ENANTIOSELECTIVE AND DOMINO INTERMOLECULAR STETTER REACTIONS

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By

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“Cualquier cosa que quieras hacer en la vida

hay que hacerla con ganas, inteligencia y corazón...

después los resultados vendrán por sí solos”

Mis padres

DEDICATION

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ABSTRACT

This thesis describes three advances in the field of NHC-catalyzed reactions. In particular, a complementary method for the enantioselective intermolecular Stetter reaction as well as the development of the first domino transformations employing the Stetter reaction as the initial step is presented.

The first chapter of this work briefly introduces the discovery and use of *N*-heterocyclic carbenes as organocatalysts, followed by a short description of the Stetter reaction. In addition, major achievements on the enantioselective intermolecular version of this transformation are also described. To conclude the chapter, a review describing early investigations and development of novel domino reactions employing acyl anion equivalents as the initial step.

Chapter two of this thesis describes a recently developed highly enantioselective synthesis of α,δ-diketoesters via an intermolecular Stetter reaction. Using this method, heteroaromatic and electron-poor aromatic aldehydes undergo conjugate addition onto γ-aryl-α,β-unsaturated-α-ketoesters, furnishing the Stetter products in moderate to excellent yields and enantioselectivities. Additionally, the synthetic usefulness of these adducts is showcased by the preparation of multiple synthetic building blocks, such as *N*-protected α-aminoesters, disubstituted δ-lactones, and trisubstituted tetrahydrofuran derivatives.

The third chapter is a good illustration of the development, study, and applications of the first domino reaction using the Stetter reaction as the initial step. This novel methodology furnishes trisubstituted indanes, featuring three contiguous stereogenic centres. The success of this transformation relies on the enolate intermediate generated from a Stetter reaction, which is used to perform a subsequent conjugate addition on a different Michael acceptor. The products,

obtained employing this protocol are later utilized for the synthesis of complex polycyclic pyrroles.

Finally, the fourth chapter of this thesis exemplifies how the endeavors in research for developing new methodologies sometimes lead to exciting discoveries. This section describes the finding of a novel and efficient approach for the synthesis of carbocyclic spiro compounds. This method consists in the homo- or cross-dimerization of *o*-formylchalcone derivatives producing spiro bis-indanes in a single operation via domino Stetter–aldol–Michael and Stetter–aldol–aldol processes. This protocol was used to prepare analogs of the core backbone present in fredericamycin A, a complex polysubstituted aromatic spiro bis-indane which exhibits antitumor antibiotic properties.

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LIST OF ABBREVIATIONS

α	observed optical rotation
$[\alpha]_D$	specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are implied)
Å	angstrom(s)
Ac	Acetyl
AIBN	2,2’-azobisisobutyronitrile
AM1	Austin model 1
aq	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad (spectral)
^{t}Bu	*tert*-butyl
°C	degrees Celsius
calcd	Calculated
CI	chemical ionization
CIF	crystallographic information file
COSY	correlation spectroscopy
Cy	Cyclohexyl
m-CPBA	*meta*-chloroperoxybenzoic acid

δ	chemical shift in parts per million
d	day(s); doublet (spectral)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDC	*N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide
EDG	electron-donating group
ee	enantiomeric excess
equiv	Equivalent
ESI	electrospray ionization
Et	Ethyl
EWG	electron-withdrawing group
FCC	flash column chromatography
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)
HPLC	high-performance liquid chromatography

HRMS	high resolution mass spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
IR	Infrared
J	coupling constant (in NMR spectroscopy)
LDA	lithium diisopropylamide
lit.	Literature value (abbreviation used with period)
M	molar (moles per litre)
M^+	parent molecular ion
m	multiplet (spectral)
Me	Methyl
Mes	mesityl (2,4,6-trimethylphenyl)
MHz	Megahertz
min	minute(s)
mol	mole(s)
mp	melting point
MS	molecular sieves
MW	microwave irradiation; molecular weight
m/z	mass-to-charge ratio
NHC	*N*-heterocyclic carbene
NOE	nuclear Overhauser effect
NMR	nuclear magnetic resonance

ORTEP	oak ridge thermal ellipsoid plot
PCC	pyridinium chlorochromate
Pd/C	palladium on charcoal
Ph	Phenyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
*i*Pr	*iso*-propyl
Pr	Propyl
PTLC	preparative thin-layer chromatography
q	quartet (spectral)
R	any alkyl substituent
rac	a prefix to denote racemic
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral); second(s)
SAM	Stetter–aldol–Michael
SAA	Stetter–aldol–aldol
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet (spectral)
t	Time
TBDPS	*tert*-butyldiphenylsilyl

TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMG	*N*,*N*,*N'*,*N'*-tetramethylguanidine
TOF	time-of-flight (in mass spectrometry)
Ts	tosyl *(para*-toluenesulfonyl [*p*-CH_3-C_6H_4-SO_2])

PART I: INTRODUCTION

CHAPTER 1: *N*-HETEROCYCLIC CARBENE–CATALYZED STETTER REACTIONS

Carbenes are molecules containing a divalent neutral carbon atom with six valence electrons, including two non-bonding electrons. For years, it was believed that these molecules were highly reactive species making their isolation an impossible task. This was true until Bertrand[1] and Arduengo,[2] independently reported the isolation of the first stable carbenes. The synthesis, isolation, and characterization by X-ray crystallography of the bisadamantyl imidazolylidene carbene allowed Arduengo to document such achievement (**Figure 1.1**).

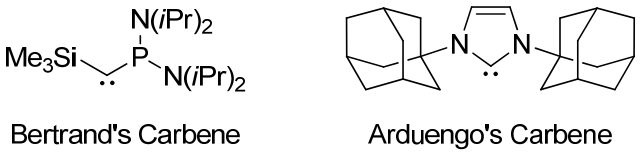


Figure 1.1 First stable carbenes isolated by Bertrand and Arduengo.

In general, carbenes can exist in either singlet (more stable) or triplet state (less stable) and their reactivity will strictly depend on the groups attached to the carbon atom. Also, these species can be electrophilic or nucleophilic. For instance, if the carbene carbon is bound to substituents with σ-electron-donating and poor π-donating character, the triplet state of the carbene will be favoured (**Figure 1.2b**). Another example is the bisadamantyl imidazolylidene carbene, in which steric and electronic factors played a pivotal role for their isolation. The bulky adamantyl groups surrounding the carbene centre provided sufficient hindrance so that the bisadamantyl imidazolylidene was kinetically stable (**Figure 1.1**). On the other hand, the role of the nitrogen atoms in the stability of the carbene was attributed to the π-donation of the lone pair

to the empty p-orbital of the carbene centre. Moreover, the electronegative character of the nitrogen atom provided a stabilizing σ-electron-withdrawal effect (**Figure 1.2c**).[3] As a result, the combination of the later two effects created a large energy gap between the singlet and triplet states. In this context, the π-donation character of a heteroatom in a heterocyclic carbene confers nucleophilic properties to heterocyclic carbenes as illustrated in **Figure 1.2d**. The central carbon is negatively charged as it shares two electrons from the neighbouring heteroatom.

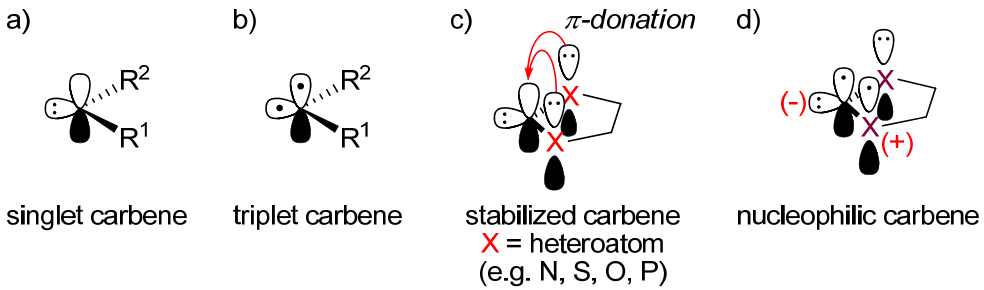
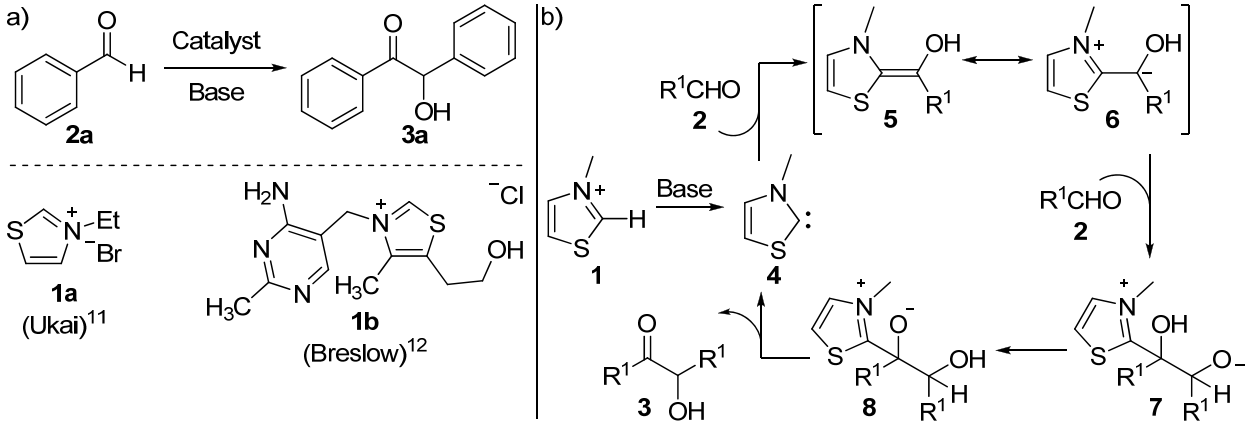


Figure 1.2 Representation of carbenes as a) singlet state, b) triplet state, c) stabilized, and d) nucleophilic carbene.

This distinctive property (nucleophilicity) has made *N*-heterocyclic carbenes (NHCs) a new class of catalysts with which chemists can develop new transformations. As a consequence, NHCs are one of the most studied species in recent years, not only because they act as strong σ donors in transition metal catalysis,[4, 5] but also because of their ability to catalyze carbon–carbon, carbon–nitrogen, and carbon–oxygen bond forming reactions.[6-13]

The first example of NHC-catalysis dates back to 1943, when Ukai and coworkers serendipitously discovered that using the carbene precursor 3-ethylthiazolium bromide (**1a**) in the presence of a base catalyzes the dimerization of benzaldehyde (**2a**) to benzoin (**3a**) (**Scheme 1.1a**).[14]

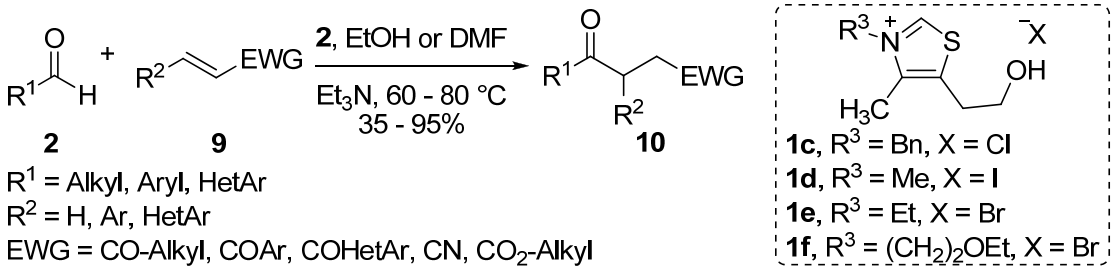
Scheme 1.1 a) Benzoin Reaction Catalyzed by Thiazolium Salt **1**, b) Mechanism of the Benzoin Reaction Proposed by Breslow.



A decade later, Breslow proposed a mechanism for this transformation during the course of his investigations of the benzoin condensation of **2a** with thiamine (**1b**) (**Scheme 1.1b**).[15] The active carbene species (**4**) is generated by treatment of the corresponding thiazolium salt **1** with a base. Carbene **4** then reacts with aldehyde **2** to form the reactive species **5**, to which its resonance form resembles to an acyl anion equivalent **6** (also called *Breslow intermediate*), thus reversing the normal mode of reactivity of the aldehyde (*umpolung*[16]). Subsequently, nucleophilic **6** attacks a second equivalent of **2** to yield the oxy-anion intermediate **7**, which after proton transfer generates **8**. Finally, this last intermediate collapses to afford the corresponding benzoin product **3**.

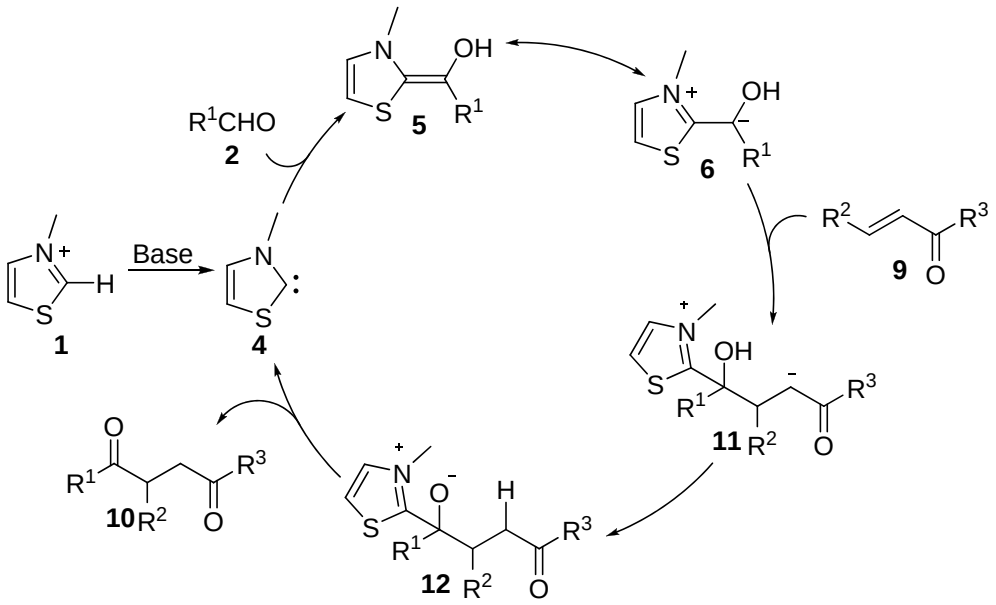
In the early 1970s, Stetter and coworkers were the first in translating the concept of addition of acyl anion equivalents (**6**) to a different class of substrates other than aldehydes, such as Michael acceptors (**Scheme 1.2**).[17, 18] This reaction works generally well with *α,β*-unsaturated ketones, nitriles, and esters. In most cases, the use of polar solvents (i.e. ethanol or *N,N*-dimethylformamide) and high temperatures (60 to 80 °C) is required.

Scheme 1.2 Early Investigations on the Conjugate Addition of Aldehydes to Electron-Poor Olefins by Stetter and Coworkers.



Mechanistically, it has been proposed that the reaction proceeds through the addition of an acyl anion equivalent **6** onto an electron-poor olefin **9** to generate the enolate intermediate **11**. Subsequent proton transfer yielding **12** and elimination of the NHC catalyst completed the catalytic cycle (**Scheme 1.3**).[19]

Scheme 1.3 Catalytic Cycle for the Stetter Reaction.



These early precedents in the literature inspired others to develop new families of NHCs that later will serve as an indispensable tool for the development of new transformations in this emerging area of research (**Figure 1.3**).

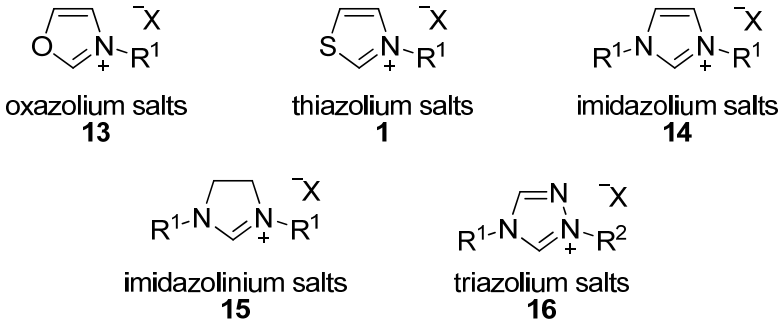
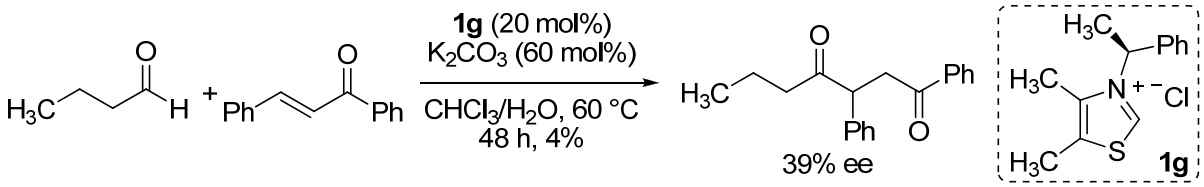


Figure 1.3 Main families of *N*-heterocyclic carbene precursor employed in organocatalyzed transformations.

1.1 THE ENANTIOSELECTIVE INTERMOLECULAR STETTER REACTION

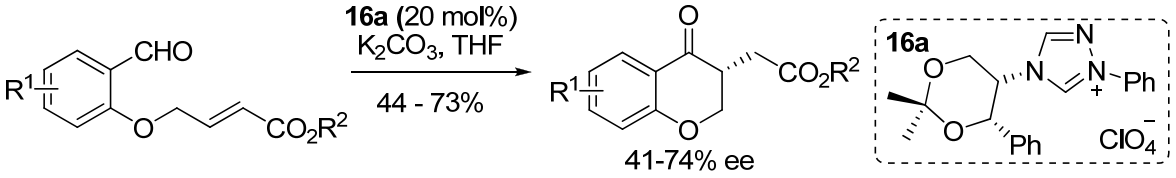
In 1996, Enders and coworkers disclosed the first enantioselective intermolecular Stetter reaction between 1-propanal and chalcone catalyzed by chiral thiazolium salt **1g**, although the reaction gave a very low yield and poor enantioselectivity (**Scheme 1.4**).[6, 20]

Scheme 1.4 The First Enantioselective Intermolecular Stetter Reaction Reported by Enders et al.



Despite initial attempts of Enders for developing an efficient method for the enantioselective intermolecular Stetter reaction, the reaction proved challenging. Therefore, the intramolecular version was quickly developed. Ciganek's first intramolecular Stetter reaction[21] inspired several other research groups in the development of new enantioselective methods. Enders and coworkers reported the first enantioselective intramolecular Stetter reaction using triazolium precatalyst **16a** (**Scheme 1.5**).[20]

Scheme 1.5 First Enantioselective Intramolecular Stetter Reaction.



The pioneering work of various research groups towards the development of chiral thiazolium[22-26] and triazolium salts[27-31] for the enantioselective benzoin condensation, served as a platform for Rovis and coworkers to design new precatalysts.[32, 33] His design consisted of the use of a system of quadrants which illustrated the steric cloud created around the Breslow intermediate (**Figure 1.4a**).[32] Additionally, the design of precatalysts was based on employing the triazolium ring as the general backbone and modifying the precatalysts by fine-tuning their electronic properties on the aryl group and the steric bulk on both the R and the aryl groups (**Figure 1.4b**).[34-36] The steric bulk on the aliphatic portion of the triazolium precatalyst was modified by using different α-amino acids. Thus, the alpha substituent (R) on the amino acid selectively shields one face of the precatalyst while the aromatic group attached to the triazolium core provides a handle for both, steric and electronic tuning. The latter was achieved by using

electron-poor (i.e. Ar = pentafluorophenyl) and electron-rich (i.e. Ar = *p*-methoxyphenyl) aryl substituents. Through extensive studies, Rovis and coworkers achieved highly enantioselective intramolecular Stetter reactions when salicylaldehyde-derived substrates were investigated for the enantioselective synthesis of chroman-4-ones (>90% ee).[33]

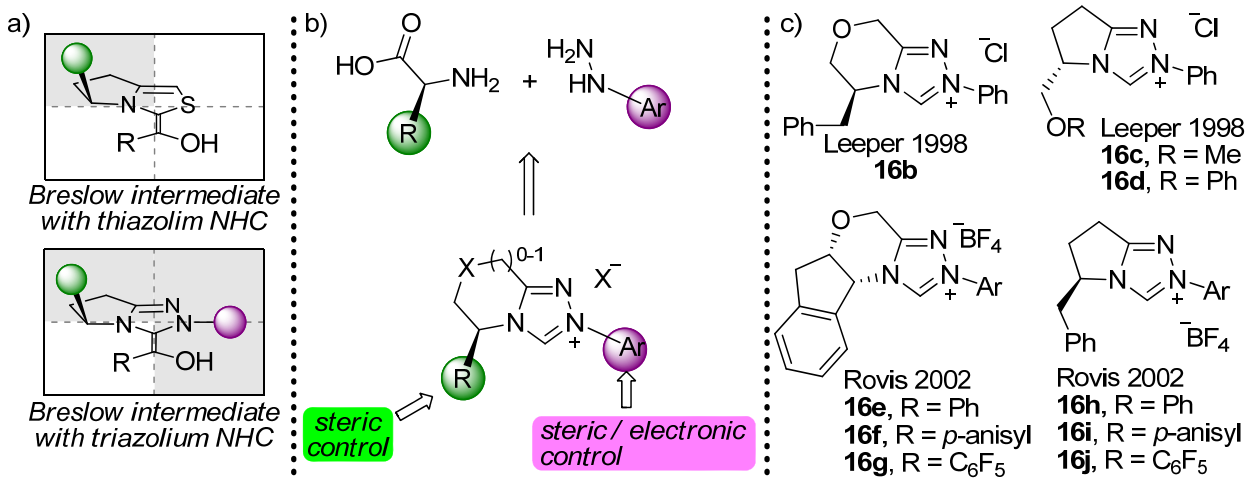


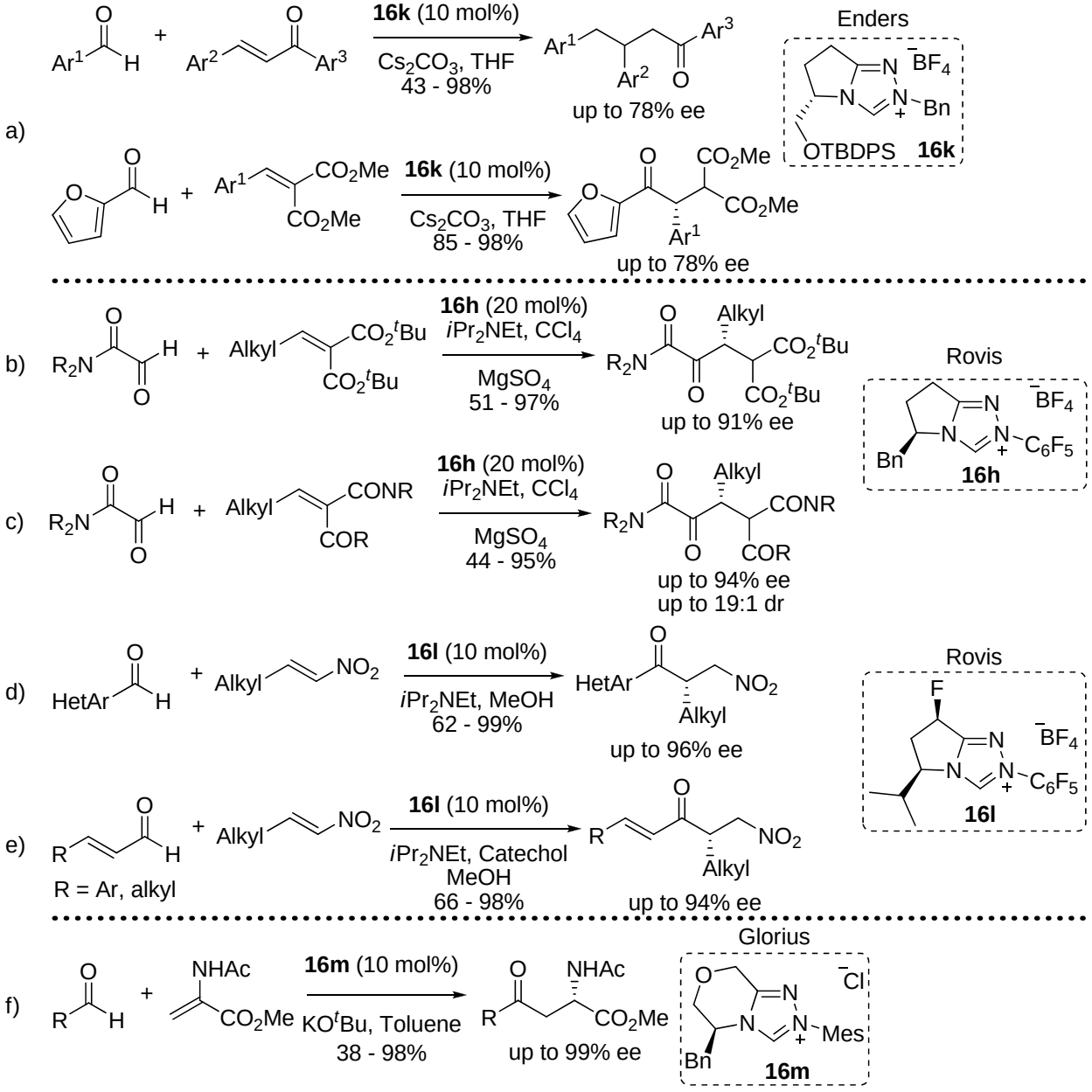
Figure 1.4 a) System of quadrants for thiazolium and triazolium NHCs, b) Fine-tuning of steric and electronic control on NHCs, c) Representative triazolium-derived precatalysts developed up to 2002.

It was not until 2008 that Enders and coworkers reported the first enantioselective intermolecular Stetter reaction achieving moderate enantioselectivities (up to 78% ee). Their work involved addition of heteroaromatic aldehydes to chalcone derivatives[37] or arylidenemalonates[38] using *N*-benzyl-derived triazolium precatalyst **16k** (**Scheme 1.6a**).

Concurrently, Rovis and coworkers employed alkylidenemalonates in combination with highly reactive glyoxamides in the presence of triazolium **16h** (**Scheme 1.6b**).[39, 40] This report disclosed the first examples of highly enantioselective intermolecular Stetter reactions (up to

91% ee). This work was followed by an enantioselective intermolecular Stetter reaction on alkylidene ketoamides achieving high levels of diastereo- and enantioselectivity (up to 19:1 dr and 98% ee) (**Scheme 1.6c**).[40]

Scheme 1.6 Recent Enantioselective Intermolecular Stetter Reactions.



In 2009, Rovis and coworkers disclosed a remarkable study on the design of the backbone-fluorinated triazolium **16l**.[41] This newly designed organocatalyst improved their enantioselectivities up to 96% ee when heteroaromatic aldehydes were used in combination with β-alkyl nitroalkenes as Stetter acceptors (**Scheme 1.6d**).

However, aromatic aldehydes were not reactive under their reaction conditions. Recently, they have proposed that the lack of reactivity in aromatic aldehydes was due to unfavourable steric interaction between the Michael acceptor and the Breslow intermediate (**Figure 1.5**).[42] In contrast, the Breslow intermediate derived from heteroaryl aldehydes did not suffer from the same interaction and provided excellent reactivity.

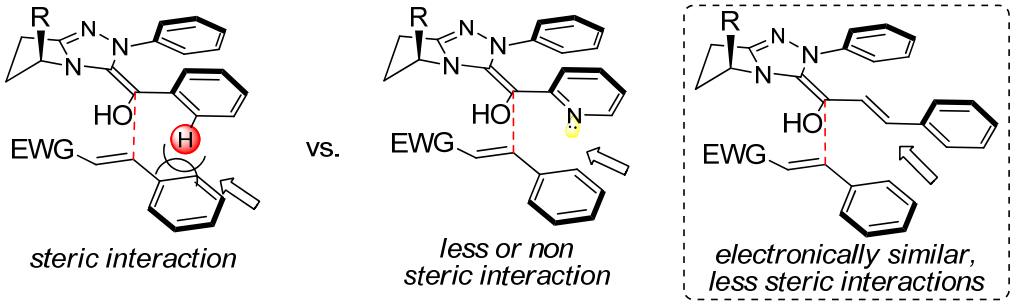


Figure 1.5 Effect of the size of the C-H bond vs. N during the conjugate addition of the Breslow intermediate to an electron-poor olefin.

As a result of the repelling interactions between the Michael acceptor and the proton of the aryl ring in the Breslow intermediate, Rovis proposed the use of α,β-unsaturated aldehydes in order to reduce the steric interactions between the electron-poor olefin and the acyl anion equivalent (**Figure 1.5**). This transformation required the use of catechol as an additive acting as a proton transfer agent during the formation of the acyl anion equivalent **17** (**Figure 1.6**),[43] thus providing very good yields and enantioselectivities (**Scheme 1.6e**).[42]

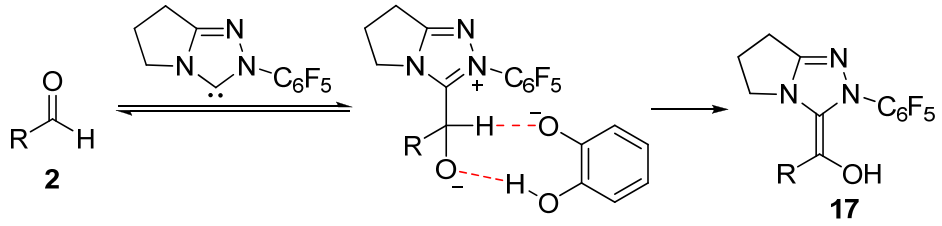


Figure 1.6 Catechol as proton transfer agent during the formation of the acyl anion equivalent.

Early this year, a group directed by Glorius disclosed a highly enantioselective synthesis of amino acid derivatives (up to 99% ee) by means of intermolecular Stetter reactions catalyzed by triazolium salt **16m**. Their work featured a diastereoselective intramolecular proton transfer during the Stetter reaction instead of the diastereoselective carbon-carbon bond formation common to other methods (**Scheme 1.6f**).[44]

Despite the remarkable progress accomplished for the Stetter reaction in recent years, several limitations remain. For instance, the use of α,β-unsaturated ketones delivered Stetter products with good to excellent enantioselectivity, although poor yields were obtained.[45] The use of aromatic aldehydes in combination with β-substituted Michael acceptors were unfruitful or gave sluggish transformation with low yield and enantioselectivity.[41]

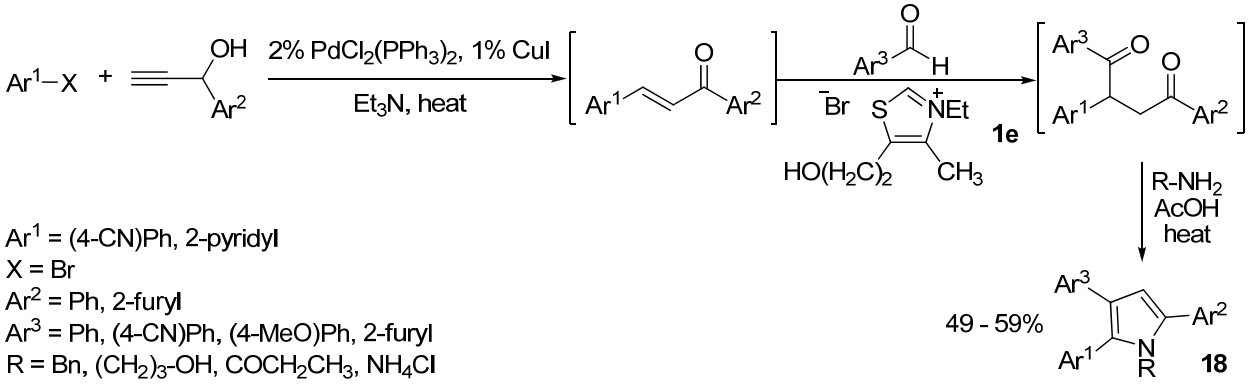
1.2 STETTER–BASED DOMINO REACTIONS

Tietze defined a domino reaction as "*a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.*"[46] The useful application of domino transformations has allowed chemists to prepare complex architectures in a single

operation. Although the concept of domino reactions was successfully applied to numerous transformations, the use of NHC-based acyl anion equivalents in this context has been largely overlooked until recent years.

In 2001, Müller and coworkers disclosed a one-pot sequence for the synthesis of pyrroles through a Sonogashira coupling followed by a Stetter reaction, then concluding with a Paal-Knorr cyclo-condensation (**Scheme 1.7**).[47]

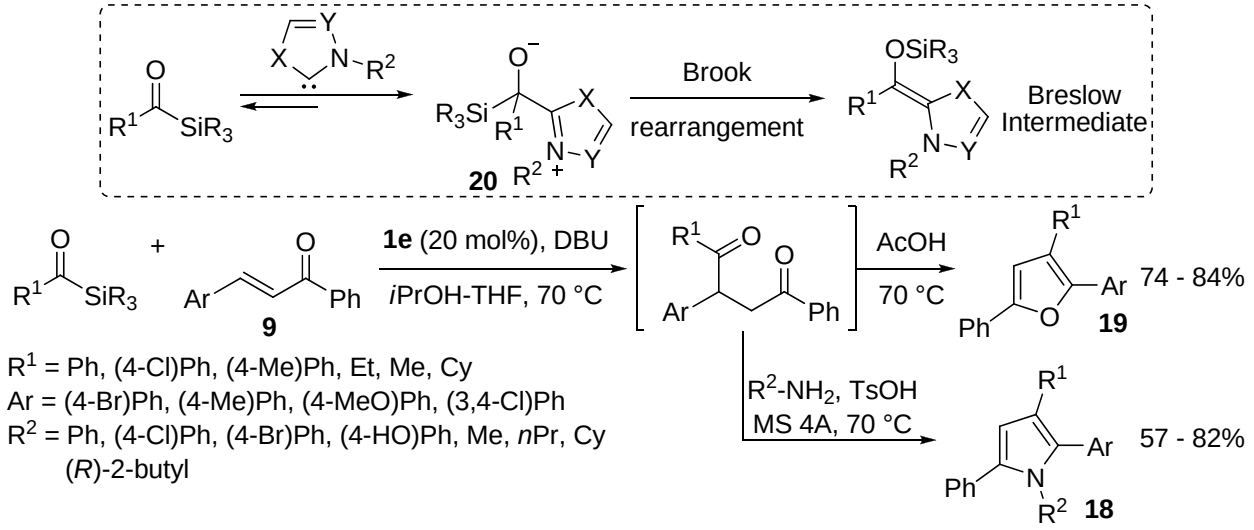
Scheme 1.7 One-pot Synthesis of Pyrroles Employing the Stetter Reaction.



Although Müller's methodology provided trisubstituted pyrroles **18** in moderate yields, it was restricted to the use of highly activated aryl-halides and propargyl alcohols.

Similarly, Scheidt and coworkers reported a general strategy for the synthesis of furans **19** and pyrroles **18**.[48] These sequential transformations were initiated by the generation of the acyl anion equivalent through the 1,2-silyl migration of intermediate **20** (**Scheme 1.8**). The scope of the one-pot procedure was general for aliphatic and aromatic acylsilanes. However, only chalcone-type acceptors **9** were employed for the synthesis of **19** and **18** furnishing the desired products in good yield.

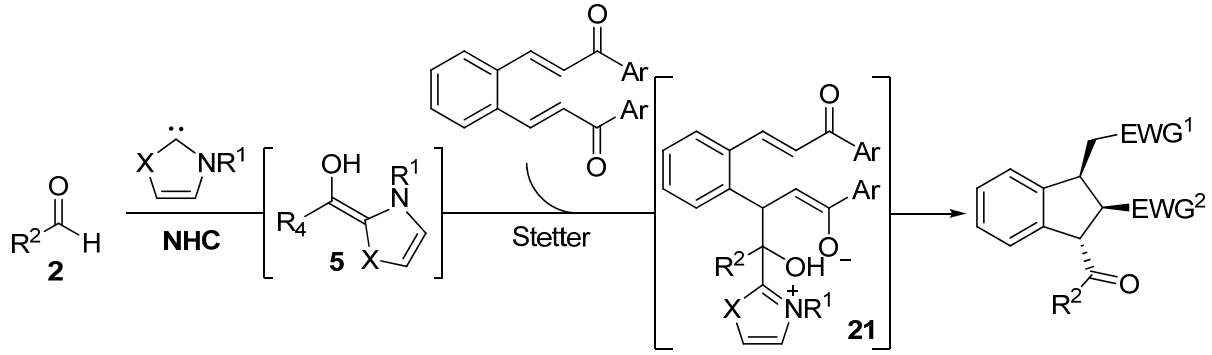
Scheme 1.8 Synthesis of Furans and Pyrroles via a Sila-Stetter–Paal-Knorr One-pot Procedure.



Although these two previous reports by Müller and Scheidt had included the Stetter reaction in a one-pot sequence for the synthesis of 5-membered ring heterocycles, these processes cannot be considered domino reactions.

The invention of the first domino transformation using the Stetter reaction as the initial step took place almost 3 years later. In 2008, our group became interested in the implementation of the Stetter reaction in domino processes. The following year, the first domino process using the Stetter reaction in the initial step was reported, giving access to trisubstituted indanes diastereoselectively.[49] The reaction consisted of intercepting the enolate intermediate **21** with a second Michael acceptor tethered to the aromatic substituent (**Scheme 1.9**).

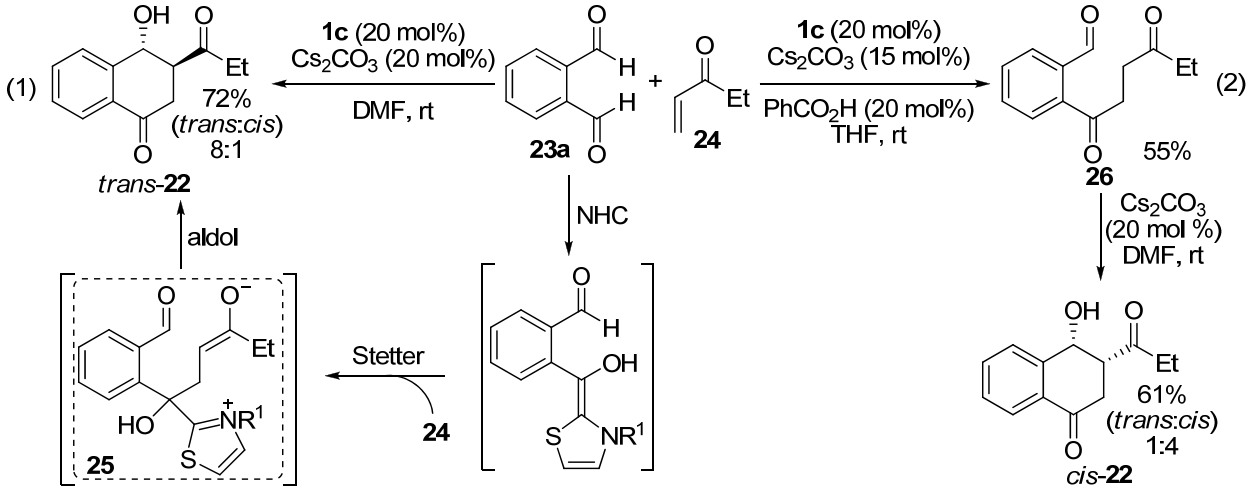
Scheme 1.9 NHC-Catalyzed Domino Stetter-Michael Reaction for the Synthesis of Indanes.



Our report on the diastereoselective synthesis of indanes was followed shortly afterwards by a series of reports from other research groups. In 2010, Ye and coworkers reported the diastereoselective synthesis of 4-hydroxytetralones **22** via a domino Stetter–aldol reaction.[50] Based on the same principle as in the domino Stetter–Michael reaction, the Ye group employed phthaldialdehyde (**23a**) as a dual reagent. One of the aldehyde functionalities on **23a**, in combination with the Michael acceptor **24** and precatalyst **1c**, performed the initial Stetter addition. Then, the enolate **25** generated from the initial 1,4-addition step cyclized onto the aldehyde furnishing the *trans*-4-hydroxytetralone **22** (**Scheme 1.10, eq 1**).

As part of this study, Ye isolated the intermediate generated after the initial Stetter reaction. The conjugate addition product **26** was then subjected to a catalytic amount of base which resulted in the formation of *cis*-4-hydroxytetralone (**22**) as the major product (**Scheme 1.10, eq 2**). In contrast to what was postulated by Gravel,[49] Ye proposed that the NHC remains as part of the intermediate during the aldol cyclization step, thus helping to control the diastereofacial selectivity during the attack on the aldehyde.

Scheme 1.10 Synthesis of 4-Hydroxytetralones via Domino Stetter–Aldol.



Presumably, the hydroxyl functionality helped stabilize the transition state by means of hydrogen bonding with the carbonyl group of the aldehyde, favouring the formation of the kinetic *trans*-product (**Figure 1.7**).

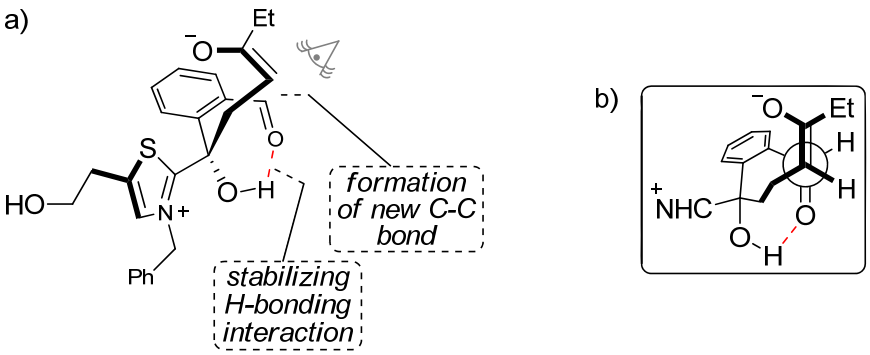
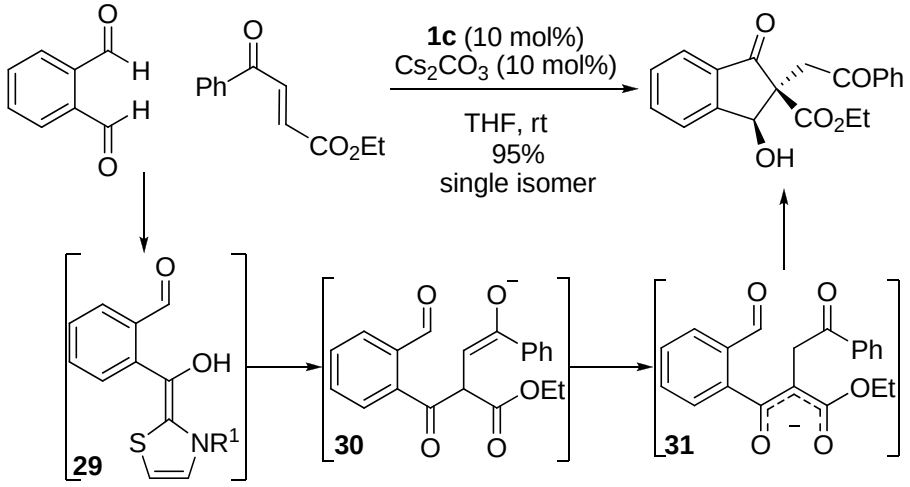


Figure 1.7 Proposed transition state for the stereoselective ring closing step during the synthesis of 4-hydroxytetralones.

Later the same year, Ye and coworkers disclosed a domino Stetter–aldol using **23a** with doubly activated Michael acceptors of type **27** to afford 2,2-disubstituted-3-hydroxyindanones (**Scheme 1.11**).[51]

Scheme 1.11 Synthesis of 3-Hydroxyindanones Via Domino Stetter–Aldol Reaction.

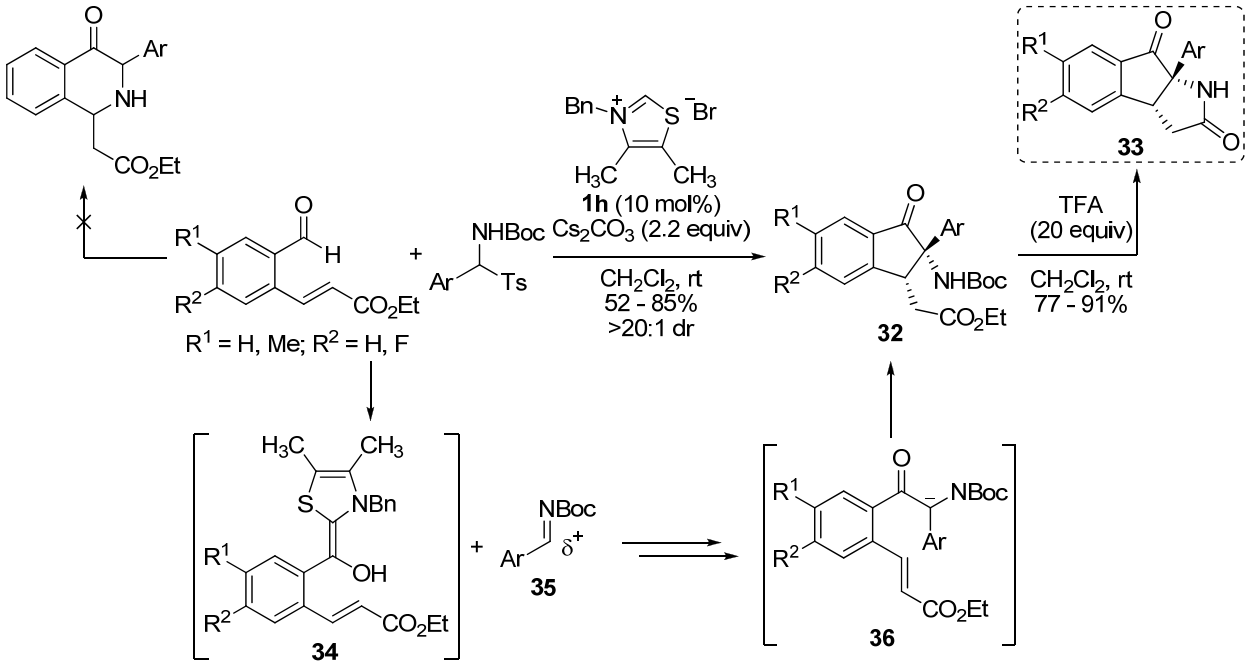


The reaction was proposed to proceed through the formation of the Breslow intermediate **29**, which in the presence of the doubly activated Michael acceptor **27** produced enolate **30**. Following this step, the acidic α-proton on **30** underwent a 1,2-proton shift to generate the more stable enolate **31**. Subsequently, the stable enolate attacked the aldehyde to form **28** (**Scheme 1.11**).

Late in 2010, with the intention of developing a facile construction of dihydroisoquinoline scaffolds, You and coworkers reported the synthesis of dihydroindenones **32** via a domino aza-benzoin–aza-Michael reaction.[52] The scope of the reaction was restricted to the use of (*E*)-ethyl 3-(2-formylphenyl)acrylates and aryl-substituted *N*-Boc imine precursors. The reaction furnished various derivatives of **32** with moderate to excellent yields and remarkable

diastereoselectivity. Additionally, products **32** served to generate pharmaceutically attractive pyrrolidine-containing tricyclic compounds **33** bearing two contiguous stereocentres. This transformation illustrated the dual role of the N-Boc imine **35** as both the electrophile in the presence of the Breslow intermediate **34** and as a nucleophile during the cyclization step on **36** to furnish **33** (**Scheme 1.12**).

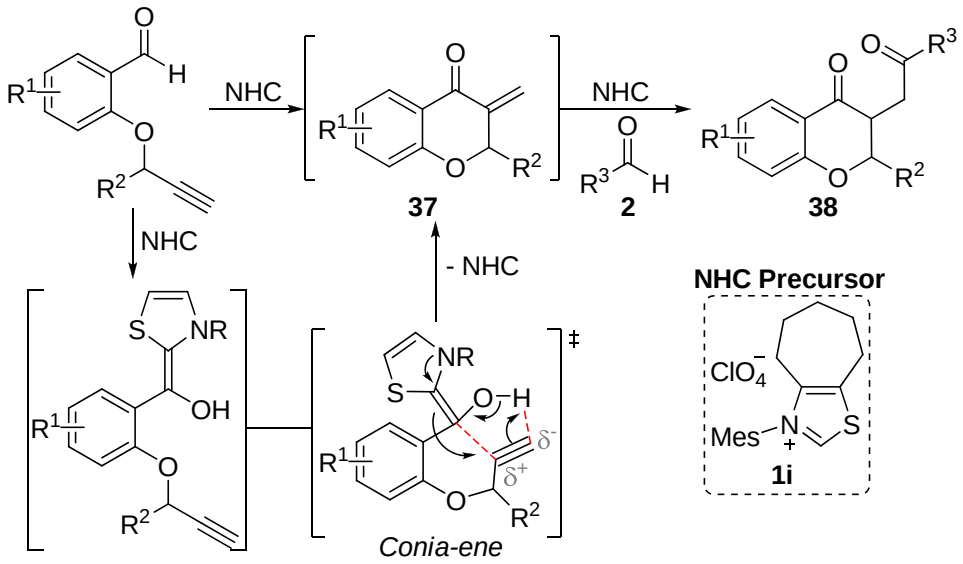
Scheme 1.12 Domino aza-Benzoin–aza-Michael Reaction Reported by You et al.



Recently, the Glorius group reported the hydroacylation of alkenes catalyzed by NHCs.[53] Glorius described the study of various electron-rich thiazolium salts of the type **1i**, whose corresponding carbenes are presumed to have higher electron density compared to *N*-aryl thiazolium salts (**Scheme 1.2**).[54] More recently, his group disclosed a novel domino process in which the initial step is an NHC-catalyzed hydroacylation of alkynes followed by a Stetter reaction to access mono- and disubstituted chroman-4-ones **38** (**Scheme 1.13**).[55]

Glorius proposed that the reaction proceeded through a concerted Conia-ene type reaction, where the enamine character of the Breslow intermediate would favour the carbon–carbon bond formation (**Scheme 1.13**). Subsequently, the opposite end of the alkyne built up a negative charge that would abstract the proton from the alcohol leading to the formation of the β,β-unsubstituted enone **37**. The reaction was effective with aromatic, heteroaromatic, and aliphatic aldehydes furnishing **38** in moderate to excellent yields (68 – 90%).

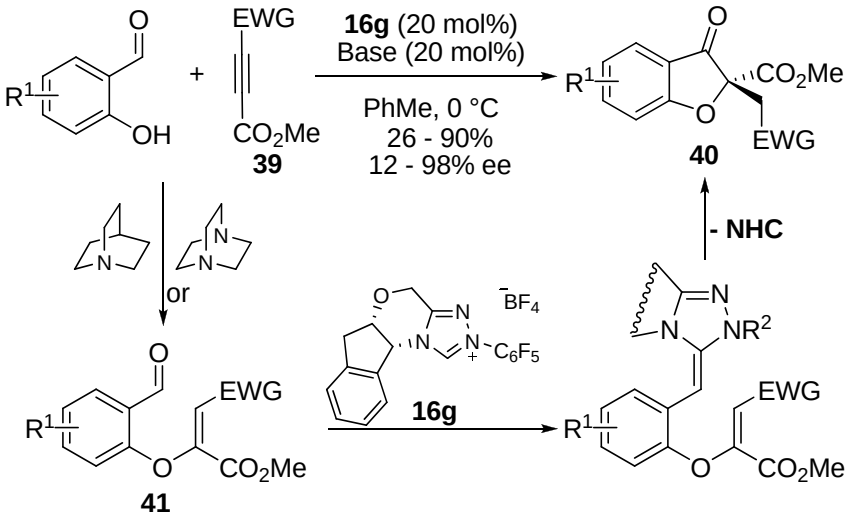
Scheme 1.13 Glorious' NHC-Catalyzed Domino Hydroacylation–Stetter Reaction for the Synthesis of Chroman-4-ones.



In recent years, several research groups have become interested in the use of combined catalytic systems for domino transformations. Recent reports in cooperative[56-59] and dual[60-62] catalysis had indicated success in this area in which two distinct catalysts are used in the same reaction. In 2010, Rovis and coworkers reported the synthesis of 2,2-disubstituted benzofuranone derivatives **40** through a domino multicatalytic enantioselective oxa-Michael–Stetter reaction

(**Scheme 1.14**).[63] They employed DABCO or quinuclidine to catalyze the oxa–Michael addition of salicyl-aldehydes to dimethyl acetylenedicarboxylate (DMAD) and derivatives (**39**). Once intermediate **41** was formed, precatalyst **16g** performed the intramolecular Stetter reaction enantioselectively to produce **40** with moderate to excellent enantioselectivity.

Scheme 1.14 Multicatalytic Domino Michael–Stetter Reaction for the Synthesis of Benzofuranone Derivatives.



1.3 CONCLUSIONS

The conjugate addition of acyl anion equivalents onto Michael acceptors (Stetter reaction) is a reaction of great value for organic chemists, as it provides a versatile method to access 1,4-bifunctional building blocks that are valuable precursors in synthesis. However, the scope of the methodology is still limited to certain combinations of aldehyde–acceptor. Although the Stetter reaction has undergone remarkable advances in recent years, several issues need to be addressed in order to make this reaction a widely used tool in synthetic chemistry.

Over the last three years, there has been an increased and sustained interest in the development of domino transformations employing *N*-heterocyclic carbene (NHC)-derived acyl anion equivalents.[49, 51, 52, 55, 60-72] Many of these domino transformations took advantage of the strategically located functionalities present in Stetter addition products. Through the judicious use of appropriate functional groups and the subtle interplay of their often competing reactivities, a wide variety of complex architectures could be generated. A key element common to many of these domino transformations was the presence of enolizable carbonyl groups following an initial Stetter reaction. The formation or interception of an enolate under the basic reaction conditions led to a cyclization event or other productive transformations.

Although the use of acyl anion equivalents in domino reactions is in its infancy, it is conceivable that such emerging protocols will find application in total synthesis of natural products or other compounds and materials of interest.

PART II: RESULTS, DISCUSSION, AND CONCLUSIONS

CHAPTER 2: HIGHLY ENANTIOSELECTIVE INTERMOLECULAR STETTER REACTIONS OF β-ARYL ACCEPTORS

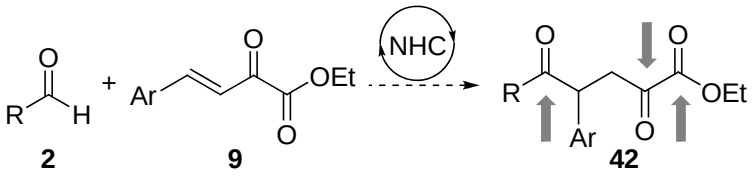
As previously discussed, the intermolecular version of the Stetter reaction has witnessed major advances in recent years.[37-42, 44] Nevertheless, several limitations still remain associated to the intermolecular version of this transformation. For instance, one of the major limitations is the substrate scope, in which the use of β-aryl substituted acceptors has not afforded high enantioselectivities (≥90% ee). In addition, simple α,β-unsaturated ketone acceptors have not delivered Stetter products with high enantioselectivity.

2.1 RESEARCH OBJECTIVE

The objective of this project was to develop a complementary protocol that would allow the use of β-aryl-substituted Michael acceptors in the enantioselective intermolecular Stetter reaction. To do so, it was decided to investigate the use of γ-aryl-β,γ-unsaturated-α-ketoesters **9** as highly electrophilic acceptors for the intermolecular Stetter reaction. It was reasoned that the highly electrophilic nature of these acceptors would allow the investigation of a wide range of catalysts under mild conditions as well as the use of a variety of aldehydes. In addition, the unique functionalities present in the resulting Stetter products **42** would provide an ideal venue for a variety of useful synthetic transformations (**Scheme 2.1**).[i]

[i] This research work was performed in collaboration with Karen Thai and François Bilodeau [Boehringer Ingelheim (Canada) Ltd.] and was published in part in the ACS journal *Organic Letters* in August 2011 (Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2011**, *13*, 4942-4945.)

Scheme 2.1 Intermolecular Stetter Reaction on γ-Aryl-β,γ-Unsaturated-α-Ketoesters and Reactive Sites on the γ-Aryl-α,δ-diketoester Product **42**.

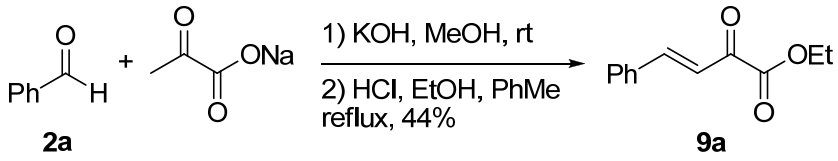


2.2 RESULTS AND DISCUSSION

2.2.1 Preliminary Investigations

To start the investigations on the Stetter reaction, it was necessary to prepare a model acceptor that would help find the optimal reactions conditions. The preparation of acceptor **9a** was performed in a two-step process using a modified procedure described by Vaijayanthi and coworkers.[73] Benzaldehyde and sodium pyruvate were reacted under strongly basic conditions to produce the corresponding carboxylic acid intermediate, which was esterified with ethanol under acidic conditions (**Scheme 2.2**).

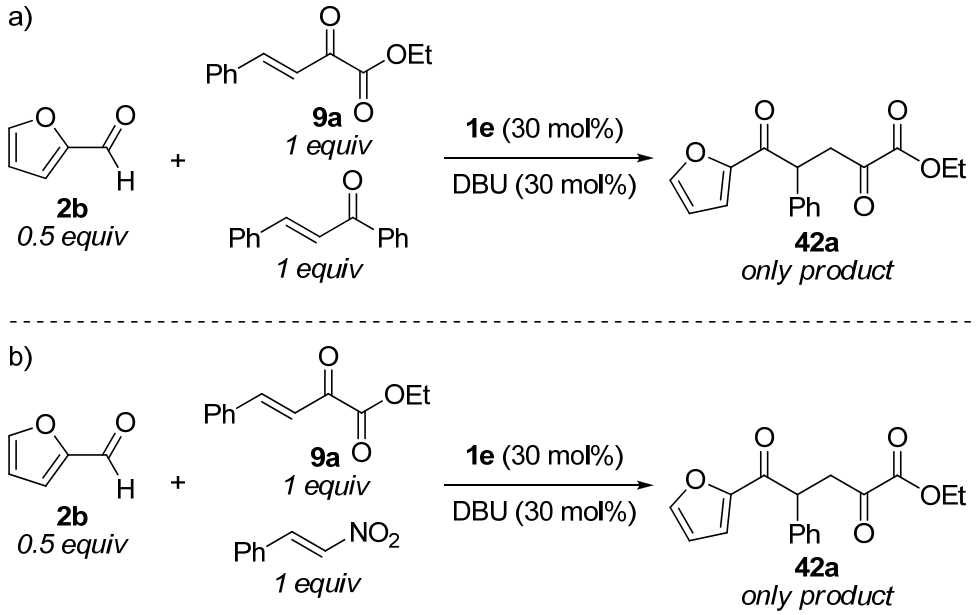
Scheme 2.2 Synthesis of Michael Acceptor **9a**.



After the successful preparation of **9a**, the studies began by comparing the reactivity of the model α-ketoester acceptor with two other phenyl-substituted acceptors, chalcone and β-nitrostyrene. Two competition reactions were performed in the presence of furfural (**2b**) as the limiting reagent and a combination of **9a** with chalcone or β-nitrostyrene employing thiazolium

salt **1e**, DBU as the base, and dichloromethane as solvent. Remarkably, the model acceptor **9a** was estimated to be at least 20 times more reactive than chalcone and β-nitrostyrene based on the fact that **42a** was the only product that could be detected after analysis of the crude sample by ^{1}H NMR spectroscopy (**Scheme 2.3**).

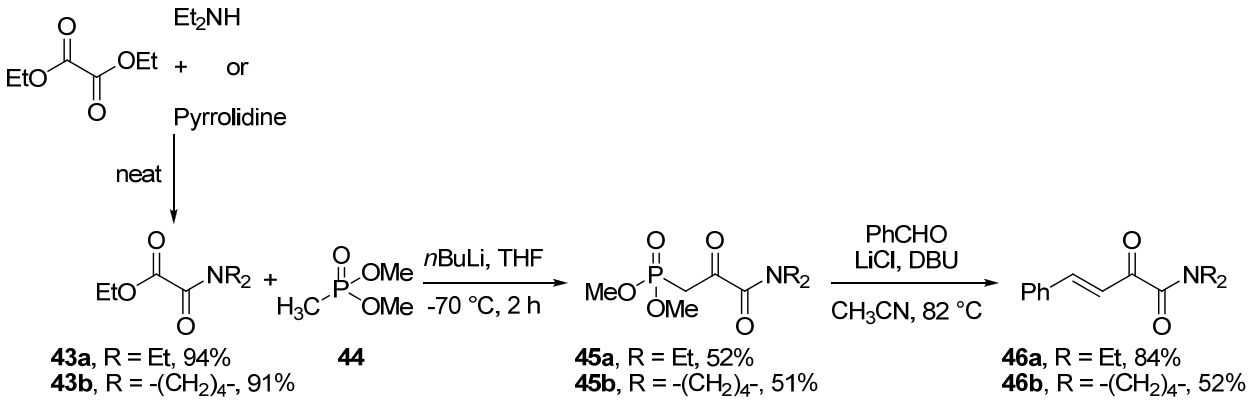
Scheme 2.3 Competition Reaction Between Model Acceptor **9a** with Chalcone or β-Nitrostyrene.



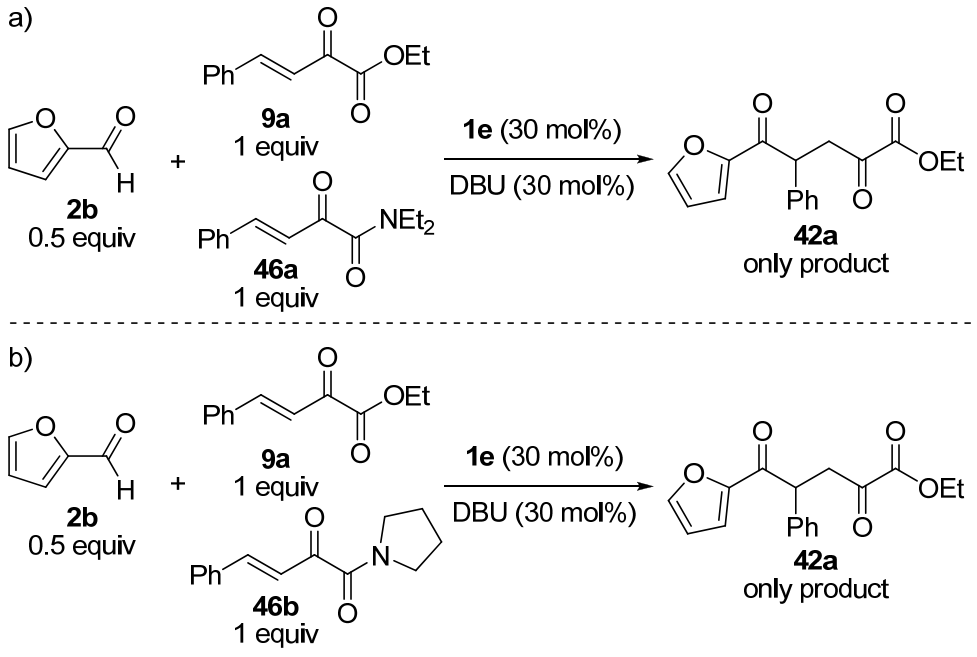
Such outstanding results demonstrate the finding of an excellent Michael acceptor which, in addition to its ease of preparation, is highly reactive for the Stetter reaction. However, the question was posed whether similar electron withdrawing groups such as α-ketoamides would behave similarly. As a result, two new Michael acceptors were prepared in order to compare their reactivity with that of **9a** (**Scheme 2.4**).

Similarly to the competition reaction shown in **Scheme 2.3**, the reactivity of **9a** was compared with that of **46a** and **46b** (**Scheme 2.5**). From these results, the reactivity of acceptor **9a** was demonstrated to be superior to that of **46a** and **46b**. Presumably, the amide moiety decreases the electron-withdrawing ability of **46**, thus reducing its reactivity.

Scheme 2.4 Synthesis of γ-Phenyl-β,γ-Unsaturated-α-Ketoamides **46a-b**.

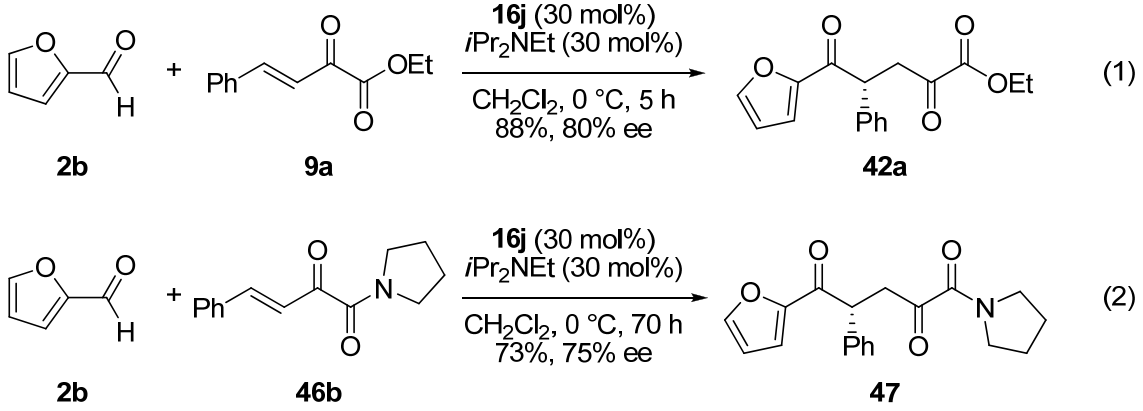


Scheme 2.5 Competition Reaction Between α-Ketoester **9a** with α-Ketoamide **46a** or α-Ketoamide **46b**.



Finally, the effect of different electron-withdrawing groups on the enantioselectivity of the Stetter reaction was studied. For this experiment, triazolium salt **16j** and acceptors **9** and **46b** were employed (**Scheme 2.6**).

Scheme 2.6 Effect of the EWG in the Michael Acceptor for the Enantioselective Intermolecular Stetter Reaction.

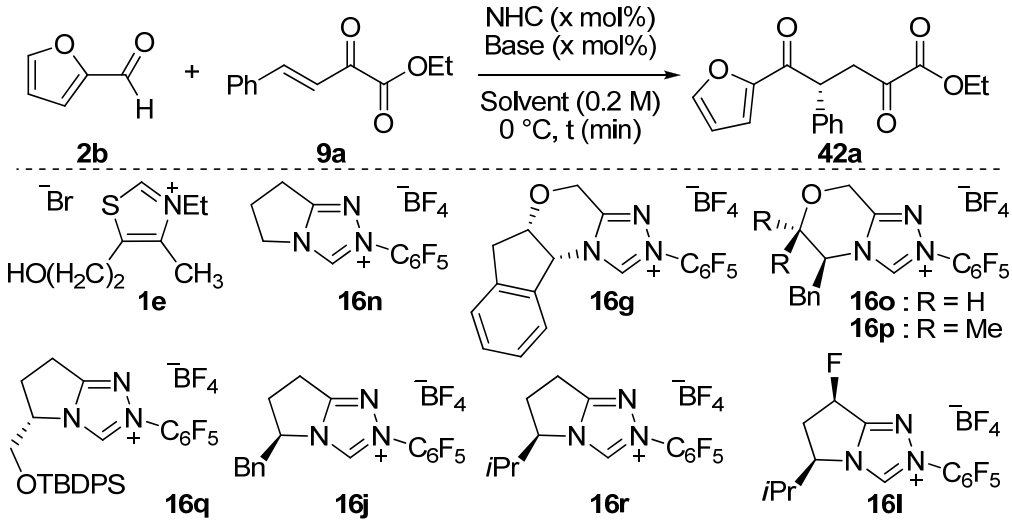


The reaction using α-ketoester **9a** furnished the desired product **42a** in very good yield and promising enantioselectivity (**Scheme 2.6, eq 1**). In contrast, α-ketoamide **46b** provided the expected product in lower yield and slightly lower enantioselectivity (**Scheme 2.6, eq 2**). Despite the large difference in reactivity between **9a** and **46b**, this experiment demonstrated that a small variation on the electron-withdrawing group did not significantly affect the enantioselectivity of the transformation.

2.2.2 Optimization of the Reaction

Having compared the reactivity of **9a** with other Michael acceptors, the reaction was then optimized using **9a** as the model substrate with furfural and various azolium salts (**Table 2.1**).

Table 2.1 Optimization of the Reaction Conditions for the Enantioselective Stetter Reaction Using **9a** as Model Acceptor and Furfural as the Model Aldehyde [a]



entry	NHC precursor (x)	base (x)	solvent	time (min)	yield (%)[b]	% ee[c]
1	**1e** (30)	DBU (30)	CH_2Cl_2	15	95	-
2	**16n** (30)	DBU (30)	CH_2Cl_2	(2 h)	90	-
3	**16n** (30)	Cs_2CO_3 (30)	CH_2Cl_2	(2 h)	88	-
4	**16n** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	(2 h)	90	-
5	**16n** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	30	77	-
6	**16n** (30)	*i*Pr_2NEt (30)	THF	30	19	-
7	**16n** (30)	*i*Pr_2NEt (30)	Toluene	30	16	-
8	**16n** (30)	*i*Pr_2NEt (30)	EtOH	30	68	-
9	**16g** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	30	20	28
10	**16o** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	(24h)	0	-
11	**16p** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	(24 h)	0	-
12	**16q** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	10	69	76 [d]

13	**16j** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	(5 h)	88	80
14	**16r** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	20	96	80
15	**16l** (30)	*i*Pr_2NEt (30)	CH_2Cl_2	(2 h)	90	86
16	**16l** (30)	*i*Pr_2NEt (100)	CH_2Cl_2	15	98	89
17	**16l** (10)	*i*Pr_2NEt (100)	CH_2Cl_2	15	98	89
18	**16l** (5)	*i*Pr_2NEt (100)	CH_2Cl_2	15	92	90
19	**16l** (1)	*i*Pr_2NEt (100)	CH_2Cl_2	(4 h)	20	82

[a] Unless otherwise noted, all reactions were performed by addition of the base to a solution of **2b** (1.5 equiv), **9a**, and precatalyst in the appropriate solvent (0.2 M) at 0 °C. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Yield of pure isolated products. [c] Enantiomeric excess determined by HPLC analysis on chiral stationary phase. [d] The opposite enantiomer was obtained.

The use of thiazolium salt **1e** and DBU as base, cleanly furnished the Stetter product **42a** in a very short time (< 10 min) (Entry 1). Although precatalyst **1e** proved to be very useful for this transformation, it will not produce **42a** enantioselectively. Additionally, it has been demonstrated by others that the use of chiral thiazolylidene catalysts typically affords poor enantioselectivities for the benzoin[22-26, 74-77] and the Stetter reactions.[78, 79] Therefore, in order to prepare enantiomerically enriched products, it was necessary to explore different azolium precatalysts such as triazolium salts. The screening of triazolium precatalysts started with the achiral triazolium salt **16n**, which under standard conditions furnished the Stetter product in excellent yield (entry 2).

With this set of conditions, two other bases (cesium carbonate and *i*Pr_2NEt) were studied. Despite the effectiveness of both bases, the use of *i*Pr_2NEt gave a cleaner transformation (entries 3-4). In addition, the use of a weaker base is desirable in order to prevent racemization of the product [pK_a values in THF (*i*Pr_2NEt = 12.5) vs. (DBU = 16.6)].[80]

Other solvents were studied. However, poor to moderate yields of the Stetter product were obtained (entries 5-8). When methanol was employed as the solvent, the Stetter adduct was formed just as fast as that performed with dichloromethane. However, analysis of the crude sample revealed that the starting material was fully consumed producing a complex mixture. In addition, it was observed that the expected Stetter product underwent transesterification with methanol.

With the optimal solvent and base, various chiral NHCs were then screened. The use of Rovis' aminoindanol-derived triazolium salt **16g**[36] gave **42a** in poor yield and enantioselectivity, presumably as a result of the steric hindrance from the catalyst (entry 9). In order to investigate the effect of the steric bulk on the NHC and its effect on the enantioselectivity, precatalysts **16o** and **16p** were examined (entries 10-11). Unfortunately, both catalysts were unreactive under the optimized reaction conditions. Switching to triazolium salt **16q**, the reaction afforded moderate yield and enantioselectivity of the opposite enantiomer (entry 12). When the reaction was performed using precatalyst **16j**, which is less sterically hindered than **16q**, **42a** was produced in very good yield and good enantioselectivity (entry 13). Similarly, triazolium salt **16r** furnished the desired product with improved yield and comparable enantioselectivity in a shorter reaction time (entry 14). The use of the recently disclosed backbone-fluorinated precatalyst **16l**[41] gave excellent enantioselectivity and comparable yield (entry 15). Despite the excellent result achieved with precatalyst **16l**, the reaction time was longer in contrast to precatalyst **16q** (2 h vs. 20 min, respectively). Therefore, it was hypothesized that the addition of 1 equivalent of base would increase the amount of deprotonated triazolium salt in solution. As a result, a substantial reduction in the reaction time (15 min) and a slight increase in the enantioselectivity were observed (to 89% ee) (entry 15 vs. 16). When the precatalyst loading was reduced to 10%, no

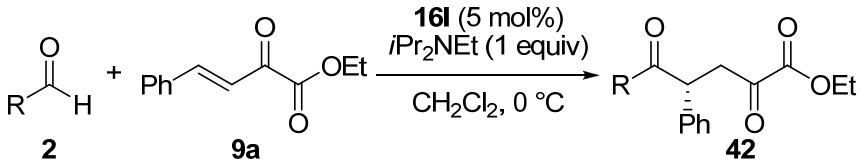
significant effect on the outcome of the reaction was observed (entry 17). Conversely, when 5 mol% of **16l** was used, the enantiomeric excess of the product increased to 90% (entry 18). The use of 1 mol% of **16l** appeared to be detrimental for this system (entry 19). After studying **16l** and other triazolium salt precatalysts in the Stetter reaction, it was observed that the activity of these catalysts is inhibited after a short period of time. As a consequence, it appears that the smaller the amount of catalyst, the less efficient the reaction will be. Therefore, the optimized conditions were established by performing the reaction at 0 °C in dry dichloromethane and employing 5 mol% of triazolium salt **16l** with 1 equivalent of Hünig's base.

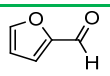
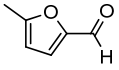
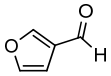
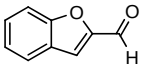
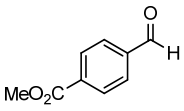
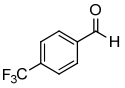
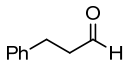
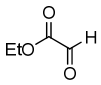
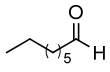
2.2.3 Scope of the Reaction

Thereafter, the scope of the reaction was studied. The extent of various aldehydes **2** was investigated in the presence of the model acceptor **9a** (**Table 2.2**).

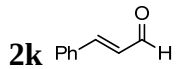
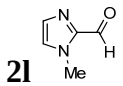
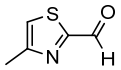
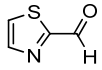
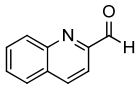
Furfural (**2b**) gave very good yield and excellent enantioselectivity in a short reaction time (entry 1). When 5-methylfurfural (**2c**) was employed, the reaction proved to be slower in contrast to the one using **2b** (entry 2). In both cases, the corresponding benzoin product was produced very rapidly (<1 min.). Also, in the case of **2c**, the conversion of the benzoin product to the desired Stetter product was found to be slower than for **2b**. Presumably, the electron-donating effect of the methyl group on **2c** affected the reactivity towards **9a**. Conversely, the reaction with 3-furaldehyde (**2d**) was sluggish (15 h), affording poor conversion to **42c** (entry 3). Thus, the position of the formyl group at C-3 on the furan ring negatively influences its reactivity due to steric reasons. The structurally analogous benzo[*b*]furan-2-carboxaldehyde (**2e**) proved comparable to **2b**, achieving complete consumption of **9a** in 10 minutes (entry 4). However, the product could not be isolated pure. In addition, the enantioselectivity was drastically reduced to 73% ee.

Table 2.2 Study of the Scope of the Enantioselective Intermolecular Stetter Reaction Employing Various Aldehydes with Model Acceptor **9a**. [a, ii]



entry	aldehyde	time (min)	product	yield (%) [b]	% ee [c]
1	**2b** 	15	**42a**	92	90
2 [d]	**2c** 	(4.5 h)	**42b**	89	84
3	**2d** 	(15 h)	**42c**	(31)	-
4	**2e** 	10	**42d**	(99)	73
5	**2a** 	(4 h)	**42e**	18	57
6 [d]	**2f** 	(3 h)	**42f**	30	68
7	**2g** 	(3 h)	**42g**	13	0
8 [d]	**2h** 	(72 h)	**42h**	(37)	65
9	**2i** 	(2.5 h)	**42i**	(60)	68
10	**2j** 	(44 h)	**42j**	17	0

[ii] Products **42b** – **d**, **42j**, **42k**, **42m**, and **42n** were prepared by Karen Thai.

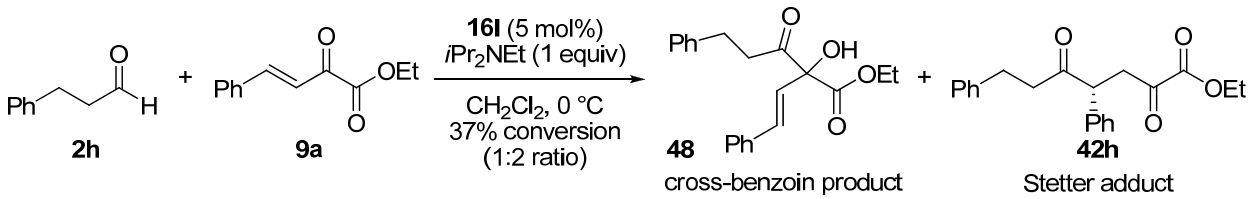
11	**2k** 	(48 h)	**42k**	<5	-
12	**2l** 	(24 h)	**42l**	41	10
13	**2m** 	90	**42m**	73	75
14	**2n** 	40	**42n**	44	76
15	**2o** 	10	**42o**	88	91
16	**2p** 	15	**42p**	94	87
17	**2q** 	30	**42q**	95	>99

[a] General reaction conditions: **2** (1.5 equiv), **9a** (1 equiv), **16l** (5 mol%), *i*Pr_2NEt (1 equiv) in dichloromethane (0.2 M) at 0 °C. [b] Yields of pure isolated products, numbers in parenthesis represent percent conversion of non-purified products. [c] Enantiomeric excess determined by HPLC analysis on chiral stationary phase. The absolute configuration was tentatively assigned by analogy to Rovis et al.[41] [d] 10 mol% of **16l** was required.

Following the study of furan-containing aldehydes, acceptor **9a** was then investigated with aryl aldehydes. The use of benzaldehyde (**2a**) resulted in a very slow transformation affording poor yield and low enantioselectivity (entry 5). When the strongly electron-poor aromatic methyl-4-formylbenzoate (**2f**) was used, it gave greater yield and moderate enantioselectivity (entry 4). Surprisingly, the use of 4-trifluoromethyl benzaldehyde (**2g**) showed a lack of reactivity under the optimized conditions affording the product in only 13% yield and as a racemic mixture (entry 5). Strangely, when **2a** and **2f** were reacted with **9a**, the reactions proceeded very rapidly within the first few minutes. After 30 minutes, it seemed that both reactions reached equilibrium and no further change was observed. Although the fate of the active carbene species cannot be ascertained at this point, Rovis and coworkers have observed

that **2a** fails to react in the presence of β-alkyl nitroalkenes and **16l** under their optimized conditions.[41] From this result, they have proposed that the lack of reactivity in aromatic aldehydes is due to steric factors between the Breslow intermediate and the Michael acceptor (**Figure 1.2**).[42] Presumably, this is true for triazolium-based NHCs given that the reaction of **2a**, **2g**, or **2h** using thiazolium salt **1c** afforded clean and complete conversion to the desired products in 4 h / 62%, 15 min / 81%, and 15 min / 83%, respectively.

When aliphatic aldehydes such as 3-phenylpropanal (**2h**) and ethyl glyoxylate (**2i**) were subjected to the optimized reaction conditions with **9a**, the formation of a cross-benzoin side product was observed along with the expected Stetter product in a 1:2 ratio (cross-benzoin : Stetter adduct) (**Scheme 2.7**), although this was not the case for aldehyde **2h**.[iii] In both cases low conversions to the desired Stetter adduct was obtained as well as moderate enantioselectivities, 65 and 68% respectively (entries 8–9).



Scheme 2.7 Cross-benzoin Product Obtained Under Optimized Conditions when 3-Phenylpropanal was Employed.

On the other hand, 1-octanal produced **42j** in low yield and 0% ee (entry 10). Given that benzaldehyde (**2a**) showed poor reactivity presumably due to steric reasons, it was decided to employ the more sterically accessible cinnamaldehyde (**2k**). Unfortunately, **2k** failed to react

[iii] Confirmation of this result and further studies on the cross-benzoin reaction between aliphatic aldehydes and **9** were later performed by Karen Thai.

under the optimized conditions (entry 11). Interestingly, four months after this experiment was performed, Rovis disclosed an enantioselective Stetter reaction of β-nitroalkenes with enals and **16l** using catechol as additive (**Scheme 1.6e**).[42]

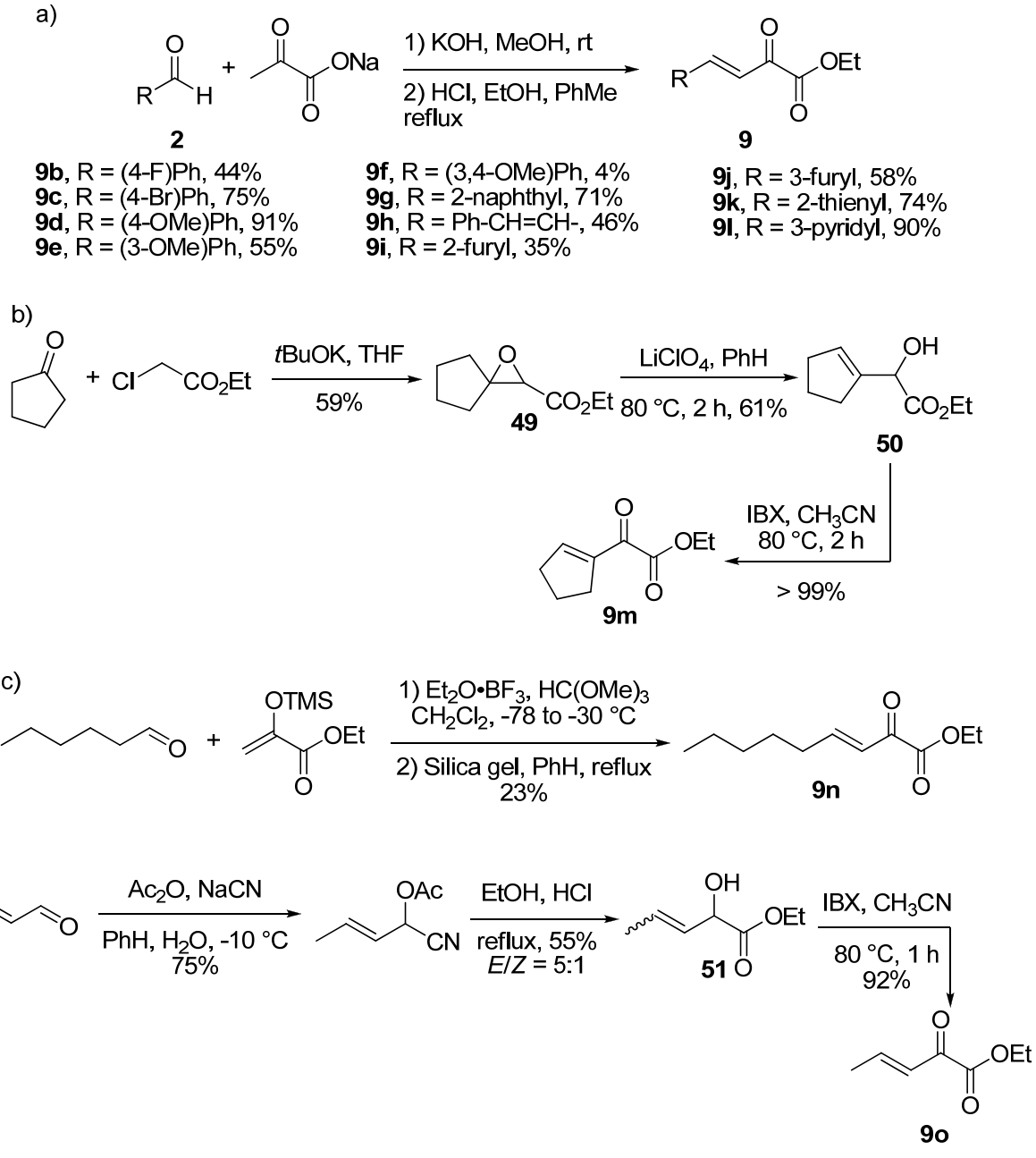
1-Methyl-1*H*-imidazole-2-carbaldehyde (**2l**) produced **42l** in modest yield and poor enantioselectivity (entry 12). Similarly, when aldehydes **2m** and **2n** were examined, they presented sluggish reactivity towards **9a**, although they produced **42m** and **42n** in moderate to low yield and moderate enantioselectivity (entries 13 – 14).

The use of pyridine-2-carboxaldehyde (**2o**) led to a more selective reaction (forming **42o**) than the use of pyrazine-2-carboxaldehyde (**2p**) to produce **42p** (91 vs. 87% ee) (entries 15–16). Remarkably, when quinoline-2-carboxaldehyde (**2q**) was employed, it furnished the Stetter adduct **42q** in excellent yield and very high enantioselectivity (entry 17). In agreement with Rovis et al., aldehydes that are less sterically hindered result in faster reactions, presumably due to the ease of Breslow intermediate formation.[41] As a result, based on such observations, shorter reaction times lead to better % ee's because the racemization of products is less extensive.

In order to study the influence of different substituents on **9**, it was necessary to prepare the corresponding γ-substituted-β,γ-unsaturated-α-ketoesters. The preparation of Michael acceptors **9b-l** was performed by following the same protocol as for **9a** (**Scheme 2.8a**). Acceptor **9m** was prepared via a three-step process starting from cyclohexanone and ethyl chloroacetate to obtain **49** from a Darzens reaction.[81] Subsequently, glycidate **49** underwent an elimination to the corresponding allylic alcohol **50**, which after treatment with IBX produced the desired α-ketoester **9m** in 31% yield over 3 steps (**Scheme 2.8b**). The aliphatic Michael acceptor **9n** was prepared from a Mukaiyama aldol reaction followed by dehydration under acidic conditions (**Scheme 2.8c**).[82] Substrate **9o** was prepared from a known protocol to obtain the corresponding

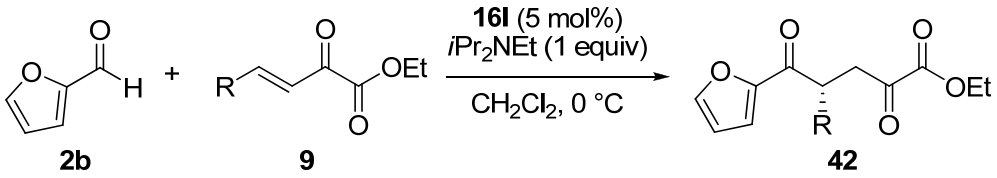
allylic alcohol **51** from crotonaldehyde.[83] After IBX oxidation, **9o** was obtained in good yield as a single isomer (**Scheme 2.8d**).

Scheme 2.8 Synthesis of γ-Substituted-β,γ-Unsaturated-α-Ketoesters **34b-l**.

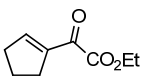


The study of the scope of the acceptor is summarized in **Table 2.3**.

Table 2.3 Study of the Scope of the Reaction Using Furfural and Various γ-Substituted-α-Ketoesters Acceptors. [a, iv]



2b **9** **42**

entry	R	time (min)	product	yield (%) [b]	% ee [c]
1[e]	(**9b**) (4-F)C_6H_5	15	**42r'**	58	74
2	(**9b**) (4-F)C_6H_5	<5	**42r**	80	90
3	(**9c**) (4-Br)C_6H_5	<5	**42s**	90	90
4	(**9d**) (4-OMe)C_6H_5	62 h	**42t**	62	0
5	(**9e**) (3-OMe)C_6H_5	<5	**42u**	96	90
6	(**9f**) 3,4-(OMe)C_6H_4	75	**42v**	86	90
7[e]	(**9g**) 2-naphthyl	20	**42w'**	84	82
8	(**9g**) 2-naphthyl	10	**42w**	97	90
9	(**9h**) Ph-CH=CH-	-	**42x**	-	-
10[d]	(**9i**) 2-furyl	24 h	**42y**	34	0
11	(**9j**) 2-thienyl	24 h	**42z**	80	0
12	(**9k**) 3-furyl	2 h	**42aa**	63	88
13	(**9l**) 3-pyridyl	5	**42ab**	(99)	77
14[d]	(**9m**) 	24 h	**42ac**	n.r. [f]	-

[iv] Products **42v'**–**ab** and their corresponding acceptors were prepared by Karen Thai.

15[d]	(**9n**) *n*-Pentyl	24 h	**42ad**	n.r. [f]	-
16	(**9o**) Me	3 h	**42ae**	(17)	-

[a] General reaction conditions: **2b** (1.5 equiv), **9** (1 equiv), **16l** (5 mol%), *i*Pr_2NEt (1 equiv) in dichloromethane (0.2 M) at 0 °C. [b] Yields of pure isolated products, numbers in parenthesis represent percent conversion. [c] Enantiomeric excess determined by HPLC analysis on chiral stationary phase. [d] 10 mol% of **16l** was required. [e] Aldehyde **2q** was used instead. [f] n.r. = no reaction

Despite the remarkable enantioselectivity achieved in the reaction between aldehyde **2q** and acceptor **9a**, such results were not consistent with other acceptors. When acceptor **9b** and **9g** were reacted with quinoline-2-carboxaldehyde, the enantioselectivity of the products **42r'** and **42w'** decreased substantially in contrast to the one obtained for **42q** (>99% ee vs. 74% or 82% ee, respectively) (entries 1 and 7). The use of electron-poor aromatic groups such as 4-fluorophenyl (**9b**) and 4-bromophenyl (**9c**) gave the corresponding products **42r** and **42s** in good yield and excellent enantioselectivity in very short reaction times (<5 min.) (entries 2–3).

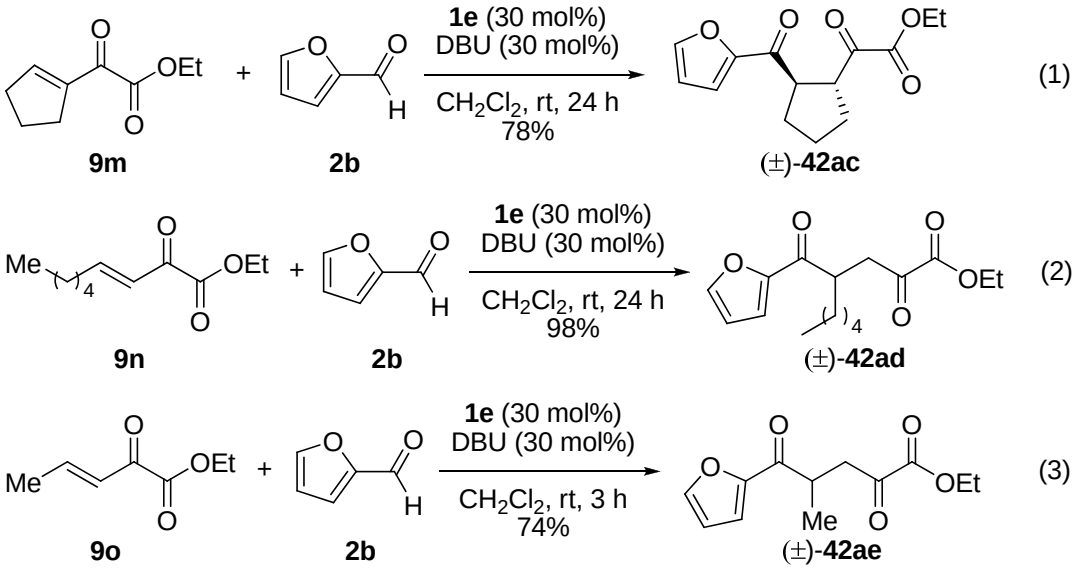
Conversely, the use of electron-rich 4-methoxyphenyl substituted acceptor (**9d**) decreased tremendously the rate of the reaction (62 hours) affording the Stetter adduct in moderate yield and as a racemic mixture (entry 4). In contrast, when the 3-methoxy substituted acceptor **9e** was subjected to the optimized reaction conditions, the desired product was rapidly produced (< 5 min.) in excellent yield and enantioselectivity (entry 5). Surprisingly, the addition of an electron-donating *para*-methoxy substituent to this acceptor (**9f**) did not adversely affect the selectivity of the reaction (entry 6), although the reaction was much slower. It is well known that a methoxy group on the *para* position is electron-donating, thus reducing the reactivity of the acceptor (**9d** and **9f**). However, when the methoxy group is located on the *meta* position, it induces an electron-withdrawing effect and, more importantly, does not affect the selectivity of the reaction (**9e** and **9f**).

The larger naphthalene substituent was well tolerated affording the product **42w** in excellent yield and enantioselectivity (entry 8). In order to study the effect of an electronically similar acceptor, the vinylogous version of **9a** was prepared (**9h)** and studied under the optimized conditions. However, **9h** proved to be poorly reactive (entry 9).

The use of the 2-heteroaryl substituted acceptors (**9i** and **9j**) demonstrated sluggish reactivity, resulting in low to moderate yields of racemic products (entries 10–11). This outcome is attributed to the strong electron-donating effect of the furan and thiophene moieties when substituted at position 2. Interestingly, the less electron-donating 3-substituted heteroaromatic acceptors (**9k** and **9l**), gave the corresponding Stetter adducts (**42aa** and **42ab**) in moderate to good yield and enantioselectivity (entries 12–13). The contrast in reactivity when using these two heterocyclic motifs is noteworthy. Whereas 2-heteroaryl aldehydes behave as excellent partners in the Stetter reaction, the use of these motifs as substituents drastically reduces the reactivity of the α-ketoester acceptor. The opposite effect is observed when 3-heteroaryl aldehydes are employed.

γ-Alkyl substituted acceptors **9m** and **9n** proved to be unreactive using precatalyst **16l** as the expected products were not detected (entries 14–15). In contrast to **9m** and **9n**, acceptor **9o** showed low reactivity towards furfural. Unfortunately, the reaction did not reach completion and several side products started to form as the reaction progressed (entry 15). On the other hand, when the three aliphatic-substituted acceptors (**9m**–**o**) were reacted with furfural and thiazolium salt **1e** as precatalyst, each Stetter product was produced efficiently, albeit in racemic form (**Scheme 2.9**).

Scheme 2.9 Intermolecular Stetter Reactions of γ-Alkyl Substituted-β,γ-Unsaturated-α-Ketoesters.



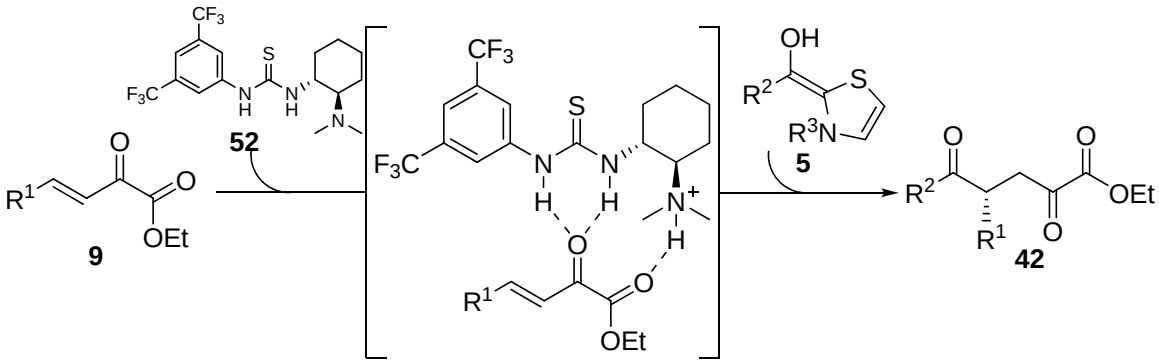
2.2.4 An Alternative Approach to the Aliphatic Acceptors

Based on the observation that aliphatic acceptors react more efficiently using thiazolium **1e** as precatalyst, it was decided to include a co-catalyst that would act as an external source of chirality for the reaction. Therefore, it was proposed to use hydrogen bonding catalysts such as Takemoto's thiourea **52**.[84, 85] This catalyst could serve three purposes, 1) to activate the Michael acceptor **9**, 2) to deprotonate the precatalyst, and 3) to provide a chiral environment that would favour the addition of the Breslow intermediate to **9** stereoselectively (**Scheme 2.10**).

In order to prevent the possibility of racemization of the Stetter adduct in the presence of the strongly basic DBU, *N,N*-diisopropylethylamine (*i*Pr_2NEt) and cesium carbonate were initially investigated for the deprotonation of thiazolium **1e**. When *i*Pr_2NEt was investigated, the desired Stetter product was not obtained. Presumably, the small quantities of NHC present in

solution were not sufficient to catalyze the reaction. On the other hand, the use of cesium carbonate cleanly afforded the desired Stetter product.

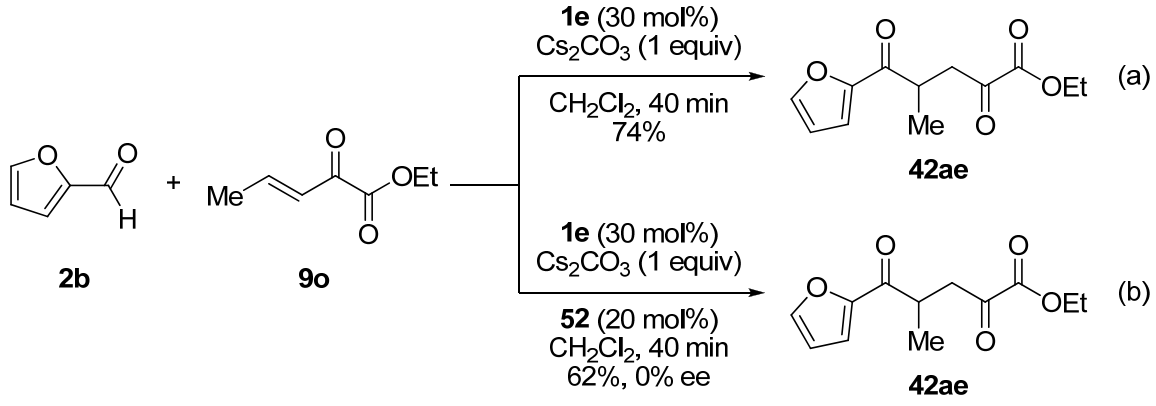
Scheme 2.10 Proposed Mode of Activation of α-Ketoester Acceptor **9** by Takemoto's Catalyst **52**.



In order to assess the effect of **52** on the background reaction, two reactions were studied simultaneously. The first one was performed in the absence of the chiral thiourea **52**, whereas the second reaction contained Takemoto's catalyst **52**. The transformation without the chiral thiourea was complete in 40 minutes, affording 74% yield of the racemic product. Although the reaction containing the thiourea as co-catalyst gave the desired product in 64% yield, it was produced as a racemic mixture (**Scheme 2.11**).

Despite the unfavourable result with Takemoto's thiourea, the fact that it is possible to perform efficiently the conjugate addition of aldehydes on aliphatic acceptors catalyzed by **1e** opens a large number of opportunities for inducing enantioselectivity in this transformation. In this context, other co-catalysts such as Lewis acids or hydrogen bond donors could be further explored.

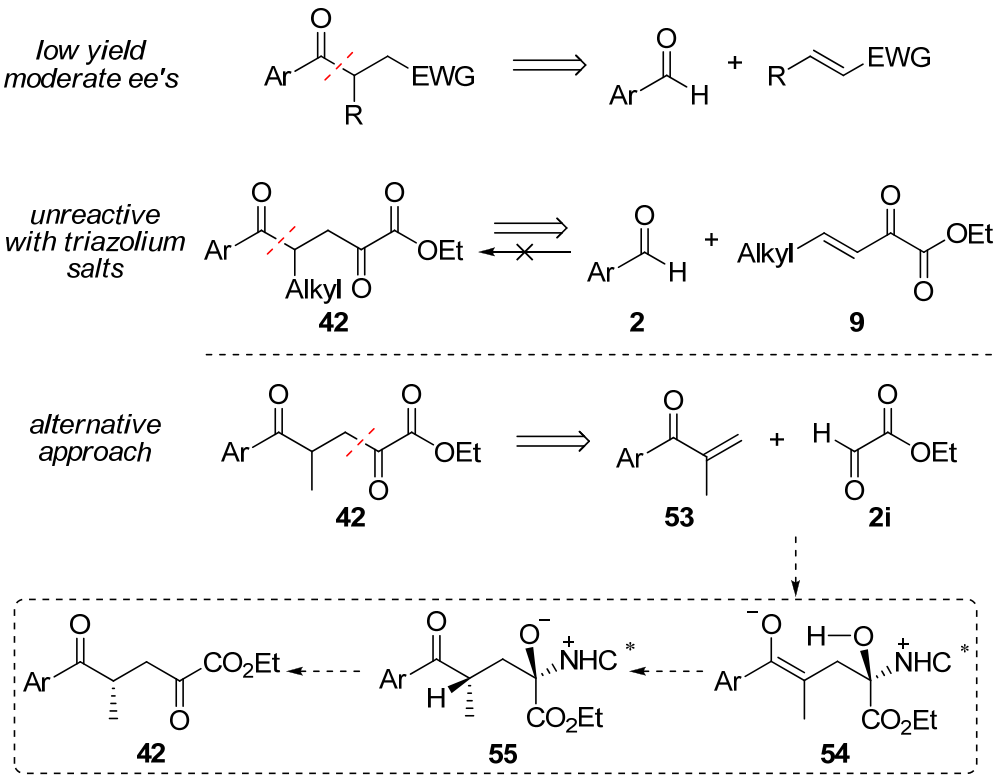
Scheme 2.11 a) Background Reaction and b) Stetter Reaction Employing Takemoto's Thiourea **52** as Co-catalyst.



The contributions detailed here had helped in expanding the scope of the intermolecular Stetter reaction; however, this reaction still faces several challenges. Some of these are: 1) the use of aromatic aldehydes with β-aryl and β-alkyl substituted acceptors, since this reaction produces the conjugate addition product in low yield and poor to moderate enantioselectivity, and 2) the use of aliphatic acceptors, as they are unreactive with triazolium salts. Therefore, it was proposed to prepare Stetter products of type **42** starting from 2-methyl-1-arylprop-2-en-1-one **53** and ethyl glyoxylate (**2i**) using a chiral triazolium salt (**Scheme 2.12**).

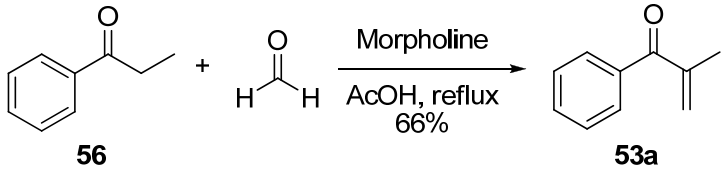
As Glorius has proposed for the synthesis of α-amino acid derivatives,[44] the proton present on the alcohol intermediate **54** would transfer stereoselectively over the top face of the *E*-enolate, thus generating a new α-stereocentre in **55**. The catalytic cycle would be concluded by the release of the catalyst producing **42**.

Scheme 2.12 Alternative Approach for the Synthesis of γ-Alkyl-δ-Aryl-α-Ketoesters.



The first step was to prepare the Michael acceptor **53a** though an α-methylenation of propiophenone (**56**) (**Scheme 2.13**).[86]

Scheme 2.13 Synthesis of 2-Methyl-1-phenylprop-2-en-1-one (**53a**).

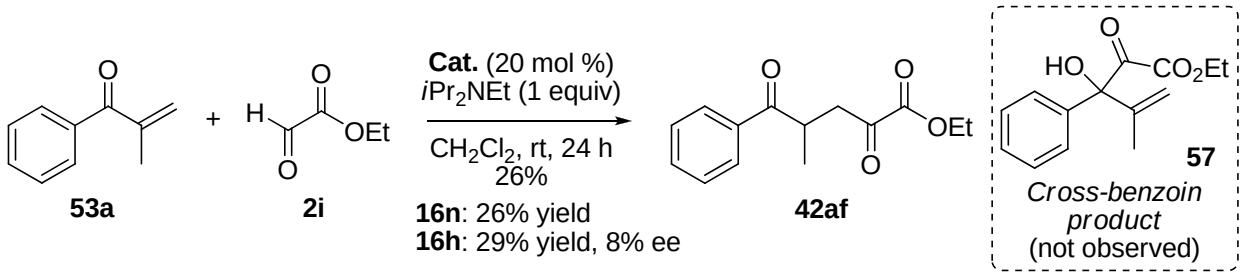


Once the Michael acceptor was successfully prepared, two reactions were set in parallel using triazolium salts **16n** and **16j** with 20% catalyst loading. At the outset of the investigation, it

was decided to run the experiment using the same solvent as that employed in the initial experiments for the Stetter methodology at ambient temperature (**Scheme 2.14**).

Despite the low catalytic activity of both triazolium salts, **16j** gave the expected 1,2,5-tricarbonyl adduct **42af** in moderate yield and poor enantioselectivity. Other attempts using precatalysts **16o**, **16q**, and **16l** were unsuccessful, producing **42af** in lower yield. It is worth mentioning that in none of these cases was the cross-benzoin product observed.

Scheme 2.14 Stetter Reaction of Ethyl Glyoxylate with 2-Methyl-1-phenylprop-2-en-1-one.

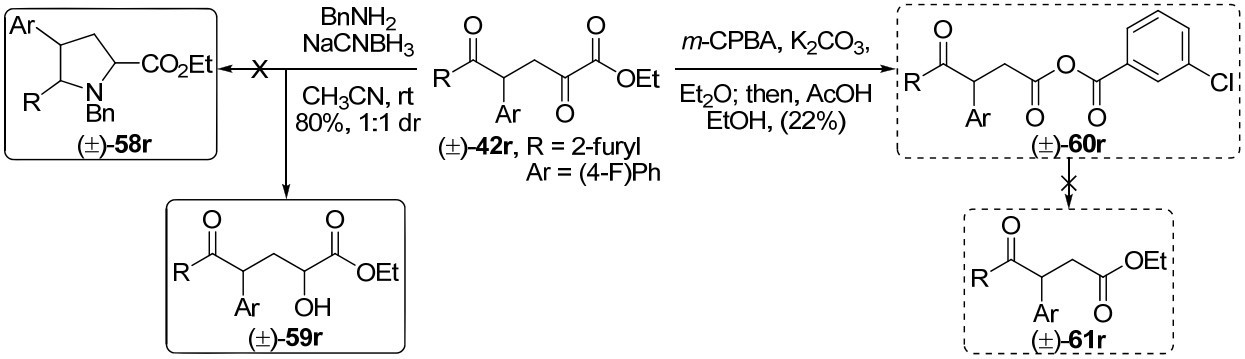


2.2.5 Chemo- and Diastereoselective Transformations of α-Ketoesters

1,4-dicarbonyl compounds are widely employed as important intermediates in the synthesis of heterocycles or natural products.[87-94] The enantioselective Stetter methodology above described provides easy access to a variety of α,δ-diketoesters enantioselectively. This type of backbone can be used to perform chemo- and diastereoselective transformations. It was envisioned that each carbonyl group could be manipulated chemoselectively by taking advantage of their inherent electronic properties. For this part of the study, (±)-**42r** was chosen as model substrate.

The first transformation was intended to be the synthesis of the ethyl ester proline derivative (±)-**58r'** through a double reductive amination.[95] However, it was found that the reduction of the α-ketone with $NaCNBH_3$ was faster than the formation of the imine, producing (±)-**59r** instead (**Scheme 2.15**). To circumvent this problem, an attempt was made to form the iminium intermediate prior to the addition of the reducing agent. However, the competing reduction of the ketone was also observed in this case.

Scheme 2.15 Chemoselective Transformations on α,δ-Diketoester (±)-**42r**.

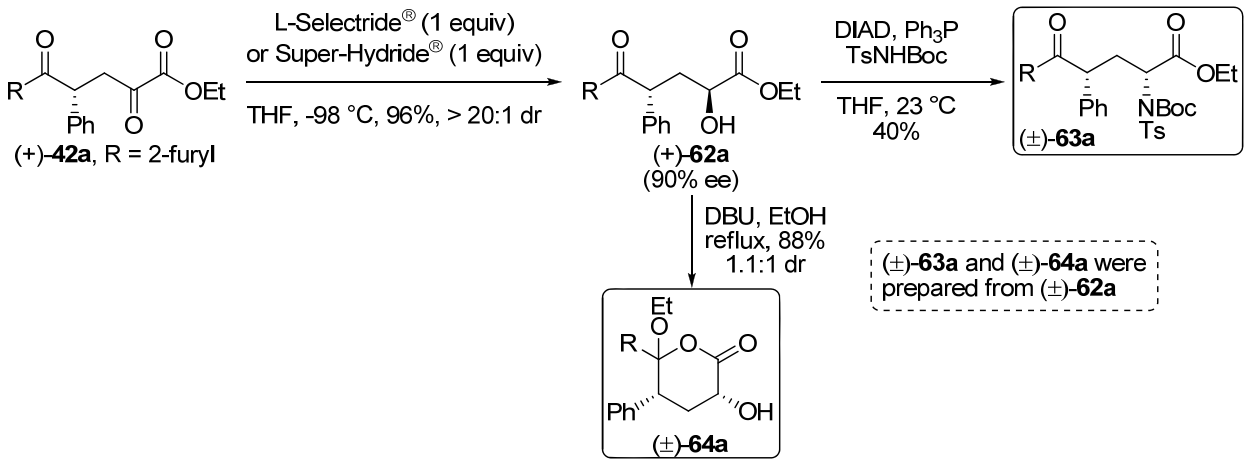


On the other hand, it was envisioned that esters, thioesters, and amides could be prepared through a Baeyer-Villiger-type oxidation on the α-ketoester.[96, 97] However, after several attempts to oxidize (±)-**42r** under various conditions, it was only possible to obtain small amounts of the anhydride (±)-**60r** which would rapidly decompose to a complex mixture.

Due to the problems encountered in the synthesis of the proline derivative and oxidation of the α-ketoester moiety, other potential and more suitable transformations on the Stetter adduct were explored. Initial investigations for the reduction of the α-ketone (+)-**42a** were performed with N-selectride, obtaining a 3:1 diastereomeric mixture of (+)-**62a**. When L-selectride or

Super-Hydride were employed as reducing agents,[v] alcohol (+)-**62a** was obtained with excellent yield and as a single diastereomer (>20:1 dr) (**Scheme 2.16**).

Scheme 2.16 Chemo- and Diastereoselective Reduction of (+)-**42a** by L-Selectride®.



The highly diastereoselective reduction could be favoured due to the coordination of the two most Lewis basic sites, the furan-carbonyl and the ester carbonyl, and a lithium ion. The 8-membered-ring transition state **65a** illustrated on **Figure 2.1** portrays the exposure of the β-face of the α-ketoester group towards the hydride delivery, whereas the α-face would be sterically hindered. Translating transition state **65a** to the Evans model for 1,3-*anti* induction,[98, 99] model **65b** shows the furan-carbonyl in *anti* position relative to the α-ketoester group in order to reduce the dipole moment, thus explaining the 1,3-anti relationship in (+)-**62a**. Although this model is employed for explaining transformations under non-chelating conditions with the Lewis basic carbonyl group, in this instance only the most Lewis basic groups chelate the lithium ion.

[v] The reduction of (+)-**42a** was also performed with $LiEt_3BH$ (Super-Hydride®). This protocol gave (+)-**62a** in comparable yield and excellent diastereoselectivity (> 20:1, same diastereomer by ^1H NMR).

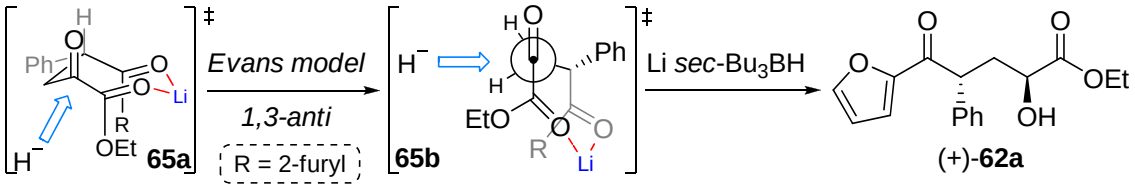


Figure 2.1 Proposed transition state for the diastereoselective reduction of (+)-**42a**.

It is worth mentioning that examples of diastereoselective reductions on substrates of this kind are not known, and diastereoselective reductions of 1,4-dicarbonyl compounds directed by a 3-aryl or alkyl group are rare.[100] More importantly, HPLC analysis of alcohol (+)-**62a** confirmed that reduction of the Stetter adduct occurred without erosion of the enantiomeric excess. *N*-Protected amino ester derivatives could also be formed from the Stetter products, as demonstrated by the transformation of a racemic sample of alcohol **62a** into (±)-**63a** in moderate yield (**Scheme 2.16**). Although this transformation gave a single diastereomer of the amino ester derivative, the stereochemical identity could not be established with certainty. The product arising from a net inversion of configuration was tentatively assigned.

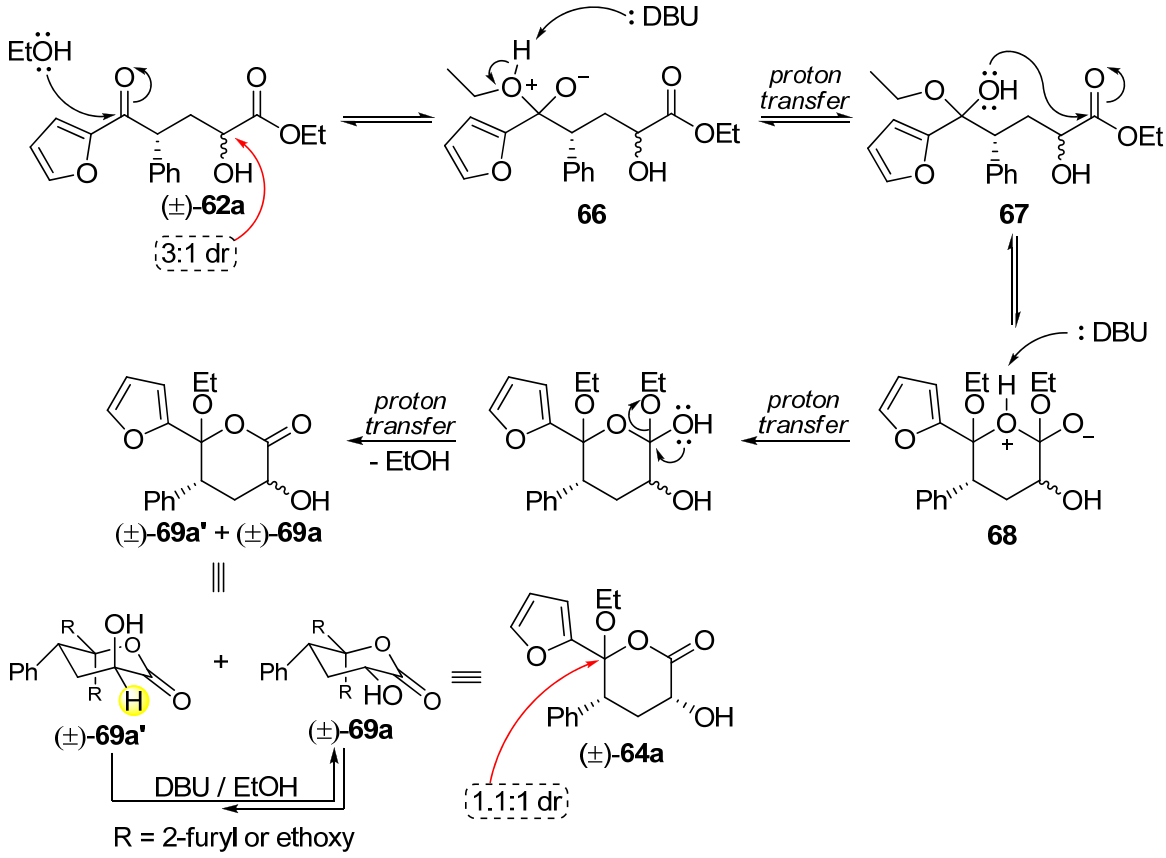
Interestingly, when the single reduction product (±)-**62a** was refluxed in ethanol and a catalytic amount of DBU, the α-hydroxylactone (±)-**64a** was produced in good yield.[vi] A proposed mechanism that accounts for the formation of (±)-**64a** is depicted in **Scheme 2.17**.

Presumably, the furyl-ketone is attacked by ethanol affording oxy-anion **66**. After proton transfer facilitated by DBU, the hemiacetal on **67** cyclizes to produce **68**. Following of a series of acid-base reactions and elimination of one molecule of ethanol, a mixture of lactones (±)-**69a'** and (±)-**69a** is afforded. Final epimerization of the stereocentre at C-2 produces the more

[vi] The starting alcohol (±)-**62a** was obtained from reduction of (±)-**42a** and N-selectride in 71% yield and 3:1 dr.

thermodynamically stable mixture of diastereomers (±)-**64a** bearing the alcohol and the phenyl groups in equatorial positions.

Scheme 2.17 Proposed Mechanism for the Cyclization of Alcohol (±)-**62a**.

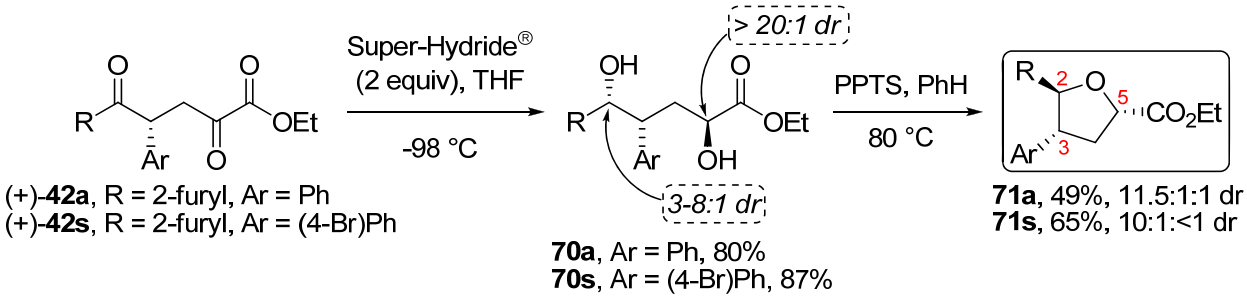


Double reduction of the ketone functionalities with Super-Hydride yielded the corresponding diol **70a**[vii] and **70s** in excellent yield (**Scheme 2.18**). Again, the α-ketoester was reduced with high diastereoselectivity (>20:1) whereas the aromatic ketone was reduced with moderate to good Felkin selectivity (3:1 dr for **70a** and 8:1 dr for **70s**) (**Figure 2.2**). Diols **70a** and **70s** were further transformed into the 2,3,5-trisubstituted tetrahydrofurans **71a** and **71s** under mildly acidic conditions. Presumably, this transformation occurs through a S_N1 mechanism furnishing the more thermodynamically stable 2,3-*trans* product. Compound **71s** was employed

[vii] Diol **70a** and tetrahydrofuran **71a** were prepared by Karen Thai.

to determine the relative configuration at C-3 and C-5 via NOE experiments (see experimental section, **Figure 5.1**) (**Scheme 2.18**).

Scheme 2.18 Double Diastereoselective Reduction of (+)-**42a** and (+)-**42s**.



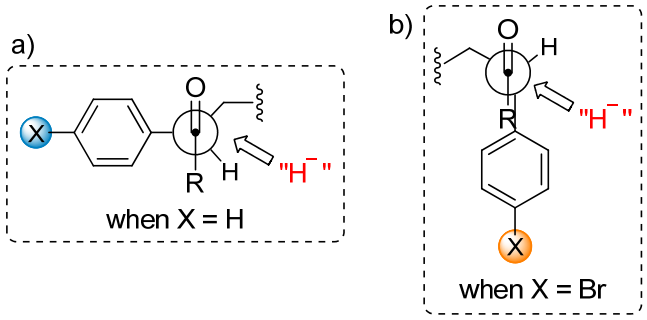
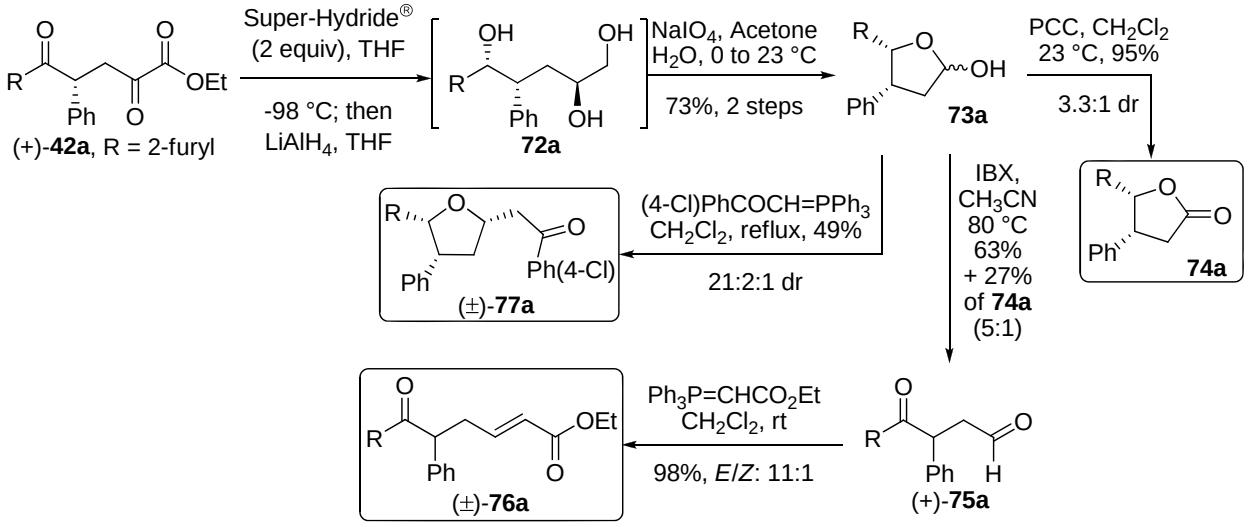


Figure 2.2 a) Felkin-Anh model that accounts for the observed selectivity for the reduction of the δ-ketone. b) Cram polar model that explains the observed selectivity when the aryl group is *para*-substituted with a bromine atom.

Finally, complete reduction of all three carbonyl groups was accomplished by reduction to the 2,5-diol followed by in situ treatment with $LiAlH_4$ to reduce the ester group. The resulting triol was used without further purification and was subjected to oxidative cleavage of the diol to afford the lactol **73a** (**Scheme 2.19**). Lactol **73a** was oxidized to the 3,4-disubstituted lactone **74a** in 95% yield. The observed 3,4-*cis* relative configuration confirms the stereochemical outcome

of the second reduction of (+)-**42a** affording **70a**, **70s**, and **72a** (see experimental section). Surprisingly, lactol **73a** could also be transformed into the corresponding γ-ketoaldehyde (+)-**75a** in 63% yield employing 2-iodoxybenzoic acid (IBX). Along with ketoaldehyde **75a**, the corresponding lactone **74a** was produced. The γ-ketoaldehyde obtained via three step reduction-oxidation process, represents the product of a formal Stetter reaction onto cinnamaldehyde. Unfortunately, due to the acidic conditions inherent to the oxidant, (+)-**75a** was obtained in only 16% ee. The newly formed aldehyde was transformed into an ε-keto-α,β-unsaturated ester ((±)-**76a**) via a Wittig olefination in excellent yield. Tetrahydrofuran (±)-**77a** was prepared from (±)-**73a** through a domino Wittig–oxa-Michael reaction with moderate diastereoselectivity (21:2:1 dr) (**Scheme 2.19**).

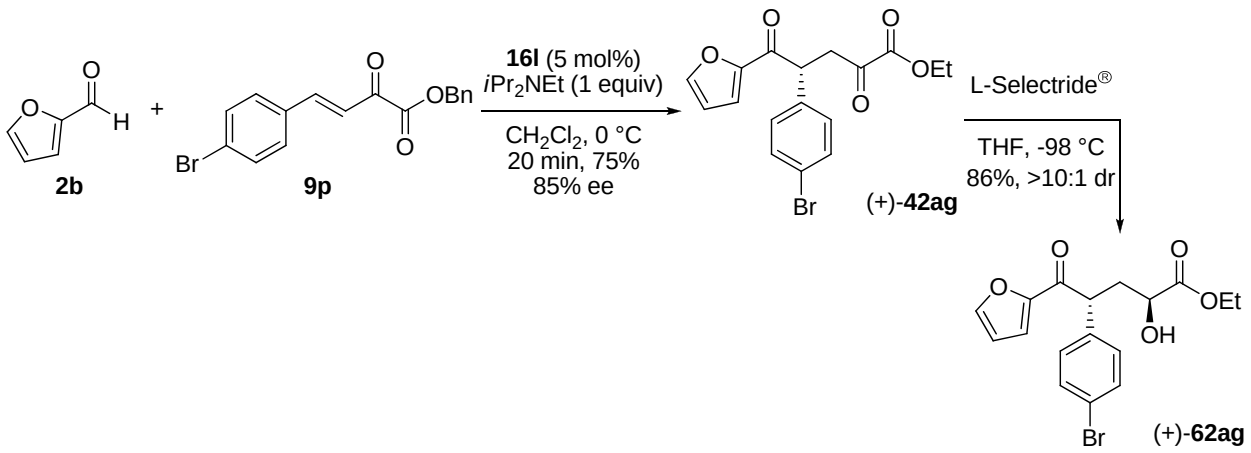
Scheme 2.19 Diastereoselective Reduction of the Three Carbonyl Groups on (+)-**42a** Towards the Synthesis of **74a**, (±)-**76a**, and (±)-**77a**.



Through the chemical derivatization of the Stetter adduct (+)-**42a** and (+)-**42s** it was possible to determine the relative configuration of each stereocentre. Additionally, the

preparation of compounds (+)-**42s** and (+)-**42ag** was targeted to obtain crystals for the determination of the absolute configuration (**Table 2.3**, entry 3 and **Scheme 2.20**, respectively).

Scheme 2.20 Synthesis of α,δ-Ketoester **42ag** and Its Reduction to Alcohol **62ag**.



Although (+)-**42s** and (+)-**42ag** were prepared and derivatized into their corresponding alcohols, it was not possible to obtain suitable crystals for X-ray analysis. Therefore, the absolute configuration of the Stetter adducts were tentatively assigned by analogy to Rovis' results given that the same precatalyst was employed for this protocol, albeit in different solvent.[41] A proposed transition state that accounts for the enantioselectivity of the Stetter reaction is shown in **Figure 2.3**.

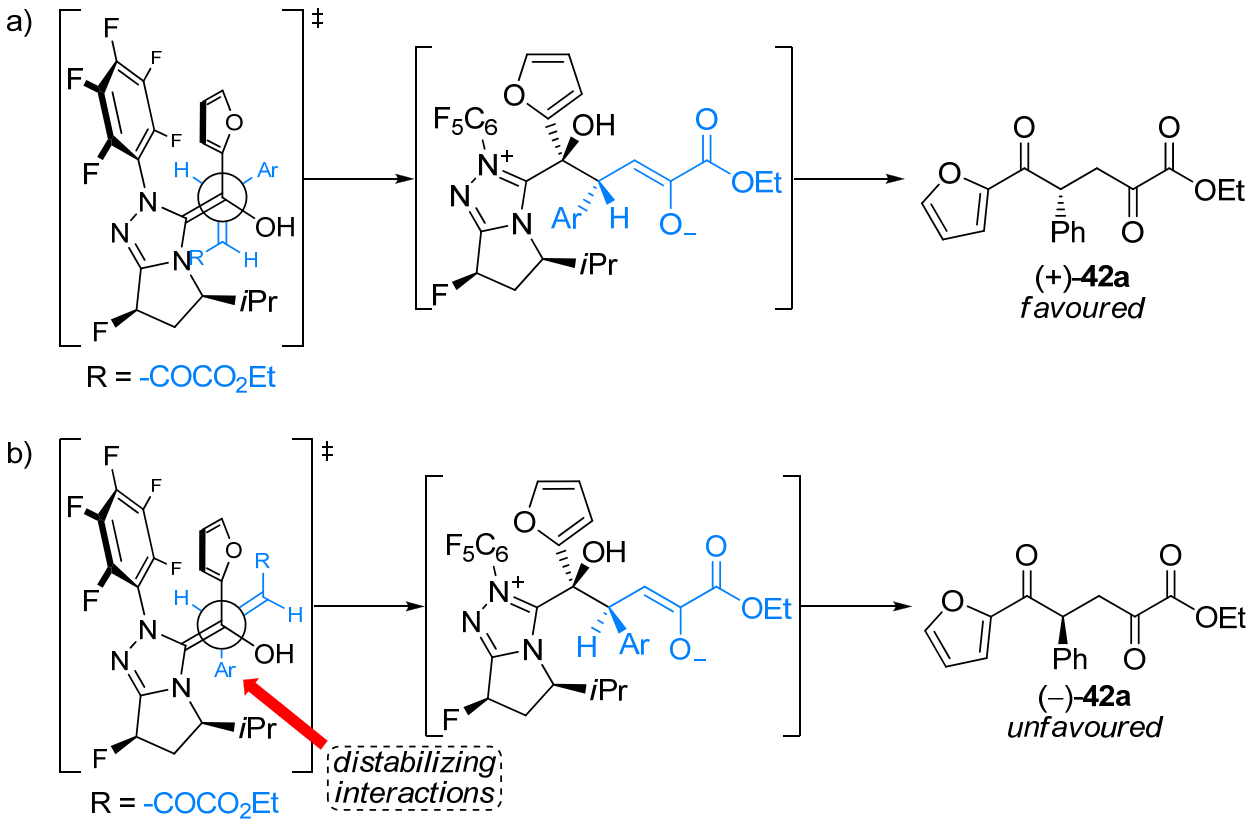


Figure 2.3 Proposed transition states for both enantiomers of **42a** during the conjugate addition step on the Stetter reaction.

2.3 CONCLUSIONS

In conclusion, the first high yielding and highly enantioselective intermolecular Stetter reactions involving β-aryl substituted Michael acceptors were developed, thus complementing current methodologies. Although this method is operative with a variety of heteroaromatic aldehydes and aromatic or heteroaromatic acceptors, reactions using aromatic aldehydes proceeded in good yield only when catalyzed by the achiral thiazolium salt **1c**. Additionally, the use of β-alkyl substituted Michael acceptors was explored. Despite their poor reactivity with triazolium precatalysts **16l**, the aliphatic substituted acceptors demonstrated a remarkable reactivity when achiral thiazolium salt **1c** was employed. Alternative methods for providing an

enantioselective control to the system such as the use of Takemoto's thiourea catalyst or a diastereoselective proton transfer were unsuccessful.

The unique functionalities present in the resulting Stetter products **42** provided an excellent opportunity to perform a variety of transformations with high chemo- and diastereoselectivity. These transformations delivered polysubstituted protected α-amino esters (**63a**), δ-lactones (**64a**), 1,4-diols (**70a** and **70s**), 2,3,5-trisubstituted tetrahydrofuran derivatives (**71a**, **71s**, and **77a**), and 3,4-disubstituted γ-lactones (**74a**). Interestingly, it was possible to prepare the formal Stetter product of cinnamaldehyde and furfural, (**75a**), along with the formal 1,6-addition product **76a**.

CHAPTER 3: DIASTEREOSELECTIVE SYNTHESIS OF INDANES VIA A DOMINO STETTER-MICHAEL REACTION[viii]

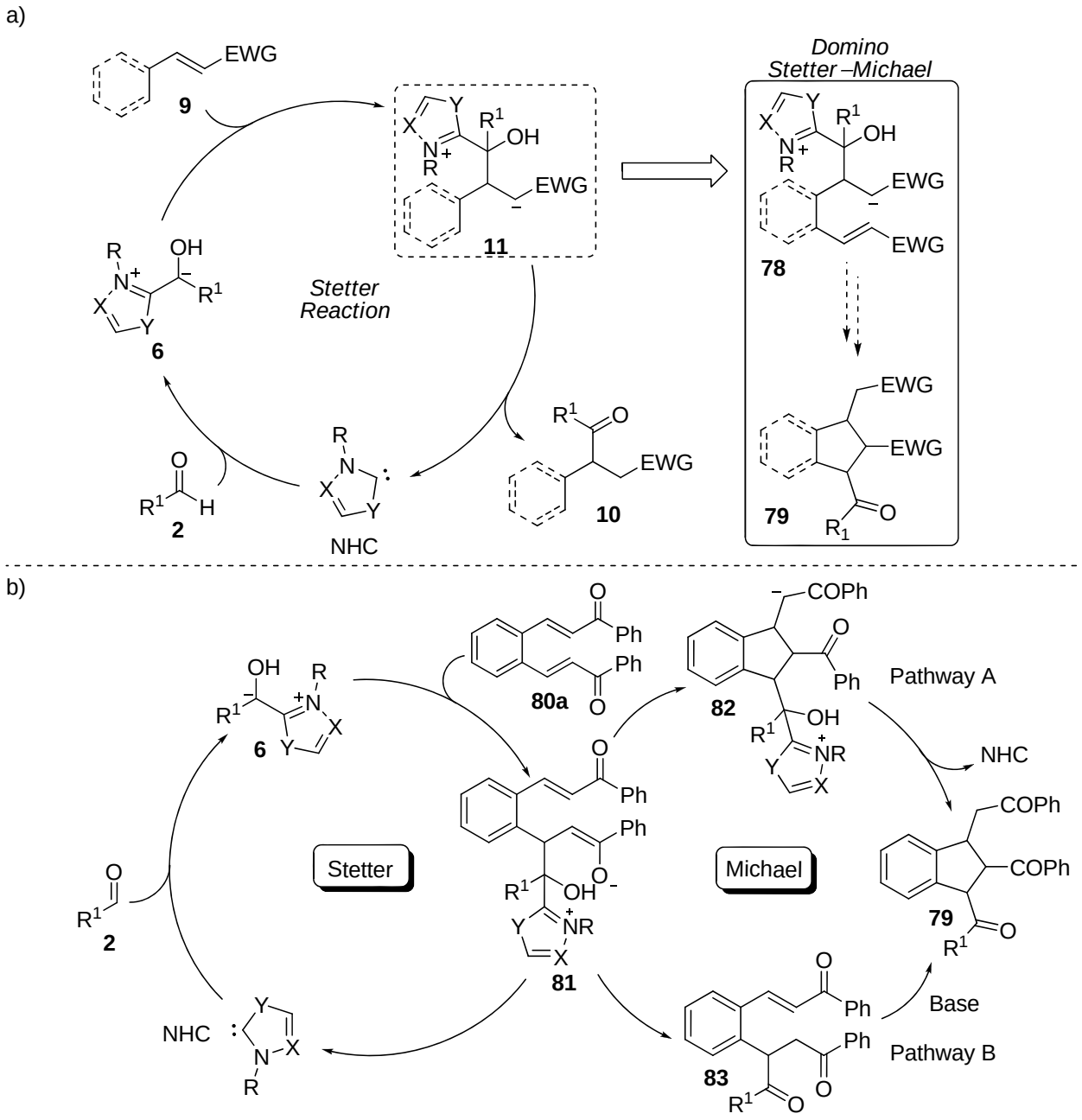
In recent years, the design of reactions utilizing domino processes has allowed chemists to synthesize molecules of considerable structural and stereochemical complexity.[4, 46, 101, 102] However, the use of acyl anion based transformations in domino reactions had been largely ignored up to 2008. Presumably, the narrow substrate scope and limited number of stereoselective methods for the Stetter reaction were seen as challenges in domino reactions.

3.1 RESEARCH OBJECTIVE

As part of the research program in organocatalysis, the Gravel group became interested in exploring the potential of implementing the Stetter reaction as the first step in a domino process to access polycyclic compounds. Mechanistically, it has been proposed that the Stetter reaction proceeds through the addition of an acyl anion equivalent (**6**) to an electron-poor olefin generating an enolate intermediate (**11**). Subsequent proton transfer and elimination of the NHC catalyst completes the catalytic cycle (**Scheme 3.1a**).[19] Interestingly, the use of the enolate intermediate (**11**) generated in this process has not been exploited in domino reactions. It was hypothesized that this enolate intermediate could perform a nucleophilic attack onto an appropriate electrophile, such as a second electron-poor olefin. If the two olefin acceptors were linked by a tether, the resulting domino Stetter–Michael reaction would proceed with concomitant cyclization (**Scheme 3.1a**).

[viii] The work described in this chapter was published in part in the ACS journal *The Journal of Organic Chemistry* in September 2009 (Sánchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 7536-7539).

Scheme 3.1 a) Proposed Use of the Enolate Intermediate on the Domino Stetter–Michael Reaction for the Synthesis of Indanes. b) Proposed Mechanism For the Synthesis of Indanes Exploring Two Possible Pathways.

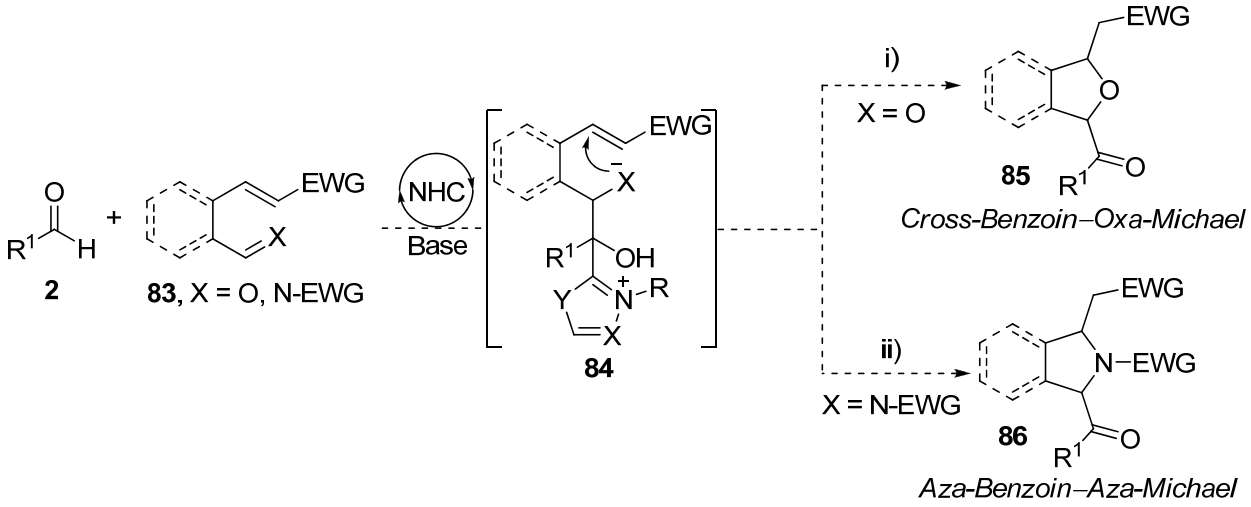


As depicted in **Scheme 3.1b**, it was envisioned that an aldehyde would react with an NHC to form a 'Breslow Intermediate' **6**,[15] which would then attack the Michael acceptor **80a** to

yield an enolate intermediate **81**. Subsequently, this intermediate can follow two possible cyclization pathways. For pathway A, enolate **81** would directly cyclize to generate the indane anion **82** followed by the release of the catalyst to furnish indane **79**. In pathway B, proton transfer and ejection of the catalyst would form a simple Stetter product **83**. Under basic reaction conditions, **83** could then regenerate the required enolate to afford the indane **79**. Overall, two carbon-carbon bonds and three contiguous stereogenic centers would be produced in one operation during the formation of the indane.

Additionally, this protocol could be applied to other domino reactions employing acyl anion equivalents (**6**) in the initial step (**Scheme 3.2**). Early experiments on the intermolecular Stetter reaction have demonstrated that the Breslow intermediate **6** reacts more rapidly with a second equivalent of aldehyde to form benzoin, rather than reacting with the electron-poor olefin, although the process is reversible.[15, 37, 39] Based on that premise, if the acyl anion equivalent **6** undergoes the initial cross-benzoin reaction with the formyl (or imino) group on **83**, the hetero-anion on **84** would cyclize to produce the cross-benzoin–oxa-Michael product **85** or the aza-benzoin–aza-Michael product **86** (**Scheme 3.2**).

Scheme 3.2 Proposed Domino Reactions Using Acyl Anion Equivalents.

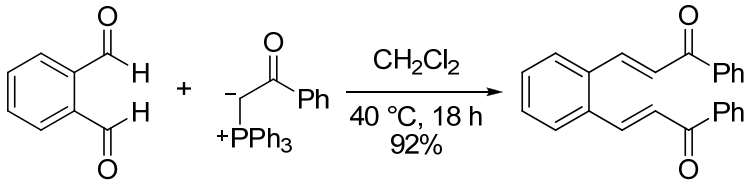


3.2 RESULTS AND DISCUSSION

3.2.1 Preliminary Investigations

The model acceptor **80a** was prepared employing a modified procedure from the literature by reacting phthaldialdehyde (**23a**) and two equivalents of (2-oxo-2-phenylethyl)triphenylphosphorane (**87a**) through a double Wittig reaction (**Scheme 3.3**).[103]

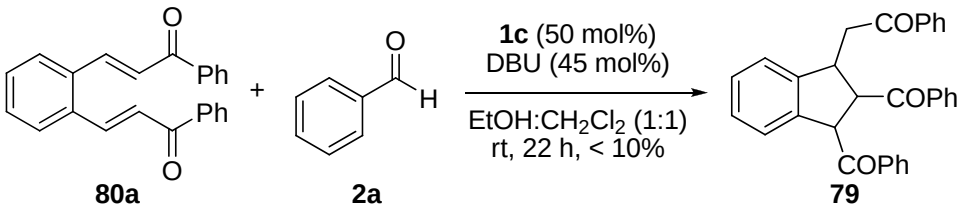
Scheme 3.3 Synthesis of Bischalcone (**80a**) Through a Double Wittig Olefination.



23a **87a** **80a**

In the early 2008, Michel Gravel initiated this project by reacting the model acceptor **80a** with benzaldehyde (**2a**) in the presence of thiazolium salt **1c** and a base to obtain the expected trisubstituted indane product **79** as a mixture of isomers in only trace amounts (**Scheme 3.4**). Results obtained with precatalyst **1c** were promising as the formation of **79** could be improved through further optimization.

Scheme 3.4 First Domino Stetter–Michael Reaction for the Synthesis of Trisubstituted Indanes.

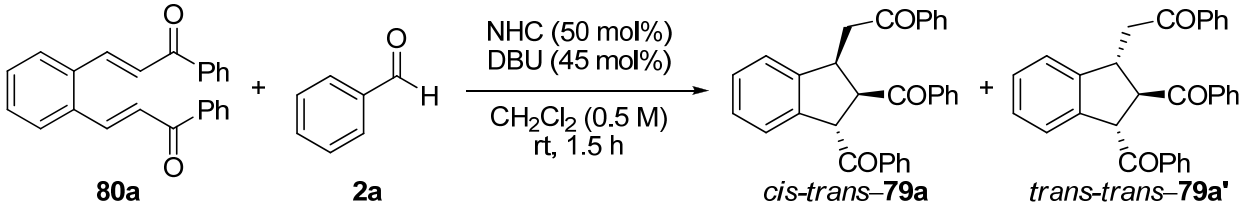


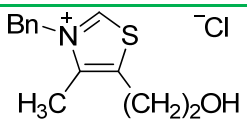
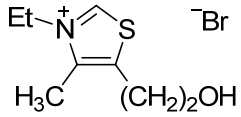
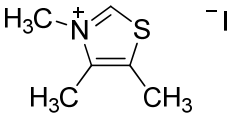
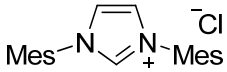
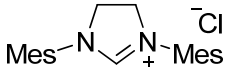
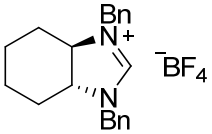
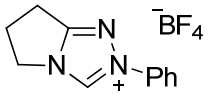
80a **2a** **79**

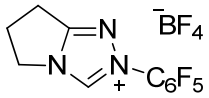
3.2.2 Optimization of the Reaction

As a result of the initial attempt to prepare indane **79**, the initial investigations began by studying the main families of NHCs employing the model acceptor **80a** and benzaldehyde for the Stetter–Michael reaction (**Table 3.1**).

Table 3.1 Effect of Azolium Salts on the Synthesis of Indanes **79**.[a]



entry	NHC precursor	yield (%)[b]	**79a**:**79a'**[c]
1	**1c** 	15	8.9:1
2	**1e** 	32	8.9:1
3	**1j** 	27	6.7:1
4	**14a** 	0	-
5	**15a** 	6	4:1
6	**15b** 	0	-
7	**16s** 	0	-

8	**16n** 		0	-

[a] All reactions were performed by addition of the base (45 mol%) to a solution of **80a** (1 equiv), **2a** (2 equiv), and NHC precursor (50 mol%) in dry dichloromethane (0.5 M) at 23 °C. [b] Yield of pure isolated products. [c] Diastereomeric ratio determined from the crude sample by ^{1}H NMR, the relative configuration of **79** was determined by NOE experiments.

Interestingly, the family of thiazolium-derived precatalysts **1c**, **1e**, and **1j** produced the desired indane in moderate yields and good diastereoselectivity (entries 1–3), for which precatalyst **1e** afforded the best result.

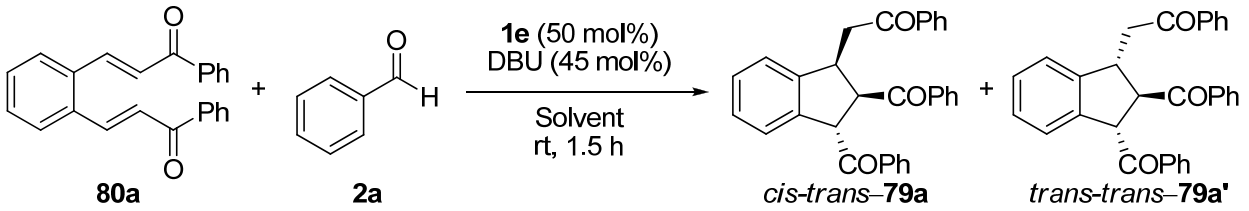
In the case of imidazolium salt **14a** and chiral imidazolinium salt **15b**, the desired domino Stetter–Michael product was not observed (entries 4 and 6).

When imidazolinium salt **15a** was employed, only small quantities of the expected domino product **79** was formed (entry 5). Disappointingly, the use triazolium salts **16s** and **16n** did not produce the trisubstituted indane.

With thiazolium salt **1e** as the optimum precatalyst, the next step was to study the effect of solvent on the domino Stetter–Michael reaction (**Table 3.2**).

When the reaction was performed with dichloromethane, **79** was obtained in moderate yield and good diastereoselectivity (entry 1). Conversely, the use of other solvents such as THF, DMF, or toluene showed to be detrimental for the yield and stereoselectivity (entries 2–4). Interestingly, the use of ethanol as solvent resulted in complete conversion into a mixture indenes **88** and **89** and only 5% of the desired indanes **79** (**Scheme 3.5a**).

Table 3.2 Effect of Solvents and Concentration on the Synthesis of Indanes **79**.

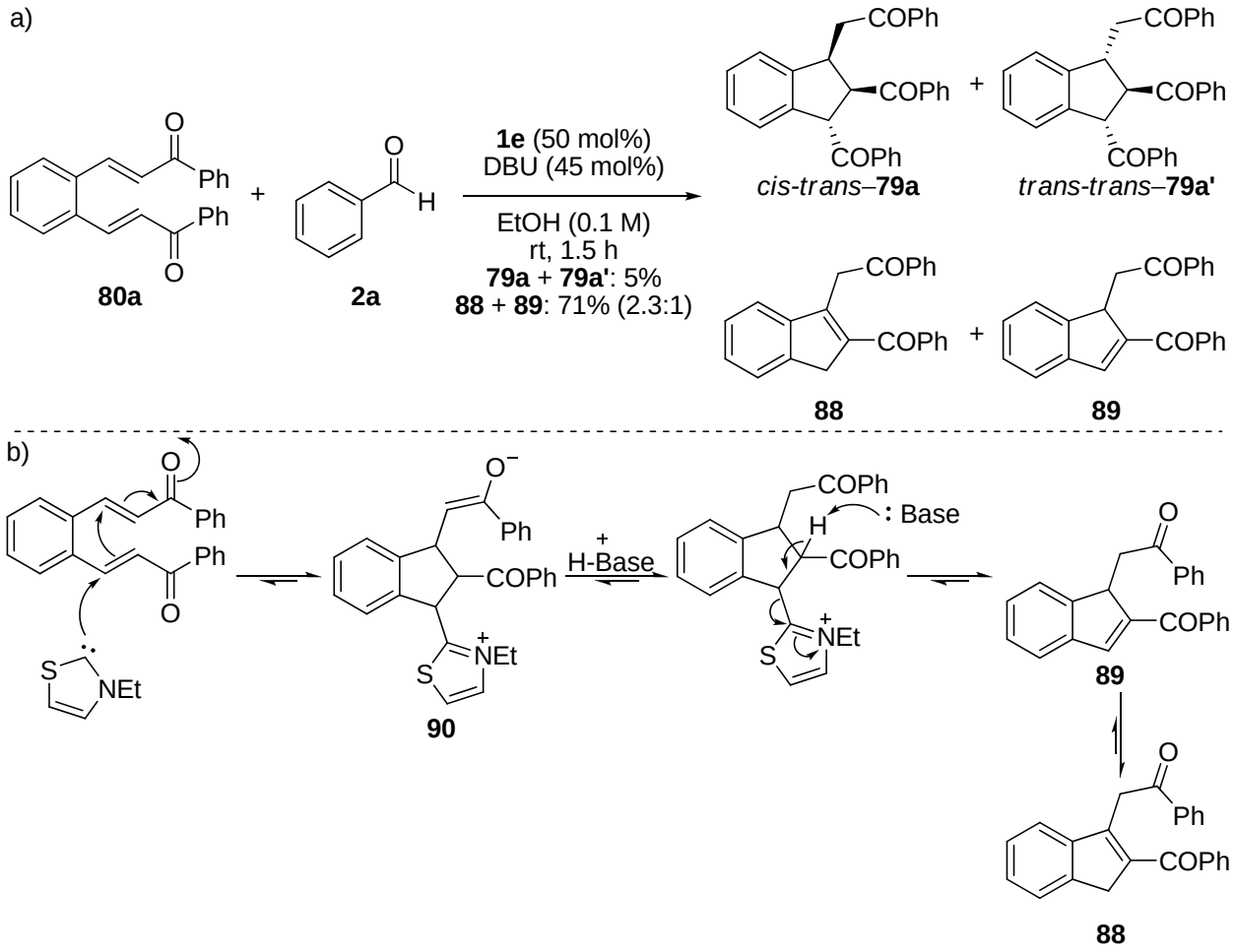


entry	solvent	[**80a**] (M)[a]	yield (%)	**79a**:**79a'**[b]
1	CH_2Cl_2	0.5	25	7.3 : 1
2	THF	0.5	25	4.1 : 1
3	DMF	0.5	22	5.3 : 1
4	Toluene	0.5	20	1.7 : 1
5[c]	Ethanol	0.1	5	6:1
6	CH_2Cl_2	1	39	5 : 1
7	CH_2Cl_2	2	38	4 : 1

[a] Concentration of the reaction is relative to **80a**. [b] The ratio of **79a**/**79a'** was determined by ^{1}H NMR on the crude reaction mixture. [c] The reaction was diluted to 0.1 M due to the poor solubility of **80a**.

The formation of these products occurred through a reaction known as Rauhut-Currier (RC) or vinylogous Morita–Baylis–Hillman reaction.[104, 105] Presumably, NHC **1e** attacks enone **80a**, producing intermediate **90**, which furnishes **89** following a protonation and elimination sequence (**Scheme 3.5b**). As a result of the basic reaction conditions, indene **89** was isomerized to **88**, hence producing the more thermodynamically stable tetrasubstituted olefin.

Scheme 3.5 a) Products Observed in the Reaction of Bischalcone **80a** and Benzaldehyde. b) Proposed Mechanism for the Formation of Rauhut–Currier Products **88** and **89**.



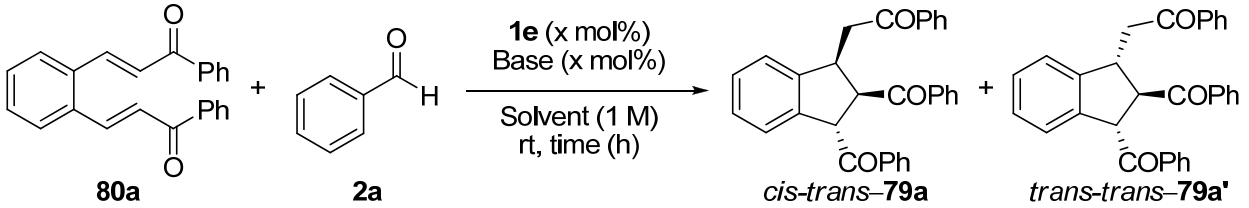
The RC reaction has been previously investigated by other research groups employing phosphines or thiolates as catalysts.[106, 107] When the reaction was discovered within the group, there were no previous reports of RC reactions catalyzed by *N*-heterocyclic carbenes as of 2008. Consequently, this result would represent the first example of a NHC-catalyzed Rauhut-Currier reaction. With this in mind, it was decided to continue our endeavours towards the optimization of the domino Stetter–Michael reaction and set aside this result for future investigations. However, Scheidt and coworkers disclosed the first RC reaction catalyzed by NHCs between

vinyl sulfones and α,β-unsaturated aldehydes in 2011,[108] and no further studies have been performed on our bischalcone manifold.

After studying different solvents, it was determined that dichloromethane was the optimum solvent. Then, the effect of the concentration of the reaction was investigated. Gratifyingly, the yield of the reaction increased as the reaction was performed at higher concentration (**Table 3.2**, entry 6). However, the diastereoselectivity of **79** decreased to 5:1. This result can be attributed to the rapid isomerization of **79a** to **79a'** promoted by DBU at higher concentrations. Further increase in the concentration of the reaction (2 M) proved to be detrimental for the diastereoselectivity of the corresponding indane without an increase in the yield (entry 7).

From the previous study depicted in **Table 3.2**, it was observed that the yield of **79** increases as the concentration increases. Therefore, it was decided to study different bases, employing the optimum solvent and precatalyst with a final concentration of 1 M relative to **80a** (**Table 3.3**). The use of other bases such as triethylamine, Hünig's base, and potassium carbonate produced the Stetter–Michael product **79** in poor conversion (entries 2–4). Interestingly, the use of cesium carbonate as base gave **79** in comparable yield to that when DBU was employed as the base; however, the diastereomeric ratio was similar in both cases (entries 1 vs. 5). Subsequently, increasing the reaction time was considered employing the best two bases, DBU and cesium carbonate. The reaction that contained DBU as base showed a significant improvement, producing the trisubstituted indane in 81% yield and similar diastereoselectivity (entry 6). In contrast to the reaction with DBU, cesium carbonate gave the desired indane in only 52% yield with a slight decrease on the stereoselectivity (entry 7). Such remarkable increment in the production of **79** may be attributed to the reversibility of benzoin under the reaction conditions.

Table 3.3 Optimization of the Reaction Conditions by Screening Bases, Studying the Effect of Time, and Precatalyst Loading Towards the Formation of Indanes.



entry	**1e** (mol%)[a]	base (x mol%)	time (h)	yield (%)[b]	**79a**:**79a'**[c]
1	50	DBU (50)	1.5	40	5:1
2	50	Et_3N (50)	1.5	(3)	9:1
3	50	$^{i}Pr_2NEt$ (50)	1.5	(2)	5:1
4	50	K_2CO_3 (50)	1.5	(5)	3:1
5	50	Cs_2CO_3 (50)	1.5	42	4:1
6	50	DBU (50)	24	81	4:1
7	50	Cs_2CO_3 (50)	24	52	3:1
8	30	DBU (28)	24	38	4:1
9	30	DBU (28)	48	64	4:1
10	20	DBU (18)	48	20	4:1

[a] Mol% of precatalyst **1e** is relative to the limiting reagent **80a**. [b] Numbers in brackets represent % conversion. [c] Diastereomeric ratios were measured by ^1H NMR on the crude reaction mixture.

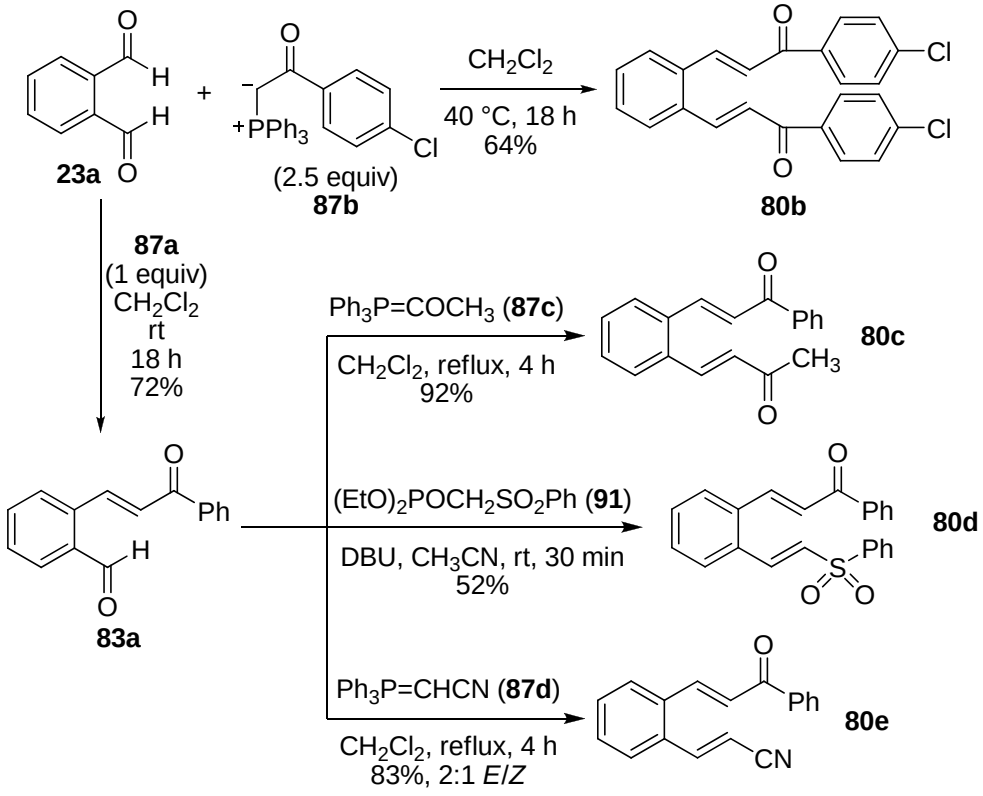
Given that the 1,4-additon on the Michael acceptor is slower than the formation of the benzoin product, the later is a reversible process that eventually will provide an equivalent of aldehyde available to react with **80a**.[18, 37, 39, 109]

With DBU as the optimum base, the precatalyst loading was decreased to 30 mol%. Unfortunately, this change was detrimental for the reaction (entry 8). Therefore, it was decided

to extend the reaction time to 48 hours producing 64% yield of the desired product (entry 9). Further reduction of **1e** to 20 mol% gave the domino Stetter–Michael in only 20% yield (entry 10).

Having established 30 mol% of **1e**, 27 mol% of DBU, and a 1 M concentration in dichloromethane as the optimum reaction conditions, other Michael acceptors were prepared to study the scope of the reaction (**Scheme 3.6**).

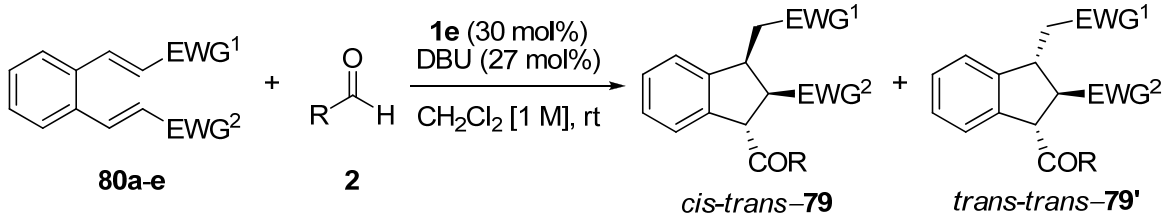
Scheme 3.6 Preparation of Symmetrical and Unsymmetrical Michael Acceptors **80b-e**.



3.2.3 Scope of the Reaction

Under the optimized conditions, a variety of functionalized aldehydes and Michael acceptors were examined to investigate the scope of the reaction (**Table 3.4**).

Table 3.4 Study of the Scope of Reaction with Symmetrical and Unsymmetrical Michael Acceptors **80** and Various Aldehydes.



entry	EWG^1	EWG^2	R	time (h)	yield (%)[a]	product	**79**:**79'**[b]
1	COPh	COPh	**2a**, Ph	48	64	**79a**	4:1
2	COPh	COPh	**2r**, (4-F)Ph	10	63	**79b**	4:1
3	COPh	COPh	**2s**, (4-Cl)Ph	30	69	**79c**	3:1
4	COPh	COPh	**2t**, (3-Cl)Ph	24	18	**79d**	4.6:1
5	COPh	COPh	**2u**, (2-Cl)Ph	24	<5	**79e**	-
6	COPh	COPh	**2v**, (4-Br)Ph	10	77	**79f**	3.3:1
7	COPh	COPh	**2w**, (4-Ac)Ph	18	82	**79g**	4:1
8[c]	COPh	COPh	**2g**, (4-CF_3)Ph	4	81	**79h**	4:1
9[c]	COPh	COPh	**2f**, (4-CO_2Me)Ph	0.5	74	**79i**	6.7:1
10	COPh	COPh	**2x**, (4-Me)Ph	48	34	**79j**	6.1:1
11	COPh	COPh	**2y**, (4-MeO)Ph	48	17	**79k**	4.9:1
12	COPh	COPh	**2z**, 2-naphthyl	11	28	**79l**	5:1
13	COPh	COPh	**2b**, 2-furyl	5	74	**79m**	4:1
14[d]	COPh	COPh	**2aa**, Ethyl	72	15(42)[e]	**79n**	1.1:1
15[d]	COPh	COPh	**2h**, Ph(CH_2)$_2$	24	33(44)[e]	**79o**	1.1:1

16[f]	COPh(4-Cl)	COPh(4-Cl)	**2v**, (4-Br)Ph	6	72	**79p**	4:1
17[f]	COPh(4-Cl)	COPh(4-Cl)	**2b**	2	72	**79q**	3.2:1
18[c]	COMe	COPh	**2f**	6	52	**79r**	2.8:1
19[g]	SO_2Ph	COPh	**2f**	5	65	**79s**	1:1.1
20[g]	CN	COPh	**2f**	24	37	**79t**	1:3

[a] Combined yield of pure isolated product diastereomers. [b] Diastereomeric ratios were determined by ^{1}H NMR on the crude reaction mixture. [c] Reaction performed at 0 °C. [d] Thiazolium salt **1c** was used as the precatalyst. [e] The number in parentheses represents the total yield of indanes (**79** + **79'**) following treatment of the uncyclized side product **83** with DBU (27 mol%). The dr for the combined products is 1:3. [f] Reaction performed at 0.2 M. [g] 1 equivalent of DBU was employed.

The use of electron-poor aldehydes **2r-w**, **2g**, and **2f**, gave the desired indane **79** in moderate to good yields and good diastereoselectivities (entries 2–9). On the other hand, it was decided to study the reactivity of chlorobenzaldehyde when the chloro group is attached to C-3 and C-2 (entries 4–5). Both aldehydes, **2t** and **2u**, proved to be much less reactive than 4-chlorobenzaldehyde (**2s**) (entry 3). Presumably, the reduced reactivity for 2-chlorobenzaldehyde (**2u**) could be attributed to steric factors.[110-113] The absence of the benzoin product typically observed during the course of these reactions supports this rationale.[37, 39]

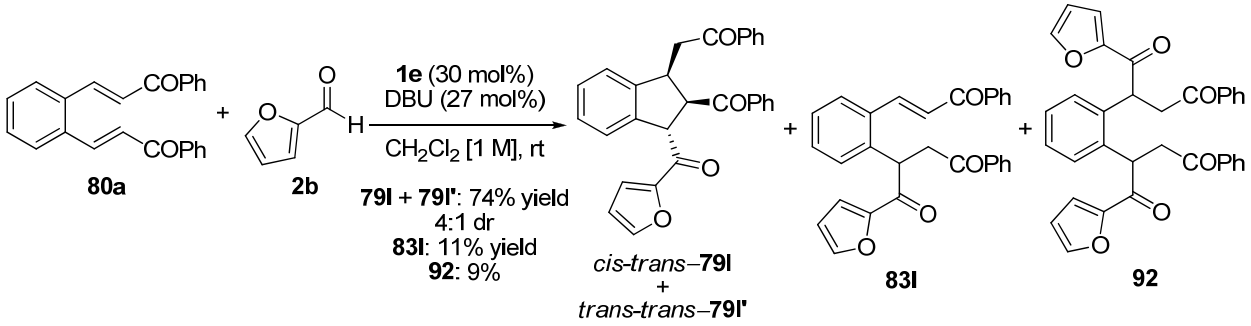
The reaction time was drastically reduced when aldehydes bearing strong electron-withdrawing groups were employed (entries 8–9). The increased reactivity of **2g** and **2f** allowed the reactions to be performed at a lower temperature. As a result, when 4-trifluoromethylbenzaldehyde (**2g**) and methyl 4-formylbenzoate (**2f**) were subjected to the reaction conditions at 0 °C, evident improvements in the diastereomeric ratio were observed (from 1.3:1 to 4:1 for **2g** and from 2:1 to 6.7:1 for **2f**).

The use of electron-rich aldehydes **2x** and **2y** displayed a tremendous decrease in reactivity furnishing indanes **79j** and **79k** in moderate and low yields, respectively and good

diastereoselectivity (entries 10–11). The use of the bulky naphthyl-2-carboxaldehyde (**2z**) furnished the desired indane in only 28% yield and good diastereoselectivity (entry 12).

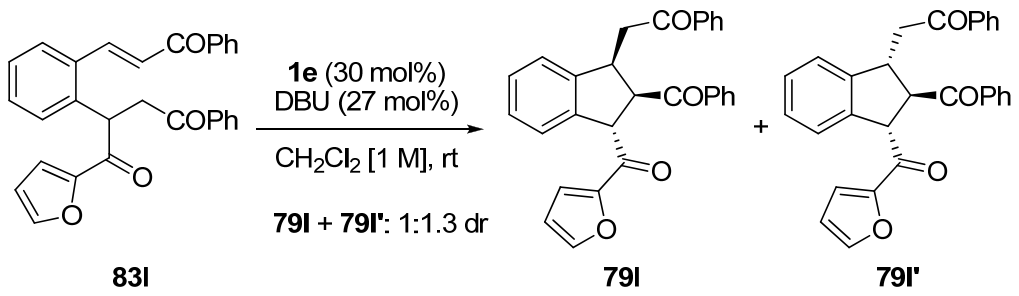
Conversely, furfural (**2b**) was very reactive, furnishing the corresponding indane in 74% yield (entry 13). Interestingly, the postulated intermediate **83l** could also be isolated from the reaction mixture, as well as the double Stetter product **92**. This side product appears to be the result of a second 'Breslow intermediate' **6** attacking the simple Stetter intermediate **83l** (**Scheme 3.7**).

Scheme 3.7 Double Stetter Addition onto Acceptor **80a**.



When intermediate **83l** was subjected to the reaction conditions, the trisubstituted indane was successfully formed. However, diastereomer **79l'** was predominant in this case. Presumably, enolization of **79l** favoured the formation of the most thermodynamically stable product **79l'** (vide infra) (**Scheme 3.8**).

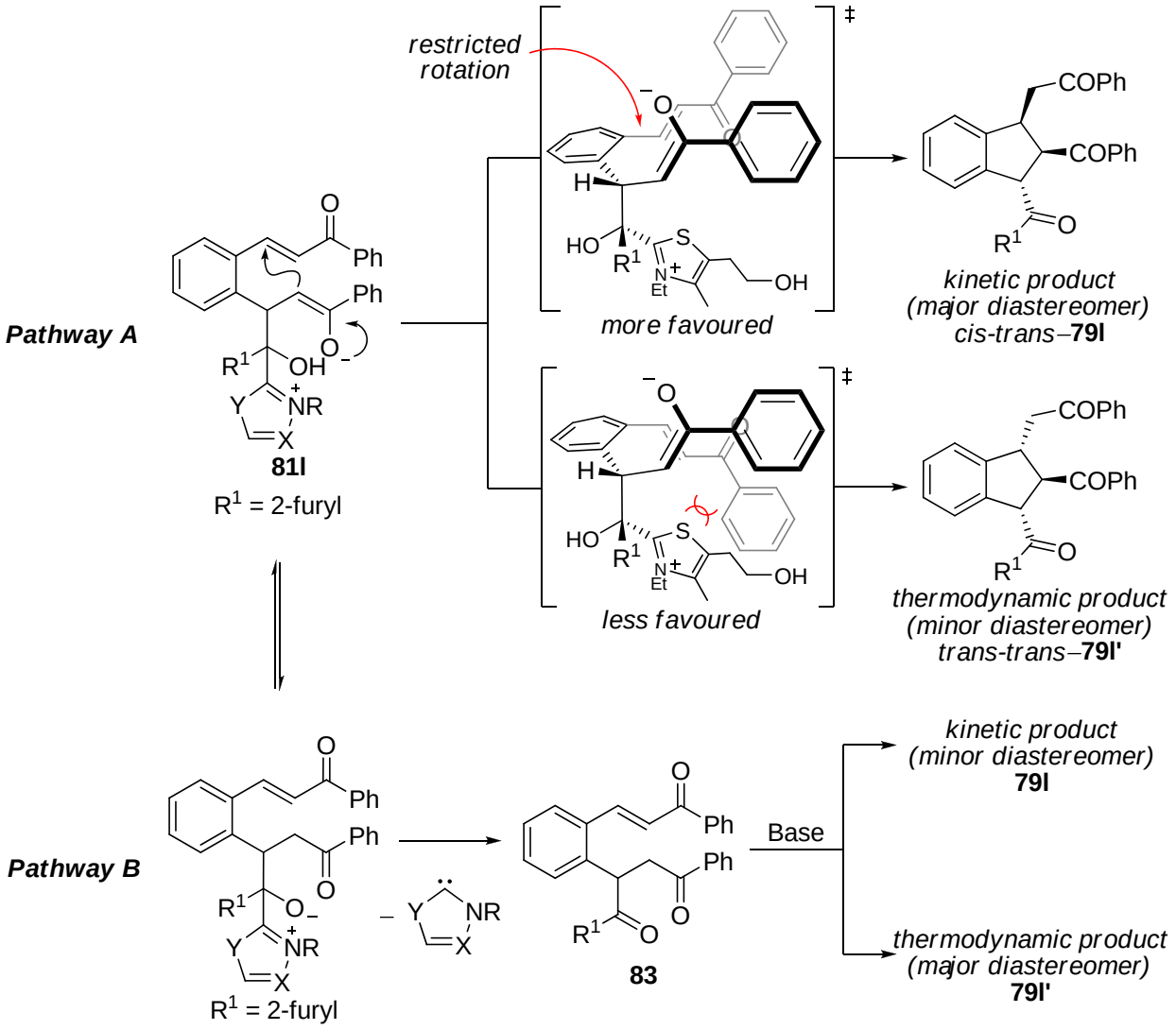
Scheme 3.8 Cyclization of Intermediate **83l** Under Reaction Conditions.



As a result of the observations made on the reaction involving acceptor **80a**, aldehyde **2b**, and precatalyst **1e**, it can be suggested that elimination of the NHC from **81l** to produce **83l** is competing with the direct cyclization pathway to form **79** (**Scheme 3.1**).

In order to explain the stereoselectivity of the reaction, it is necessary to analyze the two possible pathways that intermediate **81l** could follow to produce the indane product **79** (**Scheme 3.9**).

Scheme 3.9 Proposed Competing Pathway to Produce **79l** and **79l'**.



Through pathway A, the presence of the NHC in the molecule would allow the stereoselective formation of indane *cis*-*trans*–**79l**. Consequently, the presence of the NHC could restrict the free rotation of the enone around the sigma bond thus favouring the attack of the enolate towards the *Si* face (internal face) of the Michael acceptor. As a result, pathway A could lead to the preferred formation of the kinetic product **79l**. Therefore, once intermediate **83l** is produced, presumably the thermodynamic product *trans*-*trans*–**79l'** would be preferred (vide supra) (**Scheme 3.9**). Nevertheless, further experimental evidence is necessary to conclude which pathway is preferred towards the formation of the kinetic product **79l**.

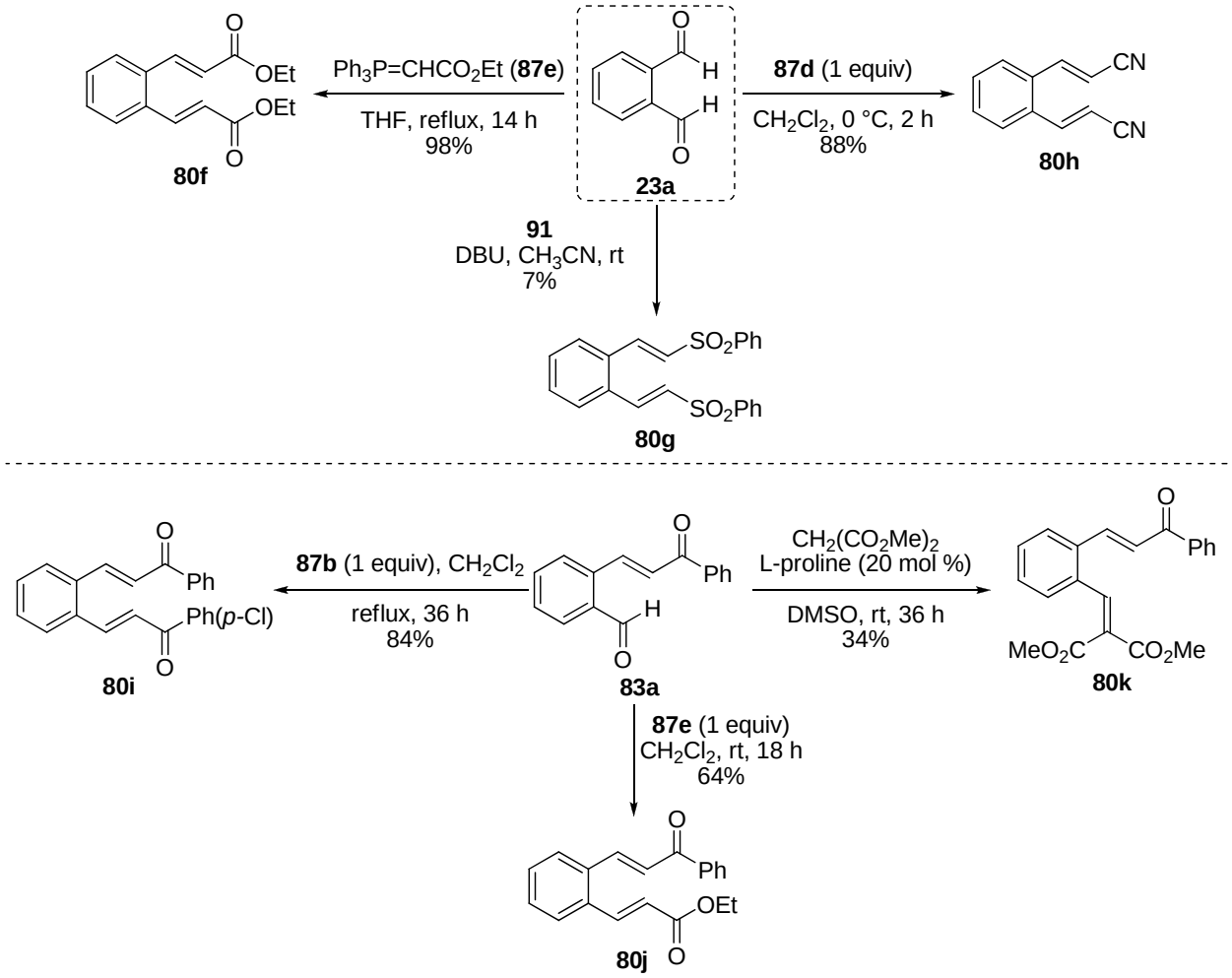
The use of poorly reactive aliphatic aldehydes at room temperature resulted in the formation of significant amounts of Stetter products **83n** and **83o**. In order to cyclize these intermediates, catalytic DBU was employed furnishing the desired indanes in moderate yields and poor diastereoselectivity (entries 14–15). As noted previously by Stetter and co-workers, the use of the *N*-benzyl-substituted thiazolium salt proved superior to its *N*-ethyl-substituted counterpart when using aliphatic aldehydes.[18]

Michael acceptors with different electron-withdrawing groups were studied as well (entries 16–20). The replacement of the benzoyl groups for 4-chlorobenzoyl groups resulted in a slight increase in the reactivity (entries 16–17). Interestingly, the presence of intermediate **83q** was also found when **2b** was employed.

None symmetrical acceptors containing different electron-poor olefins were employed in order to investigate the chemoselectivity of the intermolecular conjugate addition step (Stetter) (entries 18–20). In all cases, benzoyl-substituted olefins proved to be more reactive than acetyl-, benzenesulfonyl-, or cyano-substituted olefins, generating the indanes as single regioisomers. When **80d** ($EWG^1 = SO_2Ph$, $EWG^2 = COPh$) and **80e** ($EWG^1 = CN$, $EWG^1 = COPh$) were used,

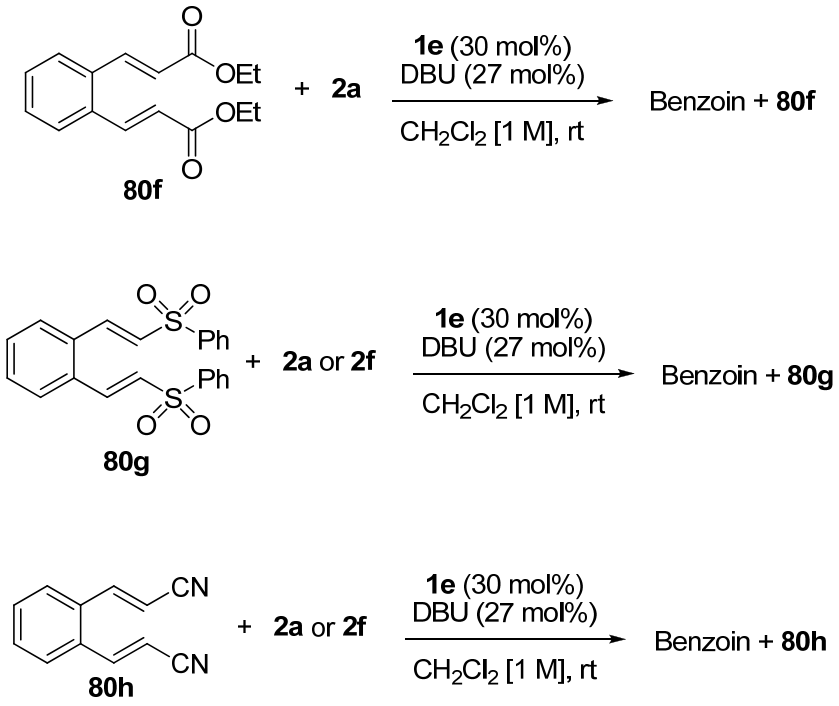
one equivalent of base was required in order to cyclize their corresponding Stetter intermediates **83s** and **83t** (entries 19–20).The picture emerging from these results is that that the steric and electronic characteristics of the aldehyde play a determinant role in the rate of the domino Stetter-Michael reaction. Additionally, the difference in the rate of the Stetter–Michael reaction between electron-deficient and electron-rich aldehydes is remarkable, where electron-poor aldehydes react very rapidly in contrast to electron-rich or hindered aldehydes that react very slow. After studying ketones as EWGs, other Michael acceptors (**80**) were studied (**Scheme 3.10**). In most cases, the preparation of these Michael acceptors was analogous to that of **80a**.

Scheme 3.10 Preparation of Michael Acceptors **80f-k**.



Under the previously optimized reaction conditions, symmetrical Michael acceptors **80f**, **80g**, and **80h** were studied (**Scheme 3.11**). Unfortunately, Michael acceptors **80f-h** proved to be unreactive, even when more reactive aldehyde **2f** was employed. In all cases, only the corresponding benzoin product was obtained. Other attempts at performing the Stetter–Michael reaction by heating were inefficient and also resulted in the recovery of unreacted acceptors **80f-h**.

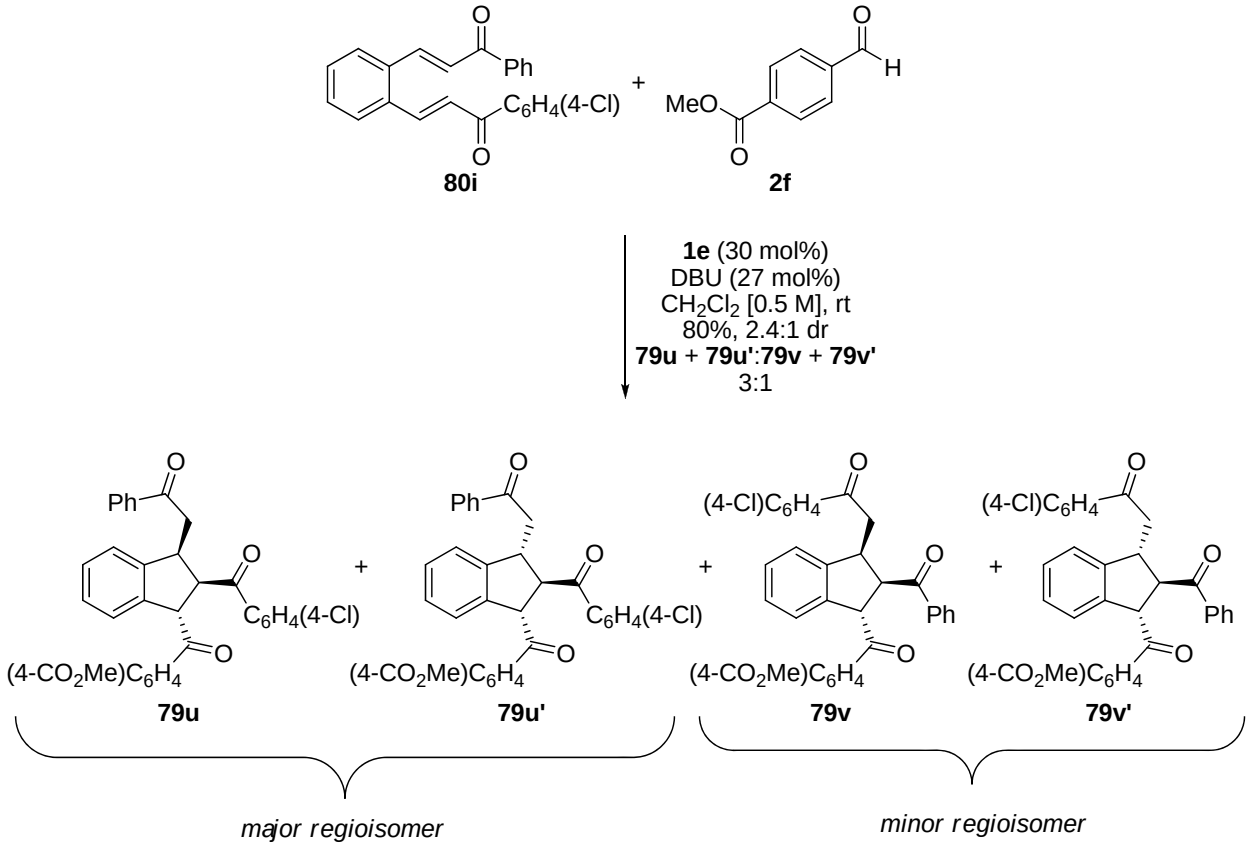
Scheme 3.11 Attempts Towards the Domino Stetter–Michael on Symmetrical Acceptors **80f**–**h**.



Similarly, acceptors **80i-k** were studied with different aldehydes. When the double Michael acceptor **80i** was reacted with aldehyde **2f**, the transformation went to completion in less than 1 hour. Unfortunately, the product **79** was generated as a mixture of regioisomers (**79u**+**79u'** and **79v**+**79v'**, 3:1) and diastereomers (2.4:1 dr) (**Scheme 3.12**). Presumably, the

Stetter reaction occurs more favourably on the side of the 4-chlorobenzoyl group than the benzoyl side on **80i**. Apparently, the difference in electron-withdrawing ability between the 4-chlorobenzoyl and the benzoyl groups is comparable, thus explaining the poor regioselectivity on **80i**.

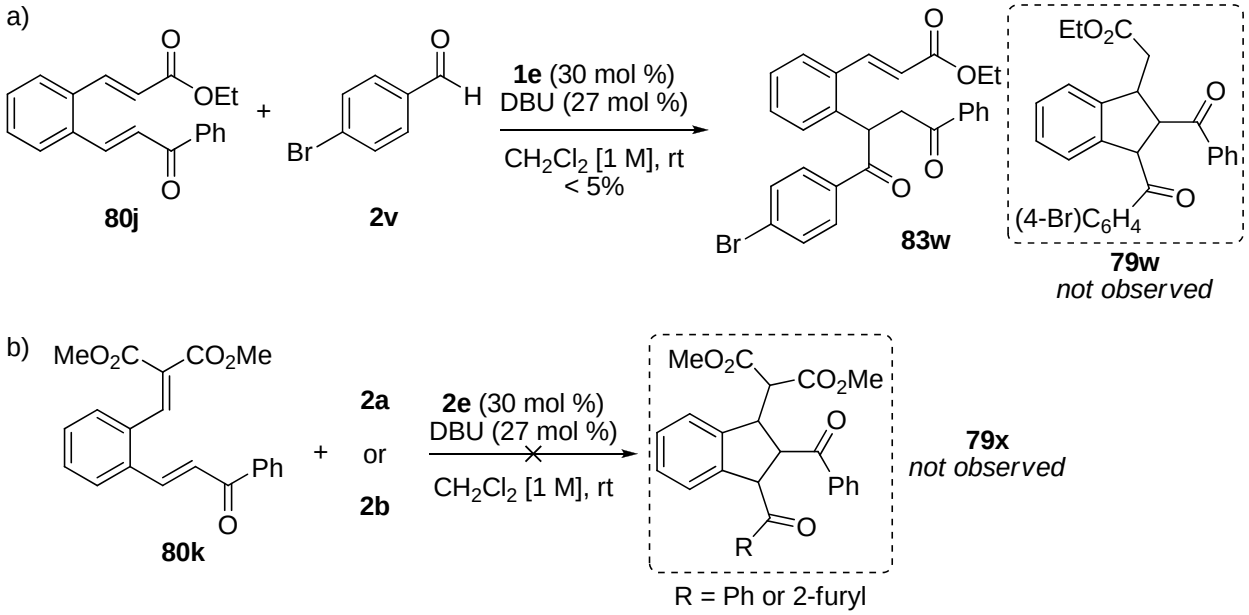
Scheme 3.12 Poorly Regioselective Stetter–Michael Reaction on Acceptor **80i**.



When acceptor **80j** was subjected to the optimized reaction conditions with 4-bromobenzaldehyde (**2v**), the formation of small amounts of the Stetter product **83w** was observed. Despite efforts to increase the yield of intermediate **83w** and favour the formation of the cyclized product, only starting materials and large amounts of the corresponding benzoin

product were recovered from the reaction mixture (**Scheme 3.13a**). It is worth mentioning that the use of ethyl ester as EWG has proven to be poorly reactive in our studies. Similarly, acceptor **80k** proved to be unreactive when benzaldehyde (**2a**) or furfural (**2b**) were employed, producing only the corresponding benzoin products (**Scheme 3.13b**).

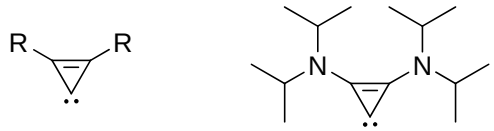
Scheme 3.13 Attempts to Synthesize Indanes **79w** and **79x**.



3.2.4 Studies with Other Type of Nucleophilic Carbenes

Although thiazolium salt **1e** was useful for producing trisubstituted indanes, these products are racemic. Therefore, we decided to study different families of chiral catalysts that could produce enantioenriched products.

The family of cyclopropenylidene carbenes **93** was investigated for the domino Stetter–Michael reaction. The cyclopropenylidene is an archetypical ring carbene that was first detected in the interstellar space and has been extensively studied by the Bertrand group (**Figure 3.1**).[114-117]

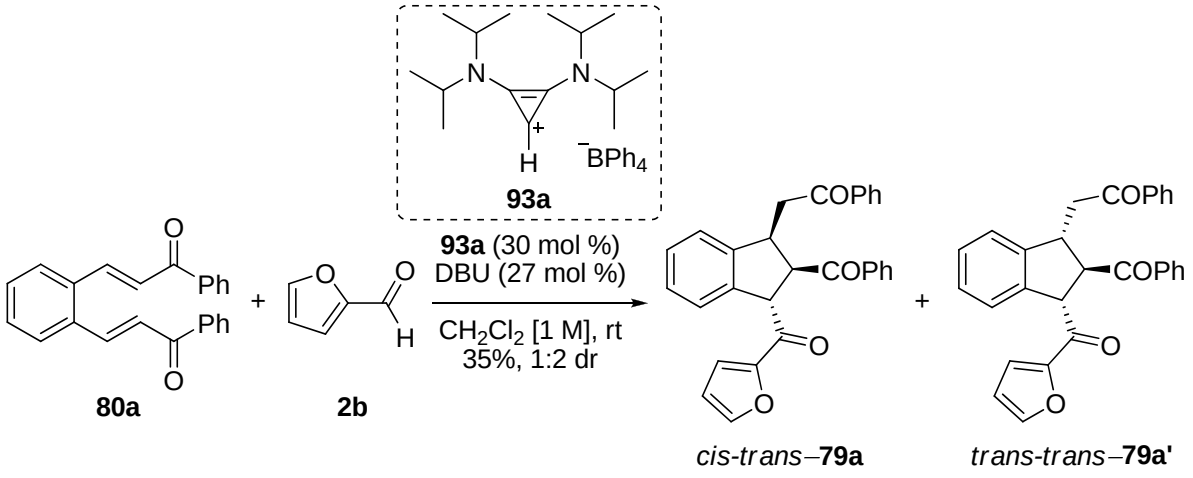


93 **93a**

Figure 3.1 Cyclopropenylidene (CP) carbenes studied by the Bertrand group.

In a recent study of various functional groups attached to the cyclopropenylidene (CP) backbone, the Bertrand group demonstrated that the presence of two amino groups in the backbone (cf. **93a**) provides stability and enhances its reactivity toward electrophilic species.[118, 119] Interestingly, with the exception of a brief mention by Tamm and coworkers,[120] no catalytic reactions have been reported when using free cyclopropenylidene **93** as an organocatalyst.[121] Therefore, it was decided to investigate the activity of **93a** on the domino Stetter–Michael reaction (**Scheme 3.14**).

Scheme 3.14 Domino Stetter–Michael Reaction Employing Bis(Diisopropylamino) Cyclopropenylidene Precatalyst **93a**.

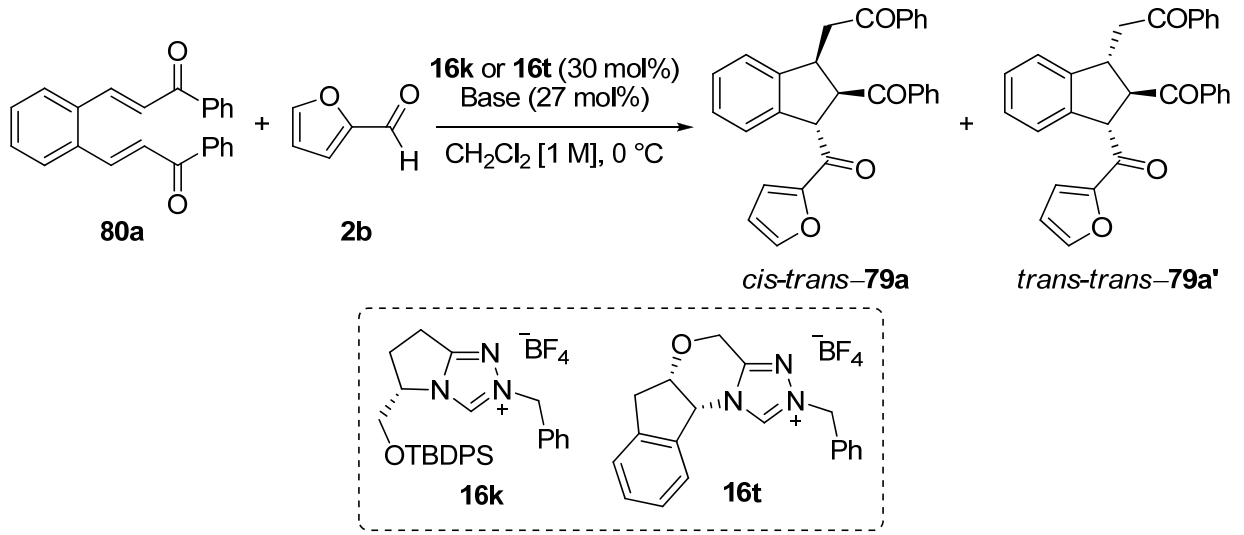


Precatalyst **93a** proved to be highly reactive, consuming **80a** in less than 45 minutes in contrast to precatalyst **1e** which took 5 h to reach completion. Despite the rapid consumption of **80a**, the reaction produced a complex mixture and only 35% yield of the desired product **79a**/**79a'** was obtained as a 1:2 mixture of diastereomers. Despite the low yield and diastereoselectivity achieved in this reaction, this result is encouraging and will serve as a starting point for the development of novel cyclopropenylidene catalysts and their application in various organocatalyzed transformations.

In 2008, Enders and co-workers disclosed the use of triazolium salt **16k** for the first enantioselective intermolecular Stetter reaction (**Scheme 1.6**).[37] In the same study, they investigated different chiral triazolium salts which proved to be reactive in the benzoin reaction but failed to catalyze the Stetter reaction. Additionally, they demonstrated that the *N*-benzyl substituent on **16k** has a dramatic impact in the reactivity of the carbene, in contrast to precatalysts bearing an *N*-aryl substituent on the triazolium salt. In view of their increased reactivity, precatalyst **16k** and **16t** were studied in the hope of developing an enantioselective version of the domino Stetter–Michael reaction (**Table 3.5**).

Although triazolium salt **16k** and DBU furnished the desired indane in excellent yield (88%), the enantioselectivity for both diastereomers was poor (entry 1). Interestingly, the thermodynamic diastereomer **79a'** was favoured despite performing the reaction at low temperature. Presumably, the mixture of **79a'**/**79a** reached thermodynamic equilibrium with the employed reaction conditions. Aiming to prevent any possible racemization and isomerization of the product, cesium carbonate was employed as base. Yet the reaction furnished **79a**/**79a'** in moderate yield as an equimolar mixture of diastereomers, and the enantioselectivity for **79a'** was only slightly improved from 14 to 25% ee (entry 2).

Table 3.5 Enantioselective Domino Stetter–Michael Reaction Employing Triazolium Catalysts **16k** and **16t**.



entry	precatalyst	base	time (h)	yield (%)[a]	dr (**79a**: **79a'**)[b]	% ee (**79a**: **79a'**)[c]
1	**16k**	DBU	7	88	1:6	6:14
2	**16k**	Cs_2CO_3	24	52	1:1	5:25
3	**16t**	DBU	2	37 (90)[d]	1:7	5:21

[a] Combined yield of pure isolated product diastereomers. [b] Diastereomeric ratios were determined by ^{1}H NMR on the crude reaction mixture. [c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. [d] Yield in parenthesis represents the total yield of indanes (**79a** + **79a'**) following treatment of the uncyclized side product **83a** with DBU (27 mol%). The dr and % ee did not change after treatment with DBU.

As a moderate improvement in the enantioselectivity of the transformation was observed, it was decided to prepare and assess the activity of precatalyst **16t** employing DBU as base. Although the reaction with the triazolium salt **16t** seems to be faster to that with precatalyst **16k**, only 37% of the desired indane was obtained along with 53% of the uncyclized Stetter product **83a** (entry 3). Once again, the formation of the thermodynamic product **79a'** was favoured over

79a and the enantioselectivity was comparable to the reaction performed with triazolium salt **16k** and cesium carbonate.

Given these results, extensive studies on the design of *N*-benzyl substituted triazolium salts need to be done in order to achieve useful levels of enantioselectivity.

3.2.5 Isomerization Studies

As a result of stereoselectivities obtained through the study of the scope of the reaction, it was considered interesting to study the stability of the *cis-trans*–**79a** indane product under basic conditions. Therefore, a sample of diastereomerically pure indane **79a** (>95:5 dr) was dissolved in dichloromethane-d_2 and treated with a catalytic amount of DBU at room temperature. An equilibrium mixture favouring diastereomer **79a'** was obtained after several hours (15:85 dr) (**Figure 3.2**).

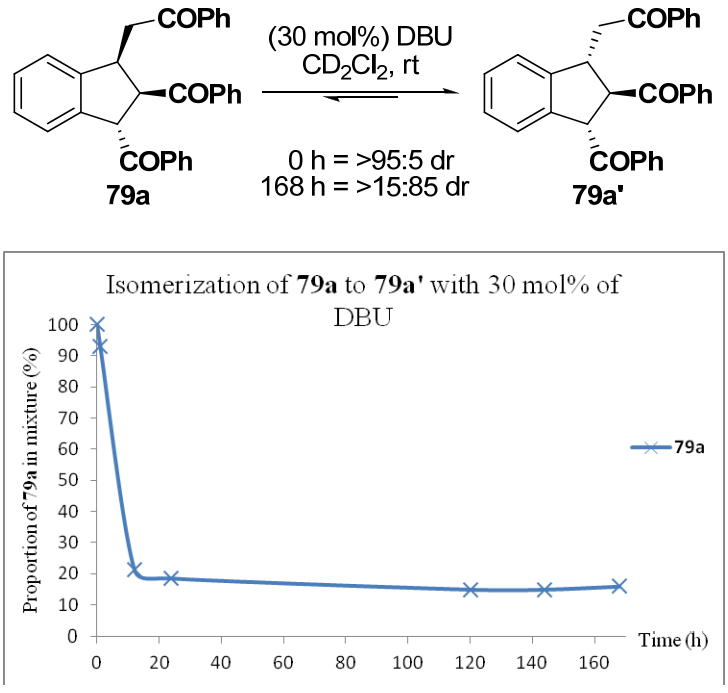


Figure 3.2 Isomerization of *cis-trans*–**79a** to *trans-trans*–**79a'** under catalytic amount of DBU.

As a result of such rapid isomerization, all possible isomers derived from **79a** (*cis-trans*–**79a**, *trans-trans*–**79a'**, *trans-cis*–**79a''**, and *trans-trans*–**79a'''**) were modeled and the ground state energies for each diastereomer were determined (**Figure 3.3**).[ix] Interestingly, it was found that from all four possible diastereomers, the thermodynamically more stable product is **79a'** followed by **79a** (6.5 kJ/mol above). This means that **79a** is produced under kinetic control during the domino transformation and **79a'** is the thermodynamic product as it has the lowest energy with respect to all other diastereomers.

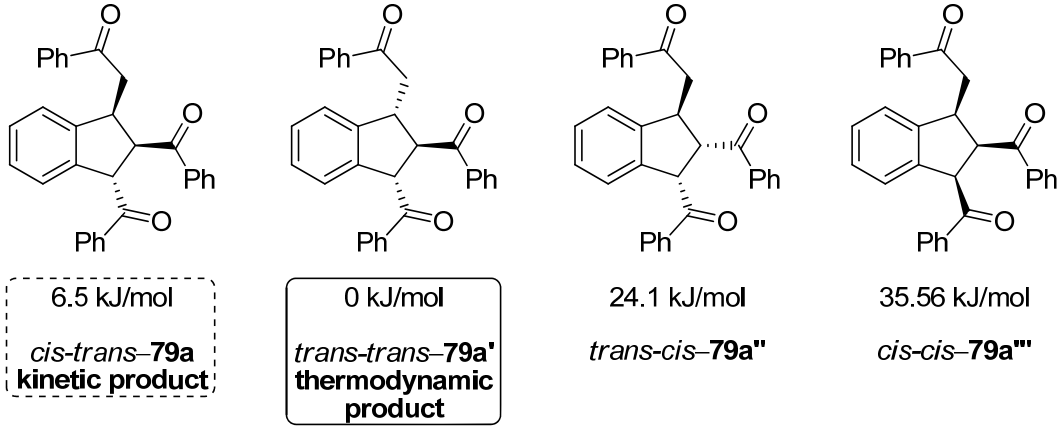


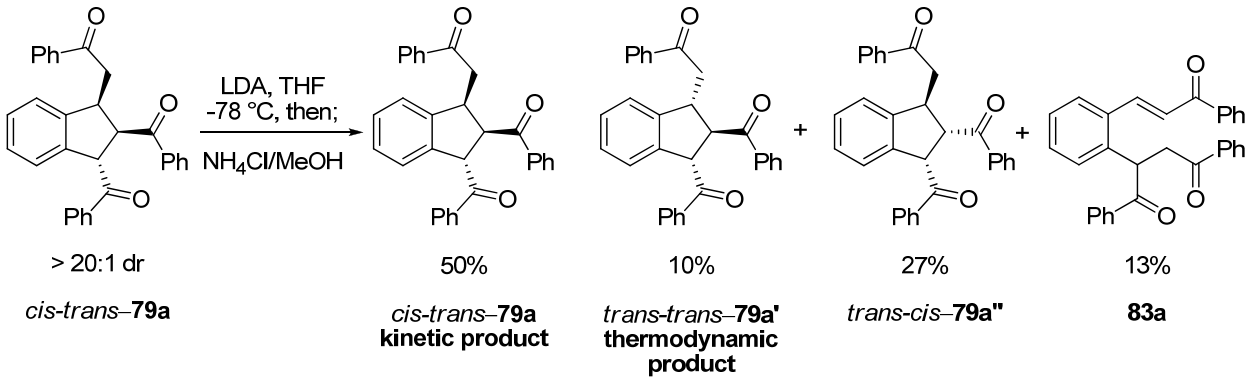
Figure 3.3 Relative ground state energies for all possible diastereomers of **79a**.

After noticing the large difference in energies between **79a** and **79a'',** the question arose whether all four possible diastereomers could be accessed through isomerization of the major isomer **79a**. The pure diastereomer **79a** (>20:1 dr) was thus subjected to LDA at low temperature, followed by quenching with a 1:1 mixture of MeOH/saturated aqueous NH_4Cl at -78 °C. Spectroscopic analysis of the sample crude revealed the presence of four products: *cis-*

[ix] All calculations were performed using the program Spartan '08 V 1.2.0 for Windows from Wavefunction, Inc. The calculations were performed by finding the equilibrium conformer using the Semi-empirical model with AM1 basis set and the ground state energy was annotated.

trans product **79a** (50%), thermodynamic isomer **79a'** in (10%), the new isomer *trans-cis*–**79a''** (27%), and the Stetter product **83a** (13%) (**Scheme 3.15**).

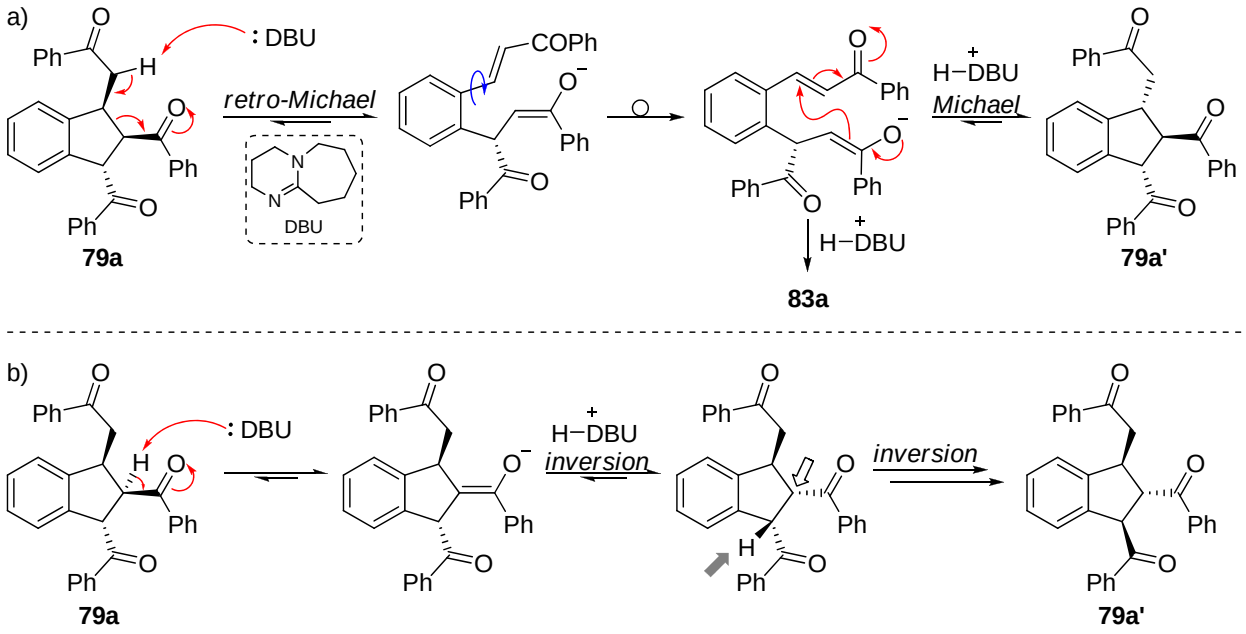
Scheme 3.15 Isomerization of the *Cis-Trans* Indane **79a**.



This result confirms that the less stable *trans-cis* isomer **79a''** was successfully obtained by deprotonation of the *cis-trans* isomer **79a**, followed by kinetically controlled protonation of the resulting enolate at -78 °C. Additionally, the isolation of intermediate **83a** suggests that the isomerization of the *cis-trans* isomer **79a** to the *trans-trans* product **79a'** occurs through a retro-Michael–Michael sequence (**Scheme 3.16a**), rather than a double inversion at C-2 and C-3 (**Scheme 3.16b**).

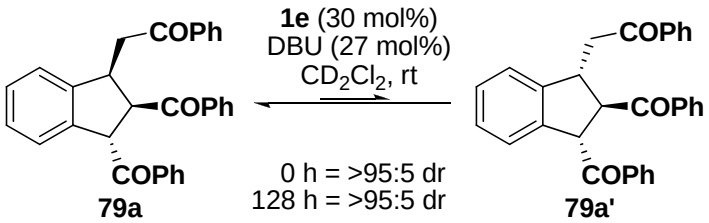
Access to enantiomerically enriched indane **79a**, would help determine which mechanism is operative. Indeed, the ability to determine which stereogenic centres undergo inversion during the isomerization process would clearly favour one mechanism over the other. This approach would be a viable way to investigate the isomerization of **79a**, assuming that there would not be racemization of the product in the process.

Scheme 3.16 Isomerization of *Cis-Trans*–**79a** into *Trans-Trans*–**79a'**.



From all these previous results, it can be concluded that the domino reaction proceeds under kinetic control, favouring **79a**. In order to confirm this observation and the results obtained from Spartan, an additional experiment was conducted. *Cis-trans* indane **79a** was subjected to reaction conditions and monitored for several hours; after 5 days, it was found that **79a** was intact and no traces of indane **79a'** was observed (**Scheme 3.17**).

Scheme 3.17 Isomerization of *Cis-Trans*–**79a** to *Trans-Trans*–**79a'** Under the Reaction Conditions.



As a result of the attempted isomerization of **79a**, it can be concluded that the predominant formation of the *cis-trans* indane **79a** arises from a diastereoselective Michael reaction rather than a subsequent equilibration, thus confirming the hypothesis previously described (**Scheme 3.9**). The *cis* selectivity observed at C1-C2 in **79a** is in sharp contrast to the *trans* selectivity observed in related processes in which indanes are formed from a Michael cyclization.[103, 122-127]

Thus, the present approach allows access to indanes that are diastereomerically and structurally distinct from previously disclosed domino methods. In order to confirm the relative configuration obtained from NOE experiments for **79a**, we obtained crystals suitable for X-ray diffraction analysis (**Figure 3.4**).

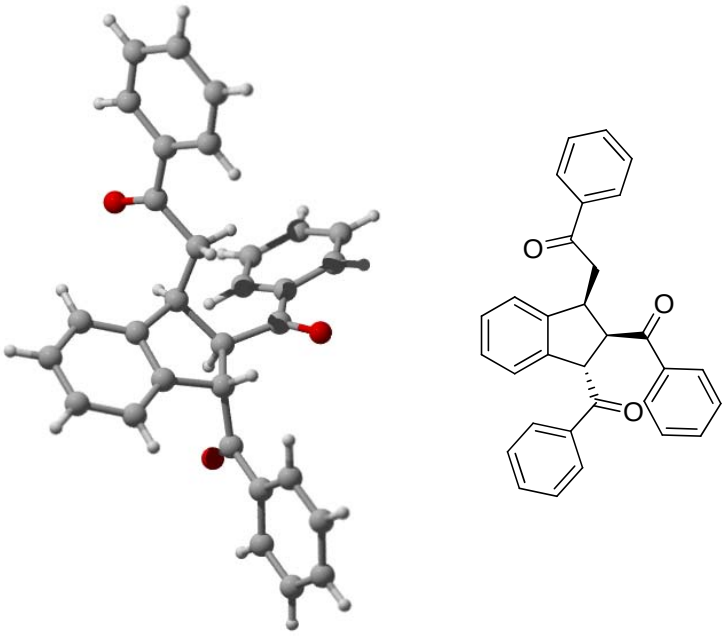
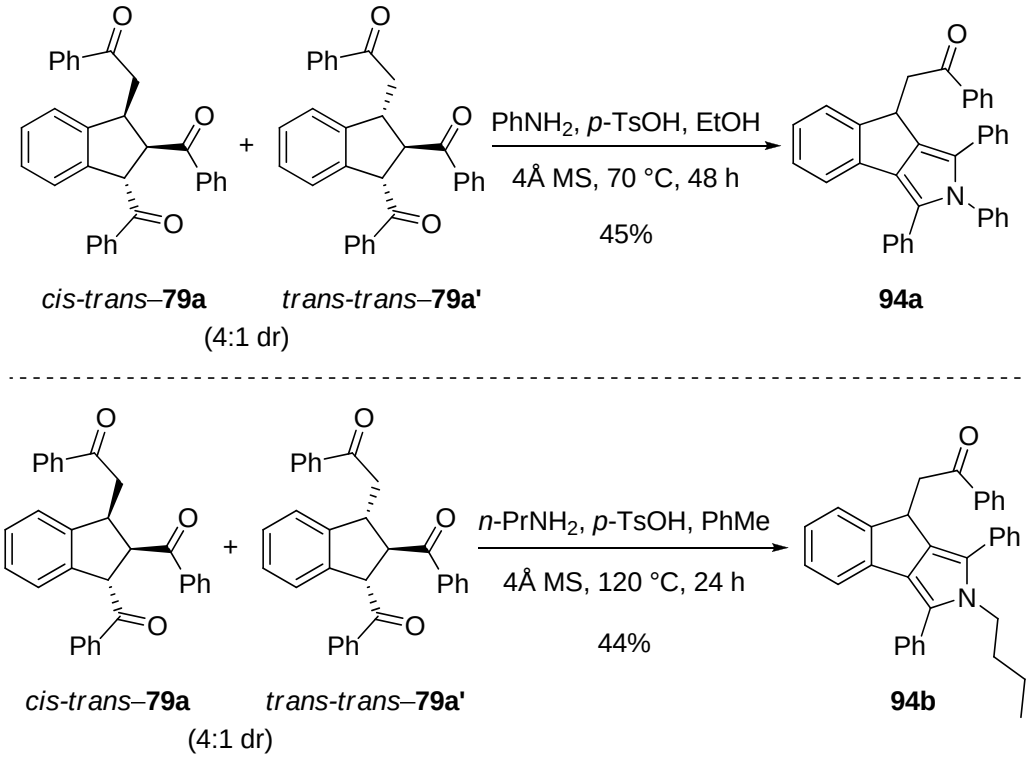


Figure 3.4 ORTEP representation for trisubstituted indane **79a**.

3.2.6 Synthesis of Pyrroles

All the indanes prepared in this study feature a 1,4-dicarbonyl pattern, which allows the preparation of complex heterocycles via the Paal-Knorr synthesis.[128, 129] As depicted in **Scheme 3.18**, fused pyrrole-containing polycyclic structures can be generated in a straightforward manner from the indanes obtained in the domino Stetter-Michael reaction.

Scheme 3.18 Synthesis of Polycyclic Pyrroles **94a** and **94b**.



3.3 CONCLUSIONS

In summary, a new NHC-catalyzed domino Stetter–Michael reaction has been developed. Aliphatic, aromatic, and heteroaromatic aldehydes were successfully employed and highly substituted indanes were synthesized with good diastereoselectivity. This methodology

represents the first example of a domino reaction involving the enolate intermediate generated from a Stetter reaction.

Various electron-withdrawing groups were studied and the use of two identical ketones, a combination of ketones, a combination of ketone-sulfone, and ketone-nitriles on the double Michael acceptor proved useful for the synthesis of indanes through a domino Stetter–Michael reaction. This new domino method for the construction of indanes is complementary to other domino reactions, providing access to a different set of diastereomer than the ones obtained by other research groups (vide supra). Additionally, this method allowed the synthesis of one major diastereomer and the preparation of two additional diastereomers out of four possible through isomerization under basic conditions. Moreover, it was determined under experimental work and computational calculations that the domino process occurs under kinetic control.

Noteworthy is the use of cyclopropenium precatalyst **93a** which proved to be useful for catalyzing our domino Stetter–Michael reaction. Despite of the low yield and low diastereoselectivity, this promising result opens a new horizon for the further development of this type of catalysts and their study in diverse transformations.

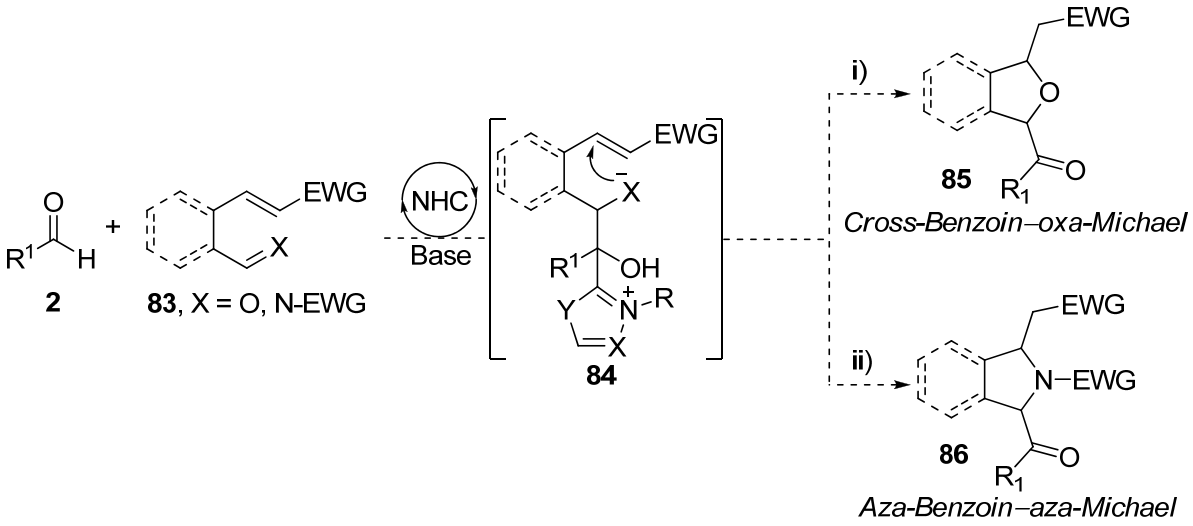
Although *N*-aryl substituted triazolium salts **16s** and **16n** did not catalyze the domino Stetter–Michael reaction, *N*-benzyl substituted triazolium salts **16k** and **16t** proved to be useful in our system affording the desired trisubstituted indane **79** in moderate to good yield and low enantioselectivity.

The presence of multiple functional groups on the resulting indane framework allows further derivatization, as demonstrated through the construction of polycyclic pyrroles **94a** and **94b**.

CHAPTER 4: SYNTHESIS OF SPIRO BIS-INDANES VIA DOMINO STETTER–ALDOL–MICHAEL AND STETTER–ALDOL–ALDOL REACTIONS

As a result of the successful development of a novel protocol for the diastereoselective synthesis of trisubstituted indanes via a domino Stetter–Michael reaction,[49] it was considered interesting to develop domino sequences that would target the synthesis of benzo[*b*]furans **85** via a domino cross-benzoin–oxa-Michael reaction and isoindolines **86** via a domino aza-benzoin–aza-Michael reaction (**Scheme 4.1**).

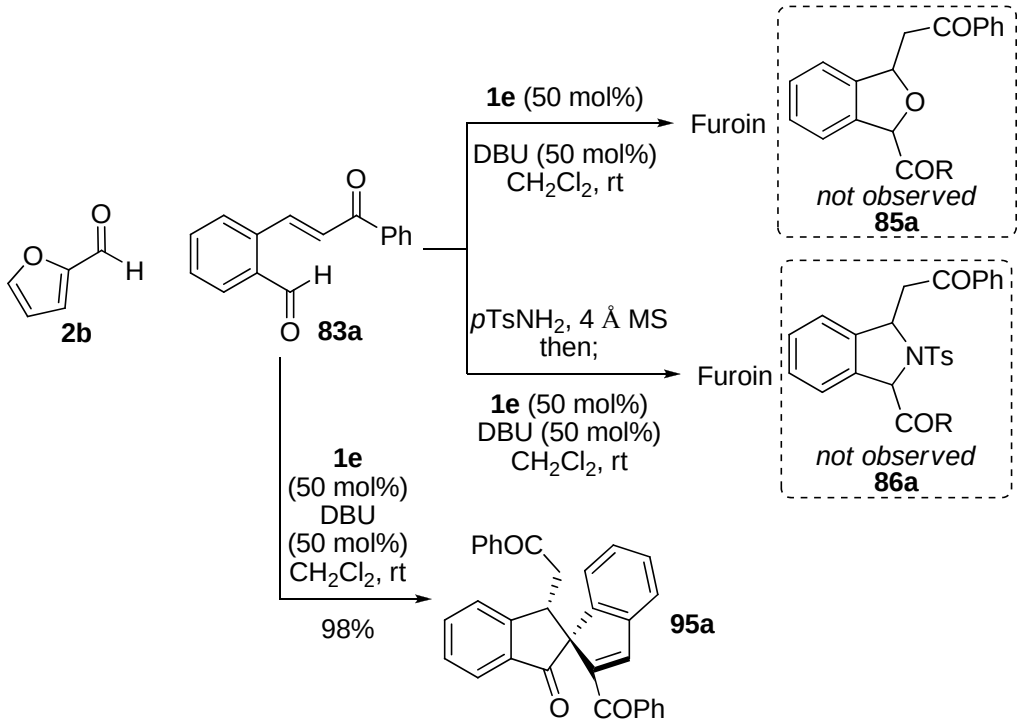
Scheme 4.1 Proposed Domino Cross-Benzoin–Oxa-Michael and Aza-Benzoin–Aza-Michael Reactions.



At the outset of the studies, both transformations were investigated employing furfural (**1c**) and *o*-formylchalcone **83a** as the model starting materials. Unfortunately, neither product **85a** nor **86a** was obtained. Instead, a complex spirocyclic structure **95a** which was derived from

two equivalents of **83a** was obtained. This exciting discovery allowed the formation of three new carbon–carbon bonds and a quaternary center in one synthetic operation (**Scheme 4.2**).[x]

Scheme 4.2 Serendipitous Discovery of the Domino Stetter–Aldol–Michael Reaction.



Interestingly, carbocyclic spiro motifs are found in a wide variety of natural products. Fredericamycin A (**96**)[130] and acutumine (**97**)[131-134] (**Figure 4.1**) are representatives of this large family of compounds which have attracted significant attention due to their biological properties and structural complexity. Other non-natural carbocyclic spiro compounds have also been studied for their medicinal properties, as exemplified by the potent estrogen receptor ligand

[x] Preliminary investigations were performed by Crystal L. Daschner as part of her Chem 483 research project. This work was developed in collaboration with Janice M. Holmes and was published in the form of a short communication to the ACS journal *Organic Letters* in November 2010 (Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M. *Org. Lett.* **2010**, *75*, 5772-5775). In June 2011, we published a full paper as an invitation from the Thieme journal *Synthesis* for the special issue in organocatalysis (Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M. *Synthesis* **2011**, 1896-1904).

98.[135] Due to the relevance of this type of carbon-skeleton, a number of synthetic methods have been devised for the synthesis of this structural motif.[136-139] The preparation of carbocyclic spiro compounds typically relied on the construction of each ring in a stepwise fashion, although a more efficient approach would involve simultaneous formation of both rings in a single operation.

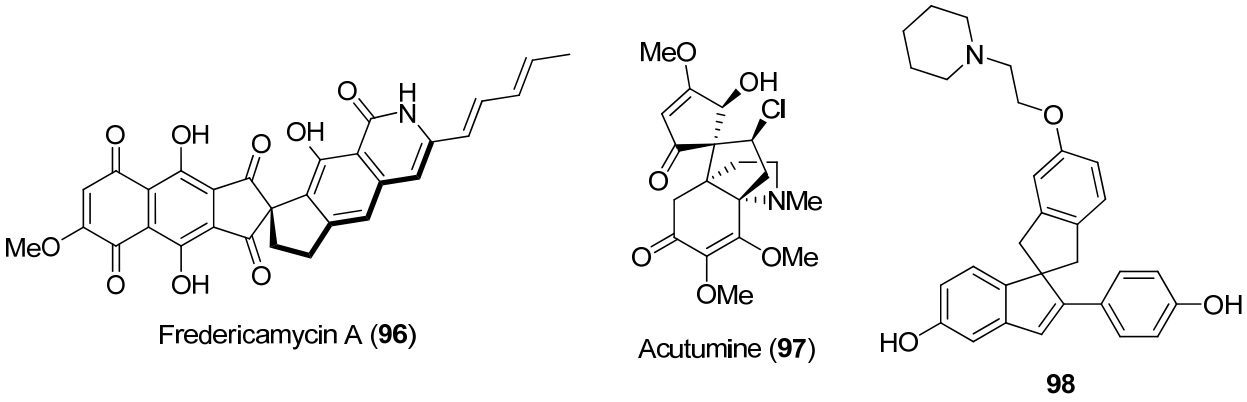


Figure 4.1 Examples of compounds containing a carbocyclic spiro motif.

4.1 RESEARCH OBJECTIVE

The serendipitous discovery of spiro bis-indane **95a** opened a new opportunity to further develop the current studies on *N*-heterocyclic carbene-catalyzed domino reactions. The objective of this project was to optimize and study the scope and limitations of the synthesis of homo spiro bis-indanes **95** through a domino Stetter–aldol–Michael (SAM) reaction and of hetero spiro bis-indanes **99** through a domino Stetter–aldol–aldol (SAA) reaction (**Scheme 4.3**). In addition, a synthetic route that allowed us to prepare the core structure of Fredericamycin A and analogs was investigated (**Figure 4.2**).

The postulated mechanism for the formation of **95a** was similar to that of the synthesis of indanes (**Scheme 4.4**).

Scheme 4.3 Domino Stetter–Aldol–Michael and Domino Stetter–Aldol–Aldol Reactions.

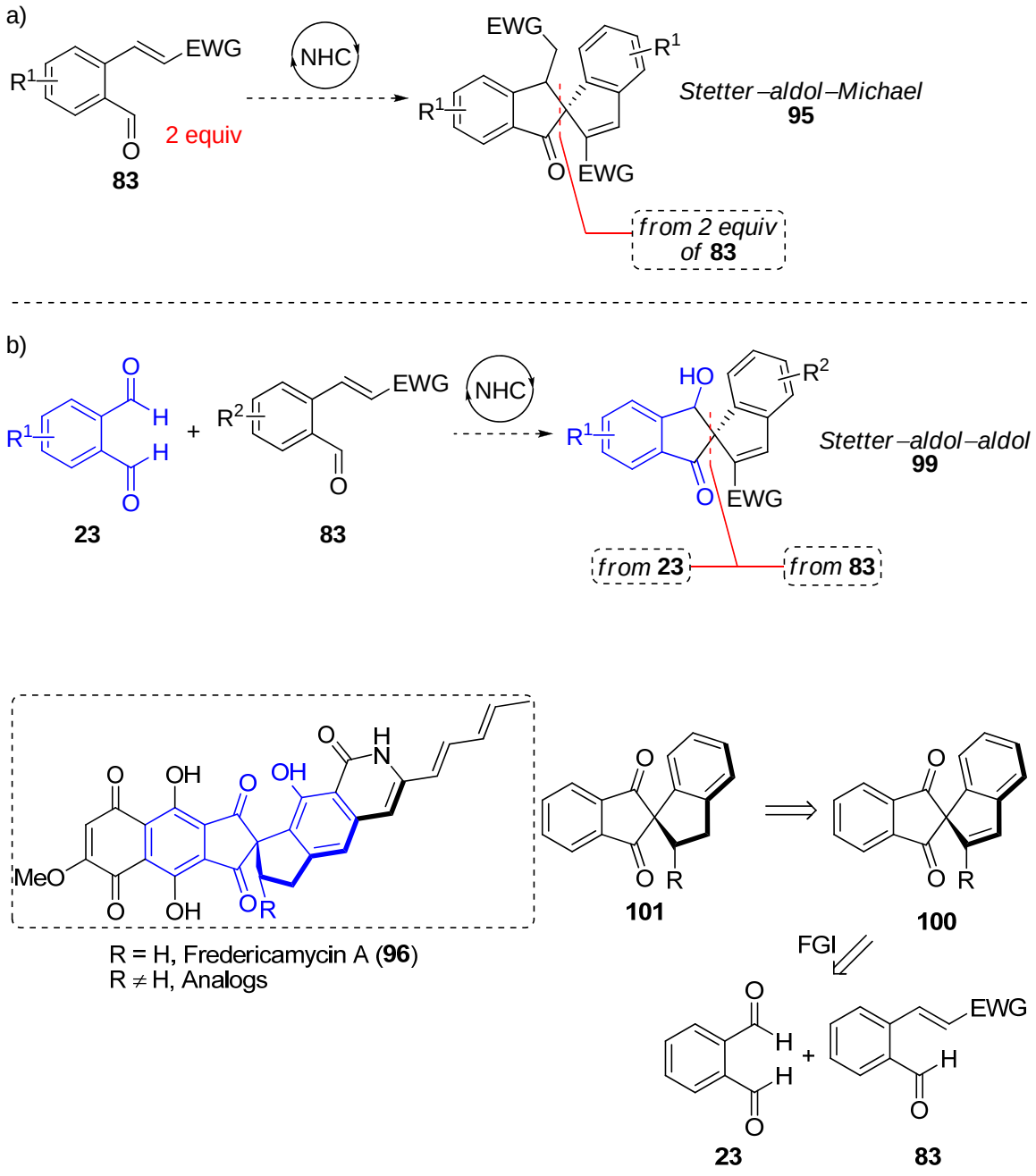
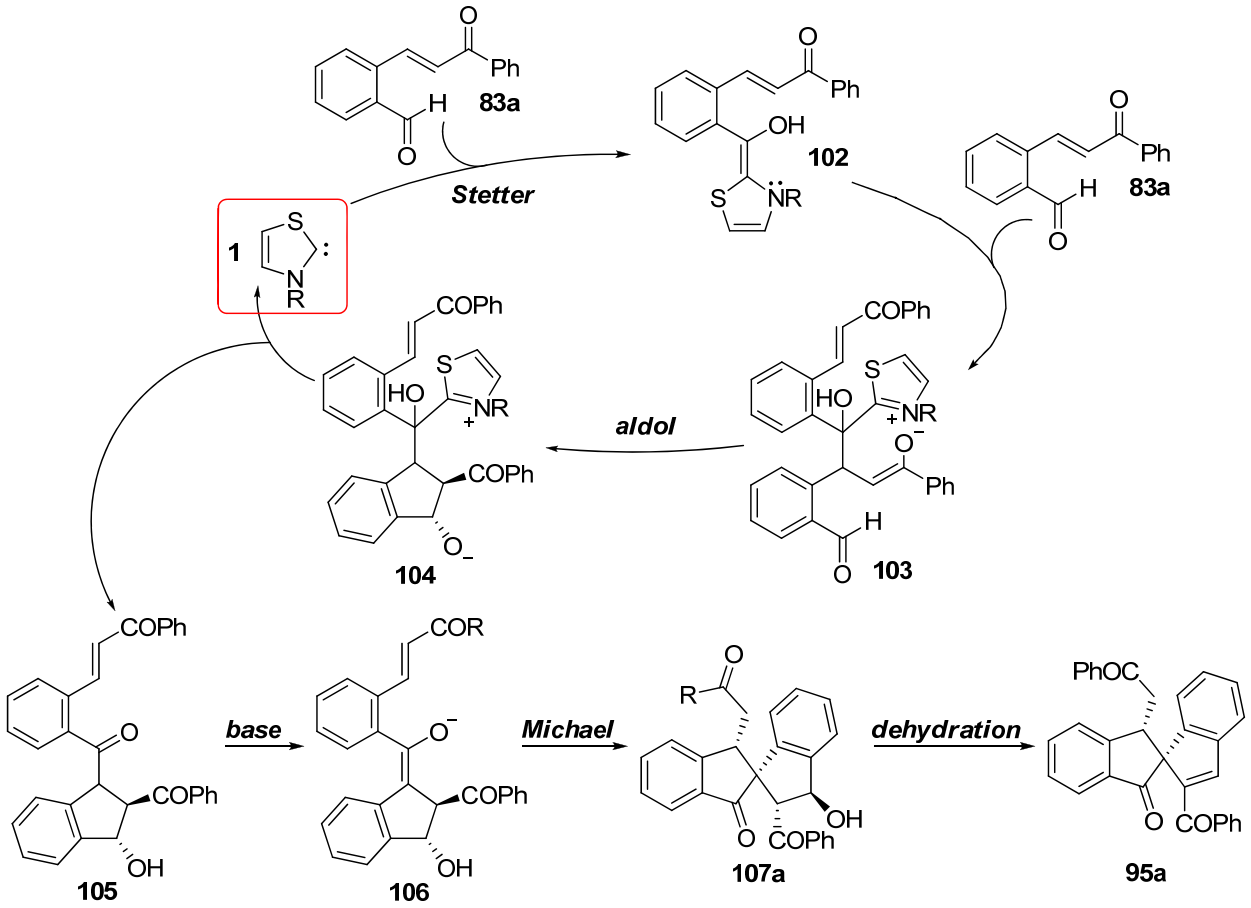


Figure 4.2 Retrosynthetic approach towards the synthesis of the core structure of fredericamycin A and analogs.

Scheme 4.4 Mechanistic Rationale for the Domino Stetter–Aldol–Michael Reaction.



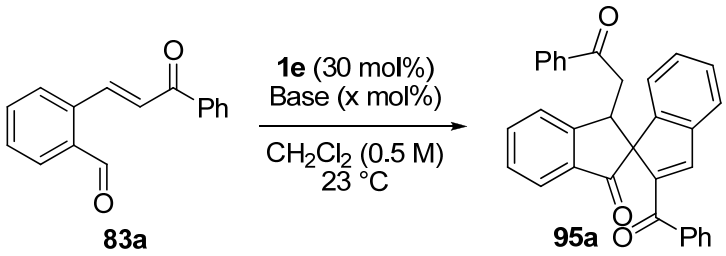
When NHC **1** reacted with **83a**, Breslow intermediate **102** was generated.[15] Subsequently, conjugate addition of **102** on the electron-poor olefin portion of a second equivalent of **83a** lead to the formation of the enolate intermediate **103**. An aldol reaction then took place,[64] followed by the elimination of the catalyst furnishing intermediate **105**. Under the basic reaction conditions, ketone **105** was deprotonated to form enolate intermediate **106** which cyclized to **107a**. According to Baldwin's rule for intramolecular cyclizations involving enolates, 5-(enolendo)-exo-trig cyclizations are disfavoured.[140] In this instance, the cyclization of **106** to **107a** falls into this classification making this particular transformation an exception to the rule. Finally, dehydration of this intermediate afforded the spiro bis-indane product **95a**.

4.2 RESULTS AND DISCUSSION

4.2.1 Optimization of the Reaction[xi]

This work began with studies aimed at finding the optimal reaction conditions and scope of the Stetter–aldol–Michael (SAM) reaction (**Table 4.1**). The first step consisted of screening the main families of NHCs, for which thiazolium salt **1e** gave the best results at 30 mol% loading. In order to achieve the best yield and diastereocontrol in this transformation, various bases were surveyed.

Table 4.1 Brief Optimization of the Reaction Conditions for the Synthesis of Spiro Bis-Indanes **95a**.



entry	base (mol%)	*t* (min)	yield (%) [a,b]	dr [c]
1	*i*Pr$_2$NEt (100)	19 h	(<10)	>20:1
2	TMG (27)	10	nr[d]	-
3	Cs_2CO_3 (9)	5 h	(<5)	-
4	DBU (100)	45	77	5:1
5	DBU (27)	35	75	20:1
6[e]	DBU (30)	15	79	17:1

[a] Combined yield of pure isolated product diastereomers. [b] Numbers in parentheses represent conversion. [c] Determined from ^{1}H NMR analysis of the crude reaction mixture. [d] nr = no reaction. [e] The reaction was performed employing 10 mol% of the thiazolium salt **1e**.

[xi] The screening of NHCs and optimization of the reaction was performed by Janice M. Holmes.

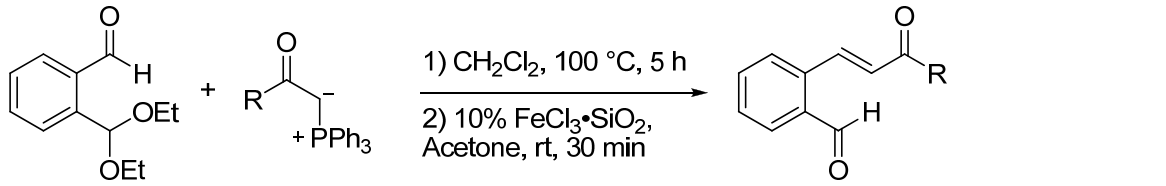
Although the use of Hünig's base in the reaction produces a single diastereomer, the yield of the desired product is very low (entry 1). The use of a stronger base such as tetramethylguanidine gives no reaction (entry 2). Similarly, cesium carbonate did not furnish the expected product (entry 3). When 1 equivalent of DBU was employed as base, **95a** was produced in 77% yield and 5:1 dr (entry 4). Reduction in the amount of DBU did not affect the yield but the diastereomer ration of **95a** increased to 20:1 (entry 5). Gratifyingly, the reduction of the catalyst loading from 30 to 10 mol% did not significantly affect the yield or diastereomeric ratio of the spiro bis-indane **95a** (entry 6).

4.2.2 Preparation of Starting Materials

In order to study the scope of the reaction, it was necessary to prepare various *o*-formylchalcone derivatives **83** for the domino SAM reaction as well as different phthaldialdehyde derivatives **23** for the domino SAA reaction (**Scheme 4.5**).[xii]

o-Formylchalcones **83b-c** and **83h-i** were prepared with a modified procedure from that previously reported by Suwa and coworkers.[141]

Scheme 4.5 Preparation of *o*-Formylchalcones **83b-c**, **h-i**.



108a

87b, R = Ph(4-Cl)
87e, R = Ph(4-OMe)
87c, R = Me
87f, R = SEt

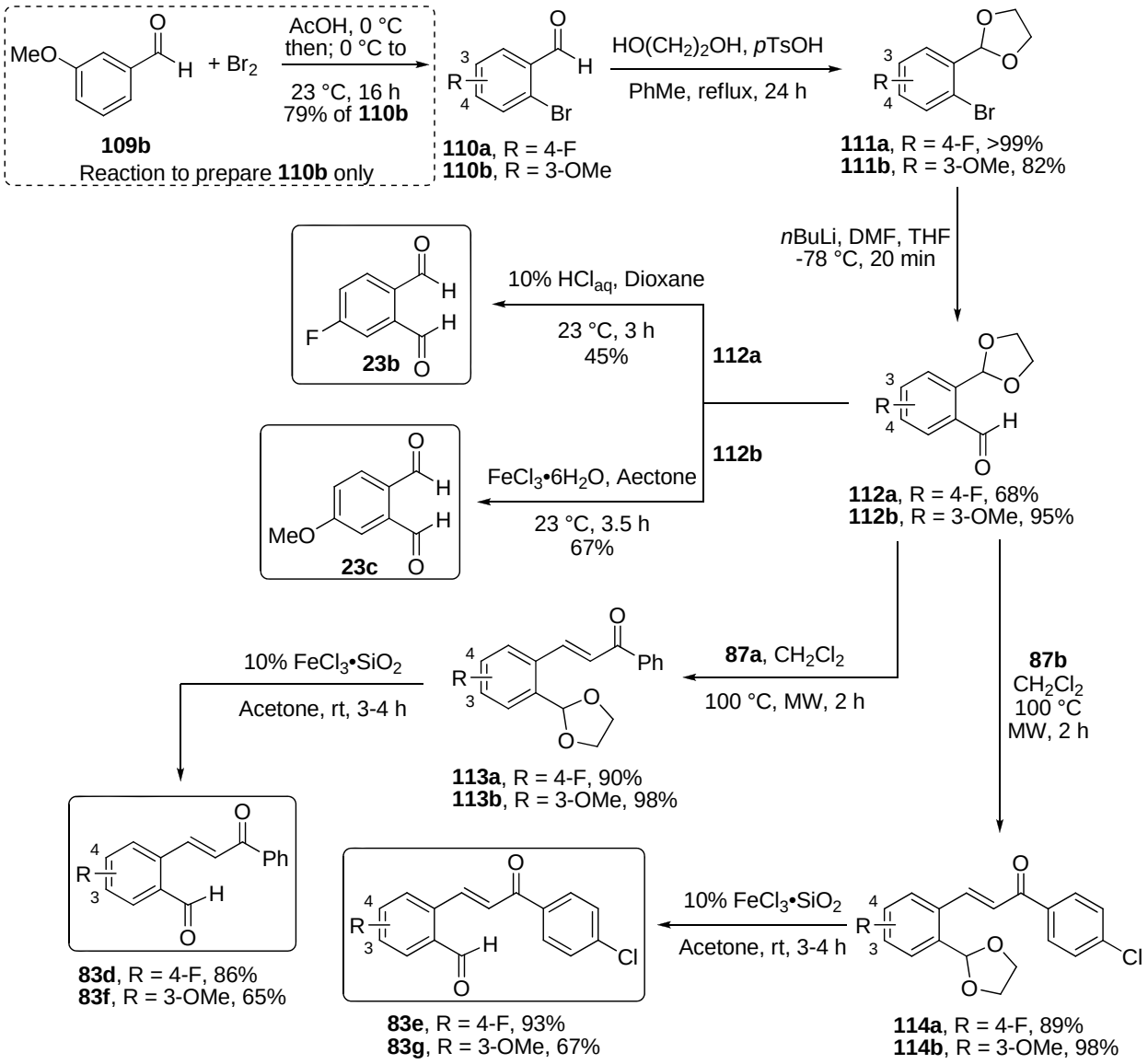
83b, R = Ph(4-Cl), 54%
83c, R = Ph(4-OMe), 81%
83h, R = Me, 74%
83i, R = SEt, 86%

yields over 2 steps

[xii] *o*-Formylchalcone **83h** was prepared by Janice M. Holmes.

Other *o*-formylchalcone (**83d-e**, **f-g**) and phthaldialdehyde (**23b-c**) derivatives were synthesized following the synthetic sequence depicted in **Scheme 4.6**.[xiii]

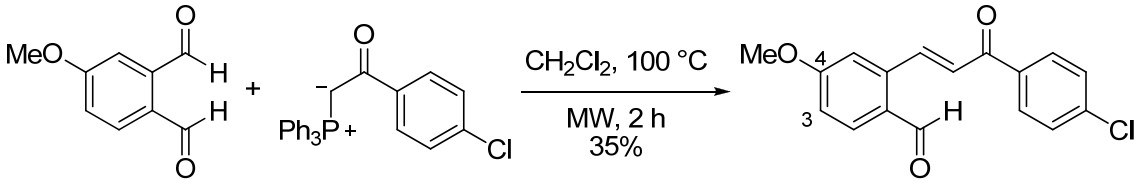
Scheme 4.6 Synthesis of *o*-Formylchalcones **83d-e**, **f-g** and Phthaldialdehyde Derivatives **23b-c**.



[xiii] *o*-Formylchalcones **83f**, **83g**, phthaldialdehyde derivative **23c**, and their corresponding precursors (**110b**, **111b**, **112b**, **113b**, **114b**) were prepared by Janice M. Holmes.

o-Formylchalcone **83j** was readily prepared from 6-formyl-3-methoxybenzaldehyde (**23c**) and phosphorane **87b** in moderate yield (**Scheme 4.7**).[xiv]

Scheme 4.7 Synthesis of *o*-Formylchalcone **83j** via Wittig Olefination Reaction.



23c **87b** **83j**

4.2.3 Scope of the Reaction

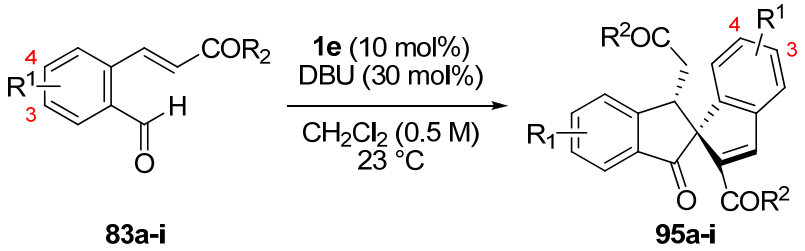
Once the optimized conditions were established, the scope of the domino Stetter–aldol–Michael reaction was studied (**Table 4.2**).[xv]

Model *o*-formylchalcone **83a** furnished the desired spiro bis-indane **95a** in good yield and excellent diastereoselectivity (entry 1). Due to the isolation of **95a** and small amounts of **107a** as single isomer, it has been proposed that the aldol reaction to produce **104** and the conjugate addition to furnish **107a** occurs with high diastereoselectivity (**Scheme 4.4**). During the Michael addition step, it has been proposed that the acceptor approaches the less hindered *Re* face of the *Z*-enolate. The observed selectivity on **107a** could be attributed to the hydrogen bond formed between the carbonyl and the alcohol, hence exposing the *Si* face of the enone activating it toward enolate attack (**Figure 4.3**).

[xiv] **83j** was prepared by Janice M. Holmes.

[xv] Products **95b**, **95f**, **95g**, and **95h** were prepared by Janice M. Holmes.

Table 4.2 Evaluation of the Scope for the Domino Stetter–Aldol–Michael (SAM) Reaction Employing Various *o*-Formylchalcone Derivatives **83**.



83a-i **95a-i**

entry	R^1	R^2	*t* (min)	product [a]	yield (%) [b,c]	dr [d]
1	H	Ph	15	**95a**	79	17:1
2	H	Ph (4-Cl)	5	**95b**	86	12:1
3	H	Ph (4-MeO)	45	**95c**	68	>20:1
4	4-F	Ph	5	**95d**	64	11:1
5	4-F	Ph (4-Cl)	15	**95e**	80	16:1
6	3-MeO	Ph	9	**95f**	85	>20:1
7	3-MeO	Ph (4-Cl)	5	**95g**	81	10:1
8	H	Me	(3.3 h)	**95h**	75	7:1
9	H	Set	(2 h)	**95i**	31	13:1

[a] The relative configuration was determined by X-ray crystallography (vide supra). [b] Combined yield of pure isolated product diastereomers. [c] Numbers in parentheses represent conversion. [d] Determined from ^{1}H NMR analysis of the crude reaction mixture.

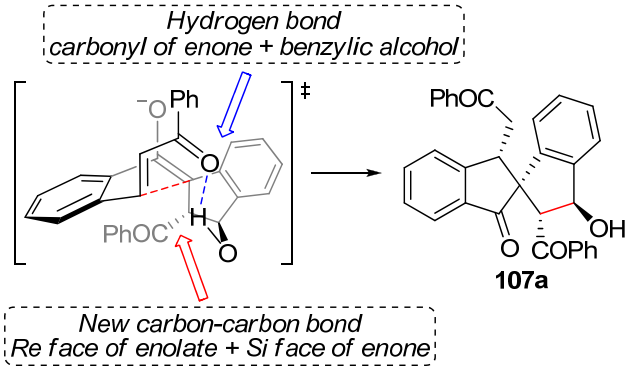
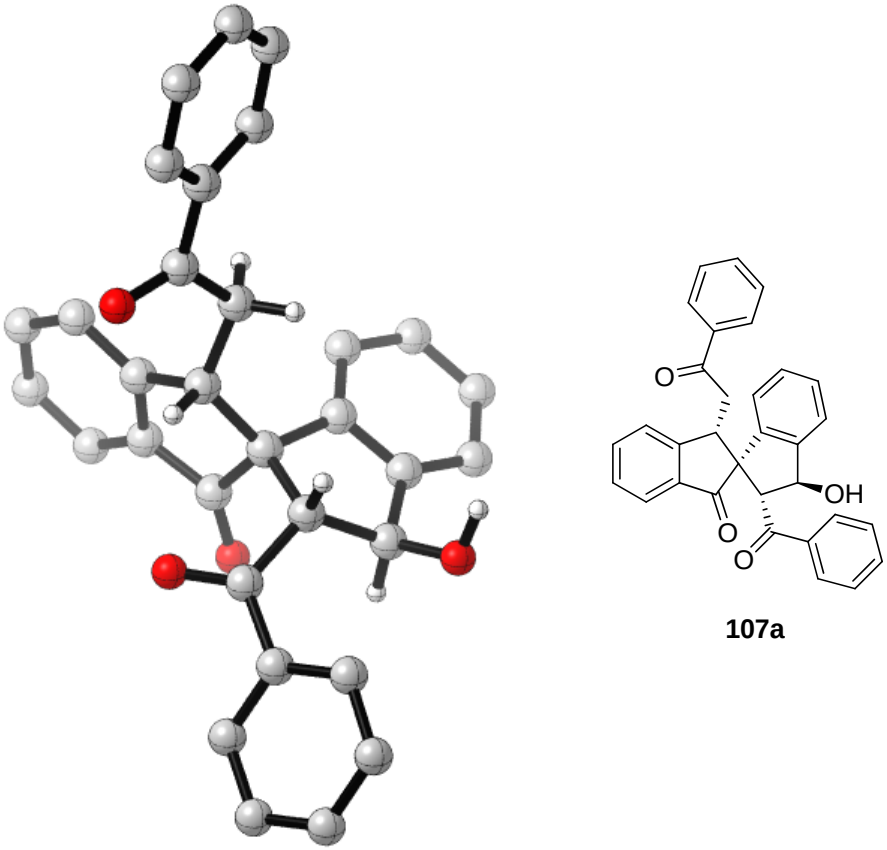


Figure 4.3 Proposed transition state for the diastereoselective Michael addition.

The structure and relative configuration of **107a** was later confirmed by X-ray analysis (**Figure 4.4**).



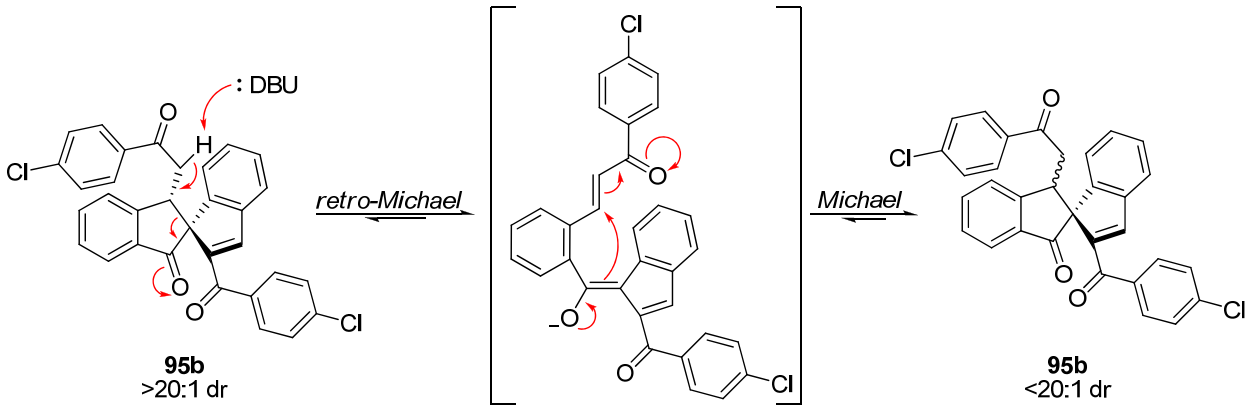
107a

Figure 4.4 ORTEP representation for alcohol intermediate **107a**.

The use of chlorine as electron-withdrawing group on the ketone portion on **83b** reduced significantly the reaction time and increased the yield of **95b** at expenses of the diastereoselectivity (entry 2). Conversely, the 4-methoxyphenylsubstituted *o*-formylchalcone derivative **83c** required of a longer reaction time to furnish the corresponding 4-methoxyphenylsubstituted spiro bis-indane **95c** (5 min. vs. 45 min.) (entry 3). Although **95c** was produced in lower yield (86% vs. 68%), a high level of diastereocontrol was achieved (12:1 vs.

>20:1 dr). Presumably, the difference in the diastereomeric ratio between **95b** and **95c** could be attributed to a retro-Michael reaction that reduces the diastereomeric ratio on species bearing electron-withdrawing groups (**Scheme 4.8**).

Scheme 4.8 Proposed Mechanism for the Reduced Diasteromeric Ratio when the Aryl Group is Substituted with an Electron-Withdrawing Group.



The reactivity of aryl ketone substrates is also greatly influenced by the type and position of the substituent (R^1) incorporated in the left portion of the acceptor **83** (entries 4-7). These results indicate that electron-withdrawing groups (relative to the aldehyde) accelerate the reaction. The results from entries 1 and 6 are particularly interesting; these show a faster reaction in the case of *m*-methoxy-substituted *o*-formylchalcone **83f**. These observations support the notion that the formation of the Breslow intermediate **102** is the rate-limiting step in the SAM sequence (**Figure 4.5**). As proposed by Rovis and coworkers, the formation of the acyl anion equivalent is the rate-limiting step during the intramolecular Stetter reaction (**Figure 1.6**).[43]

Spiro bis-indane **95d** produced crystals suitable for X-ray analysis which served for the determination of its relative configuration (**Figure 4.6**). The configuration for the remaining

spiro bis-indanes indanes was assigned by analogy to **95d** and the similarities of the chemical shifts in ^{1}H NMR spectroscopy.

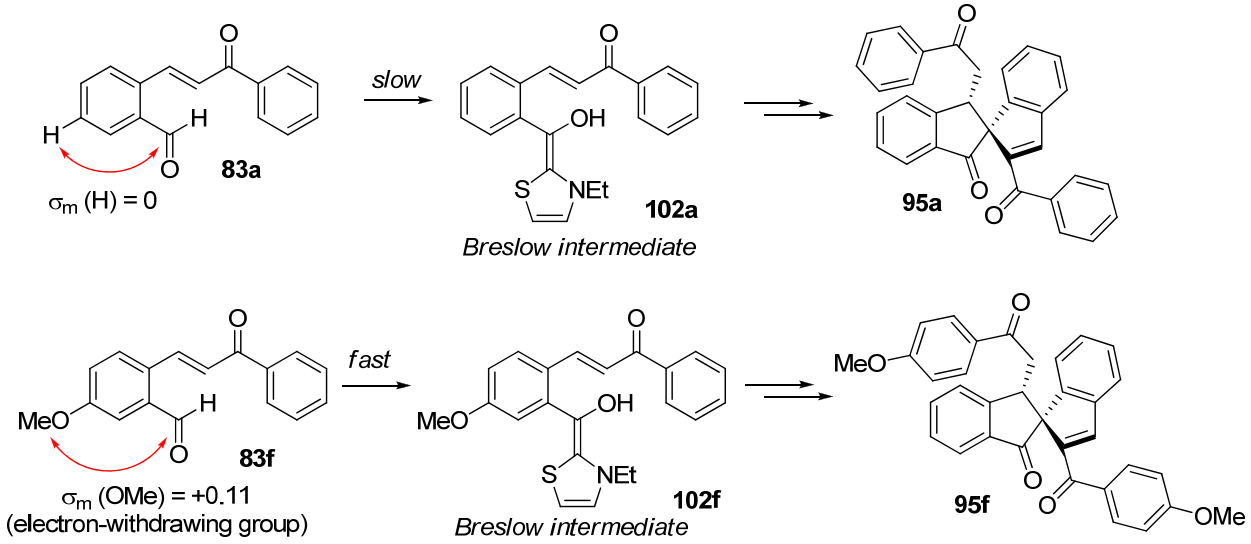


Figure 4.5 Effect of the substituent on the *o*-formylchalcone towards the formation of the Breslow intermediate **102**.

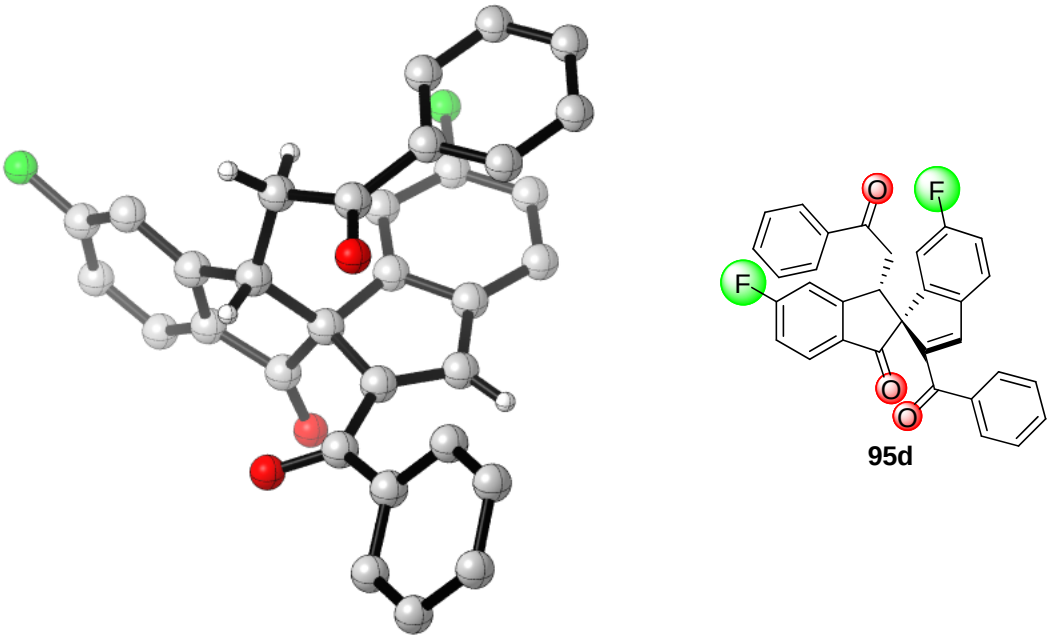


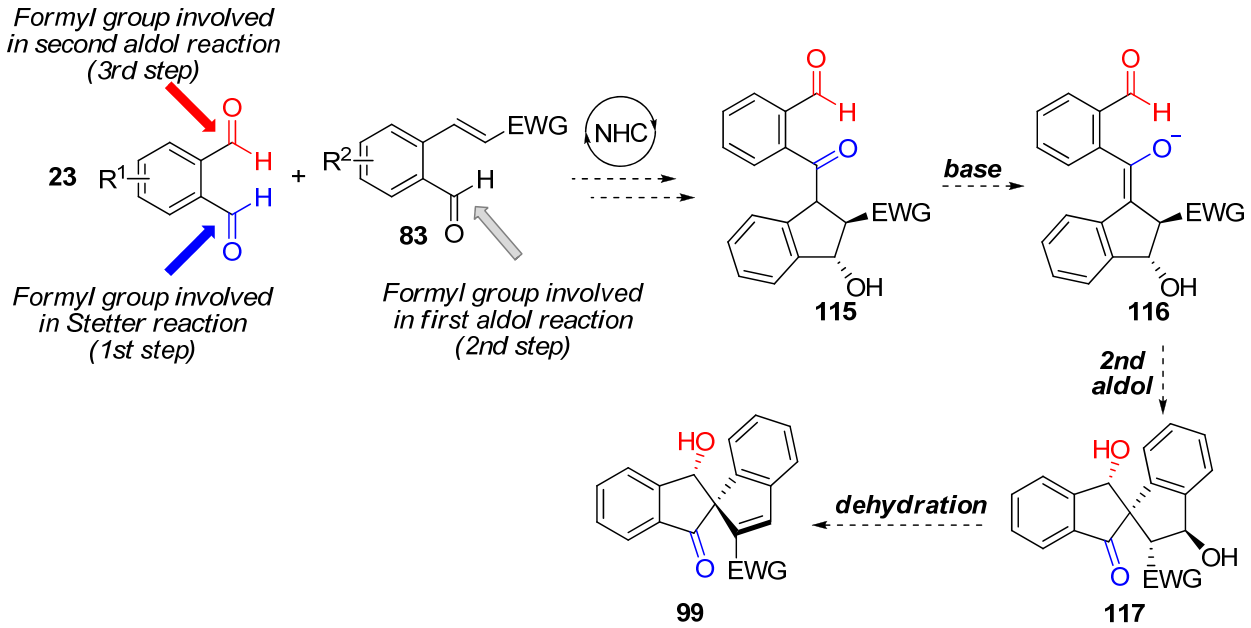
Figure 4.6 ORTEP representation for spiro bis-indane **95d**.

The use of aliphatic ketone **83h** results in good yield and moderate diastereoselectivity; however, a long reaction time was required (entry 8). Finally, thioester acceptor **83i** afforded the bis spiro-indane product with good diastereoselectivity, but in a modest yield (entry 9). The low efficiency of this transformation is presumably due to the low electron-withdrawing ability of the thioester group in contrast to ketones.

A screening of other families of acceptors revealed that esters, sulfones, and nitriles as electron-withdrawing groups do not afford the desired product under our optimized conditions. Thus, the scope of the SAM reaction seems to be limited to ketone and thioester acceptors.

Based on the understanding of the SAM reaction mechanism (**Scheme 4.4**), an analogous Stetter–aldol–aldol (SAA) process was developed. This proposed domino transformation relies on the reactivity of *o*-phthaldialdehydes **23**, in which one formyl group would be involved in the Stetter reaction and the second formyl group would be involved in a second aldol ring-closing step (**Scheme 4.9**).

Scheme 4.9 Rationale for the Domino Stetter–Aldol–Aldol Reaction.



In order to examine this hypothesis, a model reaction employing *o*-phthaldialdehyde **23a** and *o*-formylchalcone **83a** that smoothly furnished the SAA product **99a** was performed. Unfortunately, the product was obtained as an inseparable 1:1 mixture of diastereomers, in which the product probably undergoes a facile retro-aldol–aldol reaction under these conditions, leading to a thermodynamic equilibrium (see **Scheme 4.8** for a similar thermodynamic equilibration). Therefore, it was decided to oxidize the diastereomeric mixture of alcohols to a single diketone (**100**) in order to facilitate the isolation and analysis of the product. During the optimization of the reaction conditions,[xvi] it was also found that better yields could be obtained by employing 2 equivalents of acceptor **83**. In this manner, the SAA reaction could proceed to completion despite the competing SAM process forming dimer **95**. The scope of the SAA reaction is shown in **Table 4.3**.[xvii]

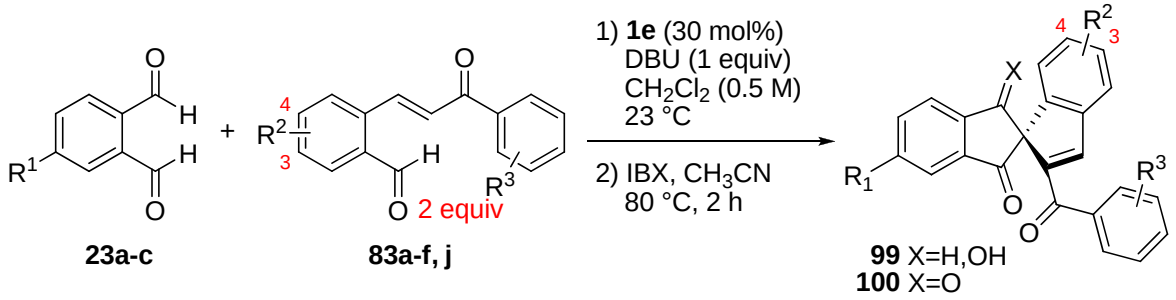
Model reaction between **23a** and **83a** gave the desired SAA product **99a** as a 1:1 mixture of diastereomers in very good yield (entry 1). It is worth mentioning that the isolation of each diastereomer was only possible for products **99a** and **99e**. Conveniently, **99a** produced crystals suitable for X-ray analysis that were used to confirm the structure of the product and its relative configuration (**Figure 4.7**).

The use of electron-withdrawing groups on the aryl ketone portion of the acceptor **83b** furnished **100b** in good yield (entry 2). Conversely, the use of the 4-methoxy group considerably increased the reaction time, affording **100c** in low yield (entry 3). When the methoxy group was installed on C3 of the acceptor **83f** also showed sluggish reactivity, furnishing **100d** in modest yield (entry 4).

[xvi] A short optimization, which consisted of the increase of the loading of catalyst **1e** and the amount of base, was performed by Janice M. Holmes.

[xvii] Products **100b**, **100d**, **100f**, and **100g** were prepared by Janice M. Holmes.

Table 4.3 Study of the Scope for the Domino Stetter–Aldol–Aldol (SAA) Reaction Employing Phthaldialdehyde Derivatives **23** and *o*-Formylchalcone Derivatives **83**.



entry	R^1	R^2	R^3	*t* (min) [a]	product	Yield (%) [b]
1 [c,d]	H	H	H	20	**99a**	71
2	H	H	4-Cl	30	**100b**	58
3	H	H	4-OMe	60	**100c**	25
4	H	3-OMe	H	100	**100d**	36
5 [d]	H	4-F	H	5	**99e**	72
6	H	4-OMe	4-Cl	15	**100f**	75
7	F	4-F	4-Cl	60	**100g**	50
8	OMe	H	H	35	**100h**	42

[a] Reaction time for the Stetter-aldol-aldol (SAA) step. [b] Yield of pure isolated product. [c] Reaction performed on a gram scale. [d] Each diastereomer of products **99a** and **99e** was isolated prior to the oxidation step.

The use of electron-withdrawing groups such as 4-fluoro and 4-methoxy (the methoxy group behaves as electron-withdrawing when is in meta position relative to the α,β-unsaturated ketone) on acceptors **83d** and **83j**, respectively, improved the reactivity of the Michael acceptors, thus reducing the reaction time and increasing the yield of the product (entries 5 and 6).

Finally, the effect of substituents on the *o*-phthaldialdehyde partner was investigated (entries 7 and 8). Surprisingly, the reaction between *o*-phthaldialdehyde substrate **23b** (R^1 = F)

and *o*-formylchalcone **83e** resulted in a very sluggish transformation producing a moderate yield of **100g** (entry 7). In contrast, the methoxy-substituted dialdehyde substrate **23c** furnished product **100h** as a single regioisomer prior to the oxidation step in a short reaction time (entry 8). This result can be attributed to the electron-donating and electron-withdrawing effect at the *para* and *meta* positions relative to the formyl group, respectively.

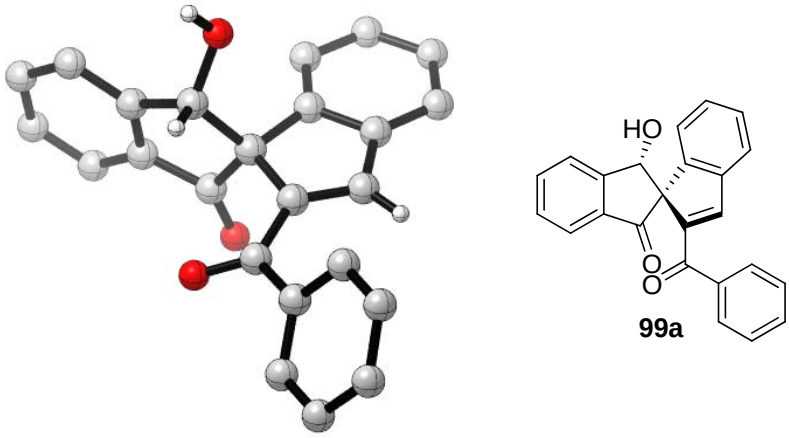


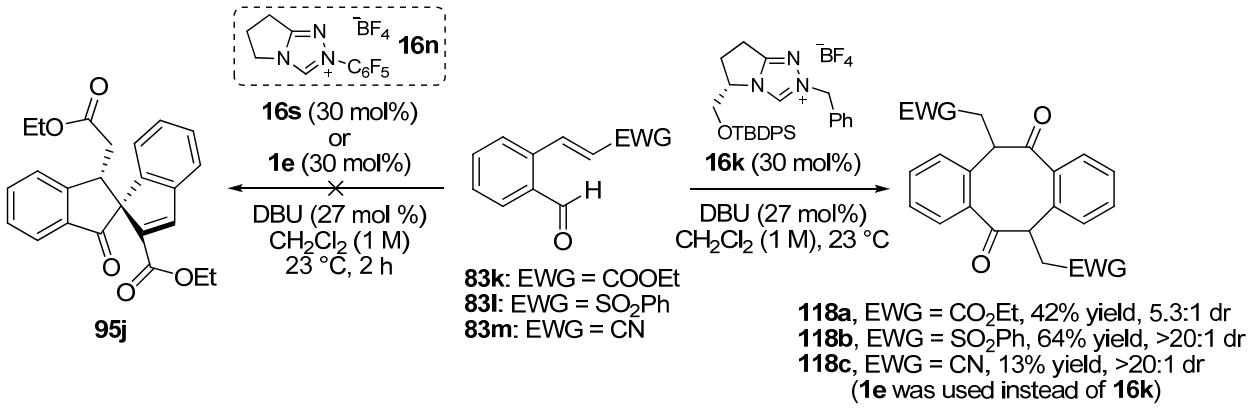
Figure 4.7 ORTEP representation for a diastereomer of **99a**.

The experimental results for the SAM reaction indicate that *o*-formylchalcone derivatives **83a-i** were very reactive Stetter acceptors. Therefore, it was decided to further study electron-withdrawing groups that are known for being poorly reactive in intermolecular Stetter reactions, such as esters and α-alkyl-α,β-unsaturated ketones.[13]

The reactivity of ester substrate **83k** using standard conditions for the Stetter reaction was investigated. However, spiro bis-indane product **95j** was not produced using either thiazolium salt **1e** or triazolium salt **16s** as precatalyst (**Scheme 4.10**). As a result, it was decided to explore the more electron-rich *N*-benzyl substituted triazolium salt **16k**.[37] Surprisingly, the dibenzo[8]annulene product **118a** was obtained when **83k** was reacted with triazolium salt **16k**.

In the same way, sulfone **83l** and cyanide **83m** furnished the corresponding dibenzo[8]annulenes **118b** and **118c**[xviii] when precatalysts **16k** and **1e** were employed, respectively.[xix]

Scheme 4.10 Synthesis of Dibenzo[8]annulenes **118a-c**.

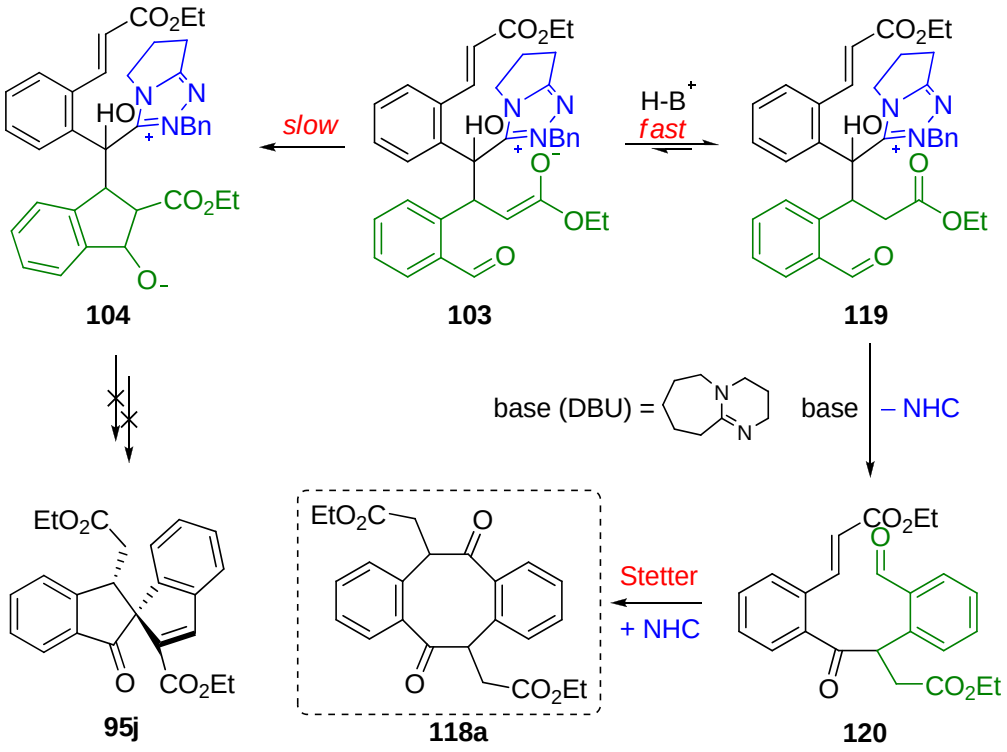


These products presumably arise from sequential inter- and intramolecular Stetter reactions. It was postulated that formation of **118** is mainly driven by rapid protonation of intermediate **103** forming intermediate **119**. Apparently, this process occurs more rapidly than the aldol ring closure leading to intermediate **104**. Subsequently, intermediate **119** releases the NHC to give intermediate **120** which undergoes a second Stetter reaction to form the eight-membered product **118a** (**Scheme 4.11**).

[xviii] The reaction of **83m** to produce **118c** was performed with catalyst **1e**.

[xix] HPLC analysis on a chiral stationary phase revealed that product **118a** was racemic, even when the reaction was performed with weaker bases to avoid racemization.

Scheme 4.11 Proposed Mechanism for the Synthesis of **118a**.



To date, it has been particularly difficult to perform intermolecular Stetter reactions on linear α-alkyl substituted Stetter acceptors.[41] This difficulty is presumably due to steric and electronic reasons. On one hand, the α-alkyl group could potentially hinder the β-carbon preventing the approach of the Breslow intermediate. On the other hand, the $A^{1,3}$ strain between the α-alkyl and the β-aryl substituents could reduce the electrophilicity of the Michael acceptor, thus forcing the β-aryl group to be perpendicular relative to the enone (**Figure 4.8**). Moreover, the α-alkyl group disrupts the conjugation between the α,β-double bond and the ketone;

therefore, the carbonyl group is located 90° relative to the olefin, hence reducing the electron-withdrawing ability of the α,β-unsaturated ketone (**Figure 4.8**).[xx]

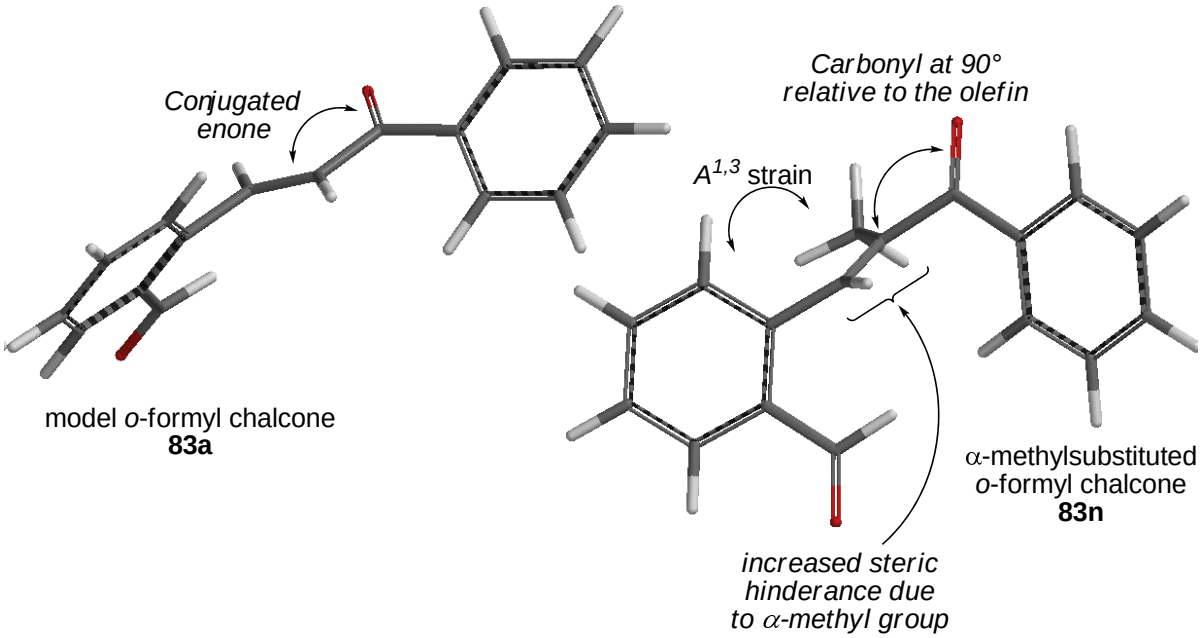


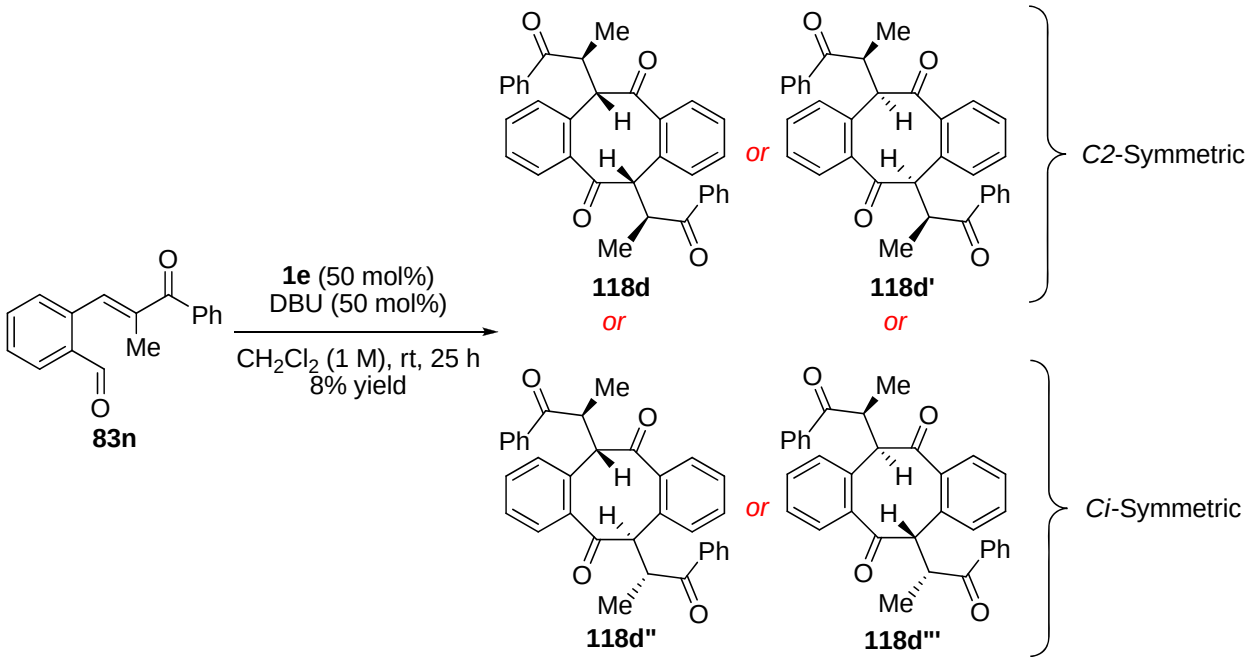
Figure 4.8 Three-dimensional representations for **83a** and **83n** illustrating the possible causes for their differences in reactivity.

As a result of the knowledge gathered on the high reactivity of *o*-formylchalcone derivatives, the use of substrate **83n** with precatalyst **1e** was then investigated. Surprisingly, the dibenzo[8]annulene **118d** was obtained in low yield (**Scheme 4.12**). For this case, presumably the enolate intermediate similar to **103** does not undergo the aldol cyclization due to steric reasons, thus leading to preferential protonation and subsequent formation of the eight-membered ring (**Scheme 4.11**). Despite the low reactivity of **83n**, the dibenzo[8]annulene

[xx] Both calculations were performed using the program Spartan '08 V 1.2.0 for Windows from Wavefunction, Inc. The calculations were performed by finding the equilibrium conformer using Molecular Mechanics / MMFF (Merck Molecular Force Field).

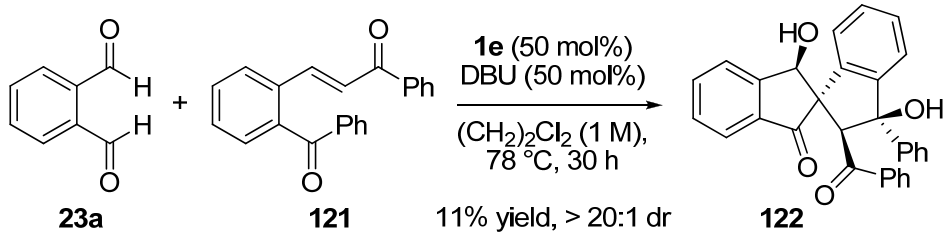
product **118d** was obtained in low yield. Although, **118d** was obtained as a mixture of diastereomers in a 2:1 ratio, it was not possible to determine which of the four possible diastereomers would be present in the mixture, as all diastereomers will give rise to one set of signals (see experimental section).

Scheme 4.12 All Possible Dibenzo[8]annulene Products From α-Methyl *o*-Formylchalcone **83n**.



Inspired by the sequential Stetter reaction on the sterically hindered *o*-formylchalcone **83n**, diketone **121** was employed for the SAA reaction. *o*-benzoylchalcone (**121**) was expected to be poorly reactive in the SAA reaction due to the increased steric hindrance in both the Stetter and the first aldol steps. Satisfactorily, acceptor **121** was prepared and reacted with phthaldialdehyde **23a**, affording the non-dehydrated SAA adduct **122** as a single diastereomer (**Scheme 4.13**).

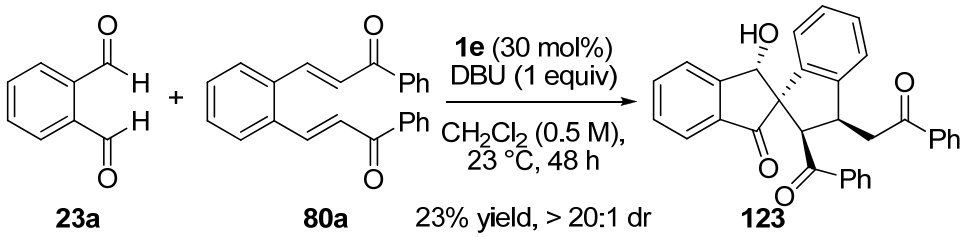
Scheme 4.13 Stetter–Aldol–Aldol Reaction Using *o*-Benzoylchalcone (**121**).



Despite the low yield, the domino SAA between **23a** and **121** is noteworthy due to the stereoselective formation of four contiguous stereogenic centres. With the aim of improving the yield, several reaction parameters were examined such as the solvent (dichloromethane, toluene, *N,N*-dimethylformamide, ethanol, and tetrahydrofuran), the precatalyst (**1e**, **16k**), portion-wise addition of precatalyst **1e**, and the temperature. However, no more than trace amounts of product were obtained in each case. Only when 50 mol% of precatalyst **1e** and 1,2-dichloroethane as solvent were used, it possible to obtain the desired product **122** in low yield (**Scheme 4.13**).

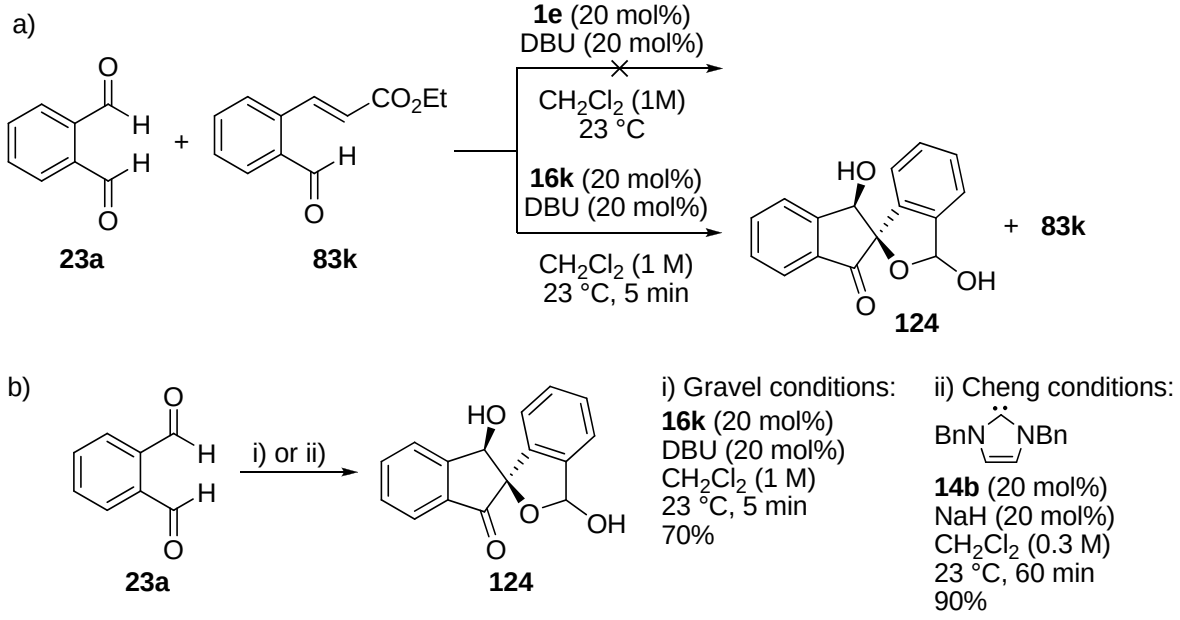
Another type of acceptor that was investigated was the double Michael acceptor **80a** which was previously employed in the synthesis of indanes discussed in Chapter 3.[49] It was hypothesized this highly electrophilic acceptor would undergo a Stetter–Michael–aldol reaction by analogy to the SAA reaction (**Scheme 4.14**). Gratifyingly, the desired product **123** was obtained in moderate yield, this result indicates the possibility of forming four contiguous stereocentres with high diastereoselectivity.

Scheme 4.14 Domino Stetter–Michael–Aldol Reaction for the Synthesis of **123**.



While studying the scope of the SAA reaction, the reactivity of ester acceptor **83k** with phthaldialdehyde **23a** was investigated. When using precatalyst **1e**, no reaction was observed. In contrast, *o*-phthaldialdehyde **23a** was completely consumed and acceptor **83k** remained intact when precatalyst **16k** was used (**Scheme 4.15a**).

Scheme 4.15 Domino Acyloin–Aldol–Aldol Reaction for the Synthesis of Lactol **124**.

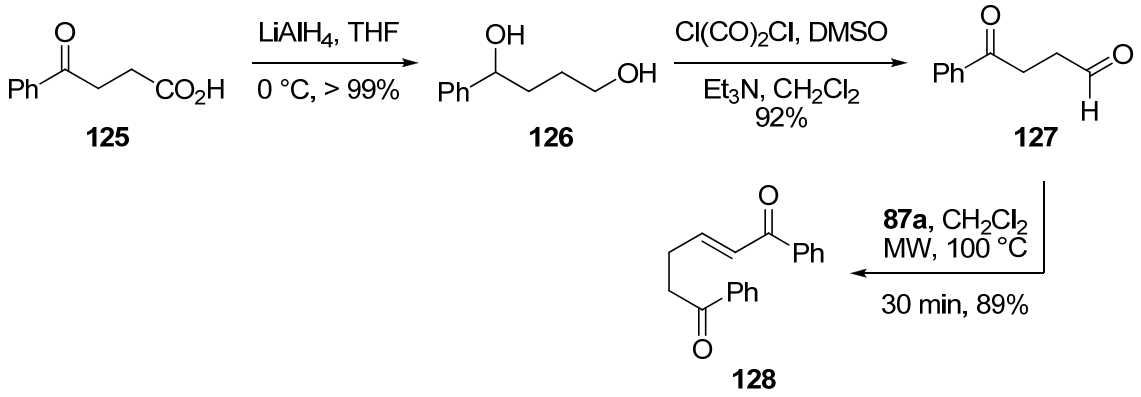


Therefore, the reaction was performed with dialdehyde **23a** alone and precatalyst **16k** furnishing the same unidentified dimeric product that was obtained in the previous transformation (**Scheme 4.15b**). Coincidentally, early in 2011 Cheng and coworkers reported the dimerization of phthaldialdehydes catalyzed by *N*,*N*'-dibenzylimidazolylidene (**14b**).[71] In this report, Cheng performed the dimerization of **23a** to give lactol **124** identifying the product by X-ray crystallography. After straight comparison of their spectroscopic data for **124** with the experiment performed employing precatalyst **16k**, the product resulted to have the same identity.

4.2.4 Synthesis of Starting Materials and Study of Aliphatic Substrates

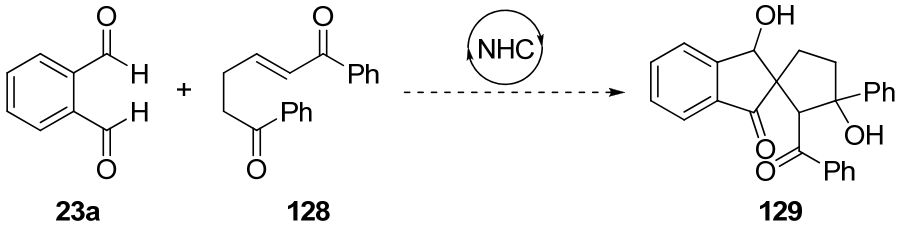
In hopes of expanding the scope of this methodology with aliphatic Michael acceptors to similar type of domino transformations, (*E*)-1,6-diphenylhex-2-ene-1,6-dione (**128**) was prepared through a short synthetic sequence (**Scheme 4.16**). Diol **126** was furnished via reduction of both carbonyl groups employing lithium aluminum hydride. Subsequent oxidation of the diol under Swern conditions produced γ-ketoaldehyde **127**, which was further reacted with ylide **87a** to give the desired 1,6-dione in 82% yield over three steps.

Scheme 4.16 Synthesis of Aliphatic Michael Acceptor **128**.



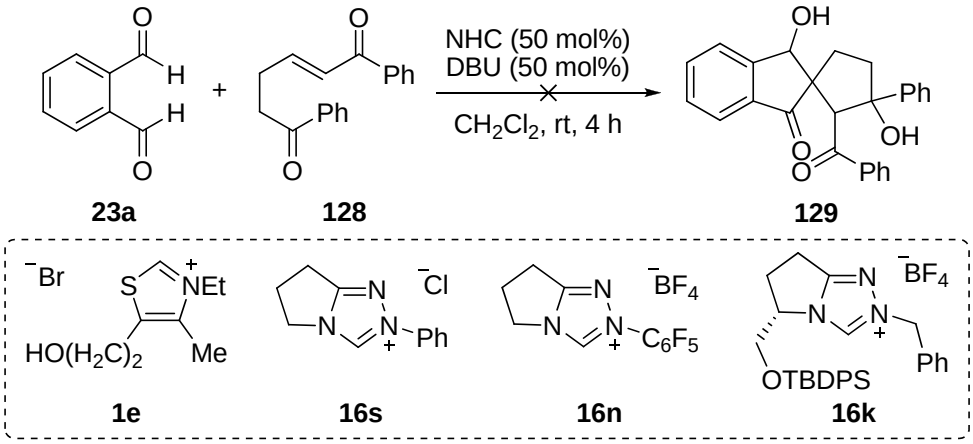
With the Michael acceptor **128** in hand, it was proposed to employ the highly reactive dialdehyde **23a** and the newly prepared acceptor **128** to produce the domino SAA product **129** (**Scheme 4.17**).

Scheme 4.17 Proposed Domino Stetter–Aldol–Aldol on Aliphatic Acceptor **128**.



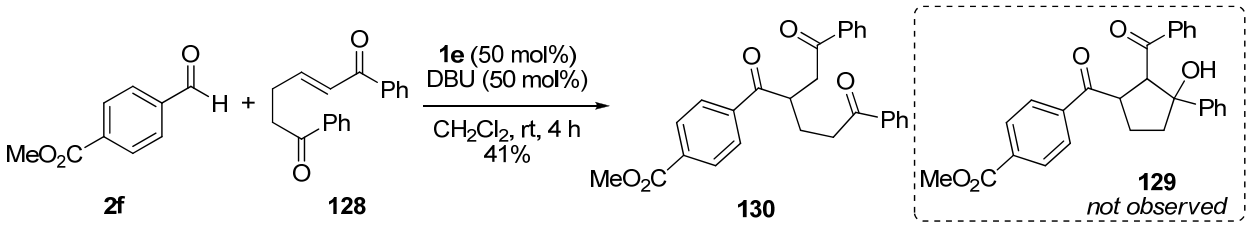
Various azolium salts were studied under the described reactions conditions (**Scheme 4.18**). Unfortunately, none of the catalysts employed gave the desired product, as only starting materials were recovered except for precatalyst **16k** that furnished lactol **124** (**Scheme 4.15**)

Scheme 4.18 Screening of Various NHC Precatalysts for the Domino SAA Reaction.



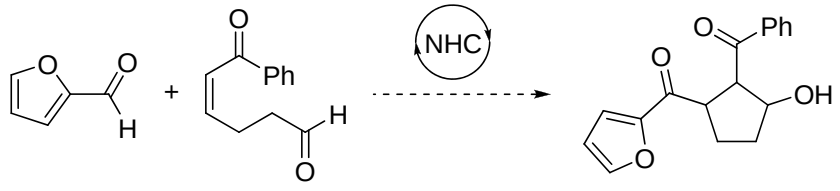
As an alternative to the use of dialdehyde **23a**, aldehyde **2f** was employed as it has proven an excellent aldehyde for the domino Stetter–Michael reaction (**Scheme 4.19**). Although **2f** underwent the Stetter reaction with **128**, the expected spiro five-membered ring product was not obtained. Attempts using excess base or heating were unsuccessful at synthesizing **130**.

Scheme 4.19 Attempts at the Synthesis of Trisubstituted Cyclopentanol **130** via a Domino Stetter–Aldol Reaction.



As a result of the failed attempts employing acceptor **128** in the domino SAA and Stetter–aldol reactions, the use of structurally different acceptors that would facilitate the cyclization step in the domino Stetter–aldol reaction was proposed (**Scheme 4.20**).

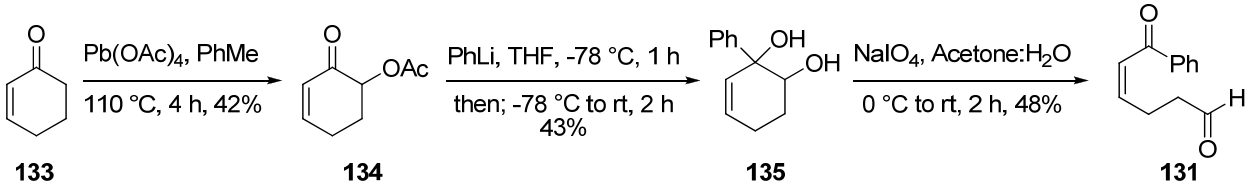
Scheme 4.20 Proposed Domino Stetter–Aldol Reaction on ε-Keto-γ,δ-Unsaturated Aldehyde **131**.



2b **131** **132**

(*Z*)-6-oxo-6-phenylhex-4-enal (**131**) was prepared via a three step sequence in moderate yield (**Scheme 4.21**).

Scheme 4.21 Synthesis of Acceptor (*Z*)-6-oxo-6-phenylhex-4-enal (**131**).

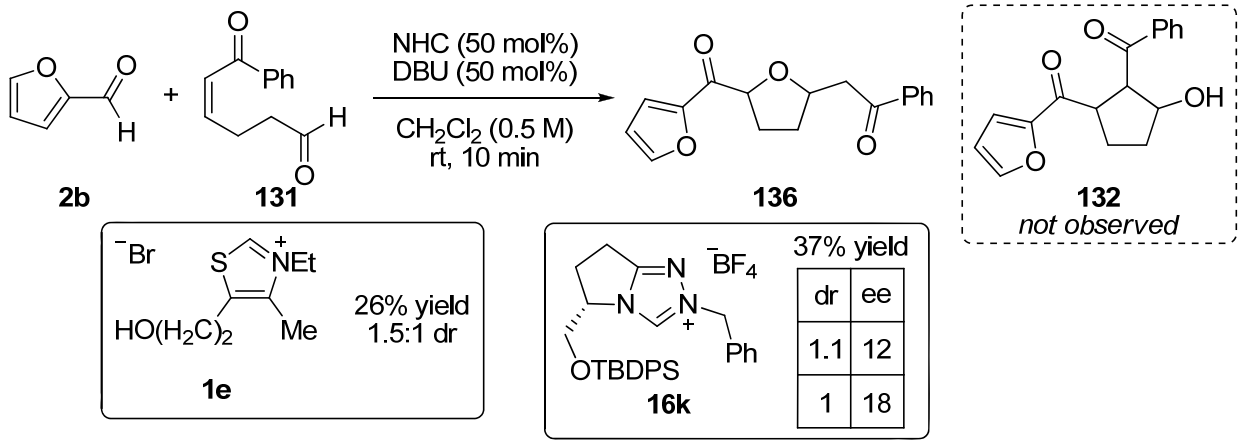


133 **134** **135** **131**

Acceptor **131** was reacted with furfural (**2b**) under standard reaction conditions, resulting in a very rapid consumption of the (*Z*)-6-oxo-6-phenylhex-4-enal (**131**) (10 min). Unexpectedly, analysis of the crude sample by ^{1}H NMR revealed that the expected 2,3-disubstituted cyclohexanol **132** was not produced. Instead, product **136** was cleanly furnished presumably via a domino cross-benzoin–oxa-Michael reaction (**Scheme 4.22**).

The reaction was later repeated using triazolium salt **16k** under similar conditions; however, the product **136** was obtained in similar low yield and poor enantioselectivity. This successful synthesis of 2,5-disubstituted tetrahydrofuran rings represents an alternative method to access this widespread motifs present in molecules with biological and medicinal properties.[142-146] Further investigations are currently being performed in the Gravel laboratory to optimize this transformation.

Scheme 4.22 Domino Cross-Benzoin–Oxa-Michael Reaction.

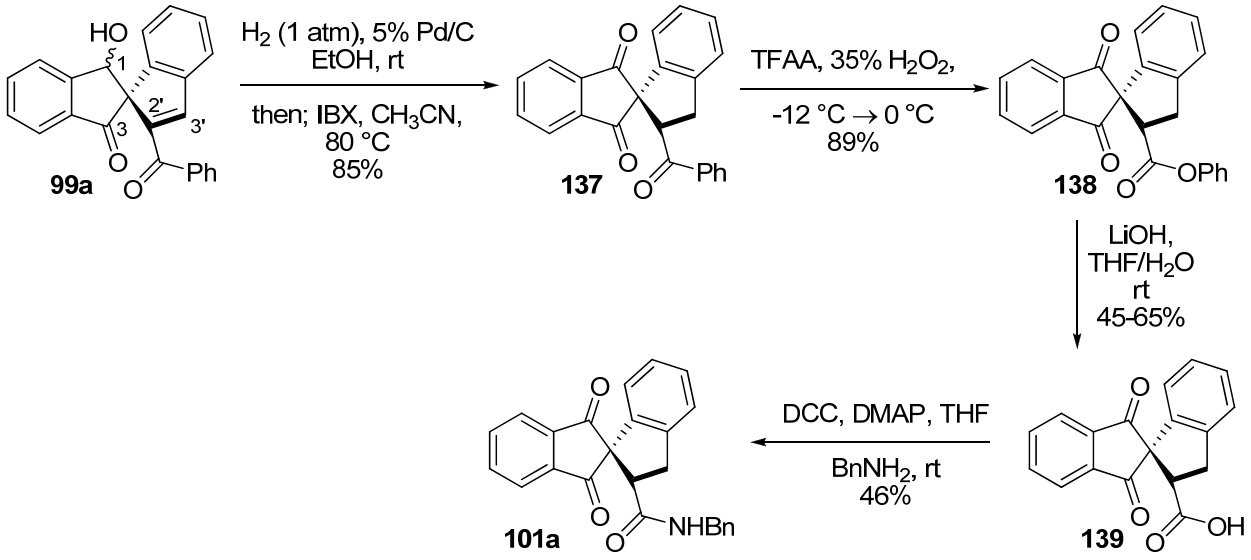


4.2.5 Synthetic Studies

At the outset of this research project, the aim was to develop a synthetic strategy that would allow the preparation of the core structure of fredericamycin A and analogs. Gratifyingly, the SAA methodology gave access to the spiro bis-indane skeleton present in the natural product. As a result, the manipulation of some functional groups on compound **99a** allowed the synthesis of product **101** (**Figure 4.2**). As depicted in **Scheme 4.23**, alcohol **99a** was cleanly transformed into the triketone **137** in high yield through a reduction-oxidation sequence. Satisfyingly, **137** underwent a completely site-selective and regioselective Baeyer-Villiger oxidation using

Emmons' protocol.[96, 147, 148] Hydrolysis of the resulting ester **138** gave the corresponding carboxylic acid **139** which was converted into *N*-benzylamide **101a** via standard amidation conditions. Through this short synthetic sequence, it was possible to prepare a derivative of the core of fredericamycin A at the C-2' position.

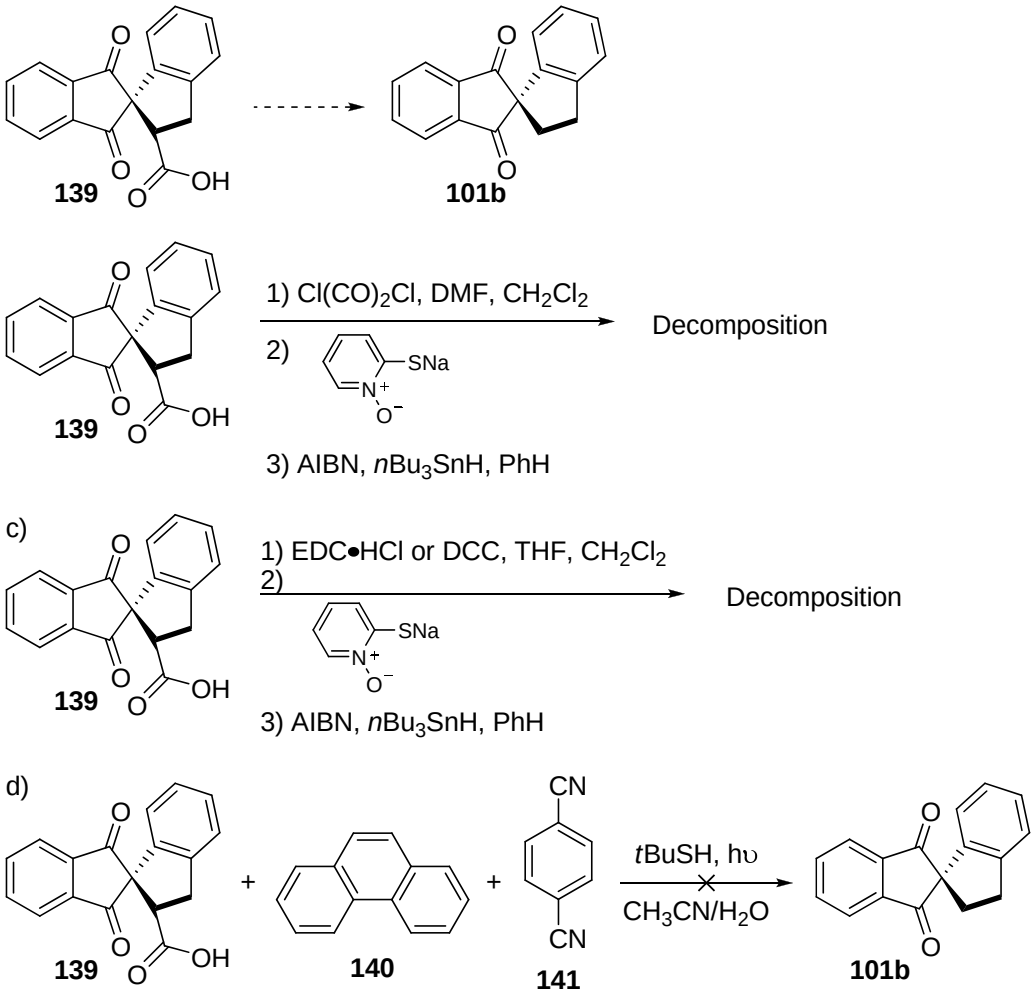
Scheme 4.23 Derivatization of Alcohol **99a** to the *N*-benzylamide derivative **101a**.



The remaining task to conclude the synthesis of the core of fredericamycin A was the removal of the carboxylic acid from **139** to produce **101b** (**Scheme 4.24a**). However, such transformation was not simple to perform. The first attempt consisted of employing the traditional Barton decarboxylation conditions by initial generation of the acid chloride followed by a radical-initiated chlorodecarboxylation.[149-151] However, starting material **139** decomposed into multiple unidentified products (**Scheme 4.24b**). Other methods employing EDC·HCl or DCC to form Barton's thioester were unsuccessful and decomposition of the starting material was observed (**Scheme 4.24c**). Recently, Hatanaka and coworkers disclosed an alternative

method for the decarboxylation of aliphatic carboxylic acids via a photogenerated cation radical of phenathrene (**140**).[152] Unfortunately, this method did not afford the desired product, but instead resulted in the quantitative recovery of the starting material (**Scheme 4.24d**).

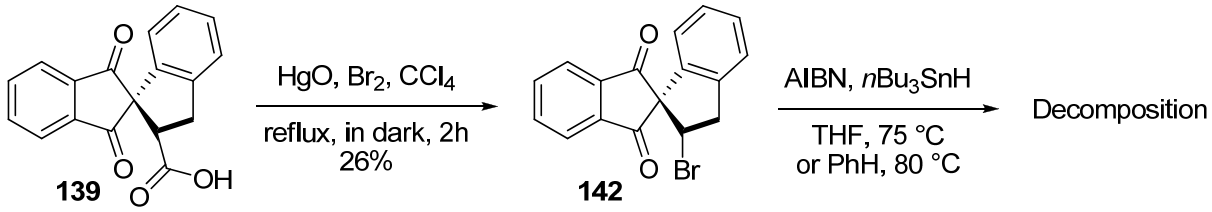
Scheme 4.24 Attempts at Decarboxylation of Substrate **139** under Barton Conditions.



Given the unsuccessful results for the decarboxylation of **139**, an alternative approach to access **101b** was taken. It was proposed to perform the Hunsdiecker reaction, which is a halogenative decarboxylation of aliphatic, α,β-unsaturated, and aromatic carboxylic acids.[153] The

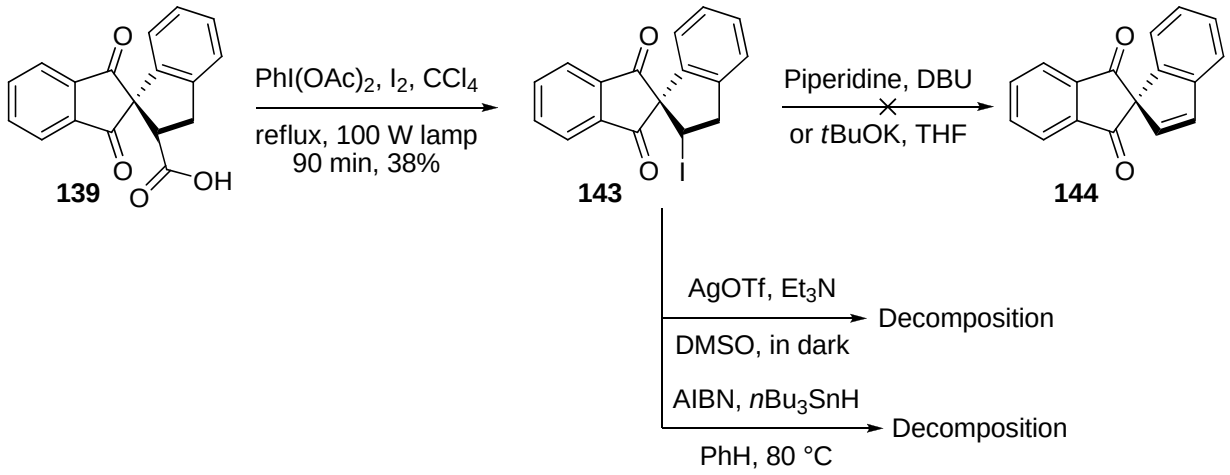
original method developed by Hunsdiecker requires the use of pure and dry silver salts, which are hard to obtain. In this case, the Cristol-Firth modification that uses red HgO was employed.[154, 155] Gratifyingly, the carboxylic acid group on **139** was successfully replaced by a bromine atom on **142**, although in modest yield (**Scheme 4.25**). Further attempts to reduce the C-2' position were unsuccessful and uniformly resulted in the decomposition of **142**.

Scheme 4.25 Halo-decarboxylation of Substrate **139**.



The Hunsdiecker-Suarez modification is an alternative method for replacing the carboxylic acid with iodine.[156] Similarly to the Cristol-Firth modification, the product **143** was prepared successfully although the yield of the transformation did not improve significantly (**Scheme 4.26**). Once the iodine was installed at the C-2' position, the formation of the olefin through the corresponding elimination of the iodine substituent followed by reduction to obtain **101b** was envisioned. Various bases such as piperidine, DBU, and potassium *tert*-butoxide were studied; however, the elimination of the halogen could not be accomplished under the studied reaction conditions (**Scheme 4.26**). The use of silver trifluoromethansulfonate to facilitate the elimination step proved unsuccessful, as the starting material turned into an insoluble black viscous semi-solid suggesting decomposition of **143**. Finally, the radical dehalogenation on C-2' with AIBN and tributyltin hydride failed and led to decomposition of the starting material (**Scheme 4.26**).

Scheme 4.26 Suarez Modification for Halogenative Decarboxylation of **139**.



Further investigations on the decarboxylation of **139** would be required in order to achieve a synthesis of the core of fredericamycin A (**96**).

4.3 CONCLUSIONS

In summary, a new series of NHC-catalyzed domino Stetter–aldol–Michael (SAM) and Stetter–aldol–aldol (SAA) reactions has been developed, featuring the formation of two rings, three new carbon–carbon bonds, and a quaternary centre.

Various Michael acceptors were surveyed for the SAM and SAA reactions. From these transformations, thioesters and ketones were shown to lead to the desired spiro bis-indane products in contrast to esters, sulfones, and nitriles. Under the appropriate conditions these latter acceptors, phthaldialdehyde (**23a**), and the α-methyl substituted *o*-formylchalcone **83n** led to dibenzo[8]annulene products **118** via a double Stetter sequence.

Additionally, the reaction with other diketone acceptors such as **121** and **80a** with phthaldialdehyde (**23a**) proceeded with high diastereocontrol producing spiro bis-indanes **122** and **123**. These products feature the formation of four contiguous stereocentres and were

obtained as single diastereomers via domino Stetter–aldol–aldol and Stetter–aldol–Michael reactions, respectively.

Aliphatic acceptors **128** and **131** were studied as well. Although, acceptor **128** was unreactive with phthaldialdehyde (**23a**), the use of methyl 4-formylbenzaldehyde (**2f**) gave the conjugate addition product without concomitant cyclization. At the beginning of this investigation, it was proposed to extend our protocol on the diastereoselective synthesis of indanes[49] to the synthesis of benzo[*b*]furans and isoindolines (**Scheme 4.2**). Although this was not possible when furfural (**2b)** and *o*-formylchalcone **83a** were employed, the use of the aliphatic acceptor (*Z*)-6-oxo-6-phenylhex-4-enal (**131**) furnished the 2,5-disubstituted tetrahydrofuran ring **136** via a cross-benzoin–oxa-Michael reaction. The discovery of this transformation opened an additional opportunity for the research group to contribute to domino reactions incorporating acyl anion equivalents using NHCs.

Finally, the domino Stetter–aldol–aldol methodology was applied to the synthesis of a simplified *N*-benzylamide analog of fredericamycin A. Despite the decarboxylation of **139** proved challenging as Barton and Hatanaka's conditions were unsuccessful, the use of Cristol-Firth-Hunsdiecker conditions and the Suarez modification for the halogenative decarboxylation successfully produced the desired C-2' halo-substituted products in modest yield.

CHAPTER 5: EXPERIMENTAL SECTION

5.1 GENERAL METHODS

Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 and was visualized with UV light and 5% phosphomolybdic acid (PMA). Silica gel SI 60 (40-63 μm) used for column chromatography was purchased from Silicycle Chemical Division. NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^1H and 125 MHz for ^{13}C. The residual solvent protons (^1H) ($CDCl_3$ 7.26 δH, D_2O 4.80 δH) or the solvent carbons (^{13}C) ($CDCl_3$ 77.23 δC) were used as internal standards for chemical shifts. High-resolution mass spectrometry (HRMS) was performed on a double focusing high-resolution spectrometer. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. All samples were prepared as a film on a KBr disc or pellet using KBr (IR grade) for IR analysis. Melting points were measured in a Terochem Scientific electrothermal digital melting point apparatus and are uncorrected. Anhydrous solvents were obtained using a Braun Solvent Purification System and stored under nitrogen over pre-dried 3 Å molecular sieves. Molecular sieves were dried by heating in a heating mantle at 300 °C (temperature measured with a thermocouple) under high vacuum (0.5 mmHg) for 24 hours.

Highly Enantioselective Intermolecular Stetter Reaction of γ-Aryl-β,γ-Unsaturated-α-Ketoesters

Unless otherwise noted, commercially available aldehydes were used without further purification. Aldehydes **2b**, **2a**, **2h**, and **2o** were purified by bulb-to-bulb distillation prior to use. All reactions were carried out under inert atmosphere employing a Schlenk tube for small scale

reactions and regular round bottom flask for large scale reactions. Pyrazine-2-carbaldehyde (**2p**) was prepared following the literature procedure.[157] Triazolium salts **16j**, **16l**, **16q**, and **16l** were prepared according to the reported procedure.[41, 158] The enantiomeric excess of enantiomerically enriched products was determined using an Agilent Technologies 1200 Series HPLC. CHIRALPAK® IA, IB, IC, and CHIRALCEL® AS-H columns were purchased from Daicel Chemical Industries, Ltd.

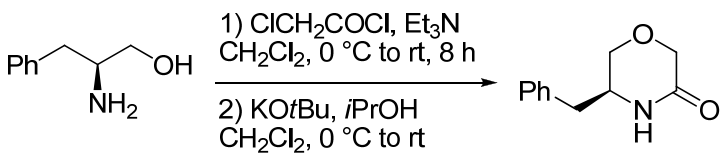
Diastereoselective Synthesis of Indanes via a Domino Stetter-Michael Reaction and Synthesis of Spiro Bis-Indanes via Domino Stetter–Aldol–Michael and Stetter–Aldol–Aldol.

Unless otherwise noted, commercially available aldehydes were used without further purification. Benzaldehyde (**2a**), 4-methylbenzaldehyde (**2x**), *p*-anisaldehyde (**2y**), and propanal (**2aa**) were purified by bulb-to-bulb distillation prior to use. All reactions were carried out under an inert atmosphere. Unless otherwise noted, all the phosphorus ylides were prepared according to procedures reported in the literature.[48, 159-162] ORTEP representations were generated using CYLview v1.0.301 BETA.

5.2 General Procedures for the Highly Enantioselective Intermolecular Stetter Reaction of γ-Aryl-β,γ-Unsaturated-α-Ketoesters

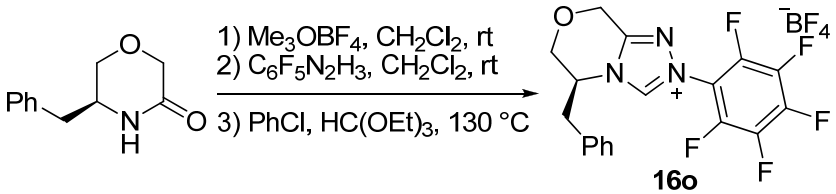
Preparation of precatalysts 16o and 16p

(*R*)-6-benzylpiperidin-2-one



In a 100 mL flame – dried round bottom flask was stirred a solution of (*S*)-2-amino-3-phenylpropan-1-ol[163] (1.00 g, 6.6 mmol, 1 equiv) and triethylamine (2.0 mL, 15 mmol, 2.2 equiv) in dichloromethane (37 mL, 0.18 M) and cooled to 0 °C. Chloroacetylchloride (0.6 mL, 7.3 mmol, 1.1 equiv) was added drop-wise to the mixture (the solution turned dark orange!). The reaction mixture was warmed to ambient temperature. After stirring for 8 h, the mixture was cooled to 0 °C and a suspension of potassium *tert*-butoxide (3.1 g, 28 mmol, 4.2 equiv) in 2-propanol (18.4 mL, 0.36 M) was added drop-wise. The mixture was warmed to ambient temperature and stirred for additional 48 h. The solvent was then removed by rotary evaporation, the crude product was washed with water (20 mL) and the organic phase was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with brine (1 x 20 mL) and dried through a column of anhydrous sodium sulfate. The solvent was evaporated and the crude product was purified by a gradient flash column chromatography (50% ethyl acetate in hexanes → 80% ethyl acetate in hexanes → 100% ethyl acetate) to afford the title compound in 37% yield (470 mg) as a light yellow oil which forms a white solid upon standing; R_f = 0.1 (50% ethyl acetate in hexanes); **mp** (°C): 93-94; $[\alpha]_D^{25}$ -85 (*c* = 1.14, $CHCl_3$); **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3212, 2920, 1676, 1454, 1349, 1123, 702; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.6, 7.1 Hz, 2H), 7.28 (dd, *J* = 7.3, 7.2 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 6.28 (brs, 1H), 4.18 (d, *J* = 16.7 Hz, 1H), 4.13 (d, *J* = 16.7 Hz, 1H), 3.90 (dd, *J* = 11.7, 3.7 Hz, 1H), 3.76 (dddd, *J* = 11.9, 8.3, 3.8, 1.7 Hz, 1H), 3.56 (dd, *J* = 11.7, 6.6 Hz, 1H), 2.88 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.73 (dd, *J* = 13.5, 8.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.1, 136.2, 129.3, 129.1, 127.3, 68.0, 67.6, 52.9, 39.5; **HRMS** (EI^+) *m/z* calcd for $C_{11}H_{13}NO_2$ $[M]^+$: 191.0946; found: 191.0945.

(*S*)-5-benzyl-2-(perfluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (16o)

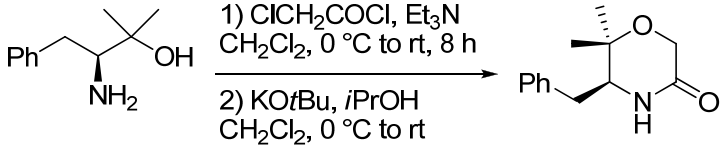


16o

In a 100 mL flame-dried round bottom flask was stirred a solution of (*S*)-5-benzylmorpholin-3-one (452 mg, 2.4 mmol, 1 equiv) in dichloromethane (12 mL, 0.2 M) under inert atmosphere. Trimethyloxonium tetrafluoroborate (349 mg, 2.4 mmol, 1 equiv) was added in one portion and the mixture was stirred for 5 h (until the solution turned clear and homogeneous). Then, pentafluorophenyl hydrazine (468 mg, 2.4 mmol, 1 equiv) was added to the previous mixture and stirred for 18 h at ambient temperature. Immediately after, the solvent was removed by rotary evaporation and the trace of solvent was removed under high vacuum for 1 h. Chlorobenzene (12 mL, 0.2 M) and triethylorthoformate (3.5 mL, 21.3 mmol, 9 equiv) were added to the flask and the mixture was stirred and heated to 130 °C for 24 h open to the atmosphere. After 24 h, an additional portion of triethylorthoformate (3.5 mL, 21.3 mmol, 9 equiv) was added to the mixture and refluxed for another 24 h (48 h total). The flask was cooled to room temperature and the solvent was removed under rotary evaporation. The flask was placed under high vacuum for 1 h and the crude product was purified by flash column chromatography (50% ethyl acetate in hexanes → 100% ethyl acetate) to afford the title compound in 30% yield (329 mg) as light yellow crystals; R_f = 0.5 (100% ethyl acetate); **mp** (°C): 168-170; $[\alpha]_D^{21}$ -32 (*c* = 0.58, acetone); **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3153, 1595, 1527, 1078, 848, 702; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.1 (s, 1H), 7.38 – 7.27 (m, 5H), 5.35 (d, *J* = 16.5 Hz, 1H), 5.21 (d, *J* = 16.5 Hz, 1H), 5.19 (m, 1H), 4.22 (d, *J* = 3.5 Hz, 2H), 3.58 (dd, *J* =

13.6, 7.1 Hz, 1H), 3.41 (dd, J = 13.6, 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.3, 152.6, 146.5, 136.1, 130.6, 130.0, 128.6, 66.4, 62.8, 59.3, 38.9 (three C signals are missing which correspond to the aromatic C-F); **HRMS** (ESI^+) m/z calcd for $C_{18}H_{13}F_5N_3O$ $[M]^+$: 382.0973; found: 382.0967.

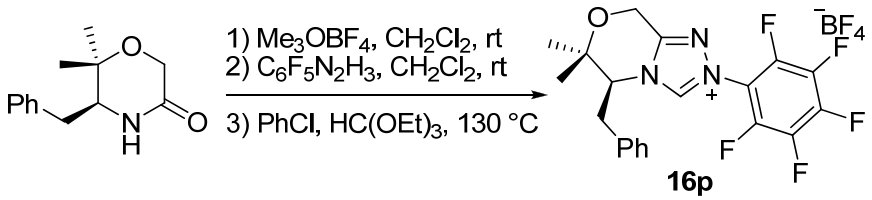
(*S*)-6-benzyl-5,5-dimethylpiperidin-2-one



In a 100 mL flame-dried round bottom flask was stirred a solution of (*S*)-3-amino-2-methyl-4-phenylbutan-2-ol[164] (1.11 g, 6.2 mmol, 1 equiv) and triethylamine (2 mL, 13.6 mmol, 2.2 equiv) in dichloromethane (34 mL, 0.18 M) and cooled to 0 °C. Chloroacetylchloride (0.5 mL, 6.8 mmol, 1.1 equiv) was then added drop-wise to the mixture (the solution turned dark purple!). The reaction mixture was warmed to ambient temperature. After stirring for 8 h, the mixture was cooled to 0 °C and a suspension of potassium *tert*-butoxide (2.9 g, 26 mmol, 4.2 equiv) in 2-propanol (17 mL, 0.36 M) was added drop-wise. The mixture was warmed to ambient temperature and stirred for additional 48 h. The solvent was removed by rotary evaporation, the crude product was washed with water (20 mL) and the organic phase was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with brine (1 x 20 mL) and dried through a column with anhydrous sodium sulfate. The solvent was evaporated and the crude product was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford the title compound in 52% yield (714 mg) as light yellow crystals; R_f = 0.18 (50% ethyl acetate in hexanes); **mp** (°C): 82-84; $[\alpha]_D^{24}$ -118 (c = 1.44, $CHCl_3$); **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3211, 2977, 1679, 1335, 1102, 847, 735, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (dd, J =

7.6, 7.2 Hz, 2H), 7.28 (dd, *J* = 7.5, 7.4 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 5.59 (brs, 1H), 4.17 (d, *J* = 17.4 Hz, 1H), 4.13 (d, *J* = 17.4 Hz, 1H), 3.57 (dd, *J* = 11.7, 2.3 Hz, 1H), 2.95 (dd, *J* = 13.5, 2.8 Hz, 1H), 2.40 (dd, *J* = 13.4, 11.8 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.9, 136.1, 129.4, 129.3, 127.5, 72.8, 63.1, 60.7, 37.7, 25.7, 19.1; **HRMS** (EI^+) *m/z* calcd for $C_{13}H_{17}NO_2$ $[M]^+$: 219.1259; found: 219.1259.

(*S*)-5-benzyl-6,6-dimethyl-2-(perfluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[3,4c][1,4] oxazin-2-ium tetrafluoroborate (16p)



16p

In a 100 mL flame-dried round bottom flask was stirred a solution of (*S*)-6-benzyl-5,5-dimethylpiperidin-2-one (500 mg, 2.3 mmol, 1 equiv) in dichloromethane (11 mL, 0.2 M) under inert atmosphere. Trimethyloxonium tetrafluoroborate (337 mg, 2.3 mmol, 1 equiv) was added in one portion and the mixture was stirred for 5h (until the solution turned clear and homogeneous). Then, pentafluorophenyl hydrazine (452 mg, 2.3 mmol, 1 equiv) was added to the previous mixture and stirred for 18 h at ambient temperature. Immediately after, the solvent removed by rotary evaporation and the trace of solvent was removed under high vacuum for 1 h. Chlorobenzene (11 mL, 0.2 M) and triethylorthoformate (3.5 mL, 20.5 mmol, 9 equiv) were added to the flask and the mixture was stirred and heated to 130 °C for 24 h at open atmosphere. After 24 h, an additional portion of triethylorthoformate (3.5 mL, 20.5 mmol, 9 equiv) was added to the mixture and refluxed for 24 h (48 h total). The flask was cooled to room temperature and the solvent was removed under rotary evaporation. The flask was placed under high vacuum for

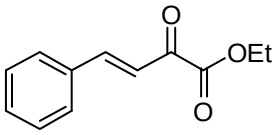
1 h and the crude product was purified by flash column chromatography (20% ethyl acetate in dichloromethane) to afford the title compound in 64% yield (731 mg) as a tan solid; R_f = 0.15 (20% ethyl acetate in dichloromethane); **mp** (°C): 76-78; $[\alpha]_D^{23}$ -59 (*c* = 1.05, acetone); **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3394, 2988, 1590, 1530, 1075, 849; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.38 – 7.33 (m, 3H), 7.12 – 7.70 (m, 2H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 5.01 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.49 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.97 (dd, *J* = 13.9, 11.1 Hz, 1H), 1.59 (s, 3H), 1.46 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.6, 145.9, 134.2, 130.0, 129.6, 128.7, 74.2, 65.1, 56.8, 36.9, 24.8, 22.6 (four C signals are missing which correspond to the pentafluorophenyl group); **HRMS** (ESI^+) *m*/*z* calcd for $C_{20}H_{17}N_3OF_5$ $[M]^+$: 410.1286; found: 410.1278.

General Procedure for the Preparation of Starting Materials (9a–e, p)

In a 100 mL round bottom flask was stirred a mixture of sodium pyruvate (1.05 equiv) and the appropriate aldehyde (1 equiv) in 50% methanol : water (1.5 M). The mixture was cooled to 0 °C with an ice-water bath for 10 min, then a freshly prepared solution of potassium hydroxide (1.5 equiv, 4.4 M) in 50% methanol : water was added to the mixture drop-wise. During the addition the solution turns a clear yellow and eventually precipitates to form thick yellow slurry. After the complete addition of the base, the reaction was allowed to warm to ambient temperature and stirred for 3 – 5 h. The reaction was quenched with 4M HCl until pH 2 and extracted with ethyl acetate (3 x 40 mL). The organic phase was dried through a column with anhydrous sodium sulfate and the solvent was removed by rotary evaporation. The residual oil was re-dissolved in ethanol (0.2 M, with respect to the aldehyde) and toluene (0.3 M, with respect to the aldehyde), then concentrated hydrochloric acid (0.8 equiv, 12.1 M) was added. The

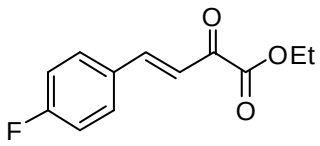
mixture was heated to 95 °C for 4 h, then cooled to ambient temperature and the solvent was removed in vacuo. The residual oil was purified by flash column chromatography to give a bright yellow product.

(*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (9a)



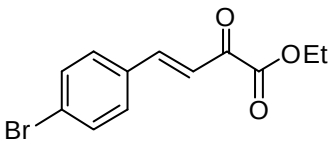
29.5 mmol scale, yellow oil, 44% yield (2.7 g); R_f = 0.28 (10% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 16.1 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.46 – 7.39 (m, 3H), 7.35 (d, *J* = 16.1 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). Spectral data matched those previously reported.[73]

(*E*)-ethyl 4-(4-fluorophenyl)-2-oxobut-3-enoate (9b)



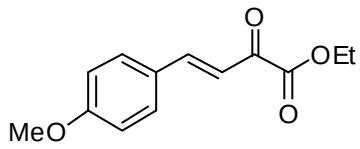
18.6 mmol scale, yellow solid, 44% yield (3.2 g); **mp** (°C): 66-68; R_f = 0.28 (10% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 16.1 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 16.1 Hz, 1H), 7.11 (t, *J* = 8.5 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). Spectral data matched those previously reported.[165]

(*E*)-ethyl 4-(4-fluorophenyl)-2-oxobut-3-enoate (9c)



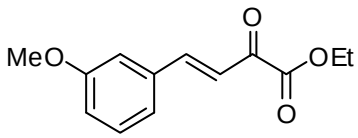
23 mmol scale, yellow solid, 75% yield (4.8 g); **mp** (°C): 66-68; R_f = 0.25 (15% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.1 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 16.1 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). Spectral data matched those previously reported.[73]

(*E*)-ethyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate (9d)



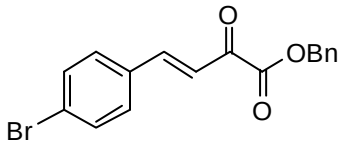
16.4 mmol scale, yellow solid, 91% yield (3.5 g); **mp** (°C): 51-52; R_f = 0.25 (20% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 16.0 Hz, 1 H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 16.0 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H). Spectral data matched those previously reported.[73]

(*E*)-ethyl 4-(3-methoxyphenyl)-2-oxobut-3-enoate (9e)



16.4 mmol scale, yellow oil, 55% yield (2.1 g); R_f = 0.30 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2982, 2837, 1729, 1693, 1607, 1239, 1078, 774; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 16.1 Hz, 1H), 7.32 (d, *J* = 16.1 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.12 (brs, 1H), 6.99 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 183.0, 162.4, 160.2, 148.5, 135.5, 130.2, 122.0, 121.0, 117.8, 113.7, 62.6, 55.5, 14.2; **HRMS** (EI^+) *m/z* calcd for $C_{18}H_{18}O_6$ $[M]^+$: 234.0892; found: 234.0891.

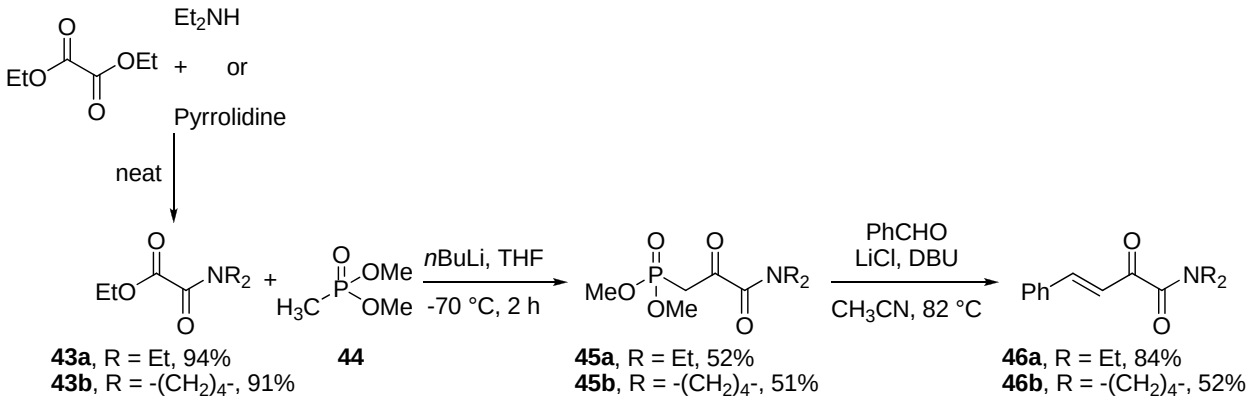
(*E*)-benzyl 4-(4-bromophenyl)-2-oxobut-3-enoate (9p)



The reaction between 4-bromobenzaldehyde (2g, 10.8 mmol, 1 equiv) and sodium pyruvate (1.2 g, 10.9 mmol, 1.01 equiv) was performed following the general procedure. The corresponding benzyl ester was prepared by stirring a solution of the carboxylic acid (10.9 mmol, 1 equiv considering complete conversion), *N,N'*-dicyclohexylcarbodiimide (2.5 g, 11.9 mmol, 1.1 equiv) and *N,N*-dimethylaminopyridine (660 mg, 5.4 mmol, 0.5 equiv) in dry THF (16 mL, 0.7 M).

After stirring for 10 min at ambient temperature, benzyl alcohol (1 mL, 10.9 mmol, 1.01 equiv) was added in one portion. The reaction was allowed to stir for 14 h, and the resulting mixture was filtered though a short column with silica gel and eluted with 20% ethyl acetate in hexanes. After filtration and concentration, the desired product formed an amorphous solid which was recrystallized from dichloromethane in hexanes to afford light yellow crystals in 42% yield (1.56 g); R_f = 0.45 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 1729, 1695, 1607, 1585, 1489, 1263, 1093, 1069, 751; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 16.1 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.46 – 7.43 (m, 4H), 7.42 – 7.35 (m, 3H), 7.32 (d, *J* = 16.1 Hz, 1H), 5.36 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 182.5, 162.1, 147.3, 134.8, 133.1, 132.6, 130.5, 129.0, 128.9 (2X), 126.4, 121.3, 68.3; **HRMS** (CI^+) *m/z* calcd for $C_{17}H_{13}BrO_3$ [M+1, NH_3]$^+$: 362.0391; found: 362.0386.

Procedure for the Preparation of α-Ketoamides (46a, 46b)



Ethyl 2-(diethylamino)-2-oxoacetate (43a)

In a 25 mL round bottom flask was stirred neat diethyl oxalate (3 mL, 22.1 mmol, 1 equiv) to which *N,N*-diethylamine (4.5 mL, 44.2 mmol, 2 equiv) was added dropwise. The

mixture was heated to reflux (90 °C) and the progress was monitored by ^{1}H NMR (2.5 h). After completion, the volatiles were removed and the crude product was purified by bulb-to-bulb distillation (145 °C, 2 torr) to afford a light yellow oil in 94% yield (3.58 g). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.32 (q, *J* = 7.1 Hz, 2H), 3.41 (q, *J* = 7.1 Hz, 2H), 3.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H) Spectral data matched those previously reported.[166]

Ethyl 2-oxo-2-(pyrrolidin-1-yl)acetate (43b)

In a 25 mL round bottom flask was stirred cold (0 °C) neat diethyl oxalate (3 mL, 22.1 mmol, 1 equiv) to which pyrrolidine (1.8 mL, 22.1 mmol, 1 equiv) was added dropwise. The mixture was stirred at ambient temperature and the progress of the reaction was monitored by ^{1}H NMR (12 h). After completion, the volatiles were removed and the crude product was purified by bulb-to-bulb distillation (185 °C, 2 torr) to afford a clear colourless liquid in 91% yield (3.4 g); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2980, 2883, 1737, 1659, 1450, 1244, 1167, 1017; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.27 (q, *J* = 7.1 Hz, 2H), 3.57 (dd, *J* = 6.8, 6.5 Hz, 2H), 3.48 (dd, *J* = 7.0, 6.8 Hz, 2H), 1.94 – 1.83 (m, 4H), 1.32 (t, *J* = 7.1, 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.4, 158.8, 62.1, 47.5, 46.1, 26.1, 24.0, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_8H_{13}NO_3$ $[M]^+$: 171.0895; found: 171.0889.

Dimethyl 3-(diethylamino)-2,3-dioxopropylphosphonate (45a)

In a 100 mL flame-dried round bottom flask was stirred a solution of *n*-butyllithium (5 mL, 10 mmol, 1 equiv, 2.12 M) in dry tetrahydrofuran (30 mL) at -70 °C. Then, a solution of dimethylmethylphosphite (**44**) (1.2 mL, 10 mmol, 1 equiv) in dry tetrahydrofuran (10 mL) was

added to the flask dropwise and stirred for 15 min followed by the slow addition of a solution of ethyl 2-(diethylamino)-2-oxoacetate (1.73 g, 10 mmol, 1 equiv) in dry tetrahydrofuran (10 mL) [This last solution was added at such a rate that the internal temperature would not go above -70 °C]. The reaction was stirred for 1 h at the same temperature and quenched with 4M hydrochloric acid until pH ca. 1. Diethyl ether (10 mL) was added and the organic layer was extracted. The aqueous layer was extracted with dichloromethane (3 x 15 mL) and all the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (50% diethyl ether in dichloromethane) to afford the title product in 52% yield (1.31 g) as light yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.73 (d, *J* = 11.3 Hz, 6H), 3.6 (d, *J* = 23.3 Hz, 2H), 3.35 (q, *J* = 7.1 Hz, 2H), 3.28 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). Spectral data matched those previously reported.[167]

Dimethyl 2,3-dioxo-3-(pyrrolidin-1-yl)propylphosphonate (45b)

Phosphonate **45b** was prepared following the previously described procedure. 10 mmol scale, clear light yellow oil, 51% yield (1.26 g); R_f = 0.15 (50% diethyl ether in dichloromethane), **FTIR** (KBr film) ν_{max} (cm^{-1}): 2957, 1719, 1642, 1448, 1266, 1027, 808; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.76 (s, 3H), 3.64 (dd, *J* = 9.8, 6.6 Hz, 2H), 3.59 (d, *J* = 22.3 Hz, 2H), 3.50 (dd, *J* = 7.0, 6.7 Hz, 2H), 1.93 – 1.85 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.6 (d, *J* = 5.6 Hz), 161.7, 53.2 (d, *J* = 6.2 Hz), 47.5, 46.7, 37.3 (d, *J* = 128.7 Hz), 26.5, 23.8; **HRMS** (EI^+) *m*/*z* calcd for $C_9H_{18}NO_5P$ $[M]^+$: 249.0766; found: 249.0767.

(*E*)-*N*,*N*-diethyl-2-oxo-4-phenylbut-3-enamide (46a)

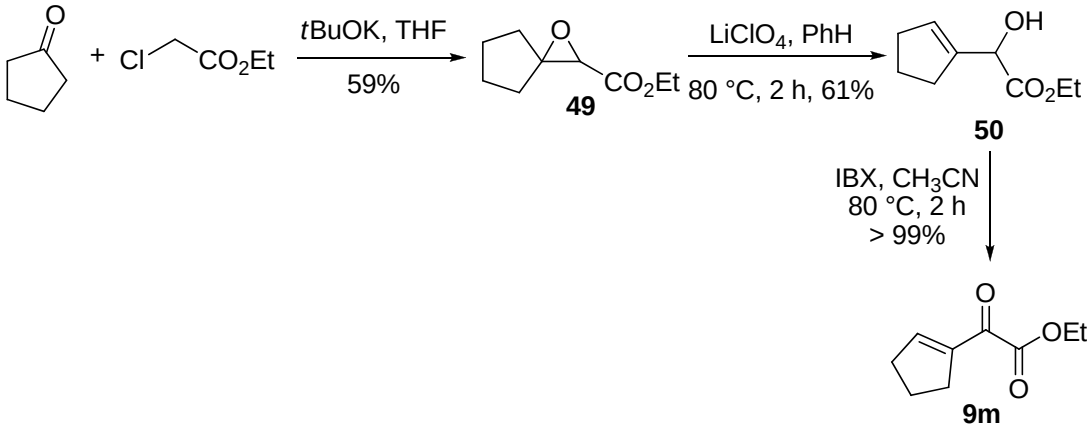
In a 100 mL flame-dried round bottom flask was stirred a suspension of dry lithium chloride (125 mg, 3 mmol, 1.5 equiv) in dry acetonitrile (16 mL). Separately, it was prepared a solution of diethyl 3-(diethylamino)-2,3-dioxopropylphosphonate (**45a**) (889 mg, 3.5 mmol, 1.8 equiv) in acetonitrile (3.5 mL + 0.5 mL for rinsing the vial) which was added to the flask in one portion. DBU (0.35 mL, 2.4 mmol, 1.2 equiv) was added followed by freshly distilled benzaldehyde (0.2 mL, 2 mmol, 1 equiv). The reaction was stirred and heated to 82 °C for 29 h. The reaction was cooled to room temperature and quenched with saturated aqueous ammonium chloride (10 mL). The solvent was removed by rotary evaporation and the remaining crude was extracted with dichloromethane (3 x 20 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford the title compound in 84% yield (382 mg) as a yellow oil; R_f = 0.3 (30% diethyl ether in dichloromethane), **FTIR** (KBr film) ν_{max} (cm^{-1}): 2977, 2937, 1639, 1557, 1449, 1201, 1120, 1073, 977, 688; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 16.4 Hz, 1H), 7.57 – 7.55 (m, 2H), 7.43 – 7.38 (m, 3H), 6.88 (d, *J* = 16.4 Hz, 1H), 3.51 (q, *J* = 7.2 Hz, 2H), 3.31 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.4, 166.8, 148.2, 134.1, 131.5, 129.2, 128.9, 123.8, 42.4, 39.3, 14.5, 12.9; **HRMS** (EI^+) *m*/*z* calcd for $C_{14}H_{17}NO_2$ $[M]^+$: 231.1259; found: 231.1257.

(*E*)-4-phenyl-1-(pyrrolidin-1-yl)but-3-ene-1,2-dione (46b)

In a 50 mL flame-dried round bottom flask was stirred a suspension of dry lithium chloride (70 mg, 1.7 mmol, 1.5 equiv) in dry acetonitrile (9 mL). Separately, it was prepared a

solution of diethyl 2,3-dioxo-3-(pyrrolidin-1-yl)propylphosphonate (**45b**) (494 mg, 2 mmol, 1.8 equiv) in acetonitrile (1.5 mL + 0.5 mL for rinsing the vial) which was added to the flask in one portion. DBU (0.2 mL, 1.3 mmol, 1.2 equiv) was added followed by freshly distilled benzaldehyde (110 μL, 1.1 mmol, 1 equiv). The reaction was stirred and heated to 82 °C for 30 h. The reaction was cooled to room temperature and quenched with saturated aqueous ammonium chloride (10 mL). The solvent was removed by rotary evaporation and the remaining crude was extracted with dichloromethane (3 x 20 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (40% ethyl acetate in hexanes) to afford the title compound in 52% yield (131 mg) as a bright yellow oil; R_f = 0.3 (30% diethyl ether in dichloromethane), **FTIR** (KBr film) ν_{max} (cm^{-1}): 2973, 2879, 1636, 1604, 1446, 1338, 1223, 1166, 1105, 766, 743, 709, 689; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 1H), 7.59 – 7.56 (m, 2H), 7.40 – 7.35 (m, 3H), 7.18 – 7.13 (m, 1H), 3.59 – 3.55 (m, 4H), 1.93 – 1.86 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.8, 164.0, 147.6, 134.3, 131.3, 129.1, 128.9, 128.8, 122.7, 122.6, 47.3, 46.1, 26.3, 23.9; **HRMS** (EI^+) *m/z* calcd for $C_{14}H_{15}NO_2$ $[M]^+$: 229.1103; found: 229.1103.

Procedure for the Preparation of Acceptor 9m



Ethyl 1-oxaspiro[2.4]heptanes-2-carboxylate (49)

To a two-necked 250 mL flame-dried round bottom flask was adapted a thermometer and then was stirred under inert atmosphere a solution of cyclopentanone (3 mL, 34 mmol, 1 equiv) and ethyl chloroacetate (3.5 mL, 34 mmol, 1 equiv) in dry tetrahydrofuran (68 mL, 0.5 M) and cooled to 0 °C with an ice-water bath. Potassium *tert*-butoxide (4.18 g, 37.3 mmol, 1.1 equiv) was added to the mixture in small portions every 20 min (1st portion of 1.18 g, six portions of 0.5 g each. *Keep internal temperature below 15 °C!*). The reaction was monitored by TLC, once completed the transformation the solvent was removed by rotary evaporation. To the solid residue was added diethyl ether (60 mL) and washed with water (30 mL) then brine (30 mL). The organic layer was dried though anhydrous sodium sulfate and the solvent was removed in vacuo. The oily residue was purified by bulb-to-bulb distillation to obtain a light yellow oil in 59% yield (4.27 g, 80% purity); R_f = 0.3 (10% ethyl acetate in hexanes), **FTIR** (KBr film) ν_{max} (cm^{-1}): 2964, 2873, 1752, 1729, 1189, 1036; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.26 – 4.20 (m, 2H), 3.51 (s, 1H), 2.00 – 1.97 (m, 1H), 1.90 – 1.65 (m, 7H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.1, 70.7, 61.4, 57.7, 33.5, 29.3, 28.2, 25.1, 14.4; **HRMS** (CI^+) *m*/*z* calcd for $C_9H_{14}O_3$ $[M+1, NH_3]^+$: 188.1286; found: 188.1281.

Ethyl 2-cyclopentyl-2-hydoxyacetate (50)

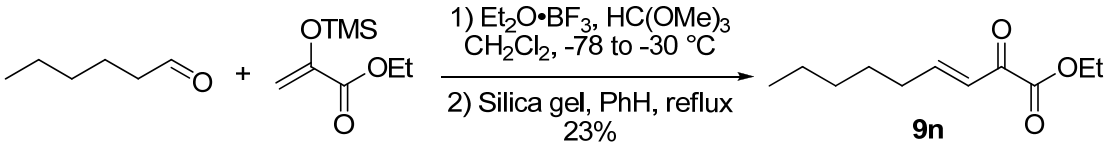
In a 10 mL round bottom flask was stired solution of ethyl 1-oxaspiro[2.4] heptane-2-carboxylate [glycidic ester **49**] (1.6 g, 9.5 mmol, 1 equiv) in benzene (4 mL, 2.4 M) to which lithium perchlorate (379 mg, 2.4 mmol, 0.25 equiv) was added. The mixture was heated to reflux (80 °C) for 2 h and cooled to ambient temperature. The mixture was washed with water (2 x 20 mL) and brine (1 x 20 mL). The organic phase was extracted with ethyl acetate (3 x 10 mL) and

dried through anhydrous sodium sulfate. The solvent was evaporated in vacuo, the residual oil was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford the title compound in 61% yield (979 mg) as colourles oil; R_f = 0.15 (10% ethyl acetate in hexanes), **FTIR** (KBr film) ν_{max} (cm^{-1}): 3493, 3050, 2955, 2850, 1734, 1196, 1073; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.79 – 5.78 (m, 1H), 4.74 (d, *J* = 5.8 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.98 (d, *J* = 6.4 Hz, 1H), 2.42 – 2.34 (m, 3H), 2.25 – 2.21 (m, 1H), 1.93 – 1.87 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.6, 141.1, 129.5, 70.5, 62.0, 32.5, 31.6, 23.4, 14.3; **HRMS** (EI^+) *m*/*z* calcd for $C_9H_{14}O_3$ $[M]^+$: 170.0942; found: 170.0945.

Ethyl 2-cyclopentyl-2-oxoacetate (9m)

In a 25 mL round bottom flask was stirred a solution of ethyl 2-cyclopentenyl-2-hydroxyacetate (**50**) (100 mg, 0.6 mmol, 1 equiv) in acetonitrile (6 mL, 0.1 M). To this solution IBX (214 mg, 0.8 mmol, 1.3 equiv) was added. The mixture was heated to reflux (80 °C) for 2 h. The reaction was cooled to ambient temperature and the solvent was removed in vacuo. The pasty residue was suspended in ethyl acetate and filtered through a short plug of silica. The filtrate was concentrated by rotary evaporation to afford the clean product in quantitative yield (>99%, 97 mg) as light yellow oil; R_f = 0.25 (10% ethyl acetate in hexanes), **FTIR** (KBr film) ν_{max} (cm^{-1}): 2963, 1735, 1669, 1606, 1160, 1027; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.13 (brs, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.63 – 2.57 (m, 4H), 1.97 – 1.90 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 183.6, 163.3, 152.7, 142.0, 62.1, 34.9, 30.4, 22.5, 14.1; **HRMS** (CI^+) *m*/*z* calcd for $C_9H_{12}O_3$ $[M+1, NH_3]^+$: 186.1130; found:186.1124.

Procedure for the Preparation of Acceptor 9n

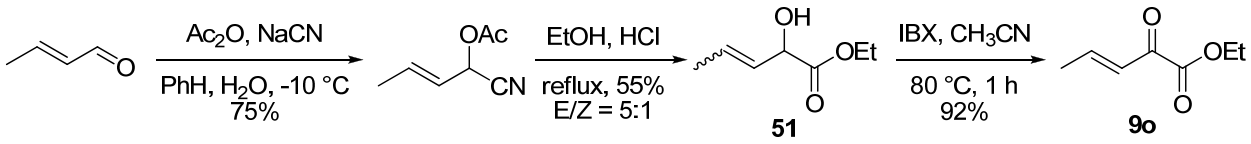


(*E*)-ethyl 2-oxonon-3-enoate (9n)

In a flame-dried 100 mL round bottom flask was stirred a solution of *n*-hexanal (1.8 mL, 13.9 mmol, 1 equiv) and trimethylorthoformate (1.7 mL, 15.3 mmol, 1.1 equiv) in dry dichloromethane (35 mL, 0.4 M). The mixture was cooled to -78 °C. Then, boron trifluoride etherate (1.9 mL, 15.3 mmol, 1.1 equiv) was added to the mixture dropwise. After 20 min, a solution of ethyl 2-(trimethylsilyloxy)acrylate (2.6 g, 13.9 mmol, 1 equiv) in dichloromethane (4 mL, 3.4 M) was added to the reaction mixture dropwise. After stirring for 30 min at -78 °C, the reaction was allowed to warm to -30 °C over 1 h, and then was stirred at 0 °C for 1 h. The mixture was quenched with saturated aqueous sodium bicarbonate (10 mL), extracted with dichloromethane (3 x 15 mL), and the organic phase was dried through anhydrous sodium sulfate. The solvent was evaporated in vacuo. The residual oil was re-dissolved in benzene (70 mL) and silica gel was added (21 g, 1.5 g/mmol). The mixture was heated to vigorous reflux for 16 h, then cooled to ambient temperature and filtered through a plug of silica gel. The silica was rinsed with diethyl ether (5 x 10 mL) and the filtrate was evaporated. The residual oil was purified by flash column chromatography to give the title product as light yellow oil in 23% yield (650 mg); **bp** (°C): 108, 1.8 torr; R_f = 0.15 (5% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2958, 2932, 2861, 1732, 1701, 1678, 1623; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 (ddd, *J* = 15.8, 6.9, 6.9 Hz, 1H), 6.63 (ddd, *J* = 15.8, 1.4, 1.4 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.29 (dddd, *J* = 7.4, 1.3, 1.3, 1.3 Hz, 2H), 1.52 – 1.46 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.28 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 183.7, 162.7, 155.3,

125.3, 62.4, 33.2, 31.5, 27.6, 22.5, 14.2, 14.1; **HRMS** (CI^+) *m/z* calcd for $C_{11}H_{18}O_3$ [M+1, NH_3]$^+$: 199.1334; found: 199.1341.

Procedure for the Preparation of Acceptor 9o



(*E*)-1-cyanobut-2-enyl acetate

In a 250 mL round bottom flask was stirred vigorously a solution of crotonaldehyde (10 mL, 120.7 mmol, 1 equiv) in toluene (30 mL, 4M relative to crotonaldehyde) and cooled to -10 °C using a frigorific mixture (ice + sodium chloride). To this solution acetic anhydride (11 mL, 120.7 mmol, 1 equiv) was added dropwise followed by the dropwise addition of an aqueous solution of sodium cyanide (8.87 g, 181 mmol, 1.5 equiv in 45 mL of distilled water [4 M relative to NaCN]) (*upon addition of the solution of sodium cyanide, the reaction mixture turns bright yellow!*). The reaction mixture was allowed to stir vigorously for 2 h at the same temperature. Then, the organic layer was extracted with toluene (3 x 20 mL) and subsequently washed with 1M acetic acid (50 mL), aqueous sodium bicarbonate (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried through anhydrous sodium sulfate and the solvent was evaporated. The crude product was purified by bulb-to-bulb distillation (110 °C, 3 torr) to afford a clear colourless oil in 75% yield (12.6 g); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.13 (dqd, *J* = 15.1, 7.2, 1.1 Hz, 1H), 5.75 (dd, *J* = 7.2, 1.1 Hz, 1H), 5.56 (dqd, *J* = 15.1, 7.2, 2.3 Hz, 1H), 2.11 (s, 3H), 1.79 (ddd, *J* = 7.2, 1.1, 1.1, 1.1 Hz, 3H). Spectral data matched those previously reported.[83]

Ethyl 2-hydroxypent-3-enoate (51)

In a 100 mL round bottom flask was stirred and heated to reflux a solution of (*E*)-1-cyanobut-2-enyl acetate (12.6 g, 90.7 mmol, 1 equiv) in ethanol (16.2 mL, 5.6 M) for 1 h. Then, a 1:1 mixture of ethanol and concentrated hydrochloric acid (8.1 mL for each, 16.2 mL in total, 5.6 M relative to (*E*)-1-cyanobut-2-enyl acetate) was slowly added from the top of the condenser to the refluxing mixture. A second portion of concentrated hydrochloric acid (4.2 mL, 149 mmol of HCl in total, 1.6 equiv) was added from the top of the condenser. The mixture was heated for 2 h and then cooled to 0 °C (*during the heating process, NH_4Cl precipitated out from solution!*). The solid was removed by filtration and the solvent was removed by rotary evaporation. The crude product was re-dissolved in diethyl ether (50 mL) and subsequently washed with saturated solution of aqueous sodium bicarbonate (until pH ca. 7) and water (10 mL). The organic phase was dried through anhydrous sodium sulfate and the solvent was removed in vacuo. The crude product was purified by bulb-to-bulb distillation (**bp** (°C): 125, 3 torr) to give a clear transparent oil in 55% yield (7.16 g); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.88 (ddq, *J* = 15.2, 6.4, 1.6 Hz, 1H), 5.51 (ddq, *J* = 15.2, 6.0, 1.6 Hz, 1H), 4.55 (dt, *J* = 6.1, 1.1 Hz, 1H), 4.23 (dddd, *J* = 20.4, 14.3, 10.7, 7.2 Hz, 2H), 3.15 (brs, 1H), 1.74 (dt, *J* = 1.6, 6.4 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). Spectral data matched those previously reported.[168]

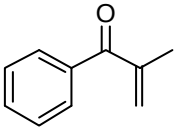
(*E*)-ethyl 2-oxopent-3-enoate (9o)

In a 25 mL round bottom flask was stirred a solution of ethyl 2-hydroxypent-3-enoate (**51**) (7.01 g, 49 mmol, 1 equiv) in acetonitrile (98 mL, 0.5 M). To this solution IBX (20.6 g, 73.5 mmol, 1.5 equiv) was added. The mixture was heated to reflux (80 °C) for 1 h. The reaction was cooled to ambient temperature and the solvent was removed in vacuo. The pasty residue was

suspended in ethyl acetate and filtered through a short plug of silica and rinsed with diethyl ether (50 mL). The filtrate was concentrated by rotary evaporation to afford the crude product which was further purified by bulb-to-bulb distillation to afford light yellow oil in 92% yield (6.37 g). **bp** (°C): 110, 3 torr; R_f = 0.5 (30% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (dq, *J* = 15.7, 6.9 Hz, 1H), 6.64 (dq, *J* = 15.7, 1.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.99 (dd, *J* = 7.0, 1.6 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). Spectral data matched those previously reported.[169]

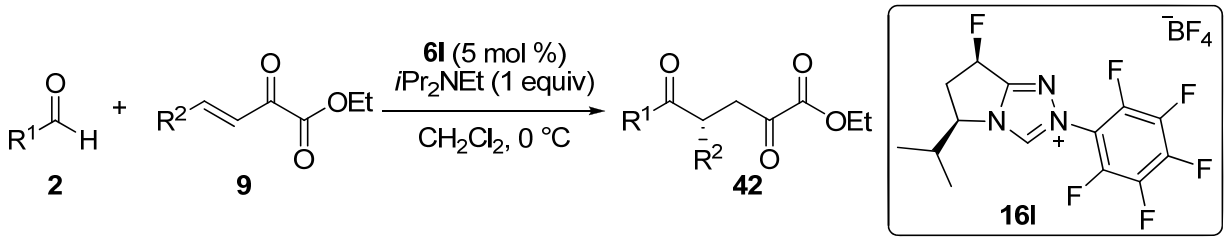
Procedure for the Preparation of Acceptor 53a

2-Methyl-1-phenylprop-2-en-1-one (53a)



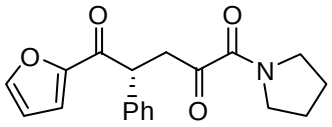
In a 50 mL round bottom flask was stirred a solution of propiophenone (1.4 mL, 10 mmol, 1 equiv), morpholine (0.55 mL, 5 mmol, 0.5 equiv), and glacial acetic acid (20 mL, 0.5 M). The reaction was heated to reflux (118 °C) and formaldehyde (5 mL, 62 mmol, 6.2 equiv, 37% in H_2O) was added dropwise in 5 portions (1 mL each hour). After complete addition of formaldehyde, the reaction was heated for additional 8 h and then the acetic acid was evaporated in vacuo. The crude product was diluted with ethyl acetate (20 mL) and successively washed with saturated aqueous sodium bicarbonate (2 x 10 mL), 1M hydrochloric acid (1 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL). The organic layer was dried through anhydrous sodium sulfate and the solvent was evaporated. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford a light yellow liquid in 66% yield (957 mg); R_f = 0.35 (10% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 5.90 (d, *J* = 1.0 Hz, 1H), 5.62 (s, 1H), 2.07 (s, 3H). Spectral data matched those previously reported.[86]

5.2.1 General Procedure for the Preparation of Stetter Products (42a–af, 47)



A 5 mL oven-dried Schlenk tube was charged with the appropriate acceptor (**9**) (1 equiv) and (*5R*,*7R*)-7-fluoro-5-isopropyl-2-(perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1c] [1,2,4] triazol-2-ium tetrafluoroborate [precatalyst] (**16l**) (0.05 equiv). The tube was evacuated with nitrogen and the solids were dissolved in CH_2Cl_2 (0.2 M). Then, the mixture was cooled to 0 °C for 5 min. Freshly distilled or prepared aldehyde (**2**) (1.5 equiv) was added, followed by a slow addition of *N*,*N*-diisopropylethylamine ($^{i}Pr_2NEt$) (1 equiv). The reaction was monitored by TLC. The reaction was quenched with AcOH (1.5 μL) and the resulting reaction mixture was purified by flash column chromatography to yield the corresponding product.

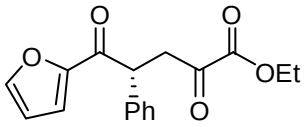
(+)-(*R*)-5-(furan-2-yl)-4-phenyl-1-(pyrrolidin-1-yl)pentane-1,2,5-trione (47)



Precatalyst **16h** (30 mol%) was employed and catalytic amount of *i*Pr_2NEt (30 mol%), 0.1 mmol scale, light yellow solid, 73% yield (21 mg); R_f = 0.25 (30% ethyl acetate in hexanes); 75% ee; $[\alpha]_D^{21}$ +131 (*c* 1.1, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 30% isopropanol in hexanes, 1.0 mL/min. Major: 14.2 min, minor: 12.0 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2974, 2881, 1716, 1672, 1637, 1466, 1393, 731, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 0.6 Hz, 1H), 7.29 – 7.27 (m, 4H), 7.24 – 7.20 (m, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.44 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.90 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.75 (dd, *J* = 18.8, 10.5 Hz, 1H), 3.51 – 3.43 (m, 4H), 3.30 (dd, *J* = 18.2, 4.1 Hz, 1H), 1.90 –

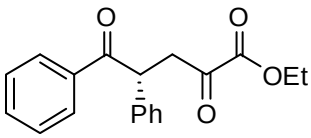
1.79 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.9, 187.5, 162.9, 152.0, 146.7, 137.8, 129.2, 128.4, 127.7, 118.7, 112.4, 48.9, 47.3, 46.3, 43.2, 26.4, 23.8; **HRMS** (EI^+) *m*/*z* calcd for $C_{19}H_{19}NO_4$ $[M]^+$: 325.1314; found: 325.1315.

(+)-(*R*)-ethyl 5-(furan-2-yl)-2,5-dioxo-4-phenylpentanoate (42a)



0.1 mmol scale, yellow oil, 92% yield (27 mg); R_f = 0.26 (20% ethyl acetate in hexanes); 90% ee; $[\alpha]_D^{24}$ +174 (*c* 1.0, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 18.3 min, minor: 14.6 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2984, 1729, 1673, 1466, 1273, 1052, 764; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 0.9 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.26 – 7.22 (m, 1H), 7.16 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.45 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.92 (dd, *J* = 9.9, 4.2 Hz, 1H), 4.30 (dddd, *J* = 7.1, 2.4, 2.4, 2.4 Hz, 2H), 3.95 (dd, *J* = 19.1, 9.9 Hz, 1H), 3.17 (dd, *J* = 19.1, 4.2 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.4, 186.9, 160.6, 152.0, 146.7, 137.7, 129.2, 128.4, 127.8, 118.6, 112.5, 62.7, 48.8, 43.0, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{17}H_{16}O_5$ $[M]^+$: 300.0997; found: 300.1000.

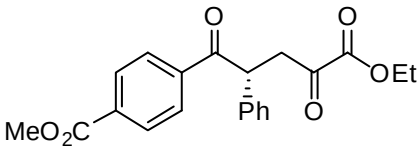
(+)-(*R*)-ethyl 2,5-dioxo-4,5-diphenylpentanoate (42e)



0.1 mmol scale, yellow oil, 18% yield (6 mg); R_f = 0.26 (20% ethyl acetate in hexanes); 57% ee; $[\alpha]_D^{23}$ +93 (*c* 0.5, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 13.8 min, minor: 10.9 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2983, 1728, 1681, 1256, 1050, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.25 (m, 4H), 7.23 – 7.20 (m, 1H), 5.13 (dd, *J* = 9.9, 4.1 Hz,

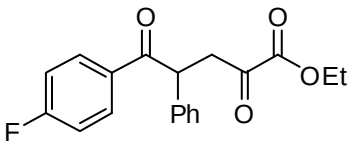
1H), 4.32 (dq, *J* = 7.1, 2.1 Hz, 2H), 3.98 (dd, *J* = 19.0, 9.9 Hz, 1H), 3.14 (dd, *J* = 19.0, 4.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.2, 192.6, 160.7, 138.2, 136.1, 133.2, 129.5, 129.1, 128.6, 128.3, 127.7, 62.7, 49.1, 44.1, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{19}H_{18}O_4$ $[M]^+$: 310.1205; found: 310.1214.

(+)-(*R*)-methyl 4-(5-ethoxy-4,5-dioxo-2-phenylpentanoyl)benzoate (42f)



0.1 mmol scale, 10 mol% of **16l** was required, yellow semi-solid, 30% yield (11 mg); R_f = 0.2 (15% ethyl acetate in hexanes); 72% ee; $[\alpha]_D^{22}$ +85 (*c* 0.7, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 27.6 min, minor: 21.2 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2924, 2852, 1727, 1686, 1280, 1108, 1051, 701; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 6.7 Hz, 2H), 7.97 (d, *J* = 6.9 Hz, 2H), 7.31 – 7.22 (m, 5H), 5.10 (dd, *J* = 10.0, 3.9 Hz, 1H), 4.33 (dddd, *J* = 7.1, 1.9, 1.9, 1.9 Hz, 2H), 4.00 (dd, *J* = 19.1, 10.0 Hz, 1H), 3.90 (s, 3H), 3.16 (dd, *J* = 19.1, 3.9 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.8, 192.5, 166.2, 160.6, 139.5, 137.5, 133.9, 129.8, 129.6, 128.9, 128.3, 127.9, 62.8, 52.5, 49.4, 44.0, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{21}H_{20}O_6$ $[M]^+$: 368.1259; found: 368.1255.

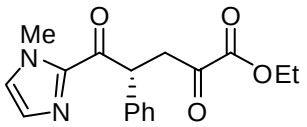
***Rac*-ethyl 5-(4-fluorophenyl)-2,5-dioxo-4-phenylpentanoate (42g)**



0.1 mmol scale, yellow oil, 13% yield (6 mg); R_f = 0.25 (10% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2985, 1730, 1690, 1324, 1170, 1130, 1067, 1016, 839, 702; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.26 – 7.23 (m, 3H), 5.09 (dd, *J* = 10.1, 3.8 Hz, 1H), 4.33 (dq, *J* = 7.1, 1.6 Hz, 2H), 4.00 (dd, *J* = 19.2,

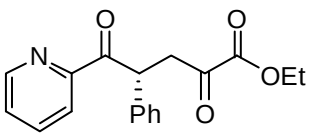
10.1 Hz, 1H), 3.18 (dd, *J* = 19.2, 3.8 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.4, 192.5, 160.6, 139.0, 137.3, 134.5 (q, *J* = 32.4 Hz), 129.7, 129.4, 128.3, 128.1, 125.7 (d, *J* = 3.7 Hz), 123.7 (d, *J* = 272.6 Hz), 62.8, 49.4, 44.1, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{20}H_{17}F_3O_4$ $[M]^+$: 378.1078; found: 378.1088.

(*R*)-ethyl 5-(1-methyl-1H-imidazol-2-yl)-2,5-dioxo-4-phenylpentanoate (42l)



0.1 mmol scale, yellow semi-solid, 41% yield (13 mg); R_f = 0.15 (30% ethyl acetate in hexanes); 10% ee; HPLC analysis – Chiralcel IA column, 30% isopropanol in hexanes, 1.0 mL/min. Major: 17.7 min, minor: 29.6 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2985, 1729, 1673, 1406, 1288, 1048, 911, 739, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 5.59 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.92 (dd, *J* = 19.2, 10.5 Hz, 1H), 3.91 (s, 3H), 3.29 (dd, *J* = 19.2, 4.1 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.5, 190.4, 160.7, 142.5, 137.9, 129.7, 128.9, 128.7, 127.5, 127.3, 62.6, 47.8, 43.2, 36.2, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{17}H_{18}N_2O_4$ $[M]^+$: 314.1266; found: 314.1258.

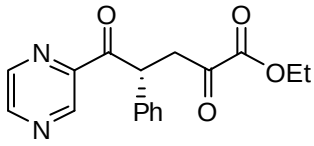
(+)-(*R*)-ethyl 2,5-dioxo-4-phenyl-5-(pyridin-2-yl)pentanoate (42o)



0.1 mmol scale, off-white crystals, 88% yield (27 mg); R_f = 0.36 (30% ethyl acetate in hexanes); 91% ee; $[\alpha]_D^{25}$ +142 (*c* 1.0, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 16.6 min, minor: 13.0 min. **mp** (°C): 82-84; **FTIR** (KBr film) ν_{max} (cm^{-1}): 2984, 1729, 1696, 1583, 1275, 1052, 703; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.1 Hz, 1H), 7.99

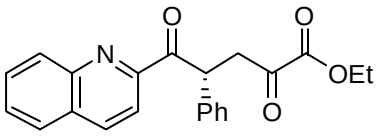
(d, *J* = 7.8 Hz, 1H), 7.74 (ddd, *J* = 7.7, 1.6 Hz, 1H), 7.40 – 7.36 (m, 3H), 7.25 (dd, *J* = 7.9, 7.3 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 5.87 (dd, *J* = 10.4, 4.1 Hz, 1H), 4.30 (dddd, *J* = 7.1, 1.4, 1.4, 1.4 Hz, 2H), 3.97 (dd, *J* = 19.3, 10.5 Hz, 1H), 3.31 (dd, *J* = 19.3, 4.1 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.4, 192.7, 160.7, 152.4, 149.1, 137.6, 136.8, 129.0, 128.9, 127.4, 127.2, 123.0, 62.6, 46.0, 43.6, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{18}H_{17}NO_4$ $[M]^+$: 311.1157; found: 311.1148.

(+)-(*R*)-ethyl 2,5-dioxo-4-phenyl-5-(pyrazin-2-yl)pentanoate (42p)



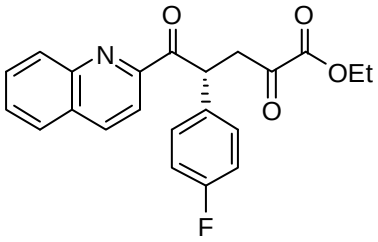
0.1 mmol scale, white solid, 94% yield (29 mg); R_f = 0.23 (25% ethyl acetate in hexanes); 87% ee; $[\alpha]_D^{23}$ +144 (*c* 1.0, CH_2Cl_2); HPLC analysis – Chiralcel IC column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 35.4 min, minor: 32.1 min. **mp** (°C): 74-76; **FTIR** (KBr film) ν_{max} (cm^{-1}): 2983, 1729, 1699, 1274, 1056, 954, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.18 (d, *J* = 1.3 Hz, 1H), 8.67 (d, *J* = 2.4 Hz, 1H), 8.61 (dd, *J* = 2.2, 1.5 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.28 – 2.25 (m, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 5.71 (dd, *J* = 10.6, 3.8 Hz, 1H), 4.32 (dddd, *J* = 7.1, 1.4, 1.4, 1.4 Hz, 2H), 4.00 (dd, *J* = 19.5, 10.6 Hz, 1H), 3.31 (dd, *J* = 19.5, 3.8 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.7, 192.6, 160.5, 147.8, 146.8, 144.7, 143.6, 136.7, 129.1, 128.9, 127.8, 62.7, 46.3, 43.5, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{17}H_{16}N_2O_4$ $[M]^+$: 312.1110; found: 312.1099.

(–)-(*R*)-ethyl 2,5-dioxo-4-phenyl-5-(quinolin-2-yl)pentanoate (42q)



0.1 mmol scale, white solid, 95% yield (34 mg); R_f = 0.28 (15% ethyl acetate in hexanes); >99% ee; $[\alpha]_D^{23}$ -96 (*c* 1.0, CH_2Cl_2); HPLC analysis – Chiralcel IB column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 9.5 min, minor: 12.1 min. **mp** (°C): 110-103; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3062, 3030, 2983, 1729, 1694, 1274, 1051, 934, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.74 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.51 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.25 (t, *J* = 7.1 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.13 (dd, *J* = 10.3, 4.3 Hz, 1H), 4.32 (dddd, *J* = 7.1, 1.5, 1.5, 1.5 Hz, 2H), 4.04 (dd, *J* = 19.3, 10.3 Hz, 1H), 3.39 (dd, *J* = 19.3, 4.3 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.5, 192.8, 160.7, 151.7, 147.2, 137.9, 136.9, 130.9, 130.0, 129.7, 129.1, 128.9, 128.8, 127.7, 127.3, 119.1, 62.7, 46.1, 43.4, 14.1; **HRMS** (EI^+) *m/z* calcd for $C_{22}H_{19}NO_4$ $[M]^+$: 361.1314; found: 361.1312.

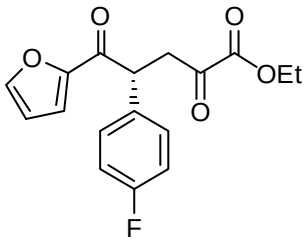
(–)-(*R*)-ethyl 4-(4-fluorophenyl)-2,5-dioxo-5-(quinolin-2-yl)pentanoate (42r')



0.1 mmol scale, yellow oil, 58% yield (22 mg); R_f = 0.2 (15% ethyl acetate in hexanes); 74% ee; $[\alpha]_D^{22}$ -71 (*c* 2.3, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 27.2 min, minor: 23.8 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2984, 1727, 1684, 1602, 1510,1222, 1160, 1051, 934, 733; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.3 Hz, 1H), 8.19 (d, *J* = 5.1 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.76 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.48 – 7.46 (m, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 6.11 (dd, *J* = 10.1, 4.5 Hz, 1H), 4.32 (dq, *J* = 7.1, 1.1 Hz, 2H), 3.99 (dd,

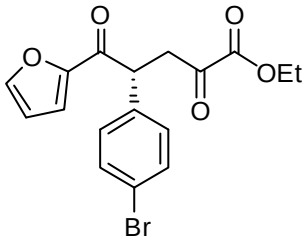
J = 19.2, 10.1 Hz, 1H), 3.40 (dd, J = 19.2, 4.6 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.3, 192.6, 162.1 (d, J = 246 Hz), 160.7, 151.7, 147.2, 137.1, 133.6, 130.9, 130.7 (d, J = 8.1 Hz), 130.1, 129.7, 128.9, 127.8, 119.1, 115.8 (d, J = 21.5 Hz), 62.7, 45.3, 43.3, 14.2; **HRMS** (EI^+) m/z calcd for $C_{22}H_{18}FNO_4$ $[M]^+$: 379.1219; found: 379.1230.

(+)-(*R*)-ethyl 4-(4-fluorophenyl)-5-(furan-2-yl)-2,5-dioxopentanoate (42r)



0.1 mmol scale, yellow oil, 88% yield (27 mg); R_f = 0.26 (15% ethyl acetate in hexanes); 91% ee; $[\alpha]_D^{22}$ +149 (*c* 1.3, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 27.2 min, minor: 23.8 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2985, 1730, 1673, 1509, 1466, 1224, 1052, 771; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 1.6, 0.6 Hz, 1H), 7.30 (dd, J = 8.7, 5.2 Hz, 2H), 7.17 (dd, J = 3.6, 0.6 Hz, 1H), 6.99 (dt, J = 6.9, 2.0 Hz, 2H), 6.47 (dd, J = 3.5, 1.7 Hz, 1H), 4.92 (dd, J = 9.7, 4.5 Hz, 1H), 4.31 (dddd, J = 7.1, 2.1, 2.1, 2.1 Hz, 2H), 3.90 (dd, J = 19.2, 9.7 Hz, 1H), 3.16 (dd, J = 19.2, 4.5 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.3, 186.8, 162.4 (d, J = 247.1 Hz), 160.5, 151.9, 146.8, 133.4 (d, J = 3.3 Hz), 130.1 (d, J = 8.1 Hz), 118.7, 116.2 (d, J = 21.6 Hz), 112.6, 62.8, 47.9, 43.0, 14.1; **HRMS** (EI^+) m/z calcd for $C_{17}H_{15}FO_5$ $[M]^+$: 318.0903; found: 318.0913.

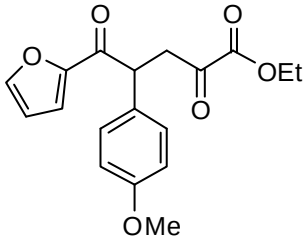
(+)-(*R*)-ethyl 4-(4-bromophenyl)-5-(furan-2-yl)-2,5-dioxopentanoate (42s)



0.3 mmol scale, yellow oil, 90% yield (102 mg); R_f = 0.17 (15% ethyl acetate in hexanes); 90% ee; $[\alpha]_D^{23}$ +113 (*c* 1.1, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 34.0 min, minor: 29.3 min. **FTIR** (KBr film) ν_{max} (cm^{-}

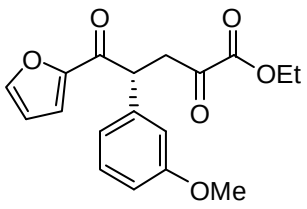
^{1}): 2983, 1729, 1673, 1567, 1487, 1465, 1393, 1270, 1221, 1052, 1011, 882, 769, 736, 593, 516; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 0.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.47 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.89 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.30 (dddd, *J* = 7.2, 1.8 Hz, 2H), 3.89 (dd, *J* = 19.2, 9.7 Hz, 1H), 3.16 (dd, *J* = 19.2, 4.4 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.1, 186.4, 160.4, 151.9, 146.9, 136.6, 132.3, 130.1, 121.9, 118.7, 112.6, 62.8, 48.1, 42.7, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{17}H_{15}BrO_5$ $[M+1]^+$: 380.0082; found: 380. 0086.

***Rac*-ethyl 5-(furan-2-yl)-4-(4-methoxyphenyl)-2,5-dioxopentanoate (42t)**



0.1 mmol scale, yellow oil, 96% yield (32 mg); R_f = 0.25 (10% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3135, 2938, 2838, 1729, 1672, 1608, 1512, 1466, 1253, 1052, 770; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 1.5, 0.6 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 3.6 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.44 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.87 (dd, *J* = 9.8, 4.4 Hz, 1H), 4.30 (dq, *J* = 7.1, 2.2 Hz, 2H), 3.90 (dd, *J* = 19.1, 9.8 Hz, 1H), 3.74 (s, 3H), 3.15 (dd, *J* = 19.1, 4.4 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.6, 187.2, 160.7, 159.3, 152.0, 146.7, 129.6, 129.5, 118.6, 114.7, 112.5, 62.7, 55.4, 48.0, 43.0, 14.2; **HRMS** (EI^+) *m*/*z* calcd for $C_{18}H_{18}O_6$ $[M]^+$: 330.1103; found: 330.1102.

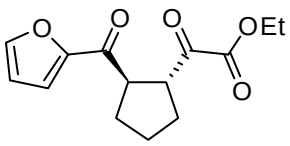
(+)-(*R*)-ethyl 5-(furan-2-yl)-4-(3-methoxyphenyl)-2,5-dioxopentanoate (42u)



0.1 mmol scale, yellow oil, 96% yield (31.7 mg); R_f = 0.25 (10% ethyl acetate in hexanes); 90% ee; $[\alpha]_D^{24}$ +164 (*c* 1.3, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0

mL/min. Major: 22.9 min, minor: 17.4 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2940, 1729, 1673, 1466, 1266, 1052, 766; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 0.9 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.84 (dd, *J* = 2.1, 1.7 Hz, 1H), 6.78 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.46 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.89 (dd, *J* = 10.0, 4.1 Hz, 1H), 4.31 (dddd, *J* = 7.1, 2.6, 2.6, 2.6 Hz, 2H), 3.94 (dd, *J* = 19.1, 10.0 Hz, 1H), 3.77 (s, 3H), 3.16 (dd, *J* = 19.1, 4.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.4, 186.7, 160.6, 160.2, 152.0, 146.8, 139.2, 130.2, 120.7, 118.7, 114.0, 113.2, 112.5, 62.7, 55.4, 48.8, 43.0, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{18}H_{18}O_6$ $[M]^+$: 330.1103; found: 330.1101.

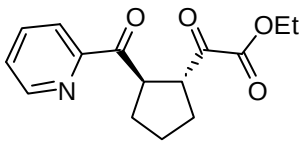
***Rac*-ethyl 2-(-2-(furan-2-carbonyl)cyclopentyl)-2-oxoacetate (42ac)**



Precatalyst **2e** (30 mol%) was employed with catalytic amount of DBU (30 mol%) at room temperature, 0.1 mmol scale, light yellow oil, 78% yield (21 mg); R_f = 0.18 (15% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3174, 2960, 2924, 2854, 1728, 1672, 1567, 1465, 1377, 1260, 1158, 926, 883, 764, 594; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (m, 1H), 7.24 (d, *J* = 3.6 Hz, 1H), 6.53 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.28 (dq, *J* = 7.1, 3.0 Hz, 2H), 4.05 (dt, *J* = 9.1, 6.7 Hz, 1H), 3.97 (dt, *J* = 8.8, 6.8 Hz, 1H), 2.22 (m, 2H), 1.89 – 1.70 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.3, 189.6, 161.4, 152.3, 146.9, 118.2, 112.5, 62.7, 49.9, 48.3, 31.6, 29.9, 26.2, 14.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{14}H_{16}O_5$ $[M]^+$: 264.0998; found: 264.0997.

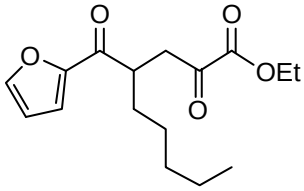
The reaction with pyridine-2-carboxaldehyde (**2o**) *and acceptor* **34m** *was just as efficient for producing the corresponding Stetter adduct as for* **42ac**.

***Rac*-ethyl 2-oxo-2-(-2-picolinoylcyclopentyl)acetate**



Precatalyst **1e** (30 mol%) was employed with catalytic amount of DBU (30 mol%) at room temperature, 0.12 mmol scale, dark yellow oil, 89% yield (29 mg); R_f = 0.25 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2960, 2873, 1727, 1695, 1629, 1266, 995, 747; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 3.9, 0.6 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.45 – 7.42 (m, 1H), 4.44 (ddd, *J* = 8.6, 7.4, 7.4 Hz, 1H), 4.25 (dq, *J* = 7.1, 2.6 Hz, 2H), 3.94 (ddd, *J* = 8.9, 7.2, 7.2 Hz, 1H), 2.18 – 2.08 (m, 2H), 1.96 – 1.88 (m, 2H), 1.82 – 1.73 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.4, 195.7, 161.6, 152.8, 148.8, 137.2, 127.3, 122.7, 62.4, 50.1, 48.8, 30.6, 30.5, 26.4, 14.2; **HRMS** (CI^+) *m/z* calcd for $C_{15}H_{17}NO_4$ [M+1, NH_3]$^+$: 276.1235; found: 276.1242.

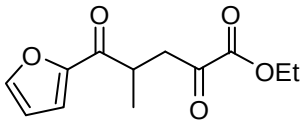
***Rac*-ethyl 4-(furan-2-carbonyl)-2-oxononanoate (42ad)**



Precatalyst **1e** (30 mol%) was employed with catalytic amount of DBU (30 mol%) at room temperature, 0.1 mmol scale, light yellow oil, 98% yield (29 mg); R_f = 0.25 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3135, 2957, 2931, 2860, 1729, 1672, 1568, 1467, 1396, 1261, 1063, 1043, 1215, 883, 765; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.23 (dd, *J* = 3.6, 0.7 Hz, 1H), 6.54 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.29 (dq, *J* = 7.2, 0.9 Hz, 2H), 3.73 – 3.68 (m, 1H), 3.44 (dd, *J* = 19.1, 9.4 Hz, 1H), 3.00 (dd, *J* = 19.1, 4.2 Hz, 1H), 1.75 – 1.69 (m, 1H), 1.55 – 1.48 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.32 – 1.19 (m, 6H), 0.83 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.1, 191.1, 160.8, 152.6, 146.7, 117.9, 112.5, 62.7, 42.1, 40.7, 32.4, 31.8, 26.9, 22.5, 14.2, 14.1; **HRMS** (CI^+) *m/z* calcd for $C_{16}H_{22}O_5$ [M+1, NH_3]$^+$: 295.1545; found:

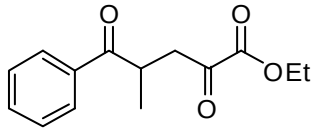
295.1546.

***Rac*-ethyl 5-(furan-2-yl)-4-methyl-2,5-dioxopentanoate (42ae)**



Precatalyst **1e** (30 mol%) was employed with catalytic amount of DBU (30 mol%) at room temperature, 0.21 mmol scale, light yellow oil, 74% yield (39 mg); R_f = 0.28 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3448, 3135, 2981, 2938, 1732, 1673, 1568, 1468, 1398, 1256, 1079, 985, 767, 594; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.24 (d, *J* = 3.5 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.6 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.79 – 3.71 (m, 1H), 3.45 (dd, *J* = 19.0, 5.0 Hz, 1H), 2.93 (dd, *J* = 19.0, 5.0 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.9, 191.1, 160.8, 151.9, 146.7, 118.0, 112.5, 62.7, 42.1, 37.1, 17.8, 14.1; **HRMS** (CI^+) *m*/*z* calcd for $C_{12}H_{14}O_5$ [M+1, NH_3]$^+$: 239.0919; found: 239.0913.

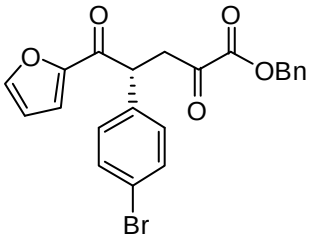
***Rac*-ethyl 4-methyl-2,5-dioxo-5-phenylpentanoate (42af)**



A 5 mL oven-dried Schlenk tube was charged with 2-methyl-1-phenylprop-2-en-1-one (**53a**) (43.8 mg, 0.3 mmol, 1 equiv) and 2-(perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**16n**) (22 mg, 0.06 mmol, 0.2 equiv). The tube was evacuated with nitrogen and the solids were dissolved in CH_2Cl_2 (1.5 mL, 0.2 M). Then, freshly cracked and distilled ethyl glyoxylate (116 μL, 1.20 mmol, 4 equiv) was added, followed by the addition of *N,*N-diisopropylethylamine (*i*Pr_2NEt) (42 μL, 0.30 mmol, 1 equiv). The reaction was monitored by TLC (24 h). The reaction was quenched with AcOH (1 μL) and the resulting reaction mixture was purified by flash column chromatography (15% ethyl acetate in hexanes) to give a pale

yellow oil in 26% yield (20 mg). R_f = 0.3 (15% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2891, 2937, 2878, 1729, 1683, 1448, 1238, 1078, 977, 704; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.9 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.02 – 3.97 (m, 1H), 3.52 (dd, *J* = 19.0, 8.6 Hz, 1H), 2.96 (dd, *J* = 19.0, 4.9 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 202.5, 193.2, 160.8, 135.8, 133.4, 128.9, 128.7, 62.7, 42.7, 36.7, 18.1, 14.2; **HRMS** (CI^+) *m/z* calcd for $C_{14}H_{17}O_4$ $[M+1, NH_3]^+$: 249.1126; found: 249.1124.

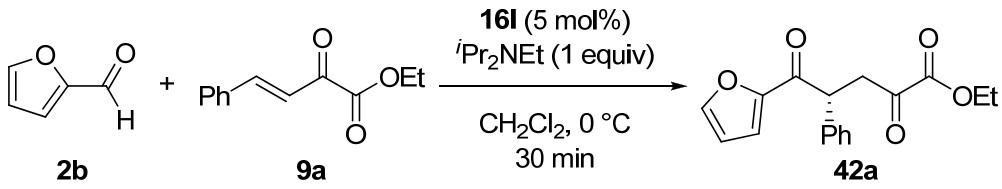
(+)-(*R*)-benzyl 4-(4-bromophenyl)-5-(furan-2-yl)-2,5-dioxopentanoate (42ag)



A 10 mL oven-dried Schlenk tube was charged with (*E*)-benzyl 4-(4-bromophenyl)-2-oxobut-3-enoate (**9p**) (300 mg, 0.87 mmol, 1 equiv) and (*5R*,*7R*)-7-fluoro-5-isopropyl-2-(perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**16l**) (18.4 mg, 0.04 mmol, 0.05 equiv). The tube was evacuated with nitrogen and the solids were dissolved in CH_2Cl_2 (4.3 mL, 0.2 M). Then, the mixture was cooled to 0 °C for 5 min. Freshly distilled furfural (**2b**) (84 μL, 0.96 mmol, 1.1 equiv) was added, followed by a slow addition of *N*,*N*-diisopropylethylamine (*i*Pr_2NEt) (122 μL, 0.87 mmol, 1 equiv). The reaction was monitored by TLC (20 min). The reaction was quenched with AcOH (10 μL) and the resulting reaction mixture was purified by FCC (15% ethyl acetate in hexanes) to yield light yellow needle-like crystals in 75% yield (288 mg); R_f = 0.23 (15% ethyl acetate in hexanes); >85% ee; $[\alpha]_D^{20}$ +101 (*c* 1.8, CH_2Cl_2); HPLC analysis – Chiralpack AS-H column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 42.7 min, minor: 44.7 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3034, 2956, 1730, 1672, 1567, 1487, 1465, 1270, 1218, 1049, 734, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, *J*

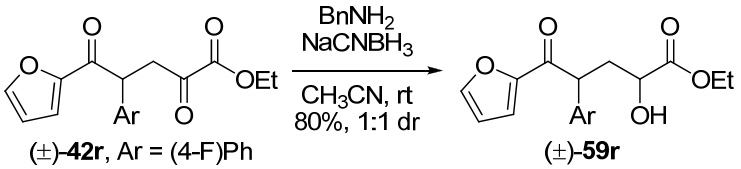
= 0.8, 0.7 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.33 (m, 5H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 3.6 Hz, 1H), 6.46 (dd, *J* = 3.5, 1.6 Hz, 1H), 5.27 (s, 2H), 4.89 (dd, *J* = 9.7, 4.4 Hz, 1H), 3.91 (dd, *J* = 19.2, 9.7 Hz, 1H), 3.17 (dd, *J* = 19.2, 4.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.7, 186.4, 160.2, 151.8, 146.9, 136.6, 134.5, 132.4, 130.1, 129.0, 128.9, 128.8, 121.9, 118.8, 112.7, 68.3, 48.0, 42.8; **HRMS** (ESI^+) *m*/*z* calcd for $C_{22}H_{17}BrO_5$ $[M+Na]^+$: 463.0151; found: 463.0137.

5.2.2 (+)-(*R*)-Ethyl-5-(furan-2-yl)-2,5-dioxo-4-phenylpentanoate (42a) *[large scale synthesis]*



Acceptor **9a** (608 mg, 2.97 mmol, 1 equiv) and precatalyst **16l** (63 mg, 0.15 mmol, 0.05 equiv) dissolved in CH_2Cl_2 (15 mL, 0.2 M) was cooled to 0 °C, under N_2. Freshly distilled 2-furfural (312 μL, 3.57 mmol, 1.2 equiv) was added, followed by a slow addition of $^{i}Pr_2NEt$ (416 μL, 2.97 mmol, 1 equiv) in CH_2Cl_2 (4.8 mL, final concentration of 0.15 M). The reaction was monitored by TLC; the reaction stops progressing after 30 min. The reaction was quenched with AcOH (170 μL, 17.4 M, 2.97 mmol), the resulting reaction mixture was purified by FCC (25% ethyl acetate in hexanes, R_f = 0.30) to yield the desired product as a yellow oil (607 mg, 88% yield, 89% ee).

***Rac*-ethyl 4-(4-fluorophenyl)-5-(furan-2-yl)-2-hydroxy-5-oxopentanoate (59r)**

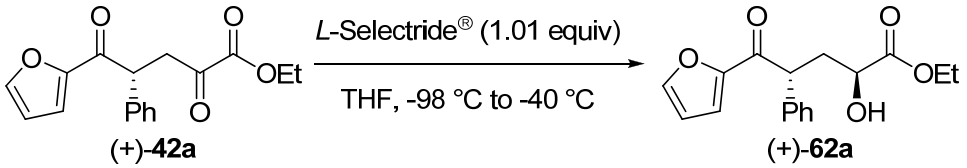


(±)-**42r**, Ar = (4-F)Ph (±)-**59r**

To a solution of ethyl 4-(4-fluorophenyl)-5-(furan-2-yl)-2,5-dioxopentanoate (±)-(**42r**) (20 mg, 0.06 mmol, 1 equiv) in dry acetonitrile (0.3 mL, 0.2 M) was added freshly distilled benzyl amine (13 μL, 0.07 mmol, 1.1 equiv) and stirred for 10 minutes. Then, sodium cyanoborohydride (8.3 mg, 0.13 mmol, 2.1 equiv) was added in one portion. The reaction was monitored by TLC and after 16 hours, glacial acetic acid (11 μL, 0.19 mmol, 3 equiv) was added. The solvent of the reaction was evaporated and the crude was then diluted with dichloromethane (5 mL). The solution was neutralized to pH 7 with aqueous saturated sodium bicarbonate and the organic layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried though anhydrous sodium sulfate, the solvent was evaporated and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford a dark yellow oil in 80% yield (16 mg). R_f = 0.18 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3330, 3064, 3030, 2981, 2928, 1732, 1673, 1601, 1566, 1508, 1465, 1393, 1284, 1224, 1160, 1095, 1029, 753; (*two diastereomers*) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.53 (m, 1H), 7.54 – 7.53 (m, 1H), 7.27 – 7.24 (m, 2H), 7.27 – 7.24 (m, 2H), 7.21 (d, *J* = 3.5 Hz, 1H), 7.18 (d, *J* = 3.5 Hz, 1H), 7.01 (t, *J* = 8.5 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 6.48 – 6.46 (m, 1H), 6.48 – 6.46 (m, 1H), 4.77 (dd, *J* = 9.1, 5.3 Hz, 1H), 4.74 (dd, *J* = 9.5, 5.3 Hz, 1H), 4.23 – 4.16 (m, 3H), 4.15 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.85 (dd, *J* = 10.4, 3.2 Hz, 1H), 2.79 (ddd, *J* = 13.8, 9.1, 4.4 Hz, 1H), 2.38 (ddd, *J* = 14.0, 9.8, 3.3 Hz, 2H), 2.25 (ddd, *J* = 14.0, 10.4, 5.3 Hz, 2H), 2.01 (ddd, *J* = 13.7, 8.1, 5.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz,

3H), 1.24 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.3, 188.1, 175.2, 174.9, 162.3 (J = 246 Hz), 162.1 (J = 246 Hz), 152.4, 152.2, 146.9, 146.8, 140.4, 134.5, 130.5 (J = 8.4 Hz), 130.3 (J = 7.6 Hz), 118.6, 118.4, 116.0 (J = 21.1 Hz), 115.8 (J = 21.1 Hz), 112.6, 112.5, 68.5, 68.0, 62.2, 62.1, 49.0, 48.2, 37.4, 37.4, 14.3, 14.2; **HRMS** (EI^+) m/z calcd for $C_{17}H_{17}FO_5$ $[M]^+$: 320.1060; found: 320.1045.

(+)-(2*S*,4*R*)-ethyl 5-(furan-2-yl)-2-hydroxy-5-oxo-4-phenylpentanoate (62a)

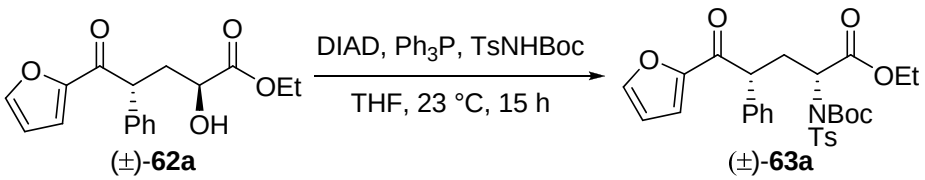


(+)-**42a** (+)-**62a**

In a 25 mL flame-dried round bottom flask was stirred a solution of (+)-(*R*)-ethyl 5-(furan-2-yl)-2,5-dioxo-4-phenylpentanoate (**42a**) (50 mg, 0.16 mmol, 1 equiv) in dry tetrahydrofuran (1.6 mL, 0.1 M). The mixture was cooled to -98 °C using a diethyl ether / $N_{2(l)}$ bath and *L*-selectride® (167 μL, 0.16 mmol, 1.01 equiv) was slowly added to the mixture. The temperature of the bath was allowed to warm slowly to -40 °C over 20 min. The reaction was quenched with saturated aqueous ammonium chloride (0.5 mL) and extracted with ethyl acetate (5 x 5 mL). The organic layer was dried through anhydrous sodium sulfate and the solvent was evaporated by rotary evaporation. The crude product was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford the title product as a light yellow oil (48 mg, 96% yield, 90% ee, dr >20:1). R_f = 0.18 (25% ethyl acetate in hexanes); $[\alpha]_D^{22}$ +85 (*c* 2.7, CH_2Cl_2); HPLC analysis – Chiralcel IC column, 25% isopropanol in hexanes, 1.0 mL/min. Major: 18.3 min, minor: 25.2 min.; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3468, 2979, 1734, 1671, 1566, 1465, 1282, 764, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 1.6, 0.6 Hz, 1H), 7.39 (d, J =

7.1 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.17 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.45 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.73 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.21 (dddd, *J* = 7.1, 3.9, 3.9, 3.9 Hz, 2H), 3.88 (dd, *J* = 10.5, 3.2 Hz, 1H), 2.78 (brs, 1H), 2.42 (ddd, *J* = 14.0, 9.6, 3.2 Hz, 1H), 2.28 (ddd, *J* = 14.0, 10.5, 5.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.4, 175.3, 152.1, 146.7, 137.8, 129.1, 128.8, 127.6, 118.4, 112.4, 68.1, 62.1, 49.9, 37.2, 14.3; **HRMS** (EI^+) *m*/*z* calcd for $C_{17}H_{18}O_5$ $[M]^+$: 302.1154 ; found: 302.1152.

***Rac*-(2*R*,4*R*)-ethyl 2-(*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonamido)-5-(furan-2-yl)-5-oxo-4-phenylpentanoate (63a)**

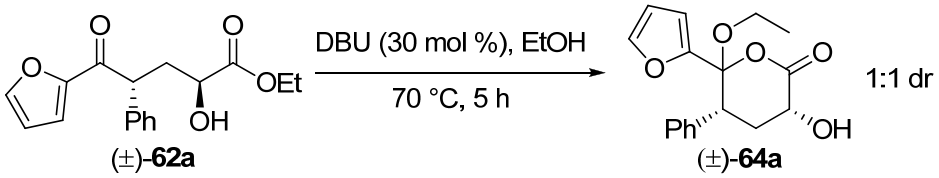


(±)-**62a** (±)-**63a**

A 5 mL oven-dried Schlenk tube was charged with *rac*-(2*S*,4*R*)-ethyl 5-(furan-2-yl)-2-hydroxy-5-oxo-4-phenylpentanoate (**62a**) (41 mg, 0.14 mmol, 1 equiv) and triphenylphosphine (71 mg, 0.27 mmol, 2 equiv). The tube was evacuated with nitrogen and the solids were dissolved with dry tetrahydrofuran (0.45 mL, 0.3 M). Then, the *N*-Tosyl-*N*-Boc amide (48 mg, 0.17 mmol, 1.3 equiv) was added to the solution and the tube was covered with aluminum foil. Diisopropylazodicarboxylate (40 μL, 0.20 mmol, 1.5 equiv) was added drop-wise to the mixture and it was allowed to stir overnight. The solvent was removed and the crude product was purified by flash column chromatography to afford an off-white foam in 40% yield (29 mg). R_f = 0.20 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2981, 1740, 1673, 1567, 1466, 1351, 1287, 1146, 764, 578; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.50 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 3H), 7.26 – 7.24 (m, 2H), 7.22 (d, *J* = 3.9

Hz, 1H), 6.43 – 6.42 (m, 1H), 5.05 (dd, *J* = 9.4, 5.0 Hz, 1H), 4.75 (dd, *J* = 10.2, 4.6 Hz, 1H), 4.17 – 4.13 (m, 2H), 3.24 (ddd, *J* = 14.0, 9.6, 3.2 Hz, 1H), 2.41 (s, 3H), 2.32 (ddd, *J* = 14.0, 10.5, 5.4 Hz, 1H), 1.26 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 187.7, 169.7, 152.5, 150.2, 146.6, 144.5, 139.0, 136.6, 129.1, 129.1, 128.8, 128.5, 127.5, 118.5, 112.3, 85.1, 61.8, 58.1, 50.5, 33.6, 27.9, 21.8, 14.1; **HRMS** (CI^+/NH_3) *m/z* calcd for $C_{29}H_{33}NO_8S$ $[M+1]^+$: 573.2270; found: 573.2259.

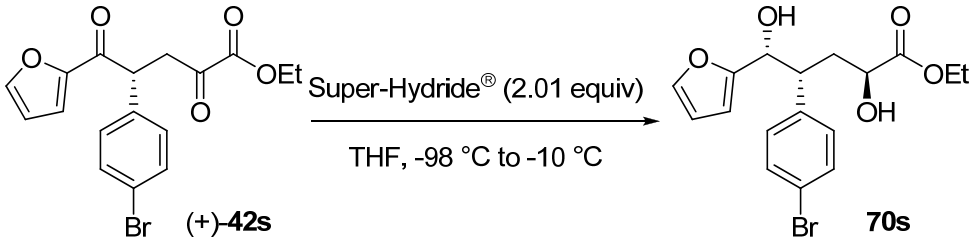
***Rac*-(*3R,5R*)-6-ethoxy-6-(furan-2-yl)-3-hydroxy-5-phenyltetrahydro-2H-pyran-2-one (64a)**



In a 5 mL Schlenk tube was stirred a solution of *rac*-ethyl 5-(furan-2-yl)-2-hydroxy-5-oxo-4-phenylpentanoate (**62a**) (65 mg, 0.21 mmol, 1 equiv) in ethanol (2.1 mL, 0.1 M) to which DBU (9.6 μL, 0.06 mmol, 0.3 equiv) was added. The mixture was heated to 70 °C for 5 h. After cooling to ambient temperature, the solvent was evaporated by rotary evaporation. The crude product was filtered though a short plug of silica gel in a Pasteur pipette. The pipette was rinsed with 50% ethyl acetate in hexanes. The filtrate was collected and the solvent was evaporated to afford pure product as pale yellow oil in 88% yield (57 mg); R_f = 0.30 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3471, 2980, 2933, 1732, 1672, 1566, 1283, 1225, 1106, 1031, 765, 700, 593; **^{1}H NMR** (500 MHz, $CDCl_3$) (*Major diastereomer*) δ 7.51 – 7.50 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.21 (m, 2H), 7.19 (d, *J* = 4.2 Hz, 1H), 6.44 – 6.43 (m, 1H), 4.76 (d, *J* = 9.1, 5.2 Hz, 1H), 4.22 – 4.15 (m, 3H), 2.99 (d, *J* = 4.8 Hz, 1H), 2.81 (ddd, *J* = 13.9, 9.2, 4.5 Hz, 1H), 2.03 (ddd, *J* = 13.9, 8.2, 5.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H);

(*Minor diastereomer*) 7.51 – 7.50 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.28 – 7.21 (m, 2H), 7.16 (d, *J* = 3.6 Hz, 1H), 6.44 – 6.43 (m, 1H), 4.73 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.12 (dddd, *J* = 10.8, 7.1, 7.1, 7.1 Hz, 1H), 3.99 (dddd, *J* = 10.7, 7.1, 7.1, 7.1 Hz, 1H), 3.87 (ddd, *J* = 10.1, 5.1, 3.3 Hz, 1H), 2.86 (d, *J* = 5.5 Hz, 1H), 2.41 (ddd, *J* = 13.9, 9.6, 3.3 Hz, 1H), 2.28 (ddd, *J* = 14.1, 10.5, 5.4 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) (*Major diastereomer*) δ 188.1, 175.3, 152.4, 146.7, 137.9, 129.1, 128.8, 127.6, 118.4, 112.4, 68.1, 62.1, 49.9, 37.3, 14.3; (*Minor diastereomer*) 188.4, 175.0, 152.2, 146.8, 138.8, 128.9, 128.7, 127.5, 118.5, 112.4, 68.6, 61.9, 49.1, 37.4, 14.2; **HRMS** (EI^+) *m*/*z* calcd for $C_{17}H_{18}O_5$ $[M]^+$: 302.1154; found: 302.1165.

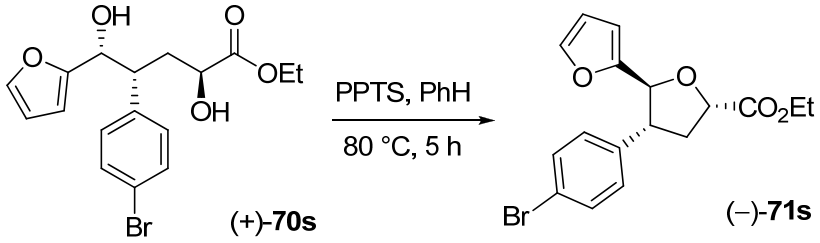
(2*S*,4*R*,5*R*)-ethyl 4-(4-bromophenyl)-5-(furan-2-yl)-2,5-dihydroxypentanoate (70s)



Super-hydride® (350 μL, 0.35 mmol, 2.02 equiv, 1.0 M in THF) was added drop-wise to a solution of (*R*)-ethyl 4-(4-bromophenyl)-5-(furan-2-yl)-2,5-dioxopentanoate (**42s**) (65 mg, 0.17 mmol, 1 equiv) in dry tetrahydrofuran (1.7 mL, 0.1 M) at -98 °C, under inert atmosphere. The reaction was allowed to slowly warm up to -10 °C over 2 h. The reaction was quenched with distilled water (50 mL), followed by the addition of 2M HCl (0.5 mL), and then neutralized with saturated aqueous $NaHCO_3$. The resulting aqueous solution was extracted with ethyl acetate (3 x 5 mL), the combined organic extracts were dried over Na_2SO_4, then concentrated under reduced pressure. The diol was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford a light yellow oil in 87% yield (38 mg, dr 8:1); R_f = 0.18 (30% ethyl acetate in

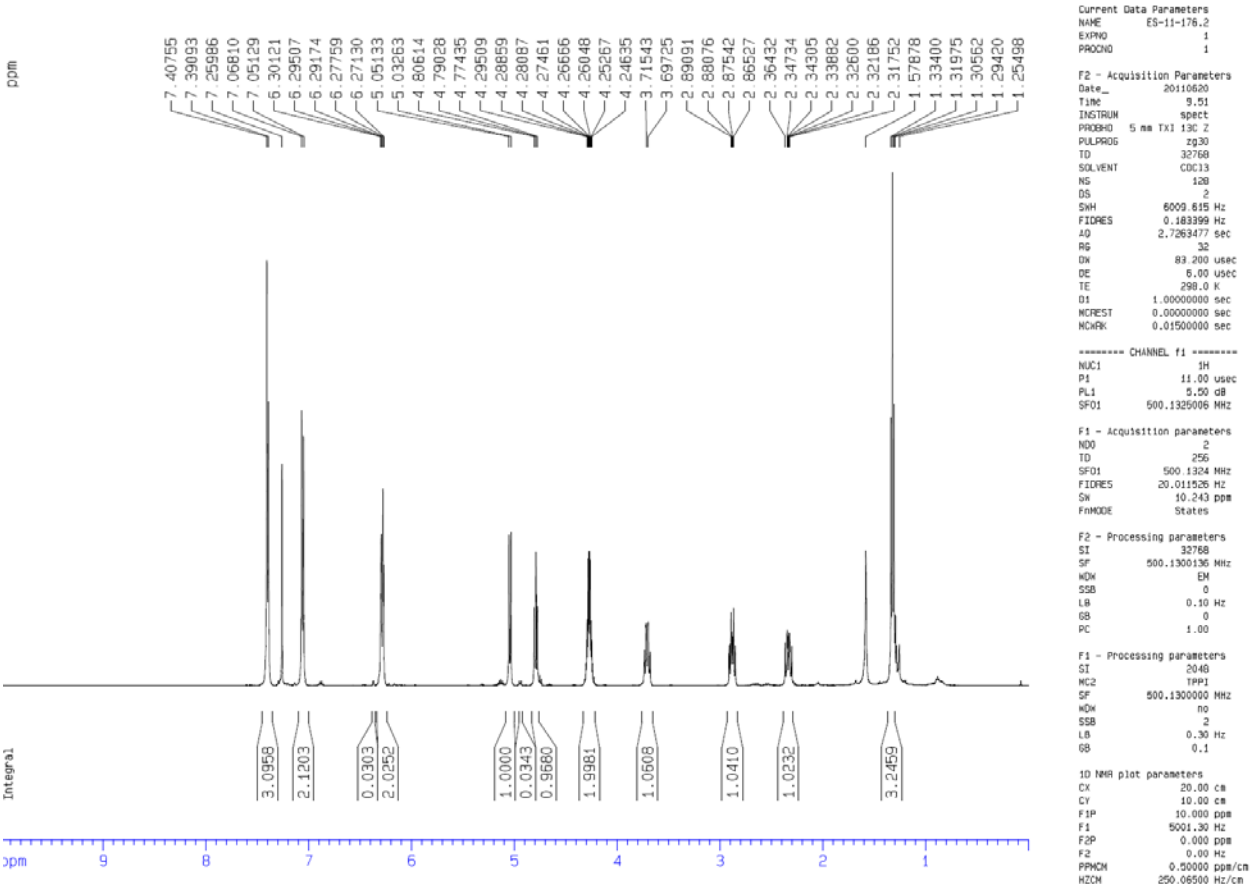
hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3447, 2981, 2929, 1730, 1488, 1215, 1099, 1010, 740; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.37 (dd, *J* = 0.8, 0.7 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.30 (dd, *J* = 2.8, 1.9 Hz, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 4.85 (d, *J* = 7.3 Hz, 1H), 4.17 (dddd, *J* = 7.1, 7.1, 7.1, 3.1 Hz, 2H), 3.73 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.47 (ddd, *J* = 11.3, 7.3, 3.9 Hz, 1H), 2.13 (ddd, *J* = 13.8, 11.7, 2.3 Hz, 1H), 1.73 (ddd, *J* = 14.7, 11.1, 3.9 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.2, 154.6, 142.2, 138.7, 131.9, 130.8, 121.3, 110.4, 107.7, 71.6, 68.3, 62.0, 47.3, 37.0, 14.3; **HRMS** (EI^+) *m*/*z* calcd for $C_{17}H_{19}BrO_5$ $[M]^+$: 382.0415; found: 382.0411.

(2*S*,4*R*,5*S*)-ethyl 4-(4-bromophenyl)-5-(furan-2-yl)tetrahydrofuran-2-carboxylate (71s)



In a Schlenk tube was stirred a solution of (+)-(2*S*,4*R*,5*R*)-ethyl 4-(4-bromophenyl)-5-(furan-2-yl)-2,5-dihydroxypentanoate (**56s**) (20 mg, 0.05 mmol, 1 equiv) in benzene (0.33 mL) to which pyridinium *p*-toluenesulfonate (1 mg, 0.003 mmol, 0.05 equiv) was added. A cold finger was adapted to the tube and heated to reflux for 5 h. After cooling to room temperature, the reaction was quenched with aqueous saturated sodium bicarbonate (1 mL). The organic phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were dried though a short column with anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford a light yellow oil (65% yield, 12 mg, dr 19:1); R_f = 0.4 (30% ethyl acetate in hexanes); $[\alpha]_D^{21}$ -4.4

(*c* 0.4, CH_2Cl_2), **FTIR** (KBr film) ν_{max} (cm^{-1}): 3120, 2980, 1747, 1491, 1374, 1206, 1091, 1010, 819, 742, 530; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.27 (d, *J* = 3.2 Hz, 1H), 5.04 (d, *J* = 9.4 Hz, 1H), 4.79 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.26 (dddd, *J* = 7.0, 7.0, 7.0, 3.2 Hz, 2H), 3.70 (ddd, *J* = 9.4, 8.9, 8.9 Hz, 1H), 2.88 (ddd, *J* = 12.8, 7.8, 7.8 Hz, 1H), 2.33 (ddd, *J* = 12.8, 10.7, 8.5 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 151.4, 143.2, 138.0, 132.0, 129.4, 121.2, 110.5, 109.7, 81.2, 76.7, 61.5, 48.8, 38.6, 14.4; **HRMS** (EI^+) *m/z* calcd for $C_{17}H_{17}BrO_4$ $[M]^+$: 364.0310; found: 364.0299.



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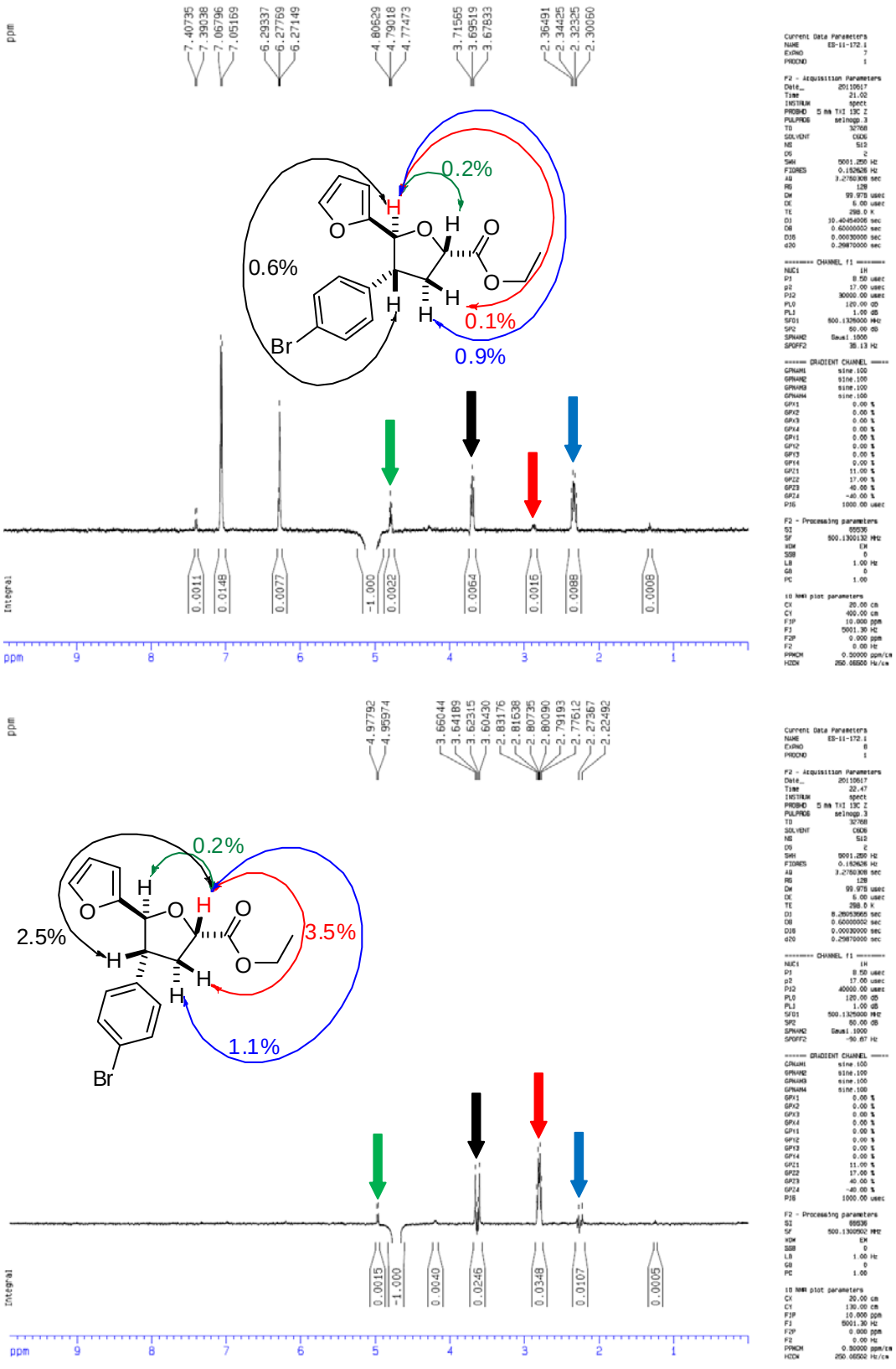
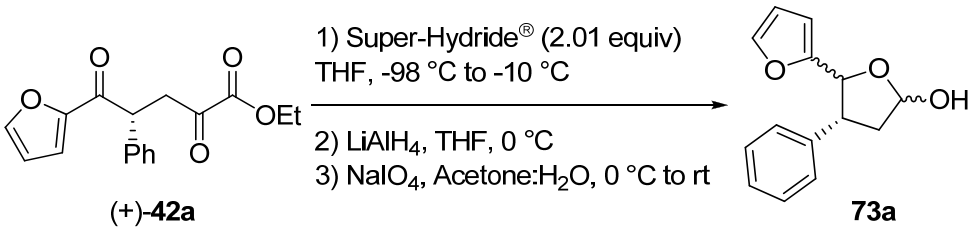


Figure 5.1 Determination of the relative configuration for (–)-**71s**.

(*R*)-5-(furan-2-yl)-4-phenyltetrahydrofuran-2-ol (73a)



(+)-**42a** **73a**

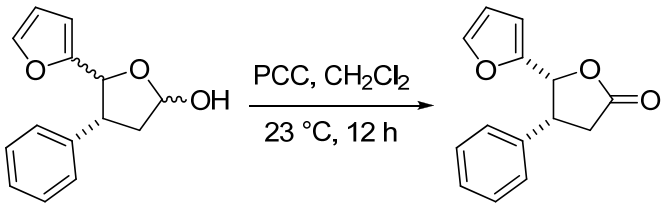
Super-hydride® (660 μL, 0.66 mmol, 2.01 equiv, 1.0 M in THF) was added drop-wise to a solution of (+)-(*R*)-ethyl 5-(furan-2-yl)-2,5-dioxo-4-phenylpentanoate (**42a**) (100 mg, 0.33 mmol, 1 equiv) in dry tetrahydrofuran (3.2 mL, 0.1 M) at -98 °C, under inert atmosphere. The reaction was allowed to slowly warm up to -10 °C over 2 h. The reaction was quenched with distilled water (0.5 mL), followed by the addition of 2M HCl (0.5 mL), and then neutralized with saturated aqueous $NaHCO_3$. The resulting aqueous solution was extracted with ethyl acetate (3 x 5 mL), the combined organic extracts were dried over anhydrous sodium sulfate, then concentrated under reduced pressure. The diol was dried under high vacuum for 2 h.

The crude diol was re-dissolved in dry tetrahydrofuran (1.9 mL, 0.1 M) and the mixture was cooled to 0 °C. To this solution, lithium aluminum hydride (340 μL, 0.33 mmol, 1 equiv, 1.0 M in Et_2O) was added drop-wise (over 1 min) and was allowed to stir for 10 min. The reaction was carefully quenched with distilled water (0.5 mL). To the mixture was successively added 15% sodium hydroxide (0.5 mL) and distilled water (1 mL). The mixture was allowed to stir for 2 h at ambient temperature, then $MgSO_4$ was added and the mixture was stirred overnight. The solution was filtered through a plug of Celite® and rinsed with THF. The filtrate was collected and the solvent evaporated under reduced pressure.

The resulting triol was re-dissolved in a mixture of acetone (2.2 mL): distilled water (1 mL), the mixture was cooled to 0 °C for 10 min and sodium periodate (142 mg, 0.66 mmol, 2 equiv) was added in one portion. The reaction was stirred for 1 h at the same temperature and

then quenched with distilled water (5 mL). The organic layer was successively extracted with ethyl acetate (3 x 10 mL), washed with brine (1 x 10 mL), and dried through anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography to afford **73a** in 74% yield (57 mg, 5.5:1.4:1.2:1 dr); R_f = 0.22 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3408, 3029, 2949, 1723, 1603, 1498, 1455, 1149, 1010, 739, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 1H), 7.19 – 7.12 (m, 3H), 7.00 (d, *J* = 6.7 Hz, 2H), 5.93 (d, *J* = 4.9 Hz, 1H), 5.91 (d, *J* = 3.0 Hz, 1H), 5.50 (d, *J* = 7.8 Hz, 1H), 4.06 (ddd, *J* = 10.2, 10.2, 7.4 Hz, 1H), 2.65 (ddd, *J* = 12.7, 12.7, 5.2 Hz, 1H), 2.32 (dd, *J* = 12.8, 7.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 152.6, 141.9, 138.3, 128.2, 128.1, 126.7, 110.0, 108.1, 98.5, 78.4, 46.7, 38.6; **HRMS** (EI^+) *m*/*z* calcd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0942; found: 230.0941.

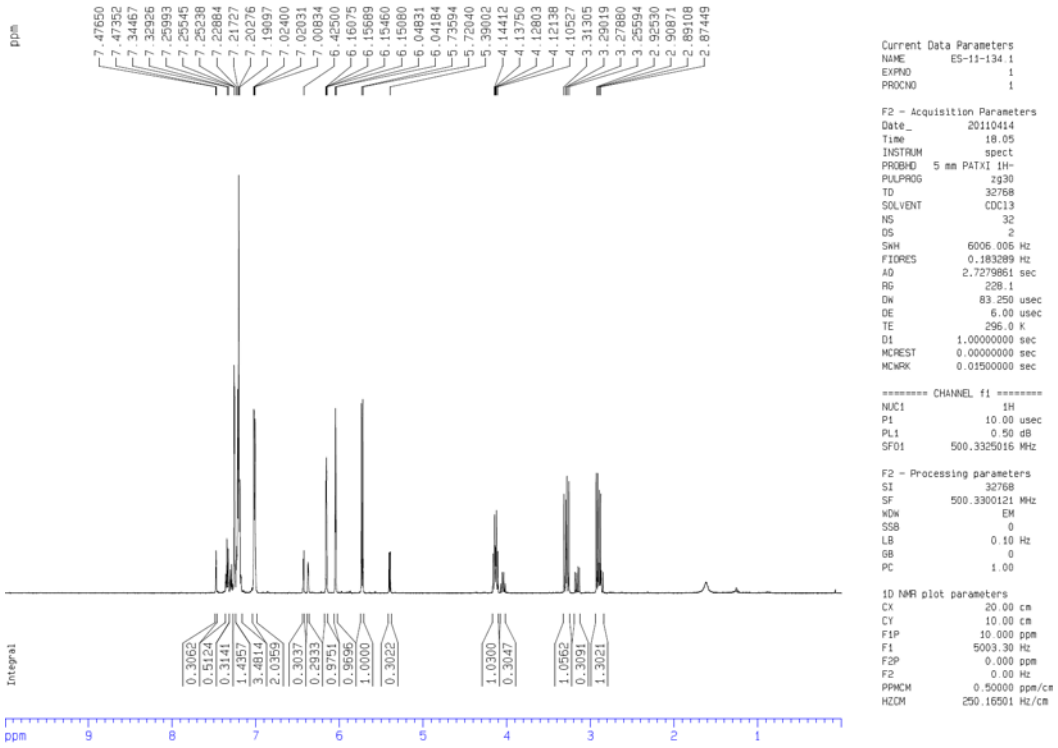
(4*R*,5*R*)-5-(furan-2-yl)-4-phenyldihydrofuran-2(3H)-one (74a)



(+)-**73a** **74a**

In a 2 dram, oven-dried vial, a stirring solution of (*R*)-5-(furan-2-yl)-4-phenyltetrahydrofuran-2-ol (15 mg, 0.07 mmol, 1 equiv) in dry dichloromethane (0.6 mL) was treated with pyridinium chlorochromate (PCC, 18 mg, 0.09 mmol, 1.5 equiv). The dark orange solution was stirred for 12 h. After completion, the mixture was filtered through a plug of Celite® and rinsed with dichloromethane. The filtrate was collected and the solvent was evaporated. The crude product was purified by preparative thin layer chromatography (PTLC) (10% ethyl acetate in toluene) to afford a light yellow oil (inseparable mixture of diastereomers: 14 mg, 94% yield,

84% ee, dr 3.3:1). R_f = 0.28 (10% ethyl acetate in toluene); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3542, 3033, 2934, 1782, 1499, 1151, 994, 745, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) (*major diastereomer*) δ 7.26 – 7.24 (m, 1H), 7.22 – 7.19 (m, 2H), 7.02 – 7.00 (m, 2H), 6.15 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.05 (d, *J* = 3.2 Hz, 1H), 5.73 (d, *J* = 7.8 Hz, 1H), 4.13 (ddd, *J* = 11.4, 8.3, 8.3 Hz, 1H), 3.28 (dd, *J* = 17.1, 11.4 Hz, 1H), 2.90 (dd, *J* = 17.1, 8.3 Hz, 1H); (*minor diastereomer*) δ 7.48 – 7.47 (m, 1H), 7.35 -7.32 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.22 – 7.19 (m, 1H), 6.43 (d, *J* = 3.2 Hz, 1H), 6.37 (dd, *J* = 5.0, 1.8 Hz, 1H), 5.40 (d, *J* = 7.8 Hz, 1H), 4.04 (q, *J* = 8.7 Hz, 1H), 3.15 (dd, *J* = 17.6, 8.7 Hz, 1H), 2.87 (dd, *J* = 17.6, 9.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) (*major diastereomer*) δ 176.0, 149.2, 143.0, 128.6, 127.7, 127.6, 127.1, 110.4, 110.3, 78.6, 45.9, 33.1; (*minor diastereomer*) δ 143.9, 135.9, 129.3, 128.1, 117.8, 115.9, 110.8, 80.5, 45.5, 36.6 (the carbon corresponding to C=O and the 4º carbon on the furan ring does not show up); **HRMS** (EI^+) *m/z* calcd for $C_{14}H_{12}O_3$ $[M]^+$: 228.0786; found: 228.0788.



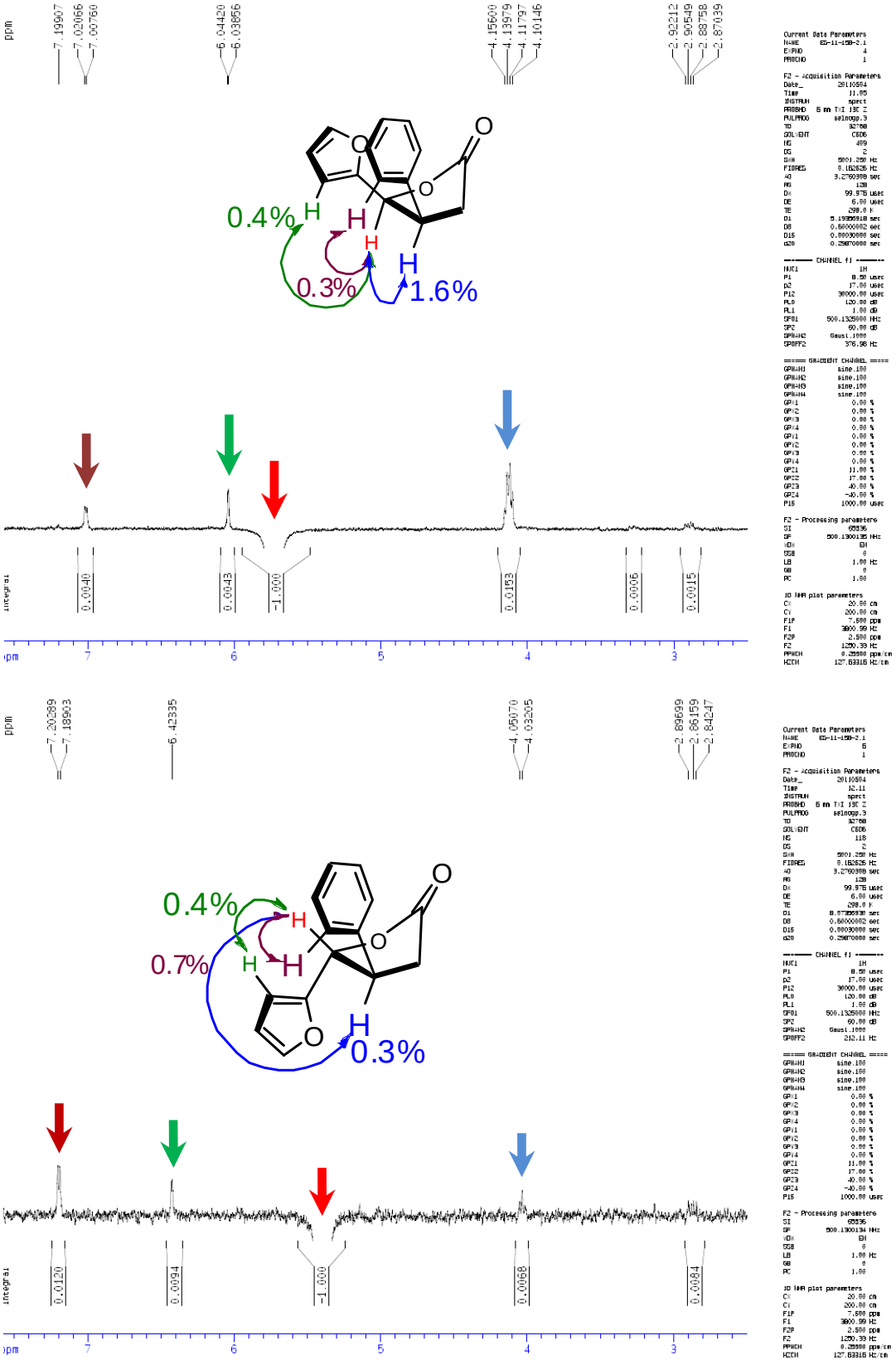
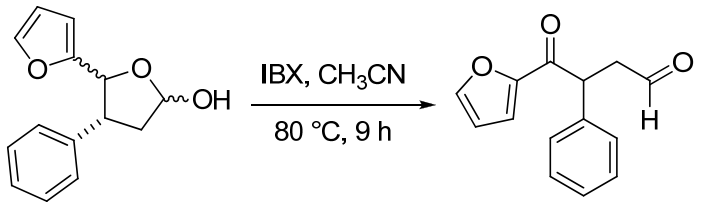


Figure 5.2 Determination of the relative configuration for **74a**.

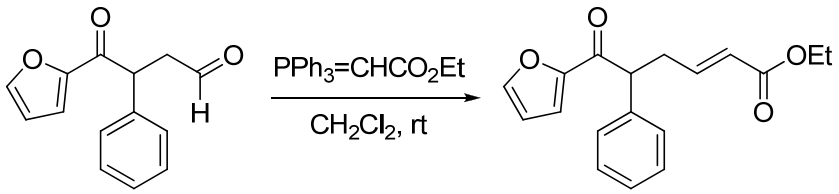
***Rac*-4-(furan-2-yl)-4-oxo-3-phenylbutanal (75a)**



73a **75a**

In a Schlenk tube was stirred a solution of 5-(furan-2-yl)-4-phenyltetrahydrofuran-2-ol (23 mg, 0.1 mmol, 1 equiv) in acetonitrile (0.3 mL, 0.3 M) at room temperature. To the solution was added 2-iodosobenzoic acid (IBX) (56 mg, 0.2 mmol, 2 equiv) in one portion. The mixture was heated at 80 °C for 9 h. The tube was allowed to cool to ambient temperature and the mixture was filtered though a fine fitted funnel. The filter cake was rinsed with ethyl acetate and the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography (15% ethyl acetate in hexanes) to afford a mixture of products. The aldehyde was obtained as dark yellow oil in 63% yield (14 mg) and lactone **60a** was isolated as light yellow oil in 27% yield (6.3 mg). R_f = 0.25 (15% ethyl acetate in toluene); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3135, 3062, 2927, 1721, 1673, 1567, 1466, 1393, 1267, 1030, 761, 735, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.53 – 7.52 (m, 1H), 7.32 – 7.27 (m, 4H), 7.25 – 7.21 (m, 1H), 7.18 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.46 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.93 (dd, *J* = 9.8, 4.4 Hz, 1H), 3.59 (dd, *J* = 18.7, 9.8 Hz, 1H), 2.84 (dd, *J* = 18.7, 4.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 187.2, 146.8, 138.0, 129.3, 128.4, 127.9, 127.8, 118.7, 112.5, 47.6, 47.4; **HRMS** (EI^+) *m*/*z* calcd for $C_{14}H_{12}O_3$ $[M]^+$: 228.0786; found: 228.0789.

***Rac*-(*E*)-ethyl 6-(furan-2-yl)-6-oxo-5-phenylhex-2-enoate (76a)**



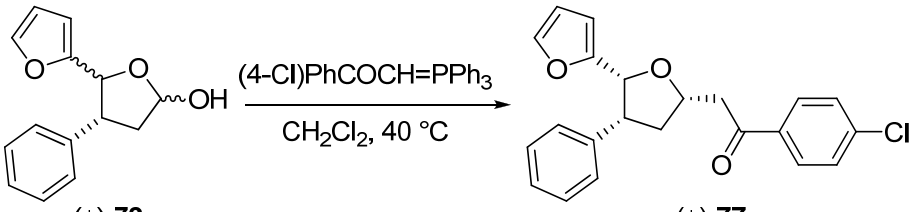
75a **76a**

To a solution of 4-(furan-2-yl)-4-oxo-3-phenylbutanal (**75a**) (14 mg, 0.06 mmol, 1 equiv) in dichloromethane (0.6 mL, 0.1 M) was added (2-ethoxy-2-oxoethyl) triphenylphosphorane (32 mg, 0.09 mmol, 1.5 equiv) in one portion. The mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to furnish off white crystals in 98% yield (2 mg (*Z*) + 17 mg (*E*), 98%). R_f = 0.25 (*Z*-isomer), 0.20 (*E*-isomer (10% ethyl acetate in hexanes); (*E*-*isomer*) **FTIR** (KBr film) ν_{max} (cm^{-1}): 2981, 1716, 1672, 1566, 1465, 1274, 1161, 1033, 764, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 1.5, 0.5 Hz, 1H), 7.33 – 7.28 (m, 4H), 7.28 – 7.22 (m, 1H), 7.16 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.85 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.46 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.49 (t, *J* = 7.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.09 (dddd, *J* = 15.1, 8.0, 7.8, 1.4 Hz, 1H), 2.68 (dddd, *J* = 14.9, 7.0, 6.9, 1.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 187.5, 166.5, 152.3, 146.8, 145.8, 138.2, 129.2, 128.4, 127.7, 123.6, 118.4, 112.6, 60.4, 52.9, 35.5, 14.4; **HRMS** (EI^+) *m/z* calcd for $C_{18}H_{18}O_4$ $[M]^+$: 298.1205; found: 298.1203.

(*Z*-isomer) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 – 7.52 (m, 1H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 6.45 (dd, *J* = 3.6, 1.4 Hz, 1H), 6.16 (ddd, *J* = 15.3, 7.5 Hz, 1H), 5.77 (d, *J* = 11.5 Hz, 1H), 4.53 (t, *J* = 7.5 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.35 (ddd, *J* = 14.5, 6.4, 6.4 Hz, 1H), 3.23 (ddd, *J* = 14.5, 7.9, 7.9 Hz,

1H), 1.27 (t, *J* = 7.1 Hz, 3H); **HRMS** (EI^+) *m/z* calcd for $C_{18}H_{18}O_4$ $[M]^+$: 298.1205; found: 298.1201.

***Rac*-1-(4-chlorophenyl)-2-(5-(furan-2-yl)-4-phenyltetrahydrofuran-2-yl)ethanone (77a)**

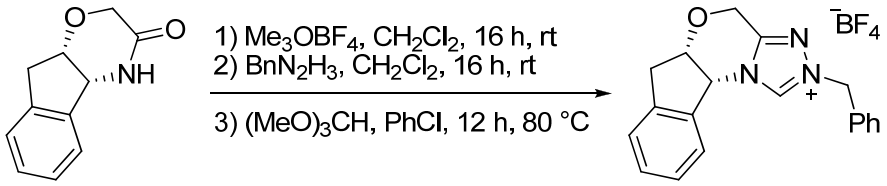


(±)-**73a** (±)-**77a**

To a solution of 5-(furan-2-yl)-4-phenyltetrahydrofuran-2-ol [(±)-**73a**] (20 mg, 0.09 mmol, 1 equiv) in dichloromethane (0.8 mL, 0.1 M) was added (4-chloro)benzoyl phosphorane (**87b**) (475 mg, 0.12 mmol, 1.5 equiv) in one portion. The reaction was heated to reflux for 4 days. After evaporation of the solvent in vacuo, the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford a light yellow oil in 49% yield (14 mg). R_f = 0.25 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3030, 2902, 1686, 1588, 1400, 1092, 1055, 993, 737, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.47 – 7.42 (m, 2H), 7.22 – 7.21 (m, 1H), 7.17 – 7.10 (m, 3H), 7.02 – 7.00 (m, 2H), 6.11 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.90 (d, *J* = 3.1 Hz, 1H), 5.24 (d, *J* = 8.2 Hz, 1H), 4.78 (dddd, *J* = 10.1, 6.2, 6.2, 6.2 Hz, 1H), 3.86 (ddd, *J* = 12.4, 7.2 Hz, 1H), 3.70 (dd, *J* = 16.5, 6.4 Hz, 1H), 3.30 (dd, *J* = 16.5, 6.2 Hz, 1H), 2.61 (ddd, *J* = 12.0, 6.5, 5.4 Hz, 1H), 2.40 (ddd, *J* = 12.2, 12.2, 10.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.3, 153.7, 142.0, 139.8, 138.2, 135.6, 130.0, 129.1, 128.2, 128.1, 126.8, 110.1, 108.6, 78.3, 76.1, 49.8, 45.1, 37.1; **HRMS** (EI^+) *m/z* calcd for $C_{22}H_{19}ClO_3$ $[M]^+$: 366.10223; found: 366.1022.

5.3 General Procedures for the Diastereoselective Synthesis of Indanes via a Domino Stetter-Michael Reaction

Synthesis of (5*aS*,10*bR*)-2-benzyl-4,5*a*,6,10*b*-tetrahydroindeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium tetrafluoroborate (16q)



16q

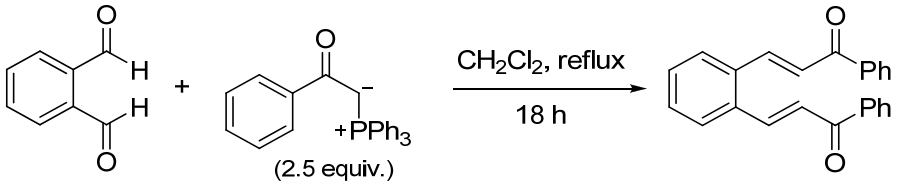
A 100 mL round bottomed flask was charged with (4a*R*,9a*S*)-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2*H*)-one[170] (685 mg, 3.62 mmol, 1 equiv) in dry dichloromethane (36 mL, 0.1 M). Trimethyloxonium tetrafluoroborate (803 mg, 5.43 mmol, 1.5 equiv) was added and the reaction mixture stirred for 16 hours at room temperature. Afterwards benzylhydrazine (552 mg, 4.52 mmol, 1.25 equiv) was added and the solution was again stirred for 16 hours. The solvent was removed in vacuo and the residue was used without further purification. Trimethyl orthoformate (38 mL, 344 mmol, 95 equiv) was added and the reaction mixture was refluxed with chlorobenzene (7.2 mL, 0.5 M) at 80 °C for 12 hours. The solvent was removed in vacuo and the product was loaded into a column using 10% acetone in chloroform and eluted with 100% chloroform to remove the non-polar impurities. Then, the mobile phase was changed to 60% ethyl acetate in hexanes and the fractions with an R_f = 0.05 were collected together [TLC solvent system $CHCl_3$/Acetone (8:2)]. The solvent was evaporated to afford a light brown solid. This was washed with a few drops of cold ethyl acetate affording the title compound as a tan solid in 49% yield (692 mg). **mp** (°C): 236-240; R_f = 0.05 (20% acetone in chloroform); **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3135, 3076, 2958, 1579, 1441, 1187, 1080; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.53 – 7.47 (m, 3H), 7.37 – 7.27 (m, 6H), 5.87 (d, *J* =

3.7 Hz, 1H), 5.62 (d, J = 14.4 Hz, 1H), 5.51 (d, J = 14.4 Hz, 1H), 4.95 – 4.86 (m, 3H), 3.27 (dd, J = 17.1, 4.6 Hz, 1H), 3.17 (d, J = 17.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.9, 142.0, 140.0, 135.3, 132.1, 129.9, 129.7, 129.5, 129.4, 128.3, 125.7, 124.1, 77.5, 61.8, 60.4, 56.5, 37.6; **HRMS** (ESI/Na^+) m/z calcd for $C_{19}H_{18}N_3O$ $[M]^+$: 304.1444; found: 304.1437.

General Procedure for the Synthesis of Electron-Poor Olefins (80a-k)

To a 50 mL round-bottomed flask containing a solution of *o*-phthaldialdehyde (**23a**) (1 equiv.) in CH_2Cl_2 (0.6 M) was added the ylide (2.5 equiv.) in one portion at room temperature (23 °C). The mixture was heated to reflux for 18 h. The reaction mixture was cooled down to ambient temperature and the solvent was removed in vacuo. The crude mixture was purified by flash column chromatography on silica gel.

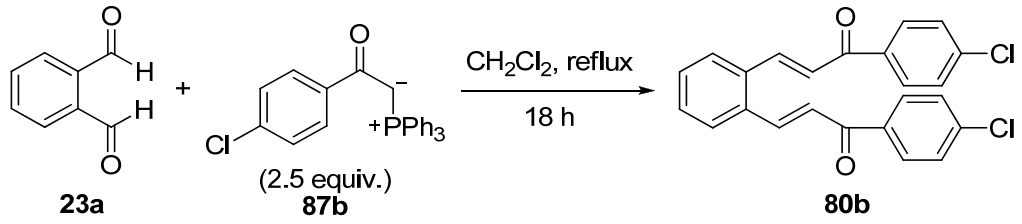
(2*E*,2'*E*)-3,3'-(1,2-phenylene)bis(1-phenylprop-2-en-1-one) (80a)



23a **87a** **80a**

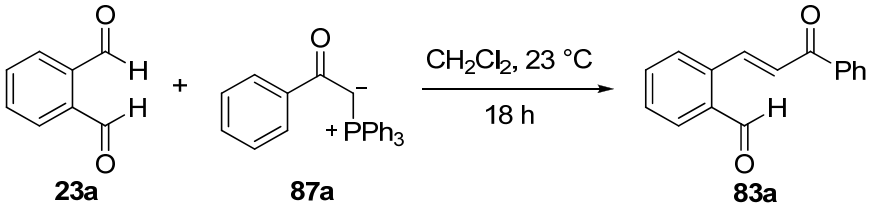
Purified with 30% ethyl acetate in hexanes, yielding 2.15 g (91%) of **80a** as light yellow or off-white thin needles. R_f = 0.30 (30% ethyl acetate in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19 (d, J = 15.5 Hz, 2H), 8.03 (d, J = 7.2 Hz, 4H), 7.76-7.70 (m, 2H), 7.60-7.56 (m, 2H), 7.52-7.45 (m, 6H), 7.43 (d, J = 15.5 Hz, 2H). All spectral data are identical to Navarro and co-workers.[103]

(2*E*,2'*E*)-3,3'-(1,2-phenylene)bis(1-(4-chlorophenyl)prop-2-en-1-one) (80b)



Purified with 30% ethyl acetate in hexanes, yielding 1.94 g (64%) of **80b** as a pale yellow solid. **mp** (°C): 135-136; R_f = 0.30 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3060, 1662, 1604, 1590, 1486, 1399, 1327, 1301; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 15.5 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.69-7.65 (m, 2H), 7.48 (d, *J* = 7.7 Hz, 6H), 7.39 (d, *J* = 15.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.8, 142.3, 139.7, 136.4, 135.5, 130.55, 130.2, 129.3, 128.5, 125.7. **HRMS** (ESI^+) *m*/*z* calcd for $C_{24}H_{17}Cl_2O_2$ $[M+1]^+$: 407.0600; found: 407.0611.

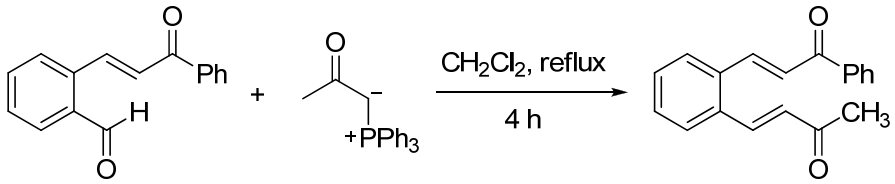
(*E*)-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (83a)



The title compound was prepared employing a modified procedure from Suwa and co-workers.[141] To a 50 mL round-bottomed flask containing a solution of *o*-phthaldialdehyde (**23a**) (1.34 g, 10 mmol, 1 equiv) in CH_2Cl_2 (13 mL) was added a solution of (benzoylmethylene)triphenylphosphorane (**87a**) (3.81 g, 10 mmol, 1 equiv) in CH_2Cl_2 (20 mL) dropwise at room temperature (23 °C) over ca. 6 minutes. The mixture was stirred at 23 °C for 18 h. The solvent was removed, and the crude was filtered through a plug of silica gel using 30%

ethyl acetate in hexanes. The fractions containing the product were collected, the solvent was evaporated in vacuo and the resulting dark brown oil was bulb-to-bulb distilled (**bp** (°C): 225/0.8 torr), yielding 1.70 g of yellow solid (72%), **mp** (°C): 57-58; R_f = 0.20 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3063, 1694, 1663, 1605, 1215, 1016, 756; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.56 (d, *J* = 15.7 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.90 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.65 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.61-7.59 (m, 2H), 7.51 (dd, *J* = 7.8, 7.4 Hz, 2H), 7.37 (d, *J* = 15.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.9, 190.7, 141.5, 137.9, 137.5, 134.5, 134.1, 133.2, 132.4, 130.2, 129.0, 128.9, 128.2, 127.6. **HRMS** (EI^+) *m*/*z* calcd for $C_{16}H_{12}O_2$ $[M]^+$: 236.0837; found: 236.0835.

(*E*)-4-(2-((*E*)-3-oxo-3-phenylprop-1-enyl)phenyl)but-3-en-2-one (80c)

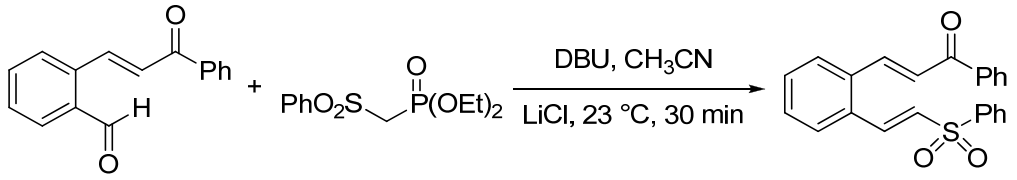


83a **87c** **80c**

To a solution of (*E*)-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (**83a**) (200 mg, 0.84 mmol, 1 equiv) in CH_2Cl_2 (2.4 mL) in a 25 mL round-bottom flask was added a solution of (triphenylphosphoranylilidene)acetone (**87c**) (321 mg, 1.01 mmol, 1.2 equiv) in CH_2Cl_2 (6 mL). The flask was fitted with a condenser and the mixture was heated to reflux for 4 h. The mixture was cooled down to room temperature (23 °C), the solvent was removed in vacuo, and the crude mixture was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes), yielding 215 mg of brown oil (92%). R_f = 0.25 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3071, 1666, 1605; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 15.5 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 16.1 Hz, 1H), 7.71-7.69 (m, 1H), 7.59 (dd, *J* = 7.6, 7.3

Hz, 2H), 7.50 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.45-7.42 (m, 3H), 6.63 (d, *J* = 16.5 Hz, 1H), 2.41 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.1, 190.0, 141.4, 140.2, 138.0, 135.2, 135.0, 133.3, 130.8, 130.5, 130.4, 128.9, 128.7, 128.1, 127.9, 126.0, 27.8. **HRMS** (EI^+) *m/z* calcd for $C_{19}H_{16}O_2$ $[M]^+$: 276.1150; found: 276.1147.

(*E*)-1-phenyl-3-(2-((*E*)-2-(phenylsulfonyl)vinyl)phenyl)prop-2-en-1-one (80d)

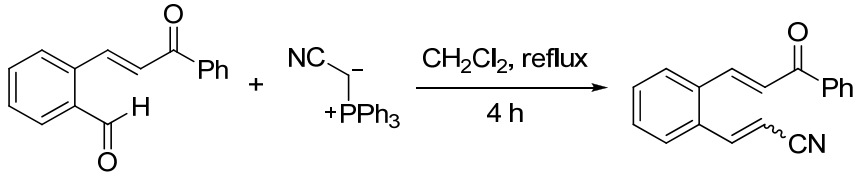


83a **91** **80d**

To a stirred solution of lithium chloride (54 mg, 1.26 mmol, 1.5 equiv.) in CH_3CN (6 mL) under nitrogen, was added a solution of diethyl phenylsulfonylmethylphosphonate (**91**)[161] (441 mg, 1.51 mmol, 1.8 equiv) in CH_3CN (1 mL). DBU (151 μL, 1.01 mmol, 1.2 equiv) was then added, followed by a solution of (*E*)-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (**83a**) (200 mg, 0.84 mmol, 1 equiv) in CH_3CN (1.4 mL). The mixture was stirred for 30 minutes at room temperature (23 °C), then quenched with a saturated solution of aqueous ammonium chloride. The acetonitrile was evaporated in vacuo, and the organic residue was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes), yielding 164 mg of a light yellow solid (52%), **mp** (°C): 144-146; R_f = 0.20 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3059, 1663, 1605, 1145; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09-8.01 (m, 4H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.63-7.59 (m, 2H), 7.55-7.48 (m, 5H), 7.45 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 15.7 Hz, 1H), 6.85 (d, *J* = 15.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)

δ 189.9, 140.9, 140.5, 139.7, 137.9, 135.7, 133.7, 133.3, 132.5, 131.1, 130.9, 130.3, 129.6, 128.9, 128.8, 128.7, 128.3, 127.9, 127.2. **HRMS** (EI^+) *m/z* calcd for $C_{23}H_{18}O_3S$ $[M]^+$: 374.0977; found: 374.0989.

3-(2-((*E*)-3-oxo-3-phenylprop-1-enyl)phenyl)acrylonitrile (80e)

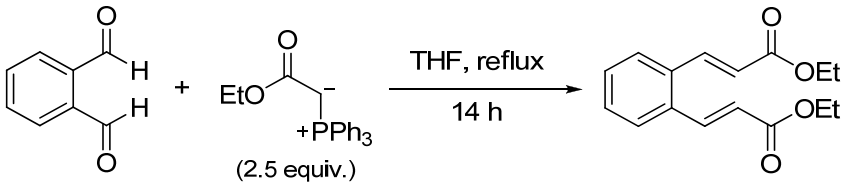


83a **87d** **80e**

To a solution of (*E*)-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (**83a**) (200 mg, 0.84 mmol, 1 equiv) in CH_2Cl_2 (2.4 mL) in a 25 mL round-bottom flask was added a solution of (triphenylphosphoranylidene)acetonitrile (**87d**) (380 mg, 1.26 mmol, 1.5 equiv) in CH_2Cl_2 (6 mL). The flask was fitted with a condenser and the mixture was heated to reflux for 4 h. The mixture was cooled down to room temperature (23 °C), the solvent was removed in vacuo and the crude mixture was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes), yielding 181 mg of a light yellow solid (83%), **mp** (°C): 67-68; R_f = 0.25 (30% ethyl acetate in hexanes); *E:Z* = (2:1), inseparable mixture of isomers. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3061, 2218, 1662, 1605, 1475, 1447; **(*E,E*-diastereomer): ^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07-8.01 (m, 3H), 7.82 (d, *J* = 16.5 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.63-7.56 (m, 1H), 7.54-7.41 (m, 6H), 5.84 (d, *J* = 16.5 Hz, 1H); **^{13}C NMR** (125 MHz, CDCl3) δ 189.7, 147.7, 140.5, 137.8, 134.8, 133.7, 133.4, 131.2, 130.5, 128.9, 128.9, 128.7, 128.2, 127.2, 117.8, 100.0. **(*E,Z*-diastereomer): ^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07-8.01 (m, 2H), 7.96 (d, *J* = 15.5 Hz, 1H), 7.91-7.89 (m, 1H), 7.75-7.73 (m, 1H), 7.63-7.56 (m, 2H), 7.54-7.41 (m, 5H), 5.65 (d, *J* = 15.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.8, 147.3, 140.8, 137.9, 134.7, 133.9, 133.3, 130.8,

130.6, 129.0, 128.7, 127.8, 126.4, 125.8, 116.7, 99.7. **HRMS** (EI^+) *m/z* calcd for $C_{18}H_{13}NO$ $[M]^+$: 259.0997; found: 259.0999.

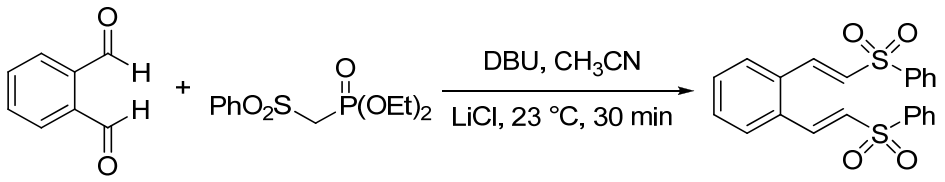
Bis-ethyl cinnamate (80f)



23a **87e** **80f**

80f was prepared following the general procedure employing phthaldialdehyde (**23a**) (1 g, 7.5 mmol, 1 equiv), THF (10 mL, 0.75 M), and (2-ethoxy-2-oxoethyl)triphenylphosphorane (**87e**) (6.49 g, 18.6 mmol, 2.5 equiv). The mixture was heated to reflux for 14 hours. The crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford a white solid in 98% yield (1.76 g). **mp** (°C): 57-59; R_f = 0.60 (40% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2985, 1710, 1703, 1636, 1625, 1314, 1215, 770; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 15.8 Hz, 2H), 7.57 – 7.56 (m, 2H), 7.41 – 7.39 (m, 2H), 6.35 (d, *J* = 15.8 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 4H), 1.35 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 141.5, 134.6, 130.2, 127.9, 122.2, 60.9, 14.5; **HRMS** (EI^+) *m/z* calcd for $C_{16}H_{18}O_2$ $[M]^+$: 274.1205; found: 274. 1204.

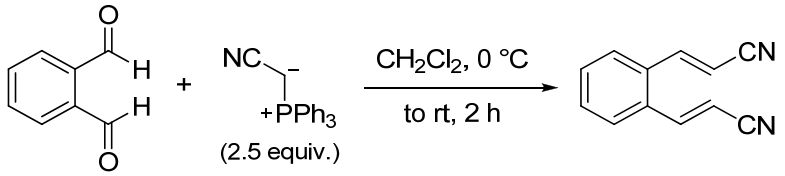
1,2-bis((*E*)-2-(phenylsulfonyl)vinyl)benzene (80g)



23a **91** **80g**

To a stirred solution of lithium chloride (190 mg, 4.5 mmol, 3 equiv) in CH_3CN (11 mL) under nitrogen, was added a solution of diethyl phenylsulfonylmethylphosphonate (**91**) (1.57 g, 5.4 mmol, 3.6 equiv) in CH_3CN (2 mL). Then, DBU (535 µL, 3.6 mmol, 2.4 equiv) was added followed by a solution of phthaldialdehyde (**23a**) (200 mg, 1.5 mmol, 1 equiv) in CH_3CN (2 mL). The mixture was stirred for 30 minutes at room temperature (23 °C), then quenched with a saturated aqueous solution of ammonium chloride. The acetonitrile was evaporated in vacuo, and the organic residue was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated by rotary evaporation. The crude product was purified by flash column chromatography (30% to 40% to 45% ethyl acetate in hexanes) to give a light yellow semisolid in 7% yield (45 mg). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3051, 1593, 1446, 1322, 1145, 1085, 970, 751; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.4 Hz, 4H), 7.88 (d, *J* = 15.3 Hz, 2H), 7.67 – 7.64 (m, 2H), 7.60 – 7.57 (m, 4H), 7.47 – 7.46 (m, 2H), 7.41 – 7.39 (m, 2H), 6.78 (d, *J* = 15.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.3, 138.8, 133.9, 132.7, 132.1, 131.1, 129.7, 128.5, 128.0; **HRMS** (EI^+) *m/z* calcd for $C_{22}H_{18}O_4S_2$ $[M]^+$: 410.0647; found: 410.0647.

(*E*)-3-(2-((*E*)-prop-2-cyano-1-enyl)phenyl) acrylonitrile (80h)

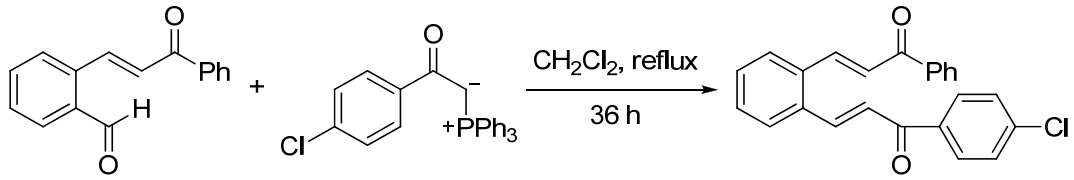


23a **87d** **80h**

80h was prepared following the general procedure employing phthaldialdehyde (**23a**) (200 mg, 1.5 mmol, 1 equiv), dichloromethane (3 mL, 0.5 M) at 0 °C, and (cyanomethyl)triphenylphosphorane (**87d**) (1.12 g, 3.7 mmol, 2.5 equiv) which was added in 5

portions (220 mg each) every 5 min. The crude was purified by flash column chromatography (40% ethyl acetate in hexanes) to afford a white solid in 88% yield (236 mg). **mp** (°C): 92-95; R_f = 0.45 (40% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3068, 2219, 1723, 1607, 1476, 1379, 1235, 782; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.43 (m, 6H), 5.89 (d, *J* = 16.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.3, 133.1, 130.9, 128.6, 116.4, 100.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{12}H_8N_2$ $[M]^+$: 180.0687; found: 180.0684.

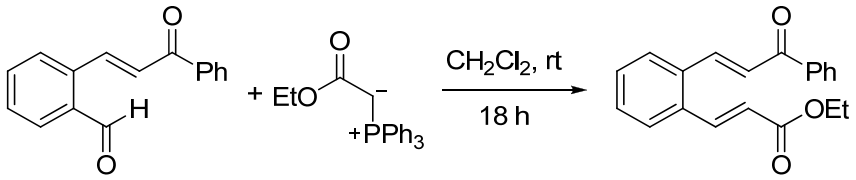
(*E*)-1-(4-chlorophenyl)-3-(2-((*E*)-3-oxo-3-phenylprop-1-enyl)phenyl)prop-2-en-1-one (80i)



83a **87b** **80e**

80i was prepared following the general procedure employing (*E*)-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (**83a**) (200 mg, 0.85 mmol, 1 equiv), (4-chlorophenacylidene)triphenyl phosphorane (**87b**) (353 mg, 0.85 mmol, 1 equiv), and dichloromethane (3 mL, 0.3 M). The crude mixture was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford a pale yellow solid in 84% yield (266 mg). **mp** (°C): 109-110; R_f = 0.3 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3061, 1663, 1604, 830, 757, 692; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 15.6 Hz, 2H), 8.03 (d, *J* = 7.3 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.71 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.48 (m, 5H), 7.36 (d, *J* = 15.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.1, 188.8, 142.3, 141.8, 139.6, 138.1, 136.4, 135.6, 135.4, 133.2, 130.5, 130.3, 130.2, 129.2, 128.9, 128.8, 128.5, 128.4, 126.2, 125.7; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{17}ClO_2$ $[M]^+$: 372.0917; found: 372.0919.

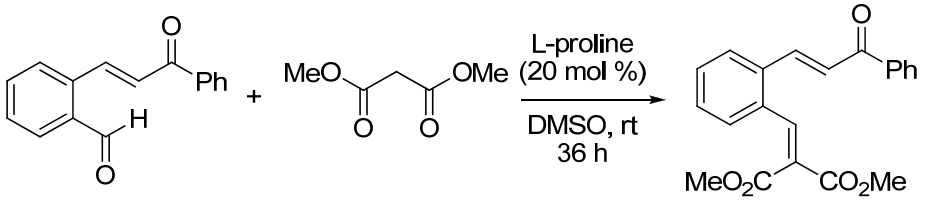
(*E*)-ethyl 3-(2-((*E*)-3-oxo-3-phenylprop-1-enyl)phenyl)acrylate (80j)



83a **87c** **80j**

80j was prepared following the general procedure employing (*E*)-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (**83a**) (436 mg, 2.1 mmol, 1 equiv), dichloromethane (7 mL, 0.3 M), and (2-ethoxy-2-oxoethyl)triphenylphosphorane (**87c**) (800 mg, 2.1 mmol, 1 equiv). The crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to give a thick light yellow oil in 64% yield (414 mg). R_f = 0.28 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2981, 1711, 1664, 1633, 1605, 1366, 1178, 1033, 1015, 761, 691; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 15.5 Hz, 1H), 8.09 (d, *J* = 15.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 2H), 7.69 – 7.68 (m, 1H), 7.65 – 7.55 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.43 – 7.40 (m, 3H), 6.36 (d, *J* = 15.8 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.9, 190.2, 166.5, 141.7, 141.6, 138.2, 135.1, 133.2, 130.3, 130.1, 128.9, 128.8, 128.2, 128.0, 126.1, 122.3, 60.9, 14.5; **HRMS** (EI^+) *m/z* calcd for $C_{20}H_{18}O_3$ $[M]^+$: 306.1256; found: 306.1245.

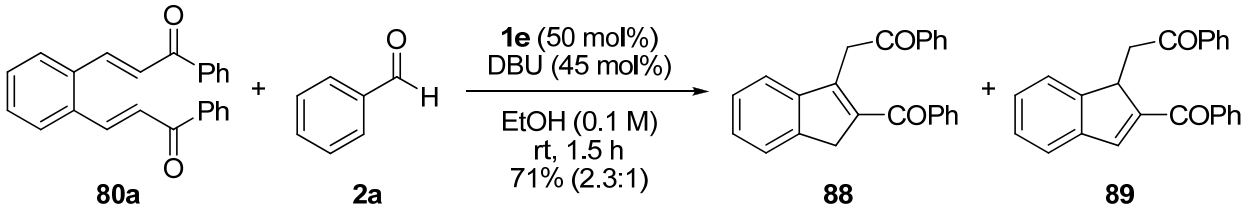
(*E*)-dimethyl 2-(2-(3-oxo-3-phenylprop-1-enyl)benzylidene)malonate (80k)



83a **80k**

In a flame-dried 10 mL round bottom flask and under nitrogen atmosphere was stirred a solution of (*E*)-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (**83a**) (359 mg, 1.5 mmol, 1 equiv) and L-proline (35 mg, 0.3 mmol, 0.2 equiv) in dry dimethyl sulfoxide (1 mL, 1.5 M) for 10 minutes. Then, dimethyl malonate (174 μL, 1.5 mmol, 1 equiv) was added. The mixture was stirred at room temperature for 36 hours. The mixture was diluted with ethyl acetate (5 mL) and washed with water (3 x 5 mL). The organic layer was dried though anhydrous sodium sulfate followed by solvent removal by rotary evaporation. The crude product was purified by flash column chromatography (15% ethyl acetate in hexanes) to afford a thick yellow oil in 34% yield (179 mg). R_f = 0.20 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2952, 1732, 1665, 1606, 1436, 1261, 1217, 1068, 1033, 979, 755, 694; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 15.6 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.37 (d, *J* = 4.0 Hz, 2H), 3.87 (s, 3H), 3.69 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.9, 166.2, 164.1, 142.2, 141.3, 138.0, 134.8, 133.9, 133.2, 130.3, 130.1, 129.1, 128.9, 128.8, 128.7, 128.3, 126.2, 52.9, 52.6; **HRMS** (EI^+) *m*/*z* calcd for $C_{21}H_{18}O_5$ $[M]^+$: 350.1154; found: 350.1159.

Rauhut-Currier Products (88, 89)



In a Schlenk flask fitted with a septum, DBU (6.7 μL, 0.047 mmol, 0.27 equiv) was added to a stirred solution of Michael acceptor (**80a**) (50 mg, 0.15 mmol, 1 equiv), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**1e**) (7.6 mg, 0.05 mmol, 0.3 equiv), and

benzaldehyde (**2a**) in ethanol (1.5 mL, 0.1 M). The mixture was stirred for 30 hours at room temperature. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulphate, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **88** and **89** as a dark yellow solids in 71% yield (2.3:1, 35 mg, combined yield). R_f (**88**) = 0.50 (10% ethyl acetate in hexanes, after developing the TLC 3X); R_f (**89**) = 0.65 (10% ethyl acetate in hexanes, after developing the TLC 3X).

2-(2-benzoyl-1H-inden-3-yl)-1-phenylethanone (88)

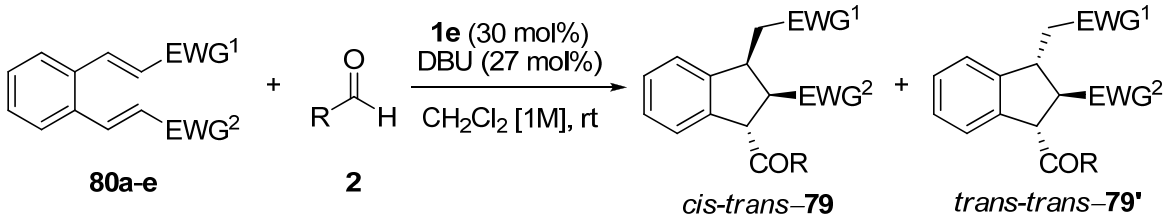
mp (°C): 118-120; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3060, 2917, 1688, 1635, 1597, 1577, 1460, 1447, 1408, 1359, 1212, 1157, 984, 910; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.3 Hz, 2H), 7.75 (d, *J* = 7.1 Hz, 2H), 7.58 – 7.50 (m, 3H), 7.46 – 7.33 (m, 7H), 4.47 (s, 2H), 3.92 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.0, 195.2, 146.3, 144.6, 143.7, 141.3, 140.3, 136.8, 133.6, 132.3, 128.8, 128.6, 128.5, 128.3, 127.9, 127.1, 124.2, 121.9, 41.0, 37.7; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{18}O_2$ $[M]^+$: 338.1307; found: 338.1313.

2-(2-benzoyl-1H-inden-1-yl)-1-phenylethanone (89)

mp (°C): 126-129; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3063, 1684, 1628, 1597, 1577, 1554, 1459, 1345, 1119, 717; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 7.3 Hz, 2H), 7.61 – 7.43 (m, 9H), 7.35 – 7.30 (m, 2H), 4.68 (d, *J* = 9.0 Hz, 1H), 4.05 (dd, *J* = 17.0, 2.2 Hz, 1H), 3.18 (dd, *J* = 17.0, 9.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.6, 193.1, 149.7,

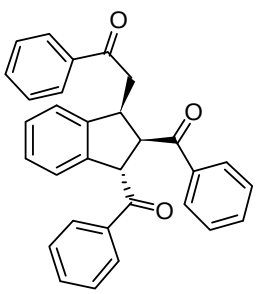
147.7, 144.4, 141.8, 139.4, 137.1, 133.3, 132.2, 129.2, 128.8, 128.6, 128.4, 127.7, 124.8, 124.4, 45.6, 39.7; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{18}O_2$ $[M]^+$: 338.1307; found: 338.1313.

5.3.1 General procedure for the preparation of indanes (79a/a'/a''–u/u')



In a Schlenk flask fitted with a septum, DBU (0.04 mmol, 0.27 equiv) was added to a stirred solution of Michael acceptor (**80a-k**) (0.15 mmol, 1 equiv), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**1e**) (0.045 mmol, 0.3 equiv), and the aldehyde (**2**) in CH_2Cl_2 (1 M). Following the addition of DBU, the septum was replaced with a reflux condenser to avoid evaporation of solvent. The mixture was stirred for the indicated time and temperature shown in **Table 3.4**. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulphate, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel.

***Rac*-((1*S*,2*R*,3*S*)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1,2-diyl)bis(phenylmethanone) (79a)**



Purified with 40% hexanes in dichloromethane, yielding 34 mg of **79a** and 8 mg of **79a'** (64% combined yield). **79a** were white crystals (recrystallized from CH_2Cl_2/2-propanol). **mp** (°C): 115-116. R_f = 0.35

(100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3064, 1680, 1596, 1579, 1448, 1217; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.7 Hz, 2H), 8.07 (d, *J* = 7.7 Hz, 2H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.66 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.61-7.55 (m, 3H), 7.51-7.47 (m, 3H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.90 (d, *J* = 9.6 Hz, 1H), 5.30 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.56 (ddd, *J* = 7.8, 7.8, 6.2 Hz, 1H), 3.14 (dd, *J* = 17.2, 8.6 Hz, 1H), 3.10 (dd, *J* = 17.2, 5.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 199.2, 198.1, 145.5, 140.3, 137.9, 137.1, 136.8, 133.9, 133.9, 133.3, 129.5, 129.2, 129.1, 128.8, 128.7, 128.2, 128.1, 127.8, 125.6, 124.4, 54.1, 52.4, 42.5, 41.1. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{24}O_3$ $[M]^+$: 444.1725; found: 444.1726.

Empirical formula: $C_{31}H_{24}O_3$
Formula weight: 444.50
Crystal Color, Habit: colourless, thin plate
Crystal dimensions (mm): 0.15 × 0.07 × 0.06
Crystal system: monoclinic
Space group: $P2_1/c$ [No. 14]
Unit cell parameters:

a (Å)	11.6926(4)
b (Å)	17.3098(6)
c (Å)	11.6041(4)
α (°)	90
β (°)	99.333(2)
γ (°)	90
V ($Å^3$)	2317.54(14)
Z^b	4

F(000) 936
Density (ρ_{calcd}): 1.274 mg/m^3
Absorption coefficient (μ): 0.641 mm^{-1}

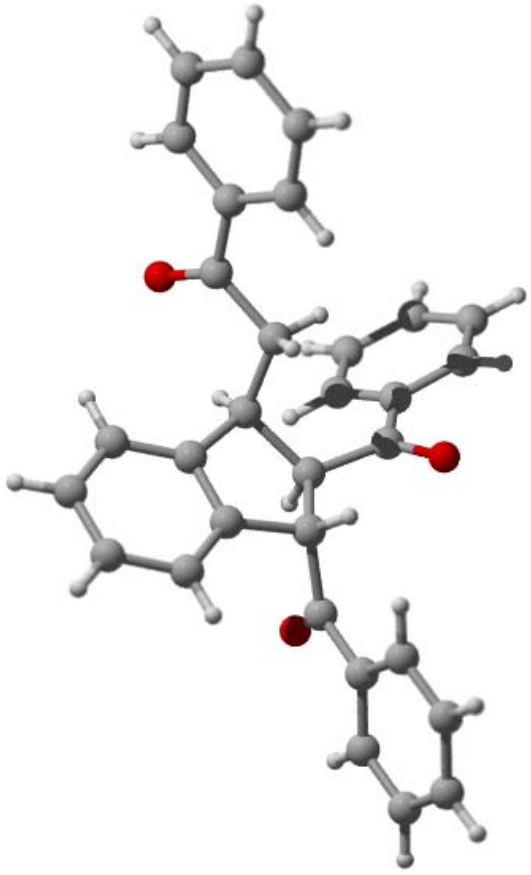


Figure 5.3 ORTEP representation for trisubstituted indane **79a**

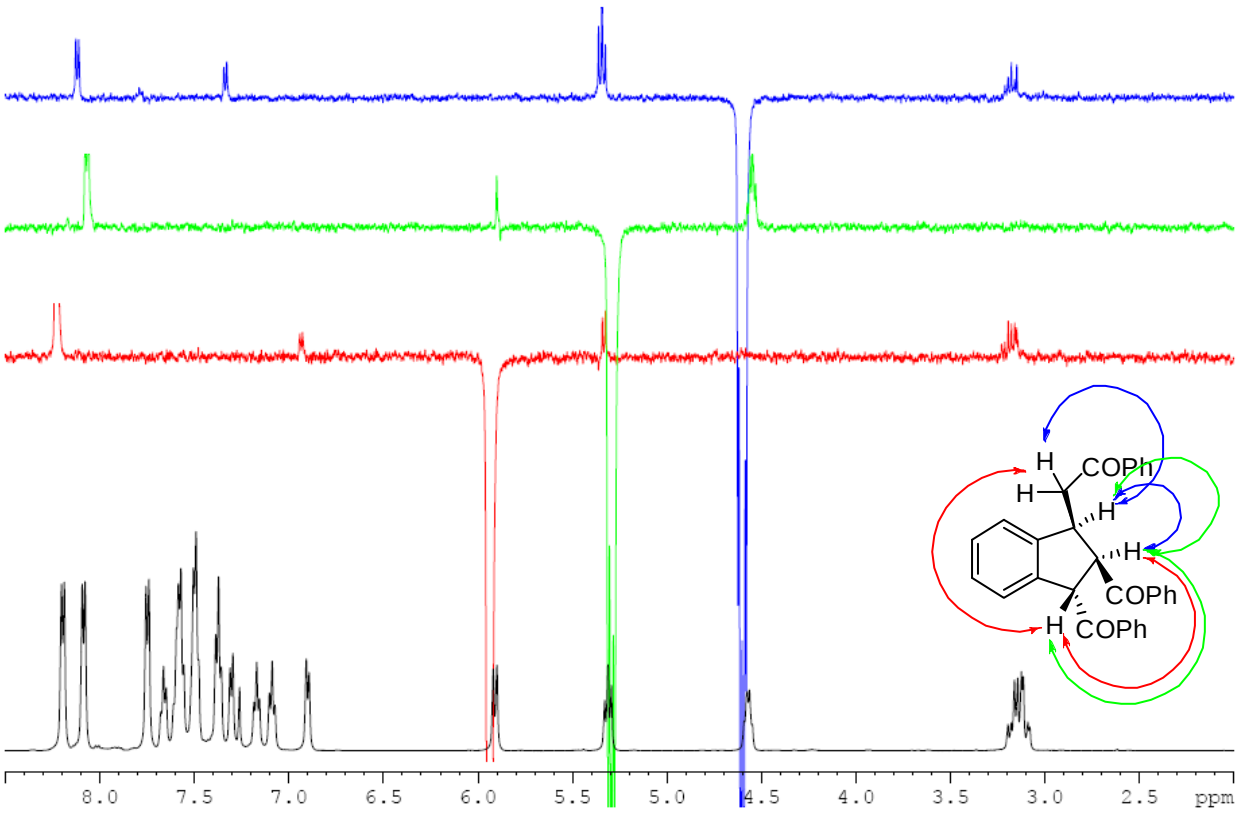
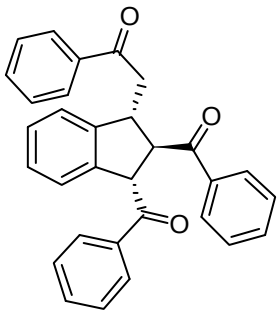


Figure 5.4 Determination of the relative configuration for indane **79a.**

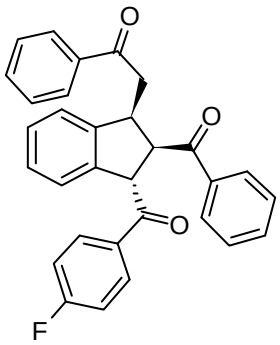
***Rac*-((1*S*,2*S*,3*S*)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1,2-diyl)bis(phenylmethanone) (79a')**



Pale yellow foam, **mp** (°C): 48-49. R_f = 0.28 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3342, 3065, 2928, 1681, 1596, 1580, 1480; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.95 (d, *J* = 7.3 Hz, 2H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.62 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 3H), 7.43 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.38 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 5.46 (d, *J* = 5.5 Hz, 1H), 4.74 (dd, *J* = 5.5, 5.5 Hz, 1H), 4.46 (ddd, *J* = 6.7, 6.4, 6.4 Hz, 1H), 3.61 (dd, *J* = 17.6, 6.0 Hz, 1H), 3.60 (dd, *J* = 17.7, 7.8 Hz, 1H);

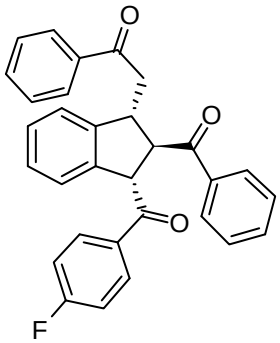
^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 199.4, 198.8, 145.7, 139.8, 137.2, 137.1, 136.9, 133.9, 133.4, 133.3, 129.5, 129.1, 128.9, 128.9, 128.8, 128.3, 127.6, 124.8, 124.8, 56.3, 54.3, 45.2, 43.8. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{24}O_3$ $[M]^+$: 444.1725; found: 444.1708.

***Rac*-2-((1*S*,2*R*,3*S*)-2-benzoyl-3-(4-fluorobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenyl ethanone (79b)**



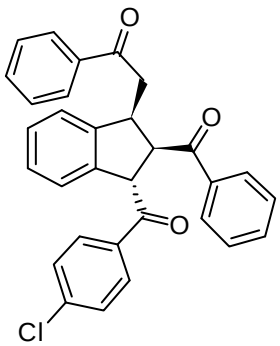
Purified with 40% hexanes in dichloromethane, yielding 35 mg of **79b** and 9 mg of **79b'** (63% combined yield). **79b** was a white foam. **mp** (°C): 178-179. R_f = 0.3 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3066, 1678, 1596, 1506, 1448, 1229; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24-8.22 (m, 2H), 8.08 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 7.1, 7.1 Hz, 1H), 7.50-7.49 (m, 3H), 7.37 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.31 (d, *J* = 7.4, 1H), 7.24 (dd, *J* = 8.6, 8.6 Hz, 2H), 7.18 (dd, *J* = 7.3 Hz, 1H), 7.10 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 5.86 (d, *J* = 9.6 Hz, 1H), 5.28 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.57 (ddd, *J* = 7.5, 7.5, 5.7 Hz, 1H), 3.16 (dd, *J* = 17.1, 8.7 Hz, 1H), 3.09 (dd, *J* = 17.1, 4.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.2, 197.9, 197.6, 167.4 (d, *J* = 256.1 Hz, C-F), 145.5, 140.1, 137.0, 136.7, 133.9, 133.3, 132.2, 132.1, 129.1, 128.8, 128.7, 128.2, 127.8, 125.7, 124.2, 116.4, 116.2, 54.4, 52.2, 42.5, 40.9. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{23}FO_3$ $[M]^+$: 462.1631; found: 462.1625.

***Rac*-2-((1*S*,2*S*,3*R*)-2-benzoyl-3-(4-fluorobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenyl ethanone (79b')**



Pale yellow solid, **mp** (°C): 56-57. R_f = 0.19 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3066, 2927, 1681, 1650, 1596, 1227; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.7 Hz, 2H), 8.07 (d, *J* = 7.7 Hz, 2H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.66 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.61-7.55 (m, 3H), 7.51-7.47 (m, 3H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.16 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.08 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.90 (d, *J* = 9.6 Hz, 1H), 5.30 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.56 (ddd, *J* = 7.8, 7.8, 6.2 Hz, 1H), 3.14 (dd, *J* = 17.2, 8.6 Hz, 1H), 3.10 (dd, *J* = 17.2, 5.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.0, 198.7, 197.8, 166.4 (d, *J* = 256.8 Hz, C-F), 145.6, 139.7, 137.1, 136.8, 133.5, 133.4, 132.2, 132.1, 128.9, 128.8, 128.5, 128.3, 127.6, 124.9, 124.6, 116.4, 116.3, 56.1, 54.5, 54.0, 43.9. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{24}O_3$ $[M]^+$: 462.1631; found: 462.1614.

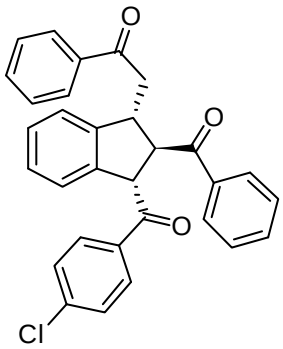
***Rac*-2-((1*S*,2*R*,3*S*)-2-benzoyl-3-(4-chlorobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenyl ethanone (79c)**



Purified with 40% hexanes in dichloromethane, yielding 37 mg of **79c** and 12 mg of **79c'** (69% combined yield). **79c** was light yellow solid. **mp** (°C): 175-176. R_f = 0.6 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3065, 1680, 1588, 1475, 1448; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.59 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.51-7.47 (m, 3H), 7.37 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.31 (d, *J* = 7.5, 1H), 7.18 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.10 (dd, *J* = 7.5, 7.5 Hz,

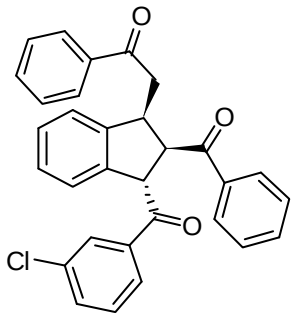
1H), 6.87 (d, *J* = 7.5 Hz, 1H), 5.85 (d, *J* = 9.6 Hz, 1H), 5.27 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.57 (ddd, *J* = 8.1, 8.1, 5.6 Hz, 1H), 3.15 (dd, *J* = 17.2, 8.7 Hz, 1H), 3.08 (dd, *J* = 17.1, 5.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.1, 198.1, 197.9, 145.5, 140.5, 140.0, 137.0, 136.7, 136.2, 133.9, 133.3, 130.9, 129.5, 129.1, 128.8, 128.7, 128.2, 128.2, 127.8, 125.7, 124.2, 54.3, 52.3, 42.51, 41.0. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{23}O_3Cl$ $[M]^+$: 478.1335; found: 478.1321.

***Rac*-2-((1*S*,2*S*,3*R*)-2-benzoyl-3-(4-chlorobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenyl ethanone (79c')**



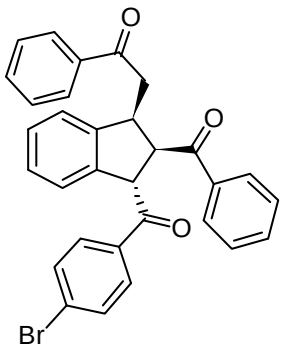
Pale yellow solid, **mp** (°C): 58-59. R_f = 0.5 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3065, 2927, 1680, 1588, 1447; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94-7.91 (m, 6H), 7.55-7.37 (m, 8H), 7.26-7.21 (m, 2H), 7.10 (dd, *J* = 6.8, 6.8 Hz, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 4.42 (d, *J* = 4.2 Hz, 1H), 4.73-4.70 (m, 1H), 4.46-4.42 (m, 1H), 3.62 (dd, *J* = 17.5, 5.2 Hz, 1H), 3.56 (dd, *J* = 17.8, 7.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.0, 198.7, 198.2, 145.6, 140.5, 139.5, 137.1, 136.8, 135.4, 133.5, 133.4, 130.8, 129.5, 128.9, 128.9, 128.8, 128.5, 128.3, 127.7, 124.9, 124.6, 56.2, 54.4, 45.0, 43.8. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{23}O_3Cl$ $[M]^+$: 478.1335; found: 478.1332.

***Rac*-2-((1*S*,2*R*,3*S*)-2-benzoyl-3-(3-chlorobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79d')**



Purified with 40% hexanes in dichloromethane, yielding 13 mg (18%), one diastereomer. **79d'** was a light yellow foam. **mp** (°C): 118-120. R_f = 0.45 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3066, 1681, 1596, 1448, 1214; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 1.7, 1.7 Hz, 1H), 8.09-8.08 (m, 3H), 7.76-7.73 (m, 2H), 7.65-7.61 (m, 2H), 7.54-7.47 (m, 4H), 7.39-7.34 (m, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5, 1H), 7.10 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 5.83 (d, *J* = 9.7 Hz, 1H), 5.26 (dd, *J* = 9.7, 8.3 Hz, 1H), 4.57 (ddd, *J* = 8.5, 8.5, 5.3 Hz, 1H), 3.16 (dd, *J* = 17.2, 8.9 Hz, 1H), 3.06 (dd, *J* = 17.2, 5.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 198.1, 197.9, 145.5, 139.9, 139.5, 137.1, 136.7, 135.6, 133.9, 133.8, 133.4, 130.5, 129.5, 129.1, 128.8, 128.7, 128.2, 128.2, 127.9, 127.6, 125.8, 124.2, 54.4, 52.5, 42.5, 41.0. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{23}O_3Cl$ $[M]^+$: 478.1335, $[M+2]^+$ 480.1336; found: 478.1332, $[M+2]^+$ 480.1327.

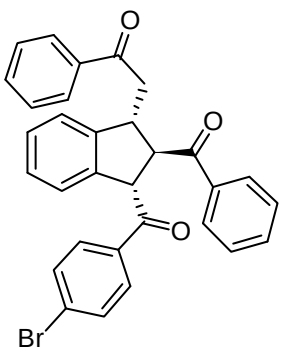
***Rac*-2-((1*S*,2*R*,3*S*)-2-benzoyl-3-(4-bromobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79f)**



Purified with 20% hexanes in dichloromethane, yielding 46 mg of **79f** and 14 mg of **79f'** (77% combined yield). **79f** was a light yellow solid. **mp** (°C): 175-176. R_f = 0.35 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3065, 1679, 1583, 1447, 1397; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.6, 7.6 Hz, 4H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.61-7.58 (m, 1H), 7.51-7.47 (m, 3H), 7.37 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.31 (d, *J* = 7.3

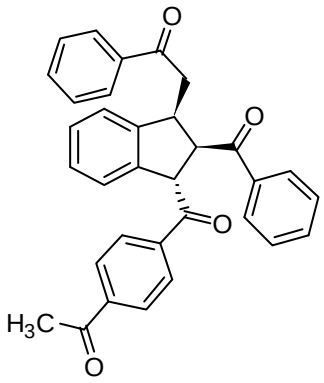
Hz, 1H), 7.18 (dd, *J* = 7.1, 7.1, 1H), 7.10 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.87 (d, *J* = 7.3 Hz, 1H), 5.84 (d, *J* = 9.5 Hz, 1H), 5.27 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.63-4.52 (m, 1H), 3.15 (dd, *J* = 17.1, 8.9 Hz, 1H), 3.07 (dd, *J* = 17.0, 4.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.1, 198.3, 197.9, 145.5, 139.9, 136.9, 136.7, 136.5, 133.9, 133.3, 132.5, 130.9, 129.3, 129.1, 128.8, 128.7, 128.2, 128.2, 128.1, 127.8, 125.7, 124.2, 54.3, 52.2, 42.5, 40.9. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{23}BrO_3$ $[M]^+$: 522.0831, $[M+2]^+$ 524.0810; found: 522.0840, $[M+2]^+$ 524.0832.

***Rac*-2-((1*S*,2*S*,3*R*)-2-benzoyl-3-(4-bromobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79f')**



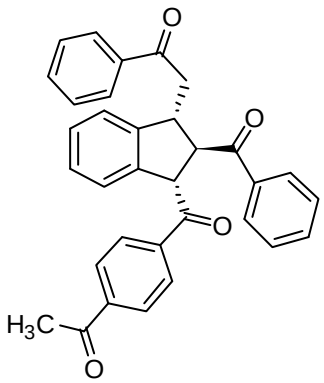
White foam, **mp** (°C): 62-63. R_f = 0.3 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3064, 1681, 1583, 1481, 1447, 1396, 1220; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.55 (dd, *J* = 7.6, 6.8 Hz, 1H), 7.51 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.44 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.30-7.21 (m, *2*H), 7.10 (dd, *J* = 7.0, 7.0 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 5.41 (d, *J* = 4.8 Hz, 1H), 4.72 (dd, *J* = 5.1, 4.4 Hz, 1H), 4.50-4.41 (m, 1H), 3.62 (dd, *J* = 17.7, 5.8 Hz, 1H), 3.56 (dd, *J* = 17.7, 7.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.9, 198.7, 198.4, 145.6, 139.5, 137.1, 136.8, 135.8, 133.5, 133.4, 132.5, 130.9, 129.3, 129.0, 129.9, 128.8, 128.5, 128.3, 127.7, 124.9, 124.7, 56.2, 54.4, 45.0, 43.8. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{23}BrO_3$ $[M]^+$: 522.0831, $[M+2]^+$ 524.0810; found: 522.0814, $[M+2]^+$ 524.0829.

***Rac*-2-((1*S*,2*R*,3*S*)-3-(4-acetylbenzoyl)-2-benzoyl-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79g)**



Purified with 100% dichloromethane, yielding 60 mg (82%) of an inseparable mixture of diastereomers. **79g+79g'** was a yellow foam. **mp** (°C): 64-65. R_f = 0.15 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3353, 3065, 2927, 2253, 1965, 1682, 1597, 1580, 1500; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.3 Hz, 2H), 8.08-8.05 (m, 2H), 7.75-7.72 (m, 2H), 7.59 (dd, *J* = 7.5, 7.3 Hz, 1H), 7.51-7.46 (m, 3H), 7.36 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 5.91 (d, *J* = 9.6 Hz, 1H), 5.28 (dd, *J* = 9.5, 8.5 Hz, 1H), 4.58 (ddd, *J* = 8.5, 8.2, 5.7 Hz, 1H), 3.16 (dd, *J* = 17.2, 8.7 Hz, 1H), 3.08 (dd, *J* = 17.2, 5.4 Hz, 1H), 2.68 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 198.9, 197.9, 197.6, 145.4, 140.9, 140.8, 139.8, 136.9, 136.6, 133.9, 133.3, 129.6, 129.1, 128.9, 128.7, 128.7, 128.2, 128.1, 127.8, 125.7, 124.2, 54.3, 52.7, 42.5, 40.9, 27.1. **HRMS** (EI^+) *m*/*z* calcd for $C_{33}H_{26}O_4$ $[M]^+$: 486.1831; found: 486.1820.

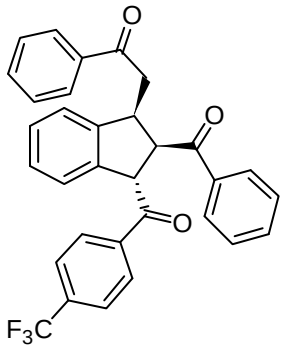
***Rac*-2-((1*S*,2*S*,3*R*)-3-(4-acetylbenzoyl)-2-benzoyl-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79g')**



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H), 8.00-7.87 (m, 4H), 7.56-7.46 (m, 4H), 7.45-7.38 (m, 4H), 7.27-7.24 (m, 1H), 7.22 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.09-7.06 (m, 1H), 6.87-6.85 (m, 1H), 5.49 (d, *J* = 5.4 Hz, 1H), 4.75 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.45 (ddd, *J* = 6.9, 5.9, 5.9 Hz, 1H), 3.63 (dd, *J* = 17.5, 5.8 Hz, 1H), 3.57 (dd, *J* = 17.8, 7.7 Hz,

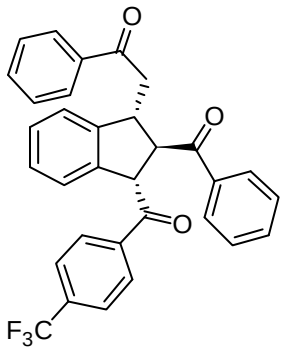
1H), 2.65 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.8, 199.0, 198.6, 197.5, 145.6, 141.1, 140.3, 139.3, 137.0, 136.7, 133.5, 133.4, 128.9, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 127.6, 124.9, 124.7, 56.5, 54.3, 44.9, 43.7, 27.1.

Rac-2-((1_S_,2_R_,3_S_)-2-benzoyl-3-(4-(trifluoromethyl)benzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79h)



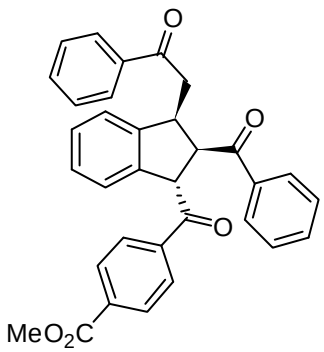
Purified with 50% hexanes in dichloromethane, yielding 50 mg of **79h** and 12 mg of **79h'** (81% combined yield). **79h** was a yellow foam. **mp** (°C): 106-107. R_f = 0.7 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3065, 1681, 1597, 1448, 1410, 1321; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 2H), 8.08 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.61 (dd, *J* = 7.0, 6.8 Hz, 1H), 7.55-7.46 (m, 3H), 7.37 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.19 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.11 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 5.91 (d, *J* = 9.6 Hz, 1H), 5.28 (dd, *J* = 9.3, 8.5 Hz, 1H), 4.59 (ddd, *J* = 7.8, 7.8, 5.1 Hz, 1H), 3.17 (dd, *J* = 17.1, 8.8 Hz, 1H), 3.08 (dd, *J* = 17.1, 4.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.9, 198.6, 197.9, 145.5, 140.5, 139.7, 136.9, 136.6, 135.1 (q, *J* = 74.4, 74.4, 41.6 Hz, CF_3), 134.0, 133.4, 129.8, 129.1, 128.8, 128.7, 128.3, 128.2, 127.9, 126.2, 126.2, 125.8, 124.1, 54.5, 52.5, 42.5, 40.9. **HRMS** (EI^+) *m/z* calcd for $C_{32}H_{23}F_3O_4$ $[M]^+$: 512.1599; found: 512.1584.

***Rac*-2-((1*S*,2*S*,3*R*)-2-benzoyl-3-(4-(trifluoromethyl)benzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79h')**



Light yellow solid, **mp** (°C): 63-64. R_f = 0.5 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3066, 1683, 1597, 1580, 1480 1448, 1322; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 2H), 7.93 (dd, *J* = 9.1, 8.5 Hz, 4H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.56 (dd, *J* = 7.1, 6.8 Hz, 1H), 7.52 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.44 (dd, *J* = 7.4, 6.9 Hz, 1H), 7.40 (dd, *J* = 7.4, 6.9 Hz, 2H), 7.31-7.20 (m, 2H), 7.11 (d, *J* = 6.9 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 1H), 5.49 (d, *J* = 4.3 Hz, 1H), 4.78-4.70 (m, 1H), 4.49-4.40 (m, 1H), 3.63 (dd, *J* = 17.5, 5.4 Hz, 1H), 3.57 (dd, *J* = 17.7, 7.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.7, 198.7, 198.6, 145.6, 139.9, 139.2, 137.0, 136.7, 135.1 (q, *J* = 65.2, 65.2, 32.0 Hz, CF_3), 133.6, 133.4, 129.7, 129.0, 128.9, 128.8, 128.6, 128.3, 127.7, 126.2, 126.2, 125.0, 124.7, 56.4, 54.3, 44.9, 43.8. **HRMS** (EI^+) *m*/*z* calcd for $C_{32}H_{23}F_3O_3$ $[M]^+$ 512.1599; found: 512.1618.

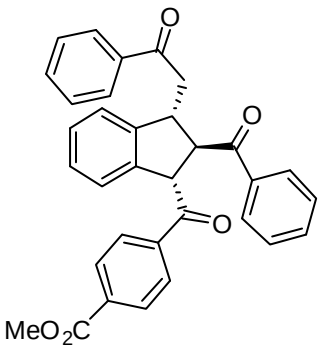
***Rac*-methyl 4-((1*S*,2*R*,3*S*)-2-benzoyl-3-(2-oxo-2-phenyl ethyl)-2,3-dihydro-1H-indene-1-carbonyl)benzoate (79i)**



Purified with 100% dichloromethane, yielding 54 mg (74%) of an inseparable mixture of diastereomers. **79i+79i'** was a yellow solid. **mp** (°C): 95-97. R_f = 0.2 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3347, 3066, 2952, 2255, 1725, 1682, 1597, 1580; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 3.4 Hz, 2H), 8.07 (d, *J* = 7.7 Hz, 2H), 7.96-7.91 (m, 2H), 7.74-7.72 (m, 2H), 7.50-7.46 (m, 3H), 7.39-7.33 (m, 3H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.17 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.09 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.84 (d, *J* = 7.4 Hz,

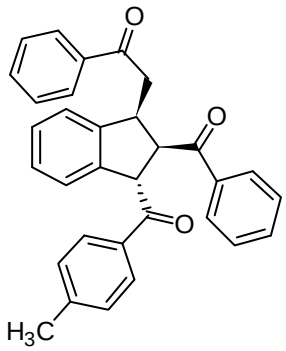
1H), 5.91 (d, *J* = 9.6 Hz, 1H), 5.29 (dd, *J* = 9.5, 8.4 Hz, 1H), 4.58 (ddd, *J* = 8.5, 8.2, 5.7 Hz, 1H), 3.97 (s, 3H), 3.17 (dd, *J* = 17.2, 8.7 Hz, 1H), 3.08 (dd, *J* = 17.2, 5.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 198.8, 197.9, 191.7, 166.3, 145.4, 141.0, 139.8, 136.9, 136.6, 134.5, 133.9, 133.3, 130.3, 129.3, 129.1, 128.7, 128.6, 128.1, 127.8, 125.7, 124.2, 56.5, 54.2, 52.7, 42.4, 40.1. **HRMS** (EI^+) *m*/*z* calcd for $C_{33}H_{26}O_5$ $[M]^+$: 502.1780; found: 502.1771.

***Rac*-methyl 4-((1*R*,2*S*,3*S*)-2-benzoyl-3-(2-oxo-2-phenyl ethyl)-2,3-dihydro-1H-indene-1-carbonyl)benzoate (79i')**



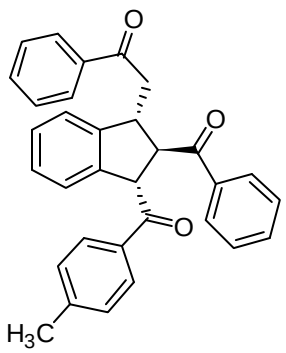
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25-8.21 (m, 2H), 8.15 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.59 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.56-7.51 (m, 2H), 7.47-7.46 (m, 2H), 7.43 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.38-7.34 (m, 1H), 7.31-7.27 (m, 1H), 7.21 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.09-7.06 (m, 1H), 6.86-6.84 (m, 1H), 5.49 (d, *J* = 5.3 Hz, 1H), 4.75 (dd, *J* = 5.5, 5.5 Hz, 1H), 4.46 (ddd, *J* = 7.1, 5.6, 5.6 Hz, 1H), 3.94 (s, 3H), 3.63 (dd, *J* = 17.6, 6.0 Hz, 1H), 3.58 (dd, *J* = 17.6, 7.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.7, 199.0, 198.6, 193.1, 166.2, 145.6, 140.4, 139.3, 137.1, 136.9, 133.4, 133.3, 130.2, 129.3, 128.9, 128.8, 128.7, 128.3, 128.2, 127.6, 124.9, 124.7, 56.5, 54.2, 52.7, 45.0, 43.7.

***Rac*-2-((1*S*,2*R*,3*S*)-2-benzoyl-3-(4-methylbenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79j)**



Purified with 40% hexanes in dichloromethane, yielding 20 mg of **79j** and 3 mg of **79j'** (34% combined yield). **79j** was a colourless crystalline solid. **mp** (°C): 165-166. R_f = 0.5 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3064, 1674, 1605, 1580, 1475, 1226; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 6.9 Hz, 2H), 8.08 (d, *J* = 7.7 Hz, 2H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.59 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.50 (dd, *J* = 6.5, 6.5 Hz, 1H), 7.48 (dd, *J* = 7.5 Hz, 2H), 7.37 (dd, *J* = 7.8, 7.3 Hz, 4H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.16 (dd, *J* = 7.5, 7.4 Hz, 1H), 7.08 (dd, *J* = 7.5, 7.4 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 5.87 (d, *J* = 9.7 Hz, 1H), 5.31 (dd, *J* = 8.6, 8.4 Hz, 1H), 4.56 (ddd, *J* = 8.3, 8.3, 5.6 Hz, 1H), 3.16 (dd, *J* = 17.2, 8.5 Hz, 1H), 3.10 (dd, *J* = 17.2, 5.5 Hz, 1H), 2.47 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 198.6, 198.1, 145.5, 144.8, 140.5, 137.1, 136.9, 135.4, 133.8, 133.3, 129.8, 129.6, 129.0, 128.8, 128.7, 128.2, 128.0, 127.7, 125.6, 124.4, 54.0, 52.3, 42.5, 41.1, 21.9. **HRMS** (EI^+) *m*/*z* calcd for $C_{32}H_{26}O_3$ $[M]^+$: 458.1881; found: 458.1883.

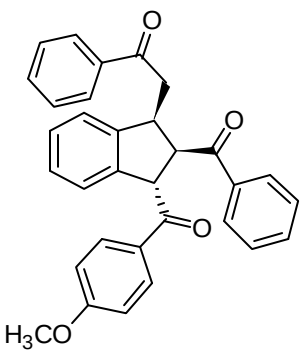
***Rac*-2-((1*S*,2*S*,3*R*)-2-benzoyl-3-(4-methylbenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79j')**



Colourless solid, **mp** (°C): 131-132. R_f = 0.4 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3064, 1677, 1604, 1579; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.50 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.43 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.39 (dd, *J* = 7.7, 7.7 Hz, 2H),

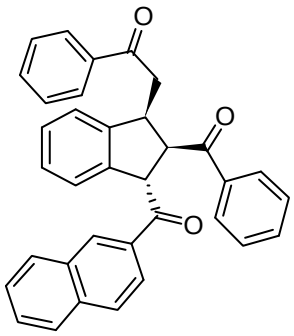
7.30 (d, *J* = 8.0 Hz, 2H), 7.27-7.23 (m, 1H), 7.21 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.08 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 5.43 (d, *J* = 5.4 Hz, 1H), 4.73 (dd, *J* = 5.5, 5.4 Hz, 1H), 4.46 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1H), 3.63 (dd, *J* = 17.9, 6.3 Hz, 1H), 3.59 (dd, *J* = 17.8, 7.6 Hz, 1H), 2.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.2, 198.9, 198.8, 145.7, 144.9, 140.0, 137.9, 134.6, 133.4, 133.4, 129.9, 129.7, 129.0, 128.9, 128.8, 128.4, 128.3, 127.6, 124.8, 124.7, 56.2, 54.3, 45.2, 43.7, 21.9. **HRMS** (EI^+) *m*/*z* calcd for $C_{32}H_{26}O_3$ $[M]^+$: 458.1881; found: 458.1878.

***Rac*-2-((1*S*,2*R*,3*S*)-2-benzoyl-3-(4-methoxybenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79k)**



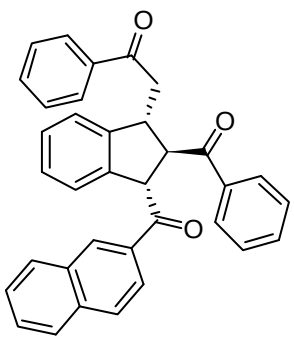
Purified with 20% hexanes in dichloromethane, yielding 13 mg (17%), one diastereomer. **79k** was a colourless solid. **mp** (°C): 142-143. R_f = 0.3 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3064, 1670, 1597, 1575, 1260; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 7.4 Hz, 2H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.59 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.50-7.46 (m, 3H), 7.36 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.16 (dd, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.84 (d, *J* = 9.7 Hz, 1H), 5.29 (dd, *J* = 9.5, 8.5 Hz, 1H), 4.55 (ddd, *J* = 8.8, 8.8, 8.2 Hz, 1H), 3.92 (s, 3H), 3.15 (dd, *J* = 17.2, 8.5 Hz, 1H), 3.09 (dd, *J* = 17.2, 5.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.4, 198.1, 197.4, 164.3, 145.5, 140.7, 137.1, 136.9, 133.8, 133.3, 131.9, 130.8, 129.1, 128.8, 128.7, 128.2, 128.0, 127.8, 125.6, 124.3, 114.3, 55.8, 54.1, 52.0, 42.6, 41.1. **HRMS** (EI^+) *m*/*z* calcd for $C_{32}H_{26}O_4$ $[M]^+$: 474.1831; found: 474.1834.

***Rac*-2-((*1S,2R,3S*)-3-(2-naphthoyl)-2-benzoyl-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79l)**



Purified with 40% hexanes in dichloromethane, yielding 17 mg of **79l** and 4 mg of **79l'** (28% combined yield). **79l** was a white crystal. **mp** (°C): 85-86. R_f = 0.6 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3061, 2253, 1962, 1674, 1626, 1596, 1580; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 2H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.66 (dd, *J* = 7.6, 6.8 Hz, 1H), 7.60 (dd, *J* = 7.7, 7.1 Hz, 2H), 7.47 – 7.53 (m, 3H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.07 (d, *J* = 9.6 Hz, 1H), 5.38 (dd, *J* = 9.2, 8.6 Hz, 1H), 4.60 (ddd, *J* = 13.6, 7.8, 7.8 Hz, 1H), 3.22 (dd, *J* = 17.1, 8.6 Hz, 1H), 3.15 (dd, *J* = 17.2, 5.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 198.9, 198.1, 145.5, 140.4, 137.1, 136.8, 136.1, 135.2, 133.9, 133.3, 132.9, 131.7, 130.1, 129.2, 129.1, 129.0, 128.8, 128.7, 128.2, 128.1, 128.0, 127.8, 127.1, 125.7, 124.7, 124.4, 54.1, 52.4, 42.5, 41.1; **HRMS** (EI^+) *m/z* calcd for $C_{35}H_{26}O_3$ $[M]^+$: 494.1882; found: 494.1889.

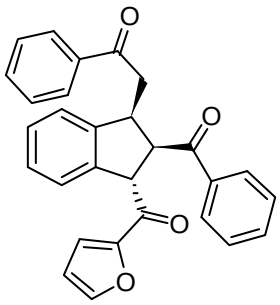
***Rac*-2-((*1S,2S,3R*)-3-(2-naphthoyl)-2-benzoyl-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79l')**



Colourless solid, **mp** (°C): 63-64. R_f = 0.5 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3060, 2926, 1679, 1626, 1596, 1579; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.06 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.98 – 7.98 (m, 7H), 7.64 (dd, *J* = 7.3, 7.1 Hz, 1H), 7.58 (d, *J* = 7.7 Hz,

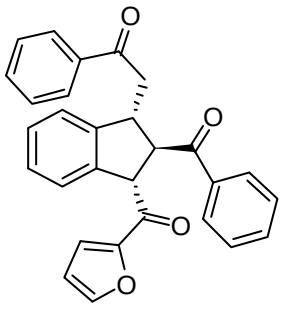
1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.24 – 7.29 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 5.64 (d, *J* = 5.4 Hz, 1H), 4.81 (t, *J* = 5.5 Hz, 1H), 4.50 (ddd, *J* = 12.8, 6.3, 6.3 Hz, 1H), 3.66 (dd, *J* = 17.8, 6.2 Hz, 1H), 3.62 (dd, *J* = 14.3, 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.3, 199.2, 198.9, 145.7, 139.9, 137.1, 136.9, 136.1, 134.5, 133.4, 133.4, 132.8, 131.6, 130.0, 129.2, 129.1, 128.9, 128.8, 128.7, 128.4, 128.4, 128.0, 127.6, 127.3, 124.9, 124.8, 124.7, 56.4, 54.4, 45.2, 43.9; **HRMS** (EI^+) *m*/*z* calcd for $C_{35}H_{26}O_3$ $[M]^+$: 494.1882; found: 494.1884.

***Rac*-2-((1*S*,2*R*,3*S*)-2-benzoyl-3-(furan-2-carbonyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79m)**



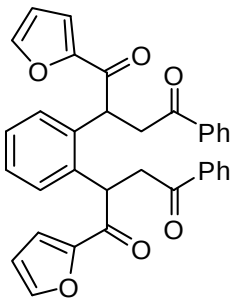
Purified with 100% dichloromethane, yielding 56 mg (74%), inseparable mixture of diastereomers. **79m+79m'** was a light yellow solid. **mp** (°C): 158-167. R_f = 0.2 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3331, 3133, 3066, 2933, 2253, 1670, 1596, 1566; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.3 Hz, 2H), 7.93 (d, *J* = 7.4 Hz, 1H), 7.76-7.70 (m, 3H), 7.61-7.55 (m, 1H), 7.52-7.45 (m, 2H), 7.36 (dd, *J* = 8.8, 7.7 Hz, 2H), 7.28 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.21-7.12 (m, 2H), 7.00 (d, *J* = 7.1 Hz, 1H), 6.67-6.63 (m, 1H), 5.66 (d, *J* = 9.5 Hz, 1H), 5.23 (dd, *J* = 8.9, 8.6 Hz, 1H), 2.55 (ddd, *J* = 14.0, 6.8, 6.8 Hz, 1H), 3.14 (dd, *J* = 17.2, 8.7 Hz, 1H), 3.08 (dd, *J* = 17.2, 4.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 198.0, 187.7, 153.2, 147.7, 145.4, 140.2, 137.0, 136.7, 133.9, 133.3, 129.0, 128.8, 128.7, 128.2, 128.1, 127.9, 125.5, 124.3, 119.7, 112.9, 53.5, 53.0, 42.7, 41.1. **HRMS** (EI^+) *m*/*z* calcd for $C_{29}H_{22}O_4$ $[M]^+$: 434.1518; Found: 434.1506.

***Rac*-2-((1*S*,2*S*,3*R*)-2-benzoyl-3-(furan-2-carbonyl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethanone (79m')**



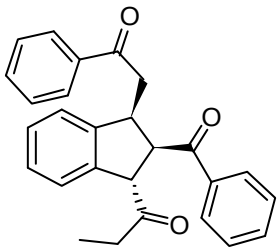
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.90 (m, 4H), 7.66 (s, 1H), 7.56-7.47 (m, 2H), 7.45-7.36 (m, 4H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.28-7.21 (m, 2H), 7.15 (dd, *J* = 7.3, 7.1 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.58 (dd, *J* = 3.5, 1.6 Hz, 1H), 5.20 (d, *J* = 5.0 Hz, 1H), 4.63 (dd, *J* = 5.0, 5.0 Hz, 1H), 4.46 (ddd, *J* = 11.9, 6.5, 6.5 Hz, 1H), 3.63 (d, *J* = 6.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.7, 198.8, 187.8, 152.5, 147.8, 145.8, 139.2, 137.1, 136.6, 133.4, 133.3, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 127.7, 124.9, 124.8, 112.9, 56.9, 53.7, 45.2, 43.7.

2,2'-(1,2-phenylene)bis(1-(furan-2-yl)-4-phenylbutane-1,4-dione) (70)



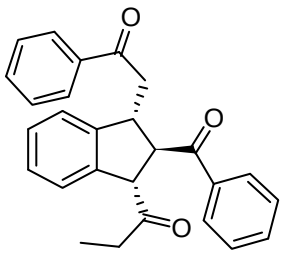
Purified with 100% dichloromethane, yielding 15 mg (9%) [0.3 mmol scale], single diastereomer. **70** was a yellow foam. **mp** (°C): 201-203. R_f = 0.10 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3140, 3070, 2922, 2257, 1673, 1596, 1568, 1467; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.4 Hz, 4H), 7.59 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.48 (dd, *J* = 7.7, 7.7 Hz, 4H), 7.41 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.25 (s, 2H), 7.22 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.10 (s, 2H), 6.37-6.34 (m, 2H), 5.85 (dd, *J* = 11.0, 1.6 Hz, 2H), 4.24 (dd, *J* = 18.2, 11.0 Hz, 2H), 3.38 (dd, *J* = 18.2, 1.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.6, 188.3, 152.9, 146.0, 136.4, 136.1, 133.7, 128.9, 128.8, 128.3, 128.1, 117.7, 112.9, 81.4, 43.6. **HRMS** (EI^+) *m*/*z* calcd for $C_{34}H_{26}O_6$ $[M]^+$: 530.1729; found: 530.1721.

***Rac*-1-((1*S*,2*R*,3*S*)-2-benzoyl-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-inden-1-yl)propan-1-one (79n)**



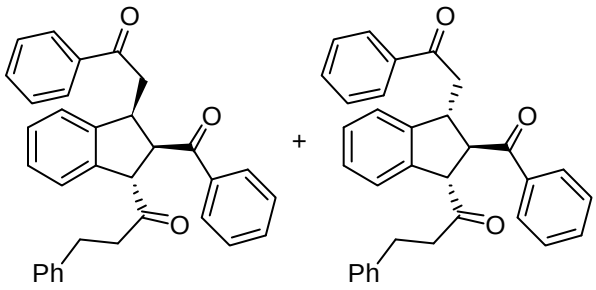
Purified with 30% hexane in dichloromethane, yielding 25 mg (42%), inseparable mixture of diastereomers. **79n+79n'** was a yellow oil. R_f = 0.45 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2936, 1711, 1681, 1596, 1447, 1227; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 6.8, 6.8 Hz, 1H), 7.49 (dd, *J* = 6.8, 6.8 Hz, 3H), 7.36 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.29-7.16 (m, 4H), 4.97 (ddd, *J* = 8.7, 8.7, 7.6 Hz, 1H), 4.97-4.95 (m, 1H), 4.52-4.42 (m, 1H), 3.12 (dd, *J* = 17.2, 8.4 Hz, 1H), 3.04 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.92-2.71 (m, 2H), 1.14 (t, *J* = 7.1, 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.9, 200.1, 198.1, 145.4, 139.7, 136.6, 136.4, 133.4, 133.3, 129.1, 128.7, 128.7, 128.1, 128.0, 127.8, 125.3, 124.1, 57.3, 54.2, 42.5, 40.7, 37.5, 7.9. **HRMS** (EI^+) *m*/*z* calcd for $C_{27}H_{24}O_3$ $[M]^+$: 396.1725; found: 396.1728.

***Rac*-1-((1*R*,2*S*,3*S*)-2-benzoyl-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-inden-1-yl)propan-1-one (79n')**



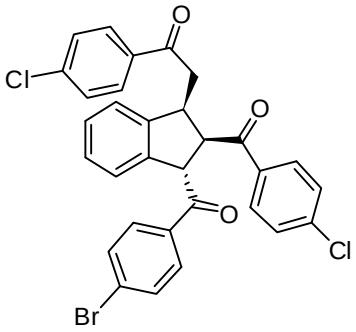
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.0, 8.0 Hz, 4H), 7.56 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.45 (dd, *J* = 7.0, 7.0 Hz, 4H), 7.32 (d, *J* = 6.5 Hz, 1H), 7.29-7.16 (m, 3H), 4.60-4.54 (m, 1H), 4.52-4.42 (m, 1H), 4.35-4.23 (m, 1H), 3.54 (dd, *J* = 18.1, 8.5 Hz, 1H), 3.49 (dd, *J* = 21.8, 9.8 Hz, 1H), 2.92-2.71 (m, 1H), 2.60 (dddd, *J* = 17.1, 6.9, 6.9, 6.9 Hz, 1H), 1.09 (t, *J* = 7.1, 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 210.3, 200.2, 198.7, 146.0, 139.0, 137.1, 137.0, 133.9, 133.4, 129.0, 128.9, 128.8, 128.5, 128.3, 127.7, 125.3, 124.7, 61.3, 53.4, 45.2, 42.8, 35.7, 8.0.

***Rac*-1-(2-benzoyl-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-inden-1-yl)-3-phenylpropan-1-one (79o+79o')**



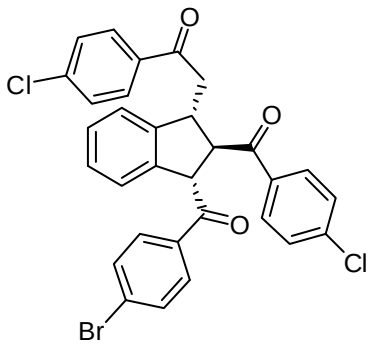
Purified with 30% hexane in dichloromethane, yielding 32 mg (44%), inseparable mixture of two diastereomers. **79o+79o'** is a yellow solid. **mp** (°C): 82-85. R_f = 0.45 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3062, 3026, 2927, 1711, 1682, 1596, 1580, 1447; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 6.8, 6.8 Hz, 1H), 7.49 (dd, *J* = 6.8, 6.8 Hz, 3H), 7.36 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.29-7.16 (m, 4H), 4.97 (ddd, *J* = 8.7, 8.7, 7.6 Hz, 1H), 4.97-4.95 (m, 1H), 4.52-4.42 (m, 1H), 3.12 (dd, *J* = 17.2, 8.4 Hz, 1H), 3.04 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.92-2.71 (m, 2H), 1.14 (t, *J* = 7.1, 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.8, 208.0, 200.1, 199.9, 198.6, 198.1, 146.0, 145.4, 141.1, 140.9, 139.3, 138.7, 137.0, 136.9, 136.6, 136.3, 133.9, 133.4, 133.3, 129.1, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 127.8, 127.7, 126.4, 126.3, 125.3, 125.3, 124.8, 124.1, 61.7, 57.7, 54.0, 53.2, 45.6, 45.1, 43.8, 42.8, 42.5, 40.6, 29.8, 29.7. **HRMS** (EI^+) *m*/*z* calcd for $C_{33}H_{28}O_3$ $[M]^+$: 472.2038; found: 472.2032.

***Rac*-2-((1*S*,2*R*,3*S*)-3-(4-bromobenzoyl)-2-(4-chlorobenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-(4-chlorophenyl)ethanone (79p)**



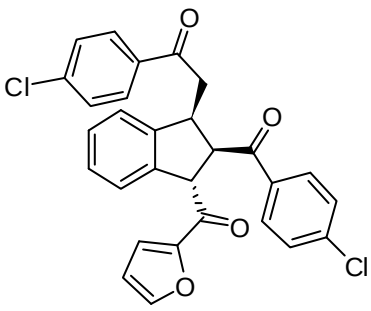
Purified with 40% hexanes in dichloromethane, yielding 32 mg of **79p** and 6 mg of **79p'** (72% combined yield, after minor diastereomer **79p'** was re-purified using 20% ethyl acetate in hexanes as eluent). **79p** was a pale yellow solid. **mp** (°C): 182-183. R_f = 0.65 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3069, 1677, 1587, 1571, 1486; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.7 Hz, 2H), 7.97 (d, *J* = 7.7 Hz, 2H), 7.68 (dd, *J* = 7.1, 6.8 Hz, 4H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 7.7, 7.7 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.20 (dd, *J* = 7.1, 6.8 Hz, 1H), 7.11 (dd, *J* = 7.1, 7.1 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.77 (d, *J* = 9.5 Hz, 1H), 5.21 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.53-5.50 (m, 1H), 3.16 (dd, *J* = 17.5, 5.8 Hz, 1H), 3.07 (dd, *J* = 17.5, 6.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.3, 197.9, 196.7, 145.2, 140.5, 139.9, 139.8, 136.4, 135.3, 135.2, 132.6, 132.5, 130.9, 130.1, 129.5, 129.4, 129.1, 128.4, 127.9, 125.4, 124.3, 53.5, 52.8, 42.5, 41.0. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{21}BrCl_2O_3$ $[M]^+$ 590.0051, $[M+2]^+$ 592.0031, $[M+4]^+$ 593.9941; found: 590.0046, 592.0023, 593.9947.

***Rac*-2-((1*S*,2*S*,3*R*)-3-(4-bromobenzoyl)-2-(4-chlorobenzoyl) -2,3-dihydro-1H-inden-1-yl)-1-(4-chlorophenyl)ethanone (79p')**



Pale yellow solid. **mp** (°C): 79-81. R_f = 0.35 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3070, 1682, 1587, 1570, 1486; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.6 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 4.3 Hz, 2H), 7.13-7.07 (m, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.35 (d, *J* = 5.6 Hz, 1H), 4.66 (dd, *J* = 5.7, 5.7 Hz, 1H), 4.40 (ddd, *J* = 8.4, 5.4, 5.4 Hz, 1H), 3.58 (dd, *J* = 17.7, 5.3 Hz, 1H), 3.51 (dd, *J* = 17.7, 8.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.8, 198.1, 197.5, 145.2, 140.1, 140.0, 139.3, 135.7, 135.2, 135.1, 132.6, 130.9, 130.3, 129.7, 129.5, 129.2, 129.1, 128.6, 127.8, 124.7, 124.6, 56.3, 54.2, 44.8, 43.8. **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{21}BrCl_2O_3$ $[M]^+$ 590.0051, $[M+2]^+$ 592.0031, $[M+4]^+$ 593.9992; found: 590.0032, 591.9994, 594.0016.

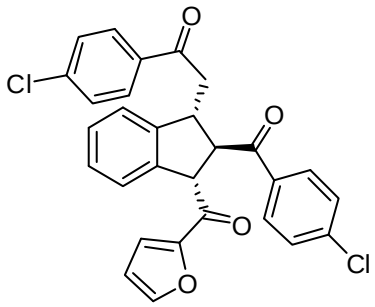
***Rac*-2-((1*S*,2*R*,3*S*)-2-(4-chlorobenzoyl)-3-(furan-2-carbonyl)-2,3-dihydro-1H-inden-1-yl)-1-(4-chlorophenyl)ethanone (79q+79q'+79q'')**



Purified with 100% dichloromethane, yielding 41 mg (72% combined yield for all three diastereomers), inseparable mixture of two diastereomers. **79q+79q'** was a light yellow foam. **mp** (°C): 68-69. R_f = 0.25 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3070, 1786, 1673, 1588; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.86 (dd, *J* = 8.5, 3.3 Hz, 1H), 7.66-7.61 (m, 2H), 7.43-7.39 (m, 2H), 7.38-7.32 (m, 2H), 7.26-7.25 (m, 2H), 7.20 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.15 (dd, *J* = 7.3, 7.3 Hz,

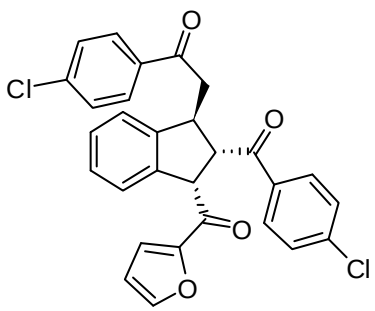
1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.64 (dd, *J* = 3.4, 1.4 Hz, 1H), 5.58 (d, *J* = 9.4 Hz, 1H), 5.18 (dd, *J* = 9.2, 8.5 Hz, 1H), 4.51 (ddd, *J* = 7.5, 7.2, 7.2 Hz, 1H), 3.18 (dd, *J* = 17.5, 6.8 Hz, 1H), 3.06 (dd, *J* = 17.5, 7.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.3, 196.8, 187.4, 153.2, 147.8, 145.2, 140.4, 140.1, 139.9, 135.3, 130.3, 130.1, 129.5, 129.3, 129.0, 129.0, 128.3, 128.0, 125.1, 124.4, 119.7, 113.0, 53.7, 52.7, 42.7, 41.1. **HRMS** (EI^+) *m*/*z* calcd for $C_{29}H_{20}Cl_2O_4$ $[M]^+$ 502.0739, $[M+2]^+$: 504.0709; found: 502.0753, 504.0715.

***Rac*-2-((1*S*,2*S*,3*R*)-2-(4-chlorobenzoyl)-3-(furan-2-carbonyl)-2,3-dihydro-1H-inden-1-yl)-1-(4-chlorophenyl)ethanone (79q')**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.66-7.61 (m, 4H), 7.49-7.46 (m, 2H), 7.43-7.39 (m, 4H), 7.38-7.32 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.61-6.60 (m, 1H), 5.14 (d, *J* = 5.0 Hz, 1H), 4.55 (dd, *J* = 5.0, 5.0 Hz, 1H), 4.42 (ddd, *J* = 6.6, 5.3, 5.3 Hz, 1H), 3.57 (d, *J* = 7.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.6, 197.7, 187.5, 152.4, 148.2, 147.9, 145.4, 142.3, 139.5, 134.9, 130.2, 129.7, 129.3, 129.2, 129.1, 128.6, 127.9, 124.8, 124.7, 119.9, 113.1, 57.1, 53.5, 45.1, 43.7.

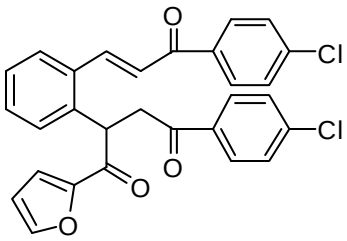
***Rac*-2-((1*S*,2*S*,3*S*)-2-(4-chlorobenzoyl)-3-(furan-2-carbonyl)-2,3-dihydro-1H-inden-1-yl)-1-(4-chlorophenyl)ethanone (79q'+79q'')**



A second purification via FCC employing 100% dichloromethane yielded 13 mg of an inseparable mixture of two diastereomers. **79q'+79q''** was a light yellow sold. **mp** (°C): 87-89. R_f = 0.15 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3070,

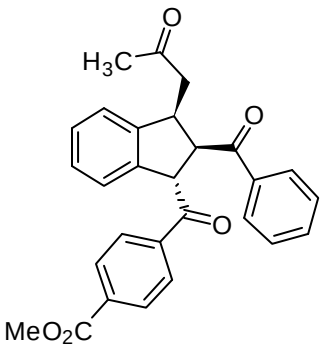
1786, 1673, 1588; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.80-7.77 (m, 2H), 7.69-7.66 (m, 2H), 7.62-7.61 (m, 1H), 7.45-7.42 (m, 3H), 7.37-7.33 (m, 2H), 7.18-7.14 (m, 2H), 6.59 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.16 (d, *J* = 8.4 Hz, 1H), 4.89 (dd, *J* = 8.2, 8.1 Hz, 1H), 4.61 (ddd, *J* = 7.9, 7.9, 5.8 Hz, 1H), 3.74 (dd, *J* = 18.0, 7.8 Hz, 1H), 3.21 (dd, *J* = 18.0, 5.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.3, 197.9, 188.7, 153.5, 147.8, 145.2, 139.9, 139.8, 139.7, 135.6, 135.6, 129.8, 129.8, 129.3, 128.9, 128.4, 127.9, 125.2, 117.5, 112.9, 77.5, 56.1, 53.8, 43.07, 42.2. **HRMS** (EI^+) *m*/*z* calcd for $C_{29}H_{20}Cl_2O_4$ $[M]^+$ 502.0739, $[M+2]^+$ 504.0709, $[M+4]^+$ 506.0580; found: 502.0753, 504.0677, 506.0596.

(*E*)-4-(4-chlorophenyl)-2-(2-(3-(4-chlorophenyl)-3-oxoprop-1-enyl)phenyl)-1-(furan-2-yl)butane-1,4-dione (83q)



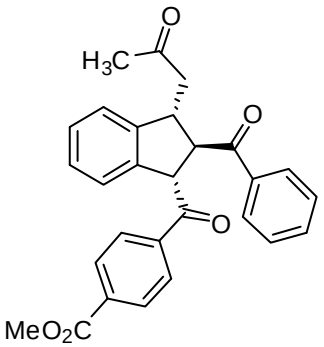
The product was purified employing 100% dichloromethane, yielding 5 mg of **83q** as a light yellow semi-solid. R_f = 0.1 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3135, 3062, 2913, 1673, 1590, 1568, 1465, 1400, 1214, 1011, 762, 737; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 15.4 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.49 – 7.31 (m, 9H), 7.18 (d, *J* = 3.5 Hz, 1H), 6.44 (dd, *J* = 3.5, 1.6 Hz, 1H), 5.54 (dd, *J* = 9.8, 3.9 Hz, 1H), 4.07 (dd, *J* = 18.0, 9.9 Hz, 1H), 3.24 (dd, *J* = 18.1, 3.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.2, 189.0, 187.4, 152.2, 146.9, 142.5, 140.0, 139.7, 138.2, 136.4, 134.8, 134.2, 131.0, 130.3, 129.8, 129.3, 129.1, 128.6, 128.1, 128.0, 125.1, 118.4, 112.6, 44.4, 42.7; **HRMS** (EI^+) *m*/*z* calcd for $C_{29}H_{20}Cl_2O_4$ $[M]^+$: 502.0738; found: 502.0727.

***Rac*-methyl 4-((1*S*,2*R*,3*S*)-2-benzoyl-3-(2-oxopropyl)-2,3-dihydro-1H-indene-1-carbonyl)benzoate (79r)**



Both products were purified with 10% ethyl acetate in hexane yielding 41 mg (52%, 0.18 mmol scale) of an inseparable mixture of two diastereomers. **79r+79r'** was a light yellow solid. R_f = 0.32 (40% ethyl acetate in hexane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2952, 2254, 1721, 1705, 1596, 1503 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (s, 4H), 8.07-8.05 (m, 1H), 7.95 (d, *J* = 7.3 Hz, 1H), 7.49 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.43 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.27 (d, *J* = 7.1 Hz, 1H), 7.22-7.18 (m, 1H), 7.09-7.04 (m, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 5.80 (d, *J* = 9.7 Hz, 1H), 5.18 (dd, *J* = 9.4, 8.4 Hz, 1H), 4.36 (ddd, *J* = 8.0, 8.0, 6.6 Hz, 1H), 3.97 (s, 3H), 2.62 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.58 (dd, *J* = 17.6, 6.4 Hz, 1H), 1.96 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.5, 200.1, 198.8, 166.3, 145.4, 141.0, 139.8, 136.6, 134.5, 134.0, 130.3, 129.3, 129.1, 128.7, 128.2, 127.8, 125.4, 124.7, 53.8, 52.8, 52.7, 45.6, 42.1, 30.9. **HRMS** (EI^+) *m*/*z* calcd for $C_{28}H_{24}O_5$ $[M]^+$: 440.1623; found: $[M^+]$ 440.1615.

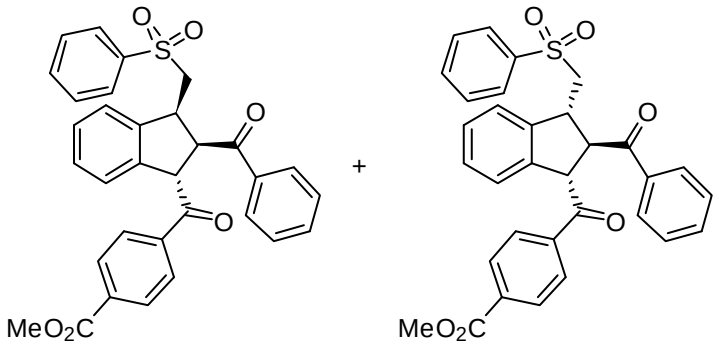
***Rac*-methyl 4-((1*R*,2*S*,3*S*)-2-benzoyl-3-(2-oxopropyl)-2,3-dihydro-1H-indene-1-carbonyl) benzoate (79r')**



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.96-7.94 (m, 1H), 7.60 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.55-7.51 (m, 1H), 7.51-7.47 (m, 1H), 7.44-7.41 (m, 1H), 7.22-7.18 (m, 1H), 7.09-7.04 (m, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 5.43 (d, *J* = 5.7 Hz, 1H), 4.64 (dd, *J* = 5.7, 5.7 Hz, 1H), 4.22, (ddd, *J* = 6.3, 6.3, 7.0 Hz, 1H), 3.95 (s, 3H), 3.07 (dd, *J* = 17.9, 6.0 Hz, 1H), 2.99 (dd, *J* = 17.9, 7.8 Hz, 1H), 2.13 (s, *J* =

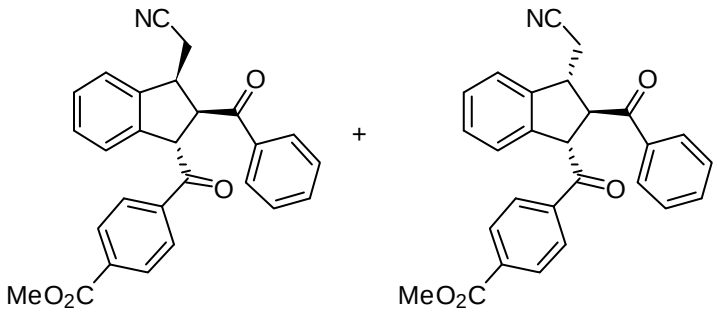
Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.2, 200.8, 198.9, 166.2, 145.3, 140.4, 139.2, 136.8, 134.6, 133.6, 130.3, 129.3, 128.9, 128.8, 128.5, 127.6, 124.2 (x2), 77.5, 56.4, 54.1, 49.6, 43.4, 30.5.

***Rac*-methyl 4-((1*S*,2*S*,3*S*) and 4-((1*R*,2*R*,3*S*)-2-benzoyl-3-(phenylsulfonylmethyl)-2,3-dihydro-1H-indene-1-carbonyl)benzoate (79s+79s')**



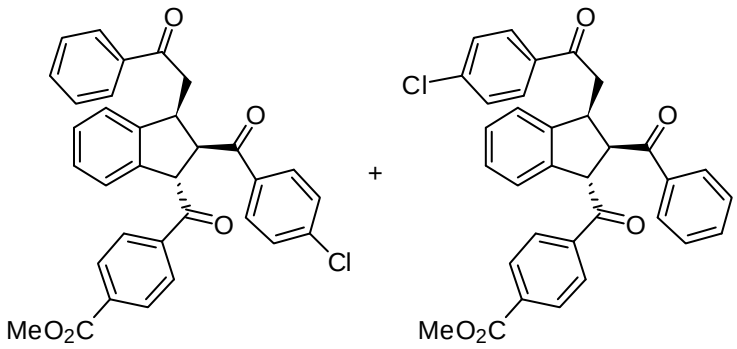
Purified with 10% ethyl acetate in hexane, yielding 53 mg (65%), inseparable mixture of two diastereomers. **79s+79s'** was a light yellow foam. R_f = 0.32 (40% ethyl acetate in hexane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2951, 1722, 1668, 1608, 1447, 1281, 1148, 1108, 1085; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 2H), 7.96-7.92 (m, 6H), 7.89-7.85 (m, 6H), 7.59-7.49 (m, 6H), 7.48-7.36 (m, 9H), 7.24-7.19 (m, 4H), 7.06-7.03, (m, 2H), 6.98-6.96 (m, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.02 (dd, *J* = 9.2, 2.2 Hz, 1H), 5.19 (d, *J* = 3.6 Hz, 1H), 4.92 (dd, *J* = 3.6, 3.6 Hz, 1H), 4.49 (ddd, *J* = 7.5, 2.9, 2.9 Hz, 1H), 4.29 (d, *J* = 17.8 Hz, 1H), 4.22 (dd, *J* = 15.1, 9.3 Hz, 1H), 4.07 (d, *J* = 17.8 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.52 (dd, *J* = 14.6, 2.8 Hz, 1H), 3.24 (dd, *J* = 15.1, 2.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.2, 198.4, 197.7, 166.7, 166.1, 146.6, 143.7, 139.9, 139.8, 139.4, 138.8, 138.4, 136.5, 135.8, 134.7, 133.9, 133.8, 133.7, 133.6, 130.8, 130.6, 130.3, 129.6, 129.55, 129.53, 129.4, 129.2, 129.1, 129.0, 128.9, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.5, 125.2, 124.9, 124.2, 121.9, 108.2, 72.7, 61.5, 59.4, 57.3, 52.9, 52.7, 52.5, 41.1, 38.2. **HRMS** (EI^+) *m*/*z* calcd for $C_{32}H_{26}O_6S$ $[M]^+$: 538.1450; found: 538.1441.

***Rac*-methyl 4-((1*S*,2*R*,3*S*) and 4-((1*R*,2*S*,3*S*)-2-benzoyl-3-(cyanomethyl)-2,3-dihydro-1H-indene-1-carbonyl)benzoate (79t+79t')**



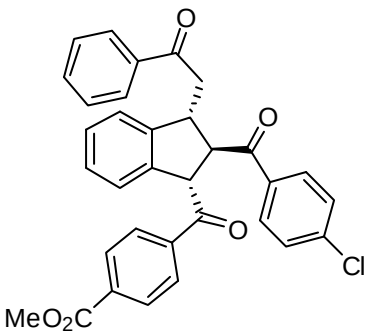
Purified with 100% dichloromethane, yielding 30 mg (37%), inseparable mixture of diastereomers. **79t+79t'** was a yellow foam. **mp** (°C): 112-114. R_f = 0.15 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2952, 2251, 1725, 1679, 1596; **^{1}H NMR** (500 MHz, $CDCl_3$) (*major isomer* **79t'**) δ 8.17 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.59 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.48 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.4 (d, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.50 (d, *J* = 4.7 Hz, 1H), 4.75 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.05 (ddd, *J* = 12.1, 12.1, 6.8 Hz, 1H), 3.96 (s, 3H), 2.98 (dd, *J* = 16.9, 9.9 Hz, 1H), 2.86 (dd, *J* = 16.9, 7.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) (*major isomer* **79t'**) δ 199.3, 198.3, 166.2, 142.4, 139.9, 139.2, 135.9, 134.8, 134.1, 130.3, 129.4, 129.3, 128.9, 128.9, 128.7, 125.0, 124.9, 118.4, 55.8, 53.5, 52.8, 44.1, 23.2. **HRMS** (EI^+) *m*/*z* calcd for $C_{27}H_{21}NO_4$ $[M]^+$: 423.1471; found: 423.1470.

***Rac*-methyl 4-((*1S,2R,3S*)-2-(4-chlorobenzoyl)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1-carbonyl) benzoate (79u) and *Rac*-methyl 4-((*1S,2R,3S*)-2-benzoyl-3-(2-(4-chlorophenyl)-2-oxoethyl)-2,3-dihydro-1H-indene-1-carbonyl)benzoate (79v)**



Purified with 100% dichloromethane, yielding 64 mg (80% combined yield for all isomers), inseparable mixture of diastereomers. **79u+79v** was a light yellow foam. R_f = 0.28 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3065, 2951, 1725, 1683, 1588, 1475, 1436, 1402, 1279, 1107, 1012, 737; (*major regioisomer* **79u**) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (s, 4H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 5.85 (d, *J* = 9.8 Hz, 1H), 5.23 (t, *J* = 9.0 Hz, 1H), 4.55 (q, *J* = 7.4 Hz, 1H), 3.97 (s, 3H), 3.18 (dd, *J* = 17.5, 6.4 Hz, 1H), 3.13 (dd, *J* = 17.4, 7.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.2, 198.6, 197.8, 166.3, 145.4, 140.9, 140.4, 139.6, 137.0, 135.2, 134.7, 133.4, 130.3, 130.1, 129.4, 129.3, 128.7, 128.4, 128.1, 127.9, 125.5, 124.2, 53.7, 53.1, 52.7, 42.4, 41.0; (*minor regioisomer* **79v**) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (s, 4H), 8.06 (d, *J* = 7.7 Hz, 2H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.52 – 7.47 (m, 4H), 7.17 (t, *J* = 6.8 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.86 (d, *J* = 9.8 Hz, 1H), 5.28 (t, *J* = 8.7 Hz, 1H), 4.55 (q, *J* = 7.4 Hz, 1H), 3.97 (s, 3H), 3.10 (d, *J* = 7.0 Hz, 2H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.1, 198.8, 196.8, 166.4, 145.3, 141.0, 140.5, 139.8, 136.7, 135.3, 134.6, 134.0, 130.4, 129.7, 129.6, 129.1, 129.0, 128.8, 128.2, 127.9, 125.6, 124.3, 54.0, 52.9, 52.8, 42.5, 41.0; **HRMS** (EI^+) *m/z* calcd for $C_{33}H_{25}ClO_5$ $[M]^+$: 536.1391; found: 536.1390.

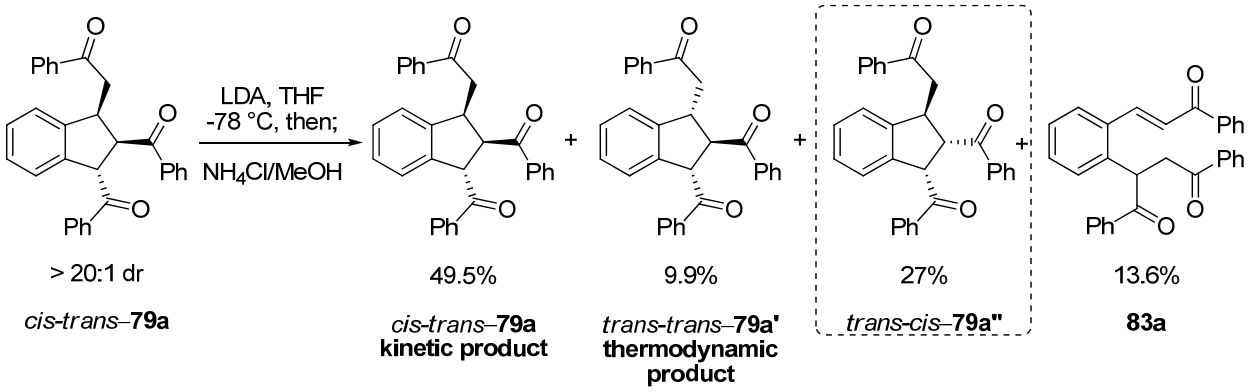
***Rac*-methyl 4-((*1S,2R,3R*)-2-(4-chlorobenzoyl)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1-carbonyl) benzoate (79u')**



79u' was a light yellow foam. R_f = 0.15 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3347, 3066, 2952, 1725, 1682, 1588, 1448, 1436, 1402, 1362, 1279, 1107, 1012, 736, 690; (*major regioisomer* **79u'**) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (s, 2H), 8.16 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.90 (t, *J* = 7.2 Hz, 3H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.42 – 7.33 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 7.3 Hz, 2H), 5.44 (d, *J* = 5.7 Hz, 1H), 4.70 (t, *J* = 5.7 Hz, 1H), 4.54 (q, *J* = 7.4 Hz, 1H), 3.98 (s, 3H), 3.62 (dd, *J* = 17.7, 5.3 Hz, 1H), 3.55 (dd, *J* = 17.7, 8.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.5, 198.7, 197.1, 167.1, 146.1, 141.0, 139.9, 139.5, 136.7, 135.1, 134.9, 132.8, 130.0, 129.8, 129.5, 129.2, 128.1, 127.8, 128.2, 126.9, 126.0, 124.7, 54.1, 52.9, 51.9, 41.8, 39.7; **HRMS** (EI^+) *m/z* calcd for $C_{33}H_{25}ClO_5$ $[M]^+$: 536.1391; found: 536.1384.

Isomerization of 79a to 79a''

((*1S,2S,3S*)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1,2-diyl)bis(phenylmethanone) (79a'')

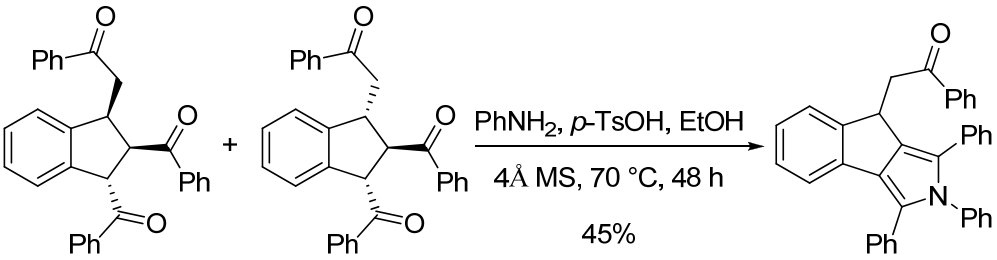


In a 10 mL round-bottom flask provided with nitrogen atmosphere and magnetic stirring, a solution of *Rac*-((*1S,2R,3S*)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1,2-diyl)bis(phenylmethanone) (**79a**) (30 mg, 0.07 mmol, 1 equiv) in THF (0.34 mL) was stirred at -78 °C, then a solution of Lithium bis(trimethylsilyl)amide (LDA) (74 μL, 0.07 mmol, 1.1 equiv, 1 M in THF) was added dropwise and the reaction was stirred at -78 °C for 15 min, then the reaction was quenched with a mixture of saturated aqueous solution of NH_4Cl and THF (1 mL, 1:1). The mixture was washed with brine and extracted with ethyl acetate (3 x 5 mL). The organic extract was dried over anhydrous sodium sulfate and the solvent was removed by rotary evaporation. The crude mixture was purified by preparative thin layer chromatography (100% dichloromethane) to afford white foam in 22% yield (7 mg). R_f = 0.35 (100% dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3064, 1681, 1596, 1579, 1477, 1247; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 4H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.42 – 7.51 (m, 4H), 7.32 – 7.38 (m, 5H), 7.17 – 7.22 (m, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 5.41 (d, *J* = 7.8 Hz, 1H), 4.98 (t, *J* = 8.1 Hz, 1H), 4.96 (ddd, *J* = 7.9, 5.5, 5.5 Hz, 1H), 3.84 (dd, *J* = 18.1, 8.1 Hz, 1H), 3.24 (dd, *J* = 18.1, 5.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 199.6,

199.5, 146.8, 140.6, 138.4, 137.4, 137.2, 133.3, 133.1, 132.9, 128.9, 128.8, 128.6, 128.4, 128.3, 128.1, 127.6, 125.2, 124.9, 56.5, 52.6, 42.9, 41.9; **HRMS** (EI^+) *m*/*z* calcd for $C_{31}H_{24}O_3$ $[M]^+$: 444.1725; found: 444.1741.

5.3.2 Procedure for the Preparation of Pyrroles (94a-b)

1-Phenyl-2-(1,2,3-triphenyl-2,8-dihydroindeno[1,2-c]pyrrol-8-yl)ethanone (94a)

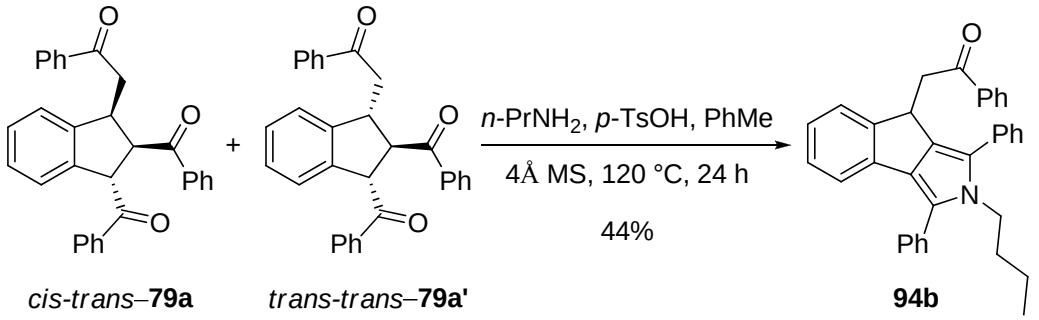


cis-trans–**79a** (4:1 dr) *trans-trans*–**79a'** **94a**

In a Schlenk flask fitted with a septum, a stirred solution of *Rac*-((1*S*,2*R*,3*S*)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1,2-diyl)bis(phenyl methanone) (4:1 dr, **79a** + **79a'**) (100 mg, 0.23 mmol, 1 equiv) in THF/MeOH (2:3, 0.5 mL, 0.5 M) containing powdered 4Å molecular sieves (25 mg) was heated to 70°C. Aniline (61.5 µL, 0.68 mmol, 3 equiv) was then added, followed by *p*-toluenesulfonic acid monohydrate (42.8 mg, 0.23 mmol, 1 equiv.). The flask was fitted with a reflux condenser and the mixture was stirred at 70°C for 48 h. The resulting mixture was then diluted with ethyl acetate (3 mL) and saturated aqueous ammonium chloride (5 mL). The organic layer was washed with brine and then dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude mixture was purified by flash column chromatography on silica gel (10% ethyl acetate/hexanes) yielding a white-yellow solid (50 mg, 45%), **mp** (°C): 216-217. R_f = 0.45 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3055, 1682, 1597, 1495, 1443, 1355; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.3 Hz, 2H),

7.51-7.48 (m, 2H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.37 (dd, *J* = 7.8, 7.5 Hz, 2H), 7.30-7.25 (m, 5H), 7.24-7.19 (m, 3H), 7.17-7.15 (m, 5H), 7.11-7.03 (m, 4H), 5.08 (dd, *J* = 9.3, 3.5 Hz, 1H), 3.33 (dd, *J* = 17.3, 3.7 Hz, 1H), 3.24 (dd, *J* = 17.3, 9.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.8, 151.3, 139.1, 137.4, 133.1, 132.8, 132.5, 132.1, 130.2, 129.3, 129.2, 129.0, 128.8, 128.6, 128.4, 128.3, 128.2, 127.6, 127.2, 127.1, 127.0, 126.6, 126.1, 125.7, 125.5, 119.7, 42.4, 38.3; **HRMS** (EI^+) *m*/*z* calcd for $C_{37}H_{27}NO$ $[M]^+$: 501.2092; found: 501.2084.

2-(1,3-diphenyl-2-propyl-2,8-dihydroindeno[1,2-c]pyrrol-8-yl)-1-phenylethanone (94b)



cis-trans–**79a** (4:1 dr) *trans-trans*–**79a'** **94b**

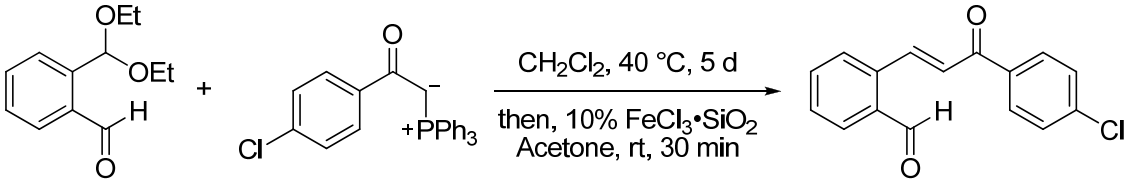
In a pressure vessel, a stirred solution of *Rac*-((1*S*,2*R*,3*S*)-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-indene-1,2-diyl)bis(phenylmethanone) (4:1 dr, **79a** + **79a'**) (50 mg, 0.11 mmol, 1 equiv.) in toluene (0.23 mL, 0.5 M) containing powdered 4Å molecular sieves (10 mg) was heated to 120°C. *n*-Propylamine (55 μL, 0.67 mmol, 6 equiv.) was then added, followed by *p*-toluenesulfonic acid monohydrate (26 mg, 0.11 mmol, 1.35 equiv). The reaction was stirred at 120°C for 24 h. The mixture was then diluted with ethyl acetate (3 mL) and saturated aqueous ammonium chloride (5 mL). The organic layer was washed with brine, dried over anhydrous sodium sulphate, and the solvent was removed in vacuo. The crude mixture was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes), yielding a yellow oil (23 mg, 44%). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3057, 2961, 1683, 1597, 1491, 1447; **^{1}H NMR** (500

MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.54-7.47 (m, 5H), 7.42-7.32 (m, 7H), 7.28 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.10 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.01 (dd, *J* = 7.4, 7.4 Hz, 1H), 4.93 (dd, *J* = 9.1, 4.0 Hz, 1H), 4.05-3.92 (m, 2H), 3.20 (dd, *J* = 17.2, 4.0 Hz, 1H), 3.09 (dd, *J* = 17.2, 9.2 Hz, 1H), 1.29-1.21 (m, 2H), 0.48 (t, *J* = 7.4, 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.8, 151.5, 137.8, 137.4, 133.5, 133.3, 133.0, 131.8, 129.9, 129.4, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 127.5, 127.3, 127.0, 126.6, 125.6, 125.0, 119.4, 47.3, 42.8, 37.9, 24.2, 11.0; **HRMS** (EI^+) *m*/*z* calcd for $C_{34}H_{29}NO$ $[M]^+$: 467.2249; found: 467.2243.

5.4 General Procedures for the Synthesis of Spiro Bis-Indanes via Domino Stetter–Aldol–Michael and Stetter–Aldol–Aldol Reactions

Preparation of starting materials (83b–e, i and 23b)

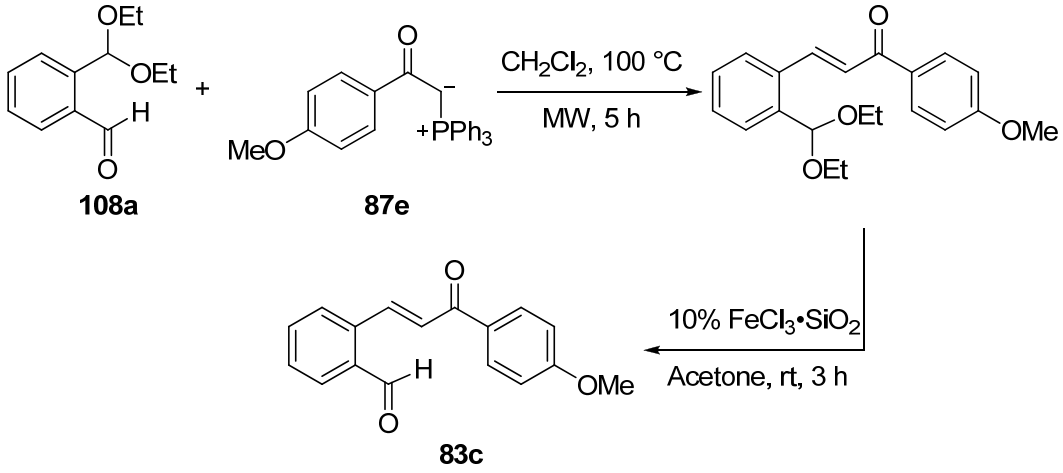
Synthesis of (*E*)-2-(3-(4-chlorophenyl)-3-oxoprop-1-enyl)benzaldehyde (83b)



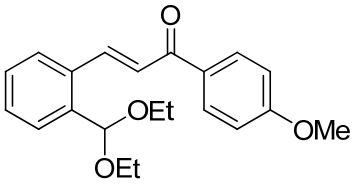
108a **87b** **83b**

In a 25 mL round-bottom flask was stirred a solution of 2-(diethoxymethyl)benzaldehyde (300 mg, 1.4 mmol, 1 equiv) in CH_2Cl_2 (5 mL, 0.3 M). To it was added solid (4-chlorophenacylidene)triphenyl phosphorane (896 mg, 2.2 mmol, 1.5 equiv). The flask was fitted with a condenser and the mixture was heated to reflux for 5 days. The mixture was cooled down to room temperature (23 °C), the solvent was removed in vacuo, and the crude mixture was filtered through a plug of silica using 30% ethyl acetate in hexanes as mobile phase. The solvent was removed and the product was re-dissolved in acetone (4.8 mL, 0.3 M). To this solution 10% $FeCl_3$•SiO_2[171] (300 mg, 1 equiv in mass) was added. After 30 minutes, the acetone was evaporated and the crude product was purified by flash column chromatography to afford a light yellow solid in 54% yield (211 mg). **mp** (°C): 115-117, R_f = 0.5 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1687, 1656, 1587, 1331, 1290, 758; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.55 (d, *J* = 15.7 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.90 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.65 (ddd, *J* = 15.0, 8.3, 7.4 Hz, 1H), 7.61 (ddd, *J* = 14.1, 7.4, 6.6 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 15.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.0, 189.6, 142.1, 139.6, 137.1, 136.2, 134.4, 134.1, 132.8, 130.4, 130.3, 129.2, 128.2, 127.0; **HRMS** (EI^+) *m/z* calcd for $C_{16}H_{11}ClO_2$ [M^+]: 270.0448; found: 270.0454.

Synthesis of 83c

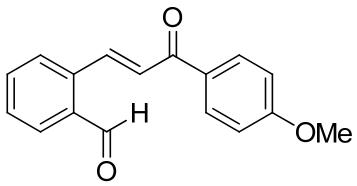


(*E*)-3-(2-(diethoxymethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one



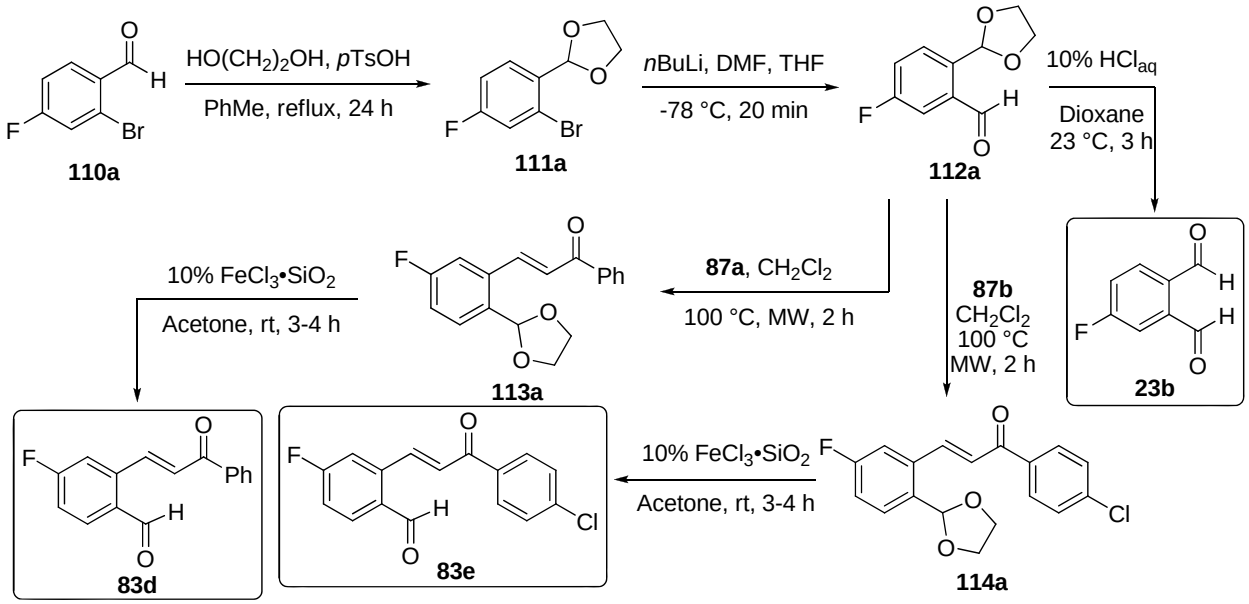
A 20 mL size vial was charged with a solution of 2-(diethoxymethyl) benzaldehyde (500 mg, 2.4 mmol, 1 equiv) and (4-methoxyphenacylidene)triphenyl phosphorane (1.17 g, 4.8 mmol, 2 equiv) in dichloromethane (8 mL, 0.3 M). The vial was crimped and set up in the microwave reactor at 100°C for 5 h at normal absorption. The solvent was then removed in vacuo and the remaining thick oil was purified by FCC using 20% ethyl acetate in hexanes as solvent system affording a light yellow oil in 88% yield (722 mg). R_f = 0.3 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2974, 1659, 1606, 1260, 1170; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 15.6 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.35 (m, 3H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.69 (s, 1H), 3.87 (s, 3H), 3.70 – 3.63 (m, 2H), 3.60 – 3.53 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.1, 163.6, 141.7, 138.4, 134.2, 131.2, 131.1, 129.7, 128.8, 127.2, 127.1, 124.4, 113.9, 100.2, 62.3, 55.6, 15.4; **HRMS** (CI^+-NH_3) *m/z* calcd for $C_{21}H_{24}O_4$ [M+1]: 340.1674; found: 340.1670.

(E)-2-(3-(4-methoxyphenyl)-3-oxoprop-1-enyl)benzaldehyde (83c)

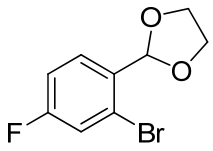


In a 25 mL round-bottom flask was stirred a solution of (*E*)-3-(2-(diethoxymethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (716 mg, 2.1 mmol, 1 equiv) in acetone (14 mL, 0.15 M) to which 10%$FeCl_3$•SiO_2 (716 mg, 0.4 mmol of $FeCl_3$, 0.18 equiv of $FeCl_3$) was added. The reaction was stirred at ambient temperature for 3 h. The resulting mixture was filtered through a plug of silica gel and eluted with ethyl acetate, the solvent was removed in vacuo and the oily residue was purified by FCC using 30% ethyl acetate in hexanes affording the title compound in 92% yield (515 mg) as yellow oil. R_f = 0.25 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2839, 1694, 1658, 1598; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.51 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.4, 7.4 Hz, 1H), 7.55 (t, *J* = 7.4, 7.4 Hz, 1H), 7.36 (d, *J* = 15.6 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.8, 188.7, 163.8, 140.3, 137.7, 134.4, 134.0, 131.9, 131.2, 130.7, 129.9, 128.2, 127.5, 114.1, 55.6; **HRMS** (EI^+) *m/z* calcd for $C_{17}H_{14}O_3$ [M^+]: 266.0942; found: 266.0936.

Synthesis of 83d, 83e, and 23b

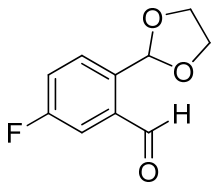


2-(2-bromo-4-fluorophenyl)-1,3-dioxolane (111a)



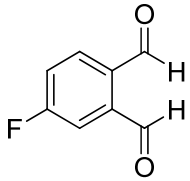
A 250 mL round-bottom flask was charged with 2-bromo-4-fluoro benzaldehyde (5 g, 24.6 mmol, 1 equiv), toluene (123 mL, 0.2 M), ethylene glycol (7 mL, 123.1 mmol, 5 equiv), and *p*-toluenesulfonic acid (141 mg, 0.74 mmol, 0.03 equiv). The mixture was refluxed for 24 h, then cooled to room temperature and transferred to a separatory funnel. The crude mixture was washed with water (2 x 50 mL), extracted with ethyl acetate (2 x 50 mL), and dried through a column with anhydrous sodium sulfate. The solvent was evaporated in vacuo affording the title compound as a light yellow oil in quantitative yield (6.1 g, >99% yield), no purification was required. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2889, 1598, 1489, 1235, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.30 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.04 (ddd, *J* = 8.5, 8.5, 2.1 Hz, 1H), 6.03 (s, 1H), 4.17 – 4.09 (m, 2H), 4.08 – 4.01 (m 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.8 (d, *J* = 252 Hz), 132.9, 129.3 (d, *J* = 8.8 Hz), 123.2 (d, *J* = 9.5 Hz), 120.3 (d, *J* = 24.6 Hz), 114.7 (d, *J* = 21.1 Hz), 102.2, 65.6; **HRMS** (CI^+/NH_3) *m/z* calcd for $C_9H_9BrFO_2$ [M+1]: 246.9769; found: 246.9765.

2-(1,3-dioxolan-2-yl)-5-fluorobenzaldehyde (112a)



A 250 mL round-bottom flask was charged with a solution of 2-(2-bromo-4-fluorophenyl)-1,3-dioxolane (**111a**) (5.75 g, 23.3 mmol, 1 equiv) in dry tetrahydrofuran (78 mL, 0.3 M) and cooled to -78 °C. Then a solution of *n*-butyllithium (16 mL, 34.9 mmol, 1.5 equiv, 2.22 M) was added dropwise and stirred for 20 minutes at the same temperature. Immediately after, *N*,*N*-dimethylformamide (3.6 mL, 46.6 mmol, 2 equiv) was added dropwise and the reaction mixture was left to warm up to 0 °C. The reaction was quenched with a solution of aqueous saturated ammonium chloride and 10 mL of water, the mixture was extracted with ethyl acetate (3 x 15 mL) and the organic phase was subsequently washed with brine (1 x 20 mL) and dried through anhydrous sodium sulfate. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford the title compound as a light yellow oil (3.12 g, 68%). R_f = 0.2 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2892, 1692, 1590, 1269, 1103, 1073; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.40 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 8.5, 5.3 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.28 (ddd, *J* = 8.3, 8.3, 2.7 Hz, 1H), 6.30 (s, 1H), 4.17 – 4.07 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.2, 163.4 (d, *J* = 250.4 Hz), 136.7 (d, *J* = 6.3 Hz), 135.4 (d, *J* = 3.3 Hz), 129.7 (d, *J* = 7.7 Hz), 120.5, (d, *J* = 21.6 Hz), 115.8 (d, *J* = 22.7 Hz), 101.1, 65.5; **HRMS** (EI^+) *m/z* calcd for $C_{10}H_9FO_3$ [M^+]: 196.0536; found: 196.0532.

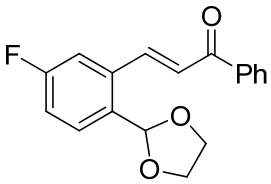
4-fluorophthalaldehyde (23b)



In a 25 mL round-bottom flask was stirred a solution of 2-(1,3-dioxolan-2-yl)-5-fluorobenzaldehyde (**112a**) (600 mg, 3.1 mmol, 1 equiv) in dioxane (7.7 mL, 0.4

M) and 10% aqueous HCl (7.7 mL, 0.4 M) at ambient temperature for 3 h. Then the reaction mixture was quenched with $NaHCO_3$ until pH ca.7 and extracted with ethyl acetate (3 x 10 mL). The organic phase was dried through anhydrous sodium sulfate and the solvent was removed in vacuo. The remaining oil was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford the title compound as a light brown solid in 45% yield (210 mg). **mp** (°C): 32-33, R_f = 0.3 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3367, 3071, 2870, 2753, 1698, 1599, 1583, 1270, 891; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.57 (d, *J* = 1.5 Hz, 1H), 10.39 (s, , 1H), 8.01 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.64 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.43 (ddd, *J* = 8.4, 8.4, 2.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.8, 190.7, 165.9 (d, *J* = 259.1 Hz), 139.3 (d, *J* = 7.1 Hz), 134.9, (d, *J* = 9.1 Hz), 133.0 (d, *J* = 3.2 Hz), 120.7 (d, *J* = 22.0 Hz), 117.5 (d, *J* = 23.2 Hz); **HRMS** (EI^+) *m/z* calcd for $C_8H_5FO_2$ [M^+]: 152.0273; found: 152.0270.

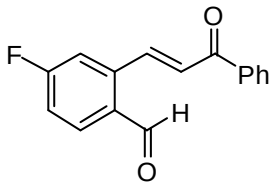
(*E*)-3-(2-(1,3-dioxolan-2-yl)-5-fluorophenyl)-1-phenylprop-2-en-1-one (113a)



A 20 mL size vial was charged with a solution of 2-(1,3-dioxolan-2-yl)-5-fluorobenzaldehyde (**112a**) (500 mg, 2.55 mmol, 1 equiv) and (phenacylidene)triphenyl phosphorane (1.94 g, 5.10 mmol, 2 equiv) in dichloromethane (8.5 mL, 0.3 M). The vial was crimped and set up in the microwave reactor at 100°C for 2 h at normal absorption. After concluded the experiment, the solvent was removed in vacuo and the remaining thick oil was purified by flash column chromatography (20% ethyl acetate in hexanes) affording **89a** as a light yellow solid in 90% yield (688 mg). **mp** (°C): 55-56, R_f = 0.4 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2891, 1664, 1609; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 8.1, 8.1 Hz, 1H), 7.59 (t, *J* = 7.3, 7.3 Hz, 1H), 7.51 (t, *J* = 7.5, 7.5 Hz, 1H), 7.43 (d, *J* = 15.6 Hz, 1H),

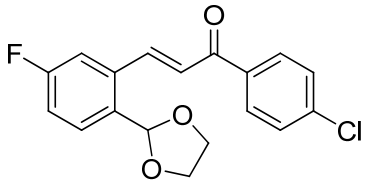
7.41 (d, *J* = 10.2 Hz, 1H), 7.11 (t, *J* = 8.2, 8.2 Hz, 1H), 4.19 – 4.04 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.2, 163.3 (d, *J* = 248.3 Hz), 140.6 (d, *J* = 2.1 Hz), 138.0, 136.7 (d, *J* = 7.8 Hz), 133.2, 132.7 (d, *J* = 2.9 Hz), 129.5 (d, *J* = 8.6 Hz), 128.8, 128.7, 125.3, 116.8 (d, *J* = 21.4 Hz), 113.7, (d, *J* = 22.5 Hz), 101.7, 65.6; **HRMS** (CI^+/NH_3) *m/z* calcd for $C_{18}H_{16}FO_3$ [M+1]: 299.1083; found: 299.1078.

(*E*)-4-fluoro-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (83d)



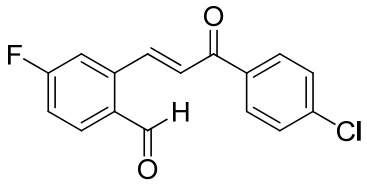
In a 25 mL round-bottom flask was stirred a solution of (*E*)-3-(2-(1,3-dioxolan-2-yl)-5-fluorophenyl)-1-phenylprop-2-en-1-one (**113a**) (570 mg, 1.91 mmol, 1 equiv) in acetone (13 mL, 0.15 M) to which 10% $FeCl_3$•SiO_2 (570 mg, 0.35 mmol of $FeCl_3$, 0.18 equiv of $FeCl_3$) was added. The reaction was stirred at ambient temperature for 4 h. The resulting mixture was filtered through a plug of silica gel and eluted with ethyl acetate, the solvent was removed in vacuo and the oily residue was purified by flash column chromatography (20% ethyl acetate in hexanes) affording the title compound in 86% yield (417 mg) as a light yellow crystal. **mp** (°C): 97-98, R_f = 0.4 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1696, 1656, 1601, 1573, 1216; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.53 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.94 (dd, *J* = 8.1, 6.0 Hz, 1H), 7.61 (dd, *J* = 7.3, 7.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 9.4 Hz, 1H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.26 (dd, *J* = 8.5, 7.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.1, 165.9 (d, *J* = 257.1 Hz), 140.5 (d, *J* = 9.0 Hz), 139.8, 137.6, 135.0 (d, *J* = 10.0 Hz), 133.4, 131.0 (d, *J* = 2.7 Hz), 128.9 (x 3C), 128.3, 117.3 (d, *J* = 22.1 Hz), 115.0 (d, *J* = 22.9 Hz); **HRMS** (EI^+) *m/z* calcd for $C_{16}H_{11}FO_2$ [M^+]: 254.0743; found: 254.0743.

(*E*)-3-(2-(1,3-dioxolan-2-yl)-5-fluorophenyl)-1-(4-chlorophenyl)prop-2-en-1-one (114a)



A 20 mL size vial was charged with a solution of 2-(1,3-dioxolan-2-yl)-5-fluorobenzaldehyde (**112a**) (500 mg, 2.55 mmol, 1 equiv) and (4-chlorophenacylidene)triphenyl phosphorane (2.12 g, 5.10 mmol, 2 equiv) in dichloromethane (8.5 mL, 0.3 M). The vial was crimped and set up in the microwave reactor at 100°C for 2 h at normal absorption. After concluded the experiment, the solvent was removed in vacuo and the remaining thick oil was purified by flash column chromatography (20% ethyl acetate in hexanes) affording **90a** as a light yellow solid in 89% yield (751 mg). **mp** (°C): 93-95, R_f = 0.4 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2892, 1665, 1611, 1588; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 15.5 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 8.1, 6.0 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.40 (m, 1H), 7.38 (d, *J* = 15.5 Hz, 1H), 7.12 (ddd, *J* = 8.3, 8.3, 1.8 Hz, 1H), 6.00 (s, 1H), 4.19 – 4.04 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.9, 163.3 (d, *J* = 248.5 Hz), 141.2, 139.7, 136.5 (d, *J* = 7.7 Hz), 136.3, 132.9, 130.2, 129.6 (d, *J* = 8.6 Hz), 129.2, 124.8, 117.0 (d, *J* = 21.4 Hz), 113.7 (d, *J* = 22.5 Hz), 101.7, 65.6; **HRMS** (CI^+/NH_3) *m/z* calcd for $C_{18}H_{15}ClFO_3$ [M+1]: 333.0693; found: 333.0692.

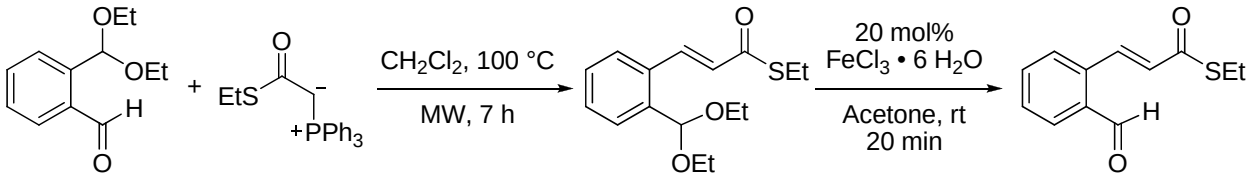
(*E*)-2-(3-(4-chlorophenyl)-3-oxoprop-1-enyl)-4-fluorobenzaldehyde (83e)



In a 25 mL round-bottom flask was stirred a solution of (*E*)-3-(2-1,3-dioxolan-2-yl)-5-fluorophenyl)-1-(4-chlorophenyl)prop -2-en-1-one (**114a**) (671 mg, 2.02 mmol, 1 equiv) in acetone (14 mL, 0.15 M) to which 10% $FeCl_3$•SiO_2 (671 mg, 0.36 mmol of $FeCl_3$, 0.18 equiv of $FeCl_3$) was added. The reaction was stirred at ambient temperature for 4 h. The resulting mixture was

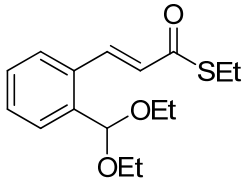
filtered through a plug of silica gel and eluted with ethyl acetate, the solvent was removed in and the solid residue was purified by flash column chromatography (since the product is highly insoluble, it had to be partially dissolved in dichloromethane to be loaded into the column) using 15% ethyl acetate in hexanes → 50% ethyl acetate in hexanes → 100% ethyl acetate affording the title compound (**83e**) in 93% yield (546 mg) as a tan solid. **mp** (°C): 155-156, R_f = 0.4 (30% ethyl acetate in hexanes). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1693, 1661, 1600, 1487, 1403; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.53 (d, *J* = 15.7 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.94 (dd, *J* = 8.2, 6.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 9.3 Hz, 1H), 7.31 (d, *J* = 15.7 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.1 (d, *J* = 143.2 Hz), 165.9 (d, *J* = 257.4 Hz), 140.6, 140.2 (d, *J* = 9.1 Hz), 139.9, 135.9, 135.5, 135.4, 131.1, 130.4, 129.2, 127.7, 117.4 (d, *J* = 22.0 Hz), 115.1 (d, *J* = 22.9 Hz); **HRMS** (EI^+) *m/z* calcd for $C_{16}H_{10}ClFO_2$ [M^+]: 288.0353; found: 288.0353.

Synthesis of 83i



108a **87f** **83i**

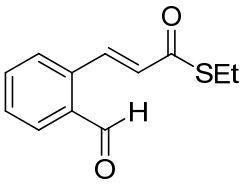
(*E*)-S-ethyl 3-(2-(diethoxymethyl)phenyl)prop-2-enethioate



In a 20 mL microwave vial 2-(diethoxymethyl) benzaldehyde (**108a**) (1 g, 4.8 mmol, 1 equiv) was dissolved in dry dichloromethane (10 mL, 0.3 M). To the resulting solution, 1-(triphenylphosphoranylidene)-*S*-ethyl propanethionate[172] (**87f**) (2.6 g, 7.2 mmol, 1.5 equiv) was added. The vial was crimped and subjected to the microwave reactor at 100°C for 24 h at normal absorption. The reaction was

concentrated and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford a yellow oil in 90% yield (1.3 g). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2975, 2930, 1658, 1615, 1057, 758; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 15.8 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.5, 7.5 Hz, 1H), 7.32 (t, *J* = 7.5, 7.5 Hz, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 5.64 (s, 1H), 3.65 (dddd, *J* = 9.0, 6.9, 6.9, 6.9 Hz, 2H), 3.55 (dddd, *J* = 9.0, 6.9, 6.9, 6.9 Hz, 2H), 3.01 (ddd, *J* = 7.4, 7.4 Hz, 2H), 1.31 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.23 (dd, *J* = 7.1, 7.1 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.2, 138.4, 138.3, 133.2, 129.9, 128.8, 127.3, 127.1, 126.9, 62.2, 23.5, 15.4, 15.0.

(*E*)-S-ethyl 3-(2-formylphenyl)prop-2-enethioate (83i)



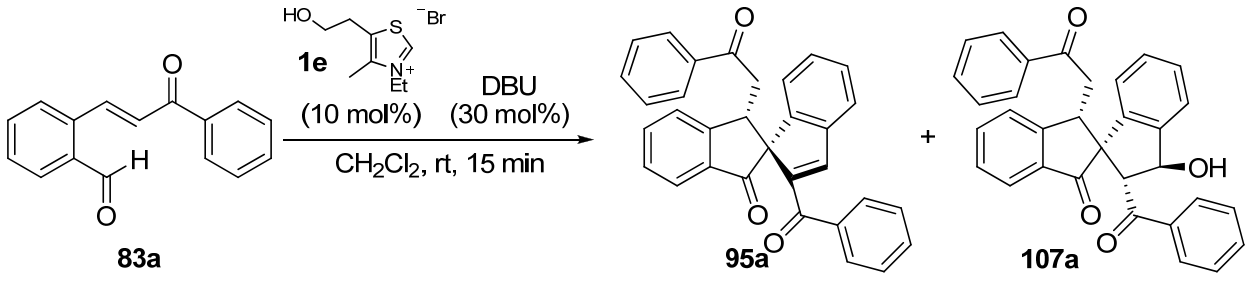
In a 25 mL round-bottom flask was stirred a solution of *(E)-S*-ethyl 3-(2-(diethoxymethyl)phenyl)prop-2-enethioate (1.14 g, 3.87 mmol, 1 equiv) in acetone (40 mL, 0.1 M) to which $FeCl_3$•6 H_2O (210 mg, 0.77 mmol, 0.2 equiv) was added. The reaction was stirred at ambient temperature for 20 min. The resulting mixture was filtered through a plug of silica gel and eluted with ethyl acetate, the solvent was removed in vacuo and the oily residue was purified by flash column chromatography (20% ethyl acetate in hexanes) affording the title compound in 96% yield (817 mg) as light yellow oil. R_f = 0.3 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2969, 2930, 2742, 1695, 1615, 1025, 759; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.47 (d, *J* = 15.7 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.56 (t, *J* = 7.2, 7.2 Hz, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 3.02 (ddd, *J* = 7.4, 7.4, 7.4 Hz, 2H), 1.32 (dd, *J* = 7.4, 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.9, 189.8, 137.0, 136.5, 134.3, 134.0, 132.7, 130.2, 129.8, 128.0, 23.6, 14.8; **HRMS** (CI^+/NH_3) *m/z* calcd for $C_{12}H_{12}O_2S$ $[M+1]^+$: 238.0901; found: 238.0900.

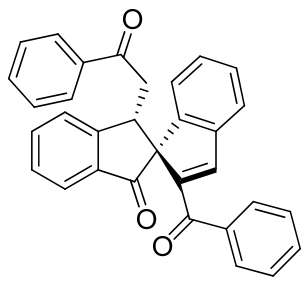
Synthesis of spiro bis-indanes via a Stetter-Aldol-Michael (SAM) sequence

5.4.1 General procedure for the preparation of spiro bis-indanes (95a-i)

In a 5 mL oven-dried Schlenk tube fitted with a septum was stirred a solution of aldehyde (**83a-i**) (1 equiv) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (0.1 equiv) in dry dichloromethane (0.5 M), then 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (0.3 equiv) was added. After stirring the mixture at ambient temperature for the indicated time shown in **Table 4.2**, the reaction was quenched with a saturated solution of aqueous ammonium chloride (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were filtered through a small pipette column containing anhydrous sodium sulfate / silica gel, the solvent was removed in vacuo. The crude product was purified by flash column chromatography employing the indicated eluent.

***Rac* -(*1'R,3S*)-2'-benzoyl-3-(2-oxo-2-phenylethyl)-1,2'-spirobis[inden]-1(3H)-one (76a) and *Rac* -(*1'S,3S*)-2'-benzoyl-3'-hydroxy-3-(2-oxo-2-phenylethyl)-2',3'-dihydro-1,2'-spirobis [inden]-1(3H)-one (107a)**

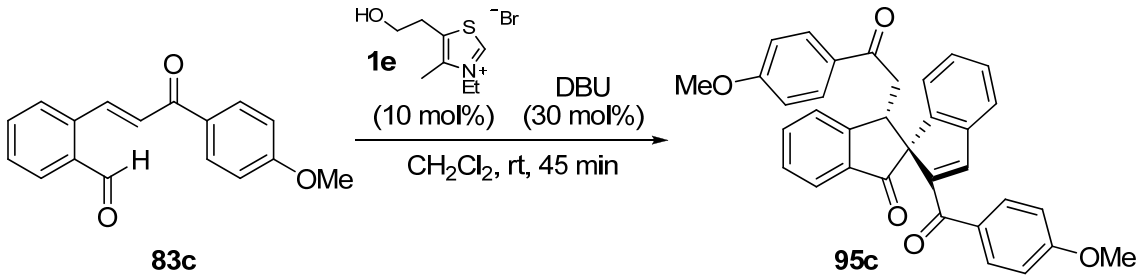




95a: 0.21 mmol scale, dr 17:1, white crystals, 79% yield, **mp** (°C): 187-189, R_f = 0.25 (30% ethyl acetate in hexanes). (<u>*major diastereomer*</u>) **FTIR** (KBr film) ν_{max} (cm^{-1}): 1716, 1682, 1629; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 3H), 7.72 (ddd, *J* = 7.6,

7.6, 1.0 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.59 – 7.53 (m, 3H), 7.61 – 7.54 (m, 3H), 7.53 – 7.48 (m, 4H), 7.47 – 7.43 (m, 1H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.19 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.13 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 4.93 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.41 (dd, *J* = 17.1, 9.3 Hz, 1H), 3.34 (dd, *J* = 17.1, 5.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.8, 197.6, 191.6, 155.4, 148.6, 145.5, 144.7, 143.7, 138.9, 137.3, 136.8, 135.4, 133.1, 132.2, 129.5, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 125.5, 125.4, 125.0, 72.4, 40.6, 39.1; **HRMS** (EI^+) *m/z* calcd for $C_{32}H_{22}O_3$ [M^+]: 454.1569; found: 454.1566.

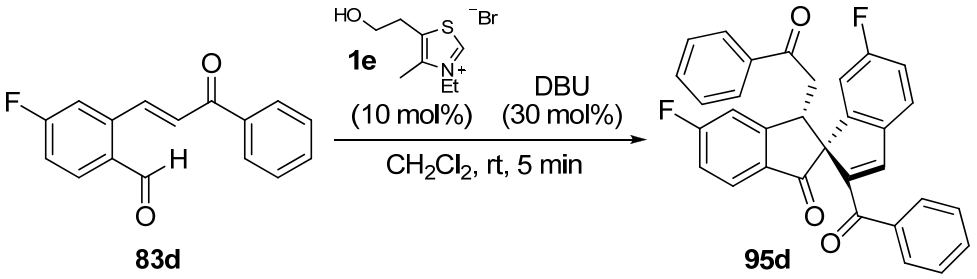
***Rac* -(*1S,1'R*)-2'-(4-methoxybenzoyl)-1-(2-(4-methoxyphenyl)-2-oxoethyl)-1,2'-spirobis [inden]-3(1H)-one (95c)**



0.19 mmol scale, dr 22:1, light yellow solid, 68% yield, **mp** (°C): 164-166. R_f = 0.2 (30% ethyl acetate in hexanes). (*major diastereomer*) **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1717, 1669, 1600, 1256, 1172, 765; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.7 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.4, 7.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.48 (t, *J* = 7.5, 7.5 Hz, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.4, 7.4 Hz, 1H), 7.12 (t, *J* = 7.4, 7.4 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 4.87 (dd, *J* = 7.9, 6.3 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.32 (dd, *J* = 16.8, 8.9 Hz, 1H), 3.26 (dd, *J* = 16.8, 5.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.8, 196.0, 190.1, 163.5, 163.1, 155.5, 149.0, 145.4, 143.8, 143.4, 137.3, 135.2, 131.7, 131.6, 130.1, 129.9, 128.3, 128.0, 127.9,

125.4, 125.1, 125.0, 123.2, 113.8, 113.7, 72.6, 55.6, 55.5, 40.6, 38.7; **HRMS** (EI^+) *m*/*z* calcd for $C_{34}H_{26}O_5$ [M^+]: 514.1780; found: 514.1790.

***Rac* -(*1'R,3S*)-2'-benzoyl-5,6'-difluoro-3-(2-oxo-2-phenylethyl)-1,2'-spirobis[inden]-1(3H)-one (95d)**



0.19 mmol scale, dr 11:1, white crystals suitable for *X-ray* analysis, 64% yield, **mp** (°C): 188-189. R_f = 0.3 (30% ethyl acetate in hexanes). (<u>*Major diastereomer*</u>) **FTIR** (KBr film) ν_{max} (cm^{-1}): 1716, 1683, 1612, 1560, 1344; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 – 7.92 (m, 3H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.61 – 7.57 (m, 1H), 7.53 – 7.47 (m, 3H), 7.45 (s, 1H), 7.36 – 7.27 (m, 4H), 7.22 (t, *J* = 8.5, 8.5 Hz, 1H), 6.90 (ddd, *J* = 8.3, 8.3, 1.9 Hz, 1H), 6.55 (dd, *J* = 8.3, 1.9 Hz, 1H), 4.91 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.40 (dd, *J* = 17.1, 9.3 Hz, 1H), 3.32 (dd, *J* = 17.1, 5.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.3, 196.7, 191.2, 167.8 (d, *J* = 257.7 Hz), 162.9 (d, *J* = 250.6 Hz), 158.2 (d, *J* = 9.7 Hz), 148.7 (d, *J* = 4.2 Hz), 147.4 (d, *J* = 8.3 Hz), 143.6, 139.6, 138.6, 136.4, 133.5, 133.3, 132.4, 129.5, 129.1, 128.7, 128.6, 128.0 (d, *J* = 10.5 Hz), 127.8, 126.6 (d, *J* = 9.2 Hz), 116.5 (d, *J* = 23.7 Hz), 115.9 (d, *J* = 23.2 Hz), 112.2 (d, *J* = 23.0 Hz), 111.1 (d, *J* = 23.2 Hz), 72.5, 40.3, 38.8; **HRMS** (EI^+) *m*/*z* calcd for $C_{32}H_{20}F_2O_3$ [M^+]: 490.1380; found: 490.1379.

Empirical formula: $C_{32}H_{20}F_2O_3$

Formula weight: 490.48

Crystal Color, Habit: colourless, block-like

Crystal dimensions (mm): 0.15 × 0.14 × 0.13

Crystal system: monoclinic

Space group: $P2_1/c$ [No. 14; non-standard setting of $P2_1/c$]

Unit cell parameters:

a (Å)	9.8701(5)
b (Å)	20.1152(11)
c (Å)	12.7485(7)
α (°)	90
β (°)	112.629(2)
γ (°)	90
V (Å^3)	2336.2(2)
Z^b	4

F(000) 1016

Density (ρ_{calcd}): 1.394 mg/m^3

Absorption coefficient (μ): 0.821 mm^{-1}

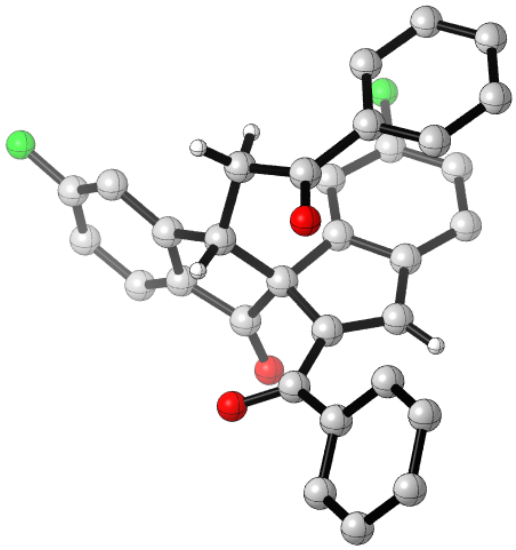
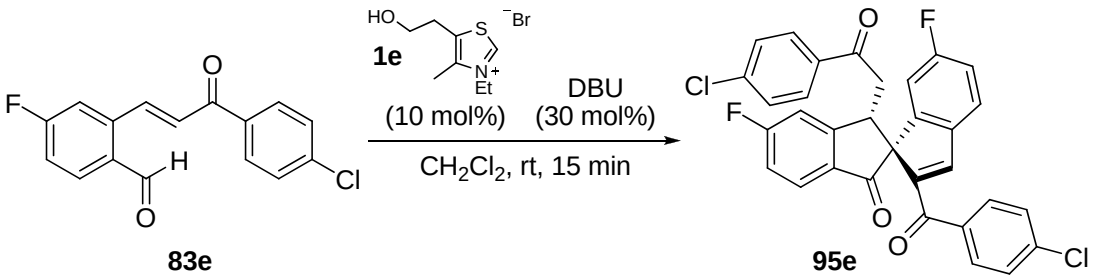


Figure 5.5 ORTEP representation for spiro bis-indane **95d**.

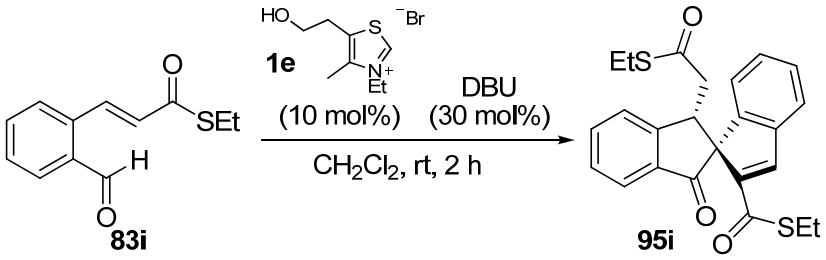
***Rac* -(*1'R,3S*)-2'-(4-chlorobenzoyl)-3-(2-(4-chlorophenyl)-2-oxoethyl)-5,6'-difluoro-1,2'-spirobis[inden]-1(3H)-one (95e)**



0.17 mmol scale (higher dilution was required due to the low solubility for **83e**, **0.1 M** in CH_2Cl_2), dr 16:1, tan solid, 80% yield, **mp** (°C): 103-105. R_f = 0.3 (20% ethyl acetate in hexanes). (*Major diastereomer*) **FTIR** (KBr film) ν_{max} (cm^{-1}): 1718, 1684, 1613, 1591; **^{1}H NMR**

(500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.3, 5.3 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.39 (s, 1H), 7.35 – 7.26 (m, 4H), 7.22 (t, *J* = 8.5, 8.5 Hz, 1H), 6.91 (ddd, *J* = 8.9, 8.9, 2.1 Hz, 1H), 6.53 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.84 (dd, *J* = 9.8, 4.4 Hz, 1H), 4.40 (dd, *J* = 17.3, 10.1 Hz, 1H), 3.31 (dd, *J* = 17.3, 4.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.9, 195.4, 190.1, 167.8 (d, *J* = 258.1 Hz), 162.9 (d, *J* = 250.9 Hz), 157.8 (d, *J* = 9.7 Hz), 148.6 (d, *J* = 4.1 Hz), 147.1 (d, *J* = 8.2 Hz), 143.4, 140.0, 139.4, 138.8, 136.8, 134.6, 133.1, 130.8, 129.1, 129.0, 128.9, 128.1 (d, *J* = 10.6 Hz), 126.7 (d, *J* = 9.1 Hz), 116.7 (d, *J* = 23.6 Hz), 116.0 (d, *J* = 23.2 Hz), 112.1 (d, *J* = 23.1 Hz), 111.1 (d, *J* = 24.0 Hz), 72.4, 40.2, 38.5; **HRMS** (EI^+) *m*/*z* calcd for $C_{32}H_{18}Cl_2F_2O_3$ [M^+]: 558.0601, 560.0583 [M+1]; found: 558.0599, 560.0569.

***Rac* -(*1S,1'R*)-S-ethyl 1-(2-(ethylthio)-2-oxoethyl)-3-oxo-1,3-dihydro-1,2'-spirobis[indene] -2'-carbothioate (95i)**



0.23 mmol scale, dr 13:1, light yellow oil, 31% yield. R_f = 0.25 (20% ethyl acetate in hexanes). (<u>*Major diastereomer*</u>) **FTIR** (KBr film) ν_{max} (cm^{-1}): 2969, 2929, 1719, 1682, 1637, 1601, 1460, 758; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 6.3 Hz, 1H), 7.84 (s, 1H), 7.70 (dddd, *J* = 7.6, 7.6, 1.1, 0.0 Hz, 1H), 7.56 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.5, 7.5 Hz, 1H), 7.33 (dddd, *J* = 7.6, 7.6, 0.9, 0.0 Hz, 1H), 7.17 (dddd, *J* =7.6, 7.6, 1.0, 0.0 Hz, 1H), 4.80 (dd, *J* = 7.5, 7.3 Hz, 1H), 3.05 – 2.94 (m, 3H), 2.79 (dddd, *J* = 13.4, 7.4, 7.4, 7.4 Hz, 1H), 2.70 (dddd, *J* = 13.4, 7.4, 7.4, 7.4 Hz, 1H), 2.50 (dd, *J* = 15.9, 8.0 Hz, 1H), 1.30 (dd, *J* =

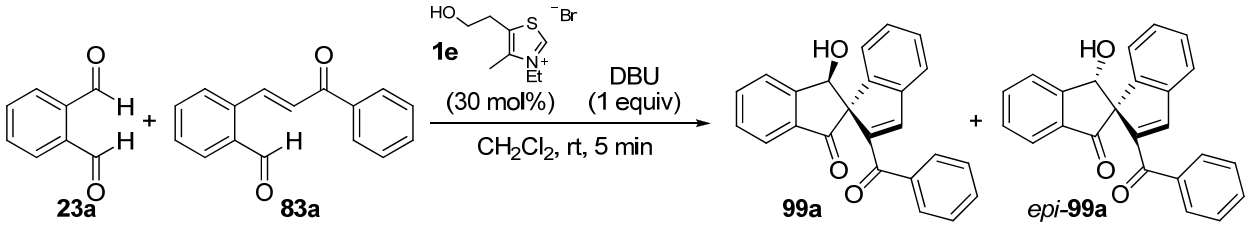
7.4, 7.4 Hz, 3H), 1.13 (dd, J = 7.4, 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.1, 196.9, 187.2, 154.6, 147.1, 145.0, 142.8, 142.0, 136.8, 135.6, 128.7, 128.5, 128.3, 125.4, 125.2, 125.1, 123.2, 71.7, 44.4, 41.1, 23.6, 23.4, 14.9, 14.8; **HRMS** (EI^+) m/z calcd for $C_{24}H_{22}O_3S_2$ [M^+]: 422.1010; found: 422.1004.

Synthesis of spiro bis-indanes via a Stetter-Aldol-Aldol (SAA) sequence

5.4.2 General procedure for the preparation of spiro bis-indanes (81a, e and *epi*-81a, e)

In a 5 mL oven-dried Schlenk tube fitted with a septum was stirred a solution of phthaldialdehyde (**23a**) (1 equiv), *o*-formyl chalcone derivative (**83a** and **d**) (2 equiv) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (0.3 equiv) in dry dichloromethane (0.5 M), then 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (1 equiv) was added. After stirring the mixture at ambient temperature for the indicated time, the reaction was quenched with a saturated solution of aqueous ammonium chloride (4 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were filtered through a small pipette column containing anhydrous sodium sulfate / silica gel. The solvent was removed in vacuo. The crude product was purified by flash column chromatography employing the indicated eluent.

***Rac* -(*1R,1'R*)-2'-benzoyl-1-hydroxy-1,2'-spirobis[inden]-3(1H)-one (99a) and *Rac* -(*1S,1'R*)-2'-benzoyl-1-hydroxy-1,2'-spirobis[inden]-3(1H)-one (*epi*-99a)**



3.7 mmol scale, dr 1:1.1, **99a**: 432 mg (33% yield), light yellow crystal, **mp** (°C): 152-154. R_f = 0.35 (10% ethyl acetate in toluene). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3421, 3066, 1716, 1552, 1341, 1064, 758; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.84 – 7.80 (m, 4H), 7.73 (s, 1H), 7.60 – 7.56 (m, 3H), 7.47 (t, *J* = 7.6, 7.6 Hz, 2H), 7.37 (t, *J* = 7.4, 7.4 Hz, 1H), 7.31 (t, *J* = 7.4, 7.4 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 5.74 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 195.6, 155.5, 149.4, 149.3, 141.9, 138.5, 136.2, 135.8, 132.9, 129.9, 129.6, 128.6, 128.5, 126.6, 125.2, 124.7, 121.8, 77.4, 74.3; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{16}O_3$ [M^+]: 352.1099; found: 352.1100.

Epi-**99a**: 492 mg (38% yield), light pink crystal, **mp** (°C): 241-244. R_f = 0.15 (10% ethyl acetate in toluene). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3428, 1690, 1621, 1553, 1343, 1292, 727; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (t, *J* = 7.6, 7.6 Hz, 2H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.81 (t, *J* = 7.3, 7.6 Hz, 1H), 7.75 (s, 1H), 7.61 – 7.57 (m, 3H), 7.50 (t, *J* = 7.7, 7.7 Hz, 2H), 7.37 (t, *J* = 7.6, 7.6 Hz, 1H), 7.23 (t, *J* = 7.6, 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.07 (d, *J* = 9.2 Hz, 1H), 1.96 (dd, *J* = 9.2, 6.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.8, 191.5, 154.0, 147.1, 146.6, 144.1, 143.5, 138.7, 136.9, 135.7, 132.4, 129.5, 129.2, 129.1, 129.0, 128.6, 125.9, 125.8, 124.8, 123.1, 75.6, 73.6; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{16}O_3$ [M^+]: 352.1099; found: 352.1095.

Empirical formula: $C_{24}H_{16}O_3$

Formula weight: 352.37

Crystal Color, Habit: colourless, block-like

Crystal dimensions (mm): 0.17 × 0.12 × 0.10

Crystal system: orthorhombic

Space group: *P*21/*P* 2ac 2ab

Unit cell parameters:

a (Å)	11.0811(4)
b (Å)	12.4394(4)
c (Å)	12.5442(4)
α (°)	90
β (°)	90(2)
γ (°)	90
V (Å^3)	21729.12(10)
Z^b	4

F(000) 736

Density (ρ_{calcd}): 1.354 mg/m^3

Absorption coefficient (μ): 0.713 mm^{-1}

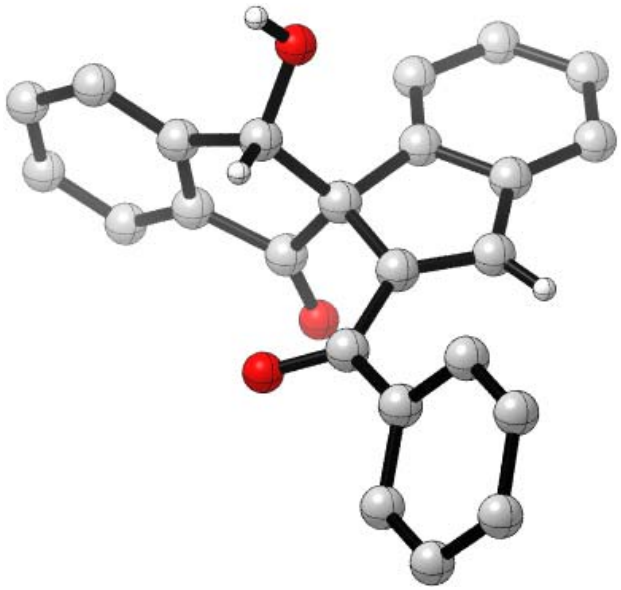
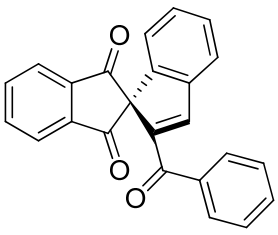


Figure 5.6 ORTEP representation for spiro bis-indane *epi*-**99a**.

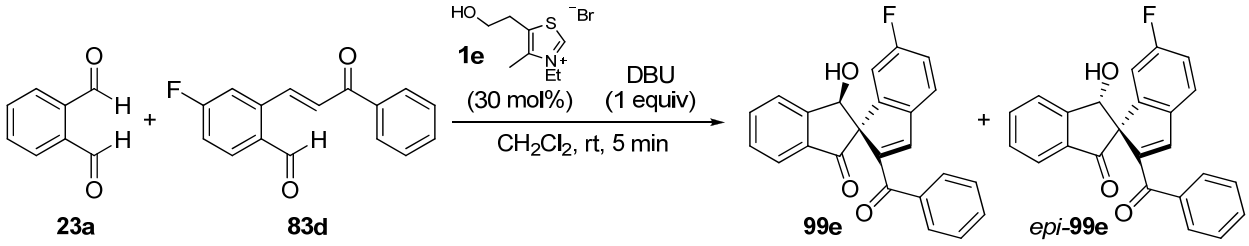
2'-benzoyl-1,2'-spirobis[indene]-1,3-dione (100a)



In a 25 mL round-bottom flask was stirred a 1:1 mixture of diastereomers of 2'-benzoyl-1-hydroxy-1,2'-spirobi[inden]-3(1*H*)-one (**99a**/*epi*-**99a**) (50 mg, 0.14 mmol, 1 equiv) in acetonitrile (1.4 mL). 2-Iodoxybenzoic acid (IBX) (80 mg, 0.28 mmol, 2 equiv) was added and the mixture was heated to 80°C for 2 h. After cooling down the mixture to ambient temperature the crude mixture was diluted with ethyl acetate and filtered through a fritted funnel and the filter-cake was washed with a mixture of 20% methanol in dichloromethane (5X). The solvent was evaporated in vacuo

and the resulting solid was quickly purified by flash column chromatography affording a light yellow solid in 98% yield (48 mg). **mp** (°C): 268-269, R_f = 0.3 (30% ethyl acetate in hexanes). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 7105, 1621, 1597, 1554, 1242, 755; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.94 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.82 (s, 1H), 7.82 – 7.80 (m, 2H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.57 (dd, *J* = 7.5, 7.3 Hz, 1H), 7.47 (t, *J* = 7.7, 7.7 Hz, 2H), 7.39 (t, *J* = 7.5, 7.5 Hz, 1H), 7.28 (t, *J* = 7.5, 7.5 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.6, 190.6, 147.8, 146.0, 145.2, 143.7, 143.6, 137.6, 135.9, 132.6, 129.7, 129.2, 129.1, 128.7, 125.6, 124.6, 122.3, 73.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{14}O_3$ [M^+]: 350.0942; found: 350.0945.

***Rac* -(*1R,1'R*)-2'-benzoyl-6'-fluoro-1-hydroxy-1,2'-spirobis[inden]-3(1H)-one (99e) and *Rac* -(*1S,1'R*)-2'-benzoyl-6'-fluoro-1-hydroxy-1,2'-spirobis[inden]-3(1H)-one (*epi*-99e)**

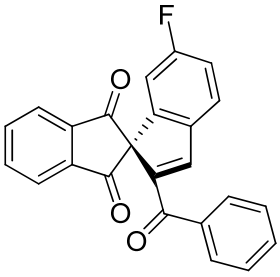


0.75 mmol scale, dr 1:1.1, **99e**: 85 mg (31% yield), light yellow crystal, **mp** (°C): 169-171. R_f = 0.3 (10% ethyl acetate in toluene). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3287, 1719, 1621, 1267, 724; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9 Hz, 1H), 7.85 – 7.78 (m, 4H), 7.68 (s, 1H), 7.59 (ddd, *J* = 12.2, 7.3, 5.2 Hz, 2H), 7.53 (dd, *J* = 8.3, 5.0 Hz, 1H), 7.47 (t, *J* = 7.7, 7.7 Hz, 2H), 7.08 (ddd, *J* = 8.9, 8.9, 2.2 Hz, 1H), 6.70 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 4.41 (d, *J* = 11.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.6, 195.2, 164.1 (d, *J* = 251.8 Hz), 155.3, 151.6 (d, *J* = 9.3 Hz), 148.3, 145.4, 138.3, 137.9, 136.5, 135.6, 133.0, 130.1, 129.6,

128.6,126.7, 126.5 (d, *J* = 9.4 Hz), 124.8, 115.9 (d, *J* = 23.2 Hz), 109.9 (d, *J* = 24.1 Hz), 77.3, 74.4; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{15}FO_3$ [M^+]: 370.1005; found: 370.1011.

Epi-**99e**: 114 mg (41%), light yellow crystal, **mp** (°C): 194-196. R_f = 0.1 (10% ethyl acetate in toluene). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3469, 1703, 1556, 1257, 762, 719; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.85 – 7.80 (m, 3H), 7.70 (s, 1H), 7.60 (ddd, *J* = 13.8, 13.8, 7.4 Hz, 2H), 7.54 (dd, *J* = 8.4, 5.1 Hz, 1H), 7.49 (dd, *J* = 7.7, 7.6 Hz, 2H), 7.07 (ddd, *J* = 8.9, 8.9, 2.3 Hz, 1H), 6.50 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.08 (s, 1H), 2.07 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.1, 191.2, 163.3 (d, *J* = 250.5 Hz), 153.7, 146.7, 146.6, 146.2, 139.3, 138.5, 136.7, 135.9, 132.5, 129.8, 129.1, 128.7, 126.8 (d, *J* = 9.1 Hz), 125.8, 125.0, 116.2 (d, *J* = 23.3 Hz), 111.6 (d, *J* = 24.3 Hz), 75.8, 73.6. **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{15}FO_3$ [M^+]: 370.1005; found: 370.0992.

2'-benzoyl-6'-fluoro-1,2'-spirobis[indene]-1,3-dione (100e)



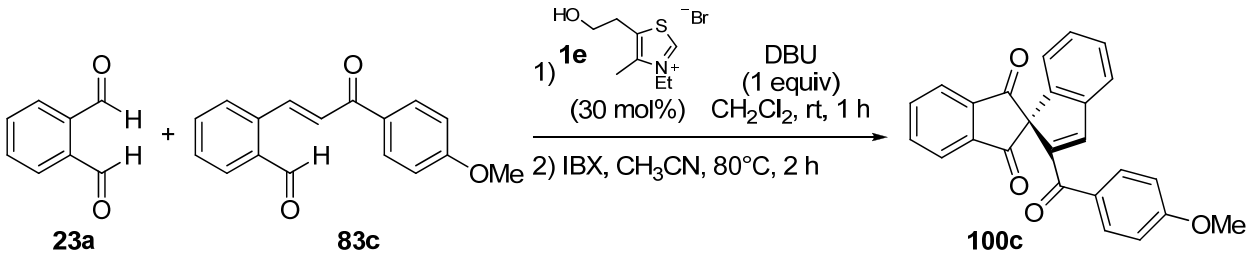
In a 25 mL round-bottom flask was stirred a 1:1 mixture of diastereomers of 2'-benzoyl-6'-fluoro-1-hydroxy-1,2'-spirobi[inden]-3(1*H*)-one (**99e**/*epi*-**99e**) (50 mg, 0.13 mmol, 1 equiv) in acetonitrile (1.4 mL, 0.1M). 2-Iodoxybenzoic acid (IBX) (76 mg, 0.27 mmol, 2 equiv) was added and the mixture was heated to 80 °C for 2 h. After cooling down the mixture to ambient temperature the crude mixture was diluted with ethyl acetate and filtered through a fritted funnel and the filter-cake was washed with a mixture of 20% methanol in dichloromethane (5X). The solvent was evaporated in vacuo and the resulting solid did not required further purification affording the title compound as a light yellow solid in 98% yield (49 mg). **mp** (°C): 214-216. R_f = 0.3 (30% ethyl acetate in hexanes). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1708, 1624, 1556, 1336,

1247, 726, 697, 508; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.97 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.76 (s, 1H), 7.57 (dd, *J* = 8.2, 5.3 Hz, 2H), 7.47 (dd, *J* = 7.7, 7.6 Hz, 2H), 7.11 (ddd, *J* = 8.8, 8.8, 2.2 Hz, 1H), 6.67 (dd, *J* = 8.1, 1.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.8, 190.2, 163.7 (d, *J* = 251.8 Hz), 147.0 (d, *J* = 9.1 Hz), 146.7, 146.0 (d, *J* = 4.0 Hz), 143.5, 139.8 (d, *J* = 2.4 Hz), 137.4, 136.2, 132.7, 129.0, 128.7, 126.8 (d, *J* = 9.2 Hz), 124.7, 116.5 (d, *J* = 23.3 Hz), 110.4 (d, *J* = 24.6 Hz), 73.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{13}FO_3$ [M^+]: 368.0848; found: 368.0839.

5.4.3 General one-pot procedure to obtain spiro bis-indane triketones (100c, g)

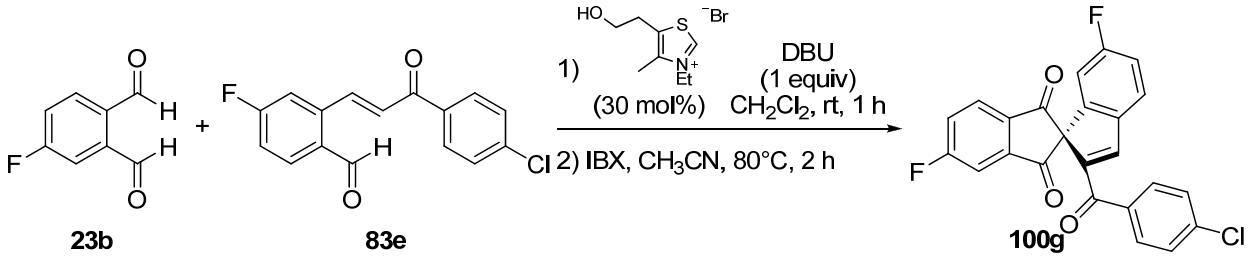
In a 5 mL oven-dried Schlenk tube fitted with a septum was stirred a solution of a phthaldialdehyde (**23a** or **23b**) (1 equiv), *o*-formyl chalcone derivative (**83c** or **83e**) (2 equiv) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (0.3 equiv) in dry dichloromethane (0.1 M), then 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (1 equiv) was added. After stirring the reaction at ambient temperature for the indicated time, the mixture was quenched with a saturated solution of aqueous ammonium chloride (4 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were filtered through a small pipette column containing anhydrous sodium sulfate / silica gel, the solvent was removed in vacuo. The crude product was re-dissolved in acetonitrile (0.3 M) and 2-iodoxybenzoic acid (IBX) (2 equiv) was added. The resulting mixture was heated for two hours and after cooling the reaction mixture to ambient temperature, the crude was filtered through a fritted funnel. The filter cake was washed with 20% methanol in dichloromethane (5X). From the resulting filtrate, the solvent was removed in vacuo and the remaining crude product was purified by flash column chromatography using 0.25% methanol in dichloromethane to afford the desired product.

2'-(4-methoxybenzoyl)-1,2'-spirobis[indene]-1,3-dione (100c)



0.17 mmol scale (16 mg, 25% yield), light yellow crystal, **mp** (°C): 177-179. R_f = 0.3 (0.25% methanol in dichloromethane). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1705, 1598, 1247, 1168, 766; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.93 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.97 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.6, 7.6 Hz, 1H), 7.27 (t, *J* = 7.5, 7.5 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.94 (t, *J* = 7.1, 7.1 Hz, 2H), 3.87 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.7, 189.1, 163.5, 146.6, 146.3, 145.0, 143.9, 143.7, 135.9, 131.4, 130.3, 129.5, 129.1, 125.3, 124.5, 122.3, 116.9, 114.3, 114.0, 113.4, 73.3, 55.7; **HRMS** (EI^+) *m/z* calcd for $C_{25}H_{16}O_4$ [M^+]: 380.1049; found: 380.1056.

***Rac*-(*R*)-2'-(4-chlorobenzoyl)-5,6'-difluoro-1,2'-spirobis[indene]-1,3-dione (100g)**

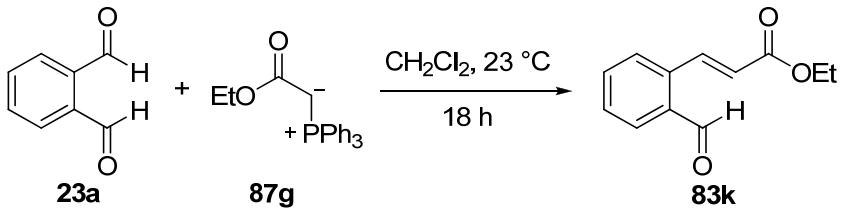


0.33 mmol scale (69 mg, 50% yield), light yellow solid, **mp** (°C): 221-224. R_f = 0.35 (0.25% methanol in dichloromethane). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1713, 1598, 1337, 1270, 993, 504; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.78 – 7.73 (m, 4H), 7.64 (ddd, *J* = 8.4, 8.4, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.4, 5.0 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.13

(ddd, J = 8.6, 8.6, 1.5 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 194.5, 193.9, 189.0, 167.8 (d, J = 261.9 Hz), 163.9 (d, J = 252.8 Hz), 146.9, 146.7 (d, J = 8.5 Hz), 146.3 (d, J = 8.9 Hz), 145.5 (d, J = 4.0 Hz), 139.7 (d, J = 0.1 Hz), 139.3, 135.7, 130.4, 129.1, 127.4 (d, J = 9.6 Hz), 127.0 (d, J = 9.3 Hz), 124.2 (d, J = 24.3 Hz), 117.9, 116.8 (d, J = 23.3 Hz), 111.3 (d, J = 23.0 Hz), 110.6 (d, J = 24.8 Hz), 73.2; **HRMS** (EI^+) m/z calcd for $C_{24}H_{11}ClF_2O_3$ [M^+]: 420.0365; found:420.0371.

Preparation of starting materials (83k, 83n, 121, 128, and 131)

Synthesis of 83k



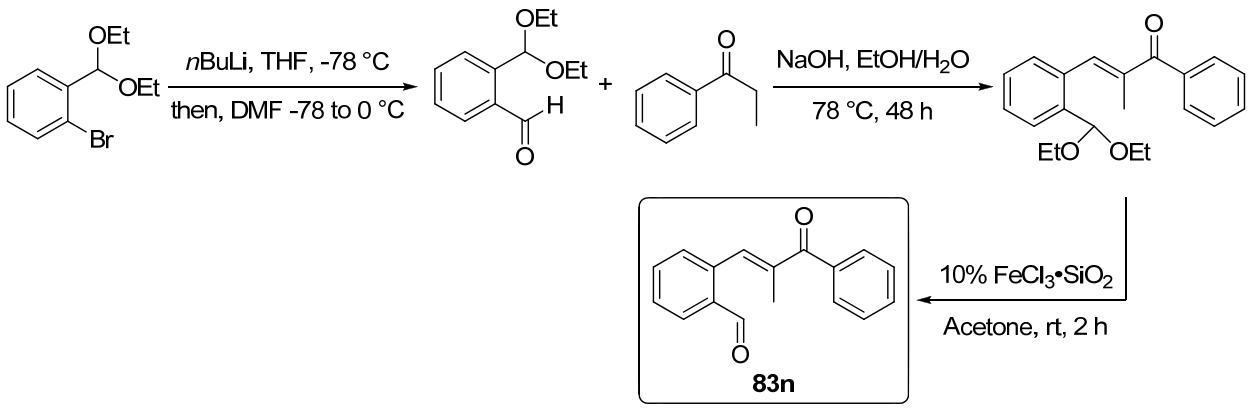
23a **87g** **83k**

(*E*)-Ethyl 3-(2-formylphenyl)acrylate (83k)

In a 100 mL round bottom flask was stirred a solution of phthaldialdehyde (**23a**) (500 mg, 3.73 mmol, 1 equiv) and (2-ethoxy-2-oxoethyl)triphenylphosphorane (**87g**) (1.29 g, 3.73 mmol, 1 equiv) in dichloromethane (37 mL, 0.1 M) at 23 °C. The mixture was stirred for 2 h and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford the title compound in 74% yield (563 mg) as a colorless oil. R_f = 0.30 (20% ethyl acetate in hexanes). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3063, 2982, 2744, 1713, 1181, 765; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.50 (d, J = 15.9 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.54 (dd, J = 7.6, 7.6 Hz, 1H), 6.36 (d, J = 15.9 Hz, 1H), 4.27 (ddd, J = 7.1, 7.1, 7.1 Hz, 2H), 1.34 (dd, J = 7.1, 7.1 Hz, 3H); **^{13}C**

NMR (125 MHz, $CDCl_3$) δ 191.9, 166.3, 141.0, 136.8, 134.1, 134.0, 132.3, 130.0, 128.1, 123.4, 60.9, 14.4; **HRMS** (CI^+/NH_3) m/z calcd for $C_{12}H_{12}O_3$ $[M+NH_4]^+$: 222.1130; found: 222.1130.

Synthesis of 83n



(*E*)-2-(2-Methyl-3-oxo-3-phenylprop-1-enyl)benzaldehyde (83n)

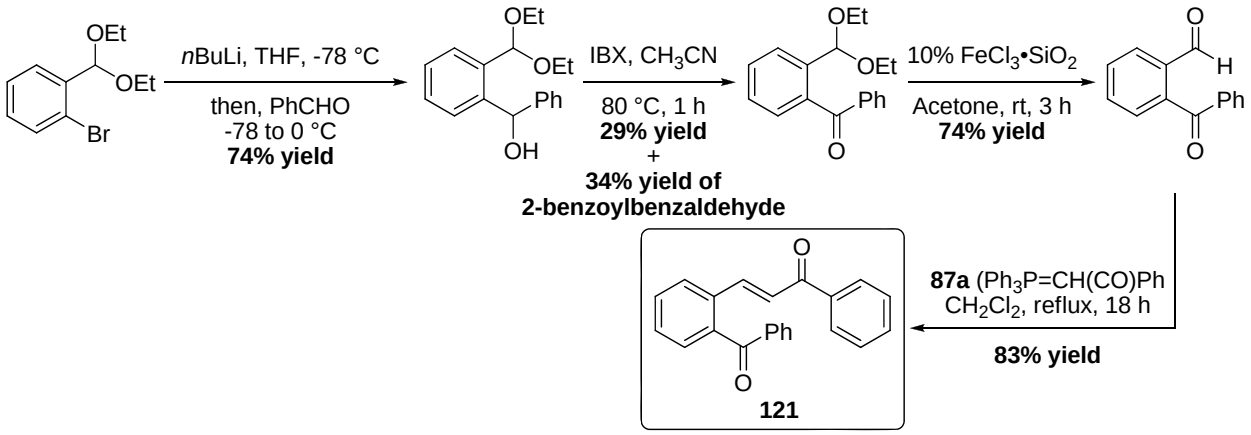
In a flame dried 100 mL round bottom flask was stirred a solution of 1-bromo-2-(diethoxymethyl)benzene (1.6 mL, 8 mmol, 1 equiv) in THF (40 mL, 0.2 M) at -78 °C, then a solution of *n*-butyllithium in hexanes (5 mL, 12 mmol, 1.5 equiv, 2.4 M) was added dropwise and stirred for 20 min. Afterwards, N,N-dimethylformamide (1.2 mL, 16 mmol, 2 equiv) was added in one portion and the mixture was allowed to slowly warm to 0 °C over 1 hour. The reaction was quenched with saturated aqueous ammonium chloride (2 mL) and water (10 mL), and the aqueous layer was extracted with ethyl acetate (3 x 20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was used without further purification for the next step. R_f = 0.7 (30% ethyl acetate in hexanes), 87% Yield (699 mg), light yellow oil.

In a 25 mL round bottom flask was stirred a solution of sodium hydroxide (220 mg, 5.48 mmol, 4 equiv) in ethanol (2 mL) and water (2.5 mL) at 0 °C. The crude aldehyde (300 mg, 1.44 mmol, 1.05 equiv) was slowly added to the flask followed by a slow addition of propiophenone

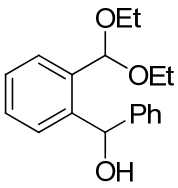
(182 μL, 1.37 mmol, 1.0 equiv). The reaction was stirred at ambient temperature for 10 min and then heated to 78 °C for 48 h. Then, the mixture was neutralized with 1M HCl to pH 7 and the aqueous layer was extracted with dichloromethane (2 x 5 mL), washed with brine (1 x 5 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (100% dichloromethane) to afford the diethylacetal α,β-unsaturated ketone in 55% yield (245 mg) as a light yellow oil.

In a 25 mL round bottom flask the diethylacetal α,β-unsaturated ketone (245 mg, 0.75 mmol, 1 equiv) was dissolved in acetone (5 mL, 0.15 M). To this solution 10% $FeCl_3$•SiO_2 (245 mg, 1 equiv in mass) was added. After 2 h, the acetone was evaporated and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford the title compound as a dark orange oil in 99% yield (186 mg). R_f = 0.15 (10% ethyl acetate in hexanes). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 3062, 2742, 1698, 1647, 1263, 1013, 705; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 3H), 7.64 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.60 – 7.48 (m, 5H), 7.38 (d, *J* = 7.6 Hz, 1H), 2.04 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.8, 192.0, 139.6, 139.2, 138.0, 137.9, 133.8, 132.2, 131.9, 130.2, 129.8, 128.8, 128.4, 14.5; **HRMS** (CI^+/NH_3) m/z calcd for $C_{17}H_{14}O_2$ $[M+1]^+$: 251.1072; found: 251.1062.

Synthesis of 85

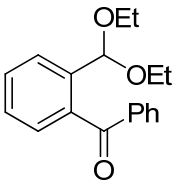


(2-(Diethoxymethyl)phenyl)(phenyl)methanol



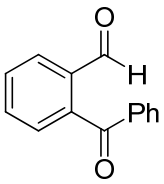
In a 100 mL flame-dried round-bottom flask was stirred a solution of 1-bromo-2-(diethoxymethyl)benzene (0.78 mL, 3.86 mmol, 1 equiv) in THF (18 mL, 0.2 M) at -78 °C, then a solution of *n*-butyllithium in hexanes (1.8 mL, 4.25 mmol, 1.1 equiv, 2.4 M) was added dropwise and stirred for 1 h. Afterwards, a solution of benzaldehyde (0.43 mL, 4.25 mmol, 1.1 equiv) in THF (1 mL) was added dropwise to the mixture and stirred for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and diluted with diethyl ether (20 mL). The aqueous layer was extracted (2 x 10 mL) with diethyl ether and the combined organic layers were sequentially washed with water (1 x 10 mL) and brine (1 x 20 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent removed in vacuo. The crude product was purified by flash column chromatography (10 % ethyl acetate in hexanes + 2% triethylamine). The pure product was obtained as yellow oil in 74% yield (816 mg). R_f = 0.3 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3425, 2975, 1451, 1056, 763, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.31 – 7.26 (m, 3H), 7.20 – 7.19 (m, 1H), 6.29 (d, *J* = 4.1 Hz, 1H), 5.52 (s, 1H), 3.74 (brs, 1H), 3.65 (dddd, *J* = 9.3, 7.1, 7.1, 7.1 Hz, 1H), 3.58 (dddd, *J* = 9.4, 7.1, 7.1, 7.1 Hz, 1H), 3.52 (dddd, *J* = 9.4, 7.1, 7.1, 7.1 Hz, 1H), 3.46 (dddd, *J* = 9.4, 7.1, 7.1, 7.1 Hz, 1H), 1.22 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.19 (dd, *J* = 7.1, 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.1, 142.4, 136.6, 129.3, 129.1, 128.3, 127.6, 127.5, 127.2, 126.7, 101.3, 72.6, 62.4, 62.2, 15.3, 15.2; **HRMS** (EI^+) m/z calcd for $C_{18}H_{22}O_3$ $[M-H_2O]^+$: 268.1463; found: 268.1453.

(2-(Diethoxymethyl)phenyl)(phenyl)methanone



In a 25 mL round bottom flask was stirred a solution of (2-(diethoxymethyl)phenyl)(phenyl)methanol (943 mg, 3.29 mmol, 1 equiv) in acetonitrile (11 mL, 0.3 M), then IBX (1.84 g, 6.58 mmol, 2 equiv) was added to the flask and the mixture was heated to reflux for 1 h. The reaction mixture was allowed to cool to ambient temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford the title compound (yellow oil, 269 mg, 0.95 mmol) and the 2-benzoylbenzaldehyde (dark yellow semi-solid, 235 mg, 1.12 mmol). The mixture represents a 63% combined yield. R_f = [diethylacetal] 0.5, [aldehyde] 0.25; (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2975, 2880, 1668, 1273, 1057, 707; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.48 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.43 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.36 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 5.67 (s, 1H), 3.56 (dddd, *J* = 8.8, 7.2, 7.2, 7.2 Hz, 2H), 3.39 (dddd, *J* = 8.8, 7.3, 7.3, 7.3 Hz, 2H), 1.02 (dd, *J* = 7.0, 7.0 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.2, 138.7, 138.2, 137.7, 133.2, 130.2, 129.8, 128.4, 127.8, 127.8, 126.8, 99.7, 62.4, 15.0; **HRMS** (EI^+) m/z calcd for $C_{18}H_{20}O_3$ [M^+]: 284.1412; found: 284.1416.

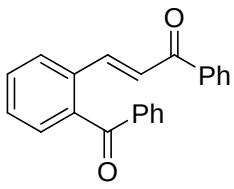
2-benzoylbenzaldehyde



In a 25 mL round bottom flask (2-(diethoxymethyl)phenyl)(phenyl)methanone (269 mg, 0.95 mmol, 1equiv) was dissolved in acetone (4.8 mL, 0.2 M). To this solution 10% $FeCl_3$•SiO_2 (269 mg, 1 equiv in mass) was added. After 3 h, the acetone was evaporated and the crude product was purified by flash column chromatography

(30% ethyl acetate in hexanes) to afford a light yellow solid in 74% yield (157 mg). **mp** (°C): 62 – 63, R_f = 0.3 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3062, 1698, 1667, 1315, 930, 714; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.01 – 8.00 (m, 1H), 7.79 – 7.77 (m, 2H), 7.70 – 7.64 (m, 2H), 7.60 – 7.57 (m, 1H), 7.49 – 7.43 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.6, 190.7, 141.4, 137.1, 135.5, 133.7, 133.4, 130.7, 130.2, 130.0, 128.9, 128.7; **HRMS** (EI^+) m/z calcd for $C_{14}H_{10}O_2$ [M^+]: 210.0680; found: 210.0667.

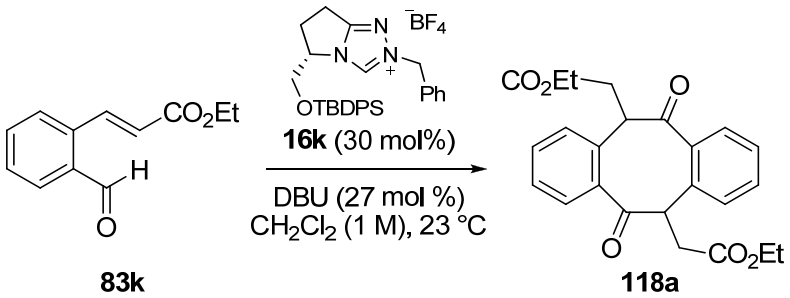
(*E*)-3-(2-benzoylphenyl)-1-phenylprop-2-en-1-one (121)



In a 25 mL round bottom flask was stirred a mixture of 2-benzoylbenzaldehyde (234 mg, 1.12 mmol, 1 equiv), (benzoyl methylene)triphenylphosphorane (**87a**) (639 mg, 1.68 mmol, 1.5 equiv) in dichloromethane (3.7 mL, 0.3 M). The mixture was stirred at reflux (40 °C) for 18 h, and then cooled to ambient temperature. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford the title compound in 83% yield (292 mg) as a yellow oil. R_f = 0.3 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3061, 1661, 1607, 1448, 1267, 928, 694, 636; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 4H), 7.78 (d, *J* = 15.9 Hz, 1H), 7.61 – 7.40 (m, 8H), 7.35 (d, *J* = 15.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.5, 190.9, 142.4, 140.0, 137.9, 137.4, 134.5, 133.8, 132.9, 130.9, 130.5, 129.6, 129.3, 128.8, 128.7, 128.6, 127.7, 125.6; **HRMS** (EI^+) m/z calcd for $C_{22}H_{16}O_2$ [M^+]: 312.1150; found: 312.1161.

5.4.4 Preparation of dibenzo[8]annulenes (118a and 118d)

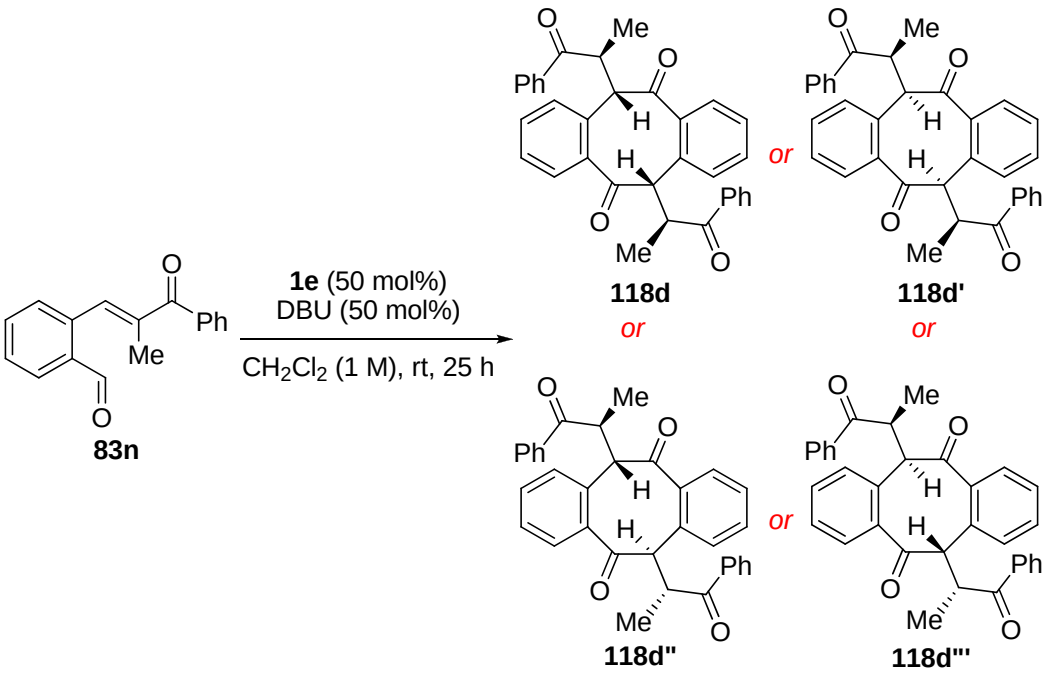
Synthesis of diethyl 2,2'-(3,4,7,8-tetrahydrodibenzo[8]annulene)diacetate (118a)



A flame-dried Schlenk tube was charged with (*E*)-ethyl 3-(2-formylphenyl)acrylate (**83k**) (50 mg, 0.24 mmol, 1 equiv) and (*S*)-2-benzyl-5-((tert-butyldiphenylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**16k**) (40 mg, 0.07 mmol, 0.3 equiv). The tube was evacuated three times and re-filled with dry nitrogen, and then the solids were dissolved in dichloromethane (0.24 mL, 1 M). Lastly, 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU) (9.7 μL, 0.065 mmol, 0.27 equiv) was added to the solution at ambient temperature. The reaction was monitored by TLC. Upon completion (10 min), it was quenched with saturated aqueous ammonium chloride (0.5 mL) and the organic layer was extracted with dichloromethane (3 × 2 mL) and filtered through a short pipette plug of anhydrous sodium sulfate / silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to furnish the title product as an inseparable mixture of diastereomers (5.3:1 dr) in 42% yield (41 mg) as colourless needle-like crystals. **mp** (°C): 135–139, R_f = 0.28 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2980, 1725, 1714, 1490, 1094; (*major diastereomer*) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.24 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 2H), 5.75 (dd, *J* = 9.3, 4.5 Hz, 2H), 4.20 (dddd, *J* = 7.2, 2.1, 2.0, 1.8 Hz, 4H), 3.10 (dd, *J* = 15.1, 9.4 Hz, 2H), 2.59 (dd, *J* = 15.2, 4.6 Hz, 2H), 1.24 (dd, *J* = 7.2, 7.2 Hz, 6H). (*minor diastereomer*)

7.37 (d, J = 7.5 Hz, 2H), 7.32 – 7.39 (m, 2H), 7.26 – 7.22 (m, 2H), 7.09 (d, J = 7.4 Hz, 2H), 5.70 (dd, J = 9.4, 4.7 Hz, 2H), 4.22 – 4.16 (m, 4H), 3.14 (dd, J = 14.9, 9.4 Hz, 2H), 2.76 (dd, J = 14.9, 4.7 Hz, 2H), 1.20 (dd, J = 7.2, 7.2 Hz, 6H); (*major diastereomer*) **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 132.0, 131.6, 128.6, 128.1, 126.9, 124.1, 120.3, 74.4, 60.9, 39.9, 14.4; **HRMS** (EI^+) m/z calcd for $C_{24}H_{24}O_6$ [M^+]: 408.1572; found: 408.1575.

***Rac*-2,2'-(3,4,7,8-tetrahydrodibenzo[8]annulene)bis (1-phenylpropan-1-one) (118d/118d')**



Following the general procedure for **118a**, the reaction was performed with (*E*)-2-(2-methyl-3-oxo-3-phenylprop-1-enyl)benzaldehyde (**83n**) (50 mg, 0.20 mmol, 1 equiv) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (25 mg, 0.10 mmol, 0.5 equiv) in dichloromethane (0.24 mL, 1 M) and DBU (15 µL, 0.10 mmol, 0.5 equiv) for 25 h. The crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to furnish the title product as an inseparable mixture of diastereomers (2:1 dr) in 8% yield (8 mg) as a light yellow oil. R_f = 0.3 (20% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2979, 2938,

1766, 1680, 1287, 1216, 972, 702; (*major diastereomer*) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.1 Hz, 2H), 7.93 – 7.87 (m, 4H), 7.68 (d, *J* = 4.5 Hz, 2H), 7.63 – 7.46 (m, 8H), 7.33 (d, *J* = 7.8 Hz, 2H), 5.91, (d, *J* = 8.8 Hz, 2H), 3.68 (ddd, *J* = 15.8, 7.1, 7.1, 7.1 Hz, 2H), 1.54 (d, *J* = 7.0 Hz, 6H); (*minor diastereomer*) 7.93 – 7.87 (m, 6H), 7.63 – 7.46 (m, 12H), 5.97 (d, *J* = 5.1 Hz, 2H), 4.10 (ddd, *J* = 12.3, 5.1, 5.1, 5.1 Hz, 2H), 1.10 (d, *J* = 7.2 Hz, 6H); (*major diastereomer*) **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.5, 170.3, 149.1, 135.9, 134.4, 134.0, 129.6, 129.1, 128.6, 126.2, 125.9, 123.4, 82.3, 47.1, 16.3; **HRMS** (EI^+) m/z calcd for $C_{34}H_{28}O_4$ [M^+]: 500.1987; found: 500.1987.

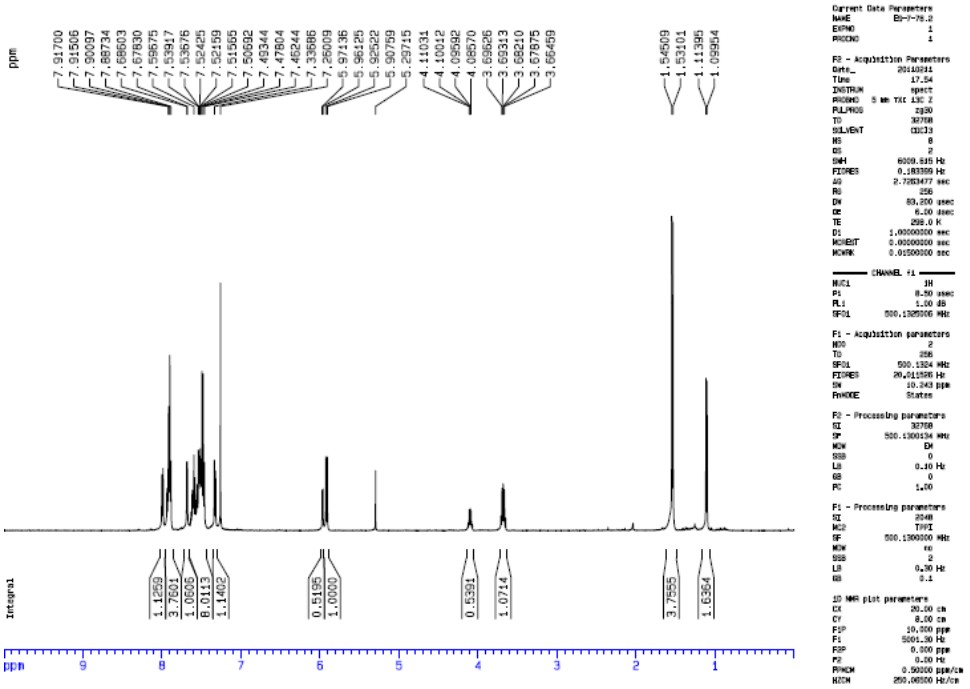
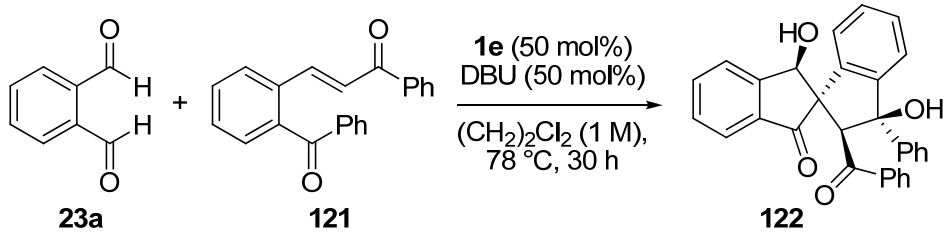


Figure 5.7 ^{1}H NMR for the mixture of diastereomers of 2,2'-(3,4,7,8-tetrahydrodibenzo[8]annulene)bis (1-phenylpropan-1-one) **118d** and **118d'**.

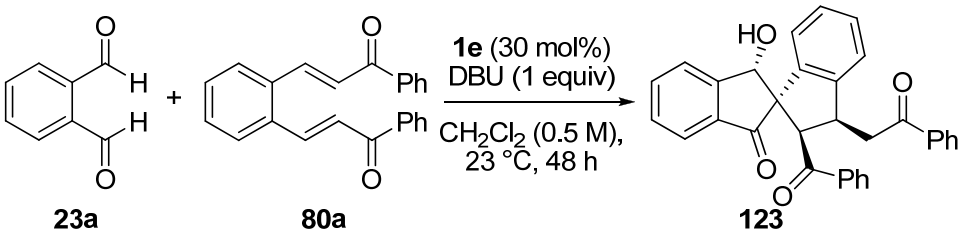
***Rac*-2'-benzoyl-1,3'-dihydroxy-3'-phenyl-2',3'-dihydro-1,2'-spirobi[inden]-3(1H)-one (122)**



A flame-dried Schlenk tube was charged with (*E*)-3-(2-benzoylphenyl)-1-phenylprop-2-en-1-one (**85**) (50 mg, 0.16 mmol, 1 equiv), *o*-phthaldialdehyde (**23a**) (32 mg, 0.24 mmol, 1.5 equiv), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (20 mg, 0.08 mmol, 0.5 equiv) in 1,2-dichloroethane (0.16 mL, 1 M). The mixture was heated to 78 °C, and then DBU was added (12 μL, 0.08 mmol, 0.5 equiv) and heated for 30 h. The reaction was quenched with saturated aqueous ammonium chloride (0.5 mL) and the organic layer was extracted with dichloromethane (3 × 2 mL) and filtered through a short pipette plug of anhydrous sodium sulfate / silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to furnish the title product in 11% yield (7.7 mg) as an orange solid. **mp** (°C): 191–194; R_f = 0.22 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3412, 3061, 1715, 1605, 1447, 1218, 957, 735, 713; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.71 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.48 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.46 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.37 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.33 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.24 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.17 (ddd, *J* = 7.6, 1.1, 1.0, 1.0 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.65 (s, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 5.43 (s, 1H), 5.34 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.7, 201.7, 153.5, 147.3, 143.7, 142.3, 136.9, 136.3, 135.8, 134.6, 129.5,

129.3, 128.9, 128.8, 128.5, 127.8, 126.5, 126.4, 124.6, 124.3, 123.8, 86.7, 72.7, 70.6, 59.0; **HRMS** (EI^+) m/z calcd for $C_{30}H_{22}O_4$ [M^+]: 446.1518; found: 446.1512.

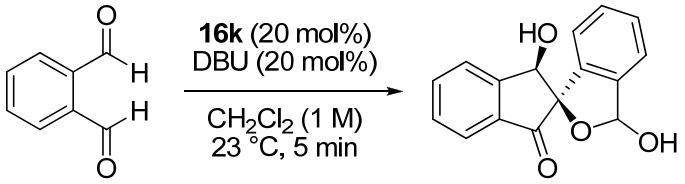
***Rac*-2'-benzoyl-1-hydroxy-3'-(2-oxo-2-phenylethyl)-2',3'-dihydro-1,2'-spirobi[inden]-3(1*H*)-one (123)**



A flame-dried Schlenk tube was charged with (2*E*,2'*E*)-3,3'-(1,2-phenylene) bis(1-phenylprop-2-en-1-one) (**80a**) (50 mg, 0.15 mmol, 1 equiv), *o*-phthaldialdehyde (**23a**) (20 mg, 0.15 mmol, 1 equiv), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (11.3 mg, 0.045 mmol, 0.3 equiv). The tube was evacuated three times and re-filled with dry nitrogen, the solids were dissolved in dichloromethane (0.3 mL, 0.5 M) followed by the addition of 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU) (22.5 μL, 0.15 mmol, 1 equiv) at ambient temperature. The reaction was monitored by thin layer chromatography. When no further change was observed (48 h), the reaction was quenched with saturated aqueous ammonium chloride (0.5 mL) and the organic layer was extracted with dichloromethane (3 × 2 mL) and filtered through a short pipette plug of anhydrous sodium sulfate / silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to furnish the title product in 23% yield (16 mg) as a light yellow solid. **mp** (°C): 167–169, R_f = 0.25 (30% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3485, 3062, 1713, 1681, 1596, 1579, 1217, 752, 690; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 10.4 Hz, 2H), 7.80 – 7.76 (m, 2H), 7.73 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.51 –

7.41 (m, 5H), 7.33 (d, J = 7.5 Hz, 1H), 7.24 (dd, J = 7.4, 7.4 Hz, 1H), 7.04 (dd, J = 7.4, 7.4 Hz, 1H), 6.44 (d, J = 7.7 Hz, 1H), 5.18 (d, J = 3.8 Hz, 1H), 4.79 (d, J = 4.8 Hz, 1H), 4.45 (ddd, J = 13.4, 10.0, 5.3 Hz, 1H), 3.78 (dd, J = 17.6, 8.3 Hz, 1H), 3.71 (dd, J = 17.6, 5.5 Hz, 1H), 2.89 (d, J = 4.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.2, 201.8, 198.9, 153.7, 146.5, 139.7, 137.1, 135.8, 135.1, 133.9, 133.4, 129.5, 129.2, 129.1, 128.8, 128.4, 127.2, 125.7, 125.3, 125.1, 124.3, 73.6, 73.4, 55.8, 46.0, 45.4; **HRMS** (EI^+) m/z calcd for $C_{32}H_{24}O_4$ [M^+]: 472.1674; found: 472.1675.

***Rac*-(*1R,1'R*)-1,3'-dihydroxy-3'H-spiro[indene-2,1'-isobenzofuran]-3(1H)-one (124)**



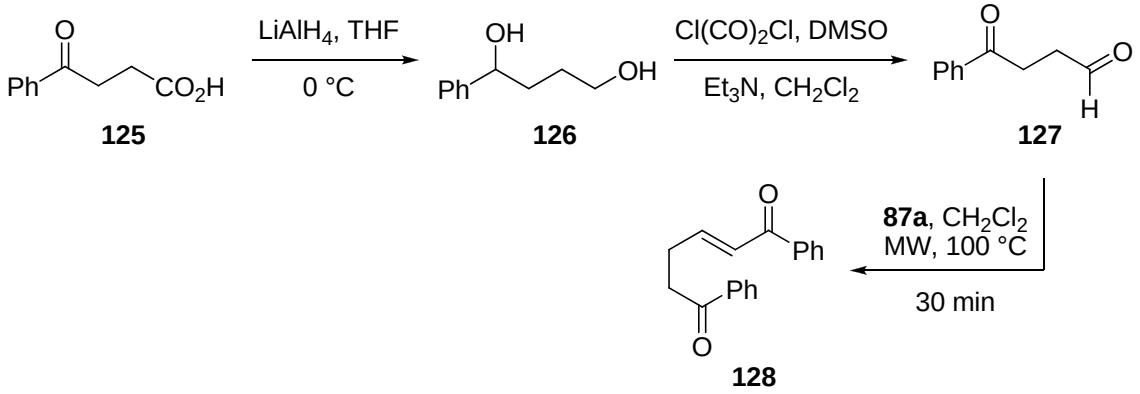
23a **124**

A flame-dried Schlenk tube was charged with phthaldialdehyde (**23a**) (50 mg, 0.37 mmol, 1 equiv) and (*S*)-2-benzyl-5-((tert-butyldiphenylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**16k**) (41 mg, 0.07 mmol, 0.2 equiv). The tube was evacuated three times and re-filled with dry nitrogen, the solids were dissolved in dichloromethane (0.4 mL, 1 M) followed by the addition of 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU) (22.5 μL, 0.15 mmol, 1 equiv) at ambient temperature. The reaction was monitored by thin layer chromatography. When no further change was observed (5 min), the reaction was quenched with saturated aqueous ammonium chloride (0.5 mL) and the organic layer was extracted with dichloromethane (3 × 2 mL) and filtered through a short pipette plug of anhydrous sodium sulfate / silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to furnish the title product in

23% yield (16 mg) as a light yellow solid. **mp** (°C): 152–154, R_f = 0.25 (30% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.95 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 7.3 Hz,1H), 7.46 – 7.51 (m, 2H), 7.33 (t, J = 8.1 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 5.49 (d, J = 6.4 Hz, 1H), 5.15 (d, J = 6.4 Hz, 1H).

Preparation of aliphatic acceptors (128 and 131)

Synthesis of (*E*)-1,6-diphenylhex-2-ene-1,6-dione (128)



1-phenylbutane-1,4-diol (90)

In a flame-dried round bottom flask was suspended $LiAlH_4$ (3.04 g, 80 mmol, 4 equiv) in dry THF (40 mL, 2 M) and the mixture was cooled to 0 °C. Benzoylpropionic acid (**125**) (3.57 g, 20 mmol, 1 equiv) in dry THF (50 mL, 0.4 M) was added dropwise using an addition funnel. The reaction mixture was stirred for 18 h allowing it to warm up to ambient temperature. After 24 h, the mixture was cooled to 0 °C and quenched with dropwise addition of water (3 mL) followed by the addition of 15% aqueous sodium hydroxide (3 mL) and water (9 mL). The quenched reaction was allowed to stir at room temperature for 1 h. Magnesium sulfate was added to the mixture and it was filtered through a plug of Celite®. The filter cake was rinsed with reagent

grade THF and the solvent was evaporated in vacuo. 3.30 g (> 99% yield) of white crystals that are formed upon standing were obtained and carried forward without purification. The spectroscopic data matches to the one reported in the literature.[173] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 4.70 (t, *J* = 6.2 Hz, 1H), 3.73 (t, *J* = 6.2 Hz, 1H), 3.70 – 3.60 (m, 2H), 2.98 (brs, 1H), 2.48 (brs, 1H), 1.88 – 1.79 (m, 3H), 1.74 – 1.59 (m, 2H).

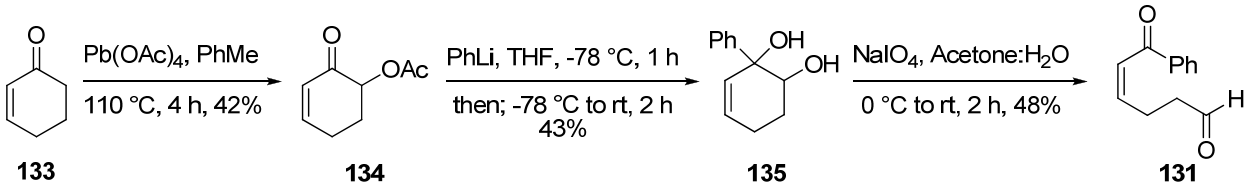
4-oxo-4-phenylbutanal (127)

In a flame-dried 500 mL round bottom flask was stirred a solution of dry DMSO (8.5 mL, 119.4 mmol, 6 equiv) in dry dichloromethane (220 mL, 0.5 M respect to DMSO) and it was cooled to -78 °C. Then, oxalyl chloride (6.7 mL, 79.6 mmol, 4 equiv) was added dropwise and the mixture was stired for 10 min at the same temperature. A solution of 1-phenylbutane-1,4-diol (**126**) in dry dichloromethane (112 mL, 0.18 M respect to **126**) was added dropwise to the mixture at -78 °C. Then triethylamine (28 mL, 199 mmol, 10 equiv) was added to the reaction flask and the mixture was allowed to reach ambient temperature. The reaction was diluted with reagent grade diethyl ether (400 mL) and the mixture was poured into a separatory funnel. The organic phase was washed successively with water (2 x 200 mL), brine (1 x 200 mL), and dried through a short column with anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford clear light yellow oil in 92% yield (2.96 g). The spectroscopic data matches that reported in the literature.[174] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.98 (t, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 3.33 (t, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 6.1 Hz, 2H).

(*E*)-1,6-diphenylhex-2-ene-1,6-dione (128)

In a 25 mL round bottom flask was stirred a mixture of 4-oxo-4-phenylbutanal (**127**) (200 mg, 1.23 mmol, 1 equiv) and (benzoyl methylene)triphenylphosphorane (**87a**) (704 mg, 1.85 mmol, 1.5 equiv) in dichloromethane (41 mL, 0.3 M). The mixture was subjected to the microwave reactor for 2 h (normal absorption, 100 °C). The solvent was removed in vacuo, and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford the title compound in 89% yield (292 mg) as a white solid. R_f = 0.3 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1682, 1623, 1595, 1447, 1371, 1267, 1198, 1008, 966, 757, 686; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 7.1 Hz, 2H), 7.59 – 7.53 (m, 2H), 7.49 – 7.44 (m, 4H), 7.10 (dt, *J* = 15.3 Hz, 1H), 6.97 (dt, *J* = 15.3, 1.3 Hz, 1H), 3.21 (t, *J* = 7.2 Hz, 2H), 2.78 (dq, *J* = 6.9, 1.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.5, 190.9, 148.0, 138.0, 136.8, 133.5, 132.9, 128.9, 128.8, 128.7, 128.2, 126.9, 37.0, 27.2; **HRMS** (EI^+) m/z calcd for $C_{18}H_{16}O_2$ [M^+]: 264.1150; found: 264.1156.

Synthesis of (*Z*)-6-oxo-6-phenylhex-4-enal (131)



2-oxocyclohex-3-enyl acetate (134)

In a 100 mL round bottom flask was heated to reflux a mixture of 2-cyclohexene-2-one (**133**) (1 mL, 10.5 mmol, 1 equiv) and lead tetraacetate (9.3 g, 21 mmol, 2 equiv) in toluene (21 mL, 0.5 M) for 4 hours. The reaction mixture was cooled to ambient temperature, diluted with diethyl ether (20 mL), and transferred to a separatory funnel. The organic phase was washed with

1M aqueous HCl and then dried through anhydrous sodium sulfate. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford an orange oil in 42% yield (682 mg). The spectroscopic data matches with the one reported in the literature.[175, 176] R_f = 0.2 (30% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.4 Hz, 2H), 7.91 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.51 – 7.43 (m, 4H), 7.10 (dt, *J* = 15.4, 6.9 Hz, 1H), 6.97 (d, *J* = 15.2 Hz, 1H), 3.22 (t, *J* = 7.3 Hz, 2H), 2.78 (t, *J* = 6.8 Hz, 2H).

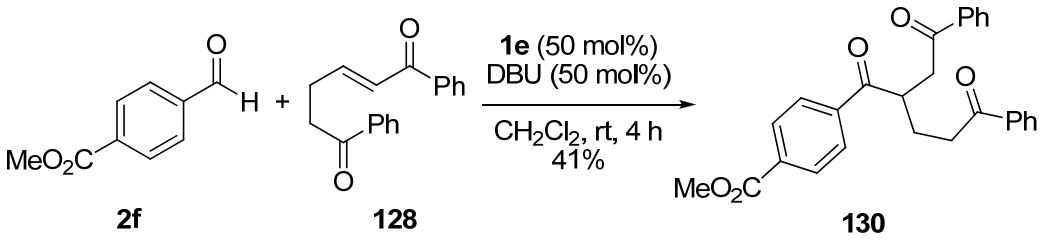
2-phenylcyclohex-3-ene-1,2-diol (135)

In a 25 mL round bottom flask was stirred a solution of 2-oxocyclohex-3-enyl acetate (**99**) (50 mg, 0.32 mmol, 1 equiv) in dry THF (2.5 mL) and cooled to -78 °C. Then, a solution of phenyllithium (1.2 mL, 0.97 mmol, 3 equiv, 0.8 M in THF) was added dropwise to the flask and stirred for 1 h at the same temperature. The temperature of the reaction was allowed to reach ambient temperature and the mixture was stirred for 2 additional hours. The reaction mixture was diluted with reagent grade ethyl acetate (5 mL) and 10% aqueous ammonium chloride was added (10 mL). The organic phase was separated, washed with brine (1 x 10 mL), and dried through anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford a yellow oil in 43% yield (79 mg, 5.4:1 dr). The spectroscopic data matches with the one reported in the literature.[175, 176] R_f = 0.28 (50% ethyl acetate in hexanes); (*major diastereomer*) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 2H), 6.00 (dt, *J* = 9.9, 3.2 Hz, 1H), 5.65 (d, *J* = 9.9 Hz, 1H), 3.80 (d, *J* = 6.7 Hz, 1H), 3.05 (brs, 1H), 2.58 (brs, 1H), 2.34 – 2.24 (m, 1H), 2.23 – 2.12 (m, 1H), 1.83 – 1.72 (m, 2H).

(*Z*)-6-oxo-6-phenylhex-4-enal (131)

In a 25 mL round bottom flask was stirred a solution of 2-phenylcyclohex-3-ene-1,2-diol (**135**) (98 mg, 0.52 mmol, 1 equiv) in acetone:water (1:1) (5 mL, 0.1 M) and cooled to 0 °C. To the mixture was added sodium periodate (221 mg, 1.03 mmol, 2 equiv) in one portion and stirred for 2 h at the same temperature then, the reaction was stirred for 2 additional hours at room temperature. The reaction was quenched with water (1 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layer was washed with brine and then dried through anhydrous sodium sulfate. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford a yellow oil in 48% yield (47 mg). The spectroscopic data matches with the one reported in the literature.[175, 176] R_f = 0.30 (30% ethyl acetate in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 11.6 Hz, 1H), 6.35 (dt, *J* = 11.6, 8.0 Hz, 1H), 2.93 (dq, *J* = 7.3, 1.4 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H).

Synthesis of methyl 4-(5-oxo-2-(2-oxo-2-phenylethyl)-5-phenylpentanoyl)benzoate (130)

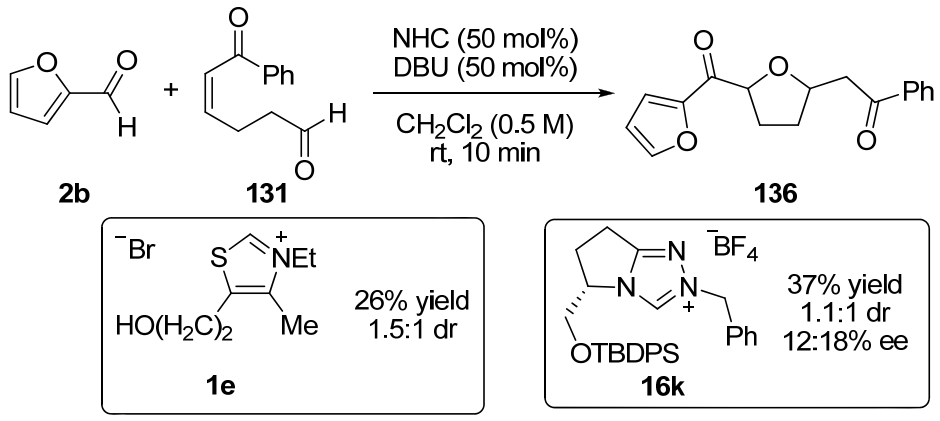


2f **128** **130**

In a 5 mL oven-dried Schlenk tube fitted with a septum was stirred a solution of (*E*)-1,6-diphenylhex-2-ene-1,6-dione (**128**) (50 mg, 0.19 mmol, 1 equiv), methyl 4-formylbenzoate (**2f**) (62.4 mg, 0.38 mmol, 2 equiv) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (24 mg, 0.1, mmol, 0.5 equiv) in dry dichloromethane (0.4 mL, 0.5 M), then 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (14 μL, 0.1 mmol, 0.5 equiv) was added. After stirring

the mixture at ambient temperature for 4 hours, the reaction was quenched with a saturated solution of aqueous ammonium chloride (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were filtered through a small pipette column containing anhydrous sodium sulfate / silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford 41% yield of a light yellow solid. **mp** (°C): , R_f = 0.22 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3346, 3060, 2951, 1723, 1682, 1597, 1448, 1280, 1108, 975, 913, 727, 648; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 7.3 Hz, 2H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 4.29 (dtd, *J* = 10.4, 6.7, 4.3 Hz, 1H), 3.78 (dd, *J* = 18.1, 9.5 Hz, 1H), 3.26 (dd, *J* = 17.8, 3.8 Hz, 1H), 3.06 – 2.98 (m, 2H), 2.25 (ddd, *J* = 14.1, 14.1, 7.0 Hz, 2H), 2.06 (ddd, *J* = 14.3, 14.3, 6.9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.0, 199.1, 198.3, 166.5, 140.4, 136.8, 136.6, 134.1, 133.6, 133.4, 130.2, 128.8 (2X), 128.7, 128.3, 128.1, 52.6, 41.3, 40.8, 35.6, 26.5; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{16}O_3$ [M^+]: 428.1624; found: 428.1622.

Synthesis of 2-(5-(furan-2-carbonyl)tetrahydrofuran-2-yl)-1-phenylethanone (136)

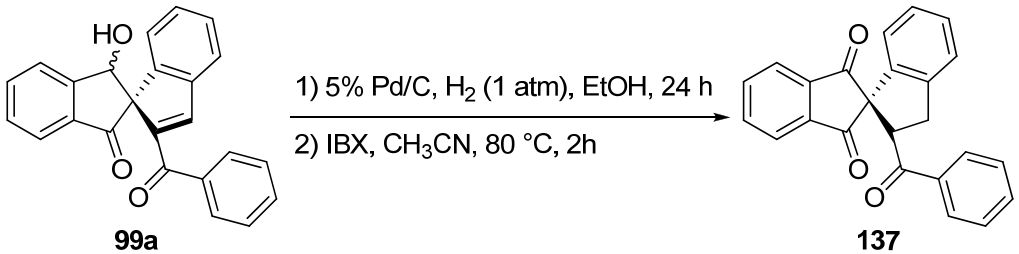


In a 5 mL oven-dried Schlenk tube fitted with a septum was stirred a solution of (*Z*)-6-oxo-6-phenylhex-4-enal (**131**) (19 mg, 0.10 mmol, 1 equiv) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**1e**) (13 mg, 0.05, mmol, 0.5 equiv) or (*S*)-2-benzyl-5-((tert-butyldiphenylsilyloxy)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**16k**) (29 mg, 0.05 mmol, 0.5 equiv) in dry dichloromethane (0.2 mL, 0.5 M). To this solution, furfural (**2b**) (13 μL, 0.15 mmol, 1.5 equiv) and 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (8 μL, 0.05 mmol, 0.5 equiv) were successively added. After stirring the mixture at ambient temperature for 10 minutes, the reaction was quenched with a saturated solution of aqueous ammonium chloride (1 mL) and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were filtered through a small pipette column containing anhydrous sodium sulfate / silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford 26% yield (8 mg, 1.5:1 dr) with precatalysts **1e** and 37% yield (11 mg, 1.1:1 dr) with precatalysts **16k** of a light yellow oil. R_f = 0.25 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3346, 3135, 2943, 1770, 1731, 1769, 1730, 1465, 1449, 1001, 756, 690; (*major diastereomer*) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H), 7.61 (dd, *J* = 0.9, 0.6 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.48 – 7.41 (m, 2H), 7.30 (d, *J* = 3.6 Hz, 1H), 6.54 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.04 (t, *J* = 7.3 Hz, 1H), 4.74 (dq, *J* = 6.0, 6.0 Hz, 1H), 3.51 (dd, *J* = 16.4, 5.7 Hz, 1H), 3.14 (dd, *J* = 16.8, 7.0 Hz, 1H), 2.31 – 2.28 (m, 2H), 2.22 – 2.16 (m, 1H), 1.74 – 1.65 (m, 1H); (*minor diastereomer*) δ 8.01 – 7.93 (m, 2H), 7.60 (dd, *J* = 0.9, 0.6 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.48 – 7.41 (m, 3H), 6.52 (dd, *J* = 3.5, 1.6 Hz, 1H), 5.08 (dd, *J* = 8.5, 4.3 Hz, 1H), 4.68 (dq, *J* = 8.1, 6.2 Hz, 1H), 3.67 (dd, *J* = 16.9, 6.2 Hz, 1H), 3.18 (dd, *J* = 17.5, 6.6 Hz, 1H), 2.46 – 2.39 (m, 2H), 2.22 – 2.16 (m, 1H), 1.74 – 1.65 (m, 1H); (*major diastereomer*) **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.8, 189.0, 147.1, 137.2, 133.5,

129.0, 128.9, 128.8, 119.2, 112.5, 80.9, 77.3, 44.6, 31.8, 30.0; (*minor diastereomer*) δ 198.2, 188.4, 147.0, 137.2, 133.4, 128.5, 128.4, 128.3, 119.9, 112.4, 80.5, 77.8, 44.7, 31.2, 29.9; **HRMS** (CI^+/NH_3) *m*/*z* calcd for $C_{17}H_{17}O_4$ [$M+1^+$]: 285.1127; found: 285.1127.

Synthesis of analogs of the core structure of fredericamycin A (101a, 142, and 143)

***Rac*-2'-benzoyl-2',3'-dihydro-1,2'-spirobis[indene]-1,3-dione (137)**

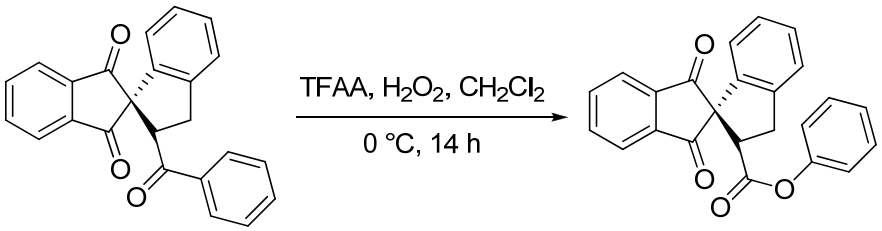


99a **137**

In a 50 mL round-bottom flask a mixture of *rac*-2'-benzoyl-1-hydroxy-1,2'-spirobi[inden]-3(1H)-one (**99a**/*epi*-**99a**) (30 mg, 0.09 mmol, 1 equiv) and 5% palladium on carbon (4 mg, 0.002 mmol, 0.02 equiv. based on palladium) in dry ethanol (0.4 mL, 0.2 M) was stirred at ambient temperature. The flask was evacuated and filled with hydrogen gas (balloon) (3 X). The reaction was monitored by ^1H NMR until complete consumption of the starting material (ca. 24 h). The crude mixture was filtered through a plug of Celite® and the filter cake was washed with dichloromethane (3 x 20 mL). The solvent was removed in vacuo. The crude product was re-dissolved in acetonitrile (0.9 mL, 0.1 M) and 2-iodoxybenzoic acid (IBX) was added (95 mg, 0.34 mmol, 4 equiv). The mixture was heated at 80 °C for 2 h and then cooled to ambient temperature. Ethyl acetate (10 mL) was added and the mixture was filtered through a fritted funnel. The filter cake was washed with dichloromethane (5 X 5 mL), the solvent was removed in vacuo and the crude product was purified by flash column chromatography affording the title compound in 85% yield (25 mg) as a pale yellow solid. **mp** (°C): 202-203, R_f = 0.25

(20% ethyl acetate in hexanes). **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1702, 1672, 1595, 1448, 1265; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.2, 7.9 Hz, 2H), 7.92 – 7.83 (m, 4H), 7.53 (t, *J* = 7.4, 7.4 Hz, 1H), 7.42 (dd, *J* = 7.9, 7.5 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5, 7.5 Hz, 1H), 7.08 (t, *J* = 7.5, 7.5 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 5.02 (dd, *J* = 11.6, 8.9 Hz, 1H), 3.79 (dd, *J* = 15.2, 12.0 Hz, 1H), 3.59 (dd, *J* = 15.3, 8.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.4, 199.1, 143.3, 143.0, 142.5, 141.3, 136.2, 136.2, 135.3, 133.5, 128.9, 128.8, 128.7, 127.5, 125.4, 124.2, 123.6, 122.6, 67.1, 59.3, 36.1; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{16}O_3$ [M^+]: 352.1099; found: 352.1102.

***Rac*-Phenyl 1,3-dioxo-1,2',3,3'-tetrahydro-1,2'-spirobis[indene]-2'-carboxylate (138)**

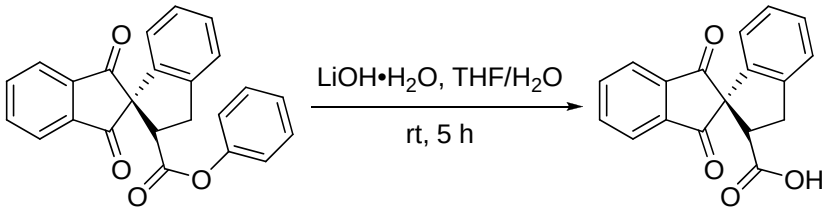


137 **138**

In a 5 mL round-bottom flask trifluoroacetic anhydride (930 µL, 6.64 mmol, 13.1 equiv) was cooled to -12 °C using an ice-salt bath for 10 min, then 35% hydrogen peroxide (138 µL, 1.57 mmol, 3.1 equiv) was added dropwise keeping the temperature below 0°C. The mixture was stirred for 10 min and then a solution of *rac*-2'-benzoyl-2',3'-dihydro-1,2'-spirobi[indene]-1,3-dione (**137**) (179 mg, 0.51 mmol, 1 equiv) in dichloromethane (5.1 mL) was added dropwise. The mixture was stirred for 14 h at 0 °C. The reaction mixture was then diluted with dichloromethane (5 mL) and water was added (5 mL). The organic layer was washed with concentrated sodium bicarbonate (until the pH of the aqueous layer was ca. 7) and brine, then dried through anhydrous sodium sulfate. The crude product was purified by flash column

chromatography to afford an off-white solid in 89% yield (166 mg). **mp** (°C): 177-179, R_f = 0.3 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3438, 3071, 2256, 1743, 1708, 1591, 1260, 1187, 729; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 – 8.13 (m, 1H), 8.05 – 8.04 (m, 1H), 7.91 – 7.88 (m, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.28 – 7.25 (m, 3H), 7.14 (t, *J* = 7.4, 7.4 Hz, 1H), 7.08 (t, *J* = 7.5, 7.5 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 7.6 Hz, 1H), 4.46 (dd, *J* = 10.0, 9.9 Hz, 1H), 3.95 (dd, *J* = 16.0, 10.7 Hz, 1H), 3.54 (dd, *J* = 16.0, 9.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.9, 198.7, 170.1, 150.4, 143.3, 143.1, 142.5, 140.9, 136.3, 135.9, 129.6, 129.0, 127.5, 126.2, 125.7, 124.4, 124.0, 122.7, 121.4, 68.2, 50.2, 34.2; **HRMS** (EI^+) *m*/*z* calcd for $C_{24}H_{16}O_4$ [M^+]: 368.1048; found: 368.1046.

***Rac*-1,3-dioxo-1,2',3,3'-tetrahydro-1,2'-spirobis[indene]-2'-carboxylic acid (139)**

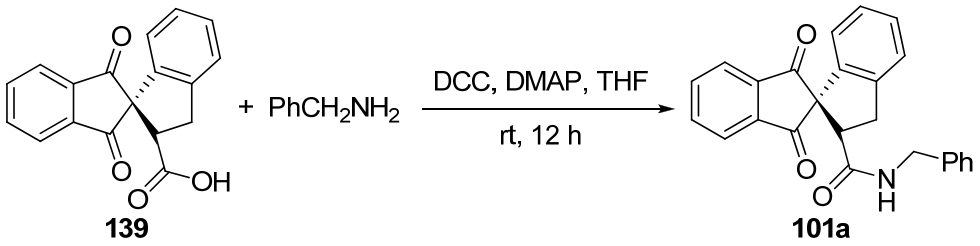


138 **139**

In a 250 mL round-bottom flask was stirred a solution of *rac*-phenyl 1,3-dioxo-1,2',3,3'-tetrahydro-1,2'-spirobi[indene]-2'-carboxylate (**138**) (423 mg, 1.15 mmol, 1 equiv) in wet THF (115 mL, 0.01 M), to which a solution of LiOH•H_2O (53 mg, 1.26 mmol, 1.1 equiv) in water (4.2 mL, 0.3 M respect to the base) was added. The reaction was stirred at ambient temperature for 5 h. The reaction mixture was quenched by adding 1M HCl until pH = 2, THF was evaporated and to the remaining oil, brine was added and the organic material was extracted with ethyl acetate (3 x 50 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (5% methanol in dichloromethane)

affording the title compound in 44% yield (149 mg) as a tan solid. Trace impurities can be removed by recrystallization from dichloromethane. **mp** (°C): 186-187, R_f = 0.3 (5% methanol in dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3398, 1750, 1701, 1243, 1124, 906, 700; **^{1}H NMR** (500 MHz, D_2O+KOH) δ 7.68 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.59 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.53 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.27 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.20 (t, *J* = 7.5, 7.5 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 3.35 (ddd, *J* = 24.1, 24.1, 9.1 Hz, 1H), 3.35 – 3.33 (m, 1H), 3.07 (ddd, *J* = 22.0, 22.0, 11.0 Hz, 1H); **^{13}C NMR** (125 MHz, D_2O+KOH / Acetone was Used as Reference) δ 210.3, 182.9, 175.9, 144.0, 140.7, 138.9, 138.1, 131.8, 130.2, 128.6, 128.2, 128.1, 127.6, 127.1, 126.9, 126.2, 125.1, 60.6, 51.3, 37.1; **HRMS** (EI^+) *m/z* calcd for $C_{18}H_{12}O_4$ [M^+]: 292.0735; found: 292.0731.

***Rac*-*N*-benzyl-1,3-dioxo-1,2',3,3'-tetrahydro-1,2'-spirobis[indene]-2'-carboxamide (101a)**

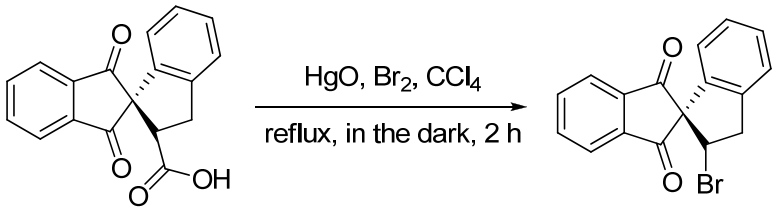


139 **101a**

In a 5 mL round-bottom flask was stirred a solution of *rac*-1,3-dioxo-1,2',3,3'-tetrahydro-1,2'-spirobi[indene]-2'-carboxylic acid (**139**) (10 mg, 0.034 mmol, 1 equiv), *N,N*-dicyclohexylcarbodiimide (10.5 mg, 0.051 mmol, 1.5 equiv), and 4-(dimethylamino)pyridine (0.4 mg, 0.003 mmol, 0.1 equiv) in dry THF (0.34 mL, 0.1 M) for 10 minutes. Immediately after, benzylamine (5.6 mL, 0.051 mmol, 1.5 equiv) was added. The mixture was stirred at room temperature for 2 h. Thereafter, the solvent was removed by rotary evaporation and the crude mixture was purified by preparative thin layer chromatography (PTLC) (30% ethyl acetate in

hexanes, developed 3X) affording **101a** in 45% yield (6 mg) as a colorless oil. R_f = 0.25 (50% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3325, 2927, 2248, 1672, 1603, 1410, 910, 730.; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.1 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.60 (ddd, *J* = 7.2, 7.2, 1.0 Hz, 1H), 7.56 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.22 – 7.14 (m, 4H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.80 (d, *J* = 15.8 Hz, 1H), 4.71 (d, *J* = 15.8 Hz, 1H), 3.69 – 3.61 (m, 2H), 3.46 – 3.38 (m, 1H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 202.5, 174.5, 151.5, 145.5, 137.8, 137.6, 135.9, 135.1, 130.9, 129.8, 128.7, 127.8, 127.4, 127.3, 126.5, 125.5, 125.4, 124.7, 94.8, 71.8, 50.0, 43.7, 35.6.; **HRMS** (EI^+) *m/z* calcd for $C_{25}H_{19}NO_3$ [M^+]: 381.1365; found: 381.1362.

***Rac*-2'-bromo-2',3'-dihydro-1,2'-spirobis[indene]-1,3-dione (142)**

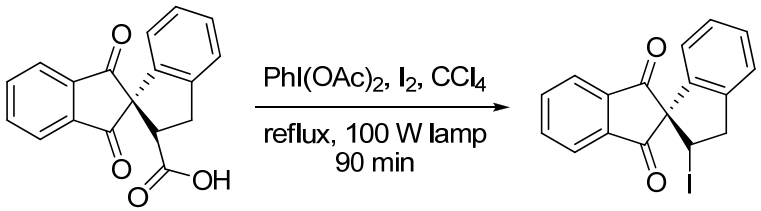


139 **142**

A 5 mL Schlenk tube wrapped in aluminum foil was charged with a solution of *rac*-1,3-dioxo-1,2',3,3'-tetrahydro-1,2'-spirobi[indene]-2'-carboxylic acid (**139**) (52 mg, 0.18 mmol, 1 equiv), red mercury oxide (39 mg, 0.18 mmol, 1 equiv), and carbon tetrachloride (1.8 mL, 0.1 M). This mixture was heated for 5 min in an oil bath at 80 °C. Immediately after, a solution of liquid bromine (2.2 μL, 0.04 mmol, 1.3 equiv) in carbon tetrachloride (44 μL) was added dropwise and the reaction was allowed to stir at 80 °C for 2 additional hours. The tube was left to cool to ambient temperature and the mixture was quenched with 1 mL of a saturated solution of $NaHCO_3$. The crude product was filtered through a pad of Celite® and the filter cake was rinsed

thoroughly with chloroform. The filtrate was consecutively washed with $NaHCO_3$ (2X) and brine (1X). Then, the organic phase was dried through anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) affording the title compound in 26% yield (15 mg) as a off-white solid. **mp** (°C): 187-189, R_f = 0.3 (30% Ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2923, 1739, 1707, 1269, 783, 762; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 2H), 7.97 – 7.93 (m, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 4.96 (dd, *J* = 10.6, 7.8 Hz, 1H), 3.83 (dd, *J* = 15.3, 10.6 Hz, 1H), 3.56 (dd, *J* = 15.3, 7.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 197.0, 143.5, 143.1, 142.3, 140.5, 136.8, 136.1, 129.2, 127.9, 124.9, 124.6, 123.8, 123.2, 69.3, 47.8, 42.1; **HRMS** (CI^+/NH_3) *m/z* calcd for $C_{17}H_{11}BrO_2$ [M+1$^+$]: 326.9843; found: 326.9854.

***Rac*-2'-iodo-2',3'-dihydro-1,2'-spirobis[indene]-1,3-dione (143)**



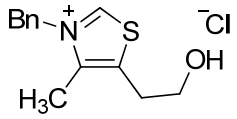
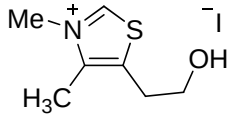
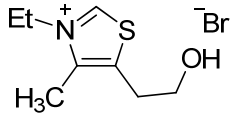
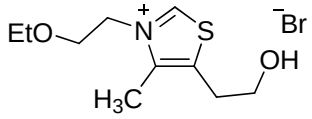
139 **143**

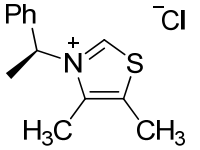
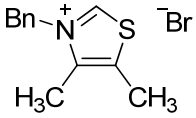
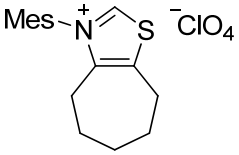
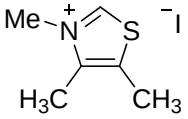
A 5 mL Schlenk tube was charged with a solution of *rac*-1,3-dioxo-1,2',3,3'-tetrahydro-1,2'-spirobi[indene]-2'-carboxylic acid (**139**) (338 mg, 1.16 mmol, 1 equiv), iodobenzene diacetate (18 mg, 0.64 mmol, 0.55 equiv), and iodine (14 mg, 0.64 mmol, 0.55 equiv) in carbon tetrachloride (89 mL, 0.013 M). This mixture was heated in an oil bath to 80 °C for 45 min (the reaction mixture turns purple). Additionally; the tube was irradiated with a 100 W tungsten lamp during the complete course of the reaction. After the first 45 min were completed, a second

portion of iodobenzene diacetate (18 mg, 0.64 mmol, 0.55 equiv), and iodine (14 mg, 0.64 mmol, 0.55 equiv) were added simultaneously and the reaction was heated at the same temperature for additional 45 min. Then, the tube was left to cool to ambient temperature and the reaction mixture was sequentially washed with sodium thiosulfate (2 x 10 mL) (the organic layer turns light yellow), water (1 x 10 mL), and brine (1 x 10 mL). Then, the organic phase was dried through anhydrous sodium sulfate, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) affording the title compound in 35% yield (152 mg) as a light yellow solid. **mp** (°C): 199-200, R_f = 0.4 (30% Ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3428, 2918, 1737, 1705, 1268, 761; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 2H), 7.97 – 7.93 (m, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 4.87 (dd, *J* = 11.1, 7.8 Hz, 1H), 3.85 (dd, *J* = 15.3, 11.1 Hz, 1H), 3.55 (dd, *J* = 15.3, 7.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.9, 198.2, 144.5, 143.5, 141.9, 140.6, 136.9, 136.2, 129.1, 127.7, 124.8, 124.5, 123.8, 123.1, 69.7, 44.1, 20.3; **HRMS** (CI^+/NH_3) *m/z* calcd for $C_{17}H_{11}IO_2$ $[M+1]^+$: 374.9904; found: 375.0268.

APPENDIX

N-HETEROCYCLIC CARBENE PRECURSORS

Number	*Thiazolium salts*
1c	
1d	
1e	
1f	

Number	*Triazolium salts*
1g	
1h	
1i	
1j	

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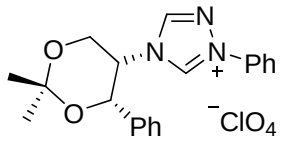
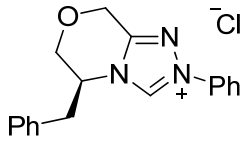
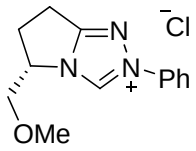
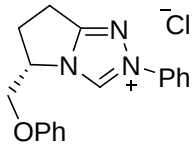
16a	
16b	
16c	
16d	

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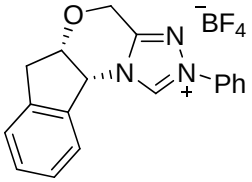
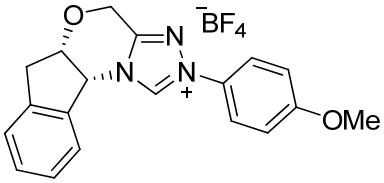
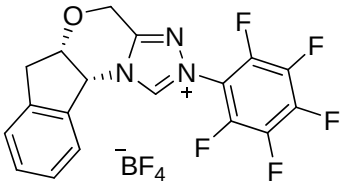
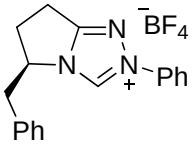
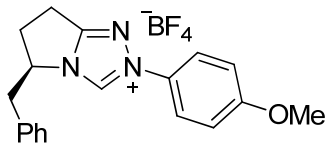
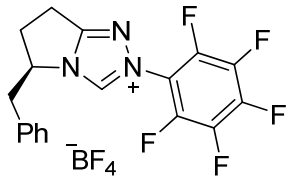
16e	
16f	
16g	
16h	

16i



16j



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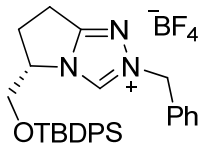
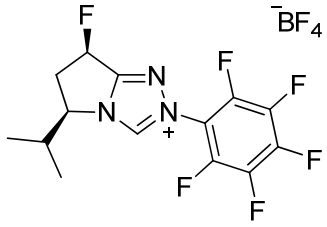


16l



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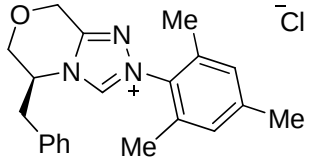
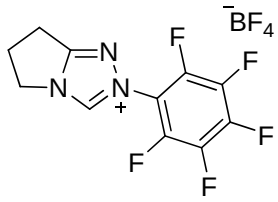


16n



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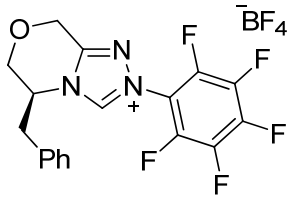
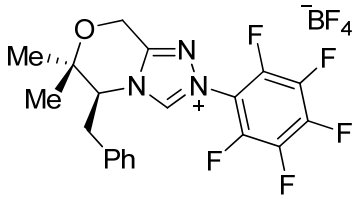


16p



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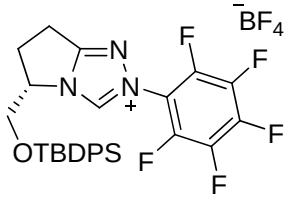
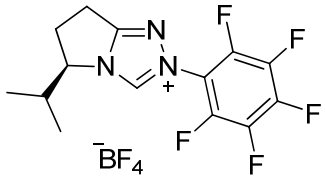


16r



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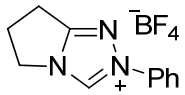

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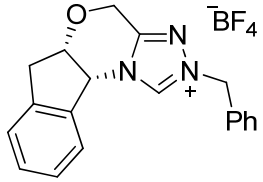
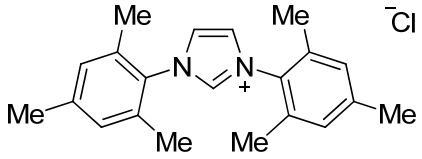
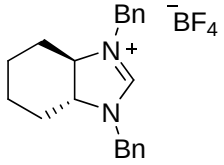


Number ***Imidazolinium salts***

15a

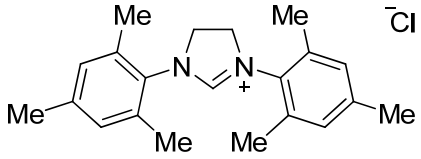


15b



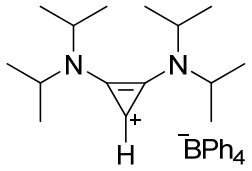
Number ***Imidazolium salts***

14a



Cyclopropenium salt

93a



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