$ (M^+): 240.1150. Found: 240.1152.



2-(2-(Thiophen-2-yl)ethyl)benzaldehyde (2.26)

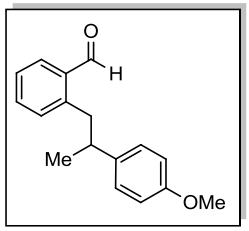
Prepared according to General Procedure D from **2.19**. Filtering through silica (Et_2O then CH_2Cl_2), concentrating on rotary then filtering through a second silica pad (EtOAc:hexanes, 1:9) afforded a pale yellow oil in 93% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 10.18 (s, 1 H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.49 (app dt, *J* = 6.9, 1.3 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.23 (d, 6.5 Hz, 1H), 7.11 (d, *J* = 5.2 Hz, 1H), 6.89 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.73 (d, *J* = 3.2 Hz, 1H), 3.37 (t, *J* = 7.7 Hz, 2H), 3.11 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 192.3 (CH), 143.7 (C), 143.4 (C), 133.8 (C), 133.7 (CH), 132.7 (CH), 131.2

(CH), 126.9 (CH), 126.8 (CH), 124.7 (CH), 123.3 (CH), 35.1 (CH_2), 31.8 (CH_2); GC/MS *m/z* calcd for $C_{13}H_{12}O_5$ (M^+): 216. Found: 216.



2-(2-(1-Tosyl-1*H*-indol-3-yl)ethyl)benzaldehyde (2.27)

Prepared under Swern conditions from **2.20**.[115] Filtering through silica (CH_2Cl_2) afforded a white solid in 91% yield. M.p. 134-135 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 10.17 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 7.0, 2.0 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.44-7.37 (m, 2H), 7.31-7.12 (m overlapping with $CHCl_3$, 6H), 3.36 (t, *J* = 7.8 Hz, 2H), 2.94 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 192.4 (CH), 144.5 (C), 143.5 (C), 135.0 (C), 133.5 (CH), 133.1 (CH), 131.0 (CH), 130.6 (C), 129.6 (CH), 126.6 (CH), 126.5 (CH), 124.4 (CH), 122.9 (CH), 122.8 (CH), 122.0 (C), 119.4 (CH), 113.5 (CH), 32.4 (CH_2), 26.8 (CH_2), 21.3 (CH_3); HRMS(EI) *m/z* calcd for $C_{24}H_{21}NO_3S$ (M^+): 403.1242. Found: 403.1234.

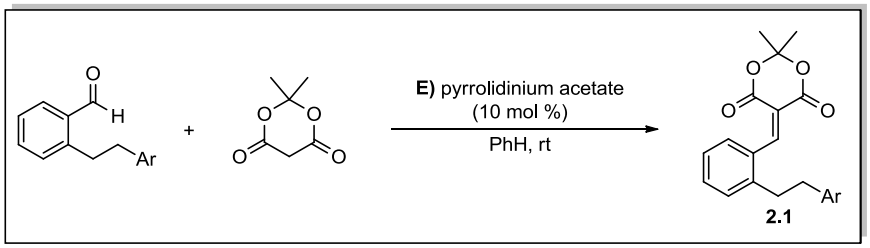


2-(2-(4-Methoxyphenyl)propyl)benzaldehyde (2.28)

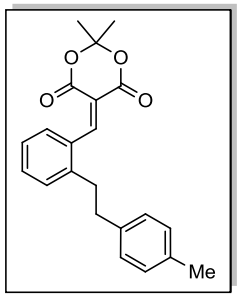
Prepared according to General Procedure D from **2.21**. Filtering through silica (Et_2O then CH_2Cl_2) afforded a tan oil in 86% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 10.15 (s, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.02 (app d, 8.2 Hz, 3H), 6.78 (d, *J* = 8.2 Hz, 2H), 3.76 (s, 3H), 3.21 (d, *J* = 7.2 Hz, 2H), 2.93 (app sextet, *J* = 7.0 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 191.9 (C), 157.7 (C), 143.2 (C), 137.8 (C), 133.7 (C), 133.0 (CH), 131.7 (CH), 131.4 (CH), 127.6 (CH), 126.3 (CH), 113.4 (CH), 54.9 (CH_3), 41.3 (CH_2), 41.1 (CH), 20.8 (CH_3); HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_2$ (M^+): 254.1307. Found: 254.1310.

Note: An improved route to this compound is thought to be realized by the following 3 step sequence in analogy to a literature protocol:[80] addition of 4-(OMe)C_6H_4MgBr to 1-(2-bromophenyl)-2-propanone (both commercially available), followed by reduction and lastly halogen exchange and trapping with an aldehyde source (ex. DMF).

General Procedure E - Knoevenagel Condensation of Benzaldehydes with Meldrum's Acid

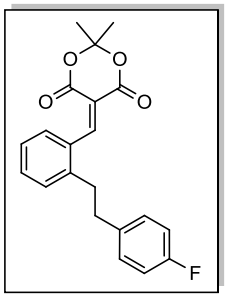


Benzylidene Meldrum's acids were prepared by Knoevenagel condensation of Meldrum's acid with benzaldehydes according to the method of Fillion and coworkers.[66] In a typical reaction, pyrrolidine (10 mol %) and acetic acid (10 mol %) were combined in dry benzene (1.0 M) and added to a solution of the benzaldehyde (1.0 equiv) and Meldrum's acid (1.1 equiv) in dry benzene (0.2 M). The solution was then capped and allowed to stir at rt (or to 50 °C if sluggish) for 24 h. Purification consisted of either diluting the reaction with EtOAc, washing the mixture with saturated $NaHCO_3$ solution, drying over $MgSO_4$, filtering, and concentrating dry or by removal of benzene by rotary evaporation and recrystallization of the resulting solid from MeOH. Flash chromatography was performed when oils were obtained.



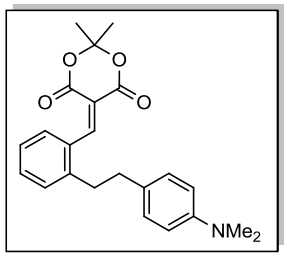
2,2-Dimethyl-5-(2-(4-methylphenethyl)benzylidene)-1,3-dioxane-4,6-dione (2.1c)

Prepared according to General Procedure E from **2.22**. Flash chromatography (EtOAc:hexanes, 1:9 to 1:5) followed by recrystallization from MeOH afforded a white solid in 26% yield. M.p. 88-89 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.55 (s, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.26-7.21 (m, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 7.9 Hz, 2H), 2.99 (t, 7.6 Hz, 2H), 2.81 (t, 7.6 Hz, 2H), 2.29 (s, 3H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.4 (C), 159.1 (C), 157.2 (CH), 142.9 (C), 137.2 (C), 135.4 (C), 132.3 (CH), 131.1 (C), 130.3 (CH), 129.8 (CH), 129.3 (CH), 128.5 (CH), 125.8 (CH), 115.3 (C), 104.4 (C), 37.5 (CH_2), 36.6 (CH_2), 27.7 (CH_3), 20.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{22}H_{22}O_4$ (M^+ -acetone): 292.1099. Found: 292.1091.



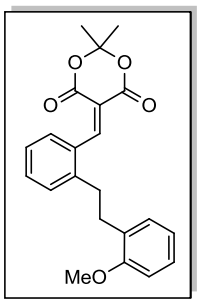
5-(2-(4-Fluorophenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1d)

Prepared according to General Procedure E from **2.23**. Recrystallization from MeOH afforded a white solid in 56% yield. M.p. 99-100 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.57 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.26-7.18 (m, 2H), 7.03-6.98 (m, 2H), 6.89 (app t, *J* = 8.6 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.4 (C), 161.3 (C, d, *J* = 242.6 Hz), 159.1 (C), 157.1 (CH), 142.4 (C), 135.9 (C, d, *J* = 3.0 Hz), 132.3 (CH), 131.1 (C), 130.2 (CH), 130.0 (CH, d, *J* = 7.9 Hz), 129.8 (CH), 125.9 (CH), 115.7 (C), 115.2 (CH, d, *J* = 21.0 Hz), 104.5 (C), 37.1, 36.4, 27.7; ^{19}F NMR ($CDCl_3$, 282 MHz) -117.4. HRMS(EI) *m/z* calcd for $C_{21}H_{19}FO_4$ (M^+ -methyl): 339.1039. Found: 339.1033.



5-(2-(4-(Dimethylamino)phenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1e)

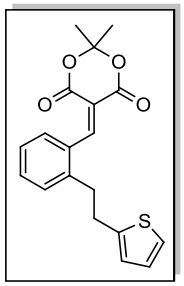
Prepared according to General Procedure E from **2.24**. Flash chromatography (EtOAc:hexanes, 1: 5) afforded a dark orange oil in 47% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.51 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.27-7.20 (m, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 2H), 2.98 (t, *J* = 7.8 Hz, 2H), 2.89 (s, 6H), 2.75 (t, *J* = 7.7 Hz, 2H), 1.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.5 (C), 159.2 (C), 157.3 (CH), 148.9 (C), 143.3 (C), 132.3 (CH), 131.2 (C), 130.3 (CH), 129.9 (CH), 129.3 (CH), 128.2 (C), 125.6 (CH), 114.4 (C), 113.1 (CH), 104.2 (C), 40.7 (CH_3), 36.9 (CH_2), 36.8 (CH_2), 27.6 (CH_3); HRMS(EI) *m/z* calcd for $C_{23}H_{25}NO_4$ (M^+): 379.1784. Found: 379.1784.



5-(2-(2-Methoxyphenethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1f)

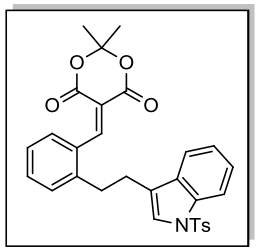
Prepared according to General Procedure E from **2.25**. Flash chromatography (EtOAc:hexanes, 1:9 to 1:5) afforded a pale yellow solid in 68% yield. M.p.

95-98 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.58 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.14 (dt, *J* = 7.5, 1.7 Hz, 1H), 6.92 (dd, *J* = 7.3, 1.8 Hz, 1H), 6.80-6.74 (m, 2H), 3.81 (s, 3H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H), 1.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.5 (C), 159.2 (C), 157.5 (CH), 157.4 (C), 143.8 (C), 132.3 (CH), 131.1 (C), 130.4 (CH), 130.3 (CH), 129.9 (CH), 128.4 (C), 127.3 (CH), 125.6 (CH), 120.5 (CH), 115.0 (C), 110.2 (CH), 104.2 (C), 54.9 (CH_3), 34.5 (CH_2), 33.2 (CH_2), 27.6 (CH_3); HRMS(EI) *m/z* calcd for $C_{22}H_{22}O_5$ (M^+): 366.1467. Found: 366.1480.



5-(2-(2-(Thiophen-2-yl)ethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1g)

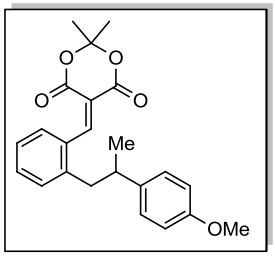
Prepared according to General Procedure E from **2.26**. Recrystallization from MeOH afforded a pale yellow solid in 43% yield over 2 crops. M.p. 90-91 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.57 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.27-7.22 (m, 2H), 7.08 (d, *J* = 5.2 Hz, 1H), 6.84 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.65 (d, *J* = 3.2 Hz, 1H), 3.07 (s, 4H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.4 (C), 159.2 (C), 157.0 (CH), 142.9 (C), 141.9 (C), 132.2 (CH), 131.4 (C), 130.2 (CH), 129.7 (CH), 127.1 (CH), 126.1 (CH), 125.2 (CH), 123.7 (CH), 115.9 (C), 104.6 (C), 36.5 (CH_2), 31.6 (CH_2), 27.8 (CH_3); HRMS(EI) *m/z* calcd for $C_{19}H_{18}O_4S$ (M^+): 342.0926. Found: 342.0934.



5-(2-(2-(1-Tosyl-1*H*-indol-3-yl)ethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1h)

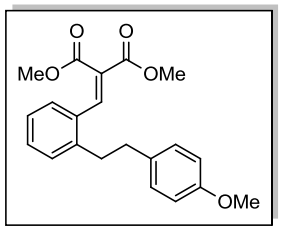
Prepared according to General Procedure E from **2.27**. Trituration with MeOH afforded a yellow solid in 35% yield. M.p. 72-74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.70 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.32-7.13 (m, 8H), 3.06 (t, *J* = 7.9 Hz, 2H), 2.89 (t, *J* = 7.9 Hz, 2H), 1.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.3 (C), 159.1 (C), 156.8 (CH), 144.6 (C), 142.2 (C), 135.1 (C), 132.1 (CH), 131.1 (C), 130.4 (C), 130.2 (CH), 129.7 (CH), 126.7 (CH), 126.1 (CH), 124.6 (CH), 123.1 (CH), 121.4 (C), 119.2 (CH), 116.6 (C), 113.6 (CH), 104.7 (C),

33.9 (CH_2), 27.7 (CH_3), 26.9 (CH_2), 21.4 (CH_3); HRMS(EI) *m/z* calcd for $C_{30}H_{27}NO_6S$ (M^+): 529.1559. Found: 529.1554.



5-(2-(2-(4-Methoxyphenyl)propyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1j)

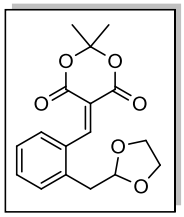
Prepared according to General Procedure E from **2.28**. Flash chromatography (EtOAc:hexanes, 1:9) afforded a yellow oil in 80% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.44 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 3.74 (s, 3H), 2.93-2.82 (m, 3H), 1.79 (s, 6H), 1.28 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.4 (C), 159.0 (C), 157.8 (C), 157.5 (CH), 142.1 (C), 136.9 (C), 131.9 (CH), 131.3 (C), 130.7 (CH), 130.2 (CH), 127.9 (CH), 125.6 (CH), 114.4 (C), 113.9 (CH), 104.2 (C), 54.9 (CH_3), 43.9 (CH_2), 41.4 (CH), 27.6 (CH_3), 27.5 (CH_3), 20.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_5$ (M^+): 380.1624. Found: 380.1631.



Dimethyl 2-(2-(4-methoxyphenethyl)benzylidene)malonate (2.1l)

Prepared by the Knoevenagel condensation of dimethyl malonate with 2-(4-methoxyphenethyl)benzaldehyde[104,109] using Brown and coworkers' method.[116] A solution of $TiCl_4$ (2.1 equiv) in CH_2Cl_2 (3M) was added dropwise under nitrogen to dry THF (0.3 M), which was cooled at 0 °C. A solution containing the aldehyde (1.0 equiv) and Meldrum's acid (1.0 equiv) in dry THF (0.2 M) was added dropwise via syringe to the $TiCl_4$·THF complex with subsequent dropwise addition of pyridine (5.0 equiv) at 0 °C. The reaction was then allowed to warm to rt and stirred until completion as monitored by TLC. The reaction was quenched by the addition of H_2O and diluted with Et_2O. The layers were then partitioned. The aqueous layer was extracted with Et_2O (2X), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2X), brine (1X), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc:hexanes, 1:9) afforded an orange oil in 22% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.00 (s, 1H), 7.28-7.24 (m, 2H), 7.18-7.10 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.70 (s,

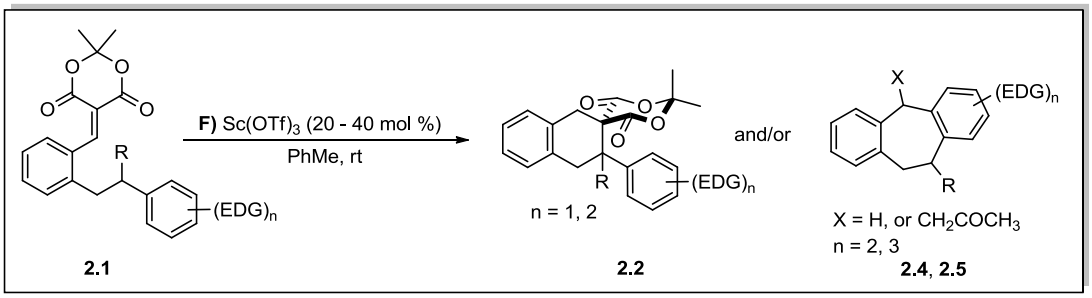
3H), 2.96-2.91 (m, 2H), 2.81-2.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 166.6 (C), 164.2 (C), 157.9 (C), 142.4 (CH), 141.2 (C), 133.1 (C), 132.1 (C), 130.0 (CH), 129.8 (CH), 129.3 (CH), 127.8 (CH), 127.2 (C), 126.3 (CH), 113.7 (CH), 55.1 (CH_3), 52.5 (CH_3), 52.3 (CH_3), 36.3 (CH_2), 36.1 (CH_2); HRMS(EI) *m/z* calcd for $C_{21}H_{22}O_5$ (M^+): 354.1467. Found: 354.1471.



5-(2-((1,3-Dioxolan-2-yl)methyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.1p)

Prepared according to General Procedure E from a known aldehyde.[117] Recrystallization from MeOH afforded a pale yellow solid in 40% yield. M.p. 106-108 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.82 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.35-7.28 (m, 2H), 5.10 (t, *J* = 4.0 Hz, 1H), 3.75 (s, 4H), 3.06 (d, *J* = 4.0 Hz, 2H), 1.81 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.7 (C), 159.3 (C), 158.9 (CH), 136.6 (C), 132.6 (C), 131.7 (CH), 131.4 (CH), 130.2 (CH), 126.4 (CH), 116.1 (C), 104.6 (C), 103.8 (CH), 65.0 (CH_2), 38.6 (CH_2), 27.6 (CH_3); HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_6$ (M^+): 318.1103. Found: 318.1101.

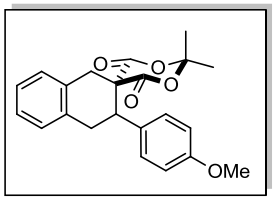
Preparation of Spiro Meldrum's Acids and Freidel-Crafts Alkylation Products



General Procedure F - [1,5]-Hydride Shift/Cyclization

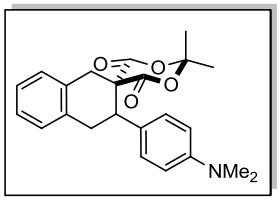
In a glove box, benzylidene Meldrum's acid **2.1** (generally 0.25 mmol), $Sc(OTf)_3$ (heated at 180 °C under high vacuum, 0.5 mm Hg for 2 h and stored in glove box), and toluene (distilled over CaH_2 then degassed, 0.1 M) were added to a glass vial equipped with a magnetic stirbar. The vial

was then capped with a septum and stirred at the appropriate temperature; reaction progress was monitored by ^{1}H NMR. Products can be purified either by diluting with CH_2Cl_2 and washing with H_2O (2X), brine (1X), drying over $MgSO_4$, filtering and concentrating by rotary or if mixtures obtained reaction can be concentrated by rotary and purified by flash chromatography (EtOAc:hexanes).



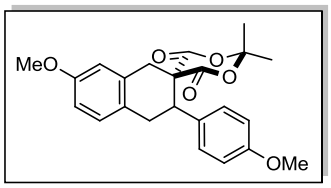
3'-(4-Methoxyphenyl)-2,2-dimethyl-3',4'-dihydro-1'*H*-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (2.2a)

Prepared according to General Procedure F from **2.1a**. Aqueous workup afforded an off-white, powdery solid in 90% yield. M.p. 180-182 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.17 (m, 4H), 7.10 (d, *J* = 7.3 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.77 – 3.66 (m, 3H), 3.23 (d, *J* = 17.1 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 1.64 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.6, 167.0, 159.4, 135.5, 131.2, 130.8, 128.4, 127.9, 126.3, 126.2 , 114.1, 105.1, 55.3, 54.0, 46.8, 37.9, 32.7, 30.1, 27.8; HRMS(EI) *m/z* calcd for $C_{22}H_{22}O_5$ (M^+): 366.1467. Found 366.1473.



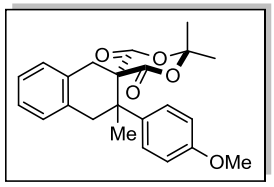
3'-(4-(Dimethylamino)phenyl)-2,2-dimethyl-3',4'-dihydro-1'*H*-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (2.2e)

Prepared according to General Procedure F from **2.1e**. Flash chromatography (EtOAc:hexanes, 1:5) afforded a white solid in 63% yield. M.p. 205-207 °C (decomposes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.16-7.09 (m, 6H), 6.65 (d, *J* = 8.8 Hz, 2H), 3.72 (d, *J* = 17.0 Hz, 1H), 3.66-3.59 (m, 2H), 3.20 (d, *J* = 16.9 Hz, 1H), 3.05-2.94 (m, 1H), 2.89 (s, 6H), 1.61 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.7 (C), 167.2 (C), 162.3 (C), 150.4 (C), 135.8 (C), 131.3 (C), 129.3 (CH), 128.4 (CH), 127.9 (CH), 126.2 (CH), 126.1 (CH), 112.7 (CH), 105.1 (C), 54.1 (C), 46.7 (CH), 40.5 (CH_3), 38.0 (CH_2), 32.7 (CH_2), 30.2 (CH_3), 27.8 (CH_3); HRMS(EI) *m/z* calcd for $C_{23}H_{25}NO_4$ (M^+): 379.1784. Found: 379.1782.



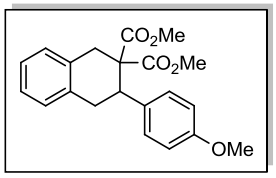
7'-Methoxy-3'-(4-methoxyphenyl)-2,2-dimethyl-3',4'-dihydro-1'*H*-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (2.2i)

Prepared according to General Procedure F from **2.1i**. Aqueous workup afforded an off-white powdery solid in 99% yield. M.p. 183-185 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.17 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.76 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.64 (s, 1 H), 3.79 (s, 6H), 3.75 – 3.61 (m, 3H), 3.19 (d, *J* = 17.4 Hz, 1H), 2.97 (dd, *J* = 15.3, 4.5 Hz, 1H), 1.63 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.6, 167.0, 159.4, 157.9, 132.2, 130.8, 129.8, 129.3, 128.2, 127.6, 114.1, 112.7, 105.1, 55.3, 55.2, 54.0, 47.2, 38.1, 31.9, 30.2, 27.7; HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_6$ (M^+) 396.1573. Found 396.1565.



3'-(4-Methoxyphenyl)-2,2,3'-trimethyl-3',4'-dihydro-1'*H*-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (2.2j)

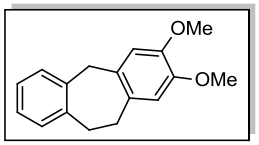
Prepared according to General Procedure F from **2.1j**. Flash chromatography (EtOAc:hexanes, 1:9) afforded a beige solid in 21% yield. M.p. 161-163 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.32 (d, *J* = 8.0 Hz, 2H), 7.15-7.12 (m, 4H), 6.87 (d, *J* = 8.2 Hz, 2H), 3.96 (d, *J* = 16.4 Hz, 1H), 3.78 (s, 3H), 3.71 (d, *J* = 17.8 Hz, 1H), 3.11 (d, *J* = 17.7 Hz, 1H), 2.67 (d, *J* = 16.4 Hz, 1H), 1.58 (s, 3H), 1.51 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.6 (C), 167.9 (C), 158.9 (C), 134.8 (C), 134.3 (C), 131.9 (C), 129.0 (CH), 128.4 (CH), 127.7 (CH), 126.1 (CH), 113.7 (CH), 104.6 (C), 57.9 (C), 55.3 (CH_3), 43.6 (C), 39.5 (CH_2), 34.0 (CH_2), 31.1 (CH_3), 26.3 (CH_3), 22.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_5$ (M^+): 380.1624. Found: 380.1635.



Dimethyl 3-(4-methoxyphenyl)-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (2.2l)

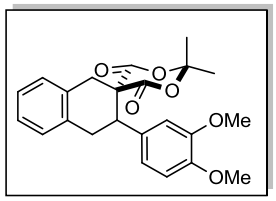
Prepared according to General Procedure F (reaction performed at 100 °C) from **2.1l**. Flash chromatography (EtOAc:hexanes, 1:4) afforded a tan oil in 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.17-7.09 (m, 4H), 7.00 (dd, *J* = 9.2, 2.5 Hz, 2H), 6.73 (dd, *J* = 9.2, 2.5

Hz, 2H), 3.93 (dd, *J* = 7.1, 3.6 Hz, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 3.57 (s, 3H), 3.63-3.55 (m, 1H, overlapping with singlets at 3.58 and 3.57 ppm), 3.32 (s, 2H), 3.11 (dd, *J* = 17.7, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 171.1 (C), 170.4 (C), 162.3 (C), 158.6 (C), 134.9 (C), 133.7 (C), 133.0 (C), 129.4 (CH), 128.9 (CH), 128.5 (CH), 126.6 (CH), 125.8 (CH), 113.5 (CH), 58.2 (C), 55.1 (CH_3), 52.7 (CH_3), 52.3 (CH_3), 42.1 (CH), 33.0 (CH_2), 31.7 (CH_2); HRMS(EI) *m/z* calcd for $C_{21}H_{22}O_5$ (M^+): 354.1467. Found: 354.1470.

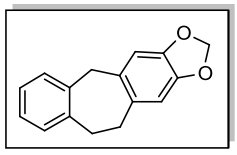


10,11-Dihydro-2,3-dimethoxy-5*H*-dibenzo[*a*,*d*]cycloheptene (3.4m) and 3'-(3,4-Dimethoxyphenyl)-2,2-dimethyl-3',4'-dihydro-1'*H*-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (2.2m)

Prepared according to General Procedure F from **2.1m**. Flash chromatography (EtOAc:hexanes, 1:12 to 1:8) first afforded **2.4m** as a white solid in 12% yield. M.p. 82-83 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.17-7.07 (m, 4H), 6.68 (s, 1H), 6.59 (s, 1H), 4.02 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.15-3.10 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 147.3 (C), 146.7 (C), 139.55 (C), 139.51 (C), 130.7 (C), 130.6 (C), 129.3 (CH), 128.6 (CH), 126.6 (CH), 126.0 (CH), 113.2 (CH), 112.8 (CH), 55.9 (CH_3), 40.4 (CH_2), 32.3 (CH_2), 32.2 (CH_2); HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_2$ (M^+): 254.1307. Found: 254.1300.

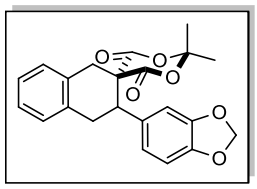


Spirocycle **2.2m** was second to elute from the above column as a tan oil in 16% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.17-7.16 (m, 3H), 7.09 (br s, 1H), 6.81 (s, 2H), 6.76 (s, 1H), 3.85 (s, 6H), 3.81-3.61 (m, 3H), 3.22 (d, *J* = 16.9 Hz, 1H), 3.05 (d, *J* = 11.4 Hz, 1H), 1.63 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.6 (C), 167.1 (C), 148.9 (C), 148.8 (C), 135.4 (C), 131.2 (C), 131.1 (C), 128.4 (CH), 127.9 (CH), 126.3 (CH), 126.2 (CH), 120.9 (CH), 111.6 (CH), 111.2 (CH), 105.1 (C), 55.9 (CH_3), 53.9 (C), 47.1 (CH), 38.2 (CH_2), 32.8 (CH_2), 30.1 (CH_3), 27.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{23}H_{24}O_6$ (M^+): 396.1573. Found: 396.1578.

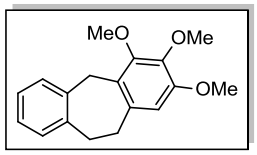


10,11-Dihydro-5*H*-benzo[4',5']cyclohepta[1',2':4,5]benzo[1,2-*d*][1,3]dioxole (2.4n) and 3'-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyl-3',4'-dihydro-1'*H*-spiro[[1,3]dioxane-5,2'-naphthalene]-4,6-dione (2.2n)

Prepared according to General Procedure F from **2.1n**. Flash chromatography (EtOAc:hexanes, 1:12) first afforded **2.4n** as a tan solid in 19% yield. M.p. 58-60 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.13-7.07 (m, 4H), 6.67 (s, 1H), 6.61 (s, 1H), 5.84 (s, 2H), 3.98 (s, 2H), 3.13-3.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 146.0 (C), 145.4 (C), 138.8 (C), 138.7 (C), 132.51 (C), 132.46 (C), 129.9 (CH), 128.9 (CH), 126.6 (CH), 125.9 (CH), 109.6 (CH), 109.3 (CH), 100.6 (CH_2), 40.6 (CH_2), 32.6 (CH_2), 32.2 (CH_2); HRMS(EI) *m/z* calcd for $C_{16}H_{14}O_2$ (M^+): 238.0994. Found: 238.0998.

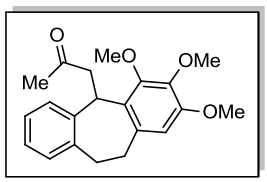


Spirocycle **2.2n** was second to elute from the above column as a white solid in 15% yield. M.p. 188-189 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.18-7.12 (m, 3H), 7.08-7.07 (m, 1H), 6.76-6.69 (m, 3H), 5.92 (s, 2H), 3.74-3.56 (m, 3H), 3.22 (d, *J* = 16.9 Hz, 1H), 3.02 (d, *J* = 13.7 Hz, 1H), 1.64 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.5 (C), 167.0 (C), 147.9 (C), 147.3 (C), 135.4 (C), 132.5 (C), 131.0 (C), 128.4 (CH), 127.9 (CH), 126.4 (CH), 126.3 (C), 122.2 (CH), 109.1 (CH), 108.5 (CH), 105.1 (C), 101.1 (CH_2), 53.8 (C), 47.2 (CH), 38.2 (CH_2), 32.9 (CH_2), 30.1 (CH_3), 27.9 (CH_3); HRMS(EI) *m/z* calcd for $C_{22}H_{20}O_6$ (M^+): 380.1260. Found: 380.1249.



10,11-Dihydro-2,3,4-trimethoxy-5*H*-dibenzo[*a*,*d*]cycloheptene (2.4o)

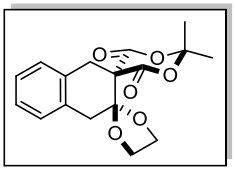
Prepared according to General Procedure F from **2.1o**. Flash chromatography (EtOAc:hexanes, 1:8) afforded a colourless oil in 22% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.19 (m, 1 H), 7.10 (m, 3H), 6.49 (s, 1H), 4.12 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 151.4 (C), 150.7 (C), 140.4 (C), 139.1 (C), 138.8 (C), 135.4 (C), 129.8 (CH), 129.5 (CH), 126.4 (CH), 126.0 (CH), 125.8 (C), 108.6 (CH), 61.4 (CH_3), 60.9 (CH_3), 56.0 (CH_3), 32.6 (CH_2), 30.8 (CH_2); HRMS(EI) *m/z* calcd for $C_{18}H_{20}O_3$ (M^+) 284.1412. Found: 284.1420.



1-(2,3,4-Trimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yl)propan-2-one (2.5o)

Prepared according to General Procedure F (reaction performed at 70 °C) from **2.1o**. Flash chromatography (EtOAc:hexanes, 1:8) first afforded **2.4o** (26% yield) followed

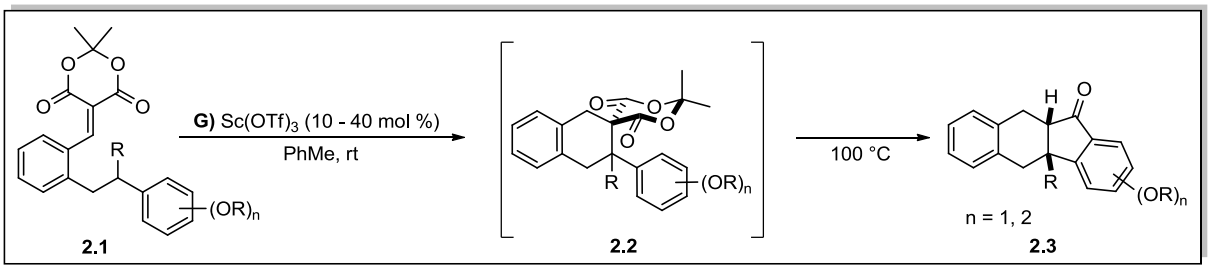
by **2.5o** as a tan solid in 21% yield. M.p. 96-97 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30 (d, *J* = 7.2 Hz, 1H), 7.12-7.05 (m, 3H), 6.41 (s, 1H), 5.12 (dd, *J* = 8.6, 5.1 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.40-3.32 (m, 2H), 3.19 (dd, *J* = 15.6, 8.6 Hz, 1H), 2.93 (dd, *J* = 15.6, 5.1 Hz, 1H), 2.96-2.79 (m, 2H, overlapping with dd at 2.93 ppm), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 206.7 (C), 151.5 (C), 151.3 (C), 140.5 (C), 140.4 (C), 139.6 (C), 135.6 (C), 131.4 (CH), 130.2 (CH), 127.3 (C), 126.9 (CH), 126.1 (CH), 109.1 (CH), 61.2 (CH_3), 60.7 (CH_3), 55.8 (CH_3), 52.8 (CH_2), 38.9 (CH), 33.7 (CH_2), 33.2 (CH_2), 30.1 (CH_3); HRMS(EI) *m/z* calcd for $C_{21}H_{24}O_4$ (M^+): 340.1675. Found: 340.1676.



Tetrahydronaphthalene spirocycle (2.2p)

Prepared according to General Procedure F (reaction performed at 50 °C) from **2.1p**. Filtration through a silica pad basified with NEt_3 (eluent = CH_2Cl_2) afforded a pale yellow oil in 22% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.14-7.04 (m, 4H), 4.05 (s, 4H), 3.59 (s, 2H), 3.07 (s, 2H), 1.84 (s, 3H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 166.1 (C), 132.9 (C), 132.6 (C), 128.5 (CH), 127.5 (CH), 126.6 (CH), 126.1 (CH), 109.8 (C), 105.9 (C), 65.6 (CH_2), 56.9 (C), 38.2 (CH_2), 36.0 (CH_2), 30.8 (CH_3), 27.6 (CH_3); HRMS(EI) *m/z* calcd for $C_{17}H_{18}O_6$ (M^+): 318.1103. Found: 318.1100.

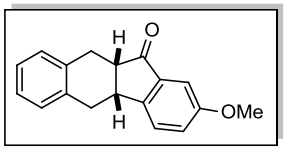
[1,5]-Hydride Shift/Cyclization/Freidel-Crafts Acylation Domino Reaction



General Procedure G - Domino Reaction

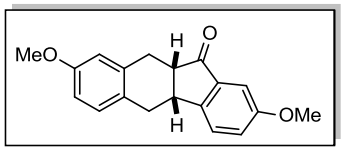
Reaction assembled as in General Procedure F and once the [1,5]-hydride shift/cyclization was complete as indicated by ^{1}H NMR (aliquots were withdrawn), the reaction vessel was immersed

in a pre-heated 100 °C oil bath and stirred until full conversion had occurred as monitored by TLC. *CAUTION*: pressure build-up since acetone and CO_2 are produced as byproducts. The reaction mixture was then diluted with CH_2Cl_2 and washed with H_2O (2X), brine (1X), dried with $MgSO_4$, filtered and concentrated by rotary. The resulting crude mixture was purified by flash chromatography (EtOAc:hexanes).



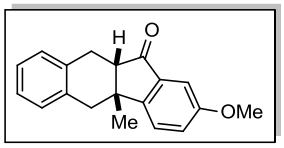
2-Methoxy-10,10a-dihydro-4b*H*-benzo[*b*]fluoren-11(5*H*)-one (2.3a)

Prepared according to General Procedure G from **2.1a**. Flash chromatography (EtOAc:hexanes, 1:5) afforded an off-white powdery solid in 78% yield. M.p. 109-110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.44 (d, *J* = 8.4 Hz, 1H), 7.19–6.99 (m, 6H), 3.76 (s, 3H), 3.72 (dd, *J* = 13.1, 6.5 Hz, 1H, overlapping with singlet at 3.76 ppm), 3.18 (dd, *J* = 14.3, 6.4 Hz, 1H), 3.09–2.93 (m, 3H), 2.76 (dd, *J* = 14.3, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3 (C), 159.5 (C), 150.7 (C), 138.5 (C), 136.9 (C), 136.8 (C), 127.5 (2 x CH), 126.6 (CH), 126.5 (CH), 126.1 (CH), 124.6 (CH), 104.5 (CH), 55.5 (CH_3), 47.8 (CH), 38.3 (CH), 34.6 (CH_2), 30.6 (CH_2); HRMS(EI) *m/z* calcd for $C_{18}H_{16}O_2$ (M^+): 264.1150. Found: 264.1150.



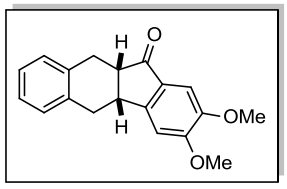
2,8-Dimethoxy-10,10a-dihydro-4b*H*-benzo[*b*]fluoren-11(5*H*)-one (2.3i)

Prepared according to General Procedure G from **2.1i**. Flash chromatography (EtOAc:hexanes, 1:5) afforded an off-white powdery solid in 55% yield. M.p. 113-115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.44 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.75-3.69 (m, 1H, overlapping with singlet at 3.73 ppm), 3.14 (dd, *J* = 14.6, 6.2 Hz, 1H), 3.11 – 2.94 (m, 3H), 2.72 (dd, *J* = 14.6, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 159.4, 158.3, 150.8, 138.4, 137.9, 128.8, 128.2, 126.1, 124.6, 113.1, 111.7, 104.4, 55.4, 55.1, 47.6, 38.4, 33.6, 30.9; HRMS(EI) *m/z* calcd for $C_{19}H_{18}O_3$ (M^+): 294.1256. Found: 294.1258.



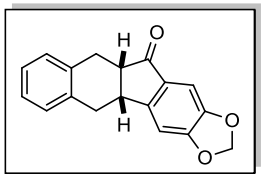
2-Methoxy-4b-methyl-10,10a-dihydro-4b*H*-benzo[*b*]fluoren-11(5*H*)-one (2.3j)

Prepared according to General Procedure G from **2.1j**. Flash chromatography (EtOAc:hexanes, 1:9 to 1:5) afforded a beige solid in 61% yield. M.p. 99-101 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.42 (d, *J* = 8.4 Hz, 1H), 7.18-6.90 (m, 6H), 3.74 (s, 3H), 3.01 (d, *J* = 6.0 Hz, 2H), 2.89 (d, *J* = 14.2 Hz, 1H), 2.84 (d, *J* = 14.2 Hz, 1H), 2.65 (t, *J* = 6.0 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.7 (C), 159.3 (C), 155.1 (C), 137.3 (C), 137.1 (C), 136.3 (C), 127.5 (CH), 127.3 (CH), 126.6 (CH), 126.4 (CH), 124.8 (CH), 124.4 (CH), 104.1 (CH), 55.9 (CH), 55.4 (CH_3), 43.3 (C), 42.5 (CH_2), 30.9 (CH_2), 29.1 (CH_3); HRMS(EI) *m/z* calcd for $C_{19}H_{18}O_2$ (M^+): 278.1307. Found: 278.1305.



2,3-Dimethoxy-10,10a-dihydro-4b*H*-benzo[*b*]fluoren-11(5*H*)-one (2.3m)

Prepared according to General Procedure G from **2.1m**. Flash chromatography (EtOAc:hexanes, 1:5) afforded a colourless oil in 52% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.48 (d, *J* = 8.7 Hz, 1H), 7.30-7.08 (m, 3H), 6.76 (s, 1H) 6.59 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75 (m, 1H), 3.13 (dd, *J* = 14.6, 6.5 Hz, 1H), 3.09–2.95 (m, 3H), 2.74 (dd, *J* = 14.6, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 206.1, 158.8, 157.2, 150.0, 138.5, 136.9, 128.8, 128.4, 126.3, 124.4, 104.4, 55.6, 55.3, 47.9, 38.6, 34.3, 30.7.



2,3-Methylenedioxy-10,10a-dihydro-4b*H*-benzo[*b*]fluoren-11(5*H*)-one (2.3n)

Prepared according to General Procedure G from **2.1n**. Flash chromatography (EtOAc:hexanes, 1:3) afforded a brown oil in 41% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.15–6.98 (m, 4H), 6.96 (s, 1H), 6.92 (s, 1H), 6.04 (s, 1H), 6.03 (s, 1H), 3.67 (dd, *J* = 13.0, 6.4 Hz, 1H), 3.16 (dd, *J* = 14.4, 6.2 Hz, 1H), 3.08–2.94 (m, 3H), 2.76 (dd, *J* = 14.4, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 206.0, 155.3, 154.5, 148.4, 136.8, 136.6, 131.9, 127.5, 127.4, 126.7, 126.5, 104.4, 102.2, 102.0, 47.5, 38.7, 34.4, 30.6; HRMS(EI) *m/z* calcd for $C_{18}H_{14}O_3$ (M^+): 278.0943. Found: 278.0941.

Chapter 3. *N*-Fused Indolines through Non-Carbonyl-Stabilized Rhodium Carbenoid C-H Insertion of *N*-Aziridinyl Imines

General methods of accessing reoccurring structural motifs or privileged scaffolds[118] are critical to structure-activity relationship (SAR) studies,[119] particularly if a compound class exhibits interesting biological properties and there is a short supply available from natural sources. This chapter focuses on the development of a selective Csp^3-H bond functionalization to access N-fused indolines from N-aziridinyl imines.

3.1. Introduction

3.1.1. The *N*-Fused Indoline Scaffold

As alluded to above the *N*-fused indoline scaffold is prevalent in a number of natural products possessing biological activity including mitomycin C (electron rich aromatic has been oxidized to the quinone), strychnine and the architecturally less complex cryptaustoline (Figure 3.1). Consequently, flexible syntheses of the core *N*-fused indolines of these structures continue to be a subject of interest to a number of research groups. Outlined below are examples of such strategies to access *N*-fused indolines.

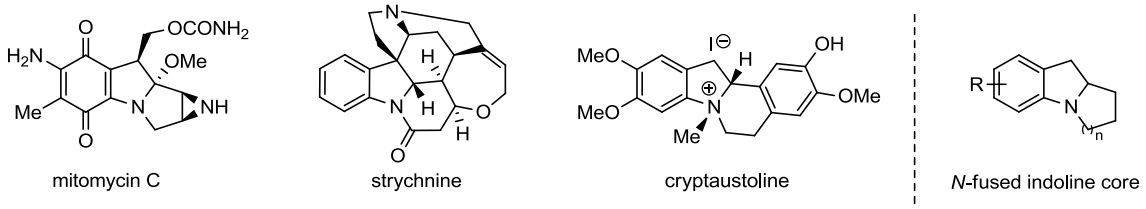


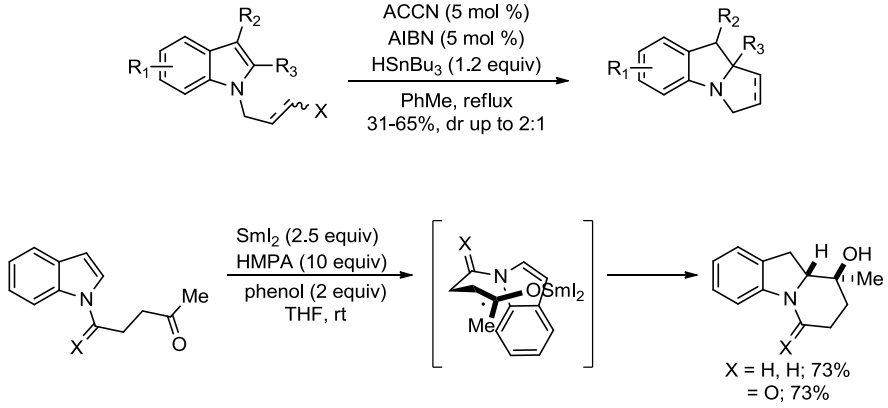
Figure 3.1. *N*-Fused Indoline Core in Natural Products

What follows below is a survey of the literature with regards to methodologies developed to access *N*-fused indolines with an emphasis on the disconnection to a benzylic carbene and an overview of rhodium (II) catalyzed C-H insertions and the reactivity of *N*-aziridinyl imines.

3.1.2. Approaches to *N*-Fused Indolines

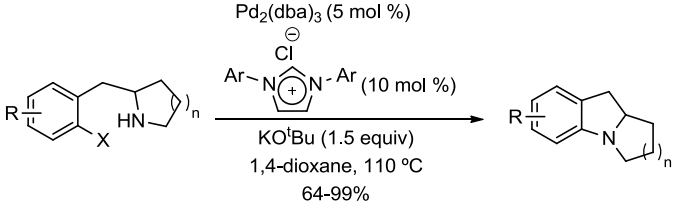
An early approach to *N*-fused indolines consisted of intramolecular radical cyclization of tethered indoles which proceeded in modest yields and relatively poor diastereoselectivities using tributylstannane and radical initiators (Scheme 3.1).[120] A related strategy using samarium ketyls was later developed by Reissig's group which afforded diastereomerically pure products in good yields (Scheme 3.1).[121] They have also applied their methodology to an elegant and concise formal total synthesis of strychnine.[122]

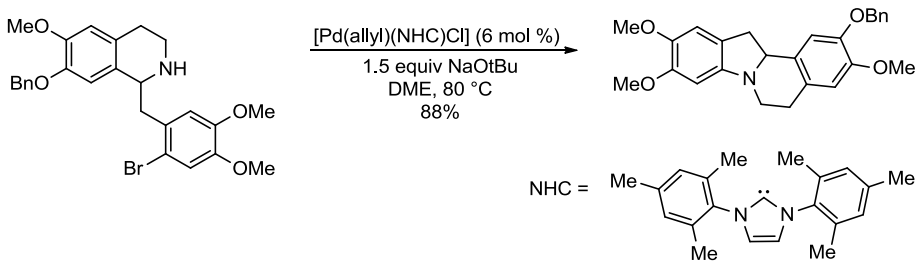
Scheme 3.1. Radical Cyclizations



Intramolecular palladium catalyzed cross-coupling has shown to be an effective approach to *N*-fused indolines as demonstrated by Doyle and coworkers (Scheme 3.2).[123] This strategy was elaborated into a tandem process by Wolfe's group[124] to construct both pendant rings and has also been utilized by Nolan's group in a formal total synthesis of racemic cryptaustoline (Scheme 3.2).[125]

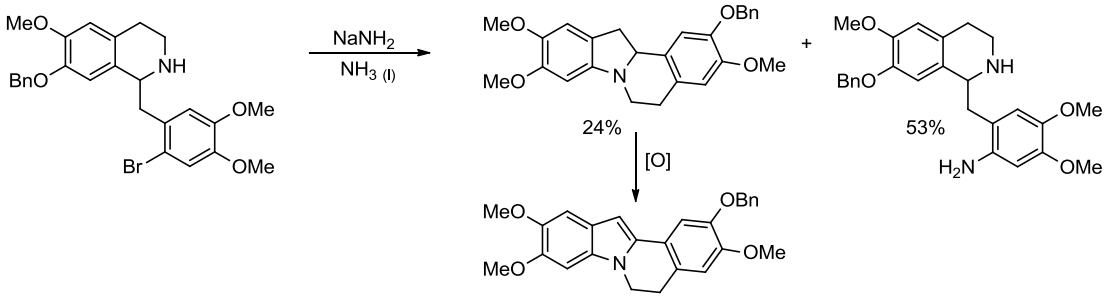
Scheme 3.2. Palladium Catalyzed Cross-Coupling and Formal Synthesis of (±)-Cryptaustoline





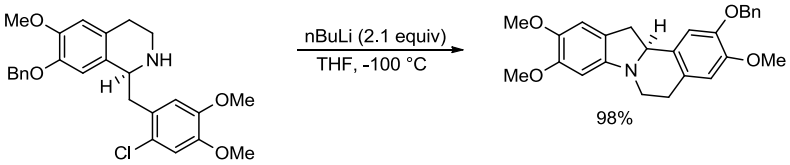
An early method of accessing *N*-fused indolines had been through the benzyne reaction as demonstrated by Kametani and coworkers enroute to an early total synthesis of (±)-cryptaustoline; however, a relatively low yield was obtained due to competitive aminolysis (Scheme 3.3).[126] The facile oxidation of the tetracyclic indoline to the corresponding indole was also noted by the authors.

Scheme 3.3. Kametani's Benzyne Reaction



Of note, this cyclization approach was also adopted by other research groups in synthesizing cryptaustoline and related alkaloids.[127] Meyers and coworkers utilized a benzyne cyclization in the last critical bond connection in their chiral auxiliary approach to a total synthesis of (+)-cryptaustoline (Scheme 3.4).[128]

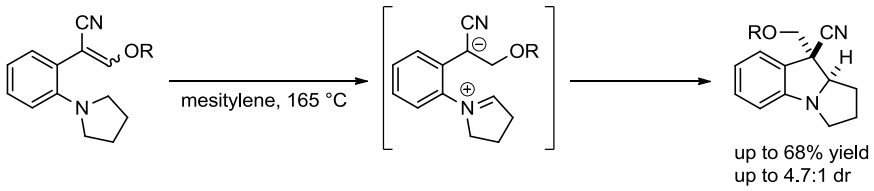
Scheme 3.4. Meyers' Benzyne Reaction



Reinhoudt, Verboom and coworkers described a conceptually different methodology by employing the *tert*-amino effect to execute a [1,6] hydride shift/cyclization protocol (Scheme

3.5).[129] This brief investigation yielded functionalized *N*-fused indolines with modest yields and diastereoselectivity.

Scheme 3.5. [1,6] Hydride Shift/Cyclization



Considerable effort has also been directed at a disconnection to a benzylic carbene. In general, mediating carbene C-H insertions with a metal to achieve highly selective reactions has been a very effective strategy and dirhodium(II) catalysts have been the most developed.[130,135] One of the major breakthroughs has been accredited to studies by Teyssié's group who found they could mediate carbene insertions with dirhodium(II) tetraacetate and derivatives thereof.[131] Subsequently, other dirhodium(II) catalysts have been prepared mainly through substitutions of dirhodium(II)tetraacetate with alternate achiral or chiral bidentate ligands in the development of this now prominent methodology to C-H insertions.

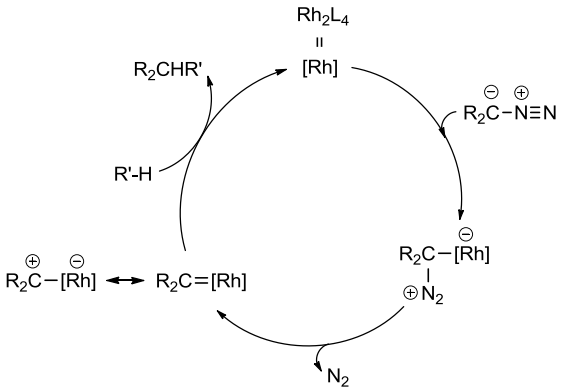
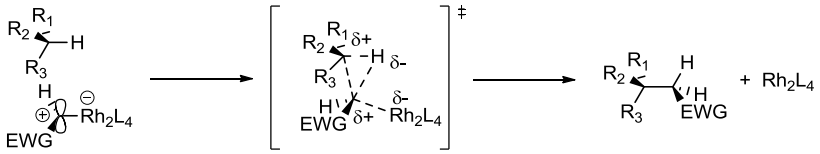


Figure 3.2. Generally Accepted C-H Insertion Mechanism

It has been shown that the selectivity of the rhodium catalyzed C-H insertion is affected by the ligands[132] and the generally accepted reaction mechanism is illustrative of electronic

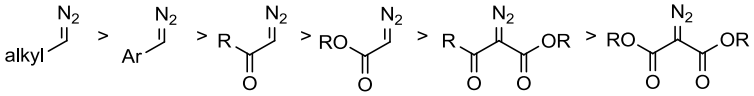
considerations (Figure 3.2).[133] The intramolecular C-H insertion follows the same pathway. Attack of the diazo compound on the metal center would be accelerated by ligands withdrawing electron density from the metal (more electrophilic metal center). However, upon irreversible nitrogen expulsion, the carbenoid carbon is electron deficient and a more electron rich metal center would better stabilize it (stabilization may include significant backbonding[134]) leading to a more selective C-H insertion reaction.[132] Doyle's group defines carbon-hydrogen insertion as "a process that occurs when a carbene associated with a stabilizing entity causes cleavage of a C-H bond concurrent, but not necessarily synchronous, with carbene-carbon and carbene-hydrogen bond formation".[135] Overlap of the empty p-orbital of the metal carbene carbon with the σ-orbital of the reacting C-H bond to initiate the mechanistic proposal of concerted but non-synchronous two bond formation (Scheme 3.6)[132,135] has been supported by calculations.[136]

Scheme 3.6. Mechanism of the C-H Insertion Step



Selectivity for C-H insertion follows the general trend of insertion into the more nucleophilic C-H bond (3°>2°>1°) providing sterically accessible and proceed with retention of configuration.[135] Dirhodium(II) carboxamidate catalysts have proven amongst the most selective for C-H insertions from diazonium substrates.[137]

a) Reactivities of diazo compounds toward Lewis acids generally follow:



b) Leading Rhodium carbenoid carbon substitution motifs:

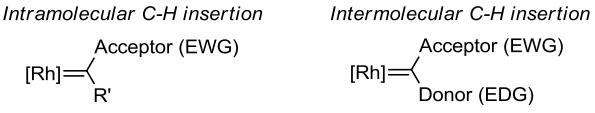


Figure 3.3. Carbenoid Carbon Substitution

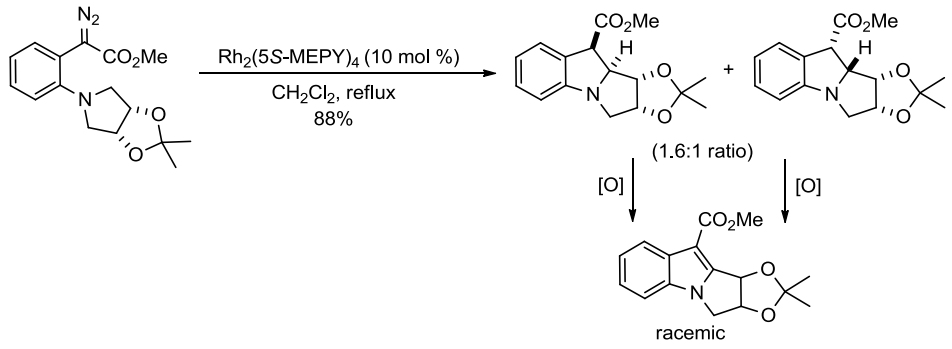
The substitution pattern of the carbenoid carbon has also been found to have considerable influence over the selectivity (Figure 3.3).[135] Diazoniums bearing two acceptors (EWGs) are much less reactive towards decomposition in the presence of a Lewis acid than diazonium substrates without acceptors. Also with regards to stability, ethyl diazoacetate is thermally stable below 120 °C, diazoaromatics are not amenable to prolonged storage and in situ generation is the preferred method for diazoalkanes.

Rhodium catalyzed, intramolecular C-H insertions from acceptor-substituted (primarily carbonyl functionalities) diazos are known to proceed with high regioselectivity to afford five membered rings (provided sterically accessible and not electronically inhibited by an electron withdrawing group), chemoselectivity and enantioselectivity (chiral carboxamidate ligands have been amongst the most successful).[135]

Recently, highly regioselective, enantioselective intermolecular C-H insertions have been described. A key to the success of this methodology was shifting the focus from ligand alterations to substrate substitution, specifically moving to donor-acceptor diazo substrates which were found to minimize dimerization pathways.[138]

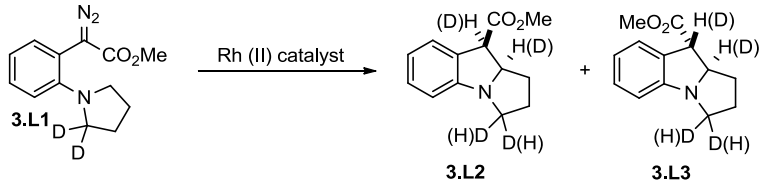
Sulikowski and coworkers found disappointing results with intramolecular C-H insertions of carbonyl-stabilized diazos to provide *N*-fused indolines under both rhodium (Scheme 3.7) and copper catalysis.[139,140] There was speculation that the poor enantioselectivity was as a result of leakage through the uncatalyzed pathway. The enantioselectivities were measured after oxidation (DDQ oxidant) of the separated diastereomers to the indole.

Scheme 3.7. Sulikowski's Carbonyl-Stabilized Rhodium Carbenoid C-H Insertions



Following these two reports, Sulikowski and coworkers devised a deuterium labelling mechanistic study[141] of their *N*-fused indoline forming reactions (Table 3.1) from carbonyl-stabilized diazo substrates with the specific goal of trying to determine whether a concerted C-H insertion or alternatively if a [1,5] hydride shift onto the metal carbenoid and then cyclization pathway was operating; the later mechanism would proceed through an iminium ion intermediate (Figure 3.4).

Table 3.1. Sulikowski's Deuterium Labelling Study



entry	conditions[a]	cis/trans (**3.L2**/**3.L3**)	k_H/k_D[b] cis (**3.L2**)	k_H/k_D[b] trans (**3.L3**)	combined yield (%)
1	toluene, reflux	31:1	1.0	1.0	91
2	$Rh_2(CF_3CO_2)_4$, CH_2Cl_2, 23 °C	1:1.5	1.2	1.5	82
3	$Rh_2(OAc)_4$, CH_2Cl_2, 23 °C	1:1.5	1.1	1.5	89
4	$Rh_2(cap)_4$, benzene, 70 °C	3:1	1.2	1.6	97

[a]Catalyst loading was 3-5 mol %. [b]Determined by integration of the ^{1}H NMR spectra after separation of **3.L2** and **3.L3**. Average of 3 experiments. The isomers have been classified as cis or trans in terms of the relationship of the H(D) to H(D) at 9 and 9a position of the indoline ring in this paper.

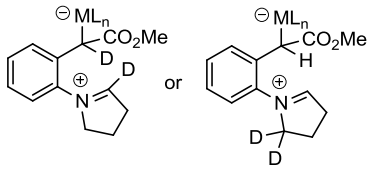


Figure 3.4. Iminium Intermediates from a Hydride Shift Mechanism

The strongest evidence found in the study supportive of a concerted C-H insertion was a consistently higher KIE leading to the trans diastereomer relative to the cis for rhodium catalyzed reactions (Table 4.1, entries 2-4). If the reaction proceeded through a hydride shift/cyclization pathway one would have expected identical KIEs for the cis and trans diastereomers since the deuterium KIE would be determined prior to the stereochemical determining cyclization step.

The larger KIE for the trans isomer relative to the cis isomer was rationalized by a stereoelectronic effect in the transition state leading to the trans isomer which would benefit from antiperiplanar orientation of the nitrogen lone pair relative to the breaking C-H bond (σ* not shown for clarity in Figure 3.5). This optimal orbital overlap could enable a more fully developed C-H bond in the transition state leading to the trans diastereomer **3.L3**. The lack of a kinetic isotope effect observed for the uncatalyzed thermal reaction (entry 1) was attributed to a lower energy barrier for insertion relative to bond rotation in the carbene intermediate. This uncatalyzed pathway was postulated to have been operating at an appreciable extent with entry 4 which required a higher temperature to proceed at a reasonable rate (less electrophilic catalyst) and displayed analogous cis selectivity to entry 1.

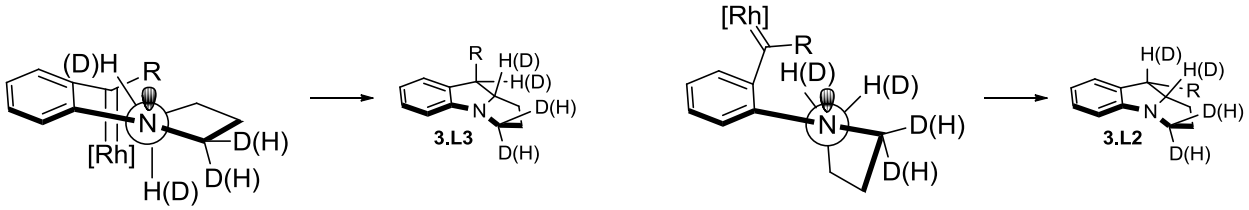
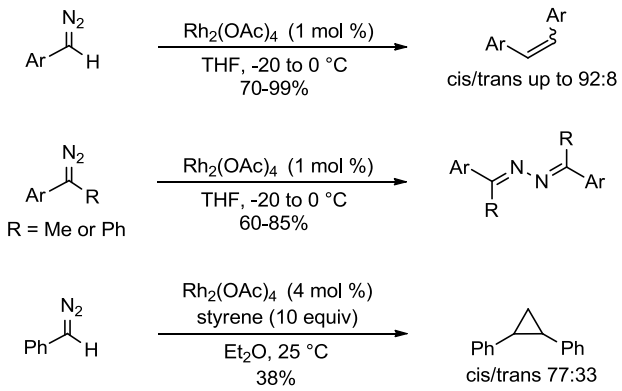


Figure 3.5. Sulikowski's Proposed Transition States

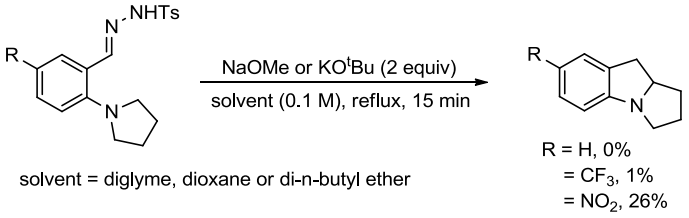
In contrast to the large body of literature for acceptor substituted (primarily carbonyl functionalities) rhodium carbenoid C-H insertions, to the best of my knowledge there has not been a non-carbonyl-stabilized rhodium carbenoid C-H insertion reported in the literature. However, it has been found that aldehyde derived aryldiazoalkanes react at low temperature in the presence of $Rh_2(OAc)_4$ to afford 'dimerized' alkenes in good yield and selectivity for the cis isomer (including a 2-$(OMe)C_6H_4$ substituted substrate that proceeded in 88% yield).[142] Alternatively, under the same conditions the keto derived aryldiazoalkanes afforded azines in good yield. Lastly, aldehyde derived aryldiazoalkanes when treated with $Rh_2(OAc)_4$ in the presence of an excess of styrene afford the cyclopropanes in fair yield but low selectivity.[143]

Scheme 3.8. Precedent for Reactions of Non-Carbonyl Stabilized Rhodium Carbenoids



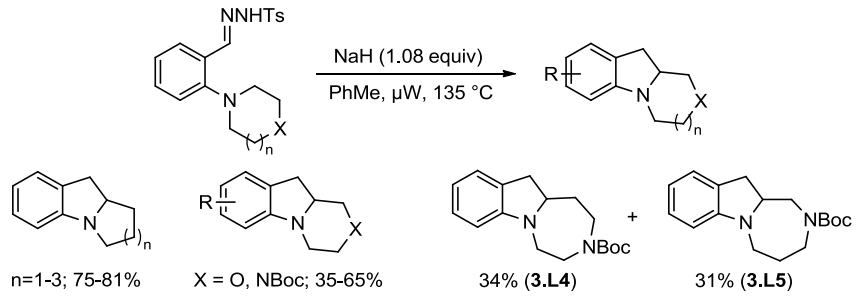
Garner and coworkers were first to report poor results from the thermal decomposition of tosylhydrazones with base in ethereal solvents (Scheme 3.9), and analogous investigations that followed were in agreement.[144]

Scheme 3.9. Carbene C-H Insertion from Tosylhydrazones

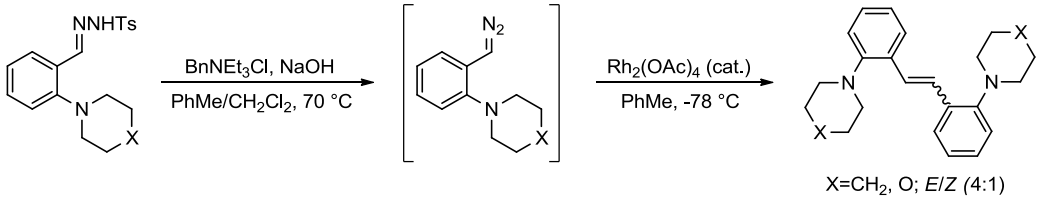


Recently it was found that the reaction could be improved under microwave conditions with sodium hydride to afford C-H insertion products in moderate to high yields from tosyl hydrazones (Scheme 3.10).[145] A limitation to the methodology was the lack of regioselectivity observed for the C-H insertion (**3.L4** and **3.L5**) although only one applicable example was reported. Furthermore, attempts to impart selectivity under rhodium catalysis were unsuccessful; instead the alkene dimers were generated as the exclusive or main product with no C-H insertion product observed (Scheme 3.11).

Scheme 3.10. Carbene C-H Insertion from Tosylhydrazones under Microwave Conditions

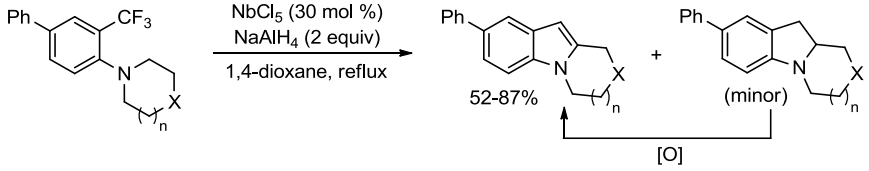


Scheme 3.11. Kehler's Attempts at Rhodium Catalysis



An interesting tandem reaction consisting of C-F bond activation followed by C-H insertion by a proposed intermittent niobium carbenoid was recently reported (Scheme 3.12).[146] The reaction conditions afforded a mixture of indole and indoline (as the minor product) which was oxidized by an external oxidant (O_2 (1 atm) in the presence of a catalytic amount of ruthenium zirconium phosphate). The authors noted that mechanistic investigations were ongoing but proposed initial formation of Nb(0) responsible for C-F bond activation.

Scheme 3.12. Niobium Carbenoid C-H Insertion

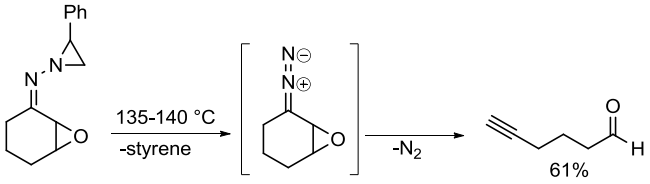


3.1.3 *N*-Aziridinyl Imines as Carbene Precursors and Anionic Acceptors

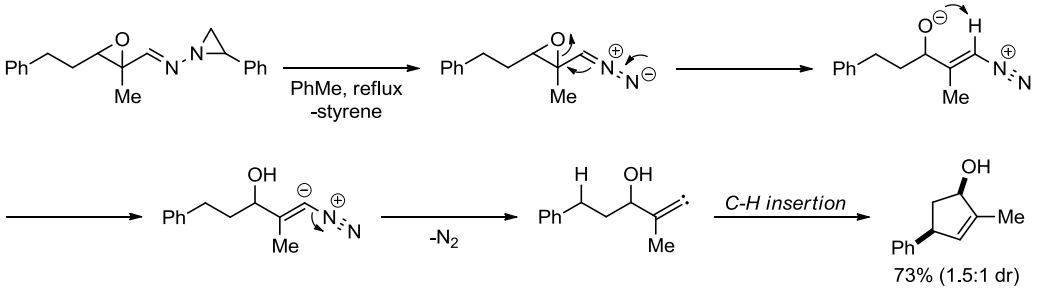
An underexplored class of diazo precursor that is directly amenable to rhodium catalysts is the *N*-aziridinyl imine (Eschenmoser hydrazone). Upon heating, strain release of the aziridine furnishes an alkene and diazo compound which contrasts with tosylhydrazones that require a

base to liberate the tosylate and then form the diazo. The fragmentation Eschenmoser described (Scheme 3.13)[147] and subsequent description of an Organic Syntheses preparation of the *N*-amino aziridines,[148] have garnered interest in reactions utilizing the functionality.[149] Somewhat surprisingly, there are only a few reports of rhodium catalyzed processes with this diazo precursor (Schemes 3.15 and 3.16) which has excluded C-H insertions thus far although thermal C-H insertions of alkylidene carbenes have been demonstrated by Kim and Cho (Scheme 3.14).[150]

Scheme 3.13. Eschenmoser's fragmentation

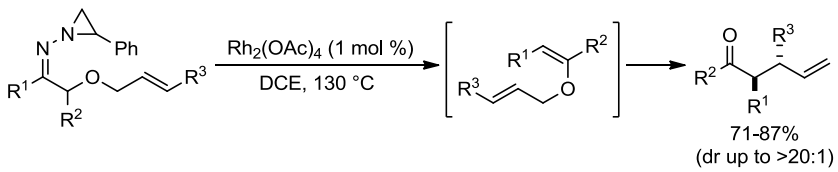


Scheme 3.14. Kim's *N*-Aziridinyl Imine Derived Alkylidine Carbene C-H Insertion



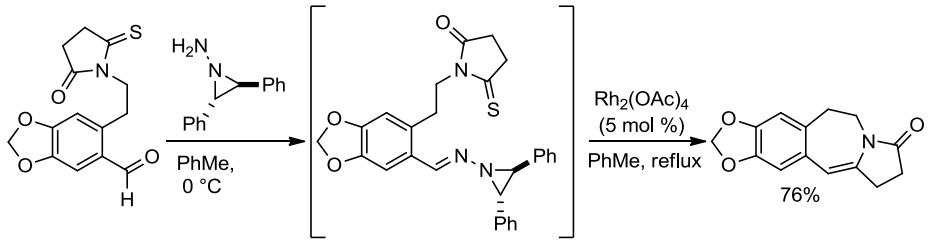
Stoltz and May described an interesting tandem reaction under rhodium catalysis (Scheme 3.15) which proceeded in good yields and diastereoselectivities.[151] The initial reaction was a 1,2-hydrogen shift (Bamford-Stevens reaction) that was followed by a Claisen [3,3] sigmatropic rearrangement.

Scheme 3.15. Stoltz's Domino Bamford Stevens/Claisen Rearrangement



Danishefsky and coworkers utilized a disubstituted amino aziridine to effect ring closure (Scheme 3.16).[152] This reaction presumably proceeds through initial attack of the nucleophilic sulfur on the generated rhodium carbenoid and leading to elimination of S.

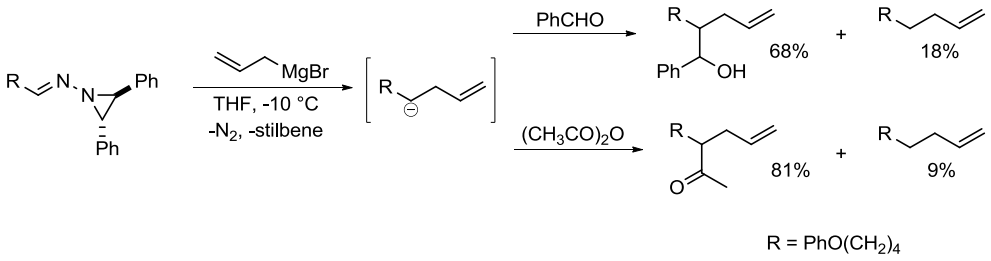
Scheme 3.16. Danishefsky's Utilization in Natural Product Synthesis



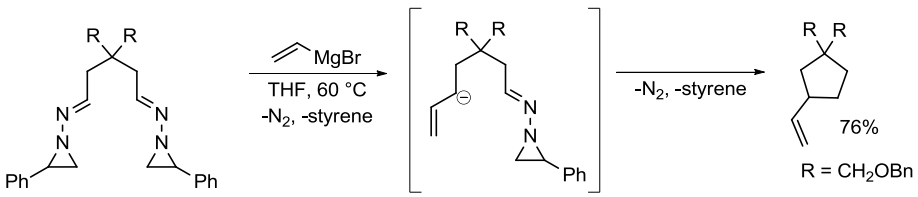
Also of interest and directly pertaining to the study in this chapter, Kim and coworkers have demonstrated the ability of *N*-aziridinyl imines to participate in anionic reactions. They have shown that organometallics can be added in high yields to Eschenmoser hydrazones and the resulting anions (following styrene and nitrogen extrusion) can be trapped intermolecularly[153] or intramolecularly (Scheme 3.17).[154]

Scheme 3.17. Anionic Reactions of *N*-Aziridinyl Imines

Intermolecular



Intramolecular



3.2. Proposal

The proposal was to investigate the viability and reaction course of *N*-aziridinyl imines, also known as Eschenmoser hydrazones, to access the privileged indoline scaffold. This class of substrate (**3.1**) was of particular interest as it potentially provided two distinct modes of reactivity to functionalize Csp^3-H bonds, namely hydride acceptor and decomposition to a benzylic carbene. In accord with the proposed [1,5] hydride shift/cyclization mechanism (Figure 3.6, path A), the benzylic carbon would act as a geminal acceptor/donor (effectively a 1,1-dipole) instead of the typical vicinal acceptor/donor (see Chapter 2 for details); the net result would be the formation of a five-membered ring as opposed to the six-membered ring created with traditionally employed acceptors. Alternatively, the *N*-aziridinyl imine could function as a carbene precursor (Figure 3.6, path B) and also deliver *N*-fused indoline **3.2** through C-H insertion.

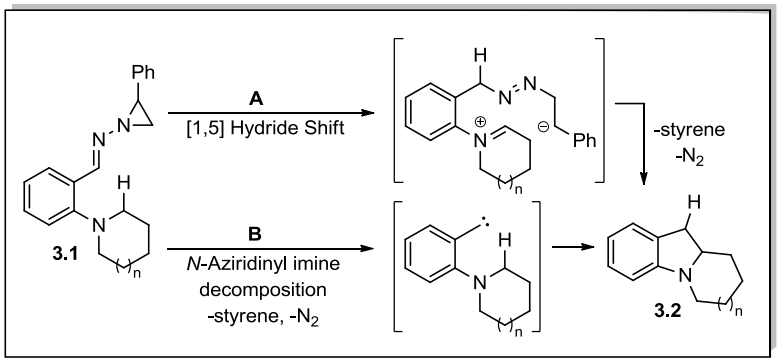


Figure 3.6. Proposal to Utilize *N*-Aziridinyl Imines to Access *N*-Fused Indolines

3.3. Results and Discussion

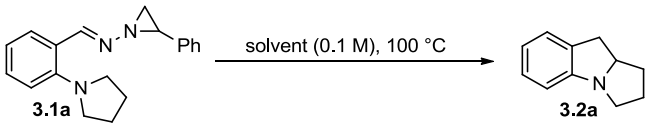
3.3.1 Development of Reaction and Exploration of Scope

Initial efforts were directed at promoting the reaction of *N*-aziridinyl imines (including **3.1a**) with Lewis and Brønsted acids and a systematic survey of these conditions known to promote [1,5]-hydride shifts according to our own experience in the area and others with different acceptors ensued.[104] Unfortunately, after much effort it was found the desired *N*-fused

indoline products were not able to be formed using this approach; consumption of starting materials were observed and ^{1}H NMR spectra were suggestive of polymerization being the deleterious pathway.

The desired *N*-fused indolines were first observed under thermal decomposition in the absence of a promoter (≥70 °C) which was found to proceed in poor yields with the exception of the formation of **3.2a** (Table 3.2 and Scheme 3.17). There was no obvious correlation between the yield of the *N*-fused indoline (**3.2a**) and the solvent polarity as both polar aprotic and non-polar solvents worked comparably well.[155]

Table 3.2. Thermal Decomposition Approach to *N*-Fused Indolines



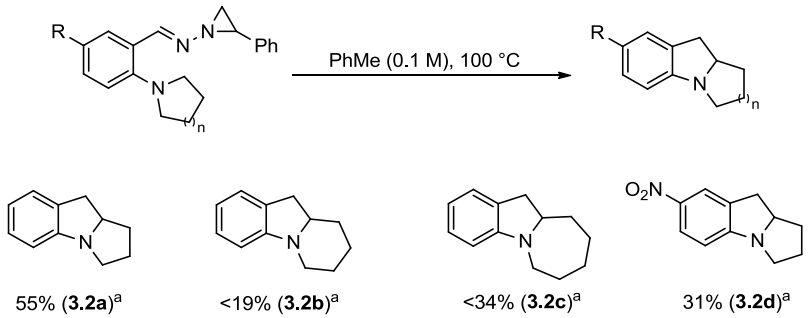
entry	solvent	time (h)	yield (%)[a]
1	PhMe	7	55
2[b]	1,2-dichloroethane	22	40
3	1,4-dioxane	4	51
4	DMF	3	53
5	NMP	3	51
6	DMPU	3	60

[a]Isolated yield after chromatography; [b]Reaction performed at reflux.

However, it was quickly realized that this thermal decomposition approach would not be of wide utility when attempts at functionalizing similar C-H bonds with different electronics or in alternate amine ring sizes resulted in poor selectivity for the *N*-fused indolines (Scheme 3.18). The poor mass balance was as a result of competitive reactions observed, which included: alkene formation (dimerization), azine formation, cyclopropanation of the stryrene released as well as some aldehdye. The product distribution was highly suggestive of the carbene pathway operating (Table 3.3, entry 1) and performing the reaction in the presence of an excess of styrene resulted in the selective formation of cyclopropanes **3.4** (trans/cis ratio of 1.6:1) by intermolecular scavenging of the carbene. Efforts were then focused on mediating the reaction with a dirhodium

(II) catalyst[156] and substrate **3.1b** which had led to the least chemoselective C-H insertion was chosen as a suitable candidate to pursue optimization.

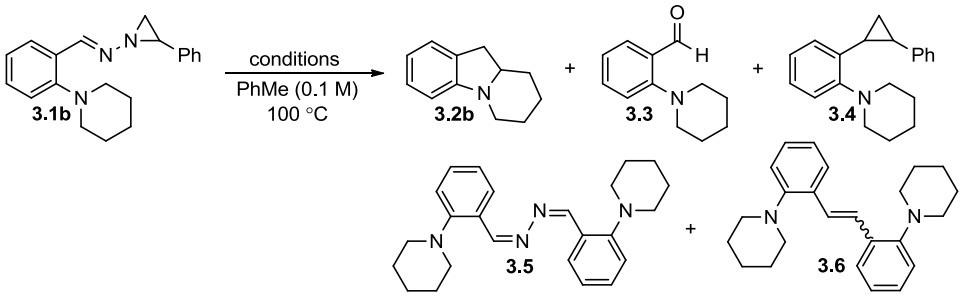
Scheme 3.18. Thermally Promoted *N*-Fused Indoline Formation

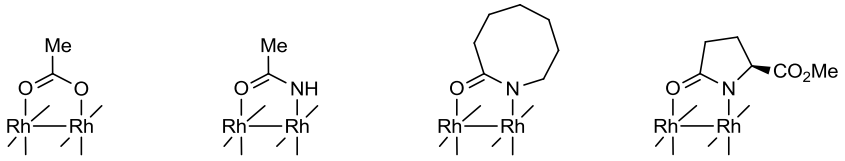


[a] Isolated yield of the indoline after chromatography.

In contrast to a recent report of tosyl hydrazone decomposition, it was found that $Rh_2(OAc)_4$ provided a significant influence over the product distribution to selectively form the desired C-H insertion product (Table 3.3, entry 3). The selectivity of rhodium carboxamidates were shown to benefit from steric effects (entry 4 vs entries 5 and 6). Negligible improvement in formation of the C-H insertion product **3.2b** was observed in additional experiments with $[Rh_2(cap)_4]$ probing higher dilution, increased catalyst loading, and slow addition of the substrate, tactics that are frequently used in metal catalyzed diazo decompositions to reduce undesired pathways including dimerization (entries 7-9). The catalyst of choice was then determined to be $[Rh_2(5S\text{-MEPY})_4]$, on the basis of its slight superiority in terms of selectivity for C-H insertion product (albeit forming racemic product)[157] and least amount of azine (**3.5**) formed. It was found that even a small percentage of azine formation, which would show to be the most commonly observed minor byproduct in this investigation, proved very difficult to separate from C-H insertion products by flash chromatography. A remedy was found by converting the azine to the aldehyde by incorporating a hydrolysis step in the workup (used as required) which permitted separation by flash chromatography (see experimental section for details).

Table 3.3. Evaluation of Reaction Parameters



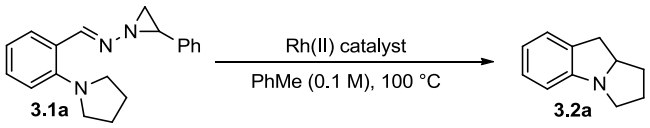


entry	conditions	time (h)	ratio[a] **3.2b**:**3.3**:**3.4**:**3.5**:**3.6**
1	-	5	24:5:64:4:3
2	10 equiv styrene	4	0:0:100 (78%):0:0
3	1 mol % $Rh_2(OAc)_4$	5	81:5:0:14:0
4	1 mol % $Rh_2(acam)_4$	5	46:4:35:2:13
5	1 mol % $Rh_2(cap)_4$	5	93 (49%):4:0:3:0
6[b]	1 mol % $Rh_2(5S\text{-MEPY})_4$	5	95 (51%):4:0:1:0
7[c]	1 mol % $Rh_2(cap)_4$	5	93 (43%):4:0:3:0
8	2 mol % $Rh_2(cap)_4$	5	96 (51%):2:0:2:0
9[d]	1 mol % $Rh_2(cap)_4$	17	89 (40%):7:0:4:0

[a]Determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures; values in parentheses correspond to isolated yield of respective component after chromatography. [b]Enantiomeric ratio of 54:46 determined by chiral HPLC on Chiralpak OD-H column, see the experimental section for details. [c]PhMe (0.05 M). [d]Syringe pump addition of **3.1b** over 9 h.

The generality of the effect of the rhodium carboxamidates on the yield of the *N*-fused indoline was echoed in examining the reaction of **3.1a** with different dirhodium catalysts (Table 3.4, entries 1-4). These reactions served to further validate the decision of continuing to pursue the examination of the reaction scope with $Rh_2(5S\text{-MEPY})_4$ and at a temperature of 100 °C (entry 4 vs entry 5).

Table 3.4. Probing the Generality of the Evaluation of Dirhodium(II) Catalysts



entry	catalyst	solvent	time (h)	yield (%)[a]
1	$Rh_2(OAc)_4$	PhMe	4	38[b]
2	$Rh_2(acam)_4$	PhMe	5	52[b]
3	$Rh_2(cap)_4{\cdot}(MeCN)_2$	PhMe	6	65
4	$Rh_2(5S\text{-MEPY})_4$	PhMe	4	74[c]
5[d,e]	$Rh_2(5S\text{-MEPY})_4$	PhMe	16	18[c]

[a]Isolated yield after chromatography; [b]Performed acidic hydrolysis workup described in General Procedure C before flash chromatography; [c]Enantiomeric ratio of 50:50 determined by chiral HPLC on a Chiralpak AD-H column, see experimental for details; [d]Reaction performed at 80 °C, resulted in primarily starting material recovery; [e]Syringe pump addition of **3.1a** over 1 h.

Gratifyingly, in examining the scope of the reaction (Figure 3.7), insertion into the C-H bond adjacent to nitrogen in alternate ring sizes proceeded in higher yields than observed with the piperidine derived substrate (**3.1b**). Furthermore, the electronics of the aromatic had a negligible effect on the process. Also, insertion into primary and secondary C-H bonds of acyclic amines was successfully demonstrated. Model studies directed at the dibenzopyrrocoline alkaloid class were found to proceed with exclusive regioselective insertion into the benzylic C-H bond to generate tetracyclic indolines (**3.2l** and **3.2m**), and subsequently were found to readily undergo oxidation to the indoles (**3.10** and **3.11** respectively).

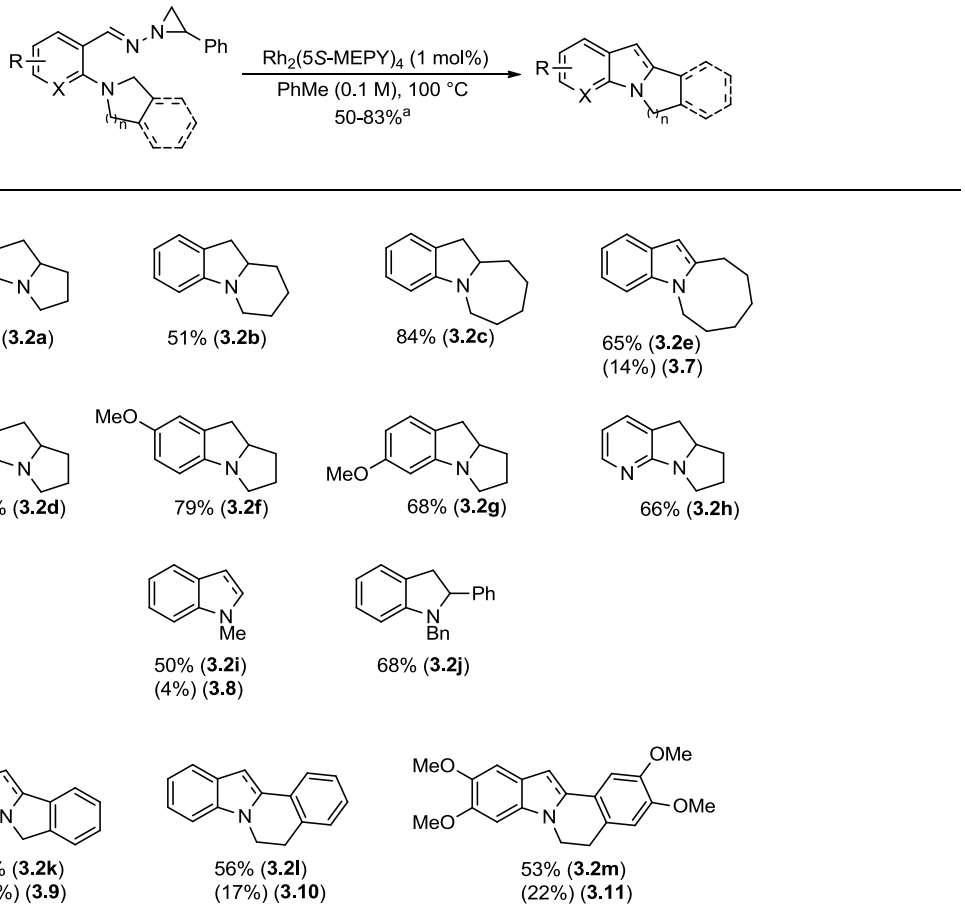
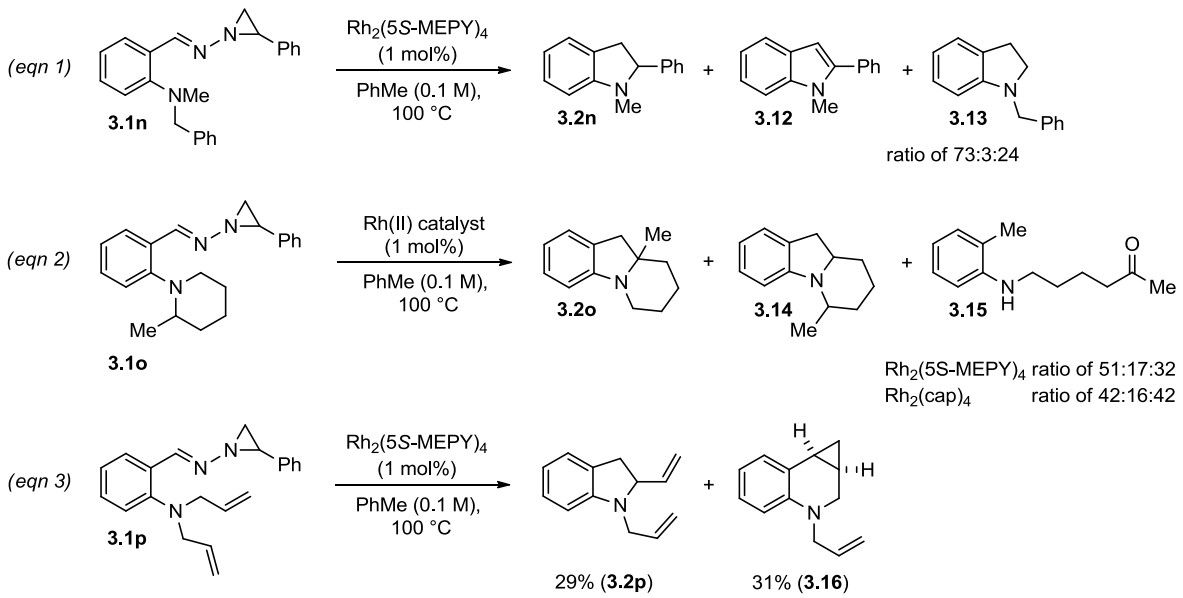


Figure 3.7. Exploring the scope of the C-H Insertion

[a] Isolated yields of the indoline and indole (in parentheses) after chromatography; indolines were found to be racemic by chiral HPLC analyses.

At this point the reaction was further probed by synthesizing a series of substrates that would present additional selectivity issues (Scheme 3.19). The poor regioselectivity (~3:1) of the C-H insertion into the *N*-methylbenzylamine hydrazone (**3.1n**) was initially an unexpected result based on electronic considerations (2° benzyl C-H being more nucleophilic than the 1° C-H); however, Doyle rationalizes this observation in analogous carbonyl-stabilized rhodium catalyzed C-H insertions as being a result of a conformational bias and therefore electronically favoured C-H insertion does not occur with as high selectivity due to it simply being not as accessible.[132]

Scheme 3.19. Further Investigations into Scope and Selectivity



Initial efforts directed at increasing functionality of the products by installing a handle at the alpha position of the amine tether have been met with limited success. Subjecting a 2-methylpiperidine based substrate (**3.1o**) to rhodium (II) carboxamidate catalysts was found to produce low regioselectivity for the C-H insertion reaction (as well as an unanticipated ring opening product **3.15**).[158] The product distribution was unaltered by changes in solvent polarity as well (PhMe, PhCl, DMF). This observation with regards to the solvent having a negligible effect on product distribution was consistent with Doyle's observation in ethyl diazoacetate dirhodium catalyzed C-H insertions in which regioisomeric products are formed.[132]

Chemoselectivity was further investigated under the optimized reaction conditions with diallylamine derived hydrazone **3.1p**, which was found to unselectively undergo C-H insertion and intramolecular cyclopropanation in forming **3.2p** and **3.16**.

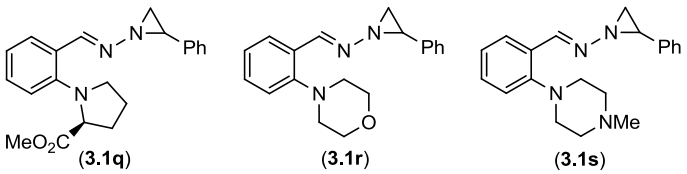
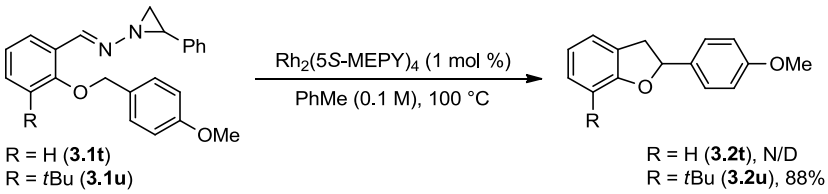


Figure 3.8. Hydrazones Bearing Less Electron Rich C-H Bonds

The substrates in Figure 3.8 were found to be poor candidates for C-H insertion under our optimized conditions; the dominant pathways were cyclopropanation of styrene and azine formation. The lowered tendency for C-H insertion can be explained by the less nucleophilic C-H bonds on the substrate due to inductively withdrawing functionalities which would limit the ability to react with the electrophilic carbenoid by destabilizing the positive charge build up in the transition state.[159]

Scheme 3.20. Application of the Thorpe-Ingold Effect to Broaden the Scope of the Reaction



R = H (**3.1t**)
R = *t*Bu (**3.1u**)

R = H (**3.2t**), N/D
R = *t*Bu (**3.2u**), 88%

An effort was also made to expand the substrate scope to the synthesis of dihydrobenzofurans (Scheme 3.20). Initial attempts yielded discouraging results and unselective reactions were observed with cyclopropanation and azine formation predominating. However, by the introduction of an ortho *tert*-butyl group (**3.1u**), the C-H insertion product (**3.2u**) was obtained in high yield (albeit racemic) which proved to be an effective strategy at restricting the conformation to increase the accessibility of the benzylic C-H bonds.

3.3.2. Total Synthesis of Cryptaustoline

Having established the ability of *N*-aziridinyl imines to undergo highly regioselective rhodium catalyzed C-H insertion in model studies aimed at the dibenzopyrrocoline alkaloids (Figure 3.9),[160] racemic cryptaustoline was identified as a promising target to highlight this methodology.

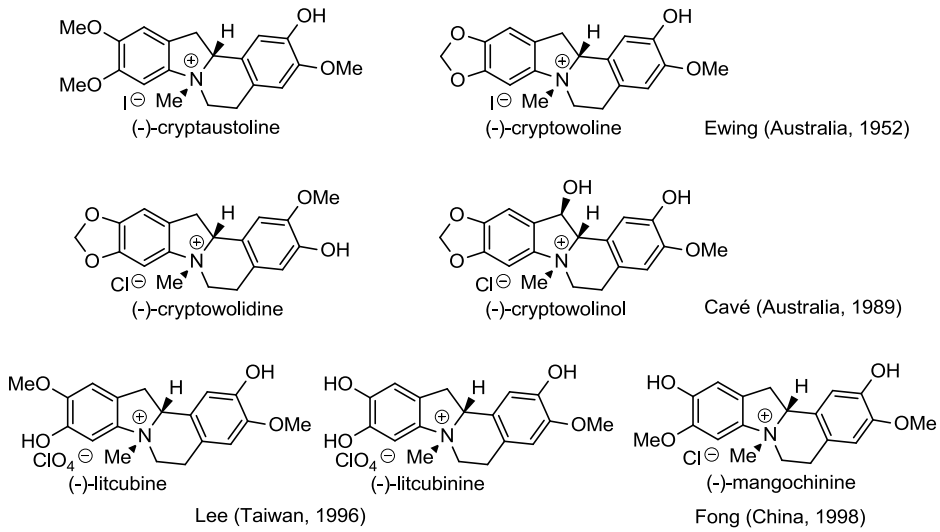
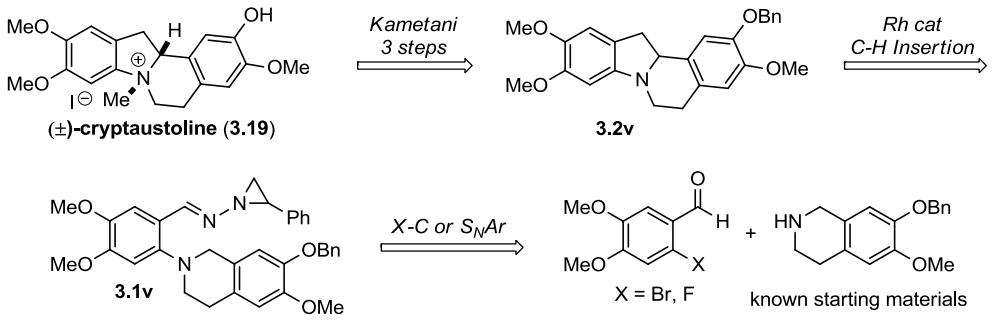


Figure 3.9. Dibenzopyrrocoline Alkaloids

(corresponding scientist, location of natural product and year discovered indicated)[161]

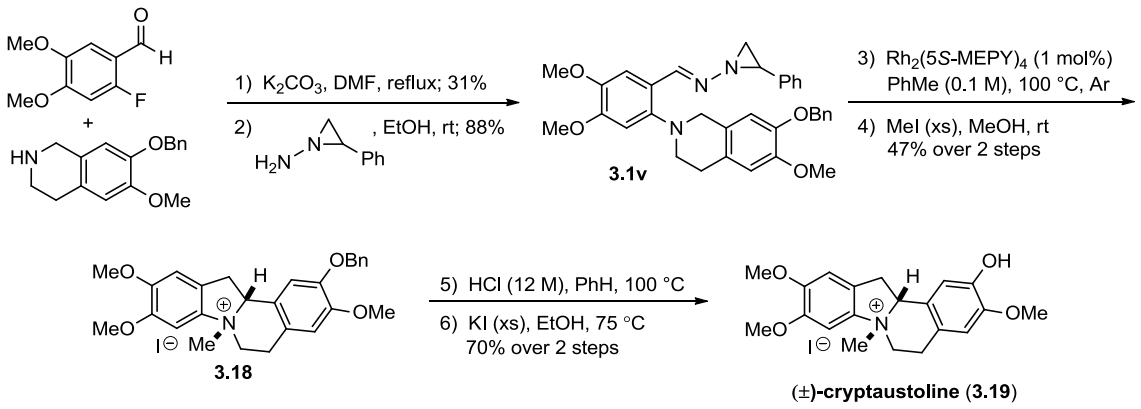
Cryptaustoline was first isolated in 1952 from the bark of *Cryptocarya bowiei* (Hook) Druce in Australia[161a] and studies directed at elucidating biological activity have been limited (paralytic activity). Compounds of similar structure[162] and those possessing the indoline[163] and tetrahydroisoquinoline[164] scaffold have been reported to exhibit anti-tumor activity amongst other bioactivity. The relative stereochemistry of cryptaustoline was determined by Takano and coworkers[165] through NOE and subsequently, Meyers' group revised previously assigned absolute chemistry.[128]

Scheme 3.21. Proposed Retrosynthesis of (±)-Cryptaustoline



The first disconnection in the proposed retrosynthesis (Scheme 3.21) was to a core structure of cryptaustoline (**3.2v**) which was identified as having been elaborated to the natural product in 3 steps (methylation, benzyl deprotection, and counter ion exchange) first reported by Kametani.[126] Our model studies had supported the viability of accessing the core of cryptaustoline from the *N*-aziridinyl imine by a highly regioselective, rhodium catalyzed C-H insertion. The requisite hydrazone (**3.1v**) was then traced back to a known vanillin derived tetrahydroisoquinoline and a commercially available 2-halobenzaldehyde. These compounds could provide the aldehyde needed to condense with the aminoaziridine through either a palladium catalyzed cross-coupling reaction or nucleophilic aromatic substitution.

Scheme 3.22. Total Synthesis of (±)-Cryptaustoline



The requisite hydrazone (**3.1v**) was readily obtained through nucleophilic aromatic substitution, followed by condensation and subjected to our optimized conditions (Scheme 3.22). Gratifyingly, the desired *N*-fused indolinium (**3.18**) was formed as a single regioisomer in moderate yield following direct methylation of the crude product to minimize the aforementioned facile oxidation. Lastly, deprotection and counterion exchange furnished the target molecule (**3.19**) whose spectroscopic data was in agreement with that of material from alternate syntheses.

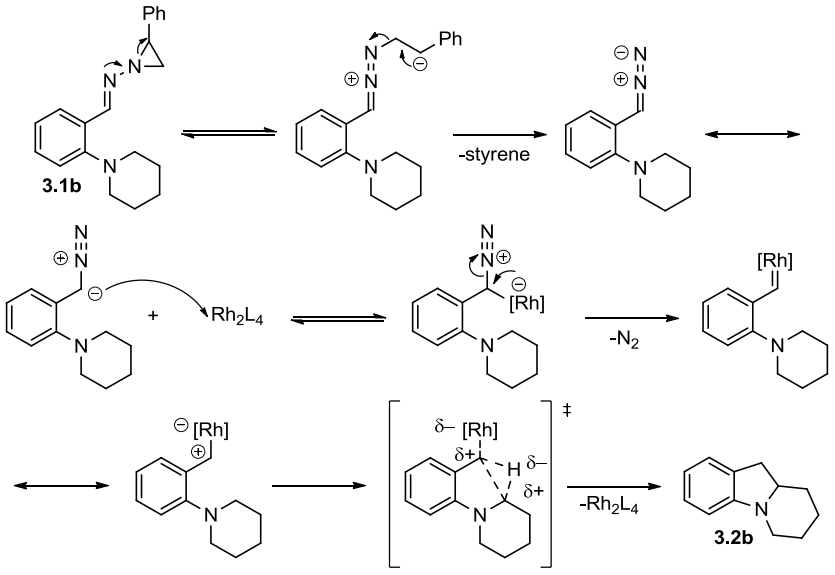


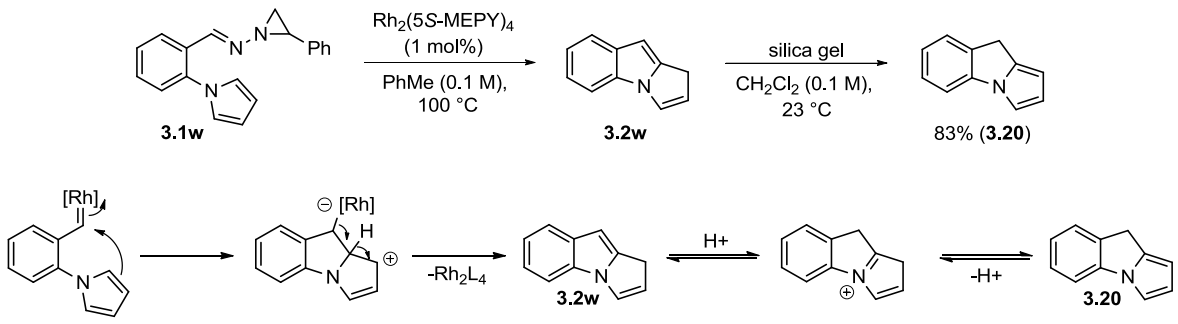
Figure 3.10. Proposed Mechanism

The strong influence of the dirhodium catalyst ligands on the product distribution, with byproducts explained as arising from a carbenoid pathway (cyclopropanes, alkene dimers and azines), are highly suggestive of a C-H insertion mechanism operating (Figure 3.10).[135] Furthermore, a hydride shift pathway would be expected to be facilitated with an electron deficient rhodium center and that was the opposite of what was observed (comparing the product distribution for $Rh_2(OAc)_4$ versus that obtained from $Rh_2(cap)_4$ and $Rh_2(5S\text{-MEPY})_4$ in accord with a C-H insertion mechanism operating.

3.3.3. Extension of the Developed Methodology

An extension of this methodology to a formal Csp^2-H insertion[166] was also demonstrated with a pyrrole substrate (**3.1w**) which was found to undergo facile isomerization from tricyclic indole (**3.2w**) to a tricyclic pyrrole (**3.20**) (Scheme 3.23). A plausible mechanism to account for these observations is given in Scheme 3.21 as well. Nucleophilic attack by the 5-position of the pyrrole on the formed rhodium carbenoid followed by 1,2-hydride transfer/elimination of dirhodium catalyst could deliver **3.2w** which then could undergo an acid catalyzed isomerization to **3.20**. The details of the mechanism remain to be investigated as well as whether **3.2w** can effectively trap other electrophiles.

Scheme 3.23. Formal Csp^2-H Insertion



Of note, the groups of Schweizer,[167,168] González-Pérez[169] and Caddick[170] reported data for similar isomerizations to **3.20** vida infra (Figure 3.11) but did not observe the intermediate indole that had been the anticipated product.

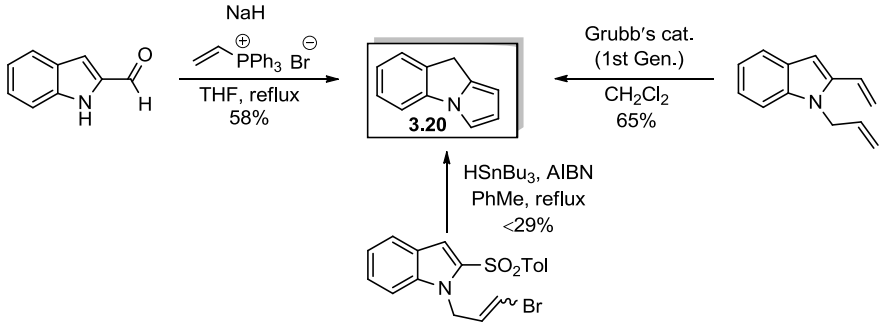


Figure 3.11. Lability of the Pyrroloindole Motif

3.4. Summary

The development of a selective, catalytic protocol of non-carbonyl-stabilized rhodium carbenoid Csp^3-H insertions enabled rapid synthesis of *N*-fused indolines and related complex heterocycles.[171] By using a rhodium carboxamidate catalyst, competing processes were minimized and C-H insertions were found to be highly regioselective for the benzylic position of tetrahydroisoquinoline derived substrates and tolerant to functionality, proceeding in moderate to high yields. Also disclosed was an expedient total synthesis of (±)-cryptaustoline, a dibenzopyrrocoline alkaloid, which highlights the methodology. An extension of the reaction conditions was also demonstrated by a formal Csp^2-H insertion in high yield.

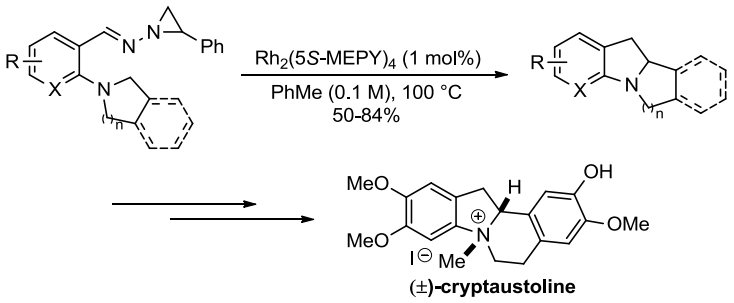


Figure 3.12. Developed Csp^3-H Insertion Protocol

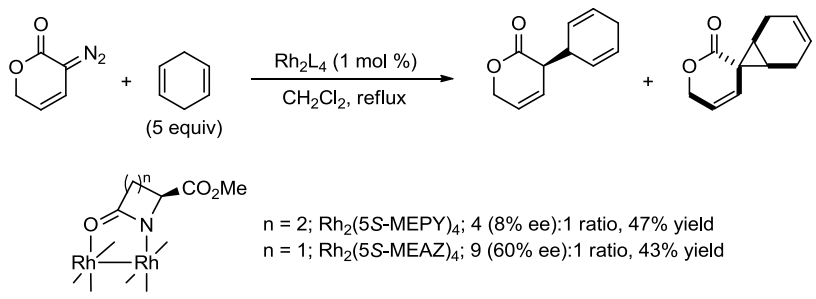
These developments should focus more attention on *N*-aziridinyl imines as carbenoid precursors, and furthermore, on the viability of aromatic stabilized/donor-substituted carbenoid C-H insertions.

3.5. Future Work

The ability to develop an enantioselective variant of this C-H insertion is still of interest, and continued work on this methodology should likely focus on screening and developing alternate catalysts, or additives.[172]

In that regard, dirhodium catalysts bearing oxaazetidinate ligands have been observed to be more reactive towards diazo decomposition than other carboxamidate dirhodium catalysts but maintain high selectivity.[133] This has been attributed to the lengthened Rh-Rh bond distance as a result of strain imparted by the bridging 4-membered ring ligand, which in turn makes the rhodium center more electrophilic. Further suppression of an uncatalyzed C-H insertion may follow as a result which may lead to increased enantioselectivity. Notably, Doyle's group has reported drastically improved enantioselectivity and chemoselectivity by using dirhodium oxaazetidinate catalysts (Scheme 3.24).[173]

Scheme 3.24. Improved Selectivity with Oxaazetidinate Ligands



3.6. Experimental

General Considerations

Reactions

Reactions were carried out in oven or flame-dried glassware under dry nitrogen atmosphere unless stated otherwise. CH_2Cl_2, THF, Et_2O and toluene were purified in solvent systems based on the published procedure.[174] DMF, DMPU, and NMP were distilled under vacuum over CaH_2 into Schlenk flasks with 4 Å molecular sieves and stored under nitrogen. Dichloroethane was distilled over CaH_2 into a Schlenk flask and stored under nitrogen. Rh_2(5*S*-MEPY)$_4$[175] and Rh_2(acam)$_4$[176] were prepared according to literature procedures from $Rh_2(OAc)_4$. Zinc powder was purified by washing with a 2% HCl solution according to the published protocol.[177] Reactions were monitored by thin-layer chromatography on commercially prepared plates. Developed plates were viewed under a UV lamp (254 nm) and with ceric ammonium molybdate stain. Flash chromatography was performed using 230-400 mesh silica gel.

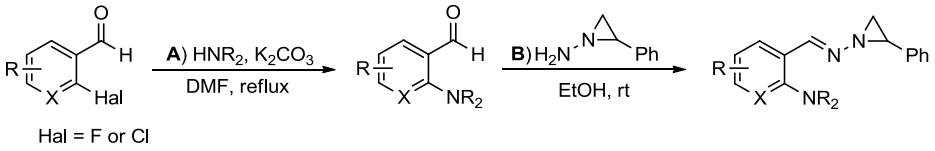
The following starting materials were prepared according to literature procedures and the spectral data obtained were in agreement with those reported and consequently, data will not be repeated here: 2-(piperidin-1-yl)benzaldehyde (**3.3**),[178] 2-(azepan-1-yl)benzaldehyde,[178] 2-(azocan-1-yl)benzaldehyde,[77] 2-(pyrrolidin-1-yl)benzaldehyde,[178] 5-nitro-2-(pyrrolidin-1-yl)benzaldehyde,[179] 5-methoxy-2-(pyrrolidin-1-yl)benzaldehyde,[180] 2-(dimethylamino)benzaldehyde,[181] 2-(dibenzylamino)benzaldehyde,[77] 2-(isoindolin-2-yl)benzaldehyde,[182] 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde,[182] 7-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline[183] [2-(4-(benzyloxy)-3-methoxyphenyl)ethanamine was

obtained from reduction of 2-(4-(benzyloxy)-3-methoxyphenyl)acetonitrile[184]], 2-(1*H*-pyrrol-1-yl)benzaldehyde,[185] 2-(benzyl(methyl)amino)benzaldehyde,[77] 2-(2-methylpiperidin-1-yl)benzaldehyde,[186] 2-(diallylamino)benzaldehyde,[187] (*S*)-methyl 1-(2-formylphenyl)pyrrolidine-2-carboxylate,[188] 2-morpholinobenzaldehyde,[178] 2-(4-methylpiperazin-1-yl)benzaldehyde,[189] and 2-((4-methoxybenzyl)oxy)benzaldehyde.[190]

Characterization

^{1}H and ^{13}C NMR spectra for all compounds were obtained in $CDCl_3$ at 300 MHz and 75 MHz, respectively unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual $CHCl_3$ (7.24 ppm), and carbon spectra were calibrated to $CDCl_3$ (77.0 ppm). The ^{1}H NMR of **3.2w** was run in acetone-d_6 and calibrated to residual acetone (2.05 ppm); the carbon spectrum was calibrated to acetone-d_6 (206.0 ppm). Carbon multiplicities (C, CH, CH_2, CH_3) were determined by combined DEPT 90/135 experiments. Melting points are uncorrected. Optical rotations were recorded in cells with 1 dm path length. Chiral HPLC analyses were performed using a Chiralcel AD-H or OD-H column (250 mm x 4.6 mm) with *i*PrOH:hexanes solvent mixtures as eluent. High resolution mass spectra were run at the University of Waterloo Mass Spectrometry facility.

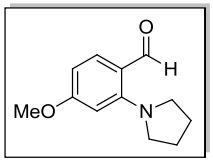
Synthesis of Starting Materials



General Procedure A - Preparation of Aminobenzaldehydes

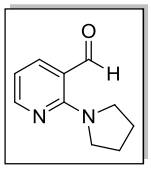
The procedure is based on the method reported by Seidel and coworkers:[77] A flame dried round bottom flask was equipped with a magnetic stir bar, 2-halogen substituted aldehyde (1 equiv), 2° amine (1.15 equiv), K_2CO_3 (1.15 equiv) and DMF (1.0 M). The reaction mixture was then refluxed under nitrogen and reaction progress was monitored by TLC. Upon completion, the

reaction was cooled to rt, diluted with water and extracted with ethyl acetate (3X). The combined organic layers were washed with sat. NH_4Cl solution (3X) and then dried over $MgSO_4$, filtered and concentrated under *vacuo*. The crude products were then purified by distillation or flash column chromatography.



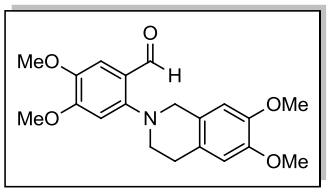
4-Methoxy-2-(pyrrolidin-1-yl)benzaldehyde (3.21)

Prepared according to General Procedure A from 2-fluoro-4-methoxybenzaldehyde (4.00 g, 25.9 mmol) and pyrrolidine (2.50 mL, 29.8 mmol); reaction was stirred for 18 h at reflux, purified eluting with EtOAc:hexanes (1:9) and isolated as a yellow oil (4.86 g, 91% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 9.92 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 6.39 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 3H), 3.38-3.33 (m, 4H), 1.99-1.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 187.7 (CH), 164.2 (C), 151.4 (C), 134.9 (CH), 117.3 (C), 103.6 (CH), 98.1 (CH), 54.8 (CH_3), 52.2 (CH_2), 25.5 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{12}H_{15}NO_2$ (M^+): 205.1103. Found: 205.1106.



2-(Pyrrolidin-1-yl)nicotinaldehyde (3.22)

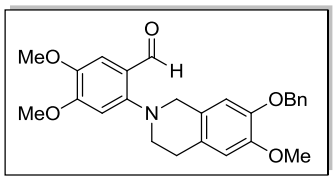
Prepared according to General Procedure A from 2-chloronicotinaldehyde (3.00 g, 21.2 mmol) and pyrrolidine (2.03 mL, 24.4 mmol); reaction was stirred for 4 h at reflux, purified eluting with EtOAc:hexanes (1:9) and isolated as an orange oil (3.01 g, 81% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 9.99 (s, 1H), 8.30 (d, *J* = 4.3 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 6.68 (dd, *J* = 7.1, 4.9 Hz, 1H), 3.52 (t, *J* = 6.0 Hz, 4H), 1.96 (t, *J* = 6.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 188.9 (CH), 156.4 (C), 152.5 (CH), 141.4 (CH), 116.1 (C), 111.6 (CH), 50.6 (CH_2), 25.3 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{10}H_{12}N_2O$ (M^+): 176.0950. Found: 176.0956.



2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4,5-dimethoxybenzaldehyde (3.23)[191]

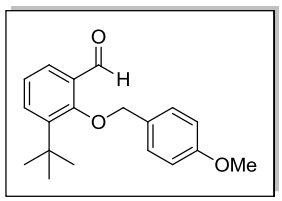
Prepared according to General Procedure A from 6-fluoroveratraldehyde (1.00 g, 5.43 mmol) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

(1.20 g, 6.24 mmol); reaction was stirred for 23 h at reflux, purified eluting with EtOAc:hexanes (1:3 to 1:1) and isolated as a pale orange solid (0.82 g, 42% yield). M.p. 142-145 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 10.27 (s, 1H), 7.34 (s, 1H), 6.67 (s, 1H), 6.65 (s, 1H), 6.58 (s, 1H), 4.18 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.36 (t, *J* = 5.7 Hz, 2H), 2.94 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 189.6 (CH), 154.6 (C), 151.9 (C), 147.6 (C), 147.4 (C), 145.1 (C), 125.9 (C), 125.8 (C), 121.9 (C), 111.5 (CH), 109.7 (CH), 108.9 (CH), 102.5 (CH), 55.92 (CH_3), 55.88 (CH_3), 55.83 (CH_3), 55.78 (CH_3), 55.2 (CH_2), 53.8 (CH_2), 28.5 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{24}NO_5$ ($[M + H]^+$): 358.1654. Found: 358.1653.



2-(7-(Benzyloxy)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4,5-dimethoxybenzaldehyde (3.24)

Prepared according to General Procedure A from 6-fluoroveratraldehyde (1.11 g, 6.03 mmol), and 7-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1.70 g, 6.33 mmol); reaction was stirred for 23 h at reflux, purified eluting with EtOAc:hexanes (1:3 to 1:2) and isolated as a pale orange solid (0.81 g, 31% yield); M.p. 48-50 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 10.25 (s, 1H), 7.43-7.27 (m, 6H), 6.68 (s, 1H), 6.63 (s, 1H), 6.58 (s, 1H), 5.11 (s, 2H), 4.11 (s, 2H), 3.88 (s, 6H), 3.87 (s, 3H), 3.35 (t, *J* = 5.6 Hz, 2H), 2.92 (t, *J* = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 189.3 (CH), 154.4 (C), 151.7 (C), 148.2 (C), 146.3 (C), 144.9 (C), 136.8 (C), 128.1 (CH), 127.4 (CH), 126.9 (CH), 126.5 (C), 125.6 (C), 121.6 (C), 111.9 (CH), 111.7 (CH), 109.5 (CH), 102.3 (CH), 70.8 (CH_2), 55.67 (CH_3), 55.66 (CH_3), 55.64 (CH_3), 54.6 (CH_2), 53.8 (CH_2), 28.3 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{28}NO_5$ ($[M + H]^+$): 434.1967. Found: 434.1971.



3-(*tert*-Butyl)-2-((4-methoxybenzyl)oxy)benzaldehyde (3.25)[192]

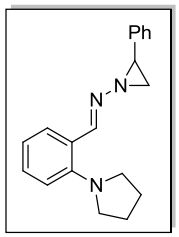
The synthesis was performed in analogy to a protocol described by Akiyama and coworkers.[193] A flame dried 500 mL round bottom flask equipped with a magnetic stir bar was charged with sodium hydride (1.80 g, 44.9 mmol, 2.0 equiv, 60% w/w in mineral oil), DMF (60 mL) and then stirred in an ice bath. A solution of 3-(*tert*-butyl)-2-hydroxybenzaldehyde[194] (4.00 g, 22.4 mmol, 1.0 equiv) in 60 mL DMF was slowly

added to the reaction flask at 0 °C under nitrogen. The resulting solution was then allowed to stir 10 min before the addition of 4-methoxybenzyl chloride (4.54 mL, 33.7 mmol, 1.5 equiv) slowly at 0 °C. The flask was then removed from the icebath and stirred at rt for 6 h. The workup began with cooling the flask in an icebath and then adding diethylamine (2.32 mL, 22.4 mmol). The crude was then extracted with diethyl ether (4X) and the combined organics were sequentially washed with 5% HCl (2X), brine (1X) and then dried with $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc:hexanes, 1:40) afforded an orange oil (1.69 g, 25% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 10.33 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 2H), 4.97 (s, 2H), 3.82 (s, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 190.4 (CH), 161.8 (C), 159.6 (C), 143.9 (C), 133.5 (CH), 130.2 (C), 128.9 (CH), 128.4 (C), 127.7 (CH), 124.0 (CH), 114.0 (CH), 80.4 (CH_2), 55.2 (CH_3), 35.2 (C), 30.8 (CH_3); HRMS (DART) *m/z* calcd for $C_{19}H_{26}NO_3$ ($[M + NH_4]^+$): 316.19127. Found: 316.18994.

General Procedure B - Preparation of N-Aziridinyl Imines

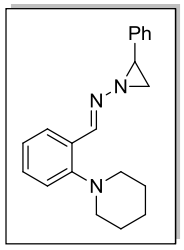
CAUTION: Proper safety precautions must be taken when 1-amino-2-phenylaziridine is handled (blast shield and when not in use store at -25 °C). 1-Amino-2-phenylaziridinium acetate has caused an explosion.[195] For details on preparation and handling see: Müller, R. K.; Joos, R.; Felix, D.; Schreiber, J.; Wintner, C.; Eschenmoser, A. *Org. Synth. Coll. Vol.* **1988**, *6*, 56.

A flame dried round bottom flask was equipped with a magnetic stir bar, aminobenzaldehyde (1 equiv), ethanol (0.2 M) and 1-amino-2-phenylaziridine (1.2-1.4 equiv) and stirred at room temperature (typically 16 to 24 h). Reaction progress was monitored via concentrating an aliquot and running ^{1}H NMR (since in many instances the R_f value of the aminobenzaldehyde was comparable to the hydrazone formed). Upon completion, the solvent was removed under vacuum, and the crude was purified by flash chromatography on silica gel (EtOAc/hexanes).



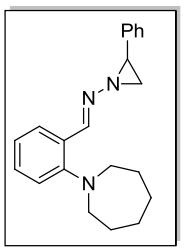
***N*-(2-(Pyrrolidin-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1a)**

Prepared according to General Procedure B from 2-(pyrrolidin-1-yl)benzaldehyde (3.00 g, 17.1 mmol) and 1-amino-2-phenylaziridine (2.75 g, 20.5 mmol). Filtration through a silica pad (EtOAc:hexanes, 1:9) afforded a yellow oil (4.85 g, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.84 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.35-7.21 (m, 6H), 6.85-6.80 (m, 2H), 3.25 (br t, *J* = 6.2 Hz, 4H), 3.13 (dd, *J* = 7.5, 5.0 Hz, 1H), 2.56 (d, *J* = 7.7 Hz, 1H), 2.42 (d, *J* = 4.8 Hz, 1H), 1.95-1.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4 (CH), 149.5 (C), 138.6 (C), 130.6 (CH), 128.6 (CH), 128.2 (CH), 127.1 (CH), 126.4 (CH), 122.9 (C), 119.2 (CH), 115.2 (CH), 52.6 (CH_2), 44.1 (CH), 40.4 (CH_2), 25.2 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}N_3$ ($[M + H]^+$): 292.1814. Found: 292.1807.



***N*-(2-(Piperidin-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1b)**

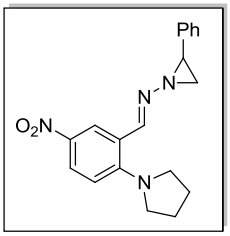
Prepared according to General Procedure B from 2-(piperidin-1-yl)benzaldehyde (**3.3**) (1.89 g, 10.0 mmol) and 1-amino-2-phenylaziridine (1.74 g, 13.0 mmol). Flash chromatography (EtOAc:hexanes, 1:9) afforded a yellow oil (2.98 g, 98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.79 (s, 1H), 7.79 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.36-7.26 (m, 6H), 7.04-6.98 (m, 2H), 3.11 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.88 (t, *J* = 5.2 Hz, 4H), 2.54 (d, *J* = 7.7 Hz, 1H), 2.45 (d, *J* = 4.8 Hz, 1H), 1.74-1.67 (m, 4H), 1.58-1.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.9 (CH), 153.2 (C), 138.3 (C), 130.5 (CH), 127.9 (CH), 127.1 (C), 126.8 (CH), 126.7 (CH), 126.0 (CH), 122.2 (CH), 118.5 (CH), 54.1 (CH_2), 43.7 (CH), 40.1 (CH_2), 25.8 (CH_2), 23.7 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{24}N_3$ ($[M + H]^+$): 306.1970. Found: 306.1974.



***N*-(2-(Azepan-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1c)**

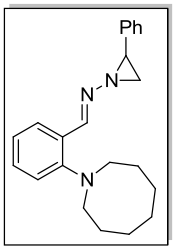
Prepared according to General Procedure B from 2-(azepan-1-yl)benzaldehyde (1.26 g, 6.20 mmol) and 1-amino-2-phenylaziridine (1.00 g, 7.40 mmol). Filtration through a silica pad (EtOAc:hexanes, 1:5) afforded an orange oil (1.98 g, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.85 (s, 1H), 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.33-

7.25 (m, 6H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 3.16 (t, *J* = 5.5 Hz, 4H), 3.12 (dd overlapping with triplet at 3.16 ppm, *J* = 7.9, 5.0 Hz, 1H), 2.54 (d, *J* = 7.5 Hz, 1H), 2.44 (d, *J* = 4.9 Hz, 1H), 1.75-1.68 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.3 (CH), 154.9 (C), 138.7 (C), 130.7 (CH), 128.2 (CH), 127.4 (CH), 127.3 (C), 127.0 (CH), 126.4 (CH), 121.9 (CH), 120.3 (CH), 56.4 (CH_2), 44.1 (CH), 40.4 (CH_2), 28.9 (CH_2), 27.1 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{26}N_3$ ($[M + H]^+$): 320.2127. Found: 320.2120.



_N_-(5-Nitro-2-(pyrrolidin-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1d)

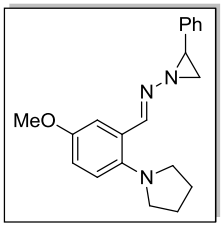
Prepared according to General Procedure B from 5-nitro-2-(pyrrolidin-1-yl)benzaldehyde (1.76 g, 8.00 mmol) and 1-amino-2-phenylaziridine (1.50 g, 11.2 mmol). The crude product was triturated in warm EtOH, filtered then washed with cold EtOH and isolated as a yellow solid (2.17 g, 81% yield). M.p. 129-131 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.91 (s, 1H), 8.45 (d, *J* = 2.8 Hz, 1H), 8.06 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.36-7.24 (m, 5H), 6.66 (d, *J* = 9.4 Hz, 1H), 3.49 (t, *J* = 6.5 Hz, 4H), 3.18 (dd, *J* = 7.8, 5.0 Hz, 1H), 2.60 (dd, *J* = 7.8, 0.6 Hz, 1H), 2.45 (dd, *J* = 5.2, 0.6 Hz, 1H), 2.02-1.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.6 (CH), 152.2 (C), 138.2 (C), 137.7 (C), 128.4 (CH), 127.3 (CH), 126.7 (CH), 126.4 (CH), 126.1 (CH), 118.8 (C), 113.4 (CH), 52.4 (CH_2), 44.4 (CH), 40.7 (CH_2), 25.8 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}N_4O_2$ ($[M + H]^+$): 337.1665. Found: 337.1671.



_N_-(2-(Azocan-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1e)

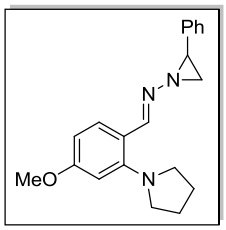
Prepared according to General Procedure B from 2-(azocan-1-yl)benzaldehyde (1.74 g, 8.00 mmol) and 1-amino-2-phenylaziridine (1.50 g, 11.2 mmol). Flash chromatography (EtOAc:hexanes, 1:12) afforded an orange oil (2.44 g, 91% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.97 (s, 1H), 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.32-7.25 (m, 6H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.14-3.09 (m, 5H), 2.55 (d, *J* = 7.6 Hz, 1H), 2.42 (d, *J* = 4.7 Hz, 1H), 1.65 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.4 (CH), 154.8 (C), 138.7 (C), 130.8 (CH), 128.3 (C), 128.2 (CH), 127.5 (CH), 127.0 (CH), 126.4 (CH), 122.4 (CH),

121.7 (CH), 55.5 (CH_2), 44.1 (CH), 40.4 (CH_2), 28.0 (CH_2), 27.4 (CH_2), 25.3 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}N_3$ ($[M + H]^+$): 334.2283. Found: 334.2277.



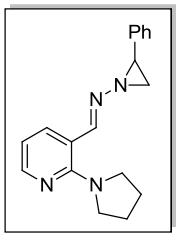
_N_-(5-Methoxy-2-(pyrrolidin-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1f)

Prepared according to General Procedure B from 5-methoxy-2-(pyrrolidin-1-yl)benzaldehyde (1.56 g, 7.60 mmol) and 1-amino-2-phenylaziridine (1.45 g, 10.8 mmol). Flash chromatography (EtOAc:hexanes, 1:12) afforded an orange oil (2.08 g, 85% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.82 (s, 1H), 7.35-7.25 (m, 6H), 6.93-6.85 (m, 2H), 3.78 (s, 3H), 3.15-3.09 (m, 5H), 2.56 (d, *J* = 7.7 Hz, 1H), 2.44 (d, *J* = 4.8 Hz, 1H), 1.92-1.87 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.1 (CH), 154.0 (C), 144.1 (C), 138.6 (C), 128.2 (CH), 127.1 (CH), 126.4 (CH), 126.1 (C), 118.0 (CH), 117.8 (CH), 110.9 (CH), 55.5 (CH_3), 53.3 (CH_2), 44.1 (CH), 40.5 (CH_2), 24.7 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{24}N_3O$ ($[M + H]^+$): 322.1919. Found: 322.1910.



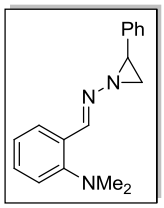
_N_-(4-Methoxy-2-(pyrrolidin-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1g)

Prepared according to General Procedure B from 4-methoxy-2-(pyrrolidin-1-yl)benzaldehyde (**3.21**) (1.56 g, 7.60 mmol) and 1-amino-2-phenylaziridine (1.43 g, 10.6 mmol). Flash chromatography (EtOAc:hexanes, 1:20 to 1:5) afforded a yellow oil (2.09 g, 86% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.79 (s, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.34-7.24 (m, 5H), 6.40 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 3.79 (s, 3H), 3.25-3.23 (m, 4H), 3.10 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.53 (d, *J* = 7.7 Hz, 1H), 2.39 (d, *J* = 4.9 Hz, 1H), 1.93-1.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 161.8 (C), 159.1 (CH), 150.9 (C), 138.8 (C), 130.1 (CH), 128.3 (CH), 127.0 (CH), 126.5 (CH), 116.1 (C), 104.6 (CH), 101.1 (CH), 55.1 (CH_3), 52.6 (CH_2), 44.0 (CH), 40.4 (CH_2), 25.3 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{20}H_{23}N_3O$ (M^+): 321.1841. Found: 321.1846.



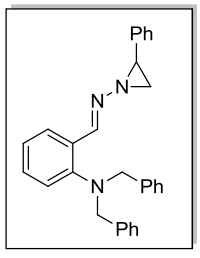
2-Phenyl-*N*-((2-(pyrrolidin-1-yl)pyridin-3-yl)methylene)aziridin-1-amine (3.1h)

Prepared according to General Procedure B from 2-(pyrrolidin-1-yl)nicotinaldehyde (**3.22**) (1.41 g, 8.00 mmol) and 1-amino-2-phenylaziridine (1.50 g, 11.2 mmol). Flash chromatography (EtOAc:hexanes, 1:4) afforded a yellow oil (2.27 g, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.79 (s, 1H), 8.16 (dd, *J* = 4.7, 1.9 Hz, 1H), 7.83 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.34-7.25 (m, 5H), 6.63 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.54 (t, *J* = 6.6 Hz, 4H), 3.12 (dd, *J* = 7.8, 4.9 Hz, 1H), 2.55 (d, *J* = 7.8 Hz, 1H), 2.42 (d, *J* = 4.9 Hz, 1H), 1.93-1.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.5 (CH), 157.3 (C), 148.9 (CH), 138.4 (C), 137.0 (CH), 128.2 (CH), 127.1 (CH), 126.3 (CH), 114.5 (C), 112.9 (CH), 50.7 (CH_2), 44.1 (CH), 40.5 (CH_2), 25.5 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{21}N_4$ ($[M + H]^+$): 293.1766. Found: 293.1763.



***N*-(2-(Dimethylamino)benzylidene)-2-phenylaziridin-1-amine (3.1i)**

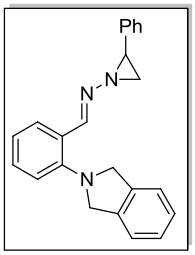
Prepared according to General Procedure B from 2-(dimethylamino)benzaldehyde (1.33 g, 8.90 mmol) and 1-amino-2-phenylaziridine (1.67 g, 12.5 mmol). Flash chromatography (EtOAc:hexanes, 1:20) afforded a yellow oil (1.56 g, 66% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.83 (s, 1H), 7.77 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.34-7.27 (m, 6H), 7.04-6.97 (m, 2H), 3.12 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.73 (s, 6H), 2.56 (d, *J* = 7.7 Hz, 1H), 2.44 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.8 (CH), 153.4 (C), 138.7 (C), 130.8 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 126.9 (C), 126.4 (CH), 122.3 (CH), 118.2 (CH), 45.2 (CH_3), 44.1 (CH), 40.6 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}N_3$ ($[M + H]^+$): 266.1657. Found: 266.1662.



***N*-(2-(Dibenzylamino)benzylidene)-2-phenylaziridin-1-amine (3.1j)**

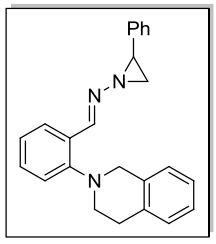
Prepared according to General Procedure B from 2-(dibenzylamino)benzaldehyde (581 mg, 1.90 mmol) and 1-amino-2-phenylaziridine (362 mg, 2.70 mmol). Flash chromatography (CH_2Cl_2:hexanes, 1:1 to EtOAc:hexanes, 1:1) afforded a yellow oil (733 mg, 91% yield). ^{1}H

NMR ($CDCl_3$, 300 MHz) 9.10 (s, 1H), 7.81 (d, *J* = 6.7 Hz, 1H), 7.34-7.14 (m, 16H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.11 (s, 4H), 3.10 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.49 (d, *J* = 7.7 Hz, 1H), 2.45 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.2 (CH), 150.5 (C), 138.4 (C), 137.3 (C), 130.4 (CH), 128.7 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 126.4 (CH), 123.4 (CH), 122.2 (CH), 57.7 (CH_2), 44.3 (CH), 40.3 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{28}N_3$ ($[M + H]^+$): 418.2283. Found: 418.2274.



_N_-(2-(Isoindolin-2-yl)benzylidene)-2-phenylaziridin-1-amine (3.1k)

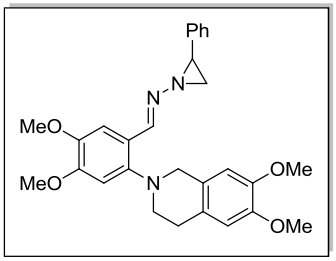
Prepared according to General Procedure B from 2-(isoindolin-2-yl)benzaldehyde (397 mg, 1.80 mmol) and 1-amino-2-phenylaziridine (334 mg, 2.50 mmol). Flash chromatography (EtOAc:hexanes, 1:9) afforded an orange oil (554 mg, 92% yield). ^1H NMR ($CDCl_3$, 300 MHz) 8.98 (s, 1H), 7.69 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.35-7.24 (m, 10H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 4.64 (s, 4H), 3.17 (dd, *J* = 4.9, 7.8 Hz, 1H), 2.59 (d, *J* = 7.8 Hz, 1H), 2.46 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.6 (CH), 148.6 (C), 138.6 (C), 138.3 (C), 130.9 (CH), 129.2 (CH), 128.4 (CH), 127.3 (CH), 127.1 (CH), 126.6 (CH), 124.3 (C), 122.2 (CH), 120.5 (CH), 116.9 (CH), 57.9 (CH_2), 44.3 (CH), 40.7 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{22}N_3$ ($[M + H]^+$): 340.1814. Found: 340.1810.



_N_-(2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)benzylidene)-2-phenylaziridin-1-amine (3.1l)

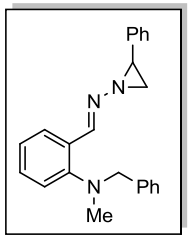
Prepared according to General Procedure B from 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (1.26 g, 5.30 mmol) and 1-amino-2-phenylaziridine (1.00 g, 7.40 mmol). Flash chromatography (EtOAc:hexanes, 1:20) afforded a tacky, yellow oil (1.63 g, 87% yield). ^1H NMR ($CDCl_3$, 300 MHz) 8.85 (s, 1H), 7.84 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.35-7.26 (m, 5H), 7.22-7.04 (m, 7H), 4.17 (s, 2H), 3.28 (t, *J* = 5.8 Hz, 2H), 3.11 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.98 (t, *J* = 5.7 Hz, 2H), 2.53 (d, *J* = 7.7 Hz, 1H), 2.43 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.0 (CH), 151.9 (C), 138.4 (C), 134.3 (C), 133.9 (C), 130.8 (CH), 128.7 (CH), 128.1 (CH), 127.6 (C), 127.3 (CH), 126.9 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH),

125.6 (CH), 122.9 (CH), 119.1 (CH), 54.6 (CH_2), 51.6 (CH_2), 43.9 (CH), 40.4 (CH_2), 28.8 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{24}N_3$ ($[M + H]^+$): 354.1970. Found: 354.1969.



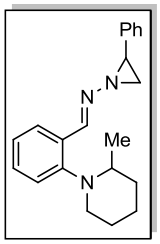
_N_-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1_H_)-yl)-4,5-dimethoxybenzylidene)-2-phenylaziridin-1-amine (3.1m)

Prepared according to General Procedure B from 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4,5-dimethoxybenzaldehyde (**3.23**) (800 mg, 2.24 mmol) and 1-amino-2-phenylaziridine (360 mg, 2.69 mmol). Flash chromatography (EtOAc:hexanes, 1:3 to 1:1) afforded a pale orange solid (971 mg, 92% yield). M.p. 58-61 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.86 (s, 1H), 7.39 (s, 1H), 7.32-7.21 (m, 5H), 6.68 (s, 1H), 6.63 (s, 1H), 6.53 (s, 1H), 4.04 (s, 2H), 3.89 (s, 3H), 3.86 (s, 6H), 3.82 (s, 3H), 3.20 (t, *J* = 5.7 Hz, 2H), 3.10 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.89 (t, *J* = 5.4 Hz, 2H), 2.50 (d, *J* = 7.6 Hz, 1H), 2.41 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.2 (CH), 151.4 (C), 147.4 (C), 147.2 (C), 146.9 (C), 145.5 (C), 138.6 (C), 128.2 (CH), 126.9 (CH), 126.4 (C), 126.3 (CH), 126.1 (C), 120.5 (C), 111.5 (CH), 108.9 (CH), 108.6 (CH), 103.4 (CH), 55.88 (CH_3), 55.79 (CH_3), 55.75 (CH_3), 55.68 (CH_3), 55.1 (CH_2), 51.9 (CH_2), 43.9 (CH), 40.5 (CH_2), 28.6 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{32}N_3O_4$ ($[M + H]^+$): 474.2393. Found: 474.2381.



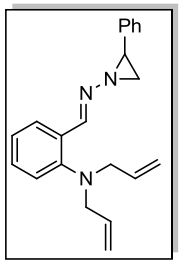
_N_-(2-(Benzyl(methyl)amino)benzylidene)-2-phenylaziridin-1-amine (3.1n)

Prepared according to General Procedure B from 2-(benzyl(methyl)amino)benzaldehyde (1.39 g, 6.2 mmol) and 1-amino-2-phenylaziridine (1.00 g, 7.4 mmol). Flash chromatography (EtOAc:hexanes, 1:40) afforded a yellow oil (1.28 g, 61% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.98 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.34-7.23 (m, 10H), 7.07-7.02 (m, 2H), 4.10 (s, 2H), 2.64 (s, 3H), 3.08 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.48 (d, *J* = 7.7 Hz, 1H), 2.40 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.3 (CH), 152.6 (C), 138.5 (C), 137.7 (C), 130.7 (CH), 128.2 (CH), 127.7 (C), 127.5 (CH), 127.0 (CH), 126.4 (CH), 122.8 (CH), 119.8 (CH), 61.8 (CH_2), 44.1 (CH), 41.5 (CH_3), 40.4 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}N_3$ ($[M + H]^+$): 342.1970. Found: 342.1968.



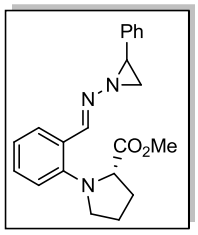
_N_-(2-(2-Methylpiperidin-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1o)

Prepared according to General Procedure B from 2-(2-methylpiperidin-1-yl)benzaldehyde (1.63 g, 8.00 mmol) and 1-amino-2-phenylaziridine (1.50 g, 11.2 mmol). Flash chromatography (EtOAc:hexanes, 1:12) afforded a yellow oil as a mixture of diastereomers (2.12 g, 83% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 9.00 (s, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.36-7.28 (m, 6H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 3.12 (app q, *J* = 6.3 Hz, 1H), 3.02-2.91 (m, 2H), 2.62 (ddd, *J* = 12.1, 8.9, 3.9 Hz, 1H), 2.53 (dd, *J* = 7.6, 4.7 Hz, 1H), 2.47 (d, *J* = 4.8 Hz, 1H), 1.79-1.64 (m, 4H), 1.47-1.36 (m, 2H), 0.81 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.4 (CH), 157.3 (CH), 152.6 (C), 152.5 (C), 138.7 (C), 130.7 (CH), 130.6 (C), 130.5 (C), 128.3 (CH), 127.1 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 126.4 (CH), 124.0 (CH), 123.9 (CH), 122.7 (CH), 122.6 (CH), 55.4 (CH), 55.3 (CH), 54.3 (CH_2), 44.3 (CH), 44.0 (CH), 40.6 (CH_2), 40.4 (CH_2), 34.1 (CH_2), 26.5 (CH_2), 23.4 (CH_2), 18.6 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{26}N_3$ ($[M + H]^+$): 320.2127. Found: 320.2116.



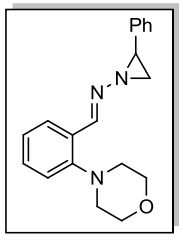
_N_-(2-(Diallylamino)benzylidene)-2-phenylaziridin-1-amine (3.1p)

Prepared according to General Procedure B from 2-(diallylamino)benzaldehyde (1.53 g, 7.60 mmol) and 1-amino-2-phenylaziridine (1.43 g, 10.6 mmol). Flash chromatography (EtOAc:hexanes, 1:12) afforded a yellow oil (2.32 g, 96% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.89 (s, 1H), 7.80 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.36-7.26 (m, 6H), 7.05-7.00 (m, 2H), 5.75 (ddt, *J* = 16.5, 10.2, 6.2 Hz, 2H), 5.14 (dd, *J* = 17.6, 1.4 Hz, 2H), 5.09 (d, *J* = 10.0 Hz, 2H), 3.61 (d, *J* = 6.1 Hz, 4H), 3.12 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.54 (d, *J* = 7.7 Hz, 1H), 2.45 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.5 (CH), 150.7 (C), 138.6 (C), 134.2 (CH), 130.3 (CH), 128.6 (C), 128.3 (CH), 127.4 (CH), 127.1 (CH), 126.4 (CH), 123.0 (CH), 121.7 (CH), 117.6 (CH_2), 56.5 (CH_2), 44.2 (CH), 40.6 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}N_3$ ($[M + H]^+$): 318.1970. Found: 318.1962.



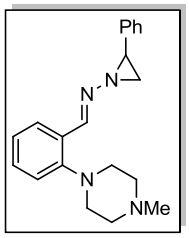
(2*S*)-Methyl 1-(2-((2-phenylaziridin-1-ylimino)methyl)phenyl)pyrrolidine-2-carboxylate (3.1q)

Prepared according to General Procedure B from (*S*)-methyl 1-(2-formylphenyl)pyrrolidine-2-carboxylate (170 mg, 0.730 mmol) and 1-amino-2-phenylaziridine (137 mg, 1.00 mmol). Flash chromatography (EtOAc:hexanes, 1:4) afforded a yellow oil as a mixture of diastereomers (254 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.85 (s, 1H), 8.84 (s, 1H), 7.68 (app dd, *J* = 8.0, 1.8 Hz, 2H), 7.33-7.23 (m, 12H), 6.94-6.90 (m, 4H), 4.28 (t, *J* = 6.4 Hz, 2H), 3.69-3.64 (m, 2H), 3.57 (s, 3H), 3.54 (s, 3H), 3.21-3.10 (m, 4H), 2.58 (dd, *J* = 7.8, 0.6 Hz, 1H), 2.54 (dd, *J* = 7.7, 0.7 Hz, 1H), 2.44 (d, *J* = 4.9 Hz, 2H), 2.41-2.27 (m, 2H), 2.07-1.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.64 (C), 173.61 (C), 158.7 (CH), 158.5 (CH), 148.0 (C), 147.9 (C), 138.6 (C), 138.5 (C), 130.6 (CH), 130.5 (CH), 128.22 (CH), 128.19 (CH), 128.16 (CH), 127.0 (CH), 126.3 (CH), 125.46 (C), 125.41 (C), 121.4 (CH), 117.6 (CH), 117.5 (CH), 63.32 (CH), 63.30 (CH), 54.0 (CH_2), 53.9 (CH_2), 51.61 (CH_3), 51.60 (CH_3), 44.0 (CH), 43.9 (CH), 40.5 (CH_2), 40.4 (CH_2), 30.3 (CH_2), 24.35 (CH_2), 24.31 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}N_3O_2$ ($[M + H]^+$): 350.1869. Found: 350.1880.



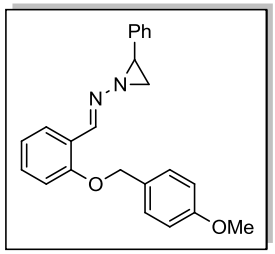
***N*-(2-Morpholinobenzylidene)-2-phenylaziridin-1-amine (3.1r)**

Prepared according to General Procedure B from 2-morpholinobenzaldehyde (1.91 g, 10.0 mmol) and 1-amino-2-phenylaziridine (1.74 g, 13.0 mmol). Flash chromatography (EtOAc:hexanes, 1:9) afforded a pale yellow solid (2.61 g, 85% yield). M.p. 100-102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.87 (s, 1H), 7.83 (d, *J* = 7.4 Hz, 1H), 7.39-7.26 (m, 6H), 7.11-7.05 (m, 2H), 3.84 (t, *J* = 4.4 Hz, 4H), 3.12 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.94 (t, *J* = 4.4 Hz, 4H), 2.55 (d, *J* = 7.7 Hz, 1H), 2.47 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.0 (CH), 152.0 (C), 138.4 (C), 131.1 (CH), 128.3 (CH), 127.6 (C), 127.5 (CH), 127.2 (CH), 126.4 (CH), 123.5 (CH), 118.8 (CH), 66.9 (CH_2), 53.3 (CH_2), 44.2 (CH), 40.5 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}N_3O$ ($[M + H]^+$): 308.1763. Found: 308.1755.



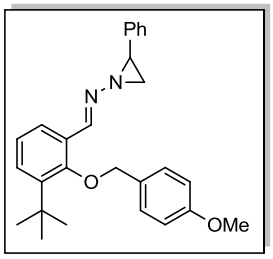
_N_-(2-(4-Methylpiperazin-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1s)

Prepared according to General Procedure B from 2-(4-methylpiperazin-1-yl)benzaldehyde (1.63 g, 8.0 mmol) and 1-amino-2-phenylaziridine (1.50 g, 11.2 mmol). Flash chromatography (EtOAc) afforded an orange oil (1.28 g, 50% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.82 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.37-7.26 (m, 6H), 7.07-7.02 (m, 2H), 3.12 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.98 (t, *J* = 4.7 Hz, 4H), 2.58-2.52 (m, 5H), 2.46 (d, *J* = 4.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.2 (CH), 152.3 (C), 138.6 (C), 131.0 (CH), 128.3 (CH), 127.6 (C), 127.4 (CH), 127.2 (CH), 126.5 (CH), 123.2 (CH), 118.9 (CH), 55.2 (CH_2), 52.9 (CH_2), 46.0 (CH_3), 44.2 (CH), 40.5 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}N_4$ (M^+): 320.2001. Found: 320.1993.



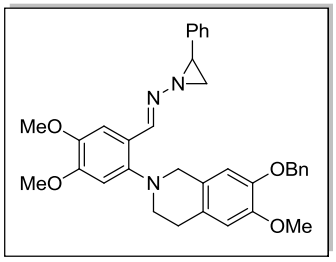
_N_-(2-(4-Methoxybenzyloxy)benzylidene)-2-phenylaziridin-1-amine (3.1t)

Prepared according to General Procedure B from 2-((4-methoxybenzyl)oxy)benzaldehyde (1.50 g, 6.2 mmol), 1-amino-2-phenylaziridine (1.00 g, 7.4 mmol) and used CH_2Cl_2 (62 mL, 0.1 M) due to insolubility of the aldehyde in EtOH. Flash chromatography (EtOAc:hexanes, 1:5) afforded a yellow solid (2.22 g, quant. yield). M.p. 98-100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.95 (s, 1H), 7.86 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.34-7.24 (m, 8H), 6.95-6.86 (m, 4H), 5.02 (s, 2H), 3.80 (s, 3H), 3.12 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.52 (d, *J* = 7.6 Hz, 1H), 2.43 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4 (C), 157.2 (C), 155.0 (CH), 138.6 (C), 131.6 (CH), 128.9 (CH), 128.5 (C), 128.3 (CH), 127.1 (CH), 126.7 (CH), 126.4 (CH), 122.8 (C), 120.9 (CH), 113.9 (CH), 112.6 (CH), 70.1 (CH_2), 55.1 (CH_3), 44.2 (CH), 40.6 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{23}N_2O_2$ ($[M + H]^+$): 359.1760. Found: 359.1754.



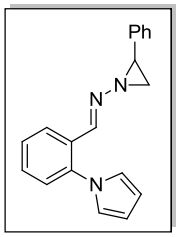
_N_-(2-(4-Methoxybenzyloxy)-3-_tert_-butylbenzylidene)-2-phenylaziridin-1-amine (3.1u)

Prepared according to General Procedure B from 3-(*tert*-butyl)-2-((4-methoxybenzyl)oxy)benzaldehyde (**3.25**) (1.50 g, 5.0 mmol) and 1-amino-2-phenylaziridine (944 mg, 7.0 mmol). Flash chromatography (EtOAc:hexanes, 1:20) afforded a yellow solid (1.28 g, 62% yield). M.p. 53-55 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.82 (s, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.40-7.26 (m, 8H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 2H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.3 Hz, 1H), 3.79 (s, 3H), 3.09 (dd, *J* = 7.3, 5.1 Hz, 1H), 2.54 (d, *J* = 7.7 Hz, 1H), 2.41 (d, *J* = 4.6 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4 (C), 157.9 (C), 156.4 (CH), 143.2 (C), 138.6 (C), 129.4 (CH), 129.0 (CH), 128.9 (C), 128.3 (CH), 128.0 (C), 127.1 (CH), 126.5 (CH), 125.9 (CH), 123.8 (CH), 113.9 (CH), 77.9 (CH_2), 55.2 (CH_3), 44.3 (CH), 40.5 (CH_2), 35.1 (C), 30.9 (CH_3); HRMS (EI) *m*/*z* calcd for $C_{27}H_{30}N_2O_2$ (M^+): 414.2307. Found: 414.2320.



_N_-(2-(7-(Benzyloxy)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4,5-dimethoxybenzylidene)-2-phenylaziridin-1-amine (3.1v)

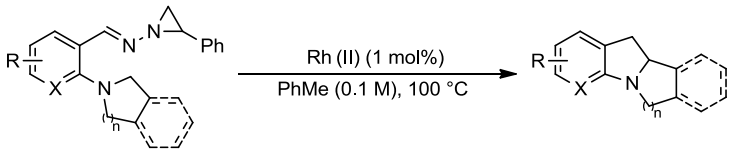
Prepared according to General Procedure B from 2-(7-(benzyloxy)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4,5-dimethoxybenzaldehyde (**3.24**) (652 mg, 1.50 mmol) and 1-amino-2-phenylaziridine (242 mg, 1.80 mmol). Flash chromatography (EtOAc:hexanes, 1:2) afforded a pale orange solid (728 mg, 88% yield). M.p. 64-66 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.82 (s, 1H), 7.42-7.24 (m, 11H, overlaps with $CHCl_3$), 6.66 (s, 1H), 6.63 (s, 1H), 6.55 (s, 1H), 5.09 (s, 2H), 3.96 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.18 (t, *J* = 5.7 Hz, 2H), 3.08 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.87 (t, *J* = 5.3 Hz, 2H), 2.46 (d, *J* = 7.6 Hz, 1H), 2.40 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.2 (CH), 151.4 (C), 148.2 (C), 146.8 (C), 146.4 (C), 145.5 (C), 138.6 (C), 137.1 (C), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 126.9 (C), 126.5 (C), 126.3 (CH), 120.5 (C), 112.1 (CH), 111.9 (CH), 108.7 (CH), 103.4 (CH), 71.1 (CH_2), 55.94 (CH_3), 55.91 (CH_3), 55.7 (CH_3), 55.0 (CH_2), 51.9 (CH_2), 43.9 (CH), 40.6 (CH_2), 28.7 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{34}H_{36}N_3O_4$ ($[M + H]^+$): 550.2706. Found: 550.2704.



***N*-(2-(1*H*-Pyrrol-1-yl)benzylidene)-2-phenylaziridin-1-amine (3.1w)**

Prepared according to General Procedure B from 2-(1*H*-pyrrol-1-yl)benzaldehyde (1.00 g, 5.80 mmol) and 1-amino-2-phenylaziridine (1.09 g, 8.20 mmol). Flash chromatography (EtOAc:hexanes, 1:9) afforded a yellow oil (1.68 g, quant. yield). ^{1}H NMR ($CDCl_3$, 500 MHz) 8.27 (s, 1H), 8.00 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.32-7.29 (m, 3H), 7.25-7.22 (m, 3H), 6.82 (app t, *J* = 1.9 Hz, 2H), 6.35 (app t, *J* = 1.9 Hz, 2H), 3.12 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.50 (d, *J* = 7.7 Hz, 1H), 2.42 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 155.3 (CH), 140.6 (C), 138.2 (C), 130.7 (CH), 129.3 (C), 128.3 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 126.36 (CH), 126.34 (CH), 122.9 (CH), 109.8 (CH), 44.1 (CH), 40.7 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}N_3$ ($[M + H]^+$): 288.1501. Found: 288.1497.

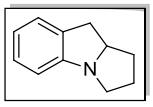
General Procedure C - Rhodium Catalyzed C-H insertion



A 20 mL screw capped sample vial was equipped with a magnetic stir bar, *N*-aziridinyl imine (1.00 mmol, 1 equiv), toluene (0.1 M), and rhodium catalyst (0.010 mmol, 2 mol % Rh), then the vial was capped and immersed into a pre-heated 100 °C oil bath. The reaction progress was monitored via TLC (EtOAc/hexanes or CH_2Cl_2/hexanes), and when complete the crude reaction mixture was passed through a short pad of silica gel (washed with EtOAc) and concentrated. A ^{1}H NMR of the crude was taken at this point to determine the selectivity and then the C-H insertion product was purified by flash chromatography using the indicated solvent gradient.

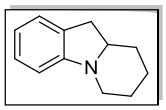
Note: In the event that trace azine was formed and proved to be resilient to separation from the products, the following acidic hydrolysis protocol was performed prior to flash chromatography: The crude reaction mixture was dissolved in CH_2Cl_2 (15 mL) and transferred to a 100 mL round bottom flask equipped with a magnetic stir bar. Then HCl (10%, 15 mL) was added and the biphasic mixture was stirred at reflux for 1 h. The workup consisted of cooling the reaction to

room temperature, then transferring the contents to a separatory funnel with CH_2Cl_2 and deionized H_2O. The contents were then slowly neutralized with a sat. $NaHCO_3$ solution. The organic layer was extracted (2x30 mL CH_2Cl_2) and then the combined organic layers were washed with deionized H_2O and brine before dried over $MgSO_4$, filtered and concentrated.



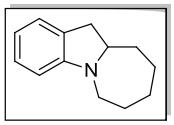
2,3,9,9a-Tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (3.2a)[196,197,120]

Prepared according to General Procedure C from imine **3.1a** (291 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 4 h reaction time. Flash chromatography (CH_2Cl_2) afforded a yellow/orange oil (117 mg, 74% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.10-7.04 (m, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 3.91 (ddt, *J* = 9.1, 5.7, 2.6 Hz, 1H), 3.41 (ddd, *J* = 10.7, 7.4, 5.0 Hz, 1H), 3.21-3.11 (m, 2H), 2.93 (dd, *J* = 16.1, 2.4 Hz, 1H), 1.92-1.75 (m, 3H), 1.37-1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 154.6 (C), 129.8 (C), 127.5 (CH), 124.8 (CH), 119.2 (CH), 110.9 (CH), 65.2 (CH), 52.2 (CH_2), 33.9 (CH_2), 31.3 (CH_2), 25.8 (CH_2); An enantiomeric ratio of 50:50 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 5.8 min, t_{R2} = 6.6 min); HRMS (EI) *m*/*z* calcd for $C_{11}H_{13}N$ (M^+): 159.1048. Found: 159.1053.



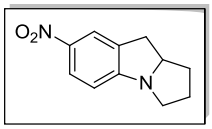
6,7,8,9,9a,10-Hexahydropyrido[1,2-*a*]indole (3.2b)[196,197,198]

Prepared according to General Procedure C from imine **3.1b** (305 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 5 h reaction time. Flash chromatography (CH_2Cl_2:hexanes, 1:9) afforded an orange oil (88 mg, 51% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.06-7.00 (m, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 7.6 Hz, 1H), 3.60 (dt, *J* = 11.9, 1.9 Hz, 1H), 3.18 (ddt, *J* = 9.0, 6.1, 2.6 Hz, 1H), 2.93 (dd, *J* = 14.8, 7.5 Hz, 1H), 2.65-2.50 (m, 2H), 1.85-1.81 (m, 2H), 1.66-1.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 151.7 (C), 129.3 (C), 127.2 (CH), 124.4 (CH), 117.4 (CH), 105.8 (CH), 65.2 (CH), 45.2 (CH_2), 35.5 (CH_2), 30.7 (CH_2), 24.6 (CH_2), 24.4 (CH_2); An enantiomeric ratio of 54:46 was measured by chiral HPLC (OD-H, hexanes, 0.5 mL/min, t_{R1} = 47.3 min, t_{R2} = 51.1 min (*major*)); HRMS (EI) *m*/*z* calcd for $C_{12}H_{15}N$ (M^+): 173.1204. Found: 173.1210.



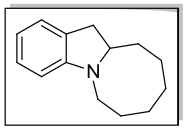
7,8,9,10,10a,11-Hexahydro-6*H*-azepino[1,2-*a*]indole (3.2c)[197]

Prepared according to General Procedure C from imine **3.1c** (319 mg, 1.00 mmol) and $Rh_2(5S\text{-MEPY})_4$ (7.7 mg, 0.010 mmol); 3 h reaction time. Flash chromatography (CH_2Cl_2:hexanes, 1:9) afforded a pale yellow oil (158 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.02 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.54 (t, *J* = 7.3 Hz, 1H), 6.30 (d, *J* = 7.8 Hz, 1H), 3.80 (dq, *J* = 8.9, 2.5 Hz, 1H), 3.41 (ddd, *J* = 12.8, 8.7, 4.2 Hz, 1H), 3.20 (dd, *J* = 15.9, 9.5 Hz, 1H), 3.02 (ddd, *J* = 12.6, 6.8, 3.8 Hz, 1H), 2.63 (dd, *J* = 15.8, 8.4 Hz, 1H), 1.89-1.40 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) 152.7 (C), 128.5 (C), 127.3 (CH), 123.7 (CH), 116.3 (CH), 105.6 (CH), 64.2 (CH), 48.2 (CH_2), 37.6 (CH_2), 37.2 (CH_2), 28.2 (CH_2), 27.1 (CH_2), 27.0 (CH_2); An enantiomeric ratio of 50:50 was measured by chiral HPLC (OD-H, hexanes, 1.0 mL/min, t_{R1} = 20.0 min, t_{R2} = 22.6 min); HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}N$ (M^+): 187.1361. Found: 187.1360.



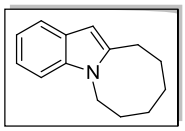
7-Nitro-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (3.2d)[199,200]

Prepared according to General Procedure C from imine **3.1d** (336 mg, 1.00 mmol) and $Rh_2(5S\text{-MEPY})_4$ (7.7 mg, 0.010 mmol); 6 h reaction time. Flash chromatography (CH_2Cl_2:hexanes, 1:1) afforded a yellow solid (170 mg, 83% yield). M.p. 37-38 °C [35 °C,[200] 47 °C [199]]; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.04 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.89 (br s, 1H), 6.41 (d, *J* = 8.7 Hz, 1H), 4.04 (dddd, *J* = 13.1, 9.5, 5.0, 3.3 Hz, 1H), 3.45 (ddd, *J* = 11.3, 8.1, 3.5 Hz, 1H), 3.24-3.14 (m, 2H), 2.97 (dd, *J* = 16.6, 2.8 Hz, 1H), 2.02-1.86 (m, 3H), 1.37-1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.6 (C), 139.5 (C), 130.7 (C), 125.8 (CH), 120.8 (CH), 107.6 (CH), 65.9 (CH), 49.5 (CH_2), 32.1 (CH_2), 30.9 (CH_2), 25.7 (CH_2); An enantiomeric ratio of 51:49 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 15.9 min, t_{R2} = 24.1 min); HRMS (EI) *m*/*z* calcd for $C_{11}H_{12}N_2O_2$ (M^+): 204.0899. Found: 204.0897

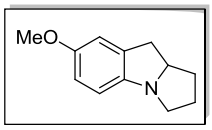


6,7,8,9,10,11,11a,12-Octahydroazocino[1,2-*a*]indole (3.2e) and 6,7,8,9,10,11-Hexahydroazocino[1,2-a]indole (3.7)

Prepared according to General Procedure C from imine **3.1e** (333 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 4 h reaction time. Flash chromatography (hexanes) afforded **3.2e** as the first product to elute and was isolated as a pale yellow oil (130 mg, 65% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.03-6.97 (m, 2H), 6.52 (t, *J* = 7.3 Hz, 1H), 6.27 (d, *J* = 7.8 Hz, 1H), 3.66 (ddt, *J* = 9.7, 6.0, 3.9 Hz, 1H), 3.43 (ddd, *J* = 14.6, 5.5, 4.2 Hz, 1H), 3.12-2.95 (m, 2H), 2.72 (dd, *J* = 15.8, 9.8 Hz, 1H), 1.94-1.49 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) 152.7 (C), 128.2 (C), 127.3 (CH), 123.9 (CH), 115.7 (CH), 104.5 (CH), 65.3 (CH), 47.4 (CH_2), 35.1 (CH_2), 32.1 (CH_2), 27.9 (CH_2), 27.4 (CH_2), 24.0 (CH_2), 23.4 (CH_2); An enantiomeric ratio of 57:43 was measured by chiral HPLC (OD-H, hexanes, 1.0 mL/min, t_{R1} = 12.2 min, t_{R2} = 14.1 min (*major*)); HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}N$ (M^+): 201.1517. Found: 201.1517.



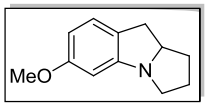
Indole **3.7** was the second product to elute from the above column and was isolated as a colourless oil (29 mg, 14% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.53 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.12 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.04 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.21 (s, 1H), 4.21 (t, *J* = 5.9 Hz, 2H), 2.85 (t, *J* = 6.1 Hz, 2H), 1.82-1.73 (m, 4H), 1.52-1.45 (m, 2H), 1.24-1.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.6 (C), 135.9 (C), 128.3 (C), 120.2 (CH), 119.8 (CH), 119.1 (CH), 108.9 (CH), 98.2 (CH), 40.5 (CH_2), 33.3 (CH_2), 29.9 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 24.1 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{14}H_{17}N$ (M^+): 199.1361. Found: 199.1357.



7-Methoxy-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (3.2f)

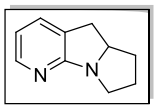
Prepared according to General Procedure C from imine **3.1f** (321 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 6 h reaction time. Flash chromatography (EtOAc:hexanes, 1:12) afforded an orange oil (150 mg, 79% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 6.67-6.62 (m, overlapping br s and dd, *J* = 2.5 Hz, 2H), 6.50 (d, *J* = 8.3 Hz, 1H), 3.91 (ddt, *J* = 9.2, 6.1, 2.8 Hz, 1H), 3.72 (s, 3H), 3.37 (ddd, *J* = 10.8, 7.2, 5.2 Hz, 1H), 3.19 -3.06 (m, 2H), 2.89 (dd, *J* = 16.2, 2.5 Hz, 1H), 1.90-1.77 (m, 3H), 1.38-1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 153.8 (C), 148.5 (C), 131.1 (C), 112.3 (CH), 111.4 (CH), 111.2 (CH), 65.5 (CH), 55.6 (CH_3),

53.0 (CH_2), 34.4 (CH_2), 31.4 (CH_2), 25.7 (CH_2); An enantiomeric ratio of 50:50 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 12.9 min, t_{R2} = 19.0 min); HRMS (EI) *m*/*z* calcd for $C_{12}H_{15}NO$ (M^+): 189.1154. Found: 189.1148.



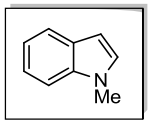
6-Methoxy-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (3.2g)

Prepared according to General Procedure C from imine **3.1g** (321 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 22 h reaction time. Flash chromatography (EtOAc:hexanes, 1:20) afforded an orange oil (129 mg, 68% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 6.92 (d, *J* = 8.0 Hz, 1H), 6.27 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 3.75 (s, 3H), 3.90 (ddt, *J* = 9.1, 5.5, 2.5 Hz, 1H), 3.38 (ddd, *J* = 10.9, 7.9, 4.4 Hz, 1H), 3.18-3.06 (m, 2H), 2.84 (dd, *J* = 15.6, 2.3 Hz, 1H), 1.90-1.75 (m, 3H), 1.33-1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 160.1 (C), 155.9 (C), 124.8 (CH), 122.0 (C), 103.8 (CH), 97.7 (CH), 65.9 (CH), 55.2 (CH_3), 51.9 (CH_2), 32.9 (CH_2), 31.2 (CH_2), 25.7 (CH_2); An enantiomeric ratio of 51:49 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 10.2 min, t_{R2} = 17.9 min); HRMS (EI) *m*/*z* calcd for $C_{12}H_{15}NO$ (M^+): 189.1154. Found: 189.1159.



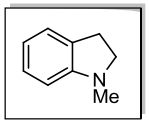
5a,6,7,8-Tetrahydro-5*H*-pyrido[3,2-*b*]pyrrolizine (3.2h)

Prepared according to General Procedure C from imine **3.1h** (292 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 16 h reaction time. Performed the aforementioned acidic hydrolysis protocol prior to flash chromatography (EtOAc:hexanes, 1:2) which afforded an orange oil (105 mg, 66% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.96 (d, *J* = 5.2 Hz, 1H), 7.22 (app dd, *J* = 7.1, 1.3 Hz, 1H), 6.54 (dd, *J* = 7.1, 5.3 Hz, 1H), 3.90 (tdd, *J* = 9.4, 5.2, 2.4 Hz, 1H), 3.67-3.58 (m, 1H), 3.40-3.32 (m, 1H), 3.12 (app dd, *J* = 16.5, 9.2 Hz, 1H), 2.88 (br d, *J* = 16.5 Hz, 1H), 1.94-1.81 (m, 3H), 1.30-1.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.9 (C), 146.6 (CH), 131.9 (CH), 123.1 (C), 114.1 (CH), 62.9 (CH), 48.3 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 25.4 (CH_2); An enantiomeric ratio of 51:49 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 0.7 mL/min, t_{R1} = 21.9 min, t_{R2} = 22.9 min); HRMS (EI) *m*/*z* calcd for $C_{10}H_{12}N_2$ (M^+): 160.1000. Found: 160.1000.

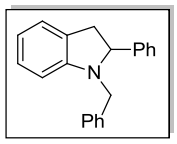


1-Methylindole (3.2i) and 1-Methylindoline (3.8)[201]

Prepared according to General Procedure C from imine **3.1i** (265 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 5 h reaction time. Flash chromatography (CH_2Cl_2:hexanes, 1:12) afforded **3.8** as the first product to elute and was isolated as a pale orange film (5 mg, 4% yield); NMR data was consistent with the literature[201] and commercial sources.

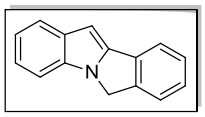


Indoline **3.2i** was the second product to elute from the above column and was isolated as a pale yellow oil (67 mg, 50% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.09-7.04 (m, 2H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 3.27 (t, *J* = 8.1 Hz, 2H), 2.92 (t, *J* = 8.1 Hz, 2H), 2.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 153.3 (C), 130.2 (C), 127.2 (CH), 124.2 (CH), 117.7 (CH), 107.2 (CH), 56.1 (CH_2), 36.2 (CH_3), 28.7 (CH_2); HRMS (EI) *m*/*z* calcd for $C_9H_{11}N$ (M^+): 133.0891; Found: 133.0897.



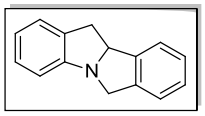
1-Benzyl-2-phenylindoline (3.2j)

Prepared according to General Procedure C from imine **3.1j** (417 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 3 h reaction time. Flash chromatography (CH_2Cl_2:hexanes, 1:9) afforded a pale yellow oil (194 mg, 68% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.43-7.40 (m, 2H), 7.35-7.26 (m, 3H), 7.23-7.18 (m, 5H), 7.06-6.99 (m, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 4.62 (t, *J* = 9.6 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 3.93 (d, *J* = 15.8 Hz, 1H), 3.37 (dd, *J* = 15.7, 9.1 Hz, 1H), 3.00 (dd, *J* = 15.7, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 152.3 (C), 142.4 (C), 138.3 (C), 128.6 (CH), 128.4 (C), 128.3 (CH), 127.64 (CH), 127.57 (CH), 127.56 (CH), 127.50 (CH), 126.8 (CH), 124.1 (CH), 117.9 (CH), 107.4 (CH), 69.3 (CH), 50.9 (CH_2), 39.4 (CH_2); An enantiomeric ratio of 41:59 was measured by chiral HPLC (OD-H, 1% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 7.0 min, t_{R2} = 13.7 min (*major*)); HRMS (EI) *m*/*z* calcd for $C_{21}H_{19}N$ (M^+): 285.1517. Found: 285.1524.

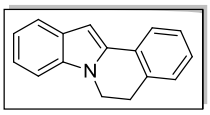


6*H*-Isoindolo[2,1-*a*]indole (3.9)[202] **and 10b,11-Dihydro-6*H*-isoindolo[2,1-*a*]indole (3.2k)**[203]

Prepared according to General Procedure C from imine **3.1k** (88 mg, 0.26 mmol) and Rh_2(5*S*-MEPY)$_4$ (2.0 mg, 0.010 mmol); 4 h reaction time. Flash chromatography, dry packed sample (EtOAc:hexanes, 1:20) afforded **3.9** as the first product to elute and was isolated as a white solid (9 mg, 17% yield). M.p. 208-210 °C (209-211 °C);[202] ^{1}H NMR ($CDCl_3$, 300 MHz) 7.70 (d, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.41-7.27 (m, 3H), 7.18 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.09 (dt, *J* = 7.4, 0.8 Hz, 1H), 6.62 (s, 1H), 5.07 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 143.9 (C), 141.7 (C), 133.9 (C), 133.1 (C), 132.8 (C), 128.1 (CH), 127.0 (CH), 123.5 (CH), 121.7 (CH), 121.5 (CH), 120.9 (CH), 119.6 (CH), 109.2 (CH), 91.3 (CH), 48.4 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{15}H_{11}N$ (M^+): 205.0891. Found: 205.0896.



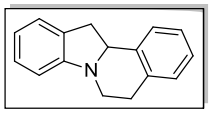
Tetracycle **3.2k** was the second product to elute from the above column and was isolated as a pale yellow solid (18 mg, 33% yield). M.p. 79-83 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29-7.18 (m, 4H), 7.11-7.04 (m, 2H), 6.80-6.73 (m, 2H), 5.19 (dd, *J* = 9.8, 0.6 Hz, 1H), 4.62 (dd, *J* = 14.8, 1.4 Hz, 1H), 4.49 (d, *J* = 14.8 Hz, 1H), 3.52 (dd, *J* = 15.9, 9.9 Hz, 1H), 3.35 (dd, *J* = 15.9, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 154.4 (C), 143.8 (C), 139.9 (C), 129.7 (C), 127.59 (CH), 127.58 (CH), 127.3 (CH), 124.7 (CH), 122.6 (CH), 122.2 (CH), 120.4 (CH), 111.9 (CH), 69.5 (CH), 59.1 (CH_2), 35.2 (CH_2); An enantiomeric ratio of 52:48 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 1.0 mL/min, t_{R1} = 8.6 min, t_{R2} = 9.1 min); HRMS (EI) *m*/*z* calcd for $C_{15}H_{13}N$ (M^+): 207.1048. Found: 207.1043.



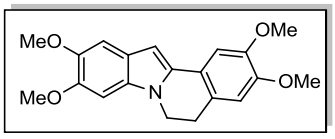
5,6-Dihydroindolo[2,1-*a*]isoquinoline (3.10)[191] **and 5,6,12,12a-Tetrahydroindolo[2,1-*a*]isoquinoline (3.2l)**

Prepared according to General Procedure C from imine **3.1l** (353 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 3 h reaction time. Flash chromatography (CH_2Cl_2:hexanes, 1:5 to 1:3) afforded **3.10** as the first product to elute and was isolated as an off white solid that turns pale green on standing while retaining integrity by ^{1}H NMR (38 mg, 17% yield). M.p. 165-167 °C (165-167 °C);[191] ^{1}H NMR ($CDCl_3$, 300 MHz) 7.75 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.9 Hz,

1H), 7.34-7.16 (m, 5H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.85 (s, 1H), 4.25 (t, *J* = 6.5 Hz, 2H), 3.19 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 136.6 (C), 135.6 (C), 132.1 (C), 129.0 (C), 128.8 (C), 128.3 (CH), 127.4 (CH), 127.2 (CH), 124.4 (CH), 121.6 (CH), 120.7 (CH), 119.8 (CH), 108.9 (CH), 96.4 (CH), 40.1 (CH_2), 29.2 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{16}H_{13}N$ (M^+): 219.1048. Found: 219.1051.



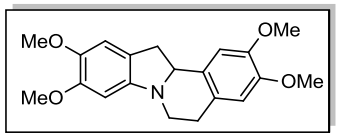
Tetracycle **3.2l** was the second product to elute from the above column and was isolated as a yellow film (124 mg, 56% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.18 (app d, *J* = 3.8 Hz, 2H), 7.13-6.98 (m, 4H), 6.65-6.59 (m, 2H), 4.88 (dd, *J* = 9.2, 3.3 Hz, 1H), 3.87 (dd, *J* = 13.8, 4.9 Hz, 1H), 3.54 (dd, *J* = 15.3, 9.4 Hz, 1H), 3.35 (dt, *J* = 13.0, 3.8 Hz, 1H), 3.14 (dd, *J* = 15.2, 4.0 Hz, 1H), 3.06 (br dt overlapping with dd at 3.14 ppm, *J* = 11.7, 5.4 Hz, 1H), 2.57 (br d, *J* = 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 150.4 (C), 139.3 (C), 134.9 (C), 129.6 (C), 128.8 (CH), 127.3 (CH), 126.4 (CH), 126.2 (CH), 125.9 (CH), 124.8 (CH), 117.9 (CH), 107.3 (CH), 62.7 (CH), 42.1 (CH_2), 36.8 (CH_2), 25.4 (CH_2); An enantiomeric ratio of 53:47 was measured by chiral HPLC (OD-H, Hexanes, 1.0 mL/min, t_{R1} = 69.7 min, t_{R2} = 78.6 min); HRMS (EI) *m*/*z* calcd for $C_{16}H_{15}N$ (M^+): 221.1204. Found: 221.1206.



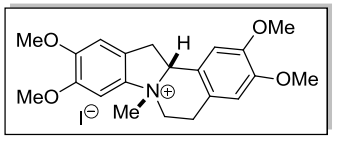
2,3,9,10-Tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline (3.11) [204,205,126,206,207,208,209] and **2,3,9,10-Tetramethoxy-5,6,12,12a-tetrahydroindolo[2,1-*a*]isoquinoline (3.2m)**[126,208,210,211]

In a glovebox, a Schlenk tube equipped with a magnetic stir bar was loaded with *N*-aziridinyl imine **3.1m** (100 mg, 0.211 mmol, 1 equiv), toluene (2.1 mL, 0.10 M; distilled over CaH_2 under N_2 and then degassed via freeze-pump-thaw method (3x)) and Rh_2(5*S*-MEPY)$_4$ (1.6 mg, 0.0021 mmol, 2 mol % Rh), then the Schlenk was sealed and capped with a rubber septum and brought out. The Schlenk tube's nitrogen atmosphere was then exchanged with argon before immersing into a pre-heated 100 °C oil bath. The reaction progress was monitored via TLC (CH_2Cl_2 then EtOAc/hexanes,1:1 respectfully), and when complete after 6 h the crude reaction mixture was passed through a short pad of silica gel (washed with EtOAc) and concentrated. A ^{1}H NMR of the crude was taken at this point to determine the selectivity (12:1 indoline **3.2m** to indole **3.11**). Flash chromatography (CH_2Cl_2 to EtOAc:hexanes, 1:1) afforded **3.11** as the first product to elute and was isolated as a white solid (16 mg, 22% yield). M.p. 192-195 °C (dec) [199 °C,[205] 200 °C

(MeOH),[207] 201-203 °C (EtOAc),[204] 202-204 °C (EtOH),[126] 204-205 °C,[209] 205-206 °C,[208] 207-208 °C (MeOH/Et_2O)[206]]; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.16 (s, 1H), 7.05 (s, 1H), 6.79 (s, 1H), 6.73 (s, 1H), 6.62 (s, 1H), 4.15 (t, *J* = 6.5 Hz, 2H), 3.94 (s, 6H), 3.92 (s, 3H), 3.89 (s, 3H), 3.10 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.4 (C), 148.3 (C), 146.8 (C), 145.2 (C), 134.6 (C), 131.1 (C), 124.0 (C), 122.0 (C), 121.6 (C), 111.3 (CH), 106.9 (CH), 102.3 (CH), 94.8 (CH), 92.6 (CH), 56.4 (CH_3), 56.3 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 40.5 (CH_2), 28.8 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}NO_4$ ([M + H]$^+$): 340.1549. Found: 340.1545.



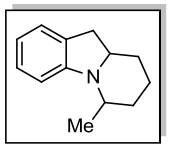
Tetracycle **3.2m** was the second product to elute from the above column and was isolated as a pale yellow film contaminated with trace **3.11** due to facile oxidation (38 mg, 53% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 6.69 (s, 1H), 6.64 (s, 1H), 6.46 (s, 1H), 6.30 (s, 1H), 4.82 (br d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.86-3.75 (m obscured by the 4 singlets, 1H), 3.45 (dd, *J* = 14.8, 9.1 Hz, 1H), 3.30 (dt, *J* = 13.0, 3.7 Hz, 1H), 3.04 (dd, *J* = 14.9, 3.1 Hz, 1H), 2.96 (br dt overlapping with dd at 3.04 ppm, *J* = 12.2, 4.3 Hz, 1H), 2.42 (br d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 149.1 (C), 147.8 (C), 147.4 (C), 144.6 (C), 142.1 (C), 130.9 (C), 127.0 (C), 120.1 (C), 111.4 (CH), 110.8 (CH), 108.9 (CH), 94.4 (CH), 63.0 (CH), 56.9 (CH_3), 56.3 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 42.8 (CH_2), 37.1 (CH_2), 24.4 (CH_2); HRMS (EI) *m/z* calcd for $C_{20}H_{23}NO_4$ (M^+): 341.1627. Found: 341.1635.



2,3,9,10-Tetramethoxy-7-methyl-6,7,12,12a-tetrahydro-5*H*-indolo[2,1-*a*]isoquinolin-7-ium iodide (3.26)[126,205,207,204,209,210,211,212,213]

In a glovebox, a Schlenk tube equipped with a magnetic stir bar was loaded with *N*-aziridinyl imine **3.1m** (100 mg, 0.211 mmol, 1 equiv), toluene (2.1 mL, 0.10 M; distilled over CaH_2 under N_2 and then degassed via freeze-pump-thaw method (3x)) and Rh_2(5*S*-MEPY)$_4$ (1.6 mg, 0.0021 mmol, 2 mol % Rh), then the Schlenk was sealed and capped with a rubber septum and brought out. The Schlenk tube's nitrogen atmosphere was then exchanged with argon before immersing into a pre-heated 100 °C oil bath. The reaction progress was monitored via TLC (CH_2Cl_2 then EtOAc:hexanes, 1:1 respectfully), and when complete after 6 h the crude reaction mixture was passed through a short pad of silica gel (washed with EtOAc) and concentrated. A ^{1}H NMR of

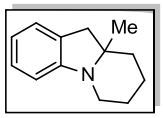
the crude was taken at this point to determine the selectivity (4:1 indoline **3.2m** to indole **3.11**) and then the readily oxidized crude reaction mixture was taken up in MeOH (0.76 mL) and an excess of iodomethane (0.76 mL) was added at room temperature according to Kametani's procedure.[126] After standing for 24 hours at room temperature, the contents of the reaction vial were filtered, and washed with cold MeOH (2 mL) to obtain a pale yellow solid (25 mg, 25% yield over 2 steps). M.p. 210-211°C (MeOH) [80-84 °C (H_2O),[212,213] 153-155 °C (H_2O),[205,207] 241-243 °C (EtOH/H_2O),[209] 242-243 °C (MeOH/H_2O),[204] 243-244 °C (EtOH),[210] 243-245 °C (EtOH/H_2O),[126] 248-249 °C (dec, MeOH)[211]]; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.14 (s, 1H), 6.78 (s, 1H), 6.71 (s, 1H), 6.66 (s, 1H), 5.07 (t, *J* = 8.4 Hz, 1H), 4.89 (d, *J* = 11.3 Hz, 1H), 4.12 (s, 3H), 3.93 (s, 3H), 3.89 (s, 9H), 3.77 (dd, *J* = 15.8, 7.4 Hz, 1H), 3.58 (dt, *J* = 11.8, 3.6 Hz, 1H), 3.48-3.30 (m, 1H), 3.20 (dd, *J* = 15.6, 9.6 Hz, 1H), 3.00 (br d, *J* = 19.0 Hz, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD, 75 MHz) 151.5 (C), 150.6 (C), 149.4 (C), 149.1 (C), 138.8 (C), 122.8 (C), 120.6 (C), 120.5 (C), 110.8 (CH), 109.1 (CH), 107.5 (CH), 101.4 (CH), 74.9 (CH), 58.6 (CH_2), 57.6 (CH_3), 56.2 (CH_3), 56.1 (CH_3), 55.8 (CH_3), 50.2 (CH_3), 36.7 (CH_2), 24.1 (CH_2); $[\alpha]^{27}_D = 0$ (*c* 0.2, EtOH) contrasted with a sample derived from natural cryptaustoline iodide $[\alpha]^{20}_D = -175$ (*c* 0.4, EtOH).[207] HRMS (ESI) *m*/*z* calcd for $C_{21}H_{26}NO_4$ ($[M - I]^+$): 356.1862. Found: 356.1855.



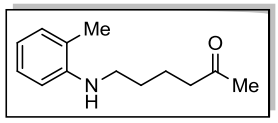
6-Methyl-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole (3.14), 9a-Methyl-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole (3.2o) and 6-(*o*-Tolylamino)hexan-2-one (3.15)

Prepared according to General Procedure C from imine **3.1o** (319 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 4 h reaction time. Flash chromatography (CH_2Cl_2/hexanes, 1:12) afforded a colourless oil (8 mg, in addition to 24 mg overlapping with **3.2o**, 4% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.04-7.00 (m, 2H), 6.55 (t, *J* = 7.3 Hz, 1H), 6.33 (d, *J* = 7.9 Hz, 1H), 3.95-3.86 (m, 1H), 3.58 (ddt, *J* = 10.7, 7.8, 2.9 Hz, 1H), 2.92 (dd, *J* = 14.8, 7.7 Hz, 1H), 2.50 (dd, *J* = 14.8, 10.4 Hz, 1H), 1.85-1.72 (m, 2H), 1.68-1.61 (m, 2H), 1.49-1.31 (m, 2H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 150.6 (C), 129.1 (C), 127.2 (CH), 124.3 (CH), 116.5 (CH), 105.4 (CH), 57.9 (CH), 45.9 (CH), 35.6 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 19.3 (CH_2), 12.1 (CH_3); An enantiomeric ratio of 50:50 was measured by chiral HPLC (OD-H, 1% *i*PrOH:hexanes, 1.0

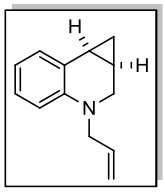
mL/min, t_{R1} = 4.9 min, t_{R2} = 5.6 min); HRMS (EI) m/z calcd for $C_{13}H_{17}N$ (M^+): 187.1361. Found: 187.1361.



N-fused indoline **3.2o** was isolated as the second product to elute from the above column and isolated as a colourless oil (48 mg, 26% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.04-6.99 (m, 2H), 6.56 (t, *J* = 7.0 Hz, 1H), 6.35 (d, *J* = 8.1 Hz, 1H), 3.47 (br dt, *J* = 14.2, 2.0 Hz, 1H), 3.13-3.03 (m, 1H), 2.80 (d, *J* = 15.1 Hz, 1H), 2.67 (d, *J* = 15.1 Hz, 1H), 1.71-1.58 (m, 3H), 1.50-1.42 (m, 2H), 1.36 (s, 3H), 1.33-1.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 150.9 (C), 128.4 (C), 127.2 (CH), 124.9 (CH), 116.6 (CH), 106.2 (CH), 63.8 (C), 44.4 (CH_2), 40.2 (CH_2), 33.2 (CH_2), 22.9 (CH_2), 21.5 (CH_3), 21.0 (CH_2); An enantiomeric ratio of 51:49 was measured by chiral HPLC (OD-H, hexanes, 1.0 mL/min, t_{R1} = 21.0 min, t_{R2} = 43.9 min); HRMS (EI) m/z calcd for $C_{13}H_{17}N$ (M^+): 187.1361. Found: 187.1361.



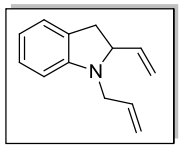
Secondary amine **3.15** was isolated as the third product to elute from the above column with ethyl acetate and isolated as a yellow oil.^{1}H NMR ($CDCl_3$, 300 MHz) 7.10 (t, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 3.54 (br s, 1H), 3.15 (t, *J* = 6.4 Hz, 2H), 2.48 (t, *J* = 6.7 Hz, 2H), 2.13 (s, 3H), 2.12 (s, 3H), 1.70-1.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.6 (C), 146.2 (C), 130.0 (CH), 127.1 (CH), 121.8 (C), 116.7 (CH), 109.5 (CH), 43.5 (CH_2), 43.2 (CH_2), 29.9 (CH_3), 29.0 (CH_2), 21.2 (CH_2), 17.4 (CH_3); HRMS (EI) *m/z* calcd for $C_{13}H_{19}ON$ (M^+): 205.1467. Found: 205.1471.



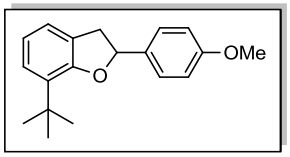
3-Allyl-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[c]quinoline (3.16) and 1-Allyl-2-vinylindoline (**3.2p**)

Prepared according to General Procedure C from imine **3.1p** (317 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 3 h reaction time. Flash chromatography (hexanes) afforded a pale orange oil (58 mg, 31% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.18 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.02 (dt, *J* = 7.8, 1.6 Hz, 1H), 6.67 (dt, *J* = 7.2, 0.6 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 5.86 (ddt, *J* = 15.9, 10.8, 5.6 Hz, 1H), 5.21 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.88 (app dd, *J* = 16.1, 5.3 Hz, 1H), 3.69 (app dd, *J* = 16.0, 5.8 Hz, 1H), 3.24 (dd, *J* = 10.7, 1.4 Hz, 1H), 3.14 (dd, *J* = 10.7, 2.1 Hz, 1H), 1.89 (dt, *J* = 8.5, 4.4 Hz, 1H), 1.78-1.70 (m, 1H), 1.29 (dd, *J* = 9.2, 4.6 Hz, 1H), 0.80 (dt, *J* = 8.3, 4.2 Hz, 1H); The relative

stereochemistry of the cyclopropanes was determined by NOESY (via irradiation of the benzylic proton at 1.89 ppm, assignment confirmed by combined HMQC and $^{1}H^{1}H$ COSY experiments, which showed an NOE with the other methine proton of the cyclopropane at 1.78 ppm; furthermore, irradiation of the methine proton at 1.78 ppm showed an NOE with the benzylic proton at 1.89 ppm). ^{13}C NMR ($CDCl_3$, 75 MHz) 143.3 (C), 133.9 (CH), 128.2 (CH), 126.9 (C), 125.7 (CH), 117.5 (CH), 117.0 (CH_2), 111.9 (CH), 53.3 (CH_2), 45.5 (CH_2), 19.4 (CH), 14.6 (CH), 7.8 (CH_2); An enantiomeric ratio of 59:41 was measured by chiral HPLC (AD-H, hexanes, 1.0 mL/min, t_{R1} = 5.0 min, t_{R2} = 6.2 min); HRMS (EI) *m*/*z* calcd for $C_{13}H_{15}N$ (M^+): 185.1204. Found: 185.1199.

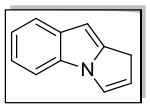


Indoline **3.2p** was second to elute from the column and isolated as an orange oil (53 mg, 29% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.06-7.01 (m, 2H), 6.63 (t, *J* = 7.4 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 5.93-5.76 (m, 2H), 5.28-5.13 (m, 4H), 4.05 (app q, *J* = 9.1 Hz, 1H), 3.82 (br dd, *J* = 16.2, 4.5 Hz, 1H), 3.56 (dd, *J* = 16.2, 6.8 Hz, 1H), 3.12 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.78 (dd, *J* = 15.5, 10.2 Hz, 1H). Further characterization was inhibited by the rapid decomposition of this indoline, plausibly by oxidation to the indole and then further to give a number of compounds.[169] A subsequent in-situ transformation in the crude reaction mixture may be an advisable direction to take in this regard.



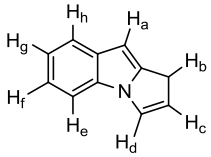
7-*tert*-Butyl-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (3.2u)

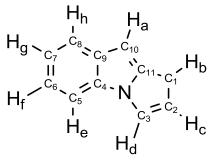
Prepared according to General Procedure C from imine **3.1u** (200 mg, 0.482 mmol) and Rh_2(5*S*-MEPY)$_4$ (3.7 mg, 0.0048 mmol); 2 h reaction time. Flash chromatography (CH_2Cl_2:hexanes, 1:9) afforded a pale yellow oil (119 mg, 88% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.31 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.80 (app t, *J* = 7.5 Hz, 1H), 5.69 (app t, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.54 (dd, *J* = 15.5, 9.4 Hz, 1H), 3.10 (dd, *J* = 15.5, 8.6 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.2 (C), 157.5 (C), 134.8 (C), 132.7 (C), 126.90 (CH), 126.89 (C), 124.8 (CH), 122.5 (CH), 120.2 (CH), 113.9 (CH), 83.2 (CH), 55.2 (CH_3), 38.5 (CH_2), 34.1 (C), 29.3 (CH_3); An enantiomeric ratio of 55:45 was measured by chiral HPLC (AD-H, 1% *i*PrOH:hexanes, 0.5 mL/min, t_{R1} = 8.7 min, t_{R2} = 9.0 min (*major*)). HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_2$ (M^+): 282.1620. Found: 282.1617.

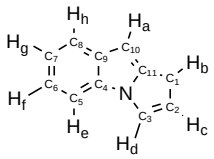


1*H*-Pyrrolo[1,2-*a*]indole (3.2w)

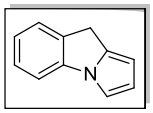
Prepared according to General Procedure C with the exception of the workup, from imine **3.1w** (200 mg, 0.700 mmol) and $Rh_2(5S\text{-MEPY})_4$ (5.4 mg, 0.0070 mmol); 2 h reaction time. After filtering the crude reaction mixture through a pad of celite (EtOAc) and concentrating in *vacuo,* obtained an orange solid (106 mg, 98% yield) that readily underwent isomerization to **3o** upon further purification attempts including silica gel, Davisil, Florisil, and neutral aluminum oxide. M.p. 60-62 °C; ^{1}H NMR (acetone-d_6, 300 MHz) 7.58-7.52 (m, 3H), 7.11 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.39 (s, 1H), 5.86 (dt, J = 4.6, 2.5 Hz, 1H), 3.53 (dd, J = 4.2, 2.0 Hz, 2H); ^{13}C NMR (acetone-d_6, 75 MHz) 143.5 (C), 133.3 (C), 130.7 (C), 127.2 (CH), 121.2 (CH), 121.1 (CH), 120.1 (CH), 114.4 (CH), 110.2 (CH), 95.9 (CH), 30.4 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{11}H_9N$ (M^+): 155.0735. Found: 155.0736.

^{1}H^{1}H COSY NMR (acetone-d_6, 300 MHz)	
proton(s) (δ)	exhibits coupling with (δ)
6.39 (H_a)	3.53 (H_b)
3.53 (H_b)	5.86 (H_c), 6.39 (H_a), 7.58-7.52 ($H_{d,e,h}$)
5.86 (H_c)	3.53 (H_b), 7.58-7.52 ($H_{d,e,h}$)
7.02 (H_f)	7.11 (H_g), 7.58-7.52 ($H_{d,e,h}$)
7.11 (H_g)	7.02 (H_f), 7.58-7.52 ($H_{d,e,h}$)
7.58-7.52 ($H_{d,e,h}$)	3.53 (H_b), 5.86 (H_c), 7.02 (H_f), 7.11 (H_g)

HMQC NMR (acetone-d_6, 300 MHz)	
proton(s) (δ)	exhibits coupling with (δ)
6.39 (H_a)	95.9 (C_{10})
3.53 (H_b)	30.4 (C_1)
5.86 (H_c)	114.4 (C_2)
7.02 (H_f)	120.1 (C_6)
7.11 (H_g)	121.2 (C_7)
7.58-7.52 ($H_{d,e,h}$)	127.2 (C_3), 110.2 (C_5), 121.1 (C_8)

HMBC NMR (acetone-d_6, 300 MHz)	
proton(s) (δ)	exhibits coupling with (δ)
6.39 (H_a)	130.7 (C_9), 133.3 (C_4), 143.5 (C_{11})
3.53 (H_b)	95.9 (C_{10}), 114.4 (C_2), 127.2 (C_3), 143.5 (C_{11})
5.86 (H_c)	-
7.02 (H_f)	110.2 (C_5), 133.3 (C_4)
7.11 (H_g)	121.1 (C_8), 130.7 (C_9)
7.58-7.52 ($H_{d,e,h}$)	95.9 (C_{10}), 120.1 (C_6), 121 (C_7/C_8), 130.7 (C_9), 133.3 (C_4)

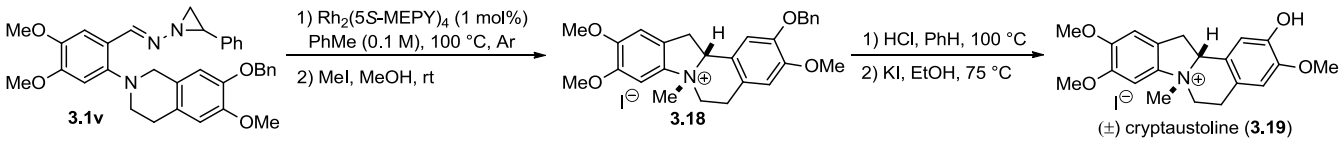
Note: The following reference misassigned a synthesis of **3.20** as **3.2w**, see: González-Pérez, P.; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2002**, *43*, 4765-4767.

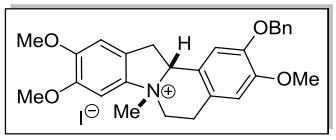


9*H*-Pyrrolo[1,2-*a*]indole (3.20)[214,215]

Prepared according to General Procedure C with the exception of the workup, from imine **3.1w** (287 mg, 1.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (7.7 mg, 0.010 mmol); 2 h reaction time. After filtering the crude reaction mixture through a pad of celite (EtOAc), concentrating in *vacuo*, and observing **3.2w** by ^{1}H NMR, proceeded to dissolve the crude in CH_2Cl_2 (10 mL) into a flask with a magnetic stir bar and added 1.00 g of silica gel and stirred for 1 h at rt. Next, the suspension was filtered over sand and concentrated before flash chromatography (hexanes) to obtain a white solid (129 mg, 83% yield). M.p. 86-88 °C [73-74 °C,[214] 87.5-90 °C[215]]; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.37 (d, *J* = 7.4 Hz, 1H), 7.29-7.24 (m, 2H), 7.08-7.05 (m, 2H), 6.36 (t, *J* = 3.0 Hz, 1H), 6.09 (dd, *J* = 3.1, 1.3 Hz, 1H), 3.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) 141.1 (C), 135.4 (C), 134.9 (C), 127.3 (CH), 125.8 (CH), 122.9 (CH), 113.0 (CH), 109.65 (CH), 109.63 (CH), 101.6 (CH), 28.9 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{11}H_9N$ (M^+): 155.0735. Found: 155.0736.

Total Synthesis of (±)-Cryptaustoline

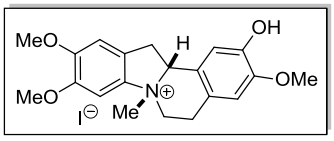




2-(Benzyloxy)-3,9,10-trimethoxy-7-methyl-6,7,12,12a-tetrahydro-5*H*-indolo[2,1-*a*]isoquinolin-7-ium iodide (3.18)[126,216,128 ,217,218]

In a glovebox, a Schlenk tube equipped with a magnetic stir bar was loaded with *N*-aziridinyl imine **3.1v** (528 mg, 0.960 mmol, 1 equiv), toluene (9.6 mL, 0.10 M; distilled over CaH_2 under N_2 and then degassed via freeze-pump-thaw method (3x)) and Rh_2(5*S*-MEPY)$_4$ (7.4 mg, 0.0096 mmol, 2 mol % Rh), then the Schlenk was sealed and capped with a rubber septum and brought out. The Schlenk tube's nitrogen atmosphere was then exchanged with argon before immersing into a pre-heated 100 °C oil bath. The reaction progress was monitored via TLC (EtOAc:hexanes:NEt_3, 3:6:1 respectfully), and when complete after 6 h the crude reaction mixture was passed through a short pad of silica gel (eluted with EtOAc) and concentrated. A ^{1}H NMR of the crude was taken at this point to determine the selectivity (11:1 indoline to indole) and then the readily oxidized crude reaction mixture was taken up in MeOH (3.55 mL) and an excess of iodomethane (3.55 mL) was added at room temperature according to Kametani's procedure.[126] After standing for 16 hours at room temperature, the contents of the vial had solidified as white fibrous crystals. Filtration and washing with cold MeOH (4 mL), afforded a white solid (162 mg) and a second crop obtained from concentration of the filtrate and recrystallization from EtOH afforded an additional 89 mg of **3.18** (251 mg total, 47% yield over 2 steps). M.p. 183-184 °C (dec, EtOH) [223-225 °C,[216] 224 °C,[128] 224-226 °C (dec, EtOH),[126] 226-228 °C,[218] 231-233 (dec)[217]]; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.11 (s, 1H), 7.43-7.28 (m, 5H), 6.75 (s, 1H), 6.73 (s, 1H), 6.68 (s, 1H), 5.16 (d, *J* = 13.0 Hz, 1H), 5.12 (d, *J* = 13.4 Hz, 1H), 5.01 (t, *J* = 8.5 Hz, 1H), 4.84 (br td, *J* = 12.2, 3.4 Hz, 1H), 4.10 (s, 3H), 3.89 (s, 6H), 3.88 (s, 3H), 3.64 (dd overlapping with ddd at 3.60 ppm, *J* = 15.8, 7.7 Hz, 1H), 3.60 (ddd, *J* = 20.6, 12.4, 3.9 Hz, 1H), 3.33 (ddd, *J* = 17.2, 11.3, 4.9 Hz, 1H), 3.08 (dd, *J* = 15.8, 9.6 Hz, 1H), 2.98 (br td, *J* =

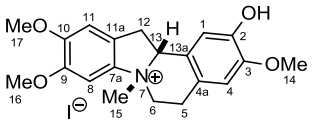
17.8, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 151.6 (C), 151.1 (C), 150.5 (C), 148.3 (C), 139.2 (C), 136.4 (C), 128.7 (CH), 128.1 (CH), 127.4 (CH), 122.1 (C), 121.5 (C), 120.4 (C), 112.1 (CH), 111.6 (CH), 107.3 (CH), 102.7 (CH), 75.0 (CH), 71.5 (CH_2), 58.6 (CH_3), 58.5 (CH_2), 56.4 (CH_3), 56.2 (CH_3), 50.9 (CH_3), 36.9 (CH_2), 24.4 (CH_2); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{30}NO_4$ ($[M - I]^+$): 432.2175. Found: 432.2168.

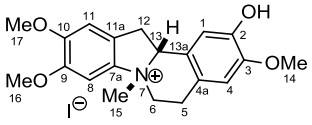


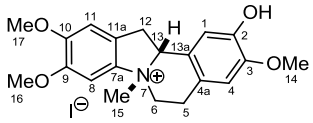
(±)-**Cryptaustoline (3.19)**[126,216,219,165,220,221]

The following 2 steps to complete the synthesis of (±)-cryptaustoline were performed according to Kametani's procedure:[126] To an oven dried round bottom flask equipped with a magnetic stir bar was added **3.18** (162 mg, 0.289 mmol), benzene (6.48 mL) and 12 M HCl (6.48 mL). The flask was then fitted with a reflux condenser and stirred for 3 h in a pre-heated 100 °C oil bath. After 3 h, the flask was allowed to cool to room temperature before placing in a freezer (-20 °C) for 1 h and then filtering. The pale yellow filter cake was washed with cold water and benzene, then dried under high vacuum. This material was then transferred to an oven dried round bottom flask equipped with a magnetic stir bar, followed by the addition of EtOH (6.48 mL) and potassium iodide (162 mg, 0.976 mmol). The flask was then sealed with a rubber septum and stirred in a pre-heated 75 °C oil bath for 1 h. The contents of the flask were then filtered and washed with boiling EtOH. Next, the filtrate was concentrated to dryness and the resultant pale yellow solid was recrystallized twice from dilute EtOH to obtain a pale yellow solid (95 mg, 70% yield over 2 steps). M.p. 223-224 °C (dec, EtOH) [214 °C (dec, MeOH),[205,207] 250-252 °C,[216] 255-256 °C,[221] 256-258 °C,[128] 259-260 °C,[220] 260 °C (dec, EtOH),[126] 261-263 °C (dec, EtOH)[218]]; ^{1}H NMR ($CDCl_3$/TFA, 10:1 respectively, 500 MHz) 7.37 (s, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 6.76 (s, 1H), 5.04 (app t, *J* = 7.1 Hz, 1H), 4.13 (br d, *J* = 10.7 Hz, 1H), 4.00 (s, 3H), 3.92 (s, 6H), 3.75 (dd, *J* = 15.7, 6.2 Hz, 1H), 3.63 (s, 3H), 3.63-3.57 (dd obscured with singlet at 3.63, 1H), 3.32 (app t, *J* = 7.4 Hz, 1H), 3.22 (dd, *J* = 15.4, 9.2 Hz, 1H), 3.05 (br d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$/TFA, 10:1 respectively, 125 MHz) 151.6 (C), 150.5 (C), 147.7 (C), 145.3 (C), 138.9 (C), 123.6 (C), 120.7 (C), 120.5 (C), 112.4 (CH), 111.0 (CH), 108.4 (CH), 101.1 (CH), 75.6 (CH), 59.8 (CH_2), 57.9 (CH_3), 56.6 (CH_3), 56.3 (CH_3), 50.8 (CH_3), 36.9 (CH_2), 24.8 (CH_2); $[\alpha]^{27}{}_D = 0$ (*c* 0.2, EtOH) contrasted with natural cryptaustoline

iodide $[\alpha]^{20}_{D}$ = -151 (*c* 0.4, EtOH).[207] HRMS (ESI) *m*/*z* calcd for $C_{20}H_{24}NO_4$ ($[M - I]^+$): 342.1705. Found: 342.1704.

$^1H^1H$ COSY NMR (CDCl$_3$/TFA, 10:1, 500 MHz)	
proton(s) (δ)	exhibits coupling with (δ)
7.37 (H_8)	-
6.90 (H_{11})	-
6.82 (H_4)	-
6.76 (H_1)	-
5.04 (H_{13})	3.75 ($H_{12\alpha}$), 3.22 ($H_{12\beta}$)
4.13 ($H_{6\alpha}$)	3.63-3.57 ($H_{6\beta}$)
4.00 (H_{16})	-
3.92 (H_{14}, H_{17})	-
3.75 ($H_{12\alpha}$)	5.04 (H_{13}), 3.22 ($H_{12\beta}$)
3.63 (H_{15})	-
3.63-3.57 ($H_{6\beta}$)	4.13 ($H_{6\alpha}$), 3.32 ($H_{5\alpha}$)
3.32 ($H_{5\alpha}$)	3.63-3.57 ($H_{6\beta}$), 3.05 ($H_{5\beta}$)
3.22 ($H_{12\beta}$)	5.04 (H_{13}), 3.75 ($H_{12\alpha}$)
3.05 ($H_{5\beta}$)	3.32 ($H_{5\alpha}$)

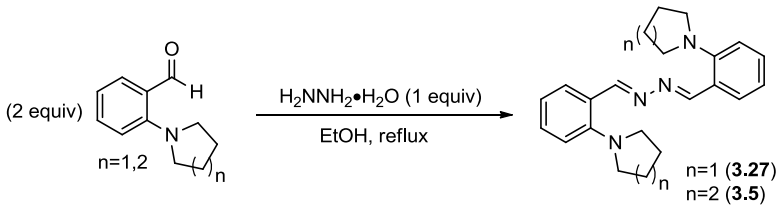
HMQC NMR (CDCl$_3$/TFA, 10:1, 500 MHz)	
proton(s) (δ)	exhibits coupling with (δ)
7.37 (H_8)	101.1 (C_8)
6.90 (H_{11})	108.4 (C_{11})
6.82 (H_4)	112.4 (C_4)
6.76 (H_1)	111.0 (C_1)
5.04 (H_{13})	75.6 (C_{13})
4.13 ($H_{6\alpha}$)	59.8 (C_6)
4.00 (H_{16})	57.9 (C_{16})
3.92 (H_{14}, H_{17})	56.6, 56.3 (C_{14}, C_{17})
3.75 ($H_{12\alpha}$)	36.9 (C_{12})
3.63 (H_{15})	50.8 (C_{15})
3.63-3.57 ($H_{6\beta}$)	59.8 (C_6)
3.32 ($H_{5\alpha}$)	24.8 (C_5)
3.22 ($H_{12\beta}$)	36.9 (C_{12})
3.05 ($H_{5\beta}$)	24.8 (C_5)

HMBC NMR ($CDCl_3$/TFA, 10:1, 500 MHz)	
proton(s) (δ)	exhibits coupling with (δ)
7.37 (H_8)	151.6 (C_{10}), 138.9 (C_{7a}), 123.6 (C_{11a})
6.90 (H_{11})	150.5 (C_9), 138.9 (C_{7a}), 123.6 (C_{11a}), 36.9 (C_{12})
6.82 (H_4)	147.7 (C_3), 145.3 (C_2), 120.7 (C_{13a}), 75.6 (C_{13})
6.76 (H_1)	147.7 (C_3), 145.3 (C_2) , 120.7 (C_{13a}), 75.6 (C_{13}), 24.8 (C_5)
5.04 (H_{13})	120.7 (C_{13a}), 112.4 (C_4), 59.8 (C_6), 50.8 (C_{15}), 36.9 (C_{12})
4.13 ($H_{6\alpha}$)	-
4.00 (H_{16})	150.5 (C_9)
3.92 (H_{14}, H_{17})	151.6 (C_{10}), 147.7 (C_3)
3.75 ($H_{12\alpha}$)	138.9 (C_{7a}), 123.6 (C_{11a})
3.63-3.57 (H_{15}, $H_{6\beta}$)	138.9 (C_{7a}), 75.6 (C_{13}), 59.8 (C_6)
3.32 ($H_{5\alpha}$)	-
3.22 ($H_{12\beta}$)	138.9 (C_{7a}), 123.6 (C_{11a}), 120.7 (C_{13a}), 75.6 (C_{13})
3.05 ($H_{5\beta}$)	-

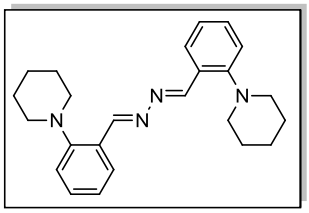
Comparison of ^{1}H NMR data of (±)-Cryptaustoline			
Position	Synthetic (Hanaoka)[216] (solvent and MHz not indicated, also no assignments were given; however, this data was said to be identical to an authentic sample obtained)	Synthetic (Takano)[165] $CDCl_3$/TFA (~10:1), 500 MHz	Synthetic $CDCl_3$/TFA (10:1), 500 MHz
1	6.77 (s)	6.70 (s, not assigned)	6.76 (s)
4	6.83 (s)	6.80 (s, not assigned)	6.82 (s)
5	not provided	3.36 (ddd, *J* = 17, 12, 4 Hz) α 3.06 (br d, *J* = 17 Hz) β	3.32 (app t, *J* = 7.4 Hz) α 3.05 (br d, *J* = 15.9 Hz) β
6	not provided	4.19 (dt, *J* = 14, 4 Hz) α 3.60 (dd, *J* = 14, 12 Hz) β	4.13 (br d, *J* = 10.7 Hz) α 3.63-3.57 (obscured by singlet) β
7 (NMe)	3.65 (s)	3.66 (s)	3.63 (s)
8	7.41 (s)	7.41 (s)	7.37 (s)
11	6.91 (s)	6.89 (s, not assigned)	6.90 (s)
12	not provided	3.75 (dd, *J* = 15, 8 Hz) α 3.23 (dd, *J* = 15, 10 Hz) β	3.75 (dd, *J* = 15.7, 6.2 Hz) α 3.22 (dd, *J* = 15.4, 9.2 Hz) β
13	5.04 (t, *J* = 8 Hz)	5.03 (dd, *J* = 10, 8 Hz)	5.04 (app t, *J* = 7.1 Hz)
OMe's	4.02 (s, OMe), 3.93 (s, OMe x 2)	4.04 (s, OMe), 3.94 (s, OMe x 2)	4.00 (s, OMe), 3.92 (s, OMe x 2)

Synthesis of Byproducts

General Procedure D – Aromatic Aldehyde Azine Formation

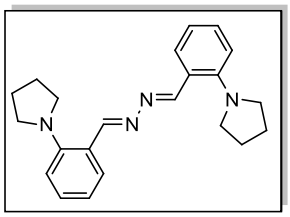


The following compounds were prepared according to Suschitzky and coworkers.[222] A round bottom flask equipped with a magnetic stir bar was charged with aldehyde (2 equiv) and hydrazine hydrate (1 equiv) in EtOH (0.2 M), fitted with a reflux condenser and immersed in a 100 °C oil bath for 20 min. On cooling the azine crystallized out. An additional recrystallization from EtOH was performed if necessary.



1,2-Bis(2-(piperidin-1-yl)benzylidene)hydrazine (3.5)[222]

Prepared according to General Procedure D from 2-(piperidin-1-yl)benzaldehyde (500 mg, 2.60 mmol) and hydrazine monohydrate (64 μL, 1.3 mmol). Filtration afforded yellow crystals (264 mg, 53% yield). M.p. 159-160 °C (EtOH) [160 °C];[222] ^{1}H NMR ($CDCl_3$, 300 MHz) 8.95 (s, 2H), 8.08 (d, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.08-7.06 (m, 4H), 2.94 (t, *J* = 5.0 Hz, 8H), 1.76-1.73 (m, 8H), 1.58-1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.5 (CH), 154.8 (C), 131.4 (CH), 127.9 (CH), 127.8 (C), 122.6 (CH), 119.0 (CH), 54.8 (CH_2), 26.3 (CH_2), 24.2 (CH_2); HRMS (ESI) *m/z* calcd for $C_{24}H_{31}N_4$ ($[M + H]^+$): 375.2549. Found: 375.2540.

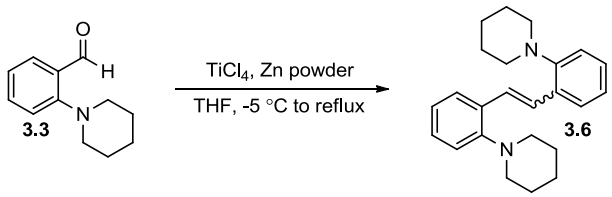


1,2-Bis(2-(pyrrolidin-1-yl)benzylidene)hydrazine (3.27)[222]

Prepared according to General Procedure D from 2-(pyrrolidin-1-yl)benzaldehyde (5.00 g, 28.5 mmol) and hydrazine monohydrate (0.88 mL, 14 mmol). A second recrystallization from EtOH afforded yellow needles (3.91 g, 79% yield). M.p. 146-147 °C (EtOH) [140 °C];[222] ^{1}H NMR ($CDCl_3$, 300 MHz) 8.99 (s, 2H), 7.89 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.27 (dt, *J* = 7.7, 1.6 Hz, 2H), 6.88-6.84 (m, 4H), 3.35-3.31 (m, 8H), 1.96-1.91 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) 161.4 (CH), 150.4 (C), 131.1

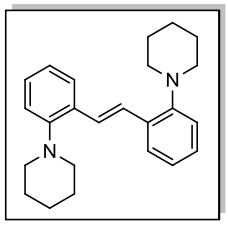
(CH), 129.3 (CH), 122.9 (C), 119.0 (CH), 115.3 (CH), 52.8 (CH_2), 25.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}N_4$ ($[M + H]^+$): 347.2236. Found: 347.2231.

Procedure for McMurry Coupling



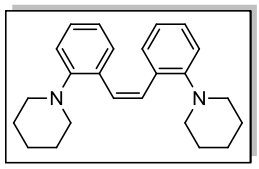
(*E*)-1-(2-(2-(Piperidin-1-yl)styryl)phenyl)piperidine (3.6*E*) and (*Z*)-1-(2-(2-(Piperidin-1-yl)styryl)phenyl)piperidine (3.6*Z*)[145b,199]

The procedure is based on the method reported by Duan and coworkers:[223] In a glovebox, freshly purified Zn powder (654 mg, 10.0 mmol) was added to a 100 mL round bottom flask equipped with a magnetic stir bar. The flask was removed from the glovebox and put under an argon atmosphere and THF (33 mL) was added. The resulting mixture was cooled in an ice/salt bath (-5 °C to 0 °C) and distilled $TiCl_4$ (0.55 mL, 5 mmol) was slowly added. The suspension was warmed to room temperature and stirred for 30 min, then heated at reflux for 2.5 h. The mixture was then cooled in an ice/salt bath (-5 °C to 0 °C) and a solution of aldehyde **3.3** (378 mg, 2.00 mmol in 12 mL THF) was slowly added. After addition, the reaction was refluxed and monitored by TLC. After 3 h, the reaction was worked up by cooling to room temperature and quenching with 10% $NaHCO_3$ solution (30 mL). The organic layer was extracted with Et_2O (2x30 mL), then washed with sat. brine solution (30 mL), before dried over $MgSO_4$, filtered and concentrated. Flash chromatography (CH_2Cl_2) produced a white solid which was a 1.3:1 mixture of *E*:*Z*-alkene **3.6*E*** and **3.6*Z*** respectively (86 mg, 25% yield). Further purification enabled separation of the isomers for characterization (detailed below).



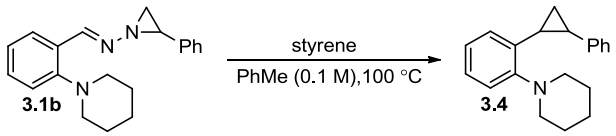
After the above initial column, **3.6*E*** was separated by recrystallization of the alkene mixture from hexanes and was isolated as a white solid. M.p. (hexanes) 174-175 °C (172 °C, alkene geometry not specified);[199] ^{1}H NMR ($CDCl_3$, 300 MHz) 7.64 (d, *J* = 7.5 Hz, 2H), 7.41 (s, 2H), 7.21 (t, *J* = 7.3 Hz, 2H), 7.06-7.00 (m, 4H), 2.92 (t, *J* = 5.0 Hz, 8H), 1.78-1.71 (m, 8H), 1.61-1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 152.2 (C), 132.4 (C), 127.8 (CH), 126.4 (CH), 125.3

(CH), 122.5 (CH), 118.6 (CH), 53.9 (CH_2), 26.6 (CH_2), 24.4 (CH_2); HRMS (EI) *m/z* calcd for $C_{24}H_{30}N_2$ (M^+): 346.2409. Found: 346.2405.



The filtrate of the above recrystallization was flashed on a column prepared with 1.5% $AgNO_3$ on silica and eluted on a gradient (CH_2Cl_2:hexanes, 1:3 to CH_2Cl_2 to EtOAc:hexanes, 1:5), to provide **3.6*Z*** as the second isomer to elute which was isolated as a white solid. M.p. 144-145 °C (172 °C, alkene geometry not specified);[199] ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25 (dd slightly overlapping with $CHCl_3$, *J* = 7.4, 1.5 Hz, 2H), 7.13 (dt, *J* = 7.7, 1.6 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.72 (dt, *J* = 7.5, 1.0 Hz, 2H), 6.66 (s, 2H), 3.01 (t, *J* = 5.1 Hz, 8H), 1.75-1.68 (m, 8H), 1.61-1.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 152.6 (C), 131.0 (C), 129.6 (CH), 127.6 (CH), 126.0 (CH), 121.2 (CH), 117.8 (CH), 53.4 (CH_2), 26.6 (CH_2), 24.4 (CH_2); HRMS (EI) *m/z* calcd for $C_{24}H_{30}N_2$ (M^+): 346.2409. Found: 346.2408.

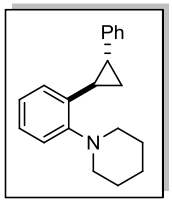
Procedure for the Cyclopropanation of Styrene



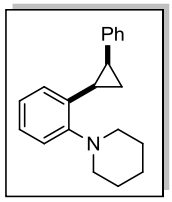
trans-1-(2-(2-Phenylcyclopropyl)phenyl)piperidine (3.4*t*) and _cis_-1-(2-(2-Phenylcyclopropyl)phenyl)piperidine (3.4*c*)

A 20 mL screw capped sample vial was equipped with a magnetic stir bar, *N*-(2-(Piperidin-1-yl)benzylidene)-2-phenylaziridin-1-amine **3.1b** (100 mg, 0.327 mmol, 1 equiv), toluene (3.30 mL, 0.1 M), and styrene containing 10-15 ppm 4-*tert*-butylcatechol as inhibitor (0.38 mL, 10 equiv), then the vial was capped and immersed into a pre-heated 100 °C oil bath. The reaction progress was monitored via TLC (EtOAc:hexanes, 1:5), and after 4 hours was deemed complete and concentrated. A crude ^{1}H NMR was taken at this point to determine the selectivity and then the cyclopropanes were purified by flash chromatography (toluene:hexanes, 1:2). The first column yielded the trans and cis cyclopropanes **3.4*t*** and **3.4*c*** as a 1.6:1 mixture respectively in high purity (71 mg, 78% yield). Additional flash chromatography was necessary to separate the isomers for characterization as detailed below. The relative stereochemistry of the cyclopropanes

was determined by NOESY (via irradiation of the benzylic protons in which the cis benzylic proton showed an NOE).



After the above initial column, an additional column (toluene:hexanes, 1:9) separated **3.4*t*** which was the first isomer to elute and was isolated as a white solid. M.p. 67-69 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28-7.24 (m, 2H), 7.16-7.13 (m, 4H), 7.01-6.96 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 2.93-2.89 (m, 2H), 2.74-2.71 (m, 2H), 2.58 (dt, *J* = 8.9, 5.9 Hz, 1H), 1.99 (dt, *J* = 8.8, 5.3 Hz, 1H), 1.56 (dt, *J* = 8.6, 5.9 Hz, 1H), 1.44-1.38 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) 153.3 (C), 143.0 (C), 136.2 (C), 128.3 (CH), 126.1 (CH), 125.5 (CH), 125.3 (CH), 123.3 (CH), 122.6 (CH), 118.6 (CH), 53.6 (CH_2), 28.8 (CH), 26.3 (CH_2), 24.31 (CH), 24.28 (CH_2), 17.4 (CH_2); HRMS (EI) *m/z* calcd for $C_{20}H_{23}N$ (M^+): 277.1830. Found: 277.1829.



After the second column above, the overlapping fractions were dry packed and a third column (EtOAc:hexanes, 1:99) separated **3.4*c*** which was the second isomer to elute and was isolated as a clear film. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.07-7.04 (m, 4H), 6.90 (d, *J* = 6.7 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.81-6.74 (m, 2H), 2.85-2.66 (m, 5H), 2.51 (dt, *J* = 8.8, 6.4 Hz, 1H), 1.74-1.61 (m, 4H), 1.57-1.37 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 154.4 (C), 139.0 (C), 132.0 (C), 128.8 (CH), 128.3 (CH), 127.4 (CH), 126.4 (CH), 125.3 (CH), 121.8 (CH), 118.7 (CH), 53.2 (CH_2), 26.6 (CH_2), 24.9 (CH), 24.4 (CH_2), 21.9 (CH), 12.1 (CH_2); HRMS (EI) *m/z* calcd for $C_{20}H_{23}N$ (M^+): 277.1830. Found: 277.1825.

Chapter 4. Carbon-Based Leaving Group in Substitution Reactions - Functionalization of sp^3-Hybridized Quaternary and Tertiary Benzylic Carbon Centers

4.1. Introduction

The direct modification/functionalization of sp^3-hybridized carbon centers through cleavage of unstrained C-C sigma bonds remains a challenging transformation in organic synthesis. The most elusive of which has been the cleavage of unstrained Csp^3-Csp^3 bonds. This chapter looks at the development of such a reaction which employs Meldrum's acid as a leaving group.

The ability of an entity to function as a leaving group is reflective of the strength of its conjugate acid as well as its resulting stability. It follows that conjugate bases of strong acids are good leaving groups. Additional factors that are known to increase the leaving group ability of an entity are the relief of ring strain and gain of aromaticity.[224] Carbon-based leaving groups, although likely not the first leaving groups that come to mind, have proven integral in synthesis, including in well-known reactions such as the haloform reaction and retro-aldol. It is intuitive to compare the pK_as of selected carbon acids at this point to the conjugate acids of some traditional leaving groups (see Figure 4.1).[225]

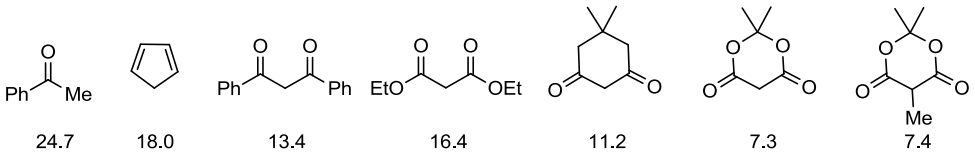


Figure 4.1. Spotlight on Carbon Acids (pK_as measured in DMSO)

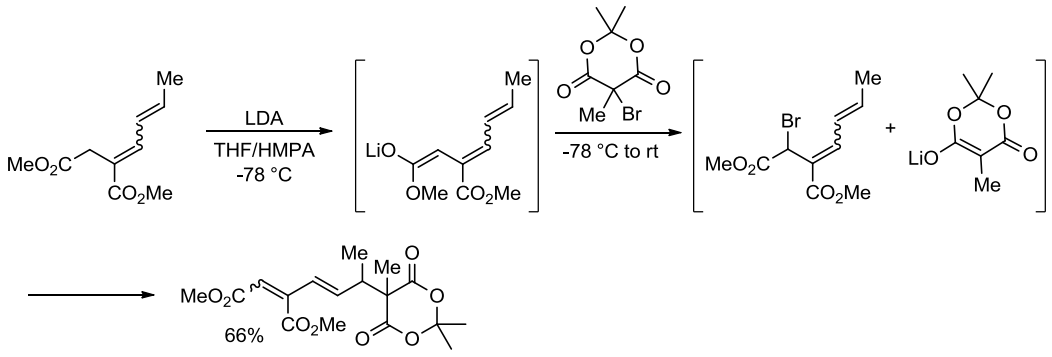
Particularly noteworthy is the high acidity of Meldrum's acid, the pK_a of which is essentially equivalent to that of acetic acid when measured in H_2O (4.83[226] vs 4.75[225] respectively) and magnitudes more acidic than related cyclic and acyclic 1,3-dicarbonyl compounds. Many experimental and computational papers have dealt with trying to rationalize

the high acidity of Meldrum's acid and attribution to the E conformation of the esters and the restricted rotation imparted by the 6-membered ring have been most prevalent.[226,227,228] Most recently, Deslongchamps presented a qualitative model to account for the observed acidity suggesting the oxonium resonance contributors of the E esters to be of utmost importance to minimize destabilizing eclipsing interactions and in doing so align the alpha C-H bonds for proton abstraction and delocalization.[229]

What follows is a survey of strategic implementations of carbon-based leaving groups in synthesis for the cleavage of unstrained Csp^3-Csp^3 bonds with an emphasis on the progression of the utilization of Meldrum's acid for this fitting role.

An early example of the use of Meldrum's acid as a leaving group is shown in Scheme 4.1. Trost reported a selective, remote alkylation of polyenolates using 5-bromo-5-methyl-Meldrum's acid and he coined this strategy "transfer alkylation".[230] The initially formed trienolate attacks the effective bromonium source displacing the anion of 5-methyl-Meldrum's acid which subsequently undergoes a 1,6-Michael addition resulting in the displacement of bromide in an S_N2' fashion. Following this report 5-bromo-5-methyl-Meldrum's acid has also shown to be an advantageous brominating reagent in certain cases.[231]

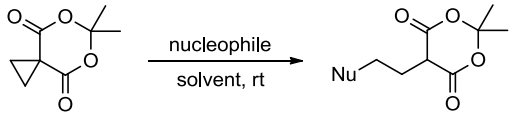
Scheme 4.1. Trost's Transfer Alkylation with 5-Bromo-5-methyl-Meldrum's Acid



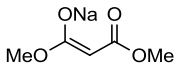
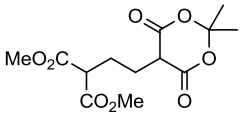
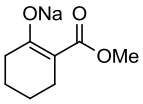
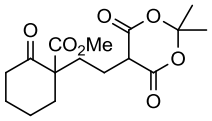
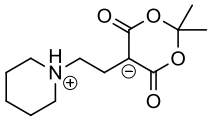
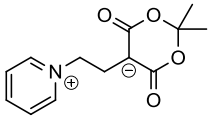
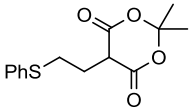
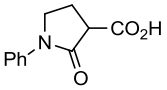
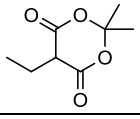
Danishefsky and Singh[227] described a series of facile C-C bond cleavages of Meldrum's acid cyclopropane **4.1** using a variety of nucleophiles (see Table 4.1) at room temperature. Interestingly, reaction with aniline delivered a lactam acid (entry 6) which could arise from the

initial opening of the cyclopropane followed by proton transfer then attack on a carbonyl with loss of acetone and carbon dioxide. The authors also found Meldrum's acid to be a superior leaving group to the analogous diethylmalonate cyclopropane which was inert under the reported hydrogenolysis conditions, and required higher temperature and afforded lower yields for the alternate nucleophiles surveyed. Musso subsequently reported a very similar hydrogenolysis reaction of **4.L1** (changed the solvent from EtOAc to MeOH) and also obtained 5-ethyl Meldrum's acid as the major product.[232]

Table 4.1. Danishefsky's Ring Opening Reactions of a Meldrum's Acid Cyclopropane

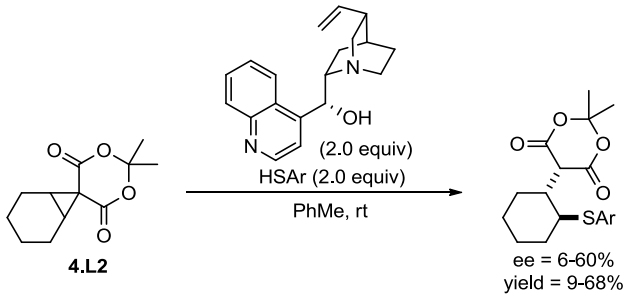


4.L1

entry	nucleophile	product	yield (%)
1			71
2			88
3	piperidine		quant.
4	pyridine		92
5	sodium thiophenoxide		85
6	aniline		quant.
7	Pd/C, H_2 (1 atm)		quant.

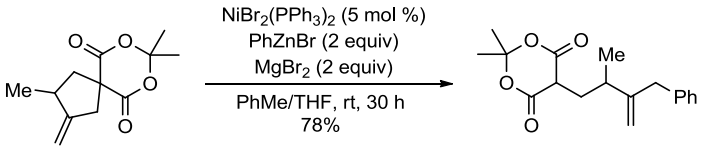
The desymmetrization of Meldrum's acid cyclopropane **4.L2** was later met with some success by the groups of Scheffold[233] and Müller.[234] Müller found that the cyclopropane could be desymmetrized with the chiral ion pair formed from thiophenols and cinchonidine (Scheme 4.2).

Scheme 4.2. Desymmetrization of a Meldrum's Acid Cyclopropane



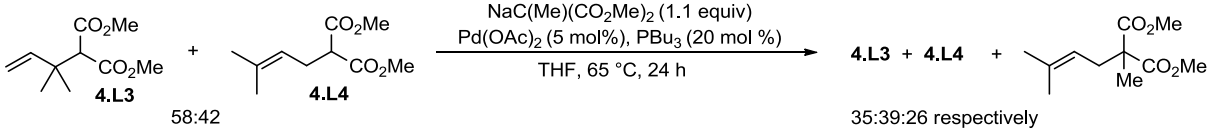
The groups of Oshima and Yorimitsu have also demonstrated that Meldrum's acid can function as an effective leaving group in a nickel catalyzed substitution reaction using an arylzinc nucleophile to open a 5-membered carbocycle (Scheme 4.3). Of note, the arylzinc reagent was prepared in situ from PhMgBr and $ZnBr_2$; optimization studies revealed that activation of the carbonyl leaving group by $MgBr_2$ was essential to a high yielding reaction.[235] The mechanism was postulated to proceed via oxidative addition (facilitated by Lewis acid complexation), transmetallation of the phenylzinc to the nickel complex followed by reductive elimination and then protonolysis of the zinc enolate in the workup.

Scheme 4.3. Nickel Catalyzed Displacement of Meldrum's Acid



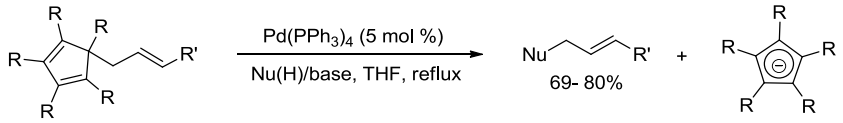
Prior to the previous report mentioned, it was demonstrated that malonates were capable as leaving groups in the Tsuji-Trost reaction (Scheme 4.4).[236] Analogous reports were made soon after using malonates,[237] 1,3-diketone[238] and 5-methyl Meldrum's acid[239] as leaving groups to effect very similar substitutions and isomerizations.

Scheme 4.4. Tsuji-Trost Reaction with a 1,3-Dicarbonyl Leaving Group



A related protocol was later developed using a cyclopentadiene as a carbon based leaving group[240] due to its highly stabilized carbanion as a result of aromatization as well as the ability to tune the sterics and electronics of cyclopentadienes (Scheme 4.5). The Tsuji-Trost allylation of allylcyclopentadienes proceeded in good yields. Interestingly, the anion of the pentaphenyl Cp was able to substitute the (*p*-AcPh)$_5$Cp owing to the difference in pK_a (the pK_a of Ph$_5$CpH is 12.5 as compared to 18.0 for CpH).[225]

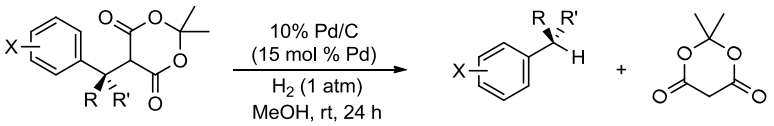
Scheme 4.5. Tsuji-Trost reaction with a Cyclopentadiene Leaving Group



R = *p*-AcPh;
Nu(H)/base = $(EtO_2C)CHMe/NaH$; $BnNHMe/Cs_2CO_3$; $Ph_5CpH/nBuLi$

In 2009 the Fillion group reported the serendipitous discovery that Meldrum's acid functions as a highly effective and convenient leaving group in the Pd-catalyzed hydrogenolysis of quaternary benzyl Meldrum's acids.[241] The reaction results in the cleavage of an unstrained benzylic Csp^3-Csp^3 bond and the formation of a Csp^3-H bond stereospecifically. A "loose" S_N2 mechanism yielding a benzylic organopalladium intermediate was suggested on the basis of the stereochemical outcome (inversion) as well as the dependency on substrate substitution to stabilize a significant amount of positive charge in the transition state (Table 4.2). The slight erosion in enantioenrichment can be rationalized to occur through β-hydride elimination of the common intermediate **4.L5** followed by hydrogenation of the resulting alkenes, or alternatively through a competitive S_N1 process.

Table 4.2. Fillion's Hydrogenolysis of Benzyl Meldrum's Acids



entry	R; R'	X	er of **1** (R/S)	er of **2** (S/R)	inversion (%)	yield (%)[a]
1	R = R' = Me	4-(OC_8H_{17})	/	/	/	76
2	R = Et; R' = Me	4-(OC_8H_{17})	98.5:1.5	96:4	97	93
3	R = R' = Me	4-Ph	/	/	/	71
4	R = Et; R' = Me	4-Ph	98:2	90.5:9.5	92	51
5	R = R' = Me	2-(OC_8H_{17})	/	/	/	65
6	R = R' = Me	3-(OC_8H_{17})	/	/	/	N/A[b]
7	R = H; R' = Me	4-(OC_8H_{17})	/	/	/	N/A [c]

[a] Isolated yields after chromatography. [b] A conversion of 9% was reported with starting material prevailing. [c] The substrate was found to be inert to the hydrogenolysis conditions.

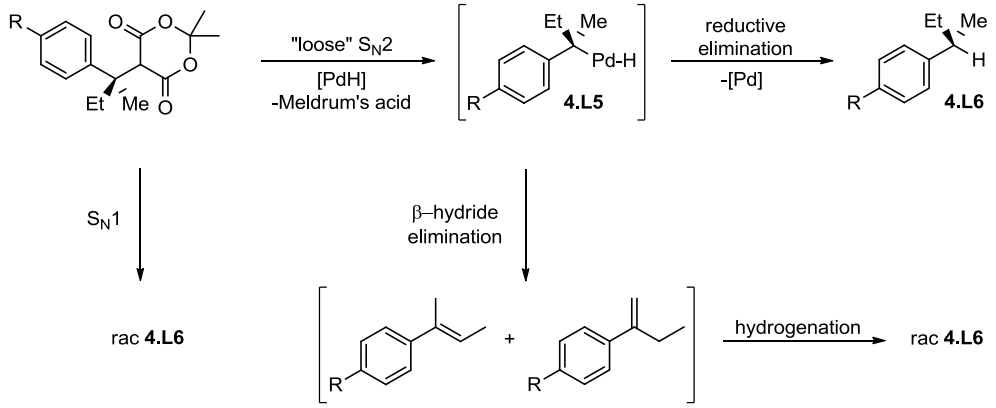
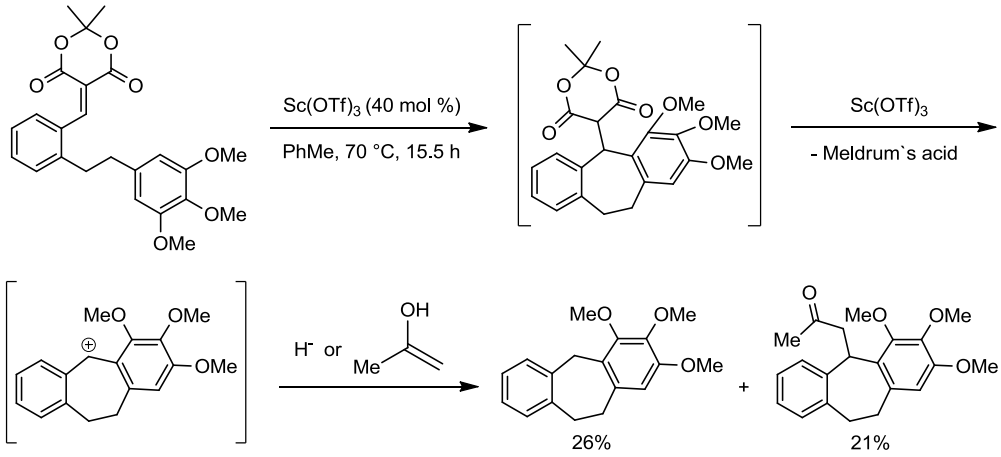


Figure 4.2. Proposed Mechanism(s)

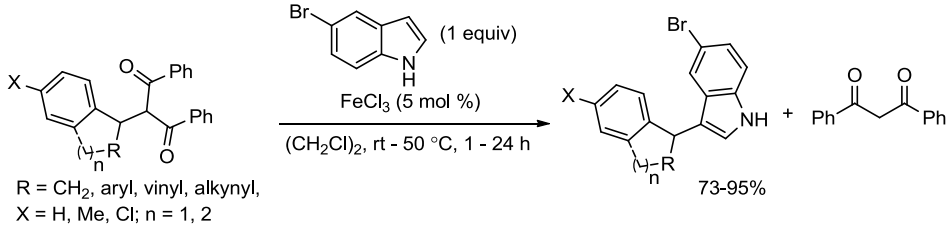
During the course of the development of a domino reaction the Fillion group also reported an interesting, unoptimized competing reaction pathway in which $Sc(OTf)_3$ promoted the cleavage of tertiary diaryl Meldrum`s acids (generated in situ).[104] Meldrum`s acid was displaced by a hydride or acetone (Scheme 4.6; for details see Chapter 3) and the reaction was proposed to go through a stabilized carbocation.

Scheme 4.6. Substitutions of Tertiary Diaryl Meldrum`s Acid



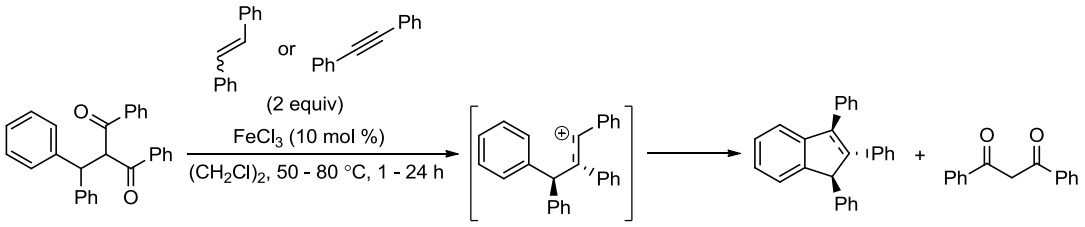
Subsequently in 2011, Li's group described a related, Fe-catalyzed substitution at tertiary sp^3-hybridized diaryl, benzylic or allylic carbon centers, with indoles and electron rich alkenes, in which 1,3-diphenylpropane-1,3-dione acted as a leaving group (Scheme 4.7).[242] They postulated the C-C bond cleavage arose from iron (III) chloride complexing with the carbonyls of the 1,3-diphenylpropane-1,3-dione moiety resulting in the formation of a stabilized carbocation intermediate. That step was found to be reversible or it could be trapped by other nucleophiles.

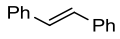
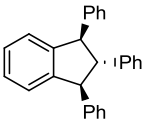
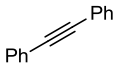
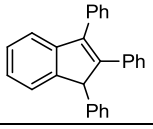
Scheme 4.7. Li's Substitutions with Dibenzoylmethane as a Leaving Group



Li's group also demonstrated the stereoselective formation of dihydroindenes as well as indene synthesis by employing stilbenes and diphenylacetylene respectively (Table 4.3). These reactions with weaker nucleophiles (relative to 5-bromoindole) proceeded in good yield having increased the catalyst loading and temperature. The results with the stilbene isomers indicated a stepwise cyclization proceeding through a cationic intermediate and leading to the thermodynamically most stable product.

Table 4.3. Li's Synthesis of Indene Derivatives via C-C Bond Scission



entry	nucleophile	product	yield (%)
1			85
2			61
3			80

4.2. Proposal

The proposal is to develop conditions to expand the Csp^3-Csp^3 cleavage of unstrained, benzyl Meldrum's acid derivatives to incorporate other nucleophiles (beyond Nu = H) and then to study the reaction mechanism through analysis of scope and stereochemistry. This proposal is of particular interest to the Fillion group, which has had much success accessing enantioenriched benzylic Meldrum's acid derivatives including the challenging quaternary center structural motif,[95] as the proposed methodology would allow for alternate functionalizations of the benzylic position and render the Meldrum's acid an auxiliary. Bearing the previous presented literature in mind, the proposed reaction was thought to be accomplished through either the use of a Lewis acid promoted cleavage or alternatively, through a carbon activation approach with a transition metal. This chapter will describe the results attained with the former approach (Figure 4.3).

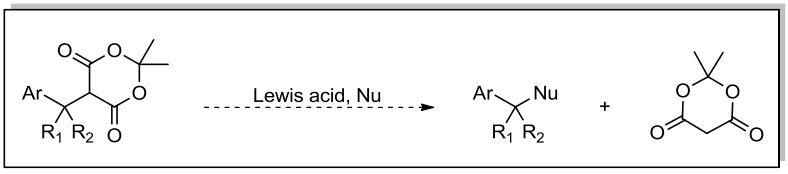
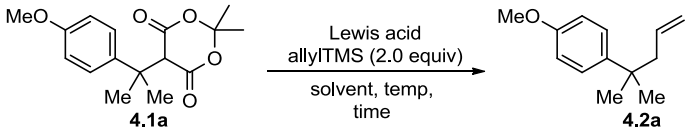


Figure 4.3. Proposal for Meldrum's Acid Substitution

4.3. Results and Discussion

Based on the Fillion group's hydrogenolysis study,[241] quaternary benzyl Meldrum's acid **4.1a** bearing a 4-alkoxy substituted aromatic was selected as a logical starting point to survey applicable reaction conditions for the desired Lewis acid promoted substitution as it had been demonstrated to provide sufficient stabilization for a developing partial positive charge in the transition state. A relatively weak carbon nucleophile, allyltrimethylsilane,[243] was chosen to establish a threshold of the desired substitution. After extensive optimization studies (Lewis acid, solvent, temperature) it was found that $AlCl_3$ and $FeCl_3$ delivered the desired substitution product in high yield (Table 4.4 entries 1 and 2 respectively) and short reaction times at room temperature. The substitution reaction was still observed with reduced amounts of Lewis acid; however, this required increased reaction time and temperature (entries 3 to 5). While a catalytic amount of $AlCl_3$ was rendered less efficient, the result with a catalytic amount of $FeCl_3$ proved comparable to the stoichiometric variant (entry 2 vs 4). The purity of the $FeCl_3$ was also found to have a negligible effect on the substitution reaction (entries 4 vs 5). At this point the generality of the $AlCl_3$ (stoichiometric) and $FeCl_3$ (catalytic) was examined.

Table 4.4. Comparison of $AlCl_3$ and $FeCl_3$ for Promoting Allyl Substitution



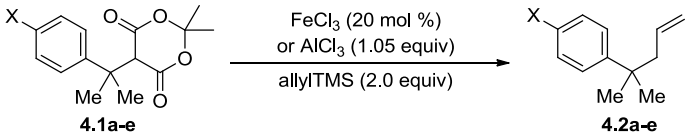
entry	Lewis acid	loading (equiv)	solvent (0.1 M)	temp	time	yield (%)[a]
1	$AlCl_3$ (99.99+%)	1.05	CH_2Cl_2	rt	20 min	quant.
2	$FeCl_3$ (97%)	1.05	CH_2Cl_2	rt	20 min	82
3	$AlCl_3$ (99.99+%)	0.20	$(CH_2Cl)_2$	50 °C	24 h	ND[b]
4	$FeCl_3$ (97%)	0.20	$(CH_2Cl)_2$	50 °C	24 h	85
5	$FeCl_3$ (99.99+%)	0.20	$(CH_2Cl)_2$	50 °C	24 h	86

[a] Isolated yields after chromatography; in all cases conversion was >95%. [b] An inseparable mixture of **4.2a**: 1-methoxy-4-(prop-1-en-2-yl)benzene (the elimination product) was obtained in a 5:1 ratio respectively.

Much to our delight, the allylation reaction stoichiometric in $AlCl_3$ proceeded in excellent yield for a sampling of *p*-substituted aromatics (Table 4.5); however, that success contrasted with

the results obtained from the $FeCl_3$ catalyzed protocol which was found to have a limited scope. The catalytic allylation only resulted in synthetically useful yields, albeit still substantially inferior, for substrates bearing a *p*-alkoxy aromatic (entries 1-2).

Table 4.5. Comparison of the Scope of General Procedure D and E for Allyl Substitution



4.1a-e **4.2a-e**

entry	X	Product	$AlCl_3$ (1.05 equiv) (General Procedure D) yield (%)[a]	$FeCl_3$ (20 mol %) (General Procedure E) yield (%)[a]
1	MeO (**4.1a**)	**4.2a**	quant.	85
2	*n*-$C_8H_{17}O$ (**4.1b**)	**4.2b**	quant.	80
3	*t*-Bu (**4.1c**)	**4.2c**	91	32
4	H (**4.1d**)	**4.2d**	89	25
5	Cl (**4.1e**)	**4.2e**	87	18

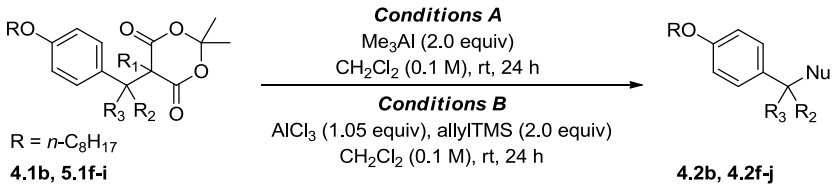
[a] Isolated yields after chromatography; in all cases conversion was >95%.

During the development of the allyl substitution reaction, conditions to effect methyl substitution were also explored and promising results were attained by the use of trimethylaluminum.[244] The results obtained for both sets of substitution conditions are detailed below in the surveying of applicable substrate substitution patterns at the benzylic position (Table 4.6). Quaternary benzyl Meldrum's acid **4.1b** was found to deliver the highest yields for both the allylation and methylation (entries 9 and 10 respectively) over the analogous tertiary and secondary substrates (entries 1-8). This trend strongly suggests the need for the substrate to have the ability to stabilize significant positive charge to permit substitution. Interestingly, it was found that methylation of the 5-position of Meldrum's acid was an effective strategy to enable the allyl substitution of secondary benzylic centers (entry 2 vs 3) and also improved the allyl substitution of tertiary centers (entry 6 vs 8). The origin of the improvement has yet to be understood (see Figure 4.5 for the proposed difference in Table 4.10 entries under Me_3Al conditions) as attempts to rationalize similar reactivity trends in Fillion's hydrogenolysis project based on differences in bond lengths, conformation (observed in x-ray crystal structures of

benzyl Meldrum's acid derivatives) or acidity of Meldrum's acid vs. 5-methyl Meldrum's acid (pK_a = 7.3 vs 7.4)[225] have been unsuccessful to date.[245]

The combined Lewis acidity and nucleophilicity upon Lewis base complexation made trimethylaluminum an ideal choice both in principal and practice with quaternary benzyl Meldrum's acid derivatives (entry 9). Extension of the methylation conditions to other related organoaluminums was met with limited success (see Figure 4.4 for an exception) as mixtures of alkyl transfer and hydride transfer were attained with Et_3Al, and competing 1,2-addition was a significant byproduct with $(allyl)_3Al$.[246]

Table 4.6. Varying the Substitution at the Benzylic Position and the 5-Position of the Meldrum's Moiety



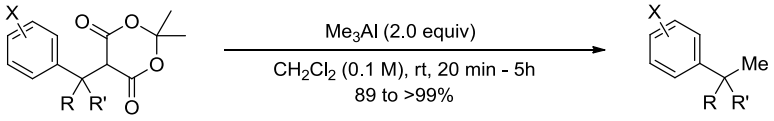
entry	substrate	Conditions	Nu	conv. (%)	yield (%)
1[a]	R_1,R_2,R_3=H (**4.1f**)	A	Me	<5	ND (**4.2f**)
2[a]	(**4.1f**)	B	allyl	<5	ND (**4.2g**)
3[a]	R_1=Me, R_2,R_3=H (**4.1g**)	A	Me	<5	ND (**4.2f**)
4[a]	(**4.1g**)	B	allyl	>95	54 (**4.2g**)
5	R_1,R_2=H, R_3=Me (**4.1h**)	A	Me	<5	ND (**4.2h**)
6	(**4.1h**)	B	allyl	>95	68 (**4.2i**)
7	R_1,R_2=Me, R_3=H (**4.1i**)	A	Me	<5	ND (**4.2h**)
8	(**4.1i**)	B	allyl	>95	77 (**4.2i**)
9[b]	R_1=H, R_2,R_3=Me (**4.1b**)	A	Me	>95	95 (**4.2j**)
10[c]	(**4.1b**)	B	allyl	>95	quant. (**4.2b**)

[a] Reaction performed in $(CH_2Cl)_2$ (0.1 M) at 50 °C. [b] Reaction time was 20 min. [c] Reaction time was 30 min.

The scope of the methyl substitution reaction on quaternary benzyl Meldrum's acid derivatives was next explored (Table 4.7) and gratifyingly, was found to proceed in excellent yields over an array of aromatic substitutions. The efficiency of the reaction was largely unaffected by sterics and electronics as mesomerically and inductively electron releasing groups, electron neutral groups and mild, inductively electron withdrawing groups produced the methyl

substitution products in high isolated yields. The exception to the table was the *p*-dimethylamino substituted aromatic (entry 5) which upon subjection, resulted in alkene formation exclusively (via elimination).

Table 4.7. Scope of the Methyl Substitution



4.1a-c, 4.1j-u **4.2j-x**

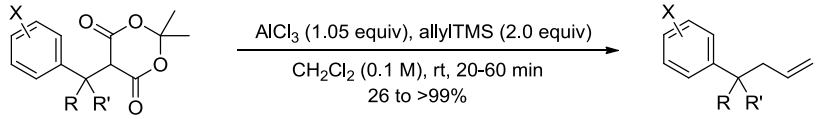
entry	X	R; R'	yield (%)[a]
1	H	R —R' = $(CH_2)_5$ (**4.1j**)	quant. (**4.2k**)
2	4-*t*-Bu	R = R' = Me (**4.1c**)	96 (**4.2l**)
3	4-(MeO)	R = R' = Me (**4.1a**)	93 (**4.2m**)
4	4-(*n*-$C_8H_{17}O$)	R = R' = Me (**4.1b**)	95 (**4.2j**)
5	4-NMe_2	R = R' = Me (**4.1k**)	N/A[b] (**4.2n**)
6	4-Cl	R —R' = $(CH_2)_5$ (**4.1l**)	quant. (**4.2o**)
7	4-F	R —R' = $(CH_2)_5$ (**4.1m**)	95 (**4.2p**)
8	2-Et	R = R' = Me (**4.1n**)	91 (**4.2q**)
9	2-(*n*-$C_8H_{17}O$)	R = R' = Me (**4.1o**)	94(**4.2r**)
10	2-F	R —R' = $(CH_2)_5$ (**4.1p**)	96 (**4.2s**)
11	3-*t*-Bu	R = R' = Me (**4.1q**)	98 (**4.2t**)
12	3-(C_6H_{13})	R = R' = Me (**4.1r**)	97 (**4.2u**)
13	3-(*n*-$C_8H_{17}O$)	R = R' = Me (**4.1s**)	89 (**4.2v**)
14	3-TMS	R = R' = Me (**4.1t**)	quant. (**4.2w**)
15	3-F	R —R' = $(CH_2)_5$ (**4.1u**)	98 (**4.2x**)

[a] In all cases, conversion was >95%; isolated yields after chromatography. [b] Elimination to form **4.4** was the major product; see experimental section for details.

Much to our chagrin, the efficiency of the allyl substitution of quaternary benzyl Meldrum's acid derivatives (Table 4.8) was found to be more sensitive to substituent effects than for the methylation protocol. However, high yields were obtained for mesomerically and inductively electron releasing groups, electron neutral groups and mild, inductively electron withdrawing groups (entries 1-4, 6-7). The *p*-dimethylamino substituted substrate (entry 5) failed to deliver the allyl substitution product, forming the alkene exclusively. Attempted resolve with the more nucleophilic allyltributylstannane (1.36×10^4 times more nucleophilic towards diarylcarbenium than allyltrimethylsilane[247]) led to the detection of only minor amounts of the

desired allyl substitution product with an inseparable mixture of alkene. This strategy of using a more nucleophilic allylating agent was found to be beneficial for entry 7, in which otherwise formed an inseparable mixture of allylsubstitution product:alkene when using allyltrimethylsilane. Of note, it was desirable to impart allyltrimethylsilane not only as an in principal more chemoselective allylating agent but also due to its ease of removal, lower toxicity, lower cost and being more atom economical than its tin analogue. The poor mass balance in the later entries (8-16) is a result of the competing elimination reaction as both alkenes and indanes were commonly observed byproducts.

Table 4.8. Scope of the Allyl Substitution



4.1a-e, 4.1k, 4.1m, 4.1o, 4.1r, 4.1q, 4.1t, 4.1v-y → **4.2a-e, 4.2y-ah**

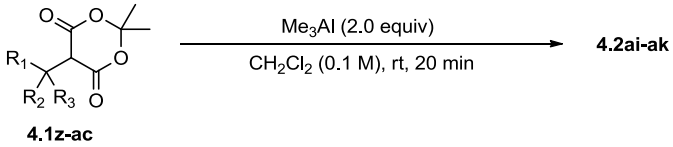
entry	X	R; R'	yield (%)[a]
1	H	R = R' = Me (**4.1d**)	89 (**4.2d**)
2	4-*t*-Bu	R = R' = Me (**4.1c**)	91 (**4.2c**)
3	4-(MeO)	R = R' = Me (**4.1a**)	quant. (**4.2a**)
4	4-(*n*-$C_8H_{17}O$)	R = R' = Me (**4.1b**)	quant. (**4.2b**)
5	4-NMe_2	R = R' = Me (**4.1k**)	N/A[b] (**4.2y**)
6	4-Cl	R = R' = Me (**4.1e**)	88 (**4.2e**)
7	4-F	R —R' = $(CH_2)_5$ (**4.1m**)	88 (**4.2z**)[c]
8	2-(MeO)	R = R' = Me (**4.1v**)	82 (**4.2aa**)
9	2-(*n*-$C_8H_{17}O$)	R = R' = Me (**4.1o**)	59 (**4.2ab**)
10	2-(*n*-$C_8H_{17}O$)	R = R' = Me (**4.1o**)	57 (**4.2ab**)[c]
11	2-F	R = R' = Me (**4.1w**)	39 (**4.2ac**)
12	3-*t*-Bu	R = R' = Me (**4.1q**)	62 (**4.2ad**)
13	3-(*n*-C_6H_{13})	R = R' = Me (**4.1r**)	59 (**4.2ae**)
14	3-TMS	R = R' = Me (**4.1t**)	68 (**4.2af**)
15	3-(MeO)	R = R' = Me (**4.1x**)	29 (**4.2ag**)[d]
16	3-F	R = R' = Me (**4.1y**)	26 (**4.2ah**)

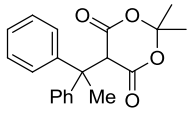
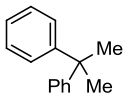
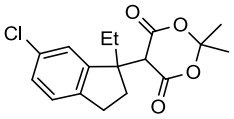
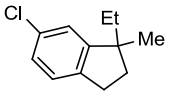
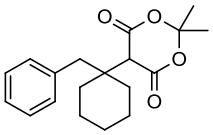
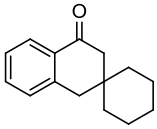
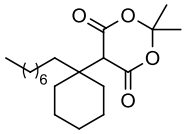
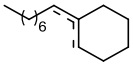
[a] In all cases, conversion was >95%; isolated yields after chromatography. [b] Elimination to form **4.4** was the major product. [c] $AllylSnBu_3$ was used as the nucleophile. [d] Reaction performed in $(CH_2Cl)_2$ at 50 °C for 24 h.

The ability of Meldrum's substrates, bearing alternative quaternary substitutions, to undergo the methylation substitution was next explored (Table 4.9). Substitution of a diaryl

quaternary substrate proceeded in excellent yield (entry 1). Electron deficient indenyl substrate (**4.1aa**) was found to afford the desired substitution product in good yield. Homobenzylic Meldrum's substrate (**4.1ab**) was found to favour intramolecular F/C acylation over the substitution reaction delivering spiro compound **4.2ak**. Furthermore, substrate **4.1ac** bearing only alkyl substituents underwent elimination to afford an unassigned mixture of alkenes.

Table 4.9. Exploration of the Methyl Substitution Reaction with Meldrum's Acid Substrates Bearing Alternate Quaternary Substitutions



entry	substrate		product		yield (%)[a]
1		**4.1z**		**4.2ai**	quant.
2		**4.1aa**		**4.2aj**	90
3		**4.1ab**		**4.2ak**	ND[b]
4		**4.1ac**			ND

[a] Isolated yields after chromatography. [b] Observed as the major product and characterized and isolated in 61% yield under the allylation conditions, for details see the experimental section.

The scope of the nucleophile was next evaluated with substrate **4.1a** (Figure 4.4) which had proven to be an ideal substrate in this study. In absence of an additional nucleophile added indane **4.5** was formed, which was also observed exclusively with less nucleophilic reagents (ex. $TMSCF_3$). MethallylTMS furnished a similar yield to the benchmark result obtained with the less nucleophilic allylTMS (methallylTMS is 1700 times more nucleophilic towards diarylcarbenium than allylTMS).[247] The allenyl and propargyl substitutions were performed in good yield from propargylTMS and allenyl$SnBu_3$, respectively. As alluded to earlier in the text, the same net

result of the hydrogenolysis protocol[241] was achieved when $^{i}Bu_3Al$ was used. TMSCN as well as the π-nucleophiles 2-methylfuran, 2-methylthiophene and 2-(trimethylsiloxy)furan resulted in good to excellent yields of the desired substitution products. Lastly, use of $TMSN_3$ demonstrated the feasibility of introducing heteroatoms at the benzylic position.

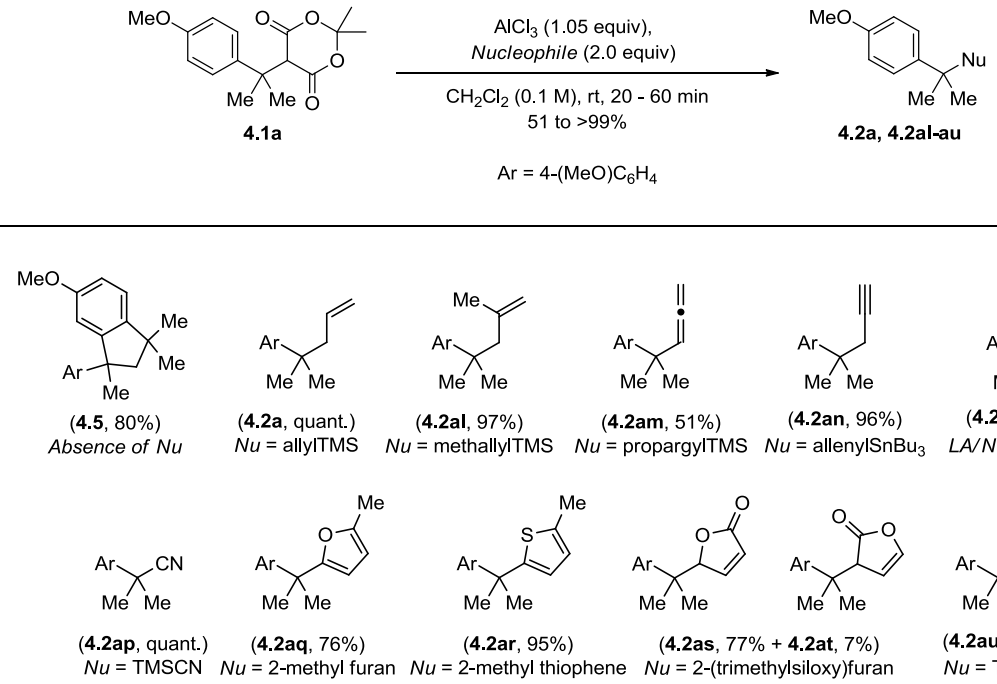


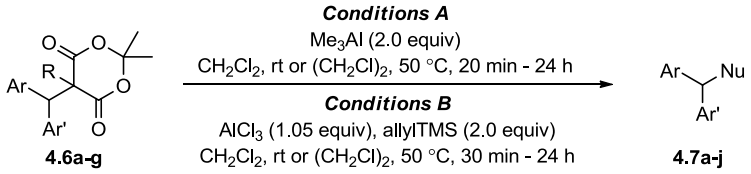
Figure 4.4. Scope of the Nucleophile

Having outlined the reaction scope with regards to quaternary benzyl Meldrum's acids, the generality of the substitution was further investigated with tertiary dibenzyl Meldrum's acid substrates (Table 4.10). The substitution reactions did prove to be generally applicable but it was quickly realized that this substrate class was more sensitive to electronics than the former examined as seen with the contrasting results of substrate **4.6a**, bearing two phenyl groups, and substrate **4.6c**, bearing two *p*-OMe substituted phenyl groups (entries 1 and 2 vs entries 5 and 6). Gratifyingly, the methylation strategy employed in Table 4.6 was effective in remedying this limitation.

An illustrative example is given with dibenzyl substrate **4.6f**, with each aromatic bearing the inductively withdrawing *p*-chloro substituent, which failed under the methylation conditions

(vigorous gas evolution, methane, observed) and also gave a poor yield of allyl substitution product. Simply increasing the nucleophilicity of the allylating agent did not increase the efficiency of the reaction (entries 12 vs 13); however, methylation of the 5-position of Meldrum's acid to form substrate **4.6g** delivered the desired substitution products in excellent yield (entries 14 and 15).

Table 4.10. Scope of Tertiary Benzylic Substitutions



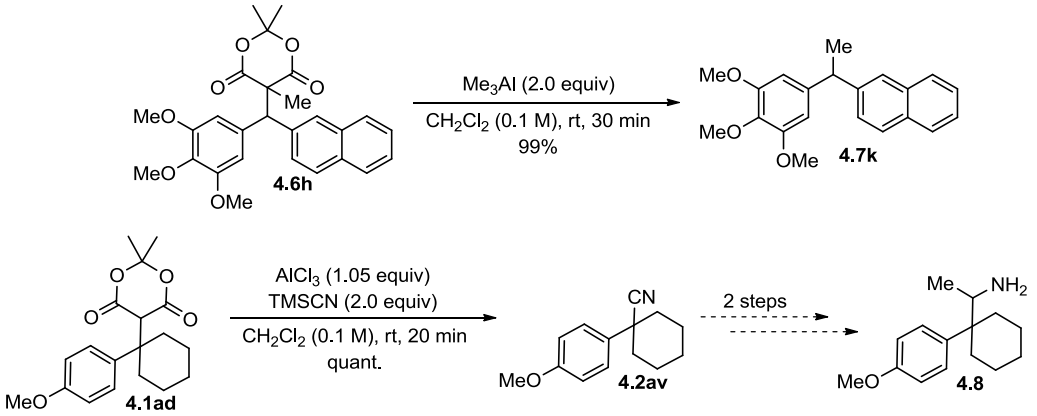
entry	Ar; Ar': R	Conditions	Nu	yield (%)
1[a]	Ar=Ar'=C_6H_5; R=H (**4.6a**)	A	Me	N/A (**4.7a**)
2	(**4.6a**)	B	allyl	50 (**4.7b**)
3	Ar=Ar'=C_6H_5; R=Me (**4.6b**)	A	Me	92 (**4.7a**)
4	(**4.6b**)	B	allyl	93 (**4.7b**)
5	Ar=Ar'=4-(MeO)C_6H_4; R=H (**4.6c**)	A	Me	quant. (**4.7c**)
6	(**4.6c**)	B	allyl	94 (**4.7d**)
7	Ar=4-(MeO)C_6H_4; Ar'=C_6H_5; R=H (**4.6d**)	A	Me	95 (**4.7e**)
8	(**4.6d**)	B	allyl	96 (**4.7f**)
9	Ar=4-(MeO)C_6H_4; Ar'=4-ClC_6H_4; R=H (**4.6e**)	A	Me	87 (**4.7g**)
10	(**4.6e**)	B	allyl	91 (**4.7h**)
11[a]	Ar=Ar'=4-ClC_6H_4; R=H (**4.6f**)	A	Me	N/A (**4.7i**)
12[b]	(**4.6f**)	B	allyl	42 (**4.7j**)
13[b,c]	(**4.6f**)	B	allyl	36 (**4.7j**)
14	Ar=Ar'=4-ClC_6H_4; R=Me (**4.6g**)	A	Me	96 (**4.7i**)
15	(**4.6g**)	B	allyl	94 (**4.7j**)

[a] Reaction did not proceed; evolution of gas suggested deprotonation of Meldrum's acid moiety. [b] Reaction was performed in $(CH_2Cl)_2$ (0.05 M) at 50 °C. [c] AllylSnBu_3 was used instead of allylTMS.

To further demonstrate the utility of the new methodology, two compounds possessing the diarylmethane and benzylic quaternary center structural motifs as well as biological activity were identified from the literature and expedient syntheses were executed (Scheme 4.8). Having readily synthesized the requisite Meldrum's precursors (**4.6h**[248] and **4.1ad**), methyl and cyanide substitution furnished **4.7k** and **4.2av** respectively in excellent yields. Compound **4.7k** is an

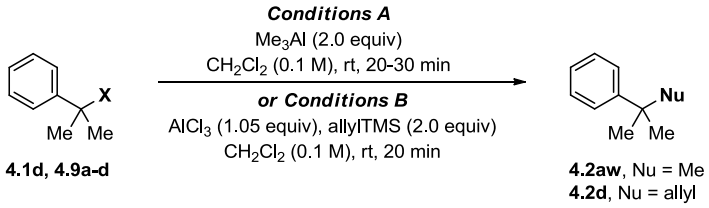
isoerianin analogue that is a potent inhibitor of tubulin polymerization.[249] Compound **4.2av** constitutes a formal synthesis of the reuptake inhibitor **4.8** which acts against the serotonin, norepinephrine and dopamine transporters.[250]

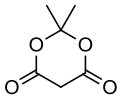
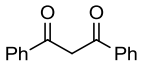
Scheme 4.8. Application to the Synthesis of Biologically Active Compounds



The efficiency of the developed Meldrum's acid displacements was then directly compared to the substitution reactions of analogous quaternary benzylic centers with alternative leaving groups (Table 4.11). The methyl substitution of Meldrum's acid **4.2d** was found to be slightly inferior to that obtained from the dibenzoyl methane (**4.9a**) and acetate (**4.9c**) derivatives; however, it proved to be advantageous in the allylation substitution which afforded **4.2d** in high yield. Poor mass balances are a result of the competing elimination reaction.

Table 4.11. Comparison of the Leaving Group in Substitution of Quaternary Benzylic Substrates

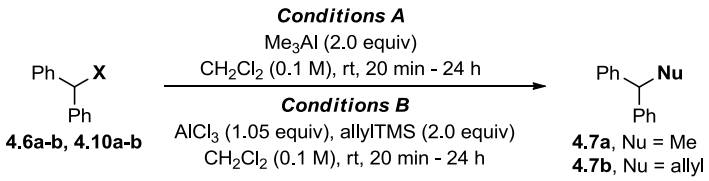


	Leaving group **X** (substrate)				
yield (%)[a]	 (**4.1d**)	 (**4.9a**)	Cl (**4.9b**)	OAc (**4.9c**)	OH (**4.9d**)
4.2aw	63	82	54	83	NA[b]
4.2d	89	62	42	46	50

[a] Average isolated yield of two experiments. [b] Deprotonation of SM which is subsequently protonated in the work up.

The efficiency of the developed Meldrum's acid displacements was then directly compared to the substitution reactions of analogous tertiary benzylic centers with alternative leaving groups (Table 4.12). As previously presented in Table 4.10, substrate **4.6b** outperforms protic analogue **4.6a** under both the methylation and allylation conditions obtaining high yields of product in both cases. Substrate **4.6b** proved to be the superior substrate for the methyl substitution as methylation of the carbonyl of dibenzoylmethane derived **4.10a** was a competing reaction and benzhydrol (**4.10b**) failed to give the desired product (evolution of gas, methane, observed). However, the allylation reaction was found to be comparable to that obtained from the dibenzoylmethane derived **4.10a** and benzhydrol (**4.10b**).

Table 4.12. Comparison of the Leaving Group in Substitution of Tertiary Benzylic Substrates

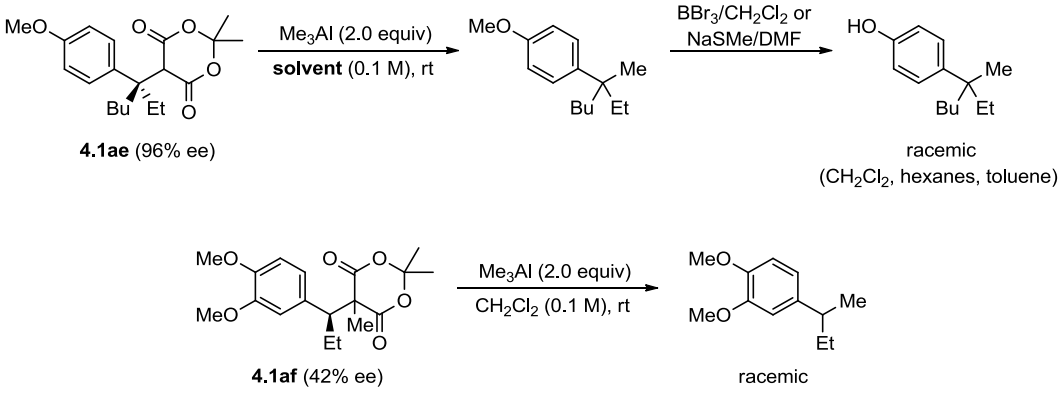


	Leaving group **X** (substrate)			
yield (%)[a]	(**4.6a**)	(**4.6b**)	(**4.10a**)	OH (**4.10b**)
4.7a	N/A[b]	92	44	N/A
4.7b	50[b]	93	92	97

[a] Isolated yields after chromatography; [b] Reaction performed in $(CH_2Cl)_2$ at 50 °C for 24 h.

A preliminary investigation into the use of enantioenriched substrates for the developed substitution reaction has been performed (Scheme 4.9).[251] Quaternary substrate **4.1ae** afforded racemic product under the generalized methyl substitution conditions as well as in less polar solvents. Deprotection of the aryl ether was necessary to effect separation on the chiral HPLC which was performed by two methods (from material obtained in CH_2Cl_2) to confirm racemization was not a result of the boron tribromide deprotection.

Scheme 4.9. Probing the Mechanism with Enantioenriched Substrates



Similarly, tertiary substrate **4.1af**, which would have less ability to stabilize a carbocation than **4.1ae**, also resulted in the formation of racemic substitution product. These results are again suggestive of an S_N1 mechanism operating.

A proposed mechanism for the methylation substitution is outlined in Figure 4.5. Initial complexation of a carbonyl of the Meldrum's acid derivative with trimethylaluminum furnishes a nucleophilic organoaluminum and a highly electrophilic carbonyl. Depending on the substitution pattern of the benzylic position the reaction can take one of three pathways: 1) C-C bond cleavage to form a stabilized carbocation or ion pair, 2) intramolecular attack by a π-nucleophile (ex. F/C acylation by an electron rich arene) or 3) deprotonation. The desired C-C bond cleavage can provide the desired S_N1 product, methyl substitution, or alternatively E1 products. An analogous mechanism for the $AlCl_3$/nucleophile system is thought to operate.

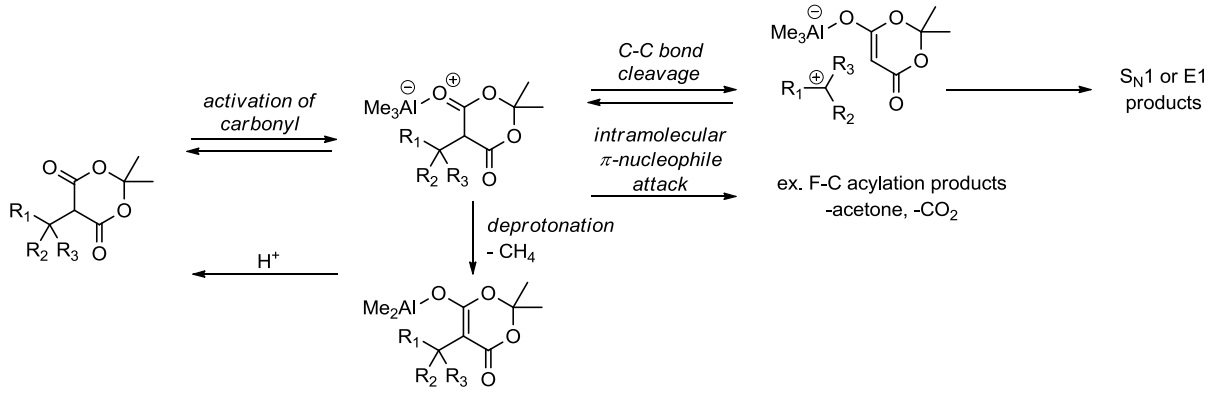


Figure 4.5. Mechanistic Proposal for the Me_3Al reactions

4.4. Summary

The investigation into expanding the substitution of Meldrum's acid can be deemed a success as two general sets of conditions employing stoichiometric Lewis acid were developed in addition to preliminary findings of a catalytic protocol (Figure 4.6).[252] The substitution reactions described transform unstrained quaternary and tertiary benzylic Csp^3-Csp^3 bonds into Csp^3-X bonds (X = C, N, H) and have even shown to be advantageous with regards to synthetic utility over the use of alternative leaving groups for substitutions at quaternary and tertiary benzylic carbon centers.

Importantly, this reaction has a broad scope both in terms of suitable substrates and nucleophiles with good to excellent yields obtained (typically >90%). Furthermore, examples of the utility was shown in synthesizing a known inhibitor of tubulin polymerization bearing the 1,1-diarylalkane structural motif as well as a formal synthesis of an inhibitor bearing a quaternary benzylic center. The mild reaction conditions, elegant simplicity of operation and readily accessible starting materials also bode well for the incorporation of this new method and concept of strategic use of carbon-based leaving groups by the synthetic community.

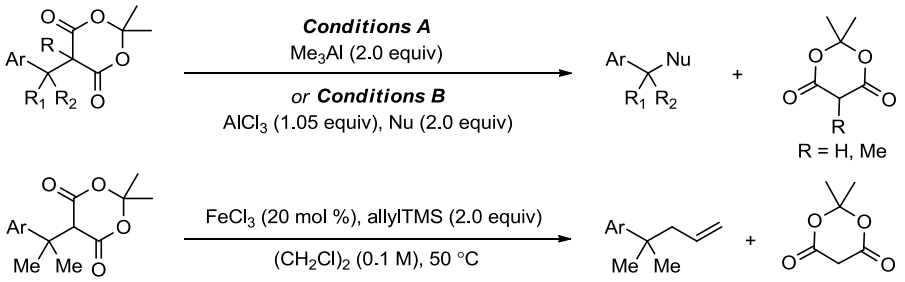


Figure 4.6. Developed Substitution Protocols

4.5. Future Work

A catalytic method to cleave benzyl Csp^3-Csp^3 bonds by way of displacement of Meldrum's acid to generate enantioenriched, highly functionalized, quaternary and tertiary centers remains a desirable process. One possible method may be envisioned as starting from racemic substrates and effecting a dynamic kinetic asymmetric transformation (DYKAT) with a chiral Lewis acid (Figure 4.7). A literature example below, as yet to be generalized, serves as an interesting proof of principle (Table 4.13).

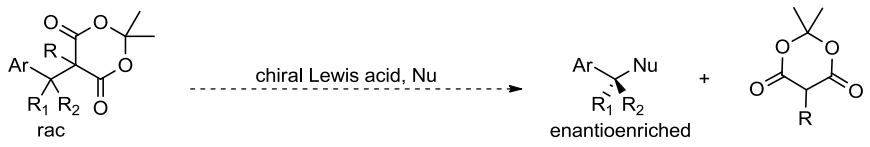
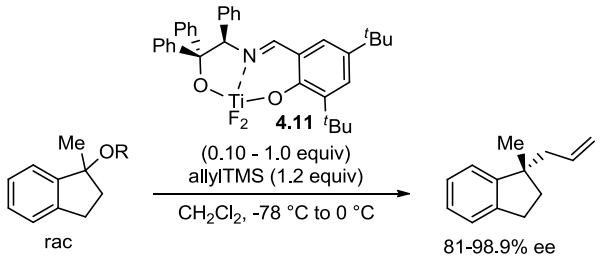


Figure 4.7. Proposed Access to Enantioenriched Benzylic Carbon Centers Through DYKAT

An attractive method of effecting S_N1 substitutions has been the direct substitution of stabilized alcohols with Lewis or Brønsted acid catalysts.[253] Braun's group has demonstrated an

elegant dynamic kinetic asymmetric transformation (DYKAT)[254] with a chiral titanium Lewis acid (**4.11**) for the formation of quaternary and tertiary benzylic carbon centers.[255] Of note a stoichiometric amount of the Lewis acid delivered the best results with the alcohol substrate; however, an improved catalytic protocol was developed by installing a siloxy leaving group. The reaction was thought to proceed by formation of diastereomeric contact ion pairs that rapidly equilibrate via the achiral indanyl carbocation and with one of the diastereomers reacting faster than the other with the allyl nucleophile.

Table 4.13. Braun's Titanium Promoted DYKAT



entry	R	**4.11** (equiv)	ee (%)	yield (%)
1	H	1.0	81	94
2	$SiMe_3$	0.10	98.9	96

4.6. Experimental

General Considerations

Reactions

THF was distilled over sodium/benzophenone ketyl before use. 1,2-Dichloroethane and DMF were distilled over CaH_2 and the former was then degassed via 3 freeze-pump-thaw cycles following distillation. HPLC grade dichloromethane and pentane were used as received from commercial sources. The following Grignard and organoaluminum reagents were obtained from commercial sources and used without further purification: MeMgBr (3.0 M in Et_2O), PhMgBr (3.0 M in Et_2O), PhMgCl (2.0 M in THF), 4-F(C_6H_4)MgBr (1.0 M in THF), 4-Cl(C_6H_4)MgBr (1.0 M in Et_2O), 4-OMe(C_6H_4)MgBr (0.5 M in THF), 3-OMe(C_6H_4)MgBr (1.0 M in THF), BnMgCl (2.0 M in THF), Me_3Al (2.0 M in heptane), $^iBu_3Al$ (1.0 M in hexanes), and DIBAL-H (1.5 M in PhMe). The other Grignards used were prepared from the corresponding aryl bromides

with magnesium in THF. Potassium carbonate was dried in an oven (140 °C) overnight prior to use. Triethylamine was distilled over CaH_2 prior to use. Chlorotrimethylsilane was also distilled prior to use. Anhydrous lithium chloride was heated in a 140 °C oil bath under vacuum (0.5 mm Hg) overnight prior to use. Anhydrous aluminum chloride (99.99+% - Al PURATREM), iron chloride (97%, reagent grade) and iron chloride (99.99+%, sublimed grade) were used as received from commercial sources. Reactions were monitored by thin-layer chromatography on commercially prepared plates. Developed plates were viewed under a UV lamp (254 nm) and with ceric ammonium molybdate stain. Flash chromatography was performed using 230-400 mesh silica gel.

The following starting materials were prepared according to literature procedures and the spectral data obtained were in agreement with those reported and consequently, data will not be repeated here: 5-(2-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.1a**),[256] 2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**4.1b**),[241] 2,2-dimethyl-5-(2-phenylpropan-2-yl)-1,3-dioxane-4,6-dione (**4.1d**),[256] 2,2-dimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**4.1h**),[241] 2,2-dimethyl-5-(1-phenylcyclohexyl)-1,3-dioxane-4,6-dione (**4.1j**),[256] 2,2-dimethyl-5-(2-(2-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**4.1o**),[241] 2,2-dimethyl-5-(2-(3-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**4.1s**),[241] 5-(2-(2-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.1v**),[256] and 5-(bis(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.6c**).[241]

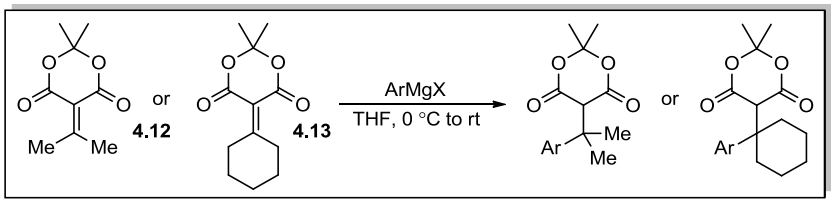
Characterization

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

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

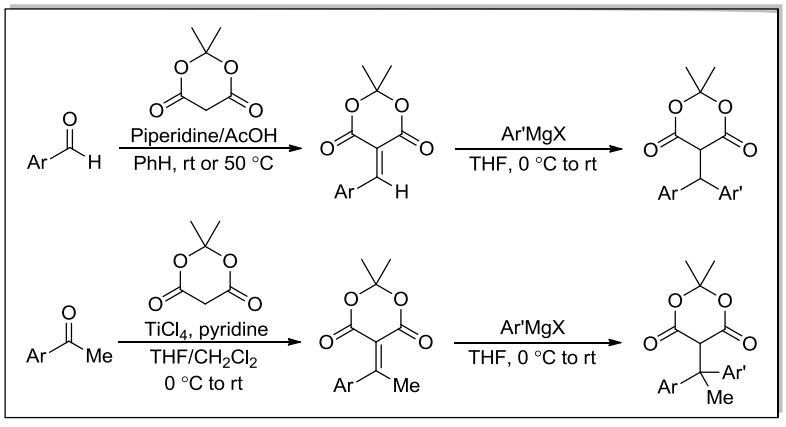
Synthesis of Starting Materials

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



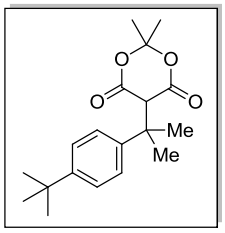
Quaternary benzyl Meldrum's acids were prepared by the addition of aryl Grignard reagents (2-3 equiv, dropwise addition or alternatively syringe pump addition at a rate of 0.34 mL/min) to a solution of 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione[257] (**4.12**) or 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione[96f] (**4.13**) in dry THF under nitrogen at 0 °C. The reaction was stirred at room temperature until completion of reaction by TLC or for 24 h. The reaction was quenched with 5% HCl at 0 °C and was extracted with EtOAc (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by recrystallization or flash chromatography as indicated.

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



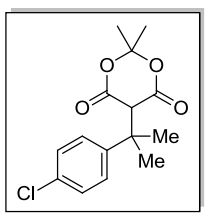
Alkylidene Meldrum's acids were prepared according to previously established literature procedures. When condensing aromatic aldehydes, the piperidinium acetate protocol[66] was used and alternatively, when condensing aromatic ketones the $TiCl_4$/pyridine method[94f] was employed unless specified otherwise.

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



5-(2-(4-*tert*-Butylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.2c)

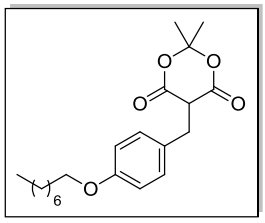
Prepared according to General Procedure A by the dropwise addition of 4-*tert*-butylphenylmagnesium bromide (55 mL, 55 mmol, 1.0 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (**4.12**) (5.00 g, 27.1 mmol) in THF (68 mL); 48 h reaction time. Recrystallization from MeOH afforded a white solid (3.02 g over 2 crops, 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-(4-Chlorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1e)

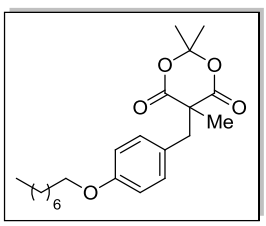
Prepared according to General Procedure A by the dropwise addition of 4-chlorophenylmagnesium bromide (20 mL, 20 mmol, 1.0 M in Et_2O) to 2,2-dimethyl-5-(propan-

2-ylidene)-1,3-dioxane-4,6-dione (**4.12**) (2.50 g, 13.6 mmol) in THF (4.5 mL); 16 h reaction time. Recrystallization from MeOH afforded a white solid (1.70 g, 42% yield). M.p. 96-98 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28 (d, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.60 (s, 1H), 1.65 (s, 3H), 1.63 (s, 6H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 163.8 (C), 143.8 (C), 132.6 (C), 128.3 (CH), 127.4 (CH), 104.9 (C), 57.1 (CH), 41.8 (C), 28.6 (CH_3), 27.6 (CH_3), 27.4 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{21}ClNO_4$ ($[M + NH_4]^+$): 314.11591. Found: 314.11698.



2,2-Dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (4.1f)

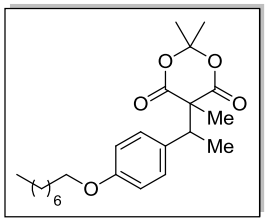
4-*n*-Octyloxybenzaldehyde[258] (15 g, 64 mmol, 1.0 equiv) and Meldrum's acid (9.69 g, 67.2 mmol, 1.05 equiv) were dissolved in EtOH (135 mL, 0.5 M) at rt. Piperidine (0.67 mL, 0.1 equiv) was added dropwise, followed by glacial acetic acid (0.4 mL, 0.1 equiv), and the resulting mixture was stirred at rt for 30 min. The reaction was placed in an ice bath and sodium cyanoborohydride (6.33 g, 100 mmol, 1.5 equiv) was added in 6 portions over 30 min. The reaction was stirred at rt overnight and concentrated under reduced pressure. The mixture was quenched with 3 M HCl and was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. Recrystallization from MeOH afforded a white solid (12 g, 52% yield). M.p. 52-53 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.19 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.70 (t, *J* = 4.8 Hz, 1H), 3.41 (d, *J* = 4.7 Hz, 2H), 1.75-1.69 (m, 5H), 1.45 (s, 3H), 1.41-1.26 (m, 10H), 0.86 (br t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.4 (C), 158.2 (C), 130.8 (CH), 128.8 (C), 114.4 (CH), 105.1 (C), 67.9 (CH_2), 48.2 (CH), 31.7 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 29.1 (2 x CH_2), 28.4 (CH_3), 27.2 (CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_5$ (M^+): 362.2093. Found: 362.2095.



2,2,5-Trimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (4.1g)

The following chemicals were added sequentially to a flame dried round bottom flask equipped with a magnetic stir bar at room temperature: 2,2-

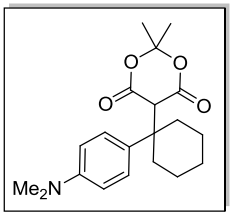
dimethyl-5-(4-(octyloxy)benzyl)-1,3-dioxane-4,6-dione (**4.1f**) (3.0 g, 8.3 mmol), K_2CO_3 (1.72 g, 12.4 mmol), DMF (9 mL), followed by addition of iodomethane (1.03 mL, 16.5 mmol) at 0 °C; the resulting reaction mixture was allowed to stir for 24 h at rt. The workup consisted of adding water and extracting with CH_2Cl_2 (3X), and then the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in Et_2O and washed with water (3X, to remove residual DMF), dried over $MgSO_4$, filtered and concentrated to afford a white solid (2.6 g, 82% yield). M.p. 53-54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.05 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.25 (s, 2H), 1.74-1.66 (m, 5H), 1.58 (s, 3H), 1.39 (quintet, *J* = 7.8 Hz, 2H), 1.34-1.25 (m, 8H), 0.95 (s, 3H), 0.86 (br t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.9 (C), 158.7 (C), 131.1 (CH), 127.2 (C), 114.7 (CH), 105.2 (C), 68.0 (CH_2), 52.3 (C), 44.2 (CH_2), 31.8 (CH_2), 29.4 (CH_3), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.4 (CH_3), 25.9 (CH_2), 25.7 (CH_3), 22.6 (CH_2), 14.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{22}H_{32}O_5$ (M^+): 376.2250. Found: 376.2240.



2,2,5-Trimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (4.1i)

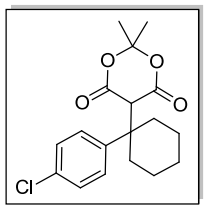
The following chemicals were added sequentially to an oven dried round bottom flask equipped with a magnetic stir bar at room temperature: 2,2-dimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**4.1h**) (2.3 g, 6.1 mmol), K_2CO_3 (1.3 g, 9.4 mmol), DMF (6 mL), followed by addition of iodomethane (1.9 mL, 30 mmol) at 0 °C; the resulting reaction mixture was allowed to stir for 17 h at rt. The workup consisted of adding water and extracting with EtOAc (3X), and then the combined organic layers were washed with sat. $NaHCO_3$ solution (2X), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography eluting with hexanes:EtOAc (5:1) afforded a clear oil (2.2 g, 94% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.03 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.86 (t, *J* = 6.6 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 1H), 1.70 (quintet, *J* = 6.8 Hz, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.37 (quintet, *J* = 6.8 Hz, 2H), 1.37-1.24 (m, 8H), 1.00 (s, 3H), 0.84 (br t, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.5 (C), 168.8 (C), 158.6 (C), 132.2 (C), 129.5 (CH), 114.4 (CH), 104.8 (C), 67.9 (CH_2), 54.4 (C), 47.9 (CH), 31.7 (CH_2), 30.2 (CH_3), 29.3

(CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.5 (CH_3), 25.9 (CH_2), 22.6 (CH_2), 22.1 (CH_3), 15.4 (CH_3), 14.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{23}H_{34}O_5$ (M^+): 390.2406. Found: 390.2401.



5-(1-(4-(Dimethylamino)phenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1k)

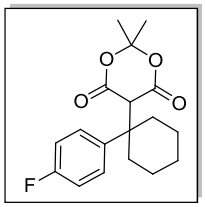
Prepared according to General Procedure A by the addition of 4-dimethylaminophenylmagnesium bromide (11.1 mL, 22.2 mmol, 2.0 M in THF) via syringe pump (0.34 mL/min) to 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.13**) (2.50 g, 11.1 mmol) in THF (17 mL); 1 h reaction time. Following the work up and removal of the solvent at rt, the crude solid was washed successively with pentane and then methanol to afford a white solid (2.26 g, 59% yield). *Note:* An initial attempt at recrystallization with methanol, which required slight heating, resulted in displacement of Meldrum's acid and the alkene was obtained). M.p. 105-106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.10 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 2H), 3.39 (s, 1H), 2.88 (s, 6H), 2.44 (br d, *J* = 8.6 Hz, 2H), 1.94-1.91 (m, 2H), 1.60 (m, 2H), 1.37 (s, 3H), 1.36-1.34 (m, 4H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.6 (C), 149.5 (C), 128.3 (CH), 126.9 (C), 112.5 (CH), 105.6 (C), 57.4 (CH), 46.8 (C), 40.4 (CH_3), 35.7 (CH_2), 30.6 (CH_3), 26.4 (CH_3), 25.8 (CH_2), 22.2 (CH_2); HRMS (DART) *m/z* calcd for $C_{20}H_{28}NO_4$ ($[M + H]^+$): 346.20183. Found: 346.20171.



5-(1-(4-Chlorophenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1l)

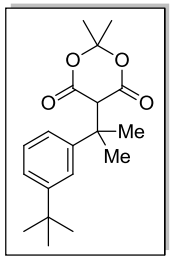
Prepared according to General Procedure A by the addition of 4-chlorophenylmagnesium bromide (17.8 mL, 17.8 mmol, 1.0 M solution in Et_2O) via syringe pump (0.34 mL/min) to 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.13**) (2.00 g, 8.92 mmol) in THF (14 mL); 2 h reaction time. Purification was achieved by: flash column chromatography of the crude combined with additional crude product obtained from the reaction vessel that was insoluble in Et_2O, eluting with hexanes:EtOAc (9:1), having dry packed the sample, and subsequent recrystallization from methanol to afford a white solid (0.650 g, 22 % yield). M.p. 126-128 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.31 (d, *J* = 8.8 Hz, 2H), 7.22 (d,

J = 8.8 Hz, 2H), 3.43 (s, 1H), 2.44 (br d, *J* = 10.9 Hz, 2H), 2.05-1.97 (m, 2H), 1.66-1.60 (m, 2H), 1.49 (s, 3H), 1.45-1.23 (m, 4H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.3 (C), 138.3 (C), 133.3 (C), 129.3 (CH), 128.7 (CH), 105.6 (C), 57.2 (CH), 46.8 (C), 35.4 (CH_2), 30.4 (CH_3), 26.5 (CH_3), 25.6 (CH_2), 22.2 (CH_2); HRMS (DART) *m/z* calcd for $C_{18}H_{25}ClNO_4$ ($[M + NH_4]^+$): 354.14721. Found: 354.14733.



5-(1-(4-Fluorophenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1m)[259]

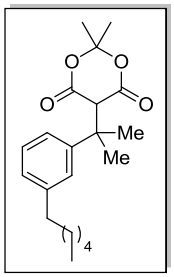
Prepared according to General Procedure A by the dropwise addition of 4-fluorophenylmagnesium bromide (7.5 mL, 7.5 mmol, 1.0 M in THF) to 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.13**) (1.12 g, 5.00 mmol) in THF (15 mL); 18 h reaction time. Recrystallization from MeOH afforded a white solid (0.760 g, 47% yield). M.p. 128-130 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.27-7.23 (m overlapping with $CHCl_3$, 2H), 7.02 (app t, *J* = 8.6 Hz, 2H), 3.44 (s, 1H), 2.44 (br d, *J* = 8.8 Hz, 2H), 2.07-1.98 (m, 2H), 1.66-1.60 (m, 2H), 1.48 (s, 3H), 1.46-1.31 (m, 4H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 164.5 (C), 161.9 (C, d, *J* = 246.0 Hz), 135.6 (C), 129.6 (CH, d, *J* = 8.0 Hz), 115.4 (CH, d, *J* = 20.7 Hz), 105.6 (C), 57.3 (CH), 46.9 (C), 35.7 (CH_2), 30.5 (CH_3), 26.5 (CH_2), 25.7 (CH_3), 22.3 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -114.9; HRMS (EI) *m/z* calcd for $C_{18}H_{21}FO_4$ (M^+): 320.1424. Found: 320.1422.



5-(2-(3-(*tert*-Butyl)phenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1q)

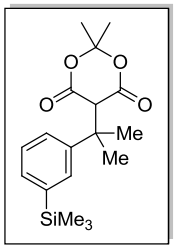
Prepared according to General Procedure A by the dropwise addition of (3-(*tert*-butyl)phenyl)magnesium bromide (7.9 mL, 11 mmol, 1.4 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (**4.12**) (1.40 g, 7.60 mmol) in THF (10 mL); 3 h reaction time. Recrystallization from MeOH afforded 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.



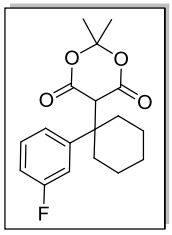
5-(2-(3-Hexylphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1r)

Prepared according to General Procedure A by the dropwise addition of (3-hexylphenyl)magnesium bromide (7.1 mL, 10 mmol, 1.4 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (**4.12**) (1.20 g, 6.52 mmol) in THF (5.2 mL); 18 h reaction time. Purification by flash column chromatography eluting on a gradient with hexanes:EtOAc (20:1 to 9:1) afforded a colourless oil (1.70 g, 75% yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.27 (s, 1H), 7.21-7.20 (m, 2H), 7.04-7.03 (m, 1H), 4.26 (s, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.77 (s, 3H), 1.62 (s overlapping with m from 1.62-1.57, 6H), 1.62-1.57 (m, 2H), 1.40 (s, 3H), 1.37-1.25 (m, 6H), 0.87 (br t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.3 (C), 144.0 (C), 143.0 (C), 128.2 (CH), 127.1 (CH), 126.4 (CH), 123.5 (CH), 105.2 (C), 57.7 (CH), 42.7 (C), 36.1 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 29.4 (CH_3), 28.9 (CH_2), 27.9 (CH_3), 27.2 (CH_3), 22.6 (CH_2), 14.1 (CH_3); HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_4$ (M^+): 346.2144. Found: 346.2149.



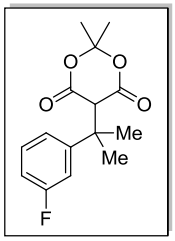
2,2-Dimethyl-5-(2-(3-(trimethylsilyl)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (4.1t)

Prepared according to General Procedure A by the dropwise addition of (3-(trimethylsilyl)phenyl)magnesium bromide (19 mL, 16 mmol, 0.84 M in THF) to 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (**4.12**) (1.48 g, 8.05 mmol) in THF (12 mL); 17 h reaction time. Recrystallization from MeOH afforded a white solid (394 mg, 15% yield). M.p. 87-88 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.46 (s, 1H), 7.39-7.37 (m, 1H), 7.31-7.30 (m, 2H), 3.52 (s, 1H), 1.68 (s, 6H), 1.57 (s, 3H), 1.08 (s, 3H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.2 (C), 143.0 (C), 140.4 (C), 131.9 (CH), 130.9 (CH), 127.7 (CH), 126.7 (CH), 105.1 (C), 57.7 (CH), 42.7 (C), 29.3 (CH_3), 27.8 (CH_3), 27.0 (CH_3), -1.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{18}H_{30}NO_4Si$ ($[M + NH_4]^+$): 352.19441. Found: 352.19346.



5-(1-(3-Fluorophenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1u)

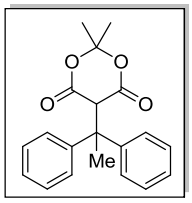
A procedure reported by Knochel and coworkers was adapted,[260] which had recently been utilized in an analogous reaction in the Fillion group to form a similar Meldrum's acid derivative.[256] To a round bottom flask flushed with argon and charged with Mg powder (428 mg, 17.6 mmol, 3.5 equiv) was added LiCl (17.6 mL, 8.82 mmol, 1.75 equiv, 0.5 M in THF), and DIBAL-H (0.05 mL, 0.07 mmol, 0.014 equiv, 1.5 M in PhMe). After 5 minutes of stirring at rt, the mixture was cooled to -20 °C and 3-bromofluorobenzene (0.77 mL, 7.1 mmol, 1.4 equiv) was added. After stirring for 1 h at -20 °C, 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.13**) (1.13 g, 5.04 mmol, 0.5 M in THF) was added and the resulting mixture was allowed to slowly warm up to rt. After 22 h, the reaction was quenched with a sat. NH_4Cl solution at 0 °C and extracted with CH_2Cl_2 (3X). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography eluting on a gradient with hexanes:EtOAc (12:1 to 9:1) afforded a colourless film (762 mg, 47% yield). An analytically pure sample was obtained by recrystallization from MeOH. M.p. 92-93 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.34-7.27 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.02-6.92 (m, 2H), 3.45 (s, 1H), 2.44-2.40 (m, 2H), 2.08-2.00 (m, 2H), 1.69-1.64 (m, 2H), 1.49 (s overlapping with m from 1.52-1.33, 3H), 1.52-1.33 (m, 4H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.2 (C), 163.0 (C, d, *J* = 244.6 Hz), 142.7 (C, d, *J* = 6.4 Hz), 130.0 (CH, d, *J* = 8.1 Hz), 123.3 (CH, d, *J* = 2.6 Hz), 115.0 (CH, d, *J* = 22.1 Hz), 114.2 (CH, d, *J* = 20.7 Hz), 105.5 (C), 56.8 (CH), 46.9 (C), 35.4 (CH_2), 30.3 (CH_3), 26.4 (CH_3), 25.5 (CH_2), 22.2 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -112.4; HRMS (DART) *m/z* calcd for $C_{18}H_{25}FNO_4$ ($[M + NH_4]^+$): 338.17676. Found: 338.17688.



5-(2-(3-Fluorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1y)

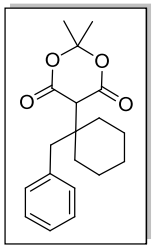
A procedure reported by Knochel and coworkers was adapted,[260] which had recently been utilized in an analogous reaction in the Fillion group to form a similar Meldrum's acid derivative.[256] To a round bottom flask flushed with argon and charged with Mg metal (428 mg, 17.6 mmol, 3.5 equiv) was added LiCl (17.6 mL, 8.82 mmol, 1.75

equiv, 0.5 M in THF), and DIBAL-H (0.05 mL, 0.07 mmol, 0.014 equiv, 1.5 M in PhMe). After 5 minutes of stirring at rt, the mixture was cooled to -20 °C and 3-bromofluorobenzene (0.77 mL, 7.1 mmol, 1.4 equiv) was added. After stirring for 1 h at -20 °C, 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (**4.12**) (928 mg, 5.04 mmol, 0.5 M in THF) was added and the resulting mixture was allowed to slowly warm up to rt. After 43 h, the reaction was quenched with a sat. NH_4Cl solution and extracted with CH_2Cl_2 (3X). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and concentrated. Recrystallization from MeOH afforded a white solid (495 mg, 35% yield). M.p. 103-105 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.31-7.26 (m, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.02 (dt, *J* = 10.9, 2.0 Hz, 1H), 6.92 (td, *J* = 8.2, 2.2 Hz, 1H), 3.64 (s, 1H), 1.66 (s, 3H), 1.63 (s, 6H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 163.7 (C), 162.7 (C, d, *J* = 243.8 Hz), 148.2 (C, d, *J* = 6.6 Hz), 129.7 (CH, d, *J* = 8.2 Hz), 121.5 (CH, d, *J* = 2.5 Hz), 113.6 (CH, d, *J* = 21.2 Hz), 113.2 (CH, d, *J* = 22.4 Hz), 104.9 (C), 56.9 (CH), 41.8 (C), 28.4 (CH_3), 27.6 (CH_3), 27.2 (CH_3); ^{19}F NMR ($CDCl_3$, 282 MHz) -112.8; HRMS (DART) *m/z* calcd for $C_{15}H_{21}FNO_4$ ($[M + NH_4]^+$): 298.14546. Found: 298.14595.



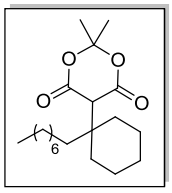
5-(1,1-Diphenylethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1z)

Prepared according to General Procedure A by dropwise addition of phenylmagnesium bromide (4 mL, 12 mmol, 3.0 M in THF) to 2,2-dimethyl-5-(1-phenylethylidene)-1,3-dioxane-4,6-dione[94a] (1.00 g, 4.06 mmol) in THF (6 mL); following addition of the Grignard and warming to rt the reaction was placed in a 50 °C oil bath and stirring was continued for 13.5 h. The reaction was worked up as outlined in General Procedure A and then the crude mixture was resubjected twice to the above conditions (20 h and 7 h reaction times respectively for the 2nd and 3rd cycle) to consume the starting material (which proved difficult to separate otherwise) as the reaction was otherwise not progressing further. Trituration with Et_2O afforded a white solid (300 mg collected over 2 crops, 23% yield). M.p. 136-137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29-7.15 (m, 10H), 4.60 (s, 1H), 2.03 (s, 3H), 1.80 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 163.0 (C), 145.2 (C), 128.1 (CH), 127.2 (CH), 126.4 (CH), 104.5 (C), 55.3 (CH), 49.2 (C), 28.2 (CH_3), 27.4 (CH_3), 27.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{24}NO_4$ ($[M + NH_4]^+$): 342.17053. Found: 342.17155.



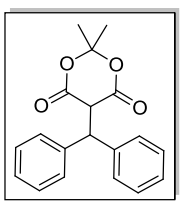
5-(1-Benzylcyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1ab)

Prepared according to General Procedure A by the addition of benzylmagnesium chloride (8.3 mL, 16.6 mmol, 2.0 M in THF) via syringe pump (0.34 mL/min) to 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.13**) (1.85 g, 8.25 mmol) in THF (13 mL); 2 h reaction time. Flash column chromatography eluting with hexanes:EtOAc (9:1) afforded a pale yellow oil (2.33 g, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29-7.16 (m, 5H), 3.58 (s, 1H), 2.92 (s, 2H), 1.94-1.89 (m, 2H), 1.70 (s, 3H), 1.68-1.42 (m overlapping with singlet at 1.62, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.7 (C), 136.9 (C), 130.9 (CH), 127.9 (CH), 126.5 (CH), 104.6 (C), 51.0 (CH), 43.0 (C), 39.8 (CH_2), 31.7 (CH_2), 28.3 (CH_3), 28.0 (CH_3), 25.3 (CH_2), 21.6 (CH_2); HRMS (DART) *m/z* calcd for $C_{19}H_{28}NO_4$ ($[M + NH_4]^+$): 334.20183. Found: 334.20210.



2,2-Dimethyl-5-(1-octylcyclohexyl)-1,3-dioxane-4,6-dione (4.1ac)

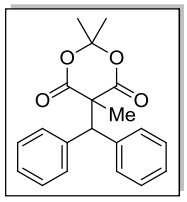
Prepared according to General Procedure A by the addition of octylmagnesium bromide (6.70 mL, 13.4 mmol, 2.0 M in THF) via syringe pump (0.34 mL/min) to 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.13**) (1.50 g, 6.69 mmol) in THF (10 mL); 1 h reaction time. Flash column chromatography eluting with hexanes:EtOAc (20:1) afforded a pale yellow oil (1.21 g, 54% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 3.48 (s, 1H), 1.71 (s, 3H), 1.66-1.63 (m overlapping with s at 1.66, 5H), 1.55-1.48 (m, 8H), 1.25 (m, 12H), 0.86 (br t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.4 (C), 104.9 (C), 52.4 (CH), 43.7 (C), 34.6 (CH_2), 33.2 (CH_2), 31.8 (CH_2), 30.2 (CH_2), 29.9 (CH_3), 29.5 (CH_2), 29.2 (CH_2), 27.6 (CH_3), 25.4 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 21.7 (CH_2), 14.0 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{35}O_4$ ($[M + H]^+$): 339.2529. Found: 339.2534.



5-Benzhydryl-2,2-dimethyl-1,3-dioxane-4,6-dione (4.6a)[261]

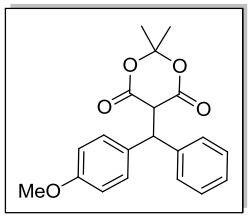
Prepared according to General Procedure B by the addition of phenylmagnesium bromide (7.47 mL, 22.4 mmol, 3.0 M solution in Et_2O) via syringe pump (0.34 mL/min) to 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione[66] (2.08 g,

8.96 mmol) in THF (8.96 mL); 12 h reaction time. Recrystallization from MeOH afforded a white solid (1.73 g, 62% yield). M.p. 134-135 °C (MeOH) [148-149 °C (ether/hexane)[261]]; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25-7.19 (m overlapping with $CHCl_3$, 10H), 5.34 (d, *J* = 2.6 Hz, 1H), 4.25 (d, *J* = 2.6 Hz, 1H), 1.69 (s, 3H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.6 (C), 140.0 (C), 129.1 (CH), 128.4 (CH), 127.1 (CH), 105.1 (C), 51.1 (CH), 49.0 (CH), 28.2 (CH_3), 27.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{19}H_{22}NO_4$ ($[M + NH_4]^+$): 328.15488. Found: 328.15597.



5-Benzhydryl-2,2,5-trimethyl-1,3-dioxane-4,6-dione (4.6b)[262]

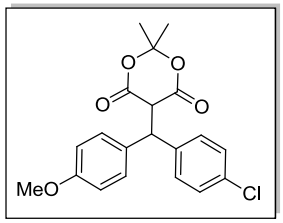
The following chemicals were added sequentially to an oven dried round bottom flask equipped with a magnetic stir bar at room temperature: 5-benzhydryl-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.6a**) (1.50 g, 4.83 mmol), K_2CO_3 (1.00 g, 7.30 mmol), DMF (4.8 mL), followed by addition of iodomethane (3.0 mL, 48 mmol) at 0 °C; the reaction was allowed to stir for 19 h at rt. The workup consisted of adding water and extracting with CH_2Cl_2 (3X), and then the combined organic layers were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. Trituration from MeOH (2X) afforded a white solid (0.458 g, 29% yield). M.p. 170-172 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.51 (dd, *J* = 7.6, 1.4 Hz, 4H), 7.32-7.21 (m overlapping with $CHCl_3$, 6H), 4.72 (s, 1H), 1.61 (s, 3H), 1.54 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.9 (C), 138.3 (C), 130.3 (CH), 128.5 (CH), 127.7 (CH), 105.2 (C), 60.6 (CH), 54.4 (C), 30.0 (CH_3), 27.7 (CH_3), 24.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{24}NO_4$ ($[M + NH_4]^+$): 342.17053. Found: 342.17069.



5-((4-Methoxyphenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.6d)[263]

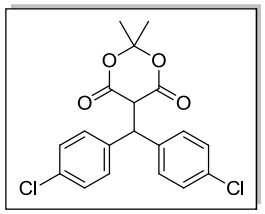
Prepared according to General Procedure B by the dropwise addition of phenylmagnesium chloride (8 mL, 16 mmol, 2.0 M in THF) to 5-(4-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione[66] (2.00 g, 7.63 mmol) in THF (76 mL); 21 h reaction time. Recrystallization from MeOH afforded a pale yellow solid (2.00 g, 77% yield). M.p. 124-125 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28-7.24 (m, 5H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.32 (d, *J* = 2.5 Hz, 1H), 4.28 (d, *J* = 2.7 Hz, 1H), 3.75 (s,

3H), 1.70 (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.8 (C), 164.6 (C), 158.5 (C), 140.3 (C), 131.9 (C), 130.4 (CH), 128.8 (CH), 128.3 (CH), 126.9 (CH), 113.6 (CH), 104.9 (C), 55.1 (CH_3), 51.1 (CH), 48.4 (CH), 28.1 (CH_3), 27.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{24}NO_5$ ($[M + NH_4]^+$): 358.16545. Found: 358.16684.



5-((4-Chlorophenyl)(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.6e)

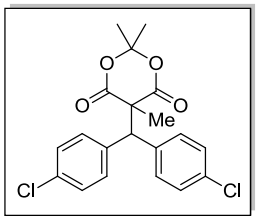
Prepared according to General Procedure B by the addition of 4-chlorophenylmagnesium bromide (15.3 mL, 15.3 mmol, 1.0 M solution in Et_2O) via syringe pump (0.34 mL/min) to 5-(4-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione[66] (2.00 g, 7.63 mmol) in THF (12 mL); 21 h reaction time. Upon quenching the reaction with 5% HCl, the extraction was performed with CH_2Cl_2 (3X) and then the combined organic layers were washed with brine (1X), dried with $MgSO_4$, filtered and concentrated. Recrystallization from MeOH afforded a white solid (1.53 g, 53% yield). M.p. 132-133 °C (MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.25 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.29 (d, *J* = 2.3 Hz, 1H), 4.22 (d, *J* = 2.6 Hz, 1H), 3.77 (s, 3H), 1.74 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.6 (C), 164.5 (C), 158.7 (C), 138.9 (C), 132.8 (C), 131.4 (C), 130.40 (CH), 130.36 (CH), 128.4 (CH), 113.8 (CH), 105.1 (C), 55.2 (CH_3), 51.1 (CH), 47.7 (CH), 28.2 (CH_3), 27.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{23}ClNO_5$ ($[M + NH_4]^+$): 392.12647. Found: 392.12662.



5-(Bis(4-chlorophenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.6f)

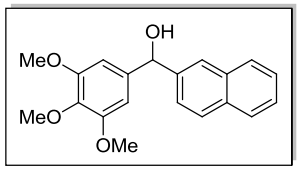
Prepared according to General Procedure B by the addition of 4-chlorophenylmagnesium bromide (13.2 mL, 13.2 mmol, 1.0 M solution in Et_2O) via syringe pump (0.34 mL/min) to 5-(4-chlorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione[66] (1.17 g, 4.39 mmol) in THF (4.4 mL); 16 h reaction time. Upon quenching the reaction with 5% HCl, the extraction was performed with CH_2Cl_2 (3X) and then the combined organic layers were washed with brine (1X), dried with $MgSO_4$, filtered and concentrated.

Recrystallization from MeOH afforded a white solid (1.41 g, 85% yield). M.p. 137-139 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.26 (d, *J* = 8.7 Hz, 4H), 7.20 (d, *J* = 8.6 Hz, 4H), 5.32 (d, *J* = 2.4 Hz, 1H), 4.21 (d, *J* = 2.6 Hz, 1H), 1.76 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.2 (C), 138.1 (C), 133.2 (C), 130.6 (CH), 128.6 (CH), 105.2 (C), 50.9 (CH), 47.5 (CH), 28.2 (CH_3), 27.4 (CH_3); HRMS (DART) *m/z* calcd for $C_{19}H_{20}Cl_2NO_4$ ($[M + NH_4]^+$): 396.07694. Found: 396.07613.



5-(Bis(4-chlorophenyl)methyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (4.6g)

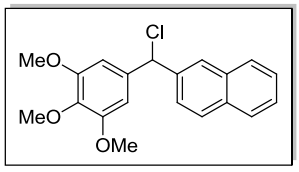
To an oven dried round bottom flask equipped with a magnetic stir bar cooled under a stream of N_2 was loaded 4,4'-(chloromethylene)bis(chlorobenzene)[264] (400 mg, 1.47 mmol), 2,2,5-trimethyl-1,3-dioxane-4,6-dione (697 mg, 4.41 mmol), K_2CO_3 (630 mg, 4.56 mmol) and DMF (4 mL, 0.4 M). The flask was then fitted with a rubber septum along with a nitrogen inlet and outlet. The mixture was stirred at rt for 10 min until vigorous evolution of CO_2 ceased and then the flask was stirred in a pre-heated 50 °C oil bath for 35.5 h. The workup consisted of cooling the reaction mixture to rt and then pouring it into a separatory funnel containing water. The organic phase was then extracted with Et_2O (3X), and the combined organic layers were washed with a sat. $NaHCO_3$ solution, dried with $MgSO_4$, filtered and concentrated. Flash column chromatography eluting with hexanes:EtOAc (12:1), having dry packed the sample, afforded unreacted 4,4'-(chloromethylene)bis(chlorobenzene) as the first compound to elute followed by a white solid (100 mg, 17% yield; 36% yield brsm). M.p. 167-168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.40 (d, *J* = 8.2 Hz, 4H), 7.27 (d overlapping with $CHCl_3$, *J* = 8.2 Hz, 4H), 4.70 (s, 1H), 1.63 (s, 3H), 1.55 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.6 (C), 136.3 (C), 133.9 (C), 131.5 (CH), 128.7 (CH), 105.3 (C), 58.9 (CH), 54.0 (C), 29.9 (CH_3), 27.9 (CH_3), 24.3 (CH_3); HRMS (DART) m/z calcd for $C_{20}H_{22}Cl_2NO_4$ ($[M + NH_4]^+$): 410.09259. Found: 410.09274.



Naphthalen-2-yl(3,4,5-trimethoxyphenyl)methanol (4.14)[265]

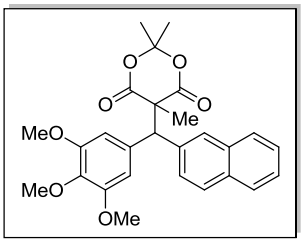
To an oven dried round bottom flask equipped with a magnetic stir bar

and cooled under a stream of N_2 was loaded 3,4,5-trimethoxybenzaldehyde (2.00 g, 10.2 mmol) and THF (15 mL). The vessel was then purged with N_2 and cooled in an icebath before adding 2-naphthylmagnesiumbromide (10.2 mL, 20.4 mmol, 2.0 M in THF) dropwise over 5 minutes; 1 h reaction time at rt. The workup consisted of cooling the vessel in an icebath, adding sat. NH_4Cl solution, and extracting with CH_2Cl_2 (3X). The combined organic layers were washed with a sat. brine solution before being dried with $MgSO_4$ then filtered and concentrated. Trituration of the crude white solid with boiling hexanes (3X) afforded a white solid free of naphthalene (2.88 g, 87% yield). M.p. 132-133 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.88-7.79 (m, 4H), 7.49-7.42 (m, 3H), 6.65 (s, 2H), 5.93 (s, 1H), 3.82 (s, 3H), 3.81 (s, 6H), 2.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 153.1 (C), 140.9 (C), 139.3 (C), 137.0 (C), 133.1 (C), 132.8 (C), 128.2 (CH), 128.0 (CH), 127.6 (CH), 126.1 (CH), 125.9 (CH), 124.9 (CH), 124.6 (CH), 103.5 (CH), 76.2 (CH), 60.7 (CH_3), 55.9 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{20}O_4$ (M^+): 324.13616. Found: 324.13558.



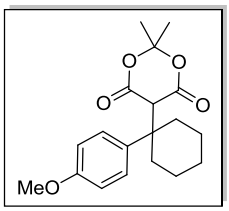
2-(Chloro(3,4,5-trimethoxyphenyl)methyl)naphthalene (4.15)

To an oven dried round bottom flask equipped with a magnetic stir bar and cooled under a stream of N_2 was loaded naphthalen-2-yl(3,4,5-trimethoxyphenyl)methanol (**4.14**) (2.00 g, 6.17 mmol) and CH_2Cl_2 (15 mL). The vessel was then purged with N_2 and cooled in an icebath before adding distilled thionyl chloride (1.80 mL, 24.7 mmol, 4 equiv) dropwise over 5 minutes. The flask was then removed from the icebath and allowed to stir at room temperature for an additional 30 minutes before concentrating the reaction to obtain a pale orange film (2.11 g, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.83-7.80 (m, 4H), 7.52-7.47 (m, 3H), 6.67 (s, 2H), 6.23 (s, 1H), 3.83 (s, 3H), 3.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 153.1 (C), 138.0 (C), 137.7 (C), 136.2 (C), 132.84 (C), 132.82 (C), 128.4 (CH), 128.1 (CH), 127.6 (CH), 126.47 (CH), 126.45 (CH), 126.41 (CH), 125.4 (CH), 105.1 (CH), 64.8 (CH), 60.8 (CH_3), 56.0 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{20}ClO_3$ ($[M + H]^+$): 343.11010. Found: 343.11099.



2,2,5-Trimethyl-5-(naphthalen-2-yl(3,4,5-trimethoxyphenyl)methyl)-1,3-dioxane-4,6-dione (4.6h)

To an oven dried round bottom flask equipped with a magnetic stir bar cooled under a stream of N_2 was loaded 2-(chloro(3,4,5-trimethoxyphenyl)methyl)naphthalene (**4.15**) (500 mg, 1.46 mmol), 2,2,5-trimethyl-1,3-dioxane-4,6-dione (692 mg, 4.38 mmol), K_2CO_3 (626 mg, 4.53 mmol) and DMF (4 mL, 0.4 M). The flask was then fitted with a rubber septum along with a nitrogen inlet and outlet. The mixture was stirred at rt for 10 min until evolution of CO_2 ceased and then the flask was stirred in a pre-heated 50 °C oil bath for 16 h. The workup consisted of cooling the reaction mixture to rt and then pouring it into a separatory funnel containing water with the aid of EtOAc and water. The layers were partitioned and then the organic phase was washed successively with water (2X), and sat. $NaHCO_3$ solution (2X) before being dried with $MgSO_4$, then filtered and concentrated. The pale yellow solid obtained was triturated with Et_2O to obtain a white solid (282 mg, 42% yield). M.p. 198-200 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.97 (s, 1H), 7.83-7.76 (m, 3H), 7.70 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.46-7.43 (m, 2H), 6.82 (s, 2H), 4.88 (s, 1H), 3.85 (s, 6H), 3.78 (s, 3H), 1.63 (s, 6H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.2 (C), 170.0 (C), 152.9 (C), 137.4 (C), 135.6 (C), 133.7 (C), 133.1 (C), 132.5 (C), 129.3 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 126.19 (CH), 126.16 (CH), 107.4 (CH), 105.1 (C), 60.7 (CH_3), 60.6 (CH), 56.0 (CH_3), 54.6 (C), 29.8 (CH_3), 27.8 (CH_3), 24.4 (CH_3); HRMS (DART) *m/z* calcd for $C_{27}H_{29}O_7$ ([M + H]$^+$): 465.19133. Found: 465.19262.

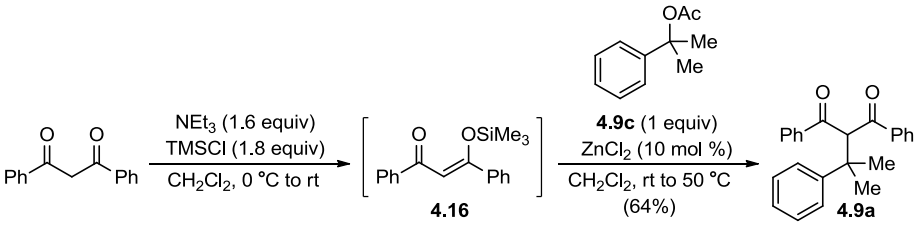


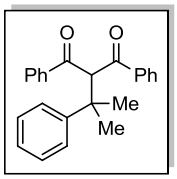
5-(1-(4-Methoxyphenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.1ad)

Prepared according to General Procedure A by the dropwise addition of 4-methoxyphenylmagnesium bromide (11.4 mL, 18.3 mmol, 1.6 M in THF) to 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.13**) (2.05 g, 9.14 mmol) in THF (14 mL); 2 h reaction time. Trituration with hexanes afforded a white solid (2.11 g, 69% yield). M.p. 123 - 125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.19 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H), 3.41 (s, 1H), 2.47-2.43 (app d, *J* = 13.9 Hz, 2H), 1.98 (app t, *J* = 10.4 Hz, 2H), 1.64 (m, 2H), 1.47 (s,

3H), 1.41-1.35 (m, 4H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.5 (C), 158.6 (C), 131.5 (C), 128.8 (CH), 113.9 (CH), 105.5 (C), 57.3 (CH), 55.1 (CH_3), 46.7 (C), 35.6 (CH_2), 30.5 (CH_3), 26.4 (CH_3), 25.7 (CH_2), 22.2 (CH_2); HRMS (DART) *m/z* calcd for $C_{19}H_{28}NO_5$ ([M + NH_4]$^+$): 350.19675. Found: 350.19659.

Preparation of 1,3-Diphenyl-2-(2-phenylpropan-2-yl)propane-1,3-dione (4.9a)

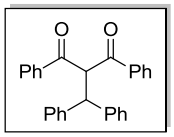




1,3-Diphenyl-2-(2-phenylpropan-2-yl)propane-1,3-dione (4.9a)

The method of preparation of **4.9a** was based on a report by Reetz and Hüttenhain,[266] and began with the *in situ* formation of 1,3-diphenyl-3-((trimethylsilyl)oxy)prop-2-en-1-one (**4.16**) as follows: a solution of dibenzoylmethane (500 mg, 2.23 mmol, 1 equiv) in CH_2Cl_2 (2.2 mL, 1.0 M) was stirred under a nitrogen atmosphere in an icebath for 7 minutes before the dropwise addition of triethylamine (0.50 mL, 3.6 mmol, 1.6 equiv). After stirring for an additional 1 h in the icebath, chlorotrimethylsilane (0.51 mL, 4.0 mmol, 1.8 equiv) was added and the reaction mixture was stirred for a further 14 h at rt. The *in situ* prepared 1,3-diphenyl-3-((trimethylsilyl)oxy)prop-2-en-1-one (**4.16**)[267] (660 mg, 2.23 mmol, 1 equiv) was then cannulated into a stirred suspension of zinc chloride (30 mg, 0.22 mmol, 10 mol %) in dichloromethane (2.2 mL, 1.0 M) under a nitrogen atmosphere at rt. This was followed by the dropwise addition of 2-phenylpropan-2-yl acetate (**4.9c**)[268] (400 mg, 2.23 mmol, 1 equiv) and the reaction mixture was then stirred in a 50 °C oil bath for 24 h. The workup consisted of cooling the reaction mixture to rt, followed by the addition of a saturated $NaHCO_3$ solution and extraction of the organic layer with CH_2Cl_2 (3X). The combined organic layers were then washed with brine (1X), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography eluting with toluene afforded a white solid (490 mg, 64% yield). M.p. 135-136 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.73 (d, *J* = 8.0 Hz, 4H), 7.46-7.38 (m, 4H), 7.30 (t, *J* = 7.6 Hz,

4H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.2 Hz, 1H), 5.90 (s, 1H), 1.64 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 194.6 (C), 147.9 (C), 138.0 (C), 132.8 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 126.2 (CH), 126.1 (CH), 63.8 (CH), 42.2 (C) 26.6 (CH_3); HRMS (DART) *m/z* calcd for $C_{24}H_{26}NO_2$ ($[M + NH_4]^+$): 360.19635. Found: 360.19719.

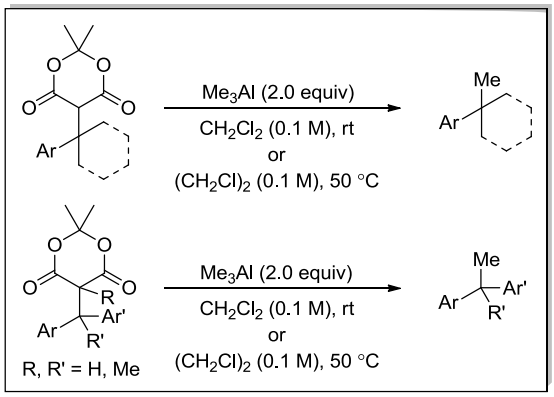


2-Benzhydryl-1,3-diphenylpropane-1,3-dione (4.10a)[269]

This protocol is based on a literature procedure.[270] In a 50 mL oven dried round bottom flask with stir bar was loaded: dibenzoylmethane (3.00 g, 13.4 mmol), benzhydrol (2.46 g, 13.4 mmol), nitromethane (13.4 mL, 1 M), and lastly *p*-toluenesulfonic acid monohydrate (0.127 g, 0.668 mmol) is added. A reflux condenser and rubber septum was attached and the assembly was purged with nitrogen then brought to reflux during which time a white solid was formed. After 20 minutes of refluxing the reaction was cooled to rt and then filtered. The filter cake was washed successively with hexane, water then benzene. The filter cake was further purified by trituration with boiling methanol and then dried under vacuum to afford a white solid (4.35 g, 83% yield). M.p. 225-228 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.81 (d, *J* = 7.5 Hz, 4H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 4H), 7.23 (d overlapping with $CHCl_3$, *J* = 7.4 Hz, 4H), 7.12 (t, *J* = 7.4 Hz, 4H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.32 (d, *J* = 11.6 Hz, 1H), 5.30 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 194.0 (C), 141.7 (C), 136.9 (C), 133.2 (CH), 128.58 (CH), 128.55 (CH), 128.51 (CH) 128.24 (CH), 126.6 (CH), 62.3 (CH), 52.4 (CH); HRMS (DART) m/z calcd for $C_{28}H_{23}O_2$ ($[M + H]^+$): 391.16980. Found: 391.16880.

Substitution Reactions

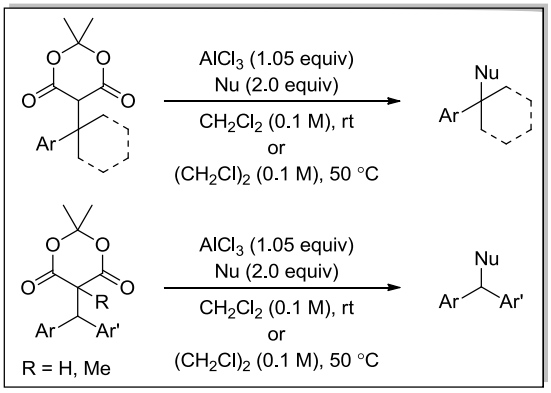
General Procedure C - Me_3Al Promoted Substitution Reactions of Benzyl Meldrum's Acids



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

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

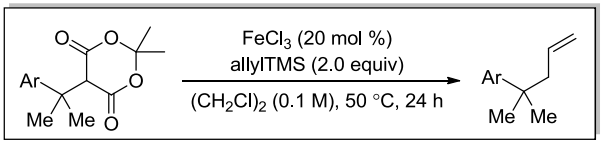
General Procedure D - $AlCl_3$ Promoted Substitution Reactions of Benzyl Meldrum's Acids



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

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

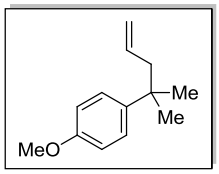
General Procedure E – $FeCl_3$ Catalyzed Allylation of Benzyl Meldrum's Acids



In a glove box, benzyl Meldrum's acid (1 equiv) and $(CH_2Cl)_2$ (0.1 M) were charged in an oven-dried sample vial with a magnetic stir bar, followed by the addition of

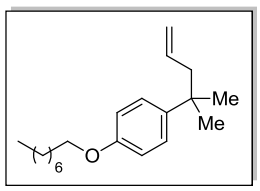
allyltrimethylsilane (2 equiv) and then iron(III) chloride (20 mol %, 97% reagent grade). The vial was then capped with a rubber septum and the reaction mixture was stirred in a pre-heated 50 °C oil bath outside of the glove box for 24 h. The workup consisted of cooling the vial in an ice bath before 5% HCl and Et_2O was slowly added to the reaction mixture. The layers were partitioned and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using silica gel and eluting with pentane. The spectral properties of the products obtained from General Procedure E (reported in Table 4.5) were identical to those from General Procedure D.

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



1-Methoxy-4-(2-methylpent-4-en-2-yl)benzene (4.2a)[271]

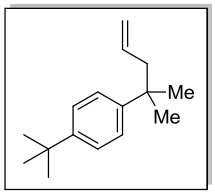
Prepared according to General Procedure D from Meldrum's derivative **4.1a** (90 mg, 0.31 mmol), allyltrimethylsilane (0.10 mL, 0.62 mmol), $AlCl_3$ (43 mg, 0.32 mmol) and CH_2Cl_2 (3.1 mL); 30 min reaction time at rt. Flash column chromatography eluting on a gradient with hexanes:EtOAc (100:0 to 9:1) afforded a pale yellow oil (58 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.57 (ddt, *J* = 17.4, 10.3, 7.2 Hz, 1H), 4.94 (d overlapping with d at 4.93 ppm, *J* = 16.9 Hz, 1H), 4.93 (d, *J* = 10.3 Hz, 1H), 3.78 (s, 3H), 2.32 (d, *J* = 7.2 Hz, 2H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.3 (C), 141.4 (C), 135.7 (CH), 126.8 (CH), 116.8 (CH_2), 113.3 (CH), 55.2 (CH_3), 48.9 (CH_2), 37.0 (C), 28.7 (CH_3); HRMS (DART) *m/z* calcd for $C_{13}H_{19}O$ ($[M + H]^+$): 191.14359. Found: 191.14393.



1-(2-Methylpent-4-en-2-yl)-4-(octyloxy)benzene (4.2b)

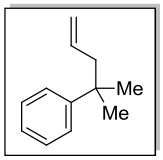
Prepared according to General Procedure D from 2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**4.1b**) (60 mg, 0.15 mmol), allyltrimethylsilane (0.05 mL, 0.3 mmol), $AlCl_3$ (22 mg, 0.16 mmol) and CH_2Cl_2 (1.5 mL); 30 min reaction time at rt. Flash column chromatography eluting

with pentane:CH_2Cl_2 (9:1), having dry packed the sample, afforded a pale yellow oil (44 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.57 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 4.96 (d overlapping with d at 4.95 ppm, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 9.9 Hz, 1H), 3.94 (t, *J* = 6.6 Hz, 2H), 2.34 (d, *J* = 7.3 Hz, 2H), 1.78 (quintet, *J* = 7.0 Hz, 2H), 1.46-1.41 (m, 2H), 1.40-1.28 (m which overlaps with s at 1.28, 14H), 0.90 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.9 (C), 141.1 (C), 135.7 (CH), 126.7 (CH), 116.7 (CH_2), 113.8 (CH), 67.8 (CH_2), 48.9 (CH_2), 36.9 (C), 31.8 (CH_2), 29.4 (2xCH_2), 29.2 (CH_2), 28.7 (CH_3), 26.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{33}O$ ($[M + H]^+$): 289.25314. Found: 289.25378.



1-(*tert*-Butyl)-4-(2-methylpent-4-en-2-yl)benzene (4.2c)

Prepared according to General Procedure D from Meldrum's derivative **4.1c** (200 mg, 0.628 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (88 mg, 0.66 mmol) and CH_2Cl_2 (6.3 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a colourless oil (123 mg, 91% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 5.61 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.00 (d overlapping with d at 4.98 ppm, *J* = 17.7 Hz, 1H), 4.98 (d, *J* = 9.4 Hz, 1H), 2.38 (d, *J* = 7.2 Hz, 2H), 1.34 (s, 9H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.0 (C), 146.2 (C), 135.8 (CH), 125.4 (CH), 124.8 CH), 116.7 (CH_2), 48.8 (CH_2), 37.1 (C), 34.2 (C), 31.4 (CH_3), 28.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{16}H_{28}N$ ($[M + NH_4]^+$): 234.22217. Found: 234.22319.



(2-Methylpent-4-en-2-yl)benzene (4.2d)[271]

Prepared according to General Procedure D from Meldrum's derivative **4.1d** (232 mg, 0.884 mmol), allyltrimethylsilane (0.28 mL, 1.8 mmol), $AlCl_3$ (124 mg, 0.930 mmol) and CH_2Cl_2 (8.8 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (126 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35-7.26 (m, 4H), 7.18-7.13 (m, 1H), 5.53 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1H), 4.94 (d overlapping with d at 4.92 ppm, *J* = 18.1 Hz, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 2.35 (d, *J* = 7.2 Hz, 2H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 149.2 (C), 135.5 (CH), 128.0 (CH), 125.8 (CH), 125.5 (CH),

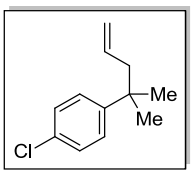
116.9 (CH_2), 48.8 (CH_2), 37.6 (C), 28.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{12}H_{17}$ ($[M + H]^+$): 161.13303. Found: 161.13253. Run #2 = 88% yield; Avg 89% yield.

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

Also prepared in analogy to General Procedure D from (2-chloropropan-2-yl)benzene (**4.9b**)[272] (202 mg, 1.31 mmol), allyltrimethylsilane (0.42 mL, 2.6 mmol), $AlCl_3$ (184 mg, 1.38 mmol) and CH_2Cl_2 (13.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (86 mg, 41% yield). The spectral properties were identical to those reported above. Run #2 = 42% yield; Avg 42% yield.

Also prepared in analogy to General Procedure D from 2-phenylpropan-2-yl acetate (**4.9c**)[268] (230 mg, 1.29 mmol), allyltrimethylsilane (0.41 mL, 2.6 mmol), $AlCl_3$ (180 mg, 1.35 mmol) and CH_2Cl_2 (12.9 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (99 mg, 48% yield). The spectral properties were identical to those reported above. Run #2 = 44% yield; Avg 46% yield.

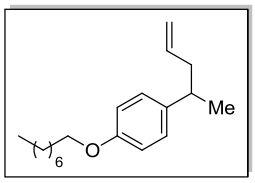
Also prepared in analogy to General Procedure D from 2-phenylpropan-2-ol (**4.9d**) (183 mg, 1.34 mmol), allyltrimethylsilane (0.43 mL, 2.7 mmol), $AlCl_3$ (188 mg, 1.41 mmol) and CH_2Cl_2 (13.4 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (106 mg, 49% yield). The spectral properties were identical to those reported above. Run #2 = 51% yield; Avg 50% yield.



1-Chloro-4-(2-methylpent-4-en-2-yl)benzene (4.2e)

Prepared according to General Procedure D from Meldrum's derivative **4.1e** (100 mg, 0.337 mmol), allyltrimethylsilane (0.11 mL, 0.67 mmol), $AlCl_3$ (48

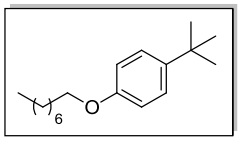
mg, 0.36 mmol), and CH_2Cl_2 (3.3 mL); 25 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a pale yellow oil (58 mg, 88% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23 (app s overlapping with $CHCl_3$, 4H), 5.50 (ddt, *J* = 17.0, 10.6, 7.3 Hz, 1H), 4.93 (d overlapping with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



1-(Octyloxy)-4-(pent-4-en-2-yl)benzene (4.2i)

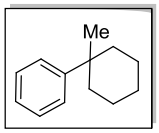
Prepared according to General Procedure D from 2,2,5-trimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**4.1i**) (187 mg, 0.479 mmol), allyltrimethylsilane (0.15 mL, 0.96 mmol), $AlCl_3$ (67 mg, 0.50 mmol) and CH_2Cl_2 (4.79 mL); 24 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (101 mg, 77% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.08 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.69 (ddt, *J* = 17.0, 10.1, 7.1 Hz, 1H), 4.97 (d slightly overlapping with d at 4.93, *J* = 15.2 Hz, 1H), 4.93 (d, *J* = 8.2 Hz, 1H), 3.91 (t, *J* = 6.6 Hz, 2H), 2.72 (sextet, *J* = 7.0 Hz, 1H), 2.38-2.18 (m, 2H), 1.75 (quintet, *J* = 7.0 Hz, 2H), 1.43-1.38 (m, 2H), 1.37-1.27 (m, 8H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.87 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.2 (C), 138.8 (C), 137.2 (CH), 127.6 (CH), 115.6 (CH_2), 114.2 (CH), 67.9 (CH_2), 42.8 (CH_2), 38.8 (CH), 31.7 (CH_2), 29.3 (2xCH_2), 29.1 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 21.6 (CH_3), 13.9 (CH_3); HRMS (DART) *m*/*z* calcd for $C_{19}H_{34}NO$ ($[M + NH_4]^+$): 292.26404. Found: 292.26424.

Alternatively prepared according to General Procedure D from 2,2-dimethyl-5-(1-(4-(octyloxy)phenyl)ethyl)-1,3-dioxane-4,6-dione (**4.1h**) (197 mg, 0.523 mmol), allyltrimethylsilane (0.20 mL, 1.05 mmol), $AlCl_3$ (73 mg, 0.55 mmol) and CH_2Cl_2 (5.2 mL); 24 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (97 mg, 68% yield). The spectral properties were identical to those reported above.



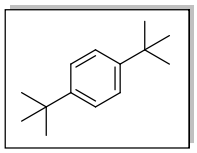
1-(*tert*-Butyl)-4-(octyloxy)benzene (4.2j)[273]

Prepared according to General Procedure C from Meldrum's derivative **4.1b** (204 mg, 0.522 mmol), Me_3Al (0.53 mL, 1.06 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (5.2 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a pale yellow oil (129 mg, 94% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30 (dd, *J* = 7.8, 2.1 Hz, 2H), 6.80 (dd, *J* = 7.8, 2.0 Hz, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 1.77 (quintet, *J* = 7.1 Hz, 2H), 1.45-1.40 (m, 2H), 1.30 (m, 17H), 0.87 (br t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 156.9 (C), 143.1 (C), 126.1 (CH), 113.9 (CH), 67.9 (CH_2), 34.0 (C), 31.8 (CH_2), 31.5 (CH_3), 29.4 (2 x CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{18}H_{31}O$ ($[M + H]^+$): 263.23749. Found: 263.23749. Run #2 = 95% yield; Avg = 95% yield.



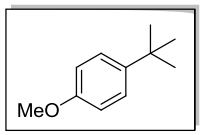
(1-Methylcyclohexyl)benzene (4.2k)[274]

Prepared according to General Procedure C from Meldrum's derivative **4.1j** (163 mg, 0.539 mmol), Me_3Al (0.54 mL, 1.1 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (5.4 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless liquid (94 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.38-7.27 (m, 4H), 7.15 (t, *J* = 7.1 Hz, 1H), 2.02-1.95 (m, 2H), 1.58-1.41 (m, 8H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 149.9 (C), 128.2 (CH), 125.8 (CH), 125.2 (CH), 37.9 (2C's: C and CH_2), 30.5 (CH_3), 26.4 (CH_2), 22.7 (CH_2); HRMS (EI) *m/z* calcd for $C_{13}H_{18}$ (M^+): 174.1409. Found: 174.1408.



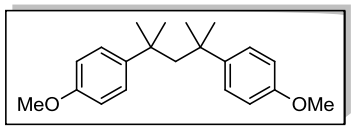
1,4-Di-*tert*-butylbenzene (4.2l)[275]

Prepared according to General Procedure C from Meldrum's derivative **4.1c** (200 mg, 0.628 mmol), Me_3Al (0.63 mL, 1.2 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (6.3 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a white solid (115 mg, 96% yield). M.p. 72-74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.41 (s, 4H), 1.41 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.0 (C), 124.9 (CH), 34.2 (C), 31.4 (CH_3); HRMS (DART) *m/z* calcd for $C_{14}H_{26}N$ ($[M + NH_4]^+$): 208.20652. Found: 208.20718.

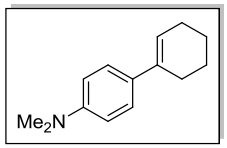


1-(*tert*-Butyl)-4-methoxybenzene (4.2m)[276] and 4,4'-(2,4-Dimethylpentane-2,4-diyl)bis(methoxybenzene) (4.17)

Prepared according to General Procedure C from Meldrum's derivative **4.1a** (198 mg, 0.677 mmol), Me_3Al (0.68 mL, 1.4 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (6.8 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane:diethyl ether (100:1) afforded **4.2m** as the first product to elute in the form of a colourless oil (103 mg, 93% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.31 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.3 (C), 143.3 (C), 126.2 (CH), 113.3 (CH), 55.2 (CH_3), 34.0 (C), 31.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{11}H_{17}O$ ($[M + H]^+$): 165.12794. Found: 165.12833.

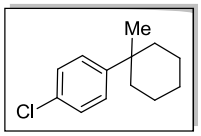


Compound **4.17** was second column to elute from the above column, having increased the solvent polarity to pentane:diethyl ether (50:1), and was isolated as a colorless oil (7 mg, 7% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.12 (d, *J* = 8.8 Hz, 4H), 6.75 (d, *J* = 8.7 Hz, 4H), 3.77 (s, 6H), 2.09 (s, 2H), 1.00 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.2 (C), 142.3 (C), 126.9 (CH), 113.0 (CH), 57.8 (CH_2), 55.2 (CH_3), 37.9 (C), 31.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{21}H_{32}NO_2$ ($[M + NH_4]^+$): 330.24330. Found: 330.24359.



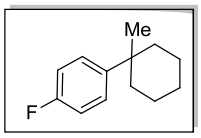
***N*,*N*-Dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-amine (4.4)**

Prepared according to General Procedure C from Meldrum's derivative **4.1k** (150 mg, 0.434 mmol), Me_3Al (0.43 mL, 0.87 mmol, 2.0 M solution in heptanes) and CH_2Cl_2 (4.3 mL); 4 h reaction time at rt. Following the extraction of the aqueous layer with Et_2O (3X) as outlined in General Procedure, the combined organic layers were washed with a sat. $NaHCO_3$ solution (2X), then dried with $MgSO_4$, filtered and concentrated to obtain a pale yellow solid (86 mg, >90% purity). M.p. 40-44 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.27 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 8.9 Hz, 2H), 5.98 (m, 1H), 2.91 (s, 6H), 2.36-2.34 (m, 2H), 2.18-2.15 (m, 2H), 1.76-1.70 (m, 2H), 1.65-1.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 149.4 (C), 135.9 (C), 131.2 (C), 125.5 (CH), 121.5 (CH), 112.5 (CH), 40.7 (CH_3), 27.3 (CH_2), 25.8 (CH_2), 23.2 (CH_2), 22.3 (CH_2); HRMS (DART) *m/z* calcd for $C_{14}H_{20}N$ ($[M + H]^+$): 202.15957. Found: 202.16049.



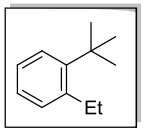
1-Chloro-4-(1-methylcyclohexyl)benzene (4.2o)

Prepared according to General Procedure C from Meldrum's derivative **4.1l** (150 mg, 0.445 mmol), Me_3Al (0.45 mL, 0.90 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (4.5 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (93 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29 (d, J = 9.2 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 1.97-1.91 (m, 2H), 1.58-1.35 (m, 8H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.4 (C), 130.9 (C), 128.2 (CH), 127.4 (CH), 37.8 (CH_2), 37.7 (C), 30.5 (CH_3), 26.3 (CH_2), 22.6 (CH_2); HRMS (EI) *m/z* calcd for $C_{13}H_{17}Cl$ (M^+): 208.1019. Found: 208.1024.



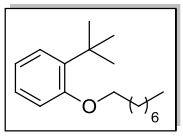
1-Fluoro-4-(1-methylcyclohexyl)benzene (4.2p)

Prepared according to General Procedure C from Meldrum's derivative **4.1m** (173 mg, 0.540 mmol), Me_3Al (0.54 mL, 1.1 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (5.4 mL); 30 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (99 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30 (dd, J = 8.7, 5.6 Hz, 2H), 6.97 (app t, J = 8.8 Hz, 2H), 1.97-1.90 (m, 2H), 1.59-1.40 (m, 8H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 160.7 (C, d, J = 241.9 Hz), 145.6 (C), 127.3 (CH, d, J = 7.5 Hz), 114.7 (CH, d, J = 20.5 Hz), 38.0 (CH_2), 37.6 (C), 30.6 (CH_3), 26.3 (CH_2), 22.6 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -118.6; HRMS (EI) *m/z* calcd for $C_{13}H_{17}F$ (M^+): 192.1314. Found: 192.1317.



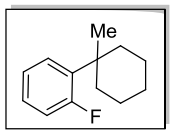
1-(*tert*-Butyl)-2-ethylbenzene (4.2q)[277]

Prepared according to General Procedure C from Meldrum's derivative **4.1n** (67 mg, 0.23 mmol), Me_3Al (0.23 mL, 0.46 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (2.3 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a yellow oil (34 mg, 91% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.34 (dd, J = 7.8, 1.2 Hz, 1H), 7.21-7.09 (m, 3H), 2.88 (q, J = 7.4 Hz, 2H), 1.40 (s, 9H), 1.25 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 147.1 (C), 143.0 (C), 131.1 (CH), 126.0 (CH), 125.9 (CH), 125.4 (CH), 35.7 (C), 31.6 (CH_3), 27.1 (CH_2), 17.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{12}H_{18}$ (M^+): 162.1409. Found: 162.1406.



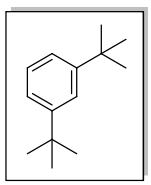
1-(*tert*-Butyl)-2-(octyloxy)benzene (4.2r)

Prepared according to General Procedure C from Meldrum's derivative **4.1o** (26 mg, 0.066 mmol), Me_3Al (0.07 mL, 0.13 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (0.66 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes:EtOAc (9:1) afforded a light yellow liquid (16 mg, 94% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.26 (d overlapping with $CHCl_3$, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.86 (t overlapping with d at 6.84 ppm, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 1.82 (quintet, *J* = 6.9 Hz, 2H), 1.52 (m, 2H), 1.37 (s, 9H), 1.24 (m, 8H), 0.87 (br t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.9 (C), 137.9 (C), 126.9 (CH), 126.5 (CH), 119.9 (CH), 111.7 (CH), 67.7 (CH_2), 34.8 (C), 31.8 (CH_2), 29.8 (CH_3), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{18}H_{31}O$ ($[M + H]^+$): 263.23749. Found: 263.23808.



1-Fluoro-2-(1-methylcyclohexyl)benzene (4.2s)

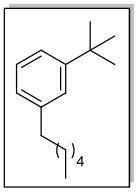
Prepared according to General Procedure C from Meldrum's derivative **4.1p**[256] (40 mg, 0.12 mmol), Me_3Al (0.12 mL, 0.24 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (1.2 mL); 1 h reaction time at rt. Flash column chromatography eluting with pentane afforded a pale yellow oil (23 mg, 96% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30 (dt, *J* = 8.1, 1.6 Hz, 1H), 7.18-7.12 (m, 1H), 7.06 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.97 (ddd, *J* = 13.2, 7.9, 1.1 Hz, 1H), 2.09-2.03 (m, 2H), 1.63-1.44 (m, 8H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 162.1 (C, d, *J* = 246.4 Hz), 136.3 (C, d, *J* = 10.4 Hz), 128.2 (CH, d, *J* = 6.0 Hz), 127.2 (CH, d, *J* = 9.0 Hz), 123.7 (CH, d, *J* = 3.2 Hz), 116.5 (CH, d, *J* = 25.0 Hz), 37.8 (C, d, *J* = 3.2 Hz), 37.2 (CH_2, d, *J* = 4.1 Hz), 26.8 (CH_3), 26.4 (CH_2), 22.7 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -109.1; HRMS (EI) *m/z* calcd for $C_{13}H_{17}F$ (M^+): 192.1314. Found: 192.1317.



1,3-Di-*tert*-butylbenzene (4.2t)[278]

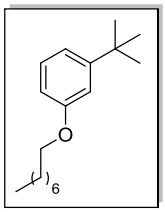
Prepared according to General Procedure C from Meldrum's derivative **4.1q** (100 mg, 0.314 mmol), Me_3Al (0.31 mL, 0.62 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (3.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane,

having dry packed the sample, afforded a pale yellow oil (59 mg, 98% yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.48 (s, 1H), 7.21-7.20 (m, 3H), 1.31 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) 150.6 (C), 127.6 (CH), 122.4 (CH), 122.2 (CH), 34.8 (C), 31.5 (CH_3); HRMS (EI) *m/z* calcd for $C_{14}H_{22}$ (M^+): 190.1722. Found: 190.1727.



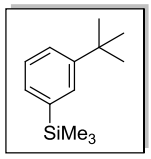
1-(*tert*-Butyl)-3-hexylbenzene (4.2u)[279]

Prepared according to General Procedure C from Meldrum's derivative **4.1r** (100 mg, 0.289 mmol), Me_3Al (0.29 mL, 0.58 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (2.9 mL); 30 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a pale yellow oil (61 mg, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.24-7.19 (m overlapping with $CHCl_3$, 3H), 7.00-6.98 (m, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.62 (quintet, *J* = 7.4 Hz, 2H), 1.31-1.26 (m overlapping with singlet at 1.31 ppm, 15H), 0.89 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 151.0 (C), 142.5 (C), 127.9 (CH), 125.4 (2 x CH), 122.5 (CH), 36.3 (CH_2), 34.6 (C), 31.8 (CH_2), 31.6 (CH_2), 31.4 (CH_3), 29.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (EI) *m/z* calcd for $C_{16}H_{26}$ (M^+): 218.2035. Found: 218.2041.



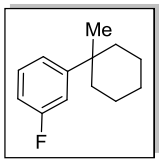
1-(*tert*-Butyl)-3-(octyloxy)benzene (4.2v)

Prepared according to General Procedure C from Meldrum's derivative **4.1s** (200 mg, 0.512 mmol), Me_3Al (0.51 mL, 1.0 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (5.1 mL); 5 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (119 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.20 (t, *J* = 7.9 Hz, 1H), 6.96-6.92 (m, 2H), 6.69 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.93 (t, *J* = 6.6 Hz, 2H), 1.76 (quintet, *J* = 7.0 Hz, 2H), 1.49-1.28 (m overlapping with singlet at 1.29, 19H), 0.87 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.9 (C), 152.8 (C), 128.9 (CH), 117.6 (CH), 112.6 (CH), 110.4 (CH), 67.8 (CH_2), 34.7 (C), 31.8 (CH_2), 31.3 (CH_3), 29.4 (2 x CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{18}H_{31}O$ ($[M + H]^+$): 263.23749. Found: 263.23847.



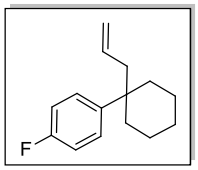
(3-(*tert*-Butyl)phenyl)trimethylsilane (4.2w)[280]

Prepared according to General Procedure C from Meldrum's derivative **4.1t** (100 mg, 0.299 mmol), Me_3Al (0.30 mL, 0.60 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (3.0 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a colourless oil (62 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.53 (s, 1H), 7.39-7.28 (m, 3H), 1.32 (s, 9H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 150.0 (C), 139.9 (C), 130.5 (CH), 129.9 (CH), 127.4 (CH), 125.9 (CH), 34.7 (C), 31.4 (CH_3), -1.0 (CH_3); HRMS (DART) *m/z* calcd for $C_{13}H_{23}Si$ ($[M + H]^+$): 207.15690. Found: 207.15600.



1-Fluoro-3-(1-methylcyclohexyl)benzene (4.2x)

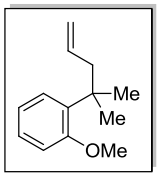
Prepared according to General Procedure C from Meldrum's derivative **4.1u** (100 mg, 0.312 mmol), Me_3Al (0.31 mL, 0.62 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (3.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a colourless oil (59 mg, 98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28-7.21 (m overlapping with $CHCl_3$, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.05 (dt, *J* = 11.6, 2.1 Hz, 1H), 6.84 (td, *J* = 8.3, 2.3 Hz, 1H), 1.98-1.91 (m, 2H), 1.60-1.41 (m, 8H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 163.1 (C, d, *J* = 242.2 Hz), 153.0 (C, d, *J* = 6.1 Hz), 129.4 (CH, d, *J* = 8.2 Hz), 121.4 (CH, d, *J* = 2.2 Hz), 113.0 (CH, d, *J* = 21.4 Hz), 112.0 (CH, d, *J* = 20.9 Hz), 38.1 (C), 37.8 (CH_2), 30.4 (CH_3), 26.3 (CH_2), 22.6 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -113.9; HRMS (DART) *m/z* calcd for $C_{13}H_{17}F$ (M^+): 192.13143. Found: 192.13084.



1-(1-Allylcyclohexyl)-4-fluorobenzene (4.2z)[281]

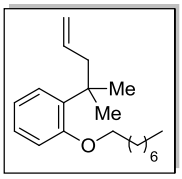
Prepared according to General Procedure D from Meldrum's derivative **4.1m** (50 mg, 0.16 mmol), allyltributyltin (0.10 mL, 0.31 mmol), $AlCl_3$ (22 mg, 0.16 mmol), and CH_2Cl_2 (1.6 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a pale yellow oil (30 mg, 88% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.24 (dd overlapping with $CHCl_3$, *J* = 8.9, 5.4 Hz, 2H), 6.98 (app t, *J* = 8.8 Hz, 2H), 5.36 (ddt, *J* = 17.7, 10.4, 7.3 Hz, 1H), 4.89-4.81 (m, 2H), 2.22 (d, *J* = 7.3 Hz, 2H),

2.01 (br dd, *J* = 13.2, 5.5 Hz, 2H), 1.61-1.31 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) 160.7 (C, d, *J* = 242.1 Hz), 142.2 (C), 134.6 (CH), 128.3 (CH, d, *J* = 7.5 Hz), 116.9 (CH_2), 114.7 (CH, d, *J* = 20.5 Hz), 48.5 (CH_2), 40.8 (C), 35.9 (CH_2), 26.4 (CH_2), 22.2 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) -118.3; HRMS (DART) *m/z* calcd for $C_{15}H_{20}F$ ($[M + H]^+$): 219.15490. Found: 219.15528.



1-Methoxy-2-(2-methylpent-4-en-2-yl)benzene (4.2aa)

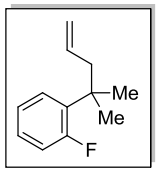
Prepared according to General Procedure D from Meldrum's derivative **4.1v** (200 mg, 0.684 mmol), allyltrimethylsilane (220 μL, 1.37 mmol), $AlCl_3$ (96 mg, 0.72 mmol) and CH_2Cl_2 (6.8 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a colourless oil (107 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23-7.18 (m, 2H), 6.93-6.87 (m, 2H), 5.52 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 4.94 (d slightly overlapping with d at 4.88 ppm, *J* = 17.1 Hz, 1H), 4.88 (d, *J* = 10.3 Hz, 1H), 3.84 (s, 3H), 2.62 (d, *J* = 7.3 Hz, 2H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.3 (C), 136.7 (CH), 136.2 (C), 127.5 (CH), 127.1 (CH), 120.2 (CH), 115.8 (CH_2), 111.3 (CH), 54.9 (CH_3), 45.1 (CH_2), 37.9 (C), 27.9 (CH_3); HRMS (DART) *m/z* calcd for $C_{13}H_{19}O$ ($[M + H]^+$): 191.14359. Found: 191.14353.



1-(2-Methylpent-4-en-2-yl)-2-(octyloxy)benzene (4.2ab)

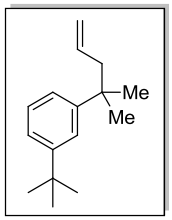
Prepared according to General Procedure D from Meldrum's derivative **4.1o** (198 mg, 0.507 mmol), allyltrimethylsilane (0.16 mL, 1.0 mmol), $AlCl_3$ (71 mg, 0.53 mmol) and CH_2Cl_2 (5.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (86 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28-7.19 (m overlapping with $CHCl_3$, 2H), 6.95-6.89 (m, 2H), 5.57 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 4.95 (d overlapping slightly with d at 4.92 ppm, *J* = 17.1 Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.03 (t, *J* = 6.5 Hz, 2H), 2.69 (d, *J* = 7.3 Hz, 2H), 1.91 (quintet, *J* = 7.0 Hz, 2H), 1.60-1.52 (m, 2H), 1.42-1.21 (m that overlaps with s at 1.42, 14H), 0.95 (br t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.7 (C), 136.7 (CH), 135.9 (C), 127.5 (CH), 127.1 (CH), 119.9 (CH), 115.8 (CH_2), 111.6 (CH), 67.7 (CH_2), 45.0 (CH_2), 37.9 (C), 31.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.9 (CH_3), 26.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{33}O$ ($[M + H]^+$): 289.25314. Found: 289.25352.

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



1-Fluoro-2-(2-methylpent-4-en-2-yl)benzene (4.2ac)

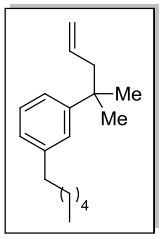
Prepared according to General Procedure D from Meldrum's derivative **4.1w** (100 mg, 0.357 mmol), allyltrimethylsilane (0.11 mL, 0.71 mmol), $AlCl_3$ (50 mg, 0.37 mmol), and CH_2Cl_2 (3.6 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a colourless oil (25 mg, 39% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) 7.23-7.14 (m, 2H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.97 (dd, *J* = 12.9, 8.1, 0.9 Hz, 1H), 5.52 (ddt, *J* = 17.1, 10.7, 7.2 Hz, 1H), 4.95 (d, *J* = 17.0 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 2.49 (d, *J* = 7.3 Hz, 2H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 161.8 (C, d, *J* = 246.0 Hz), 135.5 (CH), 135.2 (C, d, *J* = 11.2 Hz), 128.0 (CH, d, *J* = 5.8 Hz), 127.7 (CH, d, *J* = 8.9 Hz), 123.6 (CH, d, *J* = 3.3 Hz), 116.8 (CH_2), 116.2 (CH, d, *J* = 24.5 Hz), 46.0 (CH_2, d, *J* = 4.4 Hz), 37.5 (C, d, *J* = 2.9 Hz), 27.8 (CH_3, d, *J* = 2.8 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) -109.5; HRMS (DART) *m/z* calcd for $C_{12}H_{16}F$ ($[M + H]^+$): 179.12360. Found: 179.12438.



1-(*tert*-Butyl)-3-(2-methylpent-4-en-2-yl)benzene (4.2ad)

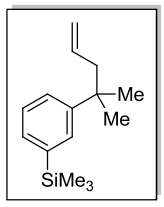
Prepared according to General Procedure D from Meldrum's derivative **4.1q** (100 mg, 0.314 mmol), allyltrimethylsilane (0.10 mL, 0.63 mmol), $AlCl_3$ (44 mg, 0.33 mmol), and CH_2Cl_2 (3.1 mL); 20 min reaction time at rt. Flash chromatography eluting with pentane, having dry packed the sample, afforded a colourless oil (42 mg, 62% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.44 (d, *J* = 1.4 Hz, 1H), 7.30-7.20 (m overlapping with $CHCl_3$, 3H), 5.64 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.04 (d overlapping with d at 5.02 ppm, *J* = 10.0 Hz, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 2.43 (d, *J* = 4.2 Hz, 2H), 1.38 (s, 9H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 150.5 (C), 148.8 (C), 135.7 (CH), 127.6 (CH), 122.9

(2 x CH), 122.4 (CH), 116.8 (CH_2), 48.9 (CH_2), 37.7 (C), 34.8 (C), 31.4 (CH_3), 28.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{16}H_{24}$ (M^+): 216.1878. Found: 216.1870.



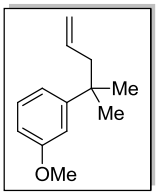
1-Hexyl-3-(2-methylpent-4-en-2-yl)benzene (4.2ae)

Prepared according to General Procedure D from Meldrum's derivative **4.1r** (100 mg, 0.289 mmol), allyltrimethylsilane (0.09 mL, 0.6 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and CH_2Cl_2 (2.9 mL); 20 min reaction time at rt. Flash chromatography eluting with pentane, having dry packed the sample, afforded a colourless oil (41 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25-7.15 (m overlapping with $CHCl_3$, 3H), 7.01 (d, *J* = 7.2 Hz, 1H), 5.58 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 4.99 (d overlapping with d at 4.98 ppm, *J* = 9.2 Hz, 1H), 4.98 (d, *J* = 17.8 Hz, 1H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.37 (d, *J* = 7.2 Hz, 2H), 1.62 (quintet, *J* = 7.8 Hz, 2H), 1.31-1.27 (m, 12H), 0.90 (br t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 149.1 (C), 142.5 (C), 135.7 (CH), 127.8 (CH), 126.0 (CH), 125.5 (CH), 123.0 (CH), 116.7 (CH_2), 48.8 (CH_2), 37.5 (C), 36.3 (CH_2), 31.7 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 28.5 (CH_3), 22.6 (CH_2), 14.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{18}H_{32}N$ ($[M + NH_4]^+$): 262.25347. Found: 262.25443.



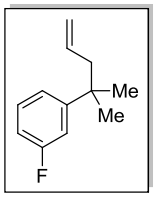
Trimethyl(3-(2-methylpent-4-en-2-yl)phenyl)silane (4.2af)

Prepared according to General Procedure D from Meldrum's derivative **4.1t** (100 mg, 0.299 mmol), allyltrimethylsilane (0.10 mL, 0.60 mmol), $AlCl_3$ (42 mg, 0.31 mmol) and CH_2Cl_2 (3.0 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (47 mg, 68% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.48 (s, 1H), 7.35-7.25 (m, 3H), 5.57 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1H), 4.95 (d overlapping with d at 4.94 ppm, *J* = 17.6 Hz, 1H), 4.94 (d, *J* = 10.0 Hz, 1H), 2.36 (d, *J* = 7.2 Hz, 2H), 1.30 (s, 6H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.2 (C), 139.8 (C), 135.6 (CH), 130.55 (CH), 130.53 (CH), 127.4 (CH), 126.4 (CH), 116.9 (CH_2), 48.8 (CH_2), 37.6 (C), 28.5 (CH_3), -1.0 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{28}NSi$ ($[M + NH_4]^+$): 250.19910. Found: 250.19972.



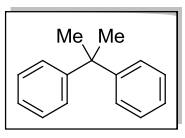
1-Methoxy-3-(2-methylpent-4-en-2-yl)benzene (4.2ag)

Prepared according to General Procedure D from Meldrum's derivative **4.1x** (179 mg, 0.613 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (86 mg, 0.64 mmol) and $(CH_2Cl)_2$ (1.5 mL, 0.4 M); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (34 mg, 29% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22 (t overlapping with $CHCl_3$, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.88 (s, 1H), 6.71 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.54 (ddt, *J* = 17.3, 10.0, 7.2 Hz, 1H), 4.94 (d overlapping with d at 4.93, *J* = 18.7 Hz, 1H), 4.93 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 2.33 (d, *J* = 7.2 Hz, 2H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4 (C), 151.1 (C), 135.5 (CH), 128.9 (CH), 118.4 (CH), 116.9 (CH_2), 112.6 (CH), 110.0 (CH), 55.1 (CH_3), 48.7 (CH_2), 37.7 (C), 28.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{13}H_{19}O$ ($[M + H]^+$): 191.14359. Found: 191.14391.



1-Fluoro-3-(2-methylpent-4-en-2-yl)benzene (4.2ah)

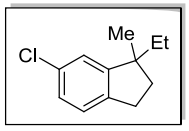
Prepared according to General Procedure D from Meldrum's derivative **4.1y** (196 mg, 0.699 mmol), allyltrimethylsilane (0.22 mL, 1.4 mmol), $AlCl_3$ (98 mg, 0.73 mmol) and CH_2Cl_2 (7.0 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a yellow oil (33 mg, 26% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29-7.22 (m overlapping with $CHCl_3$, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.02 (dt, *J* = 11.3, 2.0 Hz, 1H), 6.86 (td, *J* = 8.2, 1.8 Hz, 1H), 5.53 (ddt, *J* = 16.5, 11.1, 7.3 Hz, 1H), 4.96 (d overlapping with d at 4.95 ppm, *J* = 15.9 Hz, 1H), 4.95 (d, *J* = 11.1 Hz, 1H), 2.34 (d, *J* = 7.3 Hz, 2H), 1.25 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 162.9 (C, d, *J* = 242.5 Hz), 152.1 (C, d, *J* = 6.4 Hz), 135.0 (CH), 129.3 (CH, d, *J* = 8.1 Hz), 121.5 (CH, d, *J* = 2.6 Hz), 117.3 (CH_2), 113.0 (CH, d, *J* = 21.6 Hz), 112.3 (CH, d, *J* = 21.0 Hz), 48.7 (CH_2), 37.8 (C), 28.4 (CH_3); ^{19}F NMR ($CDCl_3$, 282 MHz) -113.9; HRMS (DART) *m/z* calcd for $C_{12}H_{16}F$ ($[M + H]^+$): 179.12360. Found: 179.12431.



Propane-2,2-diyldibenzene (4.2ai)

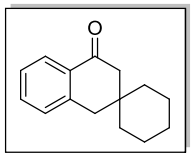
Prepared according to General Procedure C from Meldrum's derivative **4.1z** (50 mg, 0.15 mmol), Me_3Al (0.15 mL, 0.31 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (1.5 mL);

20 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a pale yellow film (30 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29-7.16 (m, 10H), 1.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 150.6 (C), 127.9 (CH), 126.8 (CH), 125.6 (CH), 42.9 (C), 30.7 (CH_3); HRMS (DART) *m*/*z* calcd for $C_{15}H_{20}N$ ([M + NH_4]$^+$): 214.15957. Found: 214.15955.



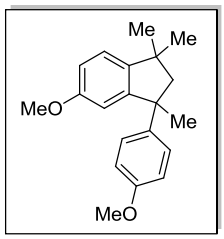
6-Chloro-1-ethyl-1-methyl-2,3-dihydro-1*H*-indene (4.2aj)

Prepared according to General Procedure C from Meldrum's derivative **4.1aa**[94f] (100 mg, 0.31 mmol), Me_3Al (0.31 mL, 0.62 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (3.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a pale yellow oil (54 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) 7.07 (s, 2H), 7.02 (s, 1H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.00 (dt, *J* = 12.6, 6.7 Hz, 1H), 1.80 (dt, *J* = 12.6, 7.6 Hz, 1H), 1.59-1.49 (m, 2H), 1.19 (s, 3H), 0.81 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 153.6 (C), 141.7 (C), 131.8 (C), 126.2 (CH), 125.5 (CH), 123.0 (CH), 47.9 (C), 38.2 (CH_2), 33.5 (CH_2), 29.8 (CH_2), 26.2 (CH_3), 9.2 (CH_3); HRMS (EI) *m*/*z* calcd for $C_{12}H_{15}Cl$ (M^+): 194.0862. Found: 194.0860.



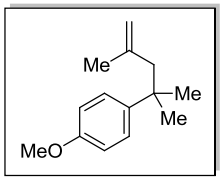
1'*H*-Spiro[cyclohexane-1,2'-naphthalen]-4'(3'*H*)-one (4.2ak)

Prepared according to General Procedure D from Meldrum's derivative **4.1ab** (150 mg, 0.47 mmol), $AlCl_3$ (66 mg, 0.50 mmol), allyltrimethylsilane (0.15 mL, 0.95 mmol) and CH_2Cl_2 (4.7 mL); 1.5 h reaction time at rt. Flash column chromatography eluting on a gradient from pentane to hexanes:EtOAc (5:1) afforded a pale yellow oil (62 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.96 (d, *J* = 7.6 Hz, 1H), 7.45 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 7.6, 1H), 2.87 (s, 2H), 2.54 (s, 2H), 1.44-1.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) 198.5 (C), 142.2 (C), 133.6 (CH), 132.1 (C), 129.4 (CH), 126.5 (CH), 126.4 (CH), 50.3 (CH_2), 41.1 (CH_2), 36.4 (CH_2), 36.3 (CH_2), 26.1 (CH_2), 21.5 (CH_2); HRMS (DART) *m*/*z* calcd for $C_{15}H_{19}O$ ([M + H]$^+$): 215.14359. Found: 215.14415.



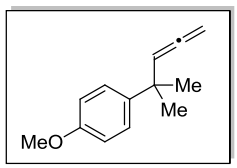
5-Methoxy-3-(4-methoxyphenyl)-1,1,3-trimethyl-2,3-dihydro-1*H*-indene (4.5)[282]

Prepared in analogy to General Procedure D from Meldrum's derivative **4.1a** (88 mg, 0.30 mmol), $AlCl_3$ (43 mg, 0.32 mmol) and CH_2Cl_2 (3.0 mL); 20 min reaction time at rt. Flash column chromatography eluting on a gradient (pentane:Et_2O, 100:0 to 100:1) afforded a yellow oil (36 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.10-7.06 (m, 3H), 6.82 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 2.4 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.34 (d, *J* = 13.0 Hz, 1H), 2.15 (d, *J* = 13.0 Hz, 1H), 1.64 (s, 3H), 1.30 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.9 (C), 157.3 (C), 150.5 (C), 144.5 (C), 143.0 (C), 127.7 (CH), 123.1 (CH), 113.24 (CH), 113.20 (CH), 109.9 (CH), 59.7 (CH_2), 55.4 (CH_3), 55.2 (CH_3), 50.1 (C), 42.2 (C), 30.9 (CH_3), 30.8 (CH_3), 30.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{20}H_{25}O_2$ ($[M + H]^+$): 297.18545. Found: 297.18582.



1-(2,4-Dimethylpent-4-en-2-yl)-4-methoxybenzene (4.2al)

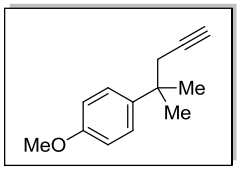
Prepared according to General Procedure D from Meldrum's derivative **4.1a** (100 mg, 0.342 mmol), methallyltrimethylsilane (0.12 mL, 0.68 mmol), $AlCl_3$ (48 mg, 0.36 mmol) and CH_2Cl_2 (3.4 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes:CH_2Cl_2 (9:1), having dry packed the sample, afforded a pale yellow oil (68 mg, 97% yield); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.73 (s, 1H), 4.52 (s, 1H), 3.79 (s, 3H), 2.34 (s, 2H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.4 (C), 143.7 (C), 141.5 (C), 126.9 (CH), 113.9 (CH_2), 113.2 (CH), 55.1 (CH_3), 52.6 (CH_2), 37.1 (C), 29.3 (CH_3), 24.4 (CH_3); HRMS (DART) *m/z* calcd for $C_{14}H_{21}O$ ($[M + H]^+$): 205.15924. Found: 205.15921.



1-Methoxy-4-(2-methylpenta-3,4-dien-2-yl)benzene (**4.2am**)

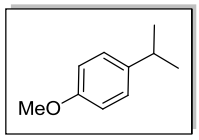
Prepared according to General Procedure D from Meldrum's derivative **4.1a** (200 mg, 0.684 mmol), trimethyl(propargyl)silane (0.20 mL, 1.4 mmol), $AlCl_3$ (96 mg, 0.72 mmol) and CH_2Cl_2 (6.8 mL); 20 min reaction time at rt. Flash column

chromatography eluting with pentane:CH_2Cl_2 (9:1), having dry packed the sample, afforded a pale yellow oil (63 mg, 49% yield). For an analytically pure sample a second flash column was run (1.5% $AgNO_3$/silica stationary phase) and eluting on a gradient (pentane:CH_2Cl_2, 100:0 to 9:1) which afforded a pale yellow oil (48 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.32 (t, *J* = 6.6 Hz, 1H), 4.80 (d, *J* = 6.6 Hz, 2H), 3.78 (s, 3H), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 206.5 (C), 157.6 (C), 141.3 (C), 126.9 (CH), 113.4 (CH), 101.5 (CH), 77.1 (CH_2), 55.2 (CH_3), 37.8 (C), 29.5 (CH_3); HRMS (DART) *m/z* calcd for $C_{13}H_{17}O$ ([M + H]$^+$): 189.12794. Found: 189.12818. Run #2 = 53% yield; Avg 51% yield.



1-Methoxy-4-(2-methylpent-4-yn-2-yl)benzene (4.2an)

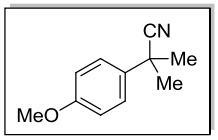
Prepared according to General Procedure D from Meldrum's derivative **4.1a** (44 mg, 0.15 mmol), allenyltributyltin[283] (100 mg, 0.304 mmol), $AlCl_3$ (21 mg, 0.16 mmol) and CH_2Cl_2 (1.5 mL); 20 min reaction time at rt. Flash column chromatography eluting on a gradient with pentane:CH_2Cl_2 (100:0 to 9:1 to 1:1), having dry packed the sample, afforded the desired product **4.2an** contaminated with trace organostannanes. A second column eluting on a gradient with pentane:CH_2Cl_2 (9:1 to 5:1), afforded a pale yellow oil (27 mg, 96% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H), 2.45 (d, *J* = 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.7 (C), 140.3 (C), 126.6 (CH), 113.4 (CH), 82.4 (C), 70.0 (CH), 55.2 (CH_3), 37.0 (C), 33.9 (CH_2), 28.4 (CH_3); HRMS (DART) *m/z* calcd for $C_{13}H_{17}O$ ([M + H]$^+$): 189.12794. Found: 189.12821.



1-Isopropyl-4-methoxybenzene (4.2ao)[284]

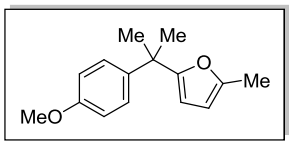
Prepared in analogy to General Procedure C from Meldrum's derivative **4.1a** (200 mg, 0.684 mmol), (^{i}Bu)$_3$Al (1.4 mL, 1.4 mmol, 1.0 M solution in hexanes), and CH_2Cl_2 (6.8 mL); 30 min reaction time at rt. Flash column chromatography eluting with CH_2Cl_2:pentane (1:9), having dry packed the sample, afforded a pale yellow liquid (83 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.14 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 2.85 (septet, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.6 (C), 141.0 (C), 127.2

(CH), 113.6 (CH), 55.2 (CH_3), 33.2 (CH), 24.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{10}H_{15}O$ ($[M + H]^+$): 151.11229. Found: 151.11235. Run #2 = 86% yield; Avg 84% yield.



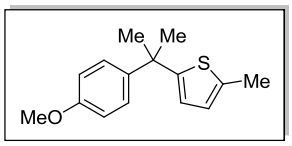
2-(4-Methoxyphenyl)-2-methylpropanenitrile (4.2ap)[285]

Prepared according to General Procedure D from Meldrum's derivative **4.1a** (100 mg, 0.342 mmol), trimethylsilyl cyanide (0.09 mL, 0.7 mmol), $AlCl_3$ (48 mg, 0.36 mmol) and CH_2Cl_2 (3.4 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes:CH_2Cl_2 (1:1), having dry packed the sample, afforded a pale yellow oil (60 mg, quant. yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.36 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 1.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.9 (C), 133.4 (C), 126.2 (CH), 124.7 (C), 114.1 (CH), 55.2 (CH_3), 36.3 (C), 29.2 (CH_3); IR (KBr) 2235 cm^{-1} (strong, C≡N stretch); HRMS (DART) *m/z* calcd for $C_{11}H_{17}N_2O$ ($[M + NH_4]^+$): 193.13409. Found: 193.13481.



2-(2-(4-Methoxyphenyl)propan-2-yl)-5-methylfuran (4.2aq)

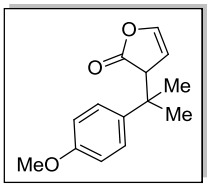
Prepared according to General Procedure D from Meldrum's derivative **4.1a** (178 mg, 0.609 mmol), 2-methylfuran (0.12 mL, 1.2 mmol), $AlCl_3$ (85 mg, 0.64 mmol) and CH_2Cl_2 (6.1 mL); 20 min reaction time at rt. Flash column chromatography eluting on a gradient (pentane:Et_2O, 100:0 to 100:0.5) afforded a yellow oil (105 mg, 75% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.15 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.92 (d, *J* = 3.0 Hz, 1H), 5.85 (d, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 2.21 (s, 3H), 1.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.8 (C), 157.7 (C), 150.6 (C), 140.4 (C), 127.0 (CH), 113.4 (CH), 105.5 (CH), 104.8 (CH), 55.2 (CH_3), 39.4 (C), 28.7 (CH_3), 13.6 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{19}O_2$ ($[M + H]^+$): 231.13850. Found: 231.13855. Run #2 = 76% yield; Avg 76% yield.



2-(2-(4-Methoxyphenyl)propan-2-yl)-5-methylthiophene (4.2ar)

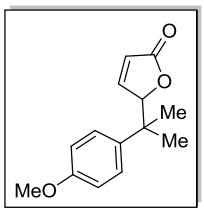
Prepared according to General Procedure D from Meldrum's derivative **4.1a** (160 mg, 0.547 mmol), 2-methylthiophene (0.10 mL, 1.1 mmol), $AlCl_3$ (77 mg, 0.57 mmol) and CH_2Cl_2 (5.5 mL); 20 min reaction time at rt. Flash column chromatography eluting on a gradient (pentane:Et_2O, 100:0 to 100:0.5) afforded a pale yellow oil

(128 mg, 95% yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.24 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 3.4 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 3.76 (s, 3H), 2.37 (s, 3H), 1.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.7 (C), 154.4 (C), 141.9 (C), 137.7 (C), 127.1 (CH), 124.1 (CH), 122.6 (CH), 113.2 (CH), 55.1 (CH_3), 40.9 (C), 31.9 (CH_3), 15.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{19}OS$ ($[M + H]^+$): 247.11566. Found: 247.11675.

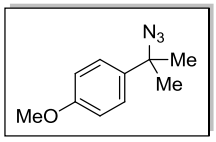


3-(2-(4-Methoxyphenyl)propan-2-yl)furan-2(3*H*)-one (4.2at) and 5-(2-(4-Methoxyphenyl)propan-2-yl)furan-2(5*H*)-one (4.2as)

Prepared according to General Procedure D from Meldrum's derivative **4.1a** (300 mg, 1.03 mmol), 2-(trimethylsiloxy)furan (0.35 mL, 2.1 mmol), $AlCl_3$ (144 mg, 1.08 mmol) and CH_2Cl_2 (10.3 mL); 30 min reaction time at rt. Flash column chromatography eluting on a gradient with hexanes:EtOAc (20:1 to 9:1), having dry packed the sample, afforded **4.2at** as the first product to elute and was isolated as a pale yellow film (16 mg, 7% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23 (d overlapping with $CHCl_3$, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.66 (app t, *J* = 2.9 Hz, 1H), 5.15 (app t, *J* = 2.9 Hz, 1H), 3.78 (s, 3H), 3.36 (app t, *J* = 2.0 Hz, 1H), 1.54 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 176.6 (C), 158.0 (C), 142.5 (CH), 138.1 (C), 126.8 (CH), 113.5 (CH), 108.5 (CH), 55.2 (CH_3), 54.3 (CH), 39.9 (C), 27.4 (CH_3), 23.6 (CH_3); IR (KBr) 1790 (strong, C=O stretch); HRMS (DART) *m/z* calcd for $C_{14}H_{20}NO_3$ ($[M + NH_4]^+$): 250.14432. Found: 250.14467.

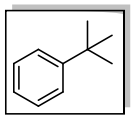


Compound **4.2as** was the second product to elute from the above column and was isolated as a white solid (183 mg, 77% yield). M.p. 81-82 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.26 (d overlapping with $CHCl_3$, *J* = 9.4 Hz, 2H), 7.10 (dd, *J* = 5.7, 1.1 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.01 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.02 (app t, *J* = 1.5 Hz, 1H), 3.78 (s, 3H), 1.47 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 173.0 (C), 158.2 (C), 154.4 (CH), 135.5 (C), 127.1 (CH), 122.3 (CH), 113.6 (CH), 90.3 (CH), 55.0 (CH_3), 40.7 (C), 25.9 (CH_3), 22.0 (CH_3); IR (KBr) 1755 (strong, C=O stretch); HRMS (DART) *m/z* calcd for $C_{14}H_{17}O_3$ ($[M + H]^+$): 233.11777. Found: 233.11797.



1-(2-Azidopropan-2-yl)-4-methoxybenzene (4.2au)[286]

Prepared according to General Procedure D from 5-(2-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione **4.1a** (200 mg, 0.684 mmol), trimethylsilyl azide (0.18 mL, 1.4 mmol), $AlCl_3$ (96 mg, 0.72 mmol) and CH_2Cl_2 (6.8 mL); 1 h reaction time at rt. Flash column chromatography eluting with hexanes:CH_2Cl_2 (9:1), having dry packed the sample, afforded a pale yellow oil (66 mg, 50% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.36 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 1.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.8 (C), 136.6 (C), 126.4 (CH), 113.7 (CH), 63.5 (C), 55.2 (CH_3), 28.4 (CH_3); IR (KBr) 2101 (v. strong, N_3 asym. stretch); HRMS (EI) *m*/*z* calcd for $C_{10}H_{13}N_3O$ (M^+): 191.1059. Found: 191.1055. Run #2 = 57% yield; Avg 54% yield.



***tert*-Butylbenzene (4.2aw)**[287]

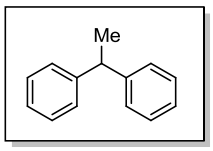
Prepared according to General Procedure C from Meldrum`s derivative **4.1d** (200 mg, 0.762 mmol), Me_3Al (0.76 mL, 1.5 mmol, 2.0 M solution in heptane) and CH_2Cl_2 (7.6 mL); 30 min reaction time at rt. Flash column chromatography eluting with pentane afforded a pale yellow tinted oil (62 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.40-7.37 (m, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.16 (t, *J* = 7.1 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 151.1 (C), 128.0 (CH), 125.4 (CH), 125.2 (CH), 34.6 (C), 31.3 (CH_3); GC/MS *m/z* calcd for $C_{10}H_{14}$ (M^+): 134. Found 134. Run #2 = 65% yield; Avg 63% yield.

Also prepared in analogy to General Procedure C from 1,3-diphenyl-2-(2-phenylpropan-2-yl)propane-1,3-dione (**4.9a**) (162 mg, 0.473 mmol), Me_3Al (0.47 mL, 0.95 mmol, 2.0 M solution in heptane) and CH_2Cl_2 (4.7 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (51 mg, 81% yield). The spectral properties were identical to those reported above. Run #2 = 80% yield; Avg 81% yield.

Also prepared in analogy to General Procedure C from (2-chloropropan-2-yl)benzene (**4.9b**) (209 mg, 1.35 mmol), Me_3Al (1.35 mL, 2.70 mmol, 2.0 M solution in heptane) and CH_2Cl_2 (13.5 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a

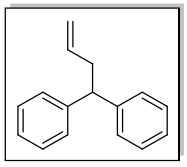
colourless oil (100 mg, 55% yield). The spectral properties were identical to those reported above. Run #2 = 53% yield; Avg 54% yield.

Also prepared in analogy to General Procedure C from 2-phenylpropan-2-yl acetate (**4.9c**)[268] (213 mg, 1.20 mmol), Me_3Al (1.20 mL, 2.40 mmol, 2.0 M solution in heptane) and CH_2Cl_2 (12.0 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (135 mg, 84% yield). The spectral properties were identical to those reported above. Run #2 = 82% yield; Avg 83% yield.



Ethane-1,1-diyldibenzene (4.7a)[290]

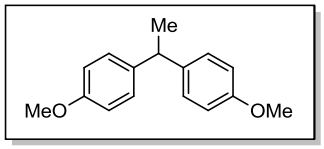
Prepared according to General Procedure C from Meldrum's derivative **4.6b** (49 mg, 0.15 mmol), Me_3Al (0.15 mL, 0.30 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (1.5 mL); 1 h reaction time at rt. Flash column chromatography eluting with pentane afforded a colourless oil (25 mg, 92% yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.28-7.26 (m, 8H), 7.19-7.13 (m, 2H), 4.18 (q, J = 7.2 Hz, 1H), 1.62 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 146.3 (C), 128.3 (CH), 127.6 (CH), 126.0 (CH), 44.7 (CH), 21.8 (CH_3); HRMS (DART) *m/z* calcd for $C_{14}H_{18}N$ ($[M + NH_4]^+$): 200.14392. Found: 200.14453.



But-3-ene-1,1-diyldibenzene (4.7b)[271]

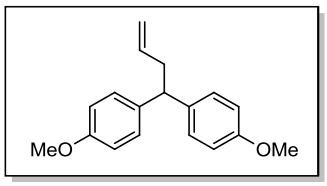
Prepared according to General Procedure D from Meldrum's derivative **4.6a** (165 mg, 0.532 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (74 mg, 0.56 mmol) and $(CH_2Cl)_2$ (5.3 mL); 24 h reaction time at 50 °C. Flash column chromatography eluting with pentane afforded a colourless oil (55 mg, 50% yield). ^{1}H NMR (acetone-d_6, 300 MHz) 7.34-7.25 (m, 8H), 7.18-7.13 (m, 2H), 5.72 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.04 (dd, J = 17.1, 1.7 Hz, 1H), 4.90 (dd, J = 10.2, 0.8 Hz, 1H), 4.06 (t, J = 7.9 Hz, 1H), 2.85 (app t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 144.5 (C), 136.8 (CH), 128.4 (CH), 127.9 (CH), 126.1 (CH), 116.3 (CH_2), 51.2 (CH), 39.9 (CH_2); HRMS (DART) *m/z* calcd for $C_{16}H_{20}N$ ($[M + NH_4]^+$): 226.15957. Found: 226.15972.

Alternatively prepared according to General Procedure D in higher yield from Meldrum's derivative **4.6b** (200 mg, 0.616 mmol), allyltrimethylsilane (0.20 mL, 1.2 mmol), $AlCl_3$ (86 mg, 0.65 mmol), and CH_2Cl_2 (6.1 mL); 30 min reaction time at rt. Flash column chromatography eluting with hexanes afforded a colourless oil (119 mg, 93% yield). The spectral properties were identical to those reported above.



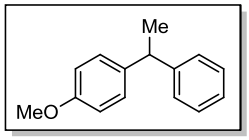
4,4'-(Ethane-1,1-diyl)bis(methoxybenzene) (4.7e)[288]

Prepared according to General Procedure C from Meldrum's derivative **4.6c** (200 mg, 0.540 mmol), Me_3Al (0.54 mL, 1.1 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (5.4 mL); 30 min reaction time at rt. Flash column chromatography eluting with hexanes:EtOAc (9:1) afforded a white solid (131 mg, quant. yield). M.p. 64-66 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.16 (d, *J* = 8.6 Hz, 4H), 6.85 (d, *J* = 8.7 Hz, 4H), 4.07 (q, *J* = 7.2 Hz, 1H), 3.79 (s, 6H), 1.62 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.7 (C), 138.9 (C), 128.4 (CH), 113.6 (CH), 55.1 (CH_3), 43.0 (CH), 22.2 (CH_3); HRMS (DART) *m/z* calcd for $C_{16}H_{22}NO_2$ ($[M + NH_4]^+$): 260.16505. Found: 260.16593.



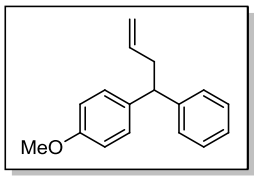
4,4'-(But-3-ene-1,1-diyl)bis(methoxybenzene) (4.7f)[289]

Prepared according to General Procedure D from Meldrum's derivative **4.6c** (120 mg, 0.324 mmol), allyltrimethylsilane (103 μL, 0.648 mmol), $AlCl_3$ (46 mg, 0.34 mmol), and CH_2Cl_2 (3.2 mL); 20 min reaction time at rt. Flash column chromatography eluting with hexanes:EtOAc (9:1) afforded a white solid (82 mg, 94% yield). M.p. 34-36 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.11 (d, *J* = 8.7 Hz, 4H), 6.80 (d, *J* = 8.7 Hz, 4H), 5.70 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.93 (d, *J* = 9.8 Hz, 1H), 3.90 (t, *J* = 7.9 Hz, 1H), 3.75 (s, 6H), 2.74 (app t, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.8 (C), 137.1 (CH), 128.7 (2C's: C, CH), 116.1 (CH_2), 113.7 (CH), 55.2 (CH_3), 49.5 (CH), 40.3 (CH_2); HRMS (DART) *m/z* calcd for $C_{18}H_{21}O_2$ ($[M + H]^+$): 269.15415. Found: 269.15338.



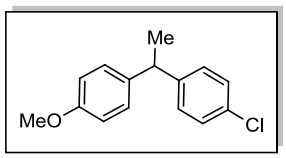
1-Methoxy-4-(1-phenylethyl)benzene (4.7e)[290]

Prepared according to General Procedure C from Meldrum's derivative **4.6d** (150 mg, 0.441 mmol), Me_3Al (0.44 mL, 0.88 mmol, 2.0 M solution in heptane), and $(CH_2Cl)_2$ (4.4 mL); 16 h reaction time at 50 °C. Flash column chromatography eluting with hexanes:EtOAc (9:1), having dry packed the sample, afforded a pale yellow oil (89 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28-7.15 (m overlapping with $CHCl_3$, 5H), 7.12 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.09 (q, J = 7.2 Hz, 1H), 3.76 (s, 3H), 1.59 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.8 (C), 146.8 (C), 138.5 (C), 128.5 (CH), 128.3 (CH), 127.5 (CH), 125.9 (CH), 113.7 (CH), 55.2 (CH_3), 43.9 (CH), 22.0 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{20}NO$ ($[M + NH_4]^+$): 230.15449. Found: 230.15450.



1-Methoxy-4-(1-phenylbut-3-en-1-yl)benzene (4.7f)[271]

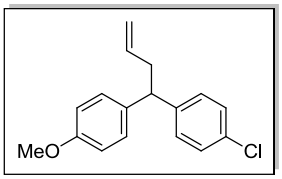
Prepared according to General Procedure D from Meldrum's derivative **4.6d** (200 mg, 0.588 mmol), allyltrimethylsilane (0.19 mL, 1.2 mmol), $AlCl_3$ (82 mg, 0.62 mmol), and CH_2Cl_2 (5.8 mL); 30 min reaction time at rt. Flash column chromatography eluting with hexanes:EtOAc (9:1) afforded a white solid (134 mg, 96% yield). M.p. 59-60 °C; ^{1}H NMR (acetone-d_6, 300 MHz) 7.31-7.12 (m, 7H), 6.83 (d, J = 8.7 Hz, 2H), 5.71 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.02 (dd, J = 17.1, 1.6 Hz, 1H), 4.89 (dd, J = 10.5, 0.9 Hz, 1H), 4.00 (t, J = 7.9 Hz, 1H), 3.74 (s, 3H), 2.80 (t overlapping with residual H_2O and HDO, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.9 (C), 144.9 (C), 136.9 (CH), 136.6 (C), 128.8 (CH), 128.4 (CH), 127.8 (CH), 126.1 (CH), 116.2 (CH_2), 113.8 (CH), 55.2 (CH_3), 50.4 (CH), 40.1 (CH_2); HRMS (DART) *m/z* calcd for $C_{17}H_{22}NO$ ($[M + NH_4]^+$): 256.17014. Found: 256.16995.



1-Chloro-4-(1-(4-methoxyphenyl)ethyl)benzene (4.7g)[291]

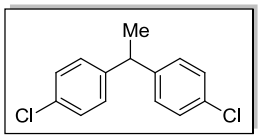
Prepared according to General Procedure C from Meldrum's derivative **4.6e** (150 mg, 0.400 mmol), Me_3Al (0.40 mL, 0.80 mmol, 2.0 M solution in heptane), and $(CH_2Cl)_2$ (4.0 mL); 23 h reaction time at 50 °C. Flash column chromatography eluting on a

gradient from pentane to hexanes:EtOAc (9:1) afforded a pale yellow oil (86 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 6.8 Hz, 2H), 7.08 (d, *J* = 7.0 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 1.57 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 157.9 (C), 145.2 (C), 137.9 (C), 131.6 (C), 128.8 (CH), 128.40 (CH), 128.39 (CH), 113.8 (CH), 55.2 (CH_3), 43.3 (CH), 21.9 (CH_3); HRMS (DART) *m/z* calcd for $C_{15}H_{19}ClNO$ ($[M + NH_4]^+$): 264.11552. Found: 264.11594.



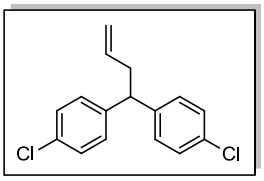
1-Chloro-4-(1-(4-methoxyphenyl)but-3-en-1-yl)benzene (4.7h)[292]

Prepared according to General Procedure D from Meldrum's derivative **4.6e** (150 mg, 0.400 mmol), allyltrimethylsilane (0.13 mL, 0.80 mmol), $AlCl_3$ (56 mg, 0.42 mmol) and $(CH_2Cl)_2$ (4.0 mL); 23 h reaction time at 50 °C. Flash column chromatography eluting with hexanes:EtOAc (20:1) afforded a pale yellow oil (99 mg, 91% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 6.9 Hz, 2H), 7.09 (d, *J* = 7.1 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.67 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 4.99 (dd slightly overlapping with d at 4.94 ppm, *J* = 17.1, 1.3 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 3.92 (t, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 2.73 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.0 (C), 134.4 (C), 136.5 (CH), 136.1 (C), 131.7 (C), 129.2 (CH), 128.7 (CH), 128.4 (CH), 116.5 (CH_2), 113.8 (CH), 55.1 (CH_3), 49.7 (CH), 39.9 (CH_2); HRMS (DART) *m/z* calcd for $C_{17}H_{21}ClNO$ ($[M + NH_4]^+$): 290.13117. Found: 290.13194.



4,4'-(Ethane-1,1-diyl)bis(chlorobenzene) (4.7i)[293]

Prepared according to General Procedure C from Meldrum's derivative **4.6g** (43 mg, 0.11 mmol), Me_3Al (0.11 mL, 0.22 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (1.1 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane afforded a white solid (26 mg, 96% yield). M.p. 48-50 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.23 (d overlapping with $CHCl_3$, *J* = 8.5 Hz, 4H), 7.09 (d, *J* = 8.4 Hz, 4H), 4.08 (q, *J* = 7.2 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 144.3 (C), 131.9 (C), 128.9 (CH), 128.6 (CH), 43.6 (CH), 21.7 (CH_3); HRMS (DART) *m/z* calcd for $C_{14}H_{12}Cl_2$ (M^+): 250.03161. Found: 250.03233.

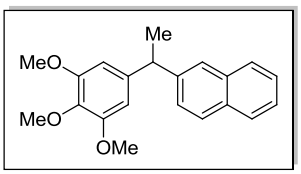


4,4'-(But-3-ene-1,1-diyl)bis(chlorobenzene) (4.7j)[289]

Prepared according to General Procedure D from Meldrum's derivative **4.6f** (75 mg, 0.20 mmol), allyltrimethylsilane (0.06 mL, 0.4 mmol), $AlCl_3$ (28 mg, 0.21 mmol) and $(CH_2Cl)_2$ (4.0 mL, 0.05 M); 6 h reaction time at 50 °C. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a pale yellow oil (23 mg, 42% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23 (d, *J* = 8.4 Hz, 4H), 7.10 (d, *J* = 8.4 Hz, 4H), 5.65 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 4.99 (dd slightly overlapping with d at 4.95 ppm, *J* = 17.3, 1.4 Hz, 1H), 4.95 (d, *J* = 9.8 Hz, 1H), 3.94 (t, *J* = 7.8 Hz, 1H), 2.73 (app t, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) 142.4 (C), 135.9 (CH), 132.1 (C), 129.2 (CH), 128.6 (CH), 116.9 (CH_2), 49.8 (CH), 39.7 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{16}H_{14}Cl_2$ (M^+): 276.0473. Found: 276.0476.

Alternatively prepared according to General Procedure D from Meldrum's derivative **4.6f** (150 mg, 0.396 mmol), allyltributyltin (0.24 mL, 0.79 mmol), $AlCl_3$ (55 mg, 0.42 mmol) and $(CH_2Cl)_2$ (7.9 mL, 0.05 M); 8 h reaction time at 50 °C. Flash column chromatography eluting with pentane, having dry packed the sample, afforded the desired product **4.7j** contaminated with trace organostannanes. A second column with the same conditions afforded a pale yellow oil (40 mg, 36% yield). The spectral properties were identical to those reported above.

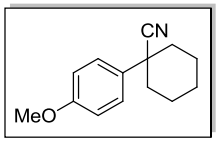
Alternatively prepared according to General Procedure D in higher yield from Meldrum's derivative **4.6g** (50 mg, 0.13 mmol), allyltrimethylsilane (0.04 mL, 0.2 mmol), $AlCl_3$ (18 mg, 0.13 mmol) and CH_2Cl_2 (1.3 mL, 0.1 M); 30 min reaction time at rt. Flash column chromatography eluting with pentane, having dry packed the sample, afforded a pale yellow oil (33 mg, 94% yield). The spectral properties were identical to those reported above.



2-(1-(3,4,5-Trimethoxyphenyl)ethyl)naphthalene (4.7k) [249c]

Prepared according to General Procedure C from Meldrum's derivative **4.6h** (100 mg, 0.215 mmol), Me_3Al (0.22 mL, 0.43 mmol, 2.0 M solution in heptane), and CH_2Cl_2 (2.2 mL); 30 min reaction time at rt. Flash column

chromatography eluting with CH_2Cl_2/hexanes (1:1 to 100:0), having dry packed the sample, afforded a pale yellow film (69 mg, 99% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.80-7.73 (m, 3H), 7.67 (s, 1H), 7.45-7.41 (m, 2H), 7.32 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.46 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 1.70 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 153.1 (C), 143.5 (C), 141.8 (C), 136.3 (C), 133.4 (C), 132.1 (C), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.6 (CH), 125.9 (CH), 125.4 (CH), 125.2 (CH), 104.9 (CH), 60.8 (CH_3), 56.0 (CH_3), 45.0 (CH), 21.8 (CH_3); HRMS (DART) *m/z* calcd for $C_{21}H_{23}O_3$ ($[M + H]^+$): 323.16472. Found: 323.16564.



1-(4-Methoxyphenyl)cyclohexanecarbonitrile (4.2av)

Prepared according to General Procedure C from Meldrum's derivitave **4.1ad** (200 mg, 0.602 mmol), trimethylsilyl cyanide (0.15 mL, 1.2 mmol), $AlCl_3$ (84 mg, 0.63 mmol) and CH_2Cl_2 (6.0 mL); 20 min reaction time at rt. Flash column chromatography eluting with pentane:CH_2Cl_2 (1:1), having dry packed the sample, afforded a colourless solid (130 mg, quant. yield). M.p. 58-60 °C (46.8 °C)[294]; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.38 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.12 (app d, *J* = 11.5 Hz, 2H), 1.85-1.65 (m, 7H), 1.27-1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.9 (C), 133.5 (C), 126.5 (CH), 122.8 (C), 114.0 (CH), 55.1 (CH_3), 43.3 (C), 37.4 (CH_2), 24.8 (CH_2), 23.5 (CH_2); IR (KBr) 2231 cm^{-1} (strong, C≡N stretch); HRMS (DART) *m/z* calcd for $C_{14}H_{21}N_2O$ ($[M + NH_4]^+$): 233.16539. Found: 233.16610.

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